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Review

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Herbicide resistance modelling: past, present and future

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Abstract

Computer simulation modelling is an essential aid in building an integrated understanding of how different factors interact to affect the evolutionary and population dynamics of herbicide resistance, and thus helps in predicting and managing how agricultural systems will be affected. In this review, why computer simulation modelling is such an important tool and framework for dealing with herbicide resistance is first discussed. The questions related to herbicide resistance that have been addressed to date using simulation modelling are then explained, and the modelling approaches that have been used are discussed, focusing first on the earlier, more general approaches, and then on some newer, more innovative approaches. How these approaches could be further developed in the future, by drawing on modelling techniques that are already employed in other areas, such as individual-based and spatially explicit modelling approaches, is then considered, as well as the possibility of better representing genetics, competition and economics, and finally the questions and issues of importance to herbicide resistance research and management that could be addressed using these new approaches are discussed. It is concluded that it is necessary to proceed with caution when increasing the complexity of models by adding new details, but, with appropriate care, more detailed models will make it possible to integrate more current knowledge in order better to understand, predict and ultimately manage the evolution of herbicide resistance.

Keywords: computer; simulation; evolution; integration; genetics

1 INTRODUCTION

Herbicide resistance is a serious agricultural issue that threatens the sustainability of world food production.[1–3] Hundreds of biotypes of weeds resistant to commonly applied herbicides are now found throughout the world.[4,5] The emergence of herbicide resistance is an evolutionary and ecological process, influenced by many interacting factors; these include the chemistry and rate of herbicides applied, other non-chemical weed management, the particular ecological and biological traits of the weed species or ecotype being studied, environmental conditions and the possible biochemical and molecular mechanisms capable of conferring effective resistance, and their underlying genetic basis. Computer simulation modelling provides an important tool for helping to build an integrated understanding of how these different factors interact to affect the evolutionary and population dynamics of herbicide resistance, and thus helps in predicting and managing how agricultural systems will be affected.

In this review, the authors (1) expand on why computer simulation modelling is such an important tool and framework for understanding, predicting and managing herbicide resistance, (2) explain what questions related to herbicide resistance have been addressed to date using simulation modelling, (3) discuss the modelling approaches that have been used, focusing first on the earlier, more general approaches, and then on some newer, more 'cutting-edge' approaches, (4) consider how these approaches could be further developed in future, by drawing on modelling techniques that are already employed in other areas, and finally (5) discuss what new questions and issues could be addressed using these new approaches. This review focuses on modelling the evolution of herbicide resistance, in contrast to other recent overviews that have taken a different or wider focus, such as modelling the evolution of resistance to pesticides and drugs in general,[6] or modelling weed population dynamics in general.[7–12] It also focuses on models that represent or simulate the dynamic evolutionary and population processes underlying the evolution of resistance, while recognising the value of many other types of modelling, such as more empirical modelling of herbicide risk assessment[13–15] or economic modelling that does not explicitly represent genetics.[16–21]

2 USE AND VALUE OF MODELLING

Computer modelling provides a tool for integrating current knowledge and hypotheses regarding the different factors and processes that influence evolution of resistance (Fig. 1). This can help

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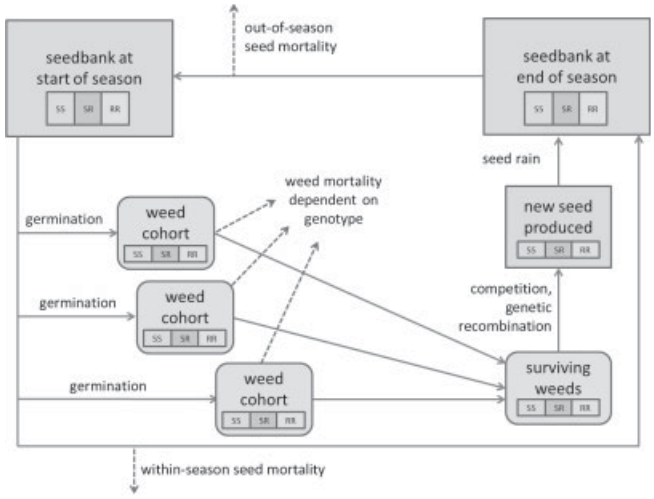

Figure 1. Conceptual model illustrating the typical dynamics simulated in a model of herbicide resistance evolution in an annual weed. The boxes usually represent the frequencies of different genotypes in the various weed and seedbank subpopulations and cohorts; sizes or densities of the subpopulations may also be represented (here, three genotypes are represented: a homozygous susceptible SS, a homozygous resistant RR and a heterozygote SR, under the assumption of a single gene, but any number is possible). A number of steps occurring within a year are simulated, resulting in transitions between the various weed and seedbank subpopulations and cohorts (solid arrows) or mortality (dashed arrows). At the start of the growing season, there exists a dormant seedbank consisting of seeds of different genotypes. One or more germination events occur, each resulting in a proportion of the seeds becoming a weed cohort (here, three germination events and cohorts are represented, but any number is possible). Herbicide application results in weed mortality, with a different mortality for different genotypes. Surviving weeds produce new seed, with the number of new seeds influenced by competition between weed cohorts and the crop, and the genotype of the new seeds determined by genetic recombination between the surviving weeds. This seed is added to the remaining dormant seedbank that has survived within-season seed mortality to form the end-of-season seedbank. Seed that survives out-of-season seed mortality then becomes the starting seedbank for the next season, and thus the simulation continues, with all these within-year processes simulated repeatedly to represent the population and evolutionary dynamics over several years. The process of evolution is driven by the differential survival of weeds under herbicide treatment, so that over a number of years the proportions and numbers of different genotypes will vary. Non-chemical weed treatments can be included in the model at almost any place; for example, harvest seed control techniques would result in a proportion of the seed produced being removed and not combined with the dormant seedbank, or higher crop sowing density might result in higher competition on the surviving weeds and thus lower seed production. Herbicide and non-chemical management can be assumed to be the same each year, or to vary from year to year. Variable environmental conditions may affect any of the processes in the model (proportion of germination for each cohort, competition, seed mortality, herbicide efficacy, etc.), or an 'average season' can be assumed in each year. Typically, the dynamics is simulated over several years, and the changing genotype frequencies and population densities are tracked until either a set number of years is reached or some other stopping criterion (such as weed population reaching a critical density threshold) is reached.

