A discrete evolutionary genetic model for the emergence of metabolic resistance

Ein zeitdiskretes genetisches Modell für die Entwicklung metabolischer Resistenz

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Summary

Metabolic resistance refers to the biochemical processes within the plant that degrade herbicides to less toxic compounds, resulting in a shift of the dose-response curve. A multi allelic fitness model is used to simulate the emergence of metabolic resistance. A diploid population with a single resistance locus is considered with K number of alleles. The joint evolutionary dynamics model as described by HUILLET and MARTINEZ (2011) is applied to the dynamics of metabolic resistance. This is achieved by relating the fitness parameters to the form of the dose response curve which is characterized by a steepness and a threshold parameter (ED_{50} value). It is assumed that the threshold parameter of individuals in a population is log-normally distributed as the result of normal genetic variation. This means that there are only very few individuals with a high degree of metabolic resistance (high threshold parameter) in a weed population if no herbicides are applied. Under the long term application of only herbicide with one mode of action, the model produces the gradual shift of the mean dose response curve of the model weed population as frequently observed in the field. The model is used to understand the dynamics of the development of metabolic resistance under field conditions.

Key words: Evolution, genetic model, metabolic resistance, multi-allelic fitness model

Zusammenfassung

Metabolische Resistenz ist die Fähigkeit eines Organismus, toxische Substanzen abzubauen, was zu einer Verschiebung von Dosis-Wirkungskurven (ED_{50}-Werte) führt. Ein generelles genetisches Modell (HUILLET und MARTINEZ, 2011) für eine diploide Population mit einem einzelnen Resistsnz-Lokus und K Allelen wurde auf das Auftreten von metabolischer Resistenz angewendet. Dazu wurden die Fitnesskoeffizienten mit einer Dosiswirkungskurve verknüpft. Die Form der Kurve ist durch einen Schwellenwert (ED_{50}-Wert) und einen Formparameter für die Steigung bestimmt. Jedes Allel A_i trägt zur Expression von einem bestimmen Schwellenwert innerhalb des Individuums bei. Es wird angenommen, dass der Schwellenwert in einer unbehandelten Population logarithmisch normalverteilt ist, d.h. die Frequenz von Individuen mit hohen ED_{50}-Werten ist äußerst gering. Das Modell liefert die Verschiebung der Dosiswirkungskurve einer Population unter der kontinuierlichen Anwendung von Herbiziden mit dem gleichen Wirkungsmechanismus und wird dazu verwendet, Managementverfahren zur Verzögerung des Auftretens der metabolischen Resistenz zu bewerten.

Stichwörter: Evolution, genetisches Modell, metabolische Resistenz, Resistenzmanagement

1. Introduction

Herbicide resistance has become a major issue for many weeds (BECKIE, 2006). There are two major groups of resistance mechanisms:

- Alteration of the herbicide site of action (target site resistance).
- Non-target site resistance comprising e.g. enhanced metabolism, sequestration and restricted translocation.

Metabolic resistance can be characterized by enzymatic degradation of pesticides within the target organism (PETIT et al., 2010) resulting in a gradual shift of the dose response curve (TAL et al., 2000; DALY & FISK, 1992). In the case of target site resistance, there are many models in the literature describing the population dynamics and genetics of sensitive and resistant biotypes (MAXWELL et al., 1990; RICHTER et al., 2002). However, there are few models for the gradual shift of dose response curves in the case of metabolic resistance. Recently, RENTON et al. (2011) published a stochastic

individual-based simulation model for polygenic metabolic resistance. It is the purpose of this paper, to present a time discrete mathematical model in a closed form relating parameters of dose response relationships to fitness coefficients in a general framework. We present here the first (monogenic) version of the model.

2. Materials and methods

2.1 General model framework

In the first model version, it is assumed that metabolic resistance is coded at a single locus. Although metabolic resistance has been found to be polygenic in recent publications (MANALIL et al., 2011), monogenic inheritance may also occur as is the case for instance in glyphosate resistance due to restricted translocation in *Lolium* spp. (POWLES et al., 2010).

