Modelling the spatio-temporal dynamics of the european corn borer in the presence of transgenic maize

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MODELISATION DE LA DYNAMIQUE SPATIO-TEMPORELLE DE LA PYRALE DU MAÏS EN PRESENCE DE MAÏS TRANSGENIQUE

MODELLING THE SPATIO-TEMPORAL DYNAMICS OF THE EUROPEAN CORN BORER IN THE PRESENCE OF TRANSGENIC MAIZE

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INTRODUCTION

Research subject

The European corn borer (ECB, *Ostrinia nubilalis* Hübner) is one of the most damaging insect pests of maize in many countries: for instance, in the North America the economic losses resulting from this pest and control costs exceed 1 billion dollars every year (Bt corn and European corn borer…, 1997). Genetically modified (transgenic) insecticidal crops that produce protein being toxic for the pest larvae due to the presence of the gene of soil bacterium *Bacillus thuringiensis* (Bt) in the plant tissues have been designed to control infestations of primary target pests in fields. Bt-transgenic plants are highly toxic to pest larvae and the high concentrations of Bt toxin they contain can almost entirely wipe out the pest during the growing season and, thus, protect the crop not only in the vegetation period but also its yield (see Velkov et al. 2003).

The Bt-plant technology provides an advantageous alternative to the widely used synthetic chemical insecticides and even the microbial Bt insecticides. All sprayed insecticides have the common drawbacks: incomplete cover of leaf surfaces, reduced influence on adult larvae, degradation by sunlight, sensitivity to heat and desiccation, and hence, the diminished toxin efficiency. Besides, the larvae bore into plant tissues shortly after hatching and the later stages of ECB bore deep into the plant stalks or ears, making traditional insecticide treatment useless (Capinera 2000; Magg et al. 2001). Bt plant-hybrids are deprived of these shortcomings, providing the highest levels of pest control in fields up to 100% efficiency (Magg et al. 2001, Velkov et al. 2003, Candolfi et al. 2004). However, the long-term exposure of the pest population to Bt toxins produced by transgenic crops may lead to the rapid genetic pest adaptation due to the selection of insects that are more fit to the toxic habitat, i.e. Bt-resistant insects and then in the absence of competition to the rapid propagation of Bt-resistant population. Due to the evolution of the Bt-resistance gene in the pest population the individuals that are susceptible to Bt-crops may be forced out by the Bt-resistant ones, what may

eventually limit the Bt-crops application in agriculture and even lead to the full loss of efficiency of so expensive transgenic technology (Sharma & Ortiz 2000, Velkov et al. 2003, Bourguet et al. 2005).

It is thought likely that target insect species will eventually develop resistance as

(i) pests are known to develop resistance to the chemical insecticides applied to crops, at high concentration, every year (Scott 1995, Taylor & Feyereisen 1996),

(ii) several generations of pests are produced each year (up to four for the European corn borer in favourable conditions (Thomas et al. 2003)), potentially accelerating the selection of Bt-resistant insects,

(iii) resistance to Bt-toxins has been selected in the laboratory, in some pest species (Huang et al. 1999a; Chaufaux et al. 2001;Tabashnik et al. 2003).

The potential threat of the emergence of Bt-resistance was discussed long before the first Bt-plant was registered. A resistance management strategy was clearly required to avoid the rapid genetic adaptation of the pest. Comins (1977) provided the first theoretical demonstration that random gene exchange between insect subpopulations exposed and not exposed to an insecticide can delay the development of resistance if the resistant allele is recessive. He also formulated two basic concepts that have later underlain a mechanism of resistance management to transgenic crops (Alstad & Andow 1995, 1998, Bourguet et al. 2004):

1) the frequency of resistant genes in the population treated by the toxin can be decreased due to an intense influx of susceptible genes from an untreated area (referred to as the refuge);

2) very intense insecticide treatment coupled with technology of reservation of untreated areas should lead to suppression of the toxin resistance in pest populations.

The evolution of the Bt-resistance gene in the genetic structure of pest population represents a complex transient non-equilibrium process which is under influence of many important factors (the dominance level and initial frequency of resistant gene, the efficiency of Bt-toxin application, the intensity of insect migration into and out of toxic area). This process may occur very rapidly, during some pest generations or, vice versa, for several decades or even hundreds of years in dependence on the above-mentioned factors. Hence, the study of problem cannot be entirely carried out in the laboratory conditions or by means of field experiments. Besides, in many countries including Russia and France the cultivation of transgenic crops is limited by the law. Thus, mathematical modelling remains one of the basic methods for investigation of spatio-temporal dynamics of agricultural ecosystems consisting of transgenic plants and insect pests. Most of the mathematical models in this area of study have been developed for identifying the mechanisms underlying the development of resistance in pest populations and predicting the rate of spread of this phenomenon.

By now, based on the results of simulation models, the “high dose-refuge” (HDR) strategy is recommended as one of the best resistance management strategies for transgenic crops (Alstad & Andow 1995; Tabashnik et al. 2004). The term the “high dose” means that Bt concentration in genetically modified plants is high enough to provide the survival of only few (less than one of a million) resistant insects. The exact definition of high dose is “25 times of the toxin concentration needed to kill susceptible larvae” (FIFRA 1998). Low levels of Bt-toxin expression in the transgenic plants is believed to be inefficient because too many Bt-resistant individuals will survive and, hence, Bt-resistance can develop much faster (Sharma & Ortiz 2000). If the “high dose” was applied as an independent strategy, several (less than one of a million) completely Bt-resistant individuals could survive on Bt fields. If these individuals not only survive but have time to mate then Bt-modified crops can quickly lose efficiency after several insect generations (Gould & Cohen 2000). Plots planted with a non-Bt crop that

can serve as a host crop for the target pest, in the close proximity of Bt fields, should act as a "refuge" for pests susceptible to Bt toxin. Their goal is to prevent or to weaken the negative effect of the "high dose", i.e., to reduce the selection pressure on the Bt-susceptible insects and thereby to limit the Bt-resistance evolution. In this case the time period required for insect adaptation to Bt toxins is expected to be 10 up to 100 times longer than in case with no "refuges" (Gould & Cohen 2000).

In most models of the development of resistance to Bt crops it is assumed that resistance is governed by a single diallelic locus[1] with a Bt-susceptible allele *s* and a Bt-resistance allele *r*. Assuming that the Bt-resistance allele is inherited in an autosomal manner, any diploid population exposed to Bt-toxin selection consists of the homozygous genotypes *ss* and *rr* and the heterozygous genotype *rs*. The HDR strategy is based on three assumptions, which must hold true for this strategy to be effective (Bourguet 2004):

1) the Bt-resistance gene must be rare in natural insect populations so that only few homozygous *rr* individuals possessing two copies of the Bt-resistant gene are likely to survive on Bt-crops;
2) the Bt-resistance gene must be recessive so that the heterozygous *rs* individuals are entirely or partially susceptible to Bt-crops;
3) spatial configuration and location of refuges within the Bt-fields must be optimal to increase the probability of breeding between Bt-resistant homozygotes *rr* emerging from Bt-crops and Bt-susceptible homozygotes *ss* emerging from refuge so that to decrease the frequency of resistance allele *r* in every subsequent generation due to their Bt-susceptible heterozygous *rs* progeny.

If all three conditions ensuring the HDR success are satisfied, the Bt-resistance evolution in the ECB population may be delayed over an economically

[1] See Appendix 1 "Abridged dictionary of main genetic terms"

feasible time period (Guse et al. 2002; Ives & Andow 2002; Onstad et al. 2002; Vacher et al. 2003).

Let us consider each of these conditions as applied to the ECB population in more details.

Initial frequency of the resistance allele. Rare resistance genes can occur in natural population due to recurrent mutations and already exist at low frequency prior to any exposure to a toxicant (Scott 1995). Surveys of the European corn borer have not yet detected alleles conferring resistance to Bt maize. The extreme scarcity of Bt-resistance allele for natural populations of *O. nubilalis* was confirmed by studies of Andow et al. (2000) and later Bourguet et al. (2003). In general, the frequency of the resistance allele for *O. nubilalis* does not exceed 10^{-3}, i.e., it is very low and satisfies the condition of efficiency of the HDR strategy.

Resistance inheritance. The second hypothesis of the HDR strategy, namely, recessive inheritance of the Bt-resistance allele in natural ECB populations is still not confirmed by laboratory analyses (Bourguet et al. 2005). However, earlier Huang et al. (1999) reported that resistance in laboratory-selected ECB population appears to be inherited as an incompletely dominant autosomal resistance gene. As far as we know, these results have not yet been observed in the field or elsewhere.

Refuges. To be effective in managing resistance, refuges must produce large number of susceptible adults relative to the number of resistant adults produced in transgenic fields. A 500:1 ratio has been recommended by Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA, 1998). The size of refuges and their arrangement within transgenic fields are crucial and impact the efficiency of refuges. The problem of the optimal refuge size and configuration is still the source of debates. There is no single-valued opinion regarding this question.

General review of the HDR strategy problems. Bt maize being the second after Bt soybean among the most important Bt crops was put into production in 1996. In 2004 it occupied 23% or 19.3 million ha of the global area planted by

transgenic crops (James 2004). The following eight countries keep leadership in producing transgenic maize occupying altogether 11.2 million ha: USA, Argentine, Canada, Philippines, Uruguay, Spain, Germany and Honduras. Such widespread and prolonged (since 1996) exposure to Bt toxin has exerted strong selection pressure, favouring the development of resistance in the target pest populations. To decrease this selection pressure, the US Environmental Protection Agency decided to put in place the HDR strategy and mandatory requirements to farmers planting Bt crops were implemented in 1995 for Bt cotton and 2000 for Bt maize (Bourguet *et al.* 2005). "All suitable non-Bt host plants for a targeted pest that are planted and managed by people" may be used as a refuge (US EPA, 1998). However, despite the fact that ECB is remarkably polyphagous and has more than 200 documented host plants, this common refuge recommendation does not fit for the ECB resistance management in Bt maize. Recent studies in the USA (Losey et al. 2001) and in northern France (Bourguet et al. 2000b; Thomas et al. 2003; Bethenod et al. 2004; Bontemps et al. 2004) have provided evidence that ECB populations on non-maize host plants cannot be viewed as alternative refuge populations because they generate races genetically differentiated from population developing on maize. Hence, solely regular non-Bt maize should be planted to ensure compatible refuges.

The US EPA stipulates that each grower planting Bt crops should couple them with some non-Bt refuge area located near the Bt field. According to the requirements of the US EPA (1998) and A Grower's Handbook… (2004), the size of non-Bt maize refuge should be between 20% to 50% of total cultivated area depending on the levels of ECB infestations. In addition, the large area of refuge is recommended to treat with insecticides to increase the crop capacity of the non-Bt field.

The current sizes of these mandatory refuges result from numerous computer simulations demonstrating that smaller refuges accelerate total population extinction and increase the rate of resistance evolution (Caprio 2001; Guse et al.

2002; Ives & Andow 2002). According to studies of Onstad et al. (2002), even infrequent use of insecticide treatment in a refuge of 20% (or less) accelerates the Bt-resistance development in the ECB population whereas for 30% refuge (or larger) such treatment does not practically influence the resistance development to Bt maize. However, growers have no economic benefit to voluntarily comply with EPA guidelines because refuge crops are less productive on average and are more risky. Most growers prefer to ignore all recommendations (Hurley et al. 1999; Mitchell et al. 2000; Jaffe 2003). The size and spatial arrangement of refuge relative to Bt fields still remain the source of debates.