in understanding and predicting herbicide resistance evolution, and thus potentially in designing and evaluating effective proactive strategies to delay or even avoid its appearance,[22,23] rather than just reactively trying to manage populations that are already resistant.[24] Modelling allows and indeed encourages herbicide resistance to be approached from evolutionary and ecological perspectives likely to yield more complete understanding and, ultimately, better management outcomes.[25,26] Many important aspects of resistance to pesticides, such as the nature of underlying mechanisms, their genetic bases and the levels of resistance they confer, can be best studied in laboratory, glasshouse or field experimentation. However, it is impossible to capture fully the long-term and large-scale dynamics of resistance evolution in such experimental systems. This is because the processes occur among millions or more usually billions of individuals, across huge areas and over many years. Experiments or trials on these scales are likely to be too expensive to be feasible, take too long to be useful and pose unjustifiable biosecurity risks by producing large numbers of resistant individuals, but computer simulation enables safe and quick virtual experiments to be conducted to investigate how various management options will affect the rate of emergence of herbicide resistance in large populations across large areas and long timeframes. Computer modelling can also represent aspects of the system that are very difficult to measure accurately in reality, such as the frequency of rare genes and the nature of soil seed banks, and the way these change with time. This can provide an insight into the way these hidden factors are likely to be affected by management factors, interact with ecological factors and affect herbicide efficacy and weed population sizes. Modelling also allows a much wider range of factors and interactions to be varied than would be possible in real experiments, giving a more complete understanding of the causal relationships determining the way in which resistance evolves.

It is also important to recognise the limitations of computer modelling as a tool for understanding and particularly for predicting herbicide resistance evolution. The accuracy of a simulation model's predictions depends on the accuracy of (1) the representation of underlying processes within the model, (2) the parameter values used in the model and (3) the definition of initial conditions.[27] Errors in model assumptions can lead to large errors in predictions.[28] For example, the rate at which herbicide resistance evolves will depend strongly on the initial frequency of resistance alleles within the population; this initial frequency may vary widely between different populations, and yet it is difficult accurately to measure this initial (or current) frequency in a given population. However, even if quantitatively accurate prediction of time to emergence of resistance is not possible because exact values for certain parameters are not known, sensitivity analysis of parameters with unknown values can be used to estimate their relative importance, thus identifying important data gaps and helping to prioritise further empirical research. Such sensitivity analysis may also reveal that relative effects do not depend on the unknown parameter values; for example, more frequent use of a herbicide may lead to faster evolution of resistance to that herbicide for a very wide range of initial frequencies of resistance alleles.

3 HERBICIDE RESISTANCE ISSUES ADDRESSED WITH MODELLING

3.1 Time to resistance

One of the first answers many managers would like a herbicide resistance model to provide is how long it will take until they have a resistance problem. Ideally, the model would be able to predict how long it will take under the current weed management strategy, and, for comparison, how long it would take under possible alternative weed management strategies. Almost all herbicide resistance models provide a prediction of 'time to resistance', with some defining this in terms of a threshold frequency of resistance within the population[29,30] and others seeking a definition of more direct relevance to the farmer, such as time until weed populations

reach a critical level, or until herbicide efficacy falls below a certain threshold.[31,32] Modelling studies then typically look at how this 'time to resistance' depends on weed management, and other ecological, biological and genetic factors • (Table 1). However it is defined, models have predicted that this 'time to resistance' is very sensitive to parameters that are almost impossible to measure in practice, and that may vary considerably between populations of the same species. In particular, the initial resistance allele frequency has a substantial effect on predicted time to resistance across a range of different models, and is likely to vary substantially in real populations – few of which remain entirely unselected in any case.[29,33,34] Therefore, much herbicide resistance modelling work has focused on predicting whether certain management options are likely to increase or decrease the time to resistance in relative terms, rather than absolute time estimates.