The phenotypic expression is characterized by a dose response relationship which is defined by only few parameters, e. g. the ED_{50} value (cf. section 2.2). We consider a diploid population with K (K arbitary large) alleles. The general theoretical frame follows the paper of Huillet and Martinez (2011). Let $x = [x_1, x_2, \ldots, x_K]$ denote the frequency distribution of alleles $A_1,\ldots,A_k$ within a population with $\sum_{i=1}^{K} x_i = 1$ and X the symmetric frequency matrix ($x_{ij} = x_{ji}$) of genotypes $A_i A_k$.

$$X = \begin{pmatrix} x_{11}\ x_{12} \cdots x_{1K} \\ x_{21}\ x_{22} \cdots x_{2K} \\ \cdots\cdots\cdots\cdots \\ x_{K1}\ x_{K2} \cdots x_{KK} \end{pmatrix}$$

In case of a diploid population with K alleles, the fitness coefficients are presented by the symmetric fitness matrix

$$W = \begin{pmatrix} w_{11}\ w_{12} \cdots w_{1K} \\ w_{21}\ w_{22} \cdots w_{2K} \\ \cdots\cdots\cdots\cdots \\ w_{K1}\ w_{K2} \cdots w_{KK} \end{pmatrix}$$

The fitness coefficients are expressed by dose response relationships. The evolutionary dynamics are acting on the parameters of these curves when herbicides are applied. In this model version, only the parameter ED_{50} is taken into account. The time discrete evolutionary dynamics is given by

$$X_{t+1} = \frac{1}{\omega(X_t)} X_t \circ W$$

where the mean fitness of the population is given by

$$\omega(X) = \sum\sum x_{kl} w_{kl}$$

The symbol $\circ$ denotes the Hadamard product of the matrices X and W.

The genetic variance is given by

$$\sigma^2 = \sum\sum x_{kl} (\omega(X) - w_{kl})^2$$

2.2 Dose response relationships

Dose response curves are described by the log-logistic model (KNEZEVIC et al., 2007)

$$S(d) = \frac{1}{1 + \exp[b(\log(d) - \log(e)]}$$

The parameter *d* denotes the dose, *b* determines the steepness of the curve and *e* is the ED_{50} value, i.e. *S(e)=0.5*. Figure 1 shows dose response curves for different values of *e*.

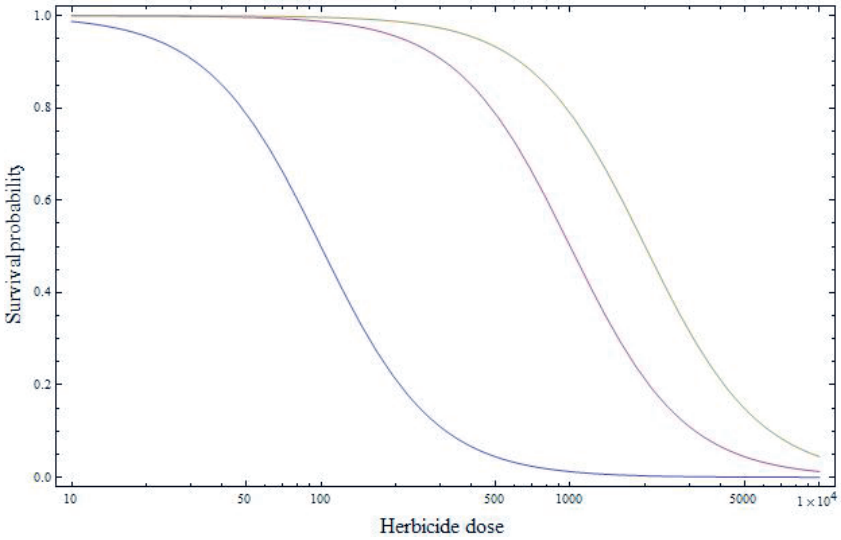

Fig. 1 Dose response curves for three ED_{50} values.

Abb. 1 *Dosis-Wirkungskurven für drei ED_{50}-Werte.*

The population dose response curve is given by the weighted superposition of dose response curves of each genotype $A_i A_k$.

$$S(d)_{pop} = \sum\sum x_{kl} w_{kl}(d)$$

2.3 Distribution of initial gene frequencies

It is assumed that the parameter *e* (ED_{50} value) is log-normally distributed within a diploid population with *K* alleles, i.e. individuals with high ED_{50} values are extremely rare.