More than 10 years other key questions concerning practical use of the HDR strategy remain unsolvable. How quickly will the Bt-resistance evolve in transgenic maize? What factors influence the rate of the Bt-resistance development? What size of the refuge will be enough to delay the Bt-resistance evolution? What configuration of the refuge will be optimal for HDR strategy to be effective? Is it possible to entirely prevent the resistance development to Bt toxin? All these and many other questions have no single-valued answer so far. Despite the fact that results of laboratory selection for the Bt-resistance and some model simulations predict that European corn borer has potential to rapidly develop the resistance to Bt maize (Huang et al. 1999; Guse et al. 2002; Ives & Andow 2002; Onstad et al. 2002), since 1996 when the first Bt maize crop has been planted in the USA none of Bt-resistant ECB individuals have been documented yet in Bt-fields (Andow et al. 2000; Bourguet et al. 2003). The difference between observed data and model forecasts is an amazing fact requiring the development of new approaches and new mathematical models being able to explain the observed phenomena and providing reliable forecasts.

Combination of the HDR strategy with biocontrol by means of pest parasitoids. Parasitoid insects are one of the major natural enemies of many pest insects. It is known that some native parasitoid-species that attack the ECB larvae are able to provide the considerable reduction of the pest density and used as the

biological control agents in the numerous Integrated Pest Management (IPM) programs (Charlet et al. 2002). Transgenic plants providing extremely high levels of resistance to invasions of pest insects (100% efficiency of Bt-maize for corn borer *O. nubilalis* according to data of Candolfi et al. 2004) may affect indirectly the parasitoid ability to control the pest density (Losey et al. 2004). For instance, in France ECB larvae collected from Bt maize displayed a lower level of parasitism by larval parasitoid *Lydella thompsoni* than did larvae collected from non-Bt maize: 0-3.17% compared to 0.60-6.28% (Bourguet at al. 2002). The field studies in the USA have also confirmed the difference of parasitism in Bt and non-Bt maize for other larval ECB parasitoid *Macrocentrus grandii* (Venditti & Steffey 2002). One of the possible reasons explaining the results obtained is the appreciable reduction of larval hosts in Bt maize. Therefore, refuges of non-Bt maize in close proximity of Bt maize fields may be required not only for Bt-resistance management of the pest but also for conservation of natural enemies (Sharma & Ortiz 2000; Venditti & Steffey 2002). Besides, reduced parasitism in Bt-fields may cause the Bt-resistance to develop more quickly than in the absence of natural enemies because isolated resistant pest in Bt maize may gain benefit from reduced parasitism, thus promoting the spread of the resistant genotype. In this case, refuges could minimize the effects of differential parasitism due to the reducing the isolation of resistant hosts within the Bt fields (White & Andow 2003).

Biological control of the ECB population by means of natural parasitoids may be extremely perspective since the refuge productivity is low due to the heavy ECB infestations that make damaged maize unfit for sale (according to Onstad et al. (2002), the carrying capacity of ECB is estimated as 22 ind/plant). Understanding the interaction between biological control and biotechnology (transgenic plants) may greatly facilitate the integration of these two important pest management strategies and increase the probability of avoiding the problems associated with the rapid pest adaptation to Bt toxin (Losey et al. 2004).

The larval parasitoid – fly *Lydella thompsoni* Herting is distinguished among the potentially important parasitoid species. This parasitoid may kill up to 30% of the second generation borers in some areas of the USA (Capinera 2000). However, in France the effectiveness of this species is much lower, the level of parasitism does not exceed 2.16% (Agusti et al. 2005).

Other ECB larval parasitoid successfully established in the United States is the wasp *Macrocentrus cingulum* Brischke (formerly *grandii* Giodanich) which not only possesses the well synchronism of adult parasitoids with preferred stages of their host but also shows sufficiently high average level of parasitism up to 45% with peak of 61% (Sked & Calvin 2005).

However, the egg parasitoid *Trichogramma ostriniae* Pang et Chen which attacks the Asian corn borer (*Ostrinia furnacalis* Guenée) with 47% natural parasitism and even 70-90% parasitism due to the both inoculative and inundative releases of the wasp is considered as the most perspective ECB parasitoid (Wang et al. 1997). *T. ostriniae* may be also effective for controlling the European corn borer because of its biological similarity to Asian species. Using an inundative release approach in sweet corn, Wang et al. (1999) achieved >40% parasitism of ECB eggs and supposed that egg parasitism of the European corn borer can reach 85%.

Thus, mathematical modelling of dynamics of system “pest – parasitoid” in heterogeneous habitat is required to understand the interaction between biotechnology and biocontrol, to investigate, whether the efficiency of the HDR strategy can be increased due to the introduction of parasitoid species into biological system in which pest is exposed to the Bt-toxin selection.

Thesis goal and problems

The goal of the PhD project is to develop and investigate the models of resistance evolution to genetically modified maize in the European corn borer (*Ostrinia nubilalis* Hubner) population. Such models should take into account the key elements of ecology and genetics of insects, adequately describe the dynamics

of pest population in the case of spatial heterogeneity caused by the use of the HDR strategy and allow investigating the efficiency of the HDR strategy both as an independent strategy and in combination with biocontrol by means of natural parasitoids.

To achieve the posed goal the following problems were formulated:

1. to develop and investigate the spatio-temporal demo-genetic model taking into account both genetics and spatial structure of the pest population;
2. to compare the demo-genetic with the conventional Fisherian approaches; to justify the validation and advantages of the demo-genetic approach, used for modelling the Bt-resistance evolution in the pest population controlled with the "high dose – refuge" strategy;
3. to find steady-state conditions of the constructed model; to investigate the stability of the stationary regimes numerically;
4. to develop bi-trophic models of systems "pest – parasitoid" and "plant resource – pest" and investigate the efficiency of the "high dose – refuge" strategy in such systems.

Research methods

We propose spatial demo-genetic models based on a reaction-diffusion system of partial differential equations (PDEs) (Murray 1983; Okubo & Levin 2001), with the modified Kostitzin model used to describe the local kinetics of competitive genotypes (Kostitzin 1936, 1937, 1938a, b, c). Diffusion describes the random movements of individuals in the habitat. In our demo-genetic models, we have slightly modified Kostitzin's equations, so as to assess genotype fitness in terms of larval survival rather than overall genotype fecundity. We also assume that all ecological characteristics of the pest (birth and mortality rates, competition coefficient) are equal for different genotypes excepting genotype fitness (Zhadanovskaya & Tyutyunov 2004; Zhadanovskaya et al. 2004a, b, 2005a, b, 2006a, b; Tyutyunov et al. 2007).

To investigate the spatio-temporal dynamics of the genetic structure of the ECB population when using different scenarios of management strategies (the HDR strategy, biocontrol and their combination), simulation models were constructed in the integrated development environment Delphi 7.0. These models allow varying all modelled characteristics of plant resource, pest and its parasitoid, defining their initial distributions in space, fixing different sizes of the ECB habitat, various sizes, arrangement and configuration of refuges.

In order to carry out numerical simulations, we discretized in space the continuous demo-genetic models with a regular grid along the spatial coordinates x, y, approximating the spatial derivatives with the central difference in each node. The obtained system of ordinary differential equations with the preset initial conditions was integrated by the Runge-Kutta method of the fourth order with automatic time step selection. The accuracy of calculations was checked on the doubled spatial grid.

The existence theorems of stationary solutions for one-level demo-genetic model in one-dimensional space were proved with methods of mathematical analysis and analysis of phase space structure created by model variables. For constructing spatially heterogeneous stationary solutions we used a shooting method, modified so that to sew together solutions obtained for two qualitatively different domains of pest habitat: Bt field and refuge. Using Matlab 7.0 and developed simulation models, we analysed numerically the stability of spatially homogeneous and heterogeneous stationary solutions.

For numerical simulations we identified model parameters on the basis of the biological characteristics estimated by Onstad et al. (2002) and Onstad & Kornkven (1999) for corn borer *Ostrinia nubilalis* and its parasitoid *Macrocentrus grandii*. For maize we used the estimates of Kovalev (2003) for.

Scientific novelty

In dissertation we validate new demo-genetic approach to modelling of the Bt-resistance evolution in pest populations. We show that the use of the classical

population genetics model (Fisher – Haldane – Wright model) coupled with diffusion terms can lead to substantial errors when predicting the evolution of the genetic structure in a spatially distributed diploid population. Developed demo-genetic models were investigated analytically and numerically. Results obtained do not contradict the observed data for the natural European corn borer populations in transgenic maize fields.

Practical value

The proposed models may be used as a basis for management techniques and development of recommendations for optimal management of Bt-resistance in natural pest populations, for solving optimization and applied problems to rational control of wildlife areas and national parks, agro-ecosystems and invasions in natural ecosystems.

Abstract of thesis chapters

The ***first chapter*** contains review of current methods of modelling of genetic processes described within the problem of resistance evolution to genetically modified insecticidal crops in pest populations, and also of spatio-temporal dynamics of populations. Advantages and disadvantages of considered modelling methods are discussed. The chapter ends with statement of scientific objectives.

The ***second chapter*** is devoted to the constructing and analytical and numerical study of demo-genetic diffusion model of Bt-resistance evolution in the European corn borer population. We show here the adequacy and advantages of the demo-genetic approach to modelling of the Bt-resistance evolution in pest population when using the HDR strategy. It is proved analytically that spatial heterogeneity caused by refuges induces the advective flux of Bt-resistance genes, and this flux delays the diffusion dispersal of Bt-resistance genes in pest population. The stationary solutions of the model were found; their stability is investigated numerically. For different scenarios of the HDR strategy the model dynamics is studied numerically. We examined the efficiency of the HDR strategy depending on the size and configuration of refuge, and pest mobility. It is shown

that with particular combinations of refuge size and pest dispersal, the HDR strategy can delay the development of Bt resistance by several hundreds or even thousands of years, and refuge aggregation increases the strategy efficiency for the middle size of ECB habitat.

The ***third chapter*** describes demo-genetic diffusion models of the two-level linear trophic chains. In the first part of the chapter we develop a demo-genetic model of system "pest-parasitoid" that allows combining the HDR strategy with biological control by means of pest parasitoid. We investigate the efficiency of combination of two strategies depending on the ECB dispersal and parasitism level. It is shown that with moderate ECB dispersal and small refuge, biocontrol can increase the efficiency of the HDR strategy.

In the second part of the chapter a bi-trophic model of system "plant resource – pest" is described. In this model the dynamics of the plant biomass is taken into account explicitly. The long-term efficiency of the HDR strategy is studied numerically. The results obtained with two-level demo-genetic model coincide qualitatively with results of one-level demo-genetic model, confirming importance of directed gene flux in frequency form of the demo-genetic model.

DEFENDED STATEMENTS

1. Spatial demo-genetic model of resistance evolution to transgenic maize in the European corn borer population is developed. The mechanism of the "high dose – refuge" strategy is modelled;
2. The stability of stationary solutions for the demo-genetic model is investigated for one-dimensional habitat. It is proved analytically that spatial heterogeneity caused by refuges induces the advective flux of Bt-resistance genes, and this flux delays the diffusion dispersal of Bt-resistance genes in pest population;
3. The model dynamics is investigated numerically for various scenarios of the HDR strategy. It is examined the efficiency of the HDR strategy depending on the size and configuration of refuge, and pest mobility;
4. Two-level demo-genetic model "plant resource – pest" that explicitly takes into account the dynamics of the plant biomass is developed. The long-term efficiency of the HDR strategy is studied numerically;
5. Two-level demo-genetic model "pest – parasitoid" that allows combining the HDR strategy with biological control by means of pest parasitoid is developed. It is investigated how the efficiency of combination of two strategies depends on the ECB dispersal and parasitism level.

CHAPTER 1

GENERAL REVIEW OF MODELLING METHODS APPLIED TO THE PROBLEM OF RESISTANCE EVOLUTION TO TRANSGENIC INSECTICIDAL CROPS IN PEST POPULATION

Modelling the dispersal of the Bt-resistance gene in the pest population focuses on two key components:

- evolution of the genetic structure of the pest population in space and in time;
- spatially heterogeneous environment caused by the subdivision of pest habitat on Bt and non-Bt patches.