3.2 Rotations and mixtures

One management option often recommended to delay the evolution of herbicide resistance is the use of herbicide rotations and mixtures/combinations, and this has been a popular topic for modelling as well (Table 1).[30,32,35] 'Combination' strategies, defined as strategies involving 'multiple intragenerational killing', can be considered to include both the application of physical mixtures of different herbicides and strategies such as 'double knockdown' that do not necessarily involve a literal mixing of different herbicides but still apply more than one herbicide within each generation.[35] Empirical studies have provided evidence that mixtures/combinations may be more effective than rotations in delaying resistance evolution through herbicide selection,[36] and modelling has supported this empirical evidence.[34,35,37,38] The issue of mixtures is growing in importance, as new crop technologies with resistance to multiple herbicides are developed.[39] Positive cross-resistance, where resistance to one herbicide also confers some resistance to another, is likely greatly to reduce the usefulness of rotations, mixtures and multiple-herbicide-resistant crop technologies as control measures;[40] to date, this issue has sometimes been ignored in modelling studies. Modelling has predicted that the efficacy of rotation and mixtures will depend on the fitness costs associated with resistance and negative cross-resistance (where resistance to one herbicide reduces resistance to another) between the herbicides used.[32,41,42]

3.3 High and low dose

Another, somewhat controversial, management issue addressed with modelling has been the question of herbicide dose, or the 'dose rate debate' as it is sometimes called (Table 1).[26,43,44] Models have consistently predicted that higher selection pressure (usually associated with higher dose) leads to faster increases in the frequency of resistance alleles within a population over time when resistance is assumed to be conferred by a single dominant gene of major effect (monogenic resistance).[29,45] However, herbicide resistance modelling has suggested that relatively low doses are likely to lead to resistant weed problems faster when effective resistance is conferred by multiple genes acting together, and any one of these genes can only confer a partial minor level of resistance (polygenic resistance).[31,46] In this case, low doses tend to allow individuals with partial levels of resistance to survive,[47,48] which then cross with individuals with partial levels of resistance conferred by other genes, producing some progeny with more of these minor genes 'stacked together' and thus higher resistance. This means that, over a number of years, weed populations can evolve resistance more quickly under low doses; in combination with the lower kill rates achieved with lower herbicide rates, this means that weed populations may increase in size considerably faster than if higher doses were used. This is one case where modelling indicates differences between resistance evolution in weeds and other organisms, with modelling for fungicide resistance indicating that low rates pose no risk of increased rates of evolution.[43] The modelling also provides an insight into why such differences might be expected between weeds and fungi, because sexual recombination is generally less frequent with fungi, and fungal populations do not generally need several years to build up populations. Modelling has also suggested that a 'revolving dose' strategy of alternating relatively high doses and relatively low doses may be effective when both polygenic and monogenic resistance genes are present at low levels in a population; the low doses reduce selection pressure for the monogenic resistance, and the high doses help to stop the accumulation of polygenic resistance alleles.[49,50] For organisms besides weeds, when it is possible to apply a pesticide dose for which the expression of resistance is recessive, modelling has predicted that a strategy combining areas of high-dose applications with areas of refuges (no dose) would be effective in delaying resistance evolution,[51–55] and it appears that the strategy has been at least somewhat effective,[55] even if limitations of the modelling and strategy must be acknowledged.[28,55] However, similar strategies in weeds have not received much attention from modellers because of the difficulty of finding situations where the required combination of an economically viable herbicide dose and a recessive expression of resistance exists.

3.4 Tillage

Soil cultivation has long been used as a weed control method, and occasional strategic tillage has been recommended for managing weeds in reduced-tillage systems,[56,57] along with harvest seed control measures.[58–60] These non-chemical control methods are promoted as ways to deal with populations that already have resistance or to delay resistance evolution by removing the need for some herbicide applications within the system. Modelling has predicted that the risk of resistance evolution can also be reduced by adding tillage to a system without removing any herbicide applications, by gaining additional weed kill through soil disturbance at sowing[38,61] or by burying resistant populations through occasional strategic soil inversion (Table 1).[62]

3.5 Interactions between management, genetics and ecology

As well as looking directly at the effect of management issues on rates of evolution of herbicide resistance rates of evolution, modelling has been used to investigate how other biological, ecological or genetic factors may influence rates of evolution, or even how biological or genetic factors may interact with management to affect rates of evolution (Table 1). Some of the factors that have been considered include the underlying genetic basis of resistance (inheritance), the mating system, gene flow, fecundity, seed dormancy and longevity of soil seed banks, and ecological fitness of different resistance genotypes.[32–34,45,62–65] For example, investigating interactions between seed dormancy and germination and the timing of when a herbicide is applied within a growing season in relation to other herbicides, and so which herbicides affect which weed cohorts, can help to explain different rates of evolution of resistance.[34,66] Many of these ecological/biological factors apply specifically to weeds, as opposed to other organism types,

justifying the development of weed-specific models. Studies have also considered how biological or genetic factors may interact with management options to influence the rate at which populations might regress from evolved resistance and become more susceptible again,[67,68] and how these factors influence the ideal weed density thresholds that should be maintained in fields.[69,70]

3.6 Spatial spread

Spatial spread of resistance through pollen and seed dispersal is another issue that has been addressed with modelling (Table 1). There has been some spatially explicit modelling of resistance evolution dynamics that has considered the spread both within and among fields.[71–77] Modelling of the spread of resistance

