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Selection and use of a mathematical model to evaluate components of resistance to Phytophthora infestans in potato

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Abstract

Five models of general epidemics, spatially homogeneous, were all shown to fit well to disease progress data for *Phytophthora infestans* on a susceptible potato cultivar. The models were: the logistic equation, the paralogistic or Vanderplank equation, two models from medical epidemiology with similar complexity, and a slightly more complex model with explicit treatment of lesion expansion. The use of the models for analysing the sensitivity of disease progress to changes in resistance components is discussed. Sensitivity analysis of the most complex model, by varying components within their range of genetic variation, indicates lesion expansion and infection efficiency as the components offering the best perspectives for resistance breeding. Improving two components simultaneously reduces disease progress slightly more than additively, but not enough to add other components to the list of breeding objectives. Pitfalls in using models for component sensitivity analysis, in the form of erroneous model initializations, are discussed, including implications for the role of components in the development of natural epidemics and in resistance breeding trials.

Additional keywords: late blight, epidemiology, resistance breeding, genetic variation, sensitivity analysis.

Introduction

Damage to crops by disease may be reduced by using completely or partially resistant cultivars that reduce pathogen build-up. Because of the swiftness with which most pathogens adapt to newly introduced completely resistant cultivars, partial resistance is nowadays favoured above complete resistance in most resistance breeding programmes, including those for potato late blight (Parlevliet, 1979; Umaerus et al., 1983).

Partial resistance consists of several components, each affecting a different stage in the life cycle of the pathogen (Parlevliet, 1979). Zadoks (1977) distinguishes five components that determine the development of epidemics and may be affected by the host plant, and thus can be used in breeding: infection efficiency (*IE*), latent period (*LP*), lesion growth rate (*LG*), infectious period (*IP*) and sporulation intensity (*SI*). To determine the relative contributions of these resistance components to the reduction of disease progress, two approaches are generally used (Jeger and Groth, 1985).

The first approach comprises the experimental determination of correlations between individual resistance components and disease progress rate. This requires extensive field experimentation using many genotypes, since no isogenic lines exist that differ for one resistance component alone. For the potato – *P. infestans* pathosystem only preliminary analyses of this nature have been performed (e.g. Pietkiewicz, 1976). Therefore, even though many studies about components of resistance to potato late blight have by now been published, it is still unclear which component has the greatest effect on disease progress. The second approach for evaluating components comprises the construction of a mathematical model of the pathosystem, and a sensitivity analysis with this model. By this, the response of yield or disease progress rate to changes in resistance component parameters is assessed.

In the present paper some of the models most frequently used for analysing epidemics are compared. The comparison is restricted to simple models, without host growth or environmental effects on parameter values. The model of which the structure most closely corresponds to the potato late blight pathosystem is used for evaluating the role of the components of resistance. The extent to which the component evaluation may be influenced by differences in model initialization, is studied in a final section.

The study presented in this paper is of a theoretical nature: models are compared and analysed. Comparisons of simulations of potato late blight with experimental data are presented elsewhere (Van Oijen, 1992).

Comparison of the different models

In resistance breeding trials, artificial inoculation is applied on relatively small plots. The resulting epidemics, developing without a strong spatial heterogeneity, are called 'general epidemics' (Zadoks and Schein, 1979). In this paragraph, five simple models of general epidemics are compared with regard to their suitability for analysing the role of resistance components in breeding trials.

Many plant disease progress curves can be described by the simple *logistic equation*. In this equation the transition of tissue from susceptible (S) to infectious fractions of the leaf area ($I = 1 - S$) is directly proportional to both S and I (Table 1). In the terminology of Hethcote (1976) such epidemiological models with S- and I-categories are called SI-models.

Since infectious leaf area in reality only remains infectious for a limited time (the infectious period, IP), an extra category of removed leaf area ($R = 1 - S - I$) can be defined, that can no longer become infected or cause infection. Such models are SIR-models. If the transition rate from I to R is taken to be directly proportional to I only, we get the *General Epidemic Model*, first published by Kermack and McKendrick in 1927 (Table 1).