1.1 Modelling population genetics

The first component concerning the evolution of the genetic structure in the pest population should take into account the important details of an insect's ecology and genetics controlling Bt-resistance. Let's consider three basic approaches to the description of the genetic processes in a population: (*i*) complex simulation models using extremely detailed biological assumptions about the population genetics and life history of the insect species (Peck et al. 1999; Caprio 2001; Guse et al. 2002; Ives & Andow 2002; Onstad et al. 2002; Storer et al. 2003; Heimpel et al. 2005), (*ii*) diffusion models based on the classical population genetics model of selection (Fisher-Haldane-Wright equations) ignoring most demographic factors and focus solely on genetic processes (Alstad & Andow 1995; Vacher et al. 2003; Cerda & Wright 2004; Tabashnik et al. 2004, 2005), (*iii*) demo-genetic models taking into account both ecology and genetics of the species (Kostitzin 1936, 1937, 1938a, b, c; Svirezhev & Pasekov 1982; Abrosov & Bogolyubov 1988; Hillier & Birch 2002a, b; Richter & Seppelt 2004; Zhadanovskaya & Tyutyunov 2004; Zhadanovskaya et al. 2004, 2005, 2006a, b; Tyutyunov et al. 2007).

Let's examine the advantages and disadvantages of each approach in details.

1.1.1 *Complex simulation models*

Onstad (1988) states that an excessive complexity is required to achieve realism in ecological models. He advocates the idea that we have to use all available information about modelling object. The complex, computer-intensive models of Bt-resistance development in insect species follow this modelling approach (Peck et al. 1999; Caprio 2001; Guse et al. 2002; Ives & Andow 2002; Onstad et al. 2002; Storer et al. 2003; Crowder et al. 2005; Heimpel et al. 2005). Complex simulation models give quite realistic prognosis of the Bt-resistance development. In bivoltine ECB population the Bt-resistance develops within 56 years for a 10% refuge when the resistance allele is recessive. If the refuge area exceeds 20% the time period for the Bt-resistance evolution exceeds 100 years (Guse et al. 2002; Onstad et al. 2002). The patch model of Ives and Andow (2002) indicates less optimistic results: only 80 generations is needed for Bt-resistance evolution with 10% refuge, or taking into account that the ECB population usually has multiple generations per year (up to 4), the time required for the resistance development may be estimated as 40 years or less. Nevertheless, the model of Ives and Andow also allows to conclude about the economic expediency of the "high dose - refuge" strategy.

However, the realism of simulation models based on their exaggerated complexity due to the over-parameterization is not justified (Ginzburg and Jensen, 2004). Ginzburg and Jensen (2004) claim that if the complexity of proposed models greatly exceeds the complexity of the problem that they seek to address, such models should be rejected. Indeed, the attempt to build the models with as much complexity and realism as possible is unreasonable because too many parameters should be measured, because some of parameters are very difficult or impossible to evaluate on the basis of existing data and because the data necessary for the estimation of all parameters are usually unavailable. In some cases, detailing of model can fall into absurdity, for instance, when the model consists of more than 17600 equations with 41000 coefficients (Onstad, 1988). The reasons

listed above strongly limit the validation of the model predictions on the basis of complex simulation models when investigating the dynamics of agro-ecosystems and ways of their management.

1.1.2 *Fisher-Haldane-Wright model*

In other models of the Bt-resistance evolution in pest populations within the framework of conceptual approach the authors neglect the insect demography and focus solely on genetic processes. They describe the pest genetics by the classical population genetics model of selection, i.e., by Fisher-Haldane-Wright model (Lenormand, Raymond, 1998; Vacher et al, 2003; Cerda, Wright, 2004; Tabashnik et al., 2004, 2005). The approach based on such conceptual model leads at least to two problems analysed by Abrosov and Bogolyubov (1988) in details.

The Fisher-Haldane-Wright model was initially developed for species with life cycles involving an alternation of the non-overlapping haploid and diploid phases (Abrosov & Bogolyubov 1988; Hastings 1997; Neal 2004; see also Fig. 1.1). When constructing the equations it is assumed that haploid and diploid individuals cannot exist simultaneously and, hence, cannot interact with each other at the ecological level, in other words, the haploid and diploid generations do not overlap. Then to describe the dynamics of the genetic structure of the whole population it is quite enough to use the equations derived only for one of the phases, haploid or diploid, but the description at the haploid (allelic) level is much simpler, and instead of the dynamics of the genotype frequencies one may consider the dynamics of allelic frequencies. This fact hampers the application of the Fisher-Haldane-Wright equations to studying the genetic processes in any diploid population because in most diploid organisms including insects, the diplophase predominates while the haplophase is strongly reduced and deprived of ecological independence (it represents gametes), i.e., it cannot persist out of diploid organism, so, diploid and haploid generations do overlap. Thus, the use of the conventional frequently-based Fisherian model for modelling the Bt-resistance development in insect populations, in particular, in the ECB population seems inadequate.

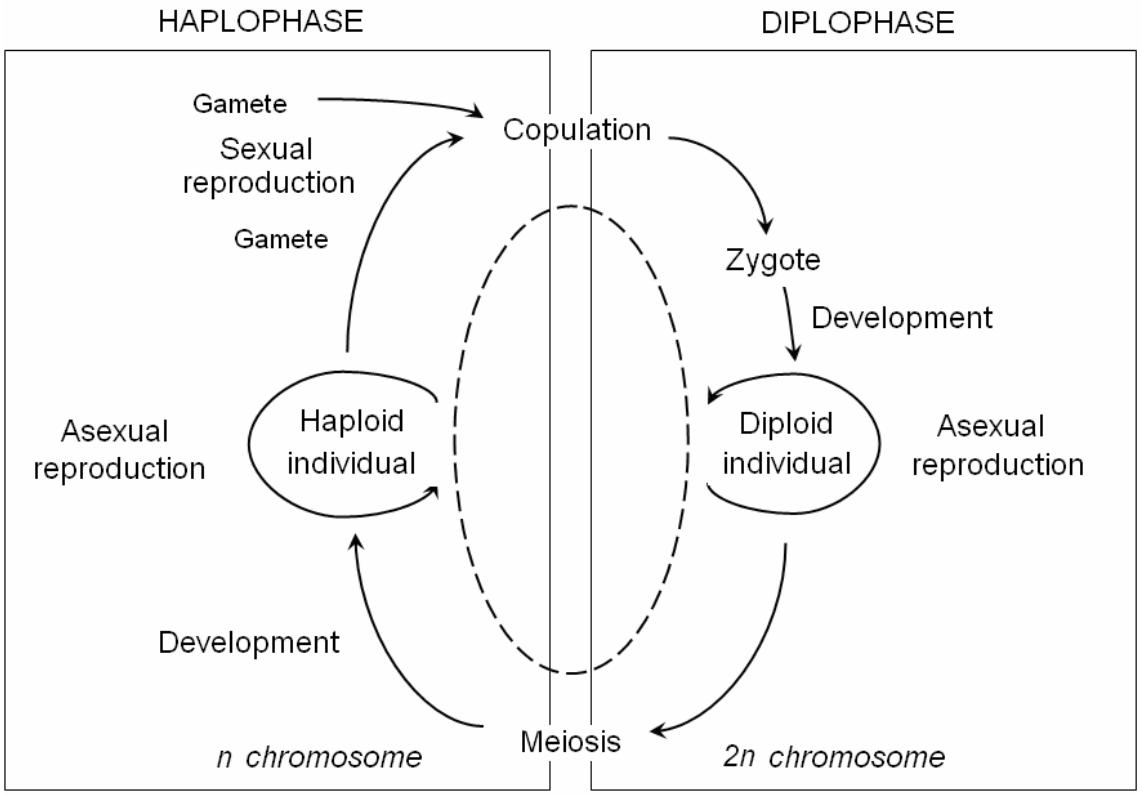


Fig. 1.1. Life cycle of a diploid organism (Abrosov & Bogolyubov 1988).

Extending the initial area of application of haploid Fisher-Haldane-Wright model is based on the inclusion of the additional hypothesis of 'gametic reservoir' according to which mating of diploid organisms and the copulation of gametes for the single parental couple are equivalent to the panmictic copulation of gametes (haploid forms). In other words, it is assumed that all gametes form the ecologically independent "pool". This allows operating the abstraction "gametic population". Under certain conditions, in a panmictic diploid population after one generation, the genotype frequencies at a single gene locus will become fixed at a particular equilibrium value (Hardy-Weinberg equilibrium). It also specifies that those equilibrium frequencies can be represented as a simple function of the allele frequencies at that locus. In the simplest case of a single diallelic locus the Hardy-Weinberg principle predicts:

$$
\begin{aligned}
u_{ss} &= p_s^2; \\
u_{rs} &= 2p_s p_r; \\
u_{rr} &= p_r^2,
\end{aligned}
\tag{1.1}
$$

where u_{ij} is the frequency of genotype *ij*, p_i is the frequency of allele *i* ($i, j = s$ or *r*). The ratio (1:1) will remain constant from generation to generation.

In addition, the hypothesis of 'gametic reservoir' requires implementation of special conditions for a diploid population:

(i) infinite population size (or sufficiently large so as to minimize the effect of genetic drift);

(ii) sexual reproduction;

(iii) no mutation;

(iv) no selection;

(v) no migration (gene flow).

For the most of insect species, including *Ostrinia nubilalis* only items (i) and (ii) are generally satisfied. In such populations, one may sometimes assume item (iii). However, items (iv) and (v) contradict properties of modelled species and character of *a-priori* non-equilibrium transient process of the Bt-resistance development in pest population. Hence, in this case both the hypothesis of 'gametic reservoir' and the assumption of Hardy-Weinberg equilibrium seem inadequate.

Moreover, it is often assumed incorrectly that the continuous Fisher-Haldane-Wright model (see, for example, Crow, 1969; Ginzburg, 1983; Ginzburg, Golenberg, 1985; Hastings, 1997; Neal, 2004) describes the dynamics of the genetic structure of population with overlapping generations:

$$
\begin{aligned}
\frac{dp_r}{dt} &= bp_r(W_r - W); \\
\frac{dN}{dt} &= N(bW - d(N)); \\
p_s + p_r &= 1,
\end{aligned}
\tag{1.2}
$$

where $W_r = W_{rs}p_s + W_{rr}p_r$ can be called the mean fitness of the resistance allele *r* (although the concept of "allelic fitness" in itself has little sense in a diploid population), $W = W_{ss}p_s^2 + 2W_{rs}p_s p_r + W_{rr}p_r^2$ is the mean population fitness. Here the case of single diallelic locus is considered: $p_s = p_s(t)$, $p_r = p_r(t)$ are the frequencies of alleles *s* and *r*, respectevely, $N = N(t)$ is the total population density, W_{ij} is the fitness of genotype *ij* ($i, j = s$ or *r*), b is the birth rate, $d(N)$ is the mortality function.

Still, system (1.2) is only the continuous approximation of the classical discrete Fisher-Haldane-Wright model for the species with non-overlapping generations and nothing more (Abrosov & Bogolyubov 1988). In itself the continuity of the model (1.2) does not give grounds to claim that the model is intended for the description of the dynamics of genetic structure in the population with overlapping generations.

As early as in 1937, V.A. Kostitzin pointed out the limitations of the application area of the classical population genetics model. He claimed that in a diploid population the selection works due to the competition of genotypes at the level of genotypic densities rather than at the level of allelic frequencies (see Abrosov & Bogolyubov 1988). Despite these limitations, the Fisher-Haldane-Wright equations and Hardy-Weinberg law remain the most commonly used. In particular, such models were used for modelling the spatio-temporal dynamics of Bt-resistance genes in insect populations (Lenormand & Raymond 1998; Peck et al. 1999; Ives & Andow 2002; Guse et al. 2002; Onstad et al. 2002; Storer et al. 2003; Vacher et al 2003; Cerda & Wright 2004; Tabashnik et al. 2004, 2005). In addition, the problem of evolution and dispersal of resistance gene in fields under the Bt-toxin selection pressure requires taking into account the spatial heterogeneity of the pest habitat. That's why models of the Bt-resistance evolution based on the classical equations of population genetics include the formal description of spatial gene dispersal, using diffusion components (Lenormand & Raymond 1998; Vacher et al 2003) or migration of fixed portion of individuals

from each cell in cellular automaton (Cerda & Wright 2004). As far as such approach to modelling the gene dispersal in spatially heterogeneous environment is justified? The above-mentioned restrictions of the Fisher-Haldane-Wright model allow us to doubt that the diffusion version of this model correctly describe the development and dispersal of the Bt-resistance gene in spatially heterogeneous pest population, and that non-spatial panmictic Fisher-Haldane-Wright model (1.2) can correctly describe the delay of resistance development to transgenic crops in insect species (see Tabashnik et al., 2004, 2005).