Table 1. Published studies that have used modelling to understand and/or predict the evolution of resistance to herbicides, ordered by publication year. The superscript next to each year is the number in the References list. For each study, the table shows whether the study explicitly tested the effect of certain management, genetic and biological/ecological factors on the evolutionary dynamics. It also shows whether the model used in the study had certain characteristics that would tend to increase model realism but at the expense of increased model complexity and/or reduced generality. Management factors include herbicide **rotation**, herbicide **mixture**, **mosaic**, i.e. spatial heterogeneity in herbicide application, herbicide **dosage**, **tillage**/cultivation or **other** management options. Genetic factors include the **initial frequ**ency of resistance alleles, the **mutation** frequency, **dominance**, the **strength** of resistance, the possibility of **cross-resistance**, the **number** of **genes** involved in resistance and **epistasis**. Biological/ecological factors include **fitness** penalties for resistance alleles, seed **dormancy** and/or longevity, **dispersal** and/or gene flow, **outcrossing** rates and **init**ial **pop**ulation **size**. Model characteristics include whether the model represents **pop**ulation **dynamics**, as opposed to just genetic dynamics, **density depend**ence, **spatial heterog**eneity and **multiple genes**/loci, and also whether the model is **stochastic**, as opposed to deterministic, whether it was **simulated** on a computer to obtain results, as opposed to being solved analytically, and whether it was explicitly constructed to represent a **specif**ic weed **species**

Year	Management factors						Genetic factors							Biological/ecological factors							Model characteristics				
	rotation	mixture	mosaic	dosage	tillage	other	initial frequ	mutation	dominance	strength	cross- resistance	number genes	epistasis	fitness	dormancy	dispersal	outcrossing	init pop size	pop dynamics	density depend.	spatial heterog.	multiple genes	stochastic	simulated	specific species
78[45]							y	y						y	y										
90[32]	y						y							y	y										
90[68]				y										y		y	y		y					y	
92[63]	y													y	y				y						y
92[70]						y										y					y			y	y
94[64]	y	y					y							y										y	
96[33]	y						y	y	y																
96[90]				y		y	y									y			y		y				y
98[49]	y			y					y										y		y		y	y	
00[93]	y				y		y											y	y		y		y	y	y
01[29]	y	y		y			y		y			y							y		y		y	y	y
01[94]	y				y			y									y	y	y				y	y	y
02[74]	y		y	y											y	y			y		y			y	
02[92]	y				y														y					y	y
03[37]	y	y															y	y	y			y	y	y	
03[66]		y				y	y		y					y	y				y			y	y	y	y
03[38]	y	y			y	y	y	y							y			y	y			y	y	y	y
04[73]																y			y		y			y	
06[86]																									
07[77]	y		y						y					y			y		y		y			y	
08[30]	y	y								y									y					y	y
08[34]	y	y		y		y	y		y					y	y		y	y	y		y			y		
08[72]	y																				y				
08[76]	y		y						y					y			y		y		y			y	
09[42]		y							y	y	y			y			y		y		y			y	
09[87]	y			y	y	y													y				y	y	y
11[31]				y					y	y		y	y						y		y		y	y	
11[88]		y					y								y			y	y				y	y	y
11[89]	y	y			y														y				y	y	y
12[46]				y					y	y		y	y						y		y		y	y	y
12[62]	y			y	y							y					y		y		y		y	y	
13[61]	y	y		y	y	y									y		y		y				y	y	y
13[91]	y	y			y	y	y								y			y	y				y	y	y
13[100]												y		y					y			y		y	
13[104]	y			y	y							y				y			y		y	y	y	y	

genes from transgenic crops has also received considerable attention,[78–80] and this modelling has potential to inform the modelling of the 'natural' emergence of resistance in weeds under selection from herbicide treatments in the way that it represents the flow of genes through pollen and possibly seed dispersal.

4 APPROACHES TO MODELLING THE EVOLUTION OF RESISTANCE

4.1 Simpler approaches

Early approaches to modelling the dynamic evolution of resistance usually aimed to capture the most important factors involved in relatively simple ways (Table 1). Simpler models also tend to be relatively general and abstract, and so they did not necessarily contain features that were specific to herbicides and weeds, but could also be thought of as representing other types of organism, although a few models were specifically developed to represent weeds.[32,45,68,81,82] In such models, the basis of resistance was usually assumed to be monogenic, and the gene was often assumed to be fully dominant, leading to an assumption of just two phenotypes – one fully susceptible and one completely resistant. These models were usually based on population density, in that their state variables represented the frequency or proportions of different alleles, genotypes or phenotypes in the population; they thus predicted when resistance might appear, but not what densities of resistant individuals to expect. These frequencies could usually take any value between 0 and 1, meaning that the discrete nature of real populations and genomes was not accounted for. These models did not typically represent seasonal variation effects or ecological aspects specific to weeds, such as dormant seed banks persisting across seasons or staggered germination within a season resulting in a number of different weed cohorts.

4.2 Adding more details of the real biological system

With time, models of herbicide resistance evolution began to include representation of more aspects of the real biological system (Table 1). In many cases this involved making the model more specific to weeds and herbicides (rather than general organisms and pesticides), and in some cases specific to particular weed species or agricultural systems (see below for examples). In other cases, genetic details were added without ecological/biological details that made the model specific to weeds.[49,83]

In the simplest approaches, actual weed population density is largely ignored, and only the frequency of the susceptible/resistant genotypes is represented. However, in reality it is weed population sizes or densities that concern farmers, and modellers have recognised this and included representation of plant and seed numbers, along with genotype frequencies (e.g. Renton *et al.*[31] and Gardner *et al.*[49]). With population densities comes the need to consider density-dependent nature of seed production, self-thinning and mortality, and intra- and interspecific resource competition. These have often been represented in fairly simple descriptive ways, such as using a hyperbolic competition function like that developed by Firbank and Watkinson,[84,85] where seed production per unit area tends towards a fixed maximum at high densities (see Renton *et al.*[31] and Diggle *et al.*[37] for examples), although more recently resistance evolution models have been linked with more complex crop growth simulation models that handle the simulation of crop–weed competition with much greater temporal and spatial resolution and biological realism.[61,86,87]