Again more realistic are SEIR-models which include latently infected leaf area ($E = 1 - S - I - R$) that has been exposed to infection, but will only become infectious after a latent period (LP). SEIR-models used in medical epidemiology assume that the rates of transition for $E - I$ and $I - R$ are directly proportional to E and I, respectively, while in plant disease models the rates of these transitions generally equal the rate of $S - E$ at times LP and $LP + IP$ earlier. SEIR-models are thus formulated as a set of continuous differential equations, the *Extended General Epidemic*

Table 1. Models of general epidemics.

Model	Type[1]	Equations[2]		Initialization	
logistic	SI	S	$= 1 - I$		
		dI/dt	$= r_1 \times S \times I$	$I(0)$	$= I_0$
General Epidemic Model	SIR	S	$= 1 - I - R$		
		dI/dt	$= r_1 \times S \times I - I/IP$	$I(0)$	$= I_0$
		dR/dt	$= I/IP$	$R(0)$	$= 0$
Extended General Epidemic Model	SEIR	S	$= 1 - E - I - R$		
		dE/dt	$= r_1 \times S \times I - E/LP$	$E(0)$	$= 0$
		dI/dt	$= E/LP - I/IP$	$I(0)$	$= I_0$
		dR/dt	$= I/IP$	$R(0)$	$= 0$
paralogistic	SEIR	S	$= 1 - E - I - R$		
			$= 1 - y$		
		E	$= y(t) - y(t - LP)$		
		I	$= y(t - LP) - y(t - LP - IP)$		
		R	$= y - E - I$		
		dy/dt	$= r_1 \times S \times I$	$y(t)$	$= f(t)$, $-LP - IP \leq t \leq 0$
BLIGHT	SIR	S	$= 1 - I - R$		
		dI/dt	$= L_1 \times da/dt + a \times dL_1/dt - I/IP$	$I(0)$	$= 0$
		R	$= L_1 \times a - I$		
		dL_E/dt	$= r_1 \times S \times I - L_E/LP$	$L_E(0)$	$= L_{EO}$
		dL_1/dt	$= L_E/LP$	$L_1(0)$	$= 0$
		da/dt	$= f(LG)$[3]	$a(0)$	$= 0$

[1] Model typification according to Hethcote (1976). SI models include susceptible (S) and infectious (I) leaf area. SIR and SEIR models add removed (R) and latent (E) leaf area.

[2] Abbreviations of leaf area fractions: S: susceptible; E: latent; I: infectious; R: removed. Abbreviations of resistance components: IP: infectious period; LP: latent period; LG: radial lesion growth rate; r_1: infection rate. Abbreviations of lesion variables: L_E: latent lesion density; L_1: sporulating lesion density; a: average lesion area.

[3] For the derivation of the function relating lesion area increase to lesion radius increase, see van Oijen (1989).

Model, for human diseases (Anderson and May, 1982), and as a time delayed differential-difference equation, the *paralogistic equation*, for plant diseases (Vanderplank, 1963) (Table 1).

Berger and Jones (1985) have indicated that a further resistance component, lesion expansion, is needed in models of diseases such as late blight, where lesions grow indefinitely without reaching a predetermined final size. Radial lesion growth rate (LG) has been added to the SEIR-model by Van Oijen (1989) using a dynamically changing frequency distribution of lesion sizes. In this model, BLIGHT, lesion growth and sporulation start at the same time after infection (the latent period, LP), so that latent lesions occupy no leaf area and the model is simplified to an SIR-model (Table 1).

The five models discussed represent the life cycle of the pathogen with increasing comprehensiveness. Therefore more resistance components can be studied with the

later models, at the cost of increased data demand for parameter estimation. However, no model includes all components distinguished by Zadoks (1977). The infection rate parameter r_1, which appears in every model (Table 1), is the product of sporulation intensity (*SI*), spore dispersal efficiency and infection efficiency (*IE*). This parameter thus combines three processes of which especially dispersal is difficult to quantify. Therefore only the remaining components are measured, while r_1 is quantified by fitting the models to measured disease progress curves.