Indeed, models based on the Fisher-Haldane-Wright equations give the pessimistic forecast, supposing the rapid Bt-resistance development which, however, is not still confirmed in fields for the ECB population. According to this approach, the resistance develops within only 10 years with relatively large 26% refuge (e.g. Vacher et al 2003). Note that the recommended standard is that a good resistance management strategy should provide efficacy of the Bt-toxin for more than 10 years (FIFRA, 1998). However, it is clear that the guaranteed ten-year period of the efficacy of the Bt-crops is unlikely to be acceptable for the producers of genetically modified crop hybrids.

Note that most of complex simulation models of Bt-resistance evolution also follow a basic principle of classical population genetics, the Hardy-Weinberg law (Peck et al. 1999; Caprio 2001; Guse et al. 2002; Ives & Andow 2002; Onstad et al. 2002; Storer et al. 2003; Neuhauser et al. 2003; Crowder et al. 2005; Heimpel et al. 2005).

The correct application of both considered approaches to the problem of resistance development to Bt-modified crops in pest populations dwelling in spatially heterogeneous habitat is problematic. Hence, it is necessary to modify the conceptual models so that to extend their area of application for the adequate description of agro-ecosystems, taking into account both genetic transformations and ecological interactions between pest insects and plants.

Demo-genetic models meet entirely these requirements. Now let's consider demo-genetic approach in details.

1.1.3 *Demo-genetic models*

V.A. Kostitzin (1937) was the first to criticize unjustified wide use of the Fisher-Haldane-Wright model and to claim that the selection works at the level of genotypic densities rather than at the level of allelic frequencies as with Fisherian equations (Kostitzin 1936; 1937; 1938a, b, c; see also Svirezhev & Pasekov 1982; Abrosov & Bogolyubov 1988). He proposed a demo-genetic approach in non-spatial cases, using Volterra's competition theory to describe interactions between genotypes in a diploid population and the evolutionary selection of more adapted genotypes as a direct result of intraspecific competition:

$$\frac{dN_i}{dt} = f_i(N) - \mu_i N_i - N_i \sum_{j=1}^{n} \alpha_{ij} N_j, \qquad i = 1,...,n, \tag{1.3}$$

where $N_i = N_i(t)$ is the density of genotype *i*; μ_i is the mortality rate of genotype *i*; α_{ij} is the competition coefficient, intraspecific ($i = j$) and interspecific ($i \neq j$); the reproduction function of genotype *i*, f_i, satisfies the Mendelian Inheritance (Table 1.1); *n* is the number of genotypes. For a diploid population in which some heritable trait is coded with diallelic gene the total number of genotypes $n = 3$. Then the reproduction functions f_i ($i = 1, 2, 3$) are:

$$\begin{aligned}
f_1 &= \frac{1}{N}\left(\varphi_{11} N_1^2 + (\varphi_{12} + \varphi_{21}) \frac{N_1 N_2}{2} + \frac{\varphi_{22} N_2^2}{4} \right); \\
f_2 &= \frac{1}{N}\left((\varphi_{12} + \varphi_{21}) \frac{N_1 N_2}{2} + \frac{\varphi_{22} N_2^2}{2} + (\varphi_{13} + \varphi_{31}) N_1 N_3 + (\varphi_{23} + \varphi_{32}) \frac{N_2 N_3}{2} \right); \\
f_3 &= \frac{1}{N}\left(\varphi_{33} N_3^2 + (\varphi_{23} + \varphi_{32}) \frac{N_2 N_3}{2} + \frac{\varphi_{22} N_2^2}{4} \right),
\end{aligned} \tag{1.4}$$

where φ_{ij} is the birth rate for pair consisting of individual of genotype *i* and individual of genotype *j* ($i, j = 1, 2, 3$); here it is implicitly assumed that all

population consists of males and females and the birth rates of pairs ♀(i), ♂(j) and ♀(j), ♂(i) may be different; $N = N_1 + N_2 + N_3$ is the total density of population. Numerical coefficients in (1.4) correspond to the portions of individuals of genotype k in the progeny of each pair (Table 1.1). One can readily see from Table 1.1 that in a case of single diallelic locus the order numbers of genotypes {1, 2, 3} in model (1.3), (1.4) are simply associated with more widely used designation of genotypes in genetics by letters {*AA*, *Aa*, *aa*}. We will use the last way of notation hereinafter.

Kostitzin's model (1.3), (1.4) allows considering influence of various ecological factors of selection on the genotypic dynamics of a population. Here the fact that the modelled biological species has no ecologically independent haplophase is crucial. It is also reasonable to assume that the sex ratio is 1:1 (see Svirezhev & Pasekov 1982; Abrosov & Bogolyubov 1988).

Table 1.1. Interaction of dominant and recessive genes (alleles) by Mendelian Inheritance for the case of single diallelic locus: portion of genotype *ij* in offspring ($i, j = A$ or a). Two alleles, dominant *A* and recessive *a*, form three genotypes in any diploid population: homozygote genotypes *AA* and *aa* and heterozygote genotype *Aa*.

Variants of mating				Portion of genotype in offspring		
♀		♂		*AA*	*Aa*	*aa*
AA	×	*AA*	=	1		
AA	×	*Aa*	=	1/2	1/2	
AA	×	*aa*	=		1	
Aa	×	*AA*	=	1/2	1/2	
Aa	×	*Aa*	=	1/4	1/2	1/4
Aa	×	*aa*	=		1/2	1/2
aa	×	*AA*	=		1	
aa	×	*Aa*	=		1/2	1/2
aa	×	*aa*	=			1

Thus, in contrast to the two previous modelling approaches, the demo-genetic approach proposed by Kostitzin allows more adequately describing the genetic processes in a diploid population for species with reduced haplophase and overlapping generations, i.e., for most of diploid organisms including corn borer *Ostrinia nubilalis*. Kostitzin's model (1.3), (1.4) underlies our research.

Note that attempts to develop demo-genetic diffusion models of Bt-resistance evolution in pest populations on basis of the Lotka-Volterra competition equations were made by Hillier & Birch (2002a, b) and Richter & Seppelt (2004). But these models are incorrect since the genetic pest structure used in them does not correspond to the Mendelian Inheritance.

To take into account simultaneously both genetics and demography of a species in the model it should be kept in mind that both processes will take place on the same temporal scale. In Darwin's theory (1859) natural selection is regarded as a weak force which becomes apparent only on the geological time scale while ecological changes in a population may be observed within one generation of animals. However, as a result of Bt-crops application more than 99.9% of susceptible insects die in each generation (Magg et al. 2001; Velkov et al. 2003; Candolfi et al. 2004), i.e., the selection is strong. In this case the changes in the genetic structure of the population will take place on the same temporal scale as ecological dynamics of population. The idea that evolutionary changes can occur on relatively short time scales can be also traced back to work of Dobzhansky (1943) who demonstrated rapid evolutionary changes coinciding with seasonal cycles in population of *Drosophila*. The conceptual model of Neuhauser et al. (2003) based on the integration of ecological and evolutionary processes in the population being under the strong selection can serve as one more argument for the justification of the adequacy of the demo-genetic approach to modelling the Bt-resistance development in insect pest populations.

All models of Bt-resistance evolution, mentioned in §§ 1.1.1-1.1.3, show that the main strategy of Bt-resistance management called the high dose – refuge

strategy and used in Bt-fields can delay the adaptation of pests to transgenic crops within time period ranging from the couple of years to several centuries (Guse et al. 2002; Ives & Andow 2002; Onstad et al. 2002; Neuhauser et al. 2003; Vacher et al. 2003; Heimpel et al. 2005), depending on several key factors such as the presence of the refuges within the Bt-fields and their size (Comins 1977; Alstad & Andow 1995; Peck et al. 1999; Guse et al. 2002; Hillier & Birch 2002б; Ives & Andow 2002; Onstad et al. 2002; Vacher et al. 2003; Cerda & Wright 2004; Tabashnik et al. 2004, 2005; Crowder et al. 2005; Heimpel et al. 2005), spatial and/or temporal distribution of refuges (Peck et al. 1999; Guse et al. 2002; Vacher et al. 2003; Cerda & Wright 2004; Crowder et al. 2005), mating behaviour (random or not) (Guse et al. 2002), the initial frequency of the Bt-resistance gene (Peck et al. 1999; Crowder et al. 2005), genotype fitness (Tabashnik et al. 2004, 2005), type of inheritance of the Bt-resistance gene (Tabashnik et al. 2005), dispersal of the pests (Comins 1977; Peck et al. 1999; Caprio 2001; Guse et al. 2002; Ives & Andow 2002; Onstad et al. 2002; Cerda & Wright, 2004; Heimpel et al. 2005), concentration of the Bt-toxin in tissues of transgenic crops (Caprio 2001; Guse et al. 2002; Onstad et al. 2002; Vacher et al. 2003; Tabashnik et al. 2004; Crowder et al. 2005), insecticide treatments (Ives & Andow 2002; Onstad et al. 2002; Cerda & Wright 2004), natural enemy attack (Neuhauser et al. 2003; Heimpel et al. 2005).

Two major perspectives of the Bt-resistance development in pest populations are investigated in mentioned works. One is focused on individual farms and the behaviour of individual growers (see, for example, Peck et al. 1999; Vacher et al. 2003). The other perspective addresses the area-wide or regional approaches to resistance management (e.g., Guse et al. 2002; Onstad et al. 2002; Crowder et al. 2005). The study of the problem at a regional scale implies that the mobility of the pest should be high enough. Unfortunately, by now there are no sufficient data about the mobility of corn borer *O.nubilalis*. The reason of data deficiency is that the estimation of such characteristic of pest spatial activity requires the complex

investigations of the large-scale movements of population density patches rather than simple observations of the fast flights of ECB adults (Hunt et al. 2001; Qureshi et al. 2005). However, among all the above-mentioned factors influencing the efficiency of the "high dose – refuge" strategy only refuge sizes, their spatial shapes within the Bt-fields, frequency of refuge rotation, the toxic level of the Bt-crops and the artificial introduction of parasitoids in Bt-fields can be really used as the management parameters while the gemographic and genetic characteristics of the pest are not actually available for modifications although they also influence the estimation of the risk of pest adaptation to Bt-toxins.

Analysis of results obtained allows the US Environmental Protection Agency to conclude (EPA 1998; EPA and USDA 1999; FIFRA 1998, 2004) that the "high dose – refuge" strategy is one of the best resistance management strategies for transgenic Bt crops (see the description of the strategy mechanism in Introduction).

The economic aspect of applying the "high dose – refuge" strategy is also important. As discussed in Introduction, refuges are much less productive than transgenic fields. From this point of view, the optimal management is required to find a compromise between short-term losses and long-term profits concerned with refuges. Hurley et al. (1999, 2001) examined the current recommendations of the US Environmental Protection Agency for the European corn borer population and found that the refuge with size exceeding 21% is economically inexpedient but a too small refuge (below 13%) is not only unprofitable but also essentially enhances the risk of the Bt-resistance development in the pest population. This group of researchers also investigated the problem whether it is profitable to use the insecticides to increase productivity of refuges. Besides, they studied the influence of the refuge sizes on the compliance of farmers with EPA recommendations of refuges and also showed that non-random mating in ECB population requires increasing the refuge size by several percents. In contrast to Hurley et al. (1999, 2001), in order to find an optimal strategy of Bt-resistance management,

Laxminarayan & Simpson (2002) and Linacre & Thompson (2004) propose extremely simple models of Bt-resistance evolution in pest population based on the classical logistic growth model. However, the excessive simplicity of Linacre & Thompson model (Linacre, Thompson 2004) and the evident errors in analytical computations made by Laxminarayan and Simpson (2002) give us a firm ground to doubt results and conclusions obtained by these researchers.