As mentioned, some herbicide resistance models have started to focus quite specifically on the details of particular species, herbicides and systems. Such modelling may, for example, focus very specifically on glyphosate resistance evolution in Palmer amaranth (*Amaranthus palmeri*) in glyphosate-resistant transgenic cotton in the southern United States[88,89] or glyphosate resistance evolution in awnless barnyard grass (*Echinochloa colona*) in glyphosate-resistant transgenic cotton in north-east Australia.[61] Herbicide resistance modelling has been applied specifically to parasitic weeds[90] and to one particular species and herbicide,[91–94] and models have been based on field data for the dynamics and relative fitness of resistant and susceptible biotypes of a particular species, making them even more specific to the context in which those data were collected.[63,81] In some cases, this specific focus has been achieved by linking evolutionary models with crop models, meaning that predictions from individual runs are specific not only to the crops and weed species but also to the soil type and historical weather of a particular field.[61,87]

As mentioned above, most earlier models of herbicide resistance evolution assumed a monogenic basis for resistance, following the fact that, for most early studied cases of resistance, when a genetic basis was identified, it was monogenic. However, there is a growing concern regarding polygenic resistance, which is more associated with problematic cross-resistance to multiple unrelated types of herbicide,[95–97] and for which selection patterns may be different from selection of monogenic resistance.[31] When earlier resistance modellers tackled the issue of polygenic resistance, they tended to use a quantitative genetics approach, based on several assumptions, including that resistance is conferred by a large number of unlinked genes, each of very small additive effect.[98] More recently, modellers have represented multiple genes and their interactions more explicitly, allowing a more detailed and realistic representation of a polygenic basis for herbicide resistance,[31,99,100] or other pesticides.[83,101,102] This explicit approach also allows for representation of the linkage disequilibrium between alleles that is likely to emerge when very strong selection pressures are driving evolutionary processes,[83] but that is ignored in the 'traditional' quantitative genetics approaches. Representing the genetics more explicitly has the advantage that initial allele frequencies, mutation frequencies and fitness penalties can also be represented separately for each resistance gene and allele; it also means that values for these parameters need to be defined and justified.

Spatial heterogeneity is another aspect of biological reality that has been added to some herbicide resistance models in more recent times. When modelling herbicide resistance, spatial heterogeneity in weed and seed densities is likely to be important, as is spatial heterogeneity in the frequencies of resistance alleles. To represent spatial heterogeneity, resistance models can take a relatively simple and implicit approach of just adding variation to parameters likely to vary across space, such as dose,[31,101,103] or they can represent space and variation in population density and genetic frequencies more explicitly. Such spatially explicit models can represent variation in space in one dimension, along a transect or gradient, or down through depths in a soil profile,[62] in two dimensions across a field or a landscape of many fields[71–77,104] or potentially in all three dimensions.

Uncertainty and stochasticity are also important aspects of herbicide resistance evolution. While earlier models tended to be deterministic, more recent models have included random stochastic processes to represent some of the uncertainty observed in real systems. For example, when weeds are sprayed with herbicide, a model can simulate that exactly 95% of susceptible plants will die

(deterministic), or that each plant in the population has a 95% chance of dying (stochastic). Stochasticity is important in resistance evolution, because it often depends on relatively rare occurrences (gene mutations, the chance survival of an intermediate resistant genotype, sexual reproduction resulting in two particular complementary resistant genes coming together in one organism to create a new strongly resistant genotype). Stochasticity can also represent sources of variation that are not explicitly modelled, such as plants having different sizes, and thus different chances of being killed by a herbicide, even if having the same resistance genes. Another source of uncertainty is basic uncertainty about how well model parameter values represent the real system. Understanding the uncertainty in predictions introduced by stochastic processes within the model and/or uncertainty in model parameter values generally requires multiple simulation runs to produce a distribution of results that represent the full range of likely outcomes (Monte Carlo simulation).[88] Another possibility is a sensitivity analysis that looks at the effect of varying each model parameter one at a time.[31,45]

Another approach that has been used in herbicide resistance modelling to some extent is individual-based modelling (IBM), as opposed to population density approaches. IBM involves explicit representation of the individuals within a population, along with their individual characteristics.[105–108] IBM approaches have been used in modelling resistance in a range of specific types of organism, including insects and parasitic nematodes,[53,54,83,101,109,110] and in more theoretical non-organism-specific studies,[111] but only to a limited extent with weeds.[31]

5 THE ROAD AHEAD

5.1 Individual-based modelling approaches

There are many open avenues for methodological development in herbicide resistance modelling, and many applications that could be addressed with these new models. IBM approaches are promising for a deeper understanding of resistance evolution and the complex interactions involved because they can incorporate more of the biological detail and variability of real systems.[106] This can represent more of the biological variation within populations, and particularly how various ecological and genetic traits of individuals may become correlated or dependent over time under certain management regimes. This would allow, for example, a better understanding of the complex interrelationships between genetics and ecological 'fitness penalties' operating at different points in the lifecycles of plants, such as reduced seed and/or pollen production, increased mortality or diminished competitiveness in certain conditions.[112] As another example, IBM could help to unravel some of the complex interactions between evolution of seed dormancy and germination traits, evolution of chemical herbicide resistance and timing of herbicide applications, and thus help in understanding observed relationships between seed dormancy and herbicide resistance.[113–116] To date, biological parameters in models, such as those controlling dormancy, competitiveness or flowering time and thus fecundity, have usually been assumed to be fixed, whereas in reality they are likely to change over generations under different simulated agronomic conditions, just like chemical resistance; IBM can help to account for this coevolution. One caution for IBM approaches is that the additional realism and better representation of biological complexity usually come at the cost of additional model complexity, which may make models more difficult to calibrate, verify and analyse.[105,106]