A second criterion for model usefulness, apart from the number of components, is whether the components are quantified in a way that allows easy and reliable measurement. Therefore in BLIGHT lesion expansion was quantified as radial growth rate of individual lesions, this being for potato late blight a more constant measure than relative or absolute growth rate of lesion area (Gees and Hohl, 1988; Van Oijen, 1989). *LP* was defined as it is generally measured: time between infection and sporulation. *IP*, on the other hand, is generally measured as the duration of sporulation of *lesions*, while for late blight, where only the shifting outer edges of lesions sporulate, the measure used in the models is the much shorter duration of sporulation of *infected tissue*. *IP* 'per lesion' would be an inconvenient model parameter, being by definition negatively correlated with *LG*, since lesions stop sporulating shortly after they have outgrown the leaf area available to them. For *IP* 'per tissue' the genetic variation is small (Lapwood, 1961; Vanderplank, 1963).

Table 2. Data of measured genetic variation for resistance components, and settings of the corresponding parameters in epidemiological models. The measured data refer to *partially* resistant cultivars, so values of zero for resistance components, which cause *complete* resistance, are not included. The model parameter values refer to a highly susceptible cultivar, with a disease progress curve as shown in Fig. 1A. Note: not all components are represented in every model.

		r_1 [1] (d^{-1})	*IP* [1] (d)	*LP* [1] (d)	*LG* [1] ($m\ d^{-1}$)
Data	field	$6.4 - 8.5 \times 10^{8}$ [3]	0.75 – 1 [4]	4-5 [4]	0.001-0.003 [5]
	laboratory	0.0026-0.0240 [3]			
Models	logistic	0.19	–	–	–
	General Epidemic	0.51	1	–	–
	Extended G. Epidemic	2.50	1	4	–
	paralogistic	2.75	1	4	–
	BLIGHT	765 [2]	1	4	0.003

[1] Abbreviations of resistance components as in Table 1.

[2] In BLIGHT, the infection rate parameter r_1 measures the increase in lesion density instead of the increase in infected leaf area, and is therefore expressed as lesions $m^{-2}\ d^{-1}$.

[3] r_1 is not a directly measurable component. Since r_1 is directly proportional to sporulation intensity (*SI*; sporangia $m^{-2}\ d^{-1}$) and infection efficiency (*IE*; %), measurements of these components are given instead. The field data refer to variation in *SI* of 4 genotypes (Lapwood, 1961), the laboratory data refer to *IE*, also of 4 genotypes (James and Fry, 1983).

[4] 4 genotypes (Lapwood, 1961).

[5] 3 genotypes (L.T. Colon, pers. comm., 1988).

Data are available of variation between potato genotypes in components of resistance to *P. infestans* (Table 2; Van Oijen, 1989). These data were used to fit each model to a disease progress curve measured in a field trial with cv. Bintje, where the percentage foliage disease had been recorded weekly (Fig. 1A). 'Bintje' is very susceptible to blight, so *IP*, *LP*, and *LG*, if included in the model, were set at the most 'susceptible' value reported, while r_1 was varied to achieve optimal fit. For each model, the resulting parameter settings (Table 2) caused good correspondence with the field data ($r^2 > 0.99$; Fig. 1A). The model curves are not identical. Disease severity approaches 100% in the logistic equation and with BLIGHT, but with the other models a lower asymptotic value is reached. In these models the infectious leaf area (I) can be shown to decrease whenever the remaining susceptible leaf area (S) drops below the threshold value of $1/(r_1 \times IP)$, which causes the epidemics to finish before S is completely infected (Anderson and May, 1982).