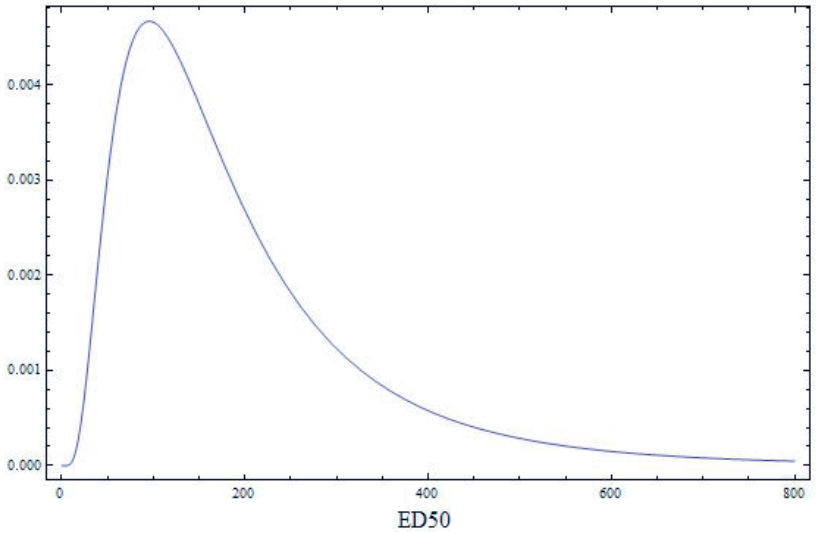

Fig. 2 Log-normal distribution of ED_{50} values within a population.

Abb. 2 *Log-normale Verteilung von ED_{50}-Werten in einer Population.*

3. Results

The model is capable of simulating the shift of dose response curves under the application of herbicides with the same mode of action. Fig. 3 shows the development in time of doses response curves under a constant herbicide dose.

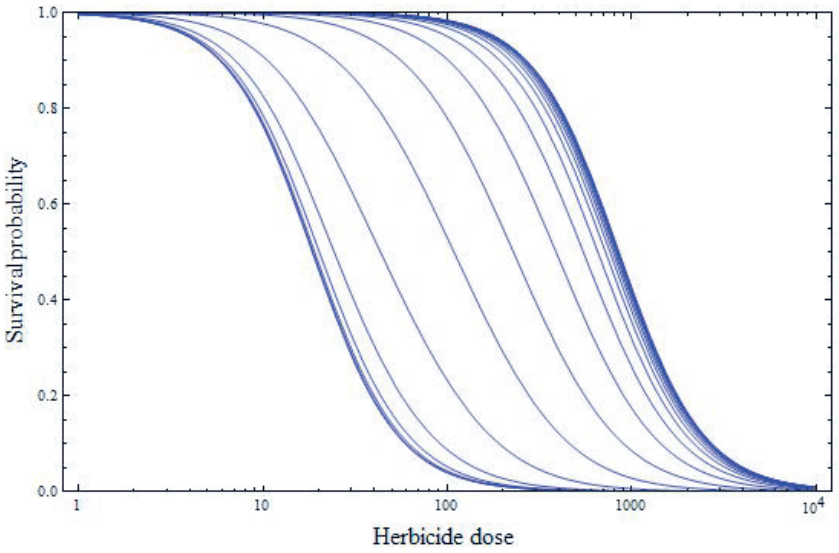

Fig. 3 Shift of the population dose response curve (from left do right) under a repeated application of herbicides with the same mode of action.

Abb. 3 *Verschiebung der Dosis-Wirkungskurve unter wiederholter Anwendung von Herbiziden mit gleichen*

3.1 Wirkungsmechanismen.

If metabolic resistance is dominant, i.e. $w_{ik} = max(w_{ii}, w_{kk})$, the shift of the dose response curve is much faster than in the recessive case, i.e. $w_{ik} = min(w_{ii}, w_{kk})$, as is shown in Fig. 4.

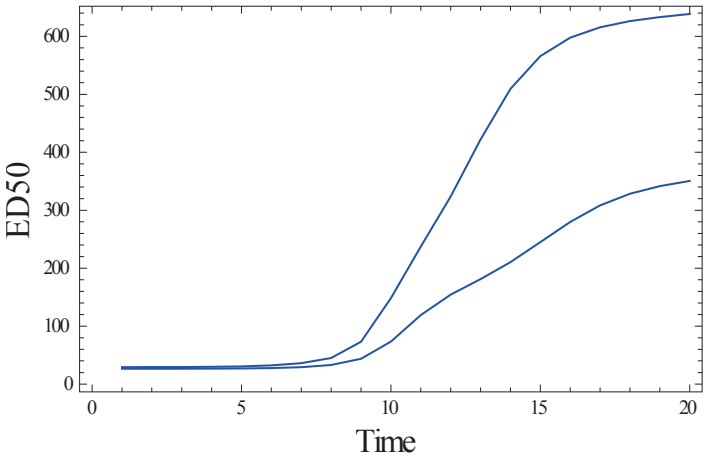

Fig. 4 Temporal development of the population ED_{50} value if the alleles coding metabolic resistance are dominant (upper curve) or recessive (lower curve).