5.2 Spatially explicit models

Making herbicide resistance models more spatially explicit may also be important. The assumptions that weed populations at the scale of a field exhibit spatially homogeneous densities and genetic frequencies, and random mating, are clearly not realistic. It has already been shown that the finite nature of weed populations can have real implications for model predictions, even when modelled populations are large and not spatially differentiated;[37] it is even more likely to be important when it is considered that real weed populations of some species may be quite patchy and have low seed dispersal. This means that the possibility for local extinction of resistance alleles will be much higher than if the population is considered to be large and spatially homogenous. Spatially explicit herbicide resistance modelling should learn from the rich field of spatially explicit modelling of dispersal and population dynamics that has already been employed in a diverse range of fields, including invasion biology, pest management, gene flow from transgenic crops and conservation.[79,80,117–122] Fortunately, recent empirical work is already providing valuable information on the dispersal of pollen and seeds that will help to inform these models.[123–126] Spatially explicit herbicide resistance models would make it possible to simulate, evaluate and design spatially targeted weed control options, such as managing resistant patches with different herbicides using targeted detection and spray technologies[127–131] or autonomous robotic vehicles.[132] They would also make it possible to understand the importance of seed and pollen dispersal in the spread of herbicide resistance, and help to predict the efficacy of management options based around limiting dispersal, such as limiting seed movement through farm equipment hygiene and crop seed screening,[133] or possibly limiting pollen flow by using barrier zones or spatial planning of land use accounting for dominant winds.[76]

5.3 Competition

It may be worth considering the level of detail at which competition for resources between plants is represented within herbicide resistance models. Plant competition, and crop–weed competition in particular, has been modelled at varying levels of biological and dynamic realism,[134] including with crop growth approaches,[135] spatially explicit individual-based approaches[136] and functional-structural approaches that represent the dynamic above- and/or below-ground architecture of competing plants in high detail.[137,138] While these approaches may be overly complex for direct inclusion in evolutionary models that represent dynamics over many years, they might still have a role for informing the representation of competition in evolutionary models, and accounting for self-thinning and compensatory growth after herbicide mortality. A related issue is the representation of environmental and weather effects in herbicide resistance models. As mentioned, when a crop model is used to simulate competition and predict seed set, the seasonal effects of specific rainfall and temperature patterns on mortality, competition and seed set can be predicted, and their influence on long-term evolutionary dynamics can be accounted for.[87] Effects of seasonal variation on seed germination timing and herbicide application efficacy may also be important, and incorporating these within herbicide resistance models should be considered.

5.4 Genetics

The representation of genetic control of resistance could be further developed. For example, resistance models have not explicitly represented the processes involved in gene amplification,

which has been shown to be an important genetic mechanism underlying resistance evolution.[49,97,139] Herbicide resistance models with more explicit representation of relatively complex polygenic genetic mechanisms exist, but to date accurate data to parameterise these models have been lacking, and so the models have mostly been used to understand how different genetics would influence the efficacy of different management options.[31] However, new genomic tools and high-throughput techniques may help to provide such information,[140,141] and there are already examples for organisms besides weeds where such information on polygenic resistance has been obtained and incorporated into models.[101,102,142] Simulation models could also be used for 'inverse modelling', working backwards from observed data regarding mortality over several generations of herbicide selection in the field or glasshouse, to identify the likely genetic bases of any observed increase in resistance, and give insights into the evolutionary history of how the resistance is likely to have evolved. More realistic representation of resistance genetics would make it possible explicitly to represent fitness penalties related to individual genes and alleles, mutation rates at different loci and possibly the influence of environmental stresses and low herbicide doses on resistance mutation frequencies and selection efficiency.[143]

5.5 Economics

Economic considerations have not been much addressed in herbicide resistance evolutionary modelling, or indeed in most modelling of resistance evolution.[6] Agricultural economists have employed relatively simple models of weed population dynamics to address important economic questions regarding weed management, but these have generally ignored herbicide resistance, compared analyses with and without resistance or perhaps used very simple models of resistance evolution that assume a given herbicide will lose efficacy after a certain number of applications.[16–21] Similarly, weed ecologists' incorporation of economics into their model frameworks has usually been of the simplest sort, analysing only basic considerations of cost. The challenge of incorporating economic evaluation with greater biological detail so that the economic costs and benefits of different resistance management options can be properly evaluated still largely remains.