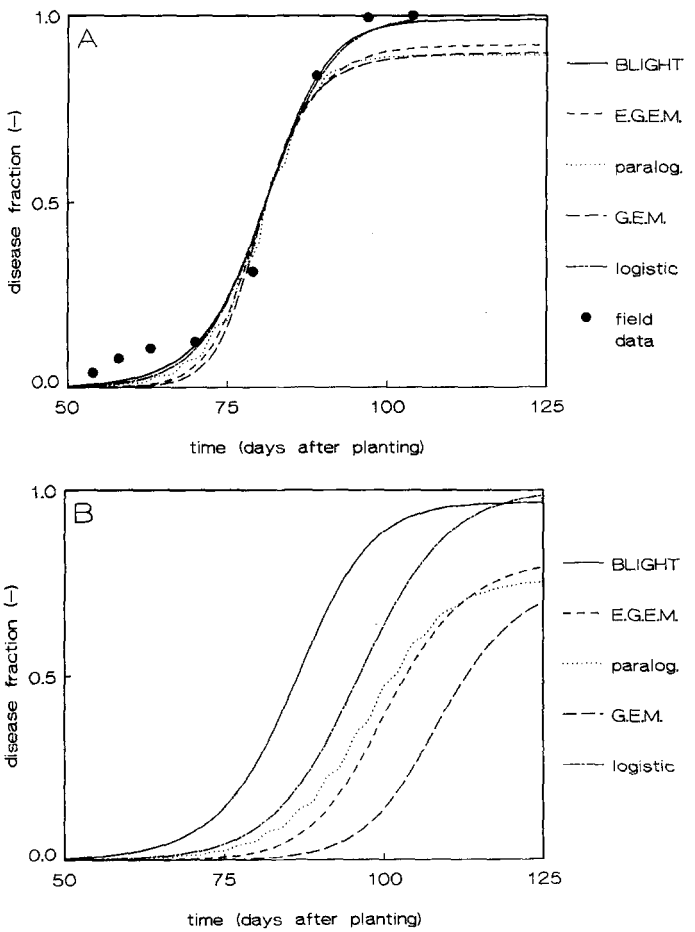

Fig. 1. Disease progress curves generated by five models. A: Best fit of the models to disease progress data for *Phytophthora infestans* on potato cultivar Bintje, field measurements 1988 (Van Oijen, 1992); B: Effect of reducing the infection rate parameter r_1 by 25%.

The models respond differently to changes in components. This is demonstrated by reducing the fitted values of r_1 by 25%. The reduction of r_1 caused widely varying increases in the time until a disease severity of 50% ($t50_1$) is reached (Fig. 1B). The most complex model, BLIGHT, showed an increase in $t50_1$ of 6 days, while the other models showed increases of 15 to 32 days. Apparently the simpler epidemiological models, that possess less resistance components, may fit to disease data equally well as the more complex models, but show greater sensitivity to changes in the components they do have. Therefore, simplifying models should be justified by extensive experimentation.

Component analysis with BLIGHT: the effect of changes in parameter values

The influence of the resistance components on disease progress was studied using BLIGHT. The sensitivity analysis of BLIGHT started with the parameter settings given in Table 2, belonging to the disease progress curve included in Fig. 1A, the 'standard curve'. Deviations from the standard curve were evoked in three ways: 1) changing individual components by 50%, 2) changing individual components according to the available genetic variation, 3) changing pairs of components.

Changing individual components by 50%. When resistance components were halved (doubled for *LP*), disease progress slowed down the most in the case of *LG*, followed by r_1 and *IP*, and finally by *LP* (Fig. 2A). *LG* represents the *radial* lesion growth rate. Changing this component thus affects *areal* growth rate quadratically, which explains the strong effect on disease progress. Changing *LP* has the least effect, which may be explained as follows. Lesions only sporulate on their outer edges. Whenever a leaflet has been infected and a lesion has started to grow, after latency, some time is needed before the whole leaflet is covered by the lesion and has showed sporulation. The time between leaflet infection and sporulation on a particular leaf spot thus depends on *LP*, *LG* and on the distance of the spot from the spore penetration site. Thus *LP* only partly determines the time course of sporulation of a lesion and so has a minor effect on disease progress.

Changing individual components according to the available genetic variation. To account for the genetic variation in components, the parameter settings were changed from the most 'susceptible' value in the genetic range to the most 'resistant' value reported (Table 2). This could not be done directly for *IE* and *SI*, because these components are lumped into r_1 in the model. The most resistant values of *IE* and *SI* are 89 and 25% lower, respectively, than the most susceptible values (Table 2), and these components were thus evaluated by reducing r_1 with the same percentages. The sensitivity analysis showed that the reported genetic variation for *LG* and *IE* suffices for strong reductions in disease progress rate, while the genetic variation for *LP*, *IP* and *SI* affects disease progress much less (Fig. 2B; Van Oijen, 1989).