1.2 Modelling spatial population dynamics

The second major component in models of Bt-resistance evolution is the spatial heterogeneity emerging as a result of applying the "high dose – refuge" strategy in pest population. There are several ways to incorporate spatial structure into models and describe spatial population interactions. Here we take into consideration only spatially explicit models describing dynamics of gene fluxes in space: systems of partial differential equations of type "reaction-diffusion" (Hillier & Birch 2002b; Medvinsky et al. 2004, 2005, 2006; Richter & Seppelt 2004; Zhadanovskaya et al., 2004a, b, 2005a, b, 2006a, b; Tyutyunov et al. 2007), cellular automata (Peck et al., 1999; Caprio, 2001; Vacher et al., 2003; Cerda, Wright, 2004) and patch models (Comins, 1977; Alstad, Andow, 1995; Guse et al., 2002; Ives, Andow, 2002; Onstad et al., 2002; Crowder et al., 2005; Heimpel et al., 2005). In all these models a space is explicitly represented using continuous spatial coordinates or discrete patches (see rewiews of Karieva 1990; Hastings 1990; Czárán 1998). Despite the fact that an explicit representation generates plenty difficulties regarding formalization of spatial species behaviour, this method is a powerful tool for studying spatial aspects of population dynamics due to their mechanistic presentation.

1.2.1 *Patch models*

The simplest way of modelling of spatial population structure underlays patch models in which a population consists of local subpopulations connected by the migration fluxes. Key factors of local habitat determine the dynamics of each

subpopulation. In the simple case, a continuous-time general model for a single species dwelling in *n*-patch habitat is:

$$\frac{dx_i}{dt} = F_i(x_i) - e_i(x_i) + \sum_{j \neq i} h_{ij}(x_1,...,x_n), \quad i, j = 1,...,n, \tag{1.5}$$

where $x_i = x_i(t)$ is the subpopulation abundance in patch *i*; $F_i(x_i)$ is the autonomous growth term for subpopulation in patch *i*; $e_i(x_i)$ and $h_{ij}(x_1,...,x_n)$ are the emigration and immigration terms, respectively.

Within the framework of such models, studying of migration mechanism assisting the population adaptation to abrupt random environmental fluctuations and demographic stochasticity have shown that even random diffusive dispersal of individuals in spatially structured habitat allows significantly decreasing the risk of subpopulation extinction due to a recolonization being a process of occupying empty patchs by migrants (Roff 1974; Dombrovsky & Tyutyunov 1985, 1987a, b; Akçakaya 1991; Burgman et al. 1993). This approach developing in theory of island biogeography (Darlington 1966; MacArthur & Wilson, 1967) has caused a so called problem SLOSS* concerning a choice of sizes and structures of wildlife areas. The rescue effect is also studied within metapopulation approach (Levins 1970; Metapopulation dynamics... 1991; Hanski 1999), the main idea of which is to investigate the birth/death processes in more complex metapopulation system "population of populations" than simple population of animals. The dynamics of such metapopulation is described by the fraction of those habitat patches that are occupied by the species (when the spatial pattern and migration nature are ignored). However, it is noteworthy that for patch models and metapopulation systems a spatial structure is given *a-priori*, i.e., it is assumed that spatial heterogeneity of a habitat accounts for the patch colonization and, finally, the efficiency of adaptation mechanisms of spatial behaviour. These models do not take into account and do not explain the mechanisms and primary reasons of autonomous appearance of heterogeneity.

This simplest method of modelling of the spatial dynamics is commonly used to describe the spatial dynamics of Bt-resistance gene in insect-pest populations (Comins 1977; Alstad & Andow 1995; Guse et al. 2002; Ives & Andow 2002; Onstad et al. 2002; Crowder et al. 2005; Heimpel et al. 2005).

1.2.2 *Cellular automata*

The authors of other models of Bt-resistance gene dispersal in heterogeneous habitat use the theory of cellular automata. This is the second popular modelling method applying to this problem (Peck et al. 1999; Caprio 2001; Vacher et al. 2003; Cerda & Wright 2004). Cellular automaton represents a set of rules, i.e., it is an algorithm that determines the interactions between spatial cells and their possible states. Such kind of models provides almost unlimited opportunities for carrying out computer simulations (Czárán, 1998).

More exact definition is that cellular automata are dynamic models that are discrete in space, time and state. A simple cellular automaton is defined by a lattice L, a state space Q, a neighbourhood template γ and a local transition function f. Each cell of L can be in a discrete state out of Q. The cells can be linked in different ways. In the simplest case they are connected geometrically according to a spatial order, such as in a one- or two-dimensional square grid or in hexagonal plots. Cells can change their states in discrete time steps. Usually cellular automata are synchronous, i.e. all cells change their states simultaneously. The fate of a cell is dependent on its neighbourhood (first-order neighbourhood consisting of the central cell and eight adjacent cells and second-order neighbourhood containing the central cell and four adjacent cells) and the corresponding transition function f. The transition rules are denoted in the following form:

$$a_{t+1}^{k} = f\left(a_t^{k-l},...,a_t^{k},...a_t^{k+l}\right), \qquad (1.6)$$

where a_t^k is the state of cell k at time t; l is the range of the neighbourhood of cell k; f is the local transition function representing the transition rules. The set of

values $\left\{a_t^k \middle| \forall k \in I\right\}$ called a configuration of the cellular automaton at time t (I is the index set) (Balzter et al, 1998).

The description of the cellular automaton with neighbourhood of second order by means of Markov chain may be found in works of Balzter et al. (1998) and Logofet & Lesnaya (2000).

This an extremely attractive (especially for modellers non-mathematicians) approach certainly deserves attention in a case of modelling of population systems that are defined by patchiness with small intensity of individual movements. However, for the mobile animals this modelling method is of little use. To describe the dispersal of mobile pests in models of Bt-resistance evolution, developers consider comparatively large cells in cellular automaton, assuming that each cell corresponds to one field the size of which may be equal to 2 km by 2 km (Peck et al., 1999; Vacher et al., 2003). Note that cellular automata constructed in such a way represent, per ce, patch models considered above in details. It is assumed that within such large cell its spatial structure is homogeneous and, actually, inaccessible to consideration. Decreasing the cell size will mean reducing pest mobility which is not a controlled parameter, in fact. Note that the essential shortcoming of cellular automata is not only the arbitrary rule of cell size determination but also fundamental impossibility to apply the analytical methods for their studying and difficulties of their use when modelling the dynamics of biological systems in continuous environment.

1.2.3 *Reaction-diffusion models*

Mathematical models based on a system of partial differential equations (PDEs) provide an opportunity of the most complete combination of analytical and simulation approaches. In theoretical biology such systems became widely used after the pioneer papers of Kolmogorov et al. (1937) and Fisher (1937) who proposed a reaction-diffusion equation describing diffusive spread of one advantageous gene in one-dimensional environment (see also Skalski 2004):

$$\frac{\partial p}{\partial t} = spq + \delta \frac{\partial^2 p}{\partial x^2}, \qquad (1.7)$$

where $p(x,t)$ is the frequency of the mutant gene at position x at time t ($x \in [0, L]$), $q = 1 - p$; s is the intensity of selection in favour of the mutant gene, supposed to be independent of p; δ is the diffusion coefficient.

Note that model (1.7) assumes the weak selection, the uniform distribution of population density, and that at each spatial point the population is in the Hardy-Weinberg equilibrium (Fisher 1937; Svirezhev & Pasekov 1982).

This modelling method has been applied to the description not only of the genetic structures of populations but also of many complex population systems and communities (Murray 1983; Svirezhev 1987; Okubo & Levin, 2001). A general model of diffusive spread of population density is:

$$\frac{\partial N}{\partial t} = F(N) + \delta \Delta N, \qquad (1.8)$$

where $N(\mathbf{x},t)$ is the population density at position $\mathbf{x}$ at time t ($\mathbf{x} \in \Omega$, Ω is the population habitat); $F(N)$ is the reaction term, i.e., function describing demographic processes in population; just as in model (1.7) the second term at the right-hand part of equation (1.8) describes the random movements of individuals in the habitat, the diffusion coefficient δ characterizes the intensity of such movements; $\Delta = \text{div grad}$ is the Laplacian of scalar variable.

There are different types of boundary conditions determining population dynamics on the boundaries of habitat Ω. We will consider here three main types (Czárán, 1998):

Passive boundary, i.e., the system is open, nothing special happens to those individuals who reach the boundaries of the area of interest.

Absorbent boundary, i.e., individuals disappear from the habitat immediately after having encountered with the edge. It is specified by the condition that the

population density is always zero at the boundary, e.g., for system (1.8) the absorbing boundary is

$$N(\mathbf{x},t)=0,\ \mathbf{x}\in\partial\Omega.$$

Reflective boundary, i.e., the boundary of an isolated habitat is impenetrable for the members of a population so that they have to turn back soon after they reach it. The appropriate formal condition to be incorporated into the models of such situations should express the fact that there are no density fluxes through the boundaries:

$$\mathbf{n}\cdot\nabla N(\mathbf{x},t)=0,\ \mathbf{x}\in\partial\Omega,$$

where $\mathbf{n}$ is the external normal to the boundary $\partial\Omega$.

Note that habitat isolation does not necessarily mean presence of the physical boundaries preventing the animal dispersal mechanically. Such isolation can be also interpreted as reluctance of individuals to leave the comfortable habitat area.

The hypothesis of random animal movements underlying reaction-diffusion models allows giving a theoretical explanation of such phenomena as patchiness of populations, appearance of dissipative stationary structures and wave regimes in spatially distributed population systems (Svirezhev & Logofet 1978; Dombrovsky & Markman 1983; Murray 1983; Svirezhev 1987; Dombrovsky et al. 1990; Ivanitsky et al. 1994). The central result obtained with reaction-diffusion models of population dynamics is the possibility of appearance of *diffusion-driven instability* or *Turing instability* (Turing, 1952): in the absence of diffusion the spatially homogeneous system is stable to small perturbations but when diffusion is non-zero the homogeneous distribution violates and stable spatial pattern arises.

However, the getting the spatially heterogeneous patterns in reaction-diffusion models requires to use non-trivial, nonlinear (which are never used in point models) functions of local kinetics (Turing 1952; Levin & Segel, 1976; Levin 1977; Mimura & Murray 1978; Svirezhev & Logofet 1978; Mimura &

Kawasaki 1980; Mimura & Yamaguti 1982; Murray 1993) or to accept the hypothesis that the system is not autonomous, i.e., there is some external periodic perturbation (Petrovskii & Malchow 1999, 2001; Savill & Hogeweg 1999; Durrett & Levin 2000; Feltham & Chaplain 2000; Malchow 2000; Venturino & Medvinsky 2001).

Note that in contrast to the frequency-based Fisherian model (1.2) the Kostitzin's model (1.3), (1.4) uses the genotype densities to describe the population dynamics, therefore one can naturally incorporate the diffusion density fluxes into this model that will be transformed into reaction-diffusion system. The local kinetics of such diffusion model will be characterized by strong non-linearity that will limit the analytical study of the model by the examination of the special cases, and the principal investigation of model dynamics will be carried out with computer simulations. To solve the proposed model numerically it is necessary to construct a difference scheme, using a discrete grid introduced in domain of spatial variable **x** (and, perhaps, in domain of time variable *t*, for example, in the finite-difference method). The system of equations obtained in such a way is, in fact, the cellular automaton but in contrast to the cellular automata considered in § 1.2.2, the spatial discretization at numerical research of reaction-diffusion models is well-grounded and the grid step is determined so that to provide the stability of used numerical method and does not depend on the biological traits of pest mobility.