5.6 Advantages and disadvantages of greater detail and realism

Incorporating greater biological detail and reality into models will have benefits. Developing new herbicide resistance models with more explicit, detailed and realistic representation of space, variability between individual, competition, effects of environment and weather and genetic mechanisms will make it possible to revisit old questions previously addressed with models. Questions regarding herbicide rotation, mixtures, combinations, doses and tillage can be revisited to see if previous results hold up when processes are represented more realistically. It will also be possible to look more closely at how results depend on a full range of possibly influential factors, and interpret results in more meaningful ways. For example, models may provide a certain prediction when the genetic basis is assumed to be monogenic and dominant, the population is assumed to be homogeneous, pollen and seed dispersal are assumed to be infinite and mating is assumed to be perfectly random. But will the prediction be the same if the genetic basis is assumed to be polygenic and recessive, the population spatiality is assumed to be heterogeneous and limited dispersal of pollen and seed and pollen competition are accounted for? And even if resistance evolves faster in terms of allele frequencies, does this mean that the farmer experiences faster growth in weed populations and quicker declines in yield and profit? New models will also make it possible to address new questions, such as the importance of gene flow through pollen or seed dispersal, or the feasibility of the spatially targeted resistant patch management mentioned previously. More detailed models will make it possible to integrate more current knowledge, from genetic and physiological mechanisms within cells to ecological processes of individual plants, populations and communities within fields, in order better to understand and predict and ultimately manage evolutionary processes operating across regions and many decades, including selection, migration, mutation and genetic drift.[6]

Incorporating greater biological detail and reality into models will also have costs. Building, calibrating, verifying, validating and analysing models costs time and money, and generally, the more detailed a model is, the more complex it will be, and the more time and money it will cost. There is also a direct cost of complexity; large complex models with many parameters are less transparent in the sense that it is less clear exactly how each parameter interacts with every other parameter to influence model outputs. This makes a complete analysis of a complex model difficult and eventually impossible, which is of course true of the real-world systems as well. For example, if the simplifying assumption is made that resistance is conferred by a single dominant gene, the model will include many fewer genetic parameters than if multiple genes are represented explicitly and separately, and different genes are allowed to have different effects and dominance and to interact with varying degrees of synergism or antagonism. In the latter case, much more testing of the effect of varying parameter values separately and in combination will be required than in the former case. Another issue is that, while simpler models can often be solved analytically to provide a complete solution,[45] more complex models usually need to be computationally simulated to obtain predictions or analyse the effect of varying parameter values (Table 1). Therefore, virtual experiments must be carefully planned to address questions and interactions of most interest and concern; while time consuming and providing less complete analysis than an analytical solution, these are still likely to be much faster, cheaper and safer than real-world experiments designed to address the same questions to the same level of generality. Nonetheless, an infinite number of models can be constructed, and an endless series of virtual experiments conducted, and so part of the ongoing goal must be to work out what details and differences really matter and where simplifications and generalisations can be made. For example, if dynamic plant growth and competition processes are represented at scales of hours and individual leaves, are results obtained that are importantly different to those obtained when plant competition is represented more simply and empirically?[65] If the spatial variation in weed density and allele frequency across a field is modelled in explicit detail at the scale of a square metre, are the predictions or greater insights achieved significantly different to those achieved when assuming the whole field to be a homogeneous mixed population? Does the model developed to represent evolution of resistance to a specific herbicide in a particular weed species in a specific cropping system in a particular region of a certain country provide important new insights compared with a similar model developed for a different species or herbicide or system or region? A balance must be sought between generality and specificity, understanding that the strength of modelling as opposed to empirical study is more

in the direction of abstraction and generality. Rather than building a new, very specific model for every new situation, a more general model can be used to investigate how characteristics of different species, herbicides, resistance genetics and agricultural systems are likely to interact with different management options to affect the evolution of resistance. If modelling predicts that a certain management option is likely to be effective, even as weed competitiveness, seed production, outcrossing levels and dormancy traits are varied across a wide range of values, then it can be concluded that there is little need empirically to identify those species traits. Or if modelling predicts that the efficacy of another management option is likely to depend strongly on the genetic basis of resistance, being highly effective for monogenic resistance but non-effective for polygenic, then research effort could be focused on better ways to identify genetic bases of resistance. A similar balance must be sought when looking at similarities and differences between organisms of different kingdoms; modellers of herbicide resistance should learn all they can from modellers of resistance evolution in insects, fungi and bacteria,[6,144,145] while also recognising that there are likely to be important differences and trying to understand what these are and what effect they have. In this way, modelling will continue to evolve and improve as a tool for integrating current knowledge and hypotheses regarding the different factors and processes that influence evolution of resistance, which will in turn help in understanding and predicting herbicide resistance better, and thus in designing and evaluating effective strategies to manage, delay or even avoid its appearance.

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Queries from the Copyeditor:

AQ1. Please confirm the inserted short title.

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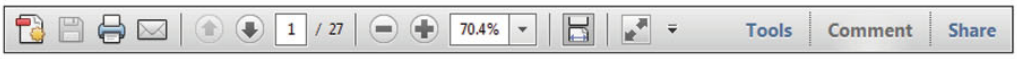
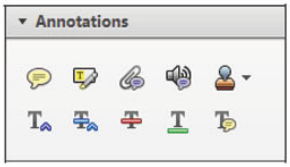
Required software to e-Annotate PDFs: Adobe Acrobat Professional or Adobe Reader (version 7.0 or above). (Note that this document uses screenshots from Adobe Reader X)
The latest version of Acrobat Reader can be downloaded for free at: http://get.adobe.com/uk/reader/

Once you have Acrobat Reader open on your computer, click on the Comment tab at the right of the toolbar:



This will open up a panel down the right side of the document. The majority of tools you will use for annotating your proof will be in the Annotations section, pictured opposite. We've picked out some of these tools below:

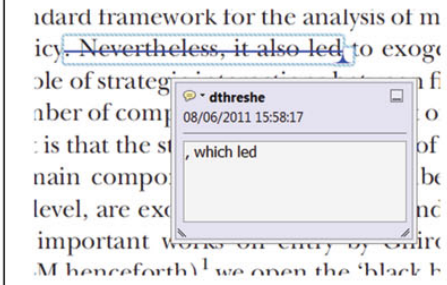


1. Replace (Ins) Tool – for replacing text.

Strikes a line through text and opens up a text box where replacement text can be entered.