Changing pairs of components. The effect of changing components simultaneously was studied next. Two of the components r_1, *LG*, *LP* and *IP* were varied, while the remaining two were kept at maximum susceptibility (Table 2). For every change the increase in $t50_1$ relative to the standard curve, was calculated. For four component

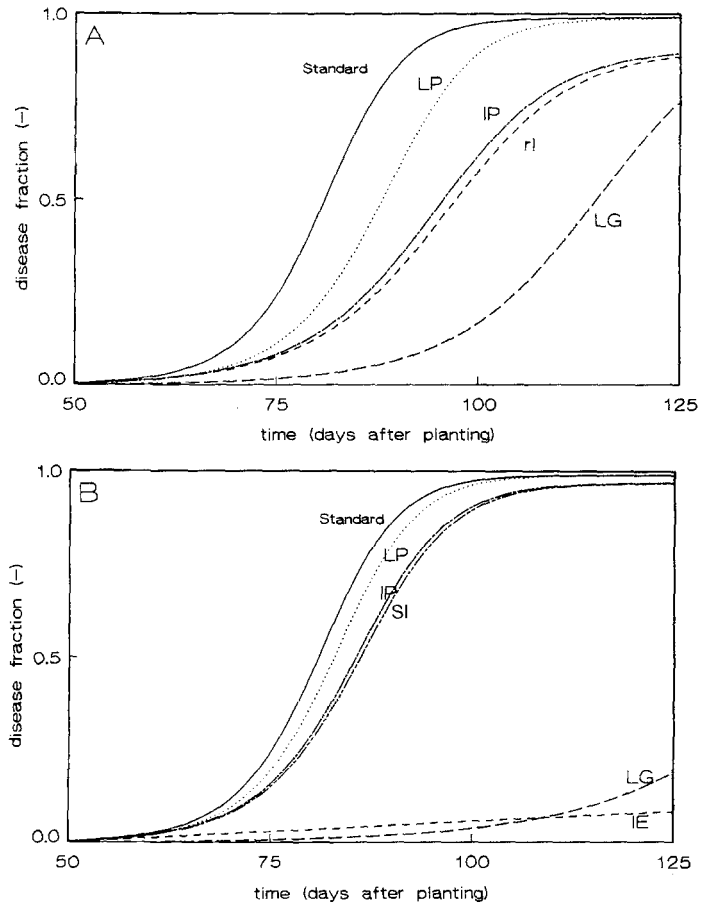

Fig. 2. Disease progress curves, simulated using BLIGHT. A: The 'Standard susceptible genotype' and hypothetical genotypes in which r_1, *IP* or *LG* were halved, or *LP* doubled; B: The 'Standard susceptible genotype' and genotypes in which *IE*, *SI* (both through r_1), *IP*, *LP* or *LG* were set to the most resistant value within the genetic ranges listed in Table 2.

pairs the iso-$t50_1$ lines, combining parameter settings causing equal increases in $t50_1$, were collected in one 'life cycle sensitivity graph' (Fig. 3; Van Oijen, 1990). As an example the simultaneous changes of *IP* and r_1, such that the individual changes would increase $t50_1$ by 10 days, are emphasized in Fig. 3A. The combination increases $t50_1$ by 27 days. This indicates a slightly stronger than additive effect on the slowing down of disease progress. The genetic variation of the components (Table 2) was visualized in a similar graph by emphasizing the collection of component values that are possible if components can be varied independently (Fig. 3B). If, on the other hand, genetic linkage between components exists, then not all combinations of values are possible and the hatched area in the graph should have been smaller. The figure shows that the genetic variation for *LP* and *IP* is insufficient to markedly increase $t50_1$, irrespective of the values of *LG* and r_1. This shows that resistance is mainly determined by the level of *LG* and r_1.