Abb. 4 *Zeitliche Entwicklung des ED_{50}-Wertes für den Fall dominanter Vererbung (obere Kurve) und rezessiver Vererbung (untere Kurve) der metabolischen Resistenz.*

Fig. 5 shows the development of the ED_{50} value under four treatment schemes (application of herbicides with the same mode of action each year, every second year, every third year, no application in between).

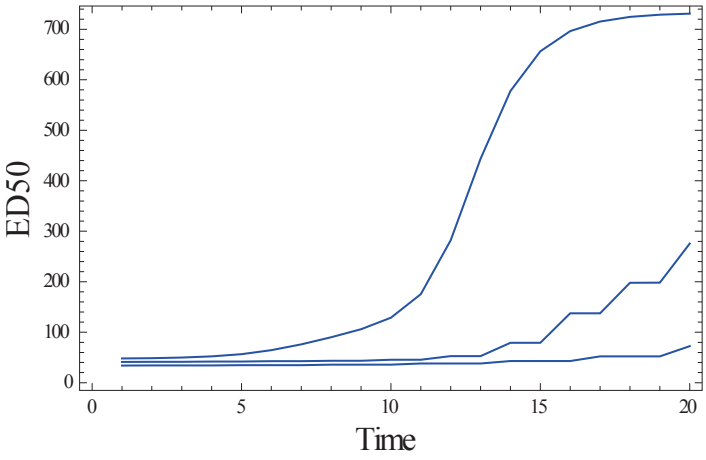

Fig. 5 Shift of ED_{50} values under three different treatment schemes. Upper curve: application of herbicides with the same mode of action each year, middle curve: application every second year, lower curve: application every third year.

Abb.5 *Retardierung der metabolischen Resistenz durch Aussetzen der Herbizidbehandlung. Obere Kurve: Anwendung von Herbiziden mit gleichen Wirkungsmechanismen jedes Jahr, mittlere Kurve: Anwendung jedes 2. Jahr, untere Kurve: Anwendung jedes dritte Jahr.*

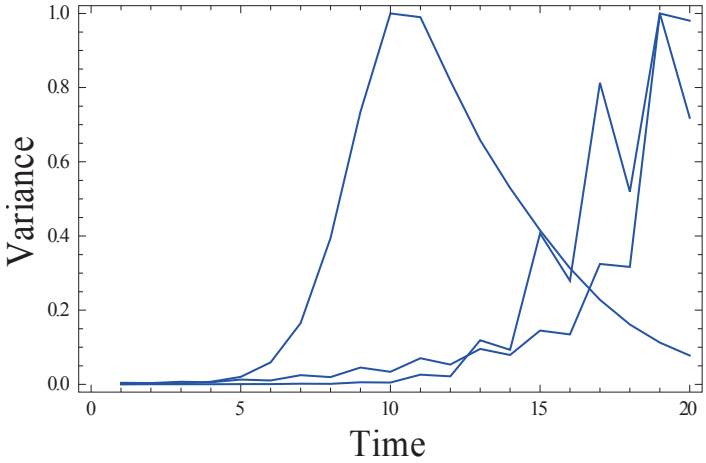

Fig. 6 Development in time of the genetic variance under the same treatment schemes as shown in Figure 5.

Fig. 6 *Zeitliche Entwicklung der genetischen Varianz unter den in Abb. 5 dargestellten Behandlungen.*

4. Discussion

The model addresses the emergence of metabolic resistance at a highly aggregated level. Model results show that the frequency of application determines the velocity of the development of metabolic resistance, i.e. the shifting of ED_{50} values, within a population. For practical applications, the model has to be integrated into a detailed life cycle model of the weed species including competition with the crop and dependence of model parameters on soil properties and climatic factors. In a further version, polygenic inheritance will be accounted for. By imbedding this extended model into a cellular automaton, it is possible to capture the spatial spread of resistant biotypes either by transport of pollen and seeds via the air or via tillage operation and other agricultural techniques.

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