How to use it

- Highlight a word or sentence.
- Click on the Replace (Ins) icon in the Annotations section.
- Type the replacement text into the blue box that appears.

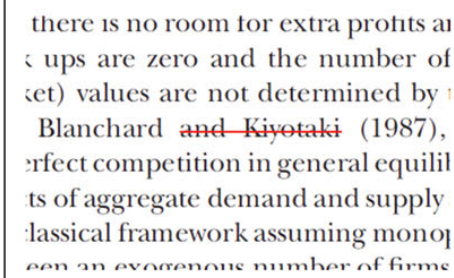


2. Strikethrough (Del) Tool – for deleting text.

Strikes a red line through text that is to be deleted.

How to use it

- Highlight a word or sentence.
- Click on the Strikethrough (Del) icon in the Annotations section.

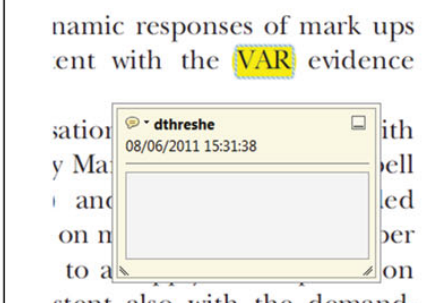


3. Add note to text Tool – for highlighting a section to be changed to bold or italic.

Highlights text in yellow and opens up a text box where comments can be entered.

How to use it

- Highlight the relevant section of text.
- Click on the Add note to text icon in the Annotations section.
- Type instruction on what should be changed regarding the text into the yellow box that appears.



4. Add sticky note Tool – for making notes at specific points in the text.

Marks a point in the proof where a comment needs to be highlighted.

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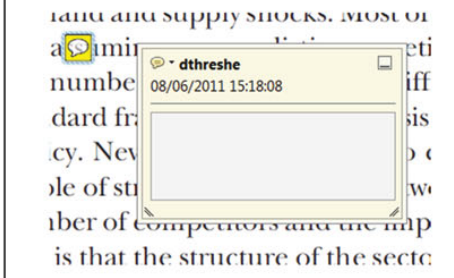

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5. Attach File Tool – for inserting large amounts of text or replacement figures.

Inserts an icon linking to the attached file in the appropriate pace in the text.

How to use it

- Click on the Attach File icon in the Annotations section.
- Click on the proof to where you'd like the attached file to be linked.
- Select the file to be attached from your computer or network.
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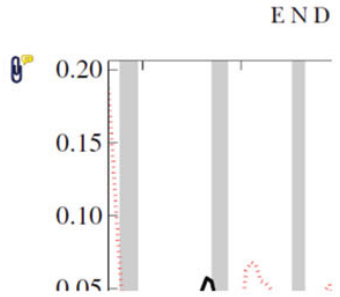

6. Add stamp Tool – for approving a proof if no corrections are required.

Inserts a selected stamp onto an appropriate place in the proof.

How to use it

- Click on the Add stamp icon in the Annotations section.
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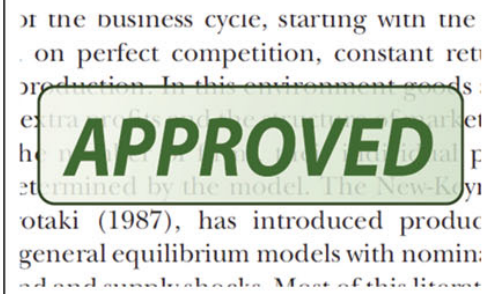
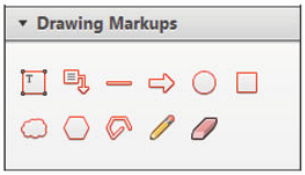


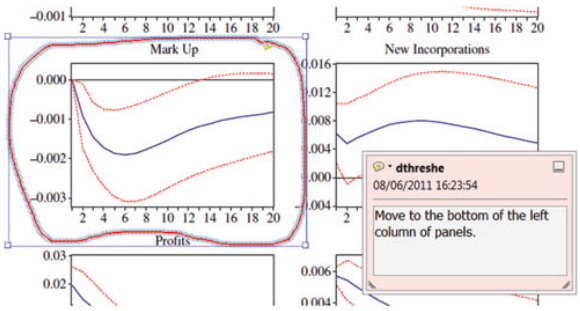


7. Drawing Markups Tools – for drawing shapes, lines and freeform annotations on proofs and commenting on these marks.

Allows shapes, lines and freeform annotations to be drawn on proofs and for comment to be made on these marks..

How to use it

- Click on one of the shapes in the Drawing Markups section.
- Click on the proof at the relevant point and draw the selected shape with the cursor.
- To add a comment to the drawn shape, move the cursor over the shape until an arrowhead appears.
- Double click on the shape and type any text in the red box that appears.



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