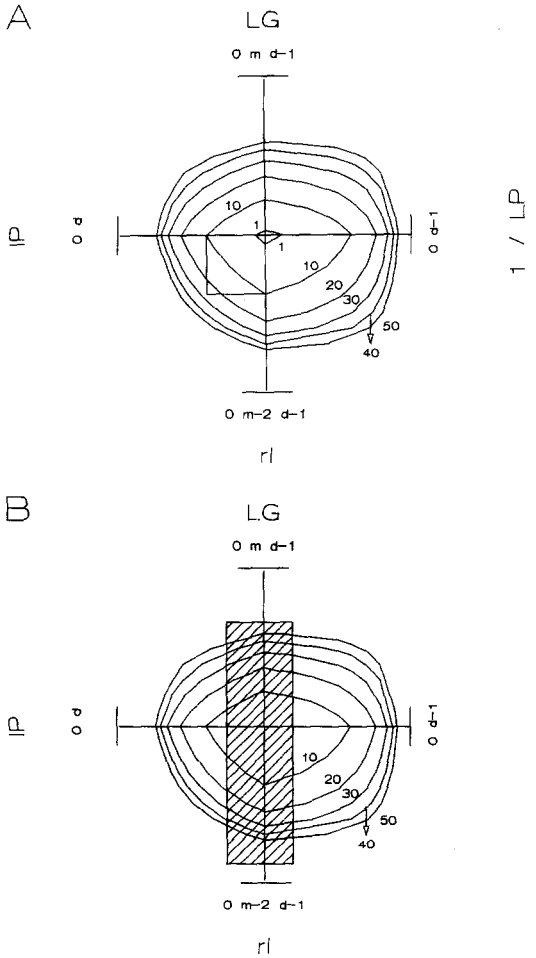

Fig. 3. 'Life cycle sensitivity graphs', calculated using BLIGHT. The graphs show the effect of varying different pairs of resistance components on the time of 50% foliage disease ($t50_l$). Axes indicate components, curved lines indicate the increase in $t50_l$, in days relative to $t50_l$ for the 'Standard' disease progress curve (Fig. 2). At the centres of the graphs, where the axes meet, all components are set at the most susceptible value within the genetic ranges listed in Table 2, i.e. the component parameter settings causing the 'Standard' disease progress curve. At the outer ends of the axes resistance is maximal, i.e. *LG*, *IP*, r_l or the reciprocal of *LP* is zero. A: The example of decreasing *IP* or r_l or both by 40%. The individual changes increase $t50_l$ by 10 days whereas the combined changes increase it by 27 days. B: The genetic variation for resistance components (indicated by the hatched area).

Component analysis with BLIGHT: the effect of changes in model initialization

The standard disease progress curve for BLIGHT (Figs 1A, 2) resulted from a low initial density of latent lesions (L_{EO} = 5 lesions m^{-2}). However, in resistance breeding trials disease is often initialized by spraying large quantities of inoculum over plots

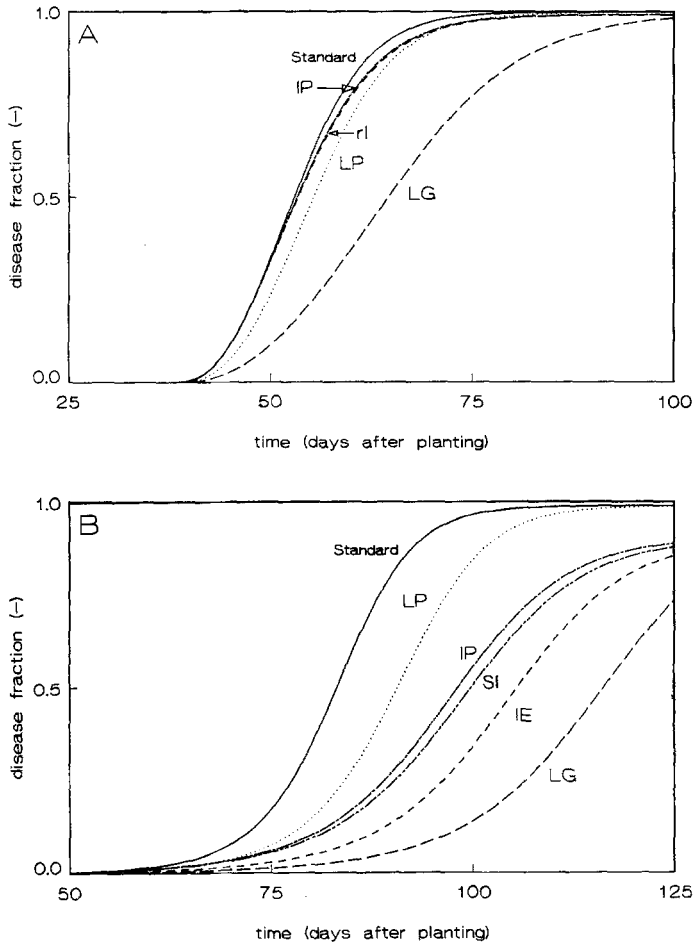

Fig. 4. Disease progress curves, simulated using BLIGHT. A: As Fig. 2A, but initial latent lesion density (L_{E0}) increased a hundredfold; B: As Fig. 2A, but L_{E0} set at zero, a temporary influx of external inoculum assumed, and *IE* and *SI* separately quantified.