Thesis problems

Based on the analysis of modelling approaches to the problem of an adequate description of the complex biological system considered above, the following tasks have been formulated:

1. to develop and investigate the spatio-temporal demo-genetic model taking into account both genetics and spatial structure of the pest population;
2. to compare the demo-genetic and the conventional Fisherian approaches; to justify the validation and advantages of the demo-genetic approach, used for modelling the Bt-resistance evolution in the pest population controlled with the “high dose – refuge” strategy;
3. to find steady-state conditions of the developed model; to investigate their stability numerically;
4. to develop bi-trophic models of systems “pest – parasitoid” and “plant resource – pest” and investigate the efficiency of the “high dose – refuge” strategy in such systems.

CHAPTER 2

DEMO-GENETIC MODEL OF THE RESISTANCE EVOLUTION TO TRANSGENIC MAIZE IN EUROPEAN CORN BORER POPULATION

2.1 The model

2.1.1 *Population genetics*

As in most models of the development of resistance to Bt crops (e.g., Alstad & Andow 1995; Peck et al. 1999; Caprio 2001; Guse et al. 2002; Hillier & Birch 2002b; Ives & Andow 2002; Vacher et al. 2003; Cerda & Wright 2004; Tabashnik et al. 2004, 2005; Heimpel et al. 2005), we assume that resistance is recessive and governed by a single diallelic locus with a Bt-susceptible allele *s* and a Bt-resistance allele *r*. Assuming that the resistance allele inherited in an autosomal manner, the pest population consists of the Bt-susceptible genotypes *ss* and *rs* and the Bt-resistant genotype *rr*. Mating is assumed to be random. Unlike the conventional approach based on the FHW model, we do not follow the Hardy-Weinberg principle to determine the relationships between allele and genotype frequencies in the pest population (see § 1.1.2).

2.1.2 *Modelling the demo-genetic dynamics of the population*

We propose a spatial demo-genetic model based on a reaction-diffusion system of PDEs, with the modified Kostitzin model (1.3), (1.4) used to describe the local kinetics of competitive genotypes. Diffusion terms specify the random movements of individuals in the habitat. In our demo-genetic model, we have slightly modified Kostitzin's equations, so as to assess genotype fitness in terms of larval survival rather than overall genotype fecundity. Peculiarity of the problem concerned with modelling of Bt-resistance gene dispersal in heterogeneous habitat stipulates such modifications. In this case, we assume that fecundity of single pair is constant and does not depend on genotypes of male and female, i.e., in Kostitzin's model (1.3), (1.4) $\varphi_{ij} = \varphi_{ji} = b = const$, where b can be interpreted as the birth rate. Note that the birth rate is assumed to be the same for all genotypes.

Taking into account the assumptions made in § 2.1.1 about genetics of modelled pest species, let us denote the index set {1, 2, 3} as {*ss*, *rs*, *rr*}. Then in model (1.3), (1.4) $N_1 = N_{ss}$, $N_2 = N_{rs}$, $N_3 = N_{rr}$ are the densities of corresponding genotypes. The term 'density of genotype' means the density of individuals pertaining to the genotype. Introducing the genotypic fitness W_{ss}, W_{rs}, $W_{rr} \in [0,1]$ associated with the genotype survival, let us assume that Bt-plants influence only the reproduction of genotypes and not the natural mortality genotypes and the competition interactions between them.

Taking into account assumptions of both demography and genetics of the pest, and assuming that insect infestation in the crop field Ω is controlled by the Bt plants, we propose a model:

$$\begin{aligned}
\frac{\partial N_{ss}}{\partial t} &= W_{ss} f_{ss}(N_{ss}, N_{rs}, N_{rr}) - \alpha_{ss} N_{ss} N - \mu_{ss} N_{ss} + \delta_{ss} \Delta N_{ss};\\
\frac{\partial N_{rs}}{\partial t} &= W_{rs} f_{rs}(N_{ss}, N_{rs}, N_{rr}) - \alpha_{rs} N_{rs} N - \mu_{rs} N_{rs} + \delta_{rs} \Delta N_{rs};\\
\frac{\partial N_{rr}}{\partial t} &= W_{rr} f_{rr}(N_{ss}, N_{rs}, N_{rr}) - \alpha_{rr} N_{rr} N - \mu_{rr} N_{rr} + \delta_{rr} \Delta N_{rr},
\end{aligned} \tag{2.1}$$

where functions f_{ss}, f_{rs}, f_{rr} describe reproduction processes of pest genotypes:

$$\begin{aligned}
f_{ss}(N_{ss}, N_{rs}, N_{rr}) &= \frac{b}{N}\left(N_{ss} + \frac{N_{rs}}{2}\right)^2;\\
f_{rs}(N_{ss}, N_{rs}, N_{rr}) &= \frac{2b}{N}\left(N_{ss} + \frac{N_{rs}}{2}\right)\left(\frac{N_{rs}}{2} + N_{rr}\right);\\
f_{rr}(N_{ss}, N_{rs}, N_{rr}) &= \frac{b}{N}\left(\frac{N_{rs}}{2} + N_{rr}\right)^2.
\end{aligned} \tag{2.2}$$

In model (2.1) $N_{ss} = N_{ss}(\mathbf{x}, t)$, $N_{rs} = N_{rs}(\mathbf{x}, t)$, $N_{rr} = N_{rr}(\mathbf{x}, t)$ are the genotype densities at position $\mathbf{x} \in \Omega$ at time t; $N = N_{ss} + N_{rs} + N_{rr}$ is the total population density; W_{ij} is the genotypic fitness; b is the birth rate; it is assumed that mortality rates μ_{ij}, competition coefficients α_{ij} and diffusion coefficients δ_{ij} may differ between genotypes ($i, j = r$ or s); Δ is Laplacian. Fitness $W_{ij} = W_{ij}(\mathbf{x})$

can be interpreted as the survival coefficient of larvae of genotype *ij* as a function of location in the habitat (toxic or non-toxic plant tissues).

The diffusion coefficient characterizes the intensity of the random movements of individuals in the habitat. We assume that there are no density fluxes through the boundaries, i.e.,

$$\nabla N_{ss} \cdot \mathbf{n} = \nabla N_{rs} \cdot \mathbf{n} = \nabla N_{rr} \cdot \mathbf{n} = 0, \quad \mathbf{x} \in \partial\Omega, \tag{2.3}$$

where $\mathbf{n}$ is the external normal to the boundary $\partial\Omega$, ∇ is the gradient.

Model (2.1), (2.3) is autonomous, and therefore does not take into account seasonal variations in environmental conditions. The model should be considered as an initial approximation to real agro-ecosystems. It does not take into account the stage structure of the pest population either, assuming instead that death and reproduction occur continuously, at constant rates. In system (2.1), the random movements of individuals take place on the large spatio-temporal scale of lifetime dispersal; micro-scale movements of pest insects are ignored.

Note that as in the original model (1.3), (1.4), in the demo-genetic model (2.1), (2.3) the sex structure is not explicitly taken into account but it is implicitly assumed that each genotype is represented by males and females. We also assume a constant 1:1 sex ratio and Mendelian inheritance. It should be kept in mind that in system (2.1) both genetic and demographic processes in the pest population and spatial movements of pest insects take place on the same temporal scale.

Validation of such approach that allows considering ecological and evolutionary processes in the population being under the strong selection on the same temporal scale is discussed above (see § 1.1.3).

2.1.3. *Modelling the "high dose - refuge" strategy*

We assume that the Bt-resistance evolution in the pest population is managed by the HDR strategy (see Introduction). Spatial heterogeneity caused by the HDR strategy is taken into account by assuming that the whole pest habitat Ω composes of several plots, each planted with a Bt or non-Bt crop. Ω_{Bt} denotes the

set of plots of Bt crop and Ω_{Ref} the refuge domain of non-Bt crop. Ω_{Bt} and Ω_{Ref} are disjoint. Any pattern of refuges can be considered.

As appears from the definition of the HDR strategy, the genotype fitness W_{ij} should be different for the Bt-crop and refuge. Let us derive explicit formulas for calculating the coefficients W_{ij}. Bourguet et al. (2000c) and Tabashnik et al. (2004) determine the dominance level of Bt-resistance as

$$h = \frac{W_{rs} - W_{ss}}{W_{rr} - W_{ss}}.$$

Values of h range from 0 (completely recessive Bt-resistance) to 1 (completely dominant Bt-resistance). Bourguet et al. (2000c) introduce the terms 'dominance level of Bt-toxin selection σ' and 'dominance level of the fitness cost c' which is paid by the genotype possessing the Bt-resistance gene for the advantage in toxic Bt-fields, defining them, respectively, as:

$$h_\sigma = \frac{W_{rs}^{Bt} - W_{ss}^{Bt}}{W_{rr}^{Bt} - W_{ss}^{Bt}}, \quad h_c = \frac{W_{rs}^{ref} - W_{ss}^{ref}}{W_{rr}^{ref} - W_{ss}^{ref}}. \tag{2.4}$$

Like Lenormand & Raymond (1998) and Vacher et al. (2003), we assume that $W_{ss}^{Bt} = 1-\sigma$, $W_{ss}^{ref} = 1$, $W_{rr}^{Bt} = W_{rr}^{ref} = 1-c$. Then from (2.4) we obtain:

$$\begin{aligned} &W_{rr} = 1-c, \quad \text{everywhere in } \Omega; \\ &W_{rs}(\mathbf{x}) = \begin{cases} 1-h_c\, c, & \mathbf{x} \in \Omega_{ref}; \\ 1-\sigma+h_\sigma(\sigma-c), & \mathbf{x} \in \Omega_{Bt}; \end{cases} \\ &W_{ss}(\mathbf{x}) = \begin{cases} 1, & \mathbf{x} \in \Omega_{ref}; \\ 1-\sigma, & \mathbf{x} \in \Omega_{Bt}, \end{cases} \end{aligned} \tag{2.5}$$

where σ is the fitness loss due to the Bt toxin; c is the fitness cost of resistance; h_σ is the dominance level of Bt-toxin selection; h_c is the dominance level of the fitness cost. Parameters σ, c, h_σ, $h_c \in [0, 1]$. Note that $h_\sigma = 1-h$, where h is the effective dominance level estimated by Tabashnik et al. (2004) (see also Vacher et al. 2004).

In particular case when (a) the selection intensity in the Bt area is maximum (i.e., 100% of susceptible insects are killed by the Bt-toxin) and (b) the resistance is recessive (i.e., all heterozygotes die in Bt-crop), $\sigma = 1$, $h_\sigma = 1$. If, in addition, it is assumed that there is no resistance cost, fitness of *ss* and *rs* genotypes become equal to zero in Ω_{Bt}, i.e., the offspring of the Bt-susceptible genotypes cannot survive in the Bt-crop while the Bt-resistant insects rr will have the maximum fitness $W_{rr} = 1$ in both Bt- and non-Bt domains:

$$W_{rr} \equiv 1, \quad \forall\, \mathbf{x} \in \Omega;$$
$$W_{ss}(\mathbf{x}) = W_{rs}(\mathbf{x}) = \begin{cases} 1, & \mathbf{x} \in \Omega_{ref}; \\ 0, & \mathbf{x} \in \Omega_{Bt}. \end{cases}$$

However, this case is extreme. In the present work we will assume that the Bt-resistance is partially recessive and the Bt-toxin has 100% efficiency of influence on the Bt-susceptible insects: $h_\sigma \geq 0$, $\sigma = 1$. These assumptions do not contradict field observations because investigations confirm neither expressed cost of Bt-resistance in the ECB population nor recessive inheritance of Bt-resistance allele (Bourguet et al. 2005; see also Introduction).

Thus, the difference between the refuge and the Bt domains is therefore determined solely on the basis of differences in pest survival coefficients between these two types of domain, according to conditions (2.5). Note that we set conditions (2.3) only for the outer boundary $\partial\Omega$, whereas the boundaries between adjacent refuges and Bt domains are permeable.

2.1.4. *Ecological simplifications in the demo-genetic model*

To better understand the influence of the HDR strategy on the Bt-resistance evolution in the pest population and to single out its effect, let us introduce some simplifications in model (2.1), (2.3). We will assume that natural mortality and competition do not depend on the genotype of individual $\mu_{ij} = \mu = const$, $\alpha_{ij} = \alpha = const$ and the mobility of different pest genotypes are the same

$\delta_{ij} = \delta = const$ $(i, j = r$ or $s)$, i.e., pest genotypes differ from each other only by their ability to survive depending on the location in the habitat Ω.

Then model (2.1), (2.3) reduces to:

$$\begin{aligned}
&\frac{\partial N_{ss}}{\partial t} = W_{ss} f_{ss}(N_{ss}, N_{rs}, N_{rr}) - \alpha N_{ss} N - \mu N_{ss} + \delta \Delta N_{ss};\\
&\frac{\partial N_{rs}}{\partial t} = W_{rs} f_{rs}(N_{ss}, N_{rs}, N_{rr}) - \alpha N_{rs} N - \mu N_{rs} + \delta \Delta N_{rs};\\
&\frac{\partial N_{rr}}{\partial t} = W_{rr} f_{rr}(N_{ss}, N_{rs}, N_{rr}) - \alpha N_{rr} N - \mu N_{rr} + \delta \Delta N_{rr},\\
&\nabla N_{ss} \cdot \mathbf{n} = \nabla N_{rs} \cdot \mathbf{n} = \nabla N_{rr} \cdot \mathbf{n} = 0, \quad \mathbf{x} \in \partial\Omega,
\end{aligned} \tag{2.6}$$

where reproduction functions f_{ij} is defined by formula (2.2).

In an entirely non-transgenic area (i.e., all $W_{ij} = 1$) and in the case of the uniformly distributed pest genotypes, summing the three equations of (2.6) generates the simple logistic equation for the growth of the whole pest population: $\frac{dN}{dt} = bN - \mu N - \alpha N^2$, where $N = N_{ss} + N_{rs} + N_{rr}$, b and μ are the constant rates of birth and death, respectively. If $b > \mu$, then the ratio $K = \frac{b-\mu}{\alpha} = \frac{\rho}{\alpha}$ (ρ is the reproduction rate of pest genotypes) is the carrying capacity of the pest population (Svirezhev & Pasekov 1982; Ginzburg & Golenberg 1985). In particular, *K* is the carrying capacity even in the case when all population consists of homozygotes of *ss* or *rr* genotype.

Despite the fact that we will consider solely the case of $b > \mu$, let us note that if $b < \mu$ zero equilibrium gets stable and determines the 'carrying capacity' in the model (2.6) while $K = \frac{b-\mu}{\alpha}$ becomes negative and unstable (see also Gabriel et al. 2005).

It is noteworthy that a population cannot consist solely of heterozygotes and the term 'carrying capacity' for *rs* genotype is artificial. However, formally,

$K_{rs} = \dfrac{b/2 - \mu}{\alpha} < K$. It means that heterozygous genotype "pays" for the reproduction of homozygote genotypes *ss* and *rr*.

Note that the demo-genetic model (2.6) can be simplified by the use of dimensionless variables and parameters: $\widetilde{t} = bt$, $\widetilde{N}_{ss} = \dfrac{N_{ss}}{K}$, $\widetilde{N}_{rs} = \dfrac{N_{rs}}{K}$, $\widetilde{N}_{rr} = \dfrac{N_{rr}}{K}$, $\widetilde{\mu} = \dfrac{\mu}{b}$, $\widetilde{\alpha} = \dfrac{\alpha K}{b} = 1 - \widetilde{\mu}$, $\widetilde{\delta} = \dfrac{\delta}{b}$. In this parameterization, $\widetilde{b} = \widetilde{K} = 1$. Thereafter, omitting tildes, we obtain:

$$
\begin{aligned}
&\frac{\partial N_{ss}}{\partial t} = W_{ss}\frac{1}{N}\left(N_{ss} + \frac{N_{rs}}{2}\right)^2 - N_{ss}N - \mu N_{ss}(1-N) + \delta\Delta N_{ss};\\
&\frac{\partial N_{rs}}{\partial t} = W_{rs}\frac{2}{N}\left(N_{ss} + \frac{N_{rs}}{2}\right)\left(\frac{N_{rs}}{2} + N_{rr}\right) - N_{rs}N - \mu N_{rs}(1-N) + \delta\Delta N_{rs};\\
&\frac{\partial N_{rr}}{\partial t} = W_{rr}\frac{1}{N}\left(\frac{N_{rs}}{2} + N_{rr}\right)^2 - N_{rr}N - \mu N_{rr}(1-N) + \delta\Delta N_{rr},\\
&\nabla N_{ss}\cdot\mathbf{n} = \nabla N_{rs}\cdot\mathbf{n} = \nabla N_{rr}\cdot\mathbf{n} = 0, \quad \mathbf{x}\in\partial\Omega.
\end{aligned}
\tag{2.7}
$$

If the whole pest habitat is a rectangle $\Omega = [0, L_x]\times[0, L_y]$, one of its sides can be normalised to any constant (e.g., L_x to 1). So, the dynamical properties of spatial solutions of model (2.6) will actually depend on three parameters: the mortality rate μ, the pest dispersal δ and the ratio of L_x/L_y (L_x and L_y are the lengthes of the habitat sides). If $L_x = L_y = L$, i.e., Ω is a square, then $\widetilde{\delta} = \dfrac{\delta}{bL^2}$, $\Omega = [0,1]\times[0,1]$.

2.1.5 *Estimation of demographic model parameters for the European corn borer*

We identified the parameters of the continuous model (2.6) on the basis of the parameter values estimated in Guse et al. (2002) for the detailed discrete model taking into account the seasonality and stage transitions of the life history of the ECB.

Let time unit be one year (365 days) and the length unit be a kilometre. The ECB is assumed to produce two generations per year. We also assume that the life span of each generation covers the period from the egg stage to the end of the adult stage (egg-to-egg cycle). The life span of the second generation is longer than the first as it includes overwintering of the larval stage.

According to Guse et al. (2002), one adult ECB female lays an average of 288 eggs during her lifetime. For estimating the instantaneous birth rate b in the continuous-time model (2.6) we use the rule $b = \frac{1}{\tau}\ln\lambda$, where λ is the lifetime fecundity in an appropriate discrete-time model and τ is the lifetime duration.

Thus, taking into account the production of two pest generations per year, the average annual birth rate b of the ECB is estimated by the weighted sum of the birth rates for the first generation b_1 and for the second generation b_2:

$$b = b_1\tau_1 + b_2\tau_2, \tag{2.8}$$

where $b_1 = \frac{1}{\tau_1}\ln\lambda$, $b_2 = \frac{1}{\tau_2}\ln\lambda$, τ_1 and τ_2 are the durations of the first and second generations, respectively. Then $b = 2\ln\lambda$. Assuming that the sex ratio is 1:1 (i.e., $\lambda = 144$), we obtain $b \approx 9.94$ yr^{-1}.

Similarly, we estimated the mean instantaneous mortality rate of the ECB μ as the sum of the mortalities of both generations:

$$\mu = \mu_1\tau_1 + \mu_2\tau_2. \tag{2.9}$$

Mortalities μ_1 and μ_2 are determined under the assumption that the decrease of the population density over a particular period of time τ_i follows the Malthusian law:

$$\frac{N(\tau_i)}{N(0)} = \exp(-\mu_i\tau_i),\ i = 1, 2, \tag{2.10}$$

where $N(0)$ is the population abundance at the initial time of the i-th period.

Then $\mu = -\ln(0.077) - \ln(0.077 \cdot 0.18) = 6.84$ yr^{-1}, where natural ECB survival coefficients are 0.077 in the summer, through the larval stages of both generations, and 0.18 in the winter diapause, for the diapausing larvae of the second generation (Guse et al. 2002). Like Guse et al. (2002), we also ignore mortality at the egg and pupal stages.

In line with Guse's model (Guse et al. 2002), we set a maximum of 22 ECB larvae/plant and 67,000 plants/ha, giving an estimate of carrying capacity $K = 147.4 \times 10^6$ larvae/km^2. The competition coefficient is therefore determined by the formula $\alpha = \frac{b-\mu}{K}$, so $\alpha = 2.1 \times 10^{-8}$ km^{2}yr^{-1}ind^{-1}.

As the large-scale diffusion coefficient δ of insect species is difficult to estimate from a small number of field observations, we will vary this coefficient from 0 to ∞, with irregular increments.

2.2 Qualitative analysis of the demo-genetic model

Let us make a qualitative investigation of system (2.6) and determine whether the stationary states of the system exist, find their number and kind of stationary distributions in space, study a problem of their stability.

Before we will pass on to the analysis of model (2.6) in spatially heterogeneous environment, let us study the behaviour of considered biological system in homogeneous habitat.

2.2.1 *Homogeneous pest habitat*

In spatially homogeneous case the dynamics of system (2.6) is entirely described by the non-spatial demo-genetic model:

$$\begin{aligned}
\frac{dN_{ss}}{dt} &= W_{ss}\frac{b}{N}\left(N_{ss}+\frac{N_{rs}}{2}\right)^2 - \alpha N_{ss}N - \mu N_{ss};\\
\frac{dN_{rs}}{dt} &= W_{rs}\frac{2b}{N}\left(N_{ss}+\frac{N_{rs}}{2}\right)\left(\frac{N_{rs}}{2}+N_{rr}\right) - \alpha N_{rs}N - \mu N_{rs};\\
\frac{dN_{rr}}{dt} &= W_{rr}\frac{b}{N}\left(\frac{N_{rs}}{2}+N_{rr}\right)^2 - \alpha N_{rr}N - \mu N_{rr}.
\end{aligned} \qquad (2.11)$$

Let us consider two subcases:

I. *Let us assume that the pest habitat consists solely of conventional* (*non-modified genetically*) *crop plants, and there are no Bt-hybrids on a cultivated field.* Then all fitness $W_{ij} = 1$ and model (2.11) coincide with the particular case of Kostitzin demo-genetic model (1.3), (1.4). Let us show that in such case the equilibria family of system (2.11) represents a parabola in three-dimensional space of phase variables (N_{ss}, N_{rs}, N_{rr}). This parabola is made up of intersection of three surfaces defined by a condition of equality of right-hand parts of equations (2.11) to zero.

Basis in phase space of model (2.11) is determined by the system of three linear-independent vectors $\mathbf{i}$, $\mathbf{j}$, $\mathbf{k}$: $\mathbf{i}(0, 0, 1)$, $\mathbf{j}(0, 1, 0)$, $\mathbf{k}(1, 0, 0)$ that specify directions of coordinate axes ON_{ss}, ON_{rs}, ON_{rr}, respectively (see Fig. 2.1). All equilibriums of system (2.11) lie in the plane ABC corresponding to the condition $N_{ss} + N_{rs} + N_{rr} = K$. Let us proceed to the new basis of the system, using the rule: the origin of the new coordinate system $O'xyz$ is located at point $O'\left(\frac{K}{2}, 0, \frac{K}{2}\right)$ and the new basis vectors $\mathbf{i}'$, $\mathbf{j}'$, $\mathbf{k}'$ specify directions of new coordinate axes $O'x$, $O'y$, $O'z$ so that vector $\mathbf{i}'$ is collinear and codirectional to vector *CA*, vector $\mathbf{j}'$ is collinear and codirectional to vector $O'B$, vector $\mathbf{k}'$ is the cross product of $\mathbf{i}' \times \mathbf{j}'$ (Fig. 2.1).

Performing in series the operations of parallel transport and rotation of system $\begin{pmatrix} N_{ss} \\ N_{rs} \\ N_{rr} \\ 1 \end{pmatrix} = \mathbf{T} * \mathbf{S} * \begin{pmatrix} x \\ y \\ z \\ 1 \end{pmatrix}$, where matrix of parallel transport $\mathbf{T}$ and rotation matrix $\mathbf{S}$ are:

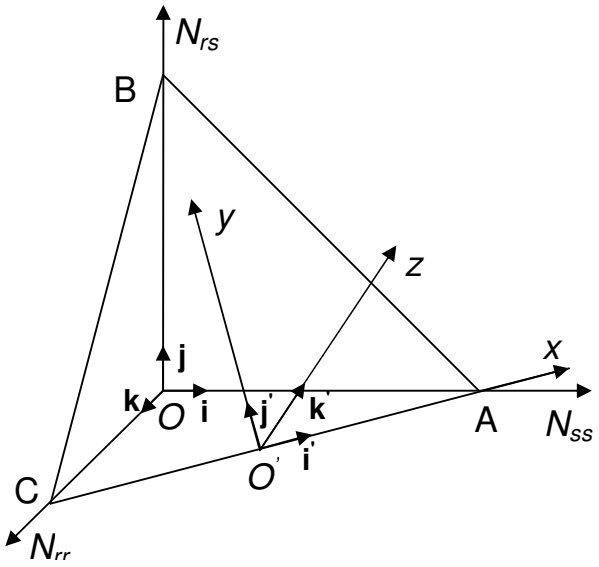


Fig. 2.1. Transition from the old basis $(\mathbf{i},\mathbf{j},\mathbf{k})$ to the new one $(\mathbf{i}',\mathbf{j}',\mathbf{k}')$. N_{ss}, N_{rs}, N_{rr} are the densities of corresponding pest genotypes.

$$\mathbf{T}=\begin{bmatrix}1 & 0 & 0 & \frac{K}{2}\\ 0 & 1 & 0 & 0\\ 0 & 0 & 1 & \frac{K}{2}\\ 0 & 0 & 0 & 1\end{bmatrix}; \qquad \mathbf{S}=\begin{bmatrix}\frac{1}{\sqrt{2}} & -\frac{1}{\sqrt{6}} & \frac{1}{\sqrt{3}} & 0\\ 0 & \frac{2}{\sqrt{6}} & \frac{1}{\sqrt{3}} & 0\\ -\frac{1}{\sqrt{2}} & -\frac{1}{\sqrt{6}} & \frac{1}{\sqrt{3}} & 0\\ 0 & 0 & 0 & 1\end{bmatrix},$$

we obtain:

$$\begin{aligned}&\dot{x}=-\sqrt{3}\alpha xz;\\ &\dot{y}=\frac{1}{\sqrt{6}}\left(\frac{b}{2}\left(\sqrt{3}z+K-\frac{6x^2}{\sqrt{3}z+K}\right)-\left(\sqrt{6}y-K\right)\left(\mu+\alpha\left(\sqrt{3}z+K\right)\right)\right);\\ &\dot{z}=-z\left(\sqrt{3}\alpha z+b-\mu\right).\end{aligned} \qquad (2.12)$$

Note that in system (2.12) the differential equations for z does not depend on other variables x and y and $z=0$ is a unique non-negative equilibrium of variable z if $b>\mu$. Then equilibriums of system (2.12) is defined by the equation of parabola located on plane ABC (Fig. 2.2): $y=\frac{3}{\sqrt{6}}\left(-\frac{x^2}{K}+\frac{K}{2}\right)$ that also defines the equilibria family of system (2.11).

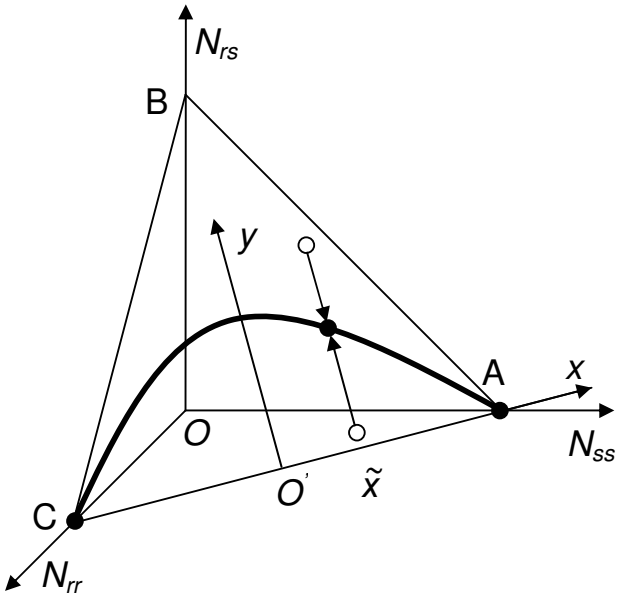


Fig. 2.2. Equilibrium family of system (2.11) is a parabola (thick solid line) on plane ABC. N_{ss}, N_{rs}, N_{rr} are the densities of corresponding pest genotypes.

Let us examine the stability of obtained equilibrium states. Jacobean matrix of system (2.12) is:

$$\mathbf{J}=\begin{bmatrix} -\sqrt{3}\alpha z & 0 & -\sqrt{3}\alpha x \\ -\dfrac{\sqrt{6}bx}{\sqrt{3}z+K} & -\mu-\alpha\left(\sqrt{3}z+K\right) & \dfrac{1}{\sqrt{2}}\left(\dfrac{b}{2}\left(1+\dfrac{6x^2}{\left(\sqrt{3}z+K\right)^2}\right)-\alpha\left(\sqrt{6}y-K\right)\right) \\ 0 & 0 & -2\sqrt{3}\alpha z-b+\mu \end{bmatrix}$$

Then, using the formula $\left|\mathbf{J}-\lambda\mathbf{E}\right|\Big|_{x,\,y=\frac{3}{\sqrt{6}}\left(-\frac{x^2}{K}+\frac{K}{2}\right),\,z=0}=0$, where $\mathbf{E}$ is the unit matrix with appropriate size, we get the characteristic equation:

$$\lambda^3+\lambda^2(2b-\mu)+\lambda b(b-\mu)=0. \qquad (2.13)$$

Thus, the stability conditions following from the negativity of real parts of eigenvalues of (2.13) $\lambda_1=-b$, $\lambda_2=\mu-b$ are determined by the strict positivity of

the birth rate b and the strict prevalence of birth rate over death rate $b > \mu$. Note that $\lambda_0 = 0$ is also a root of characteristic equation (2.13).

Let us introduce the definition of allelic frequencies, expressing them via genotype densities: $p_s = \dfrac{N_{ss} + \dfrac{1}{2} N_{rs}}{N}$ is the frequency of the susceptible allele, $p_r = \dfrac{N_{rr} + \dfrac{1}{2} N_{rs}}{N}$ is the frequency of the resistance allele, $p_s + p_r = 1$. Then the following theorems of a invariability of allelic frequencies when there is no selection are true.

Theorem 1. If in demo-genetic model (2.6) $\Omega = \Omega_{ref}$ then for any initial point $\left(N_{ss}^0, N_{rs}^0, N_{rr}^0\right)$ lying on the plane ABC defined by equation $N_{ss} + N_{rs} + N_{rr} = K$ (Fig. 2.2) the allelic frequencies are invariable with time: $p_r(t) = p_r(0)$, $p_s(t) = p_s(0)$ $\forall\, t \in [0, \infty)$.

It means that system reaches the equilibrium point located on the parabola and moving to the equilibrium occurs along axis $O'y$ with invariable allelic frequencies in population.

Proof. Let us express the new basic variables (x, y, z) via old ones (N_{ss}, N_{rs}, N_{rr}):

$$(\mathbf{T} * \mathbf{S})^{-1} * \begin{pmatrix} N_{ss} \\ N_{rs} \\ N_{rr} \\ 1 \end{pmatrix} = \begin{pmatrix} x \\ y \\ z \\ 1 \end{pmatrix}, \text{ where } (\mathbf{T} * \mathbf{S})^{-1} = \begin{pmatrix} \frac{1}{\sqrt{2}} & 0 & -\frac{1}{\sqrt{2}} & 0 \\ -\frac{1}{\sqrt{6}} & \frac{2}{\sqrt{6}} & -\frac{1}{\sqrt{6}} & \frac{K}{\sqrt{6}} \\ \frac{1}{\sqrt{3}} & \frac{1}{\sqrt{3}} & \frac{1}{\sqrt{3}} & -\frac{K}{\sqrt{3}} \\ 0 & 0 & 0 & 1 \end{pmatrix}.$$

Note that if the initial point belongs to the plane ABC, i.e., it has coordinates $(x_0, y_0, 0)$, then with time the trajectory of the system does not leave the plane:

$z(t)=0$, $\forall\, t>0$. Therefore, fixing some arbitrary point $x=\tilde{x}=const$ on axis $O'x$ and assuming $z=0$, we get:

$$\begin{aligned} N_{ss} + \ N_{rs} + N_{rr} &= K; \\ N_{ss} \qquad\quad - N_{rr} &= \sqrt{2}\tilde{x}; \\ -N_{ss} + 2N_{rs} - N_{rr} &= \sqrt{6}y - K. \end{aligned}$$

Then the allelic frequencies $p_s = \dfrac{N_{ss}+\dfrac{1}{2}N_{rs}}{N} = \dfrac{1}{2} + \dfrac{\tilde{x}}{\sqrt{2}K}$ and $p_r = \dfrac{N_{rr}+\dfrac{1}{2}N_{rs}}{N} = \dfrac{1}{2} - \dfrac{\tilde{x}}{\sqrt{2}K}$, where $N = N_{ss}+N_{rs}+N_{rr} = K$ on the plane ABC. Moreover, owing to the arbitrary choice of value $\tilde{x}$ these expressions for the allelic frequencies will be true for any $\tilde{x} \in \left[-\dfrac{K}{\sqrt{2}},\ \ \dfrac{K}{\sqrt{2}}\right]$ on axis $O'x$.

Thus, Theorem 1 is proved ■

We will also prove a more general form of Theorem 1.

Theorem 2. If in demo-genetic model (2.6) $\Omega = \Omega_{ref}$ then for any initial point $\left(N_{ss}^0, N_{rs}^0, N_{rr}^0\right)$: $N_{ss}^0 \ge 0$, $N_{rs}^0 \ge 0$, $N_{rr}^0 \ge 0$, the allelic frequencies are invariable with time: $p_r(t) = p_r(0)$, $p_s(t) = p_s(0)$ $\forall\, t \in [0, \infty)$.

In other words, even if the initial point does not belong to the plane ABC (Fig. 2.2), then during the evolution of the system to one point of the equilibrium family located on the parabola, the allelic frequencies also remain invariable in the population. However, in contrast to the previous case, transition to the equilibrium occurs with displacement along axis $O'x$ regarding the initial position.

Proof. Let the initial point do not belong to the plane ABC and have coordinates $\left(N_{ss}^0, N_{rs}^0, N_{rr}^0\right)$, where $N_{ss}^0 \ge 0$, $N_{rs}^0 \ge 0$, $N_{rr}^0 \ge 0$, or (x_0, y_0, z_0) in new coordinate system $O'xyz$. Since in system (2.12) the differential equation for z does not

depend on other variables of the system, x and y, given the initial condition $z(0)=z_0$, we have:

$$z(t)=\frac{z_0 K}{-\sqrt{3}z_0+e^{(b-\mu)t}\left(K+\sqrt{3}z_0\right)}.$$

Then, substituting this expression into the differential equation $\dot{x}=-\sqrt{3}\alpha\, x\, z$ and solving the Cauchy problem obtained, we find:

$$x(t)=\frac{x_0 K}{-\sqrt{3}z_0 e^{-(b-\mu)t}+K+\sqrt{3}z_0}.$$

If $t\to\infty$ and $b>\mu$, $z(t)\to 0$ and $x(t)\to\frac{x_0 K}{K+\sqrt{3}z_0}$. This means that with time the system evolves to the point located on the plane ABC, deviating from x