of healthy plants. Many of the lesions that are formed during the epidemic then are directly caused by this large temporary influx of external inoculum. This obscures the polycyclic nature of the disease and may reduce the importance of those resistance components that affect the build-up of inoculum during later infection cycles in the epidemic. Simulations confirm this point. If the initial latent lesion density is raised to 500 lesions m^{-2}, the time before these first lesions start to grow (*LP*) and the subsequent rate of growth of these lesions (*LG*) are the dominant components (Fig. 4A), while the components that only affect later pathogen generations (r_1 and *IP*) are less important. However, the high initial lesion density reduces $t50_1$ at all component values, to the extent that differences between component effects are minimized (Fig. 4A).

The previous analyses started from fixed numbers of initial latent lesions. Such model initializations do not fully apply to resistance breeding trials with artificial

inoculation. In such trials genotypical differences in *IE* affect the effectiveness of the inoculation itself and thus cause differences between genotypes in the density of the first generation of lesions. To determine the magnitude of this error, and to establish the importance of *IE* in resistance breeding trials with artificial inoculation, a simulation was carried out where r_1 was split into *IE*, dispersal efficiency and *SI*. The model was initialized by assuming a temporary influx of external inoculum into a healthy crop. The result of the simulation (Fig. 4B) confirms that *IE* is more important in breeding trials than was apparent from changing r_1 in the simulations with a fixed initial lesion density (Fig. 2A).

Discussion

The logistic and paralogistic equations are the most prominent models in plant disease epidemiology. The logistic equation is too simple to be of much use in component analysis. The more comprehensive paralogistic equation has been criticized by Jeger (1986) for its mathematical untractability and the fact that its structure, a time delayed differential-difference equation, does not correspond to the vast theory of linked differential equations in medical epidemiology. Jeger therefore recommends using the human disease SEIR-model discussed above. However, lesion growth rate was not introduced in any of these models. In BLIGHT this resistance component was introduced and it was demonstrated that it strongly affects disease progress.

The sensitivity analyses show that, while disease progress is most sensitive to *LG* (Fig. 2A), genetic variation for *IE* is large enough to offer equally good perspectives for resistance breeding (Fig. 2B). Although improving two components simultaneously may lead to slightly stronger than additive effects (Fig. 3A), genetic variation for *IP* and *LP* is not sufficient to warrant breeding for improvement of these components (Fig. 3B). If, however, genetic linkage between these components and *LG* or *IE* exists, they may still be useful for indirect selection.

In BLIGHT, sensitivity of disease progress to changes in *LP* is less than in the paralogistic equation, which was analysed extensively by Zadoks (1971). The difference is partly caused by differences in model structure, the greater sensitivity in the paralogistic being related to its smaller number of parameters, as explained above. The method of model initialization, however, also affects the outcome of sensitivity analyses. The analyses show that a high level of initial inoculum may not only alter the ranking of the components, but may also obscure differences between genotypes that would have become apparent in natural epidemics, initiated from lower levels of inoculum whereafter more disease cycles would take place (Fig. 2A compared to 4A). Differences between genotypes with respect to *IE* may be obscured if the models are initialized with fixed numbers of first generation lesions, thereby ignoring that varietal differences in *IE* also affect the effectiveness of the artificial inoculation (Fig. 4B).

This analysis shows that the proper use of multi-component models may help in avoiding some of the pitfalls, when evaluating the role of resistance components in breeding research. The necessity of considering lesion growth rate, the importance of studying effects of simultaneous changes of more than one component, and the need for correct model initialization, have been demonstrated. If, furthermore, the genetic variation for the different resistance components is taken into account, the main components can be identified, as were *LG* and *IE* in the case of potato late blight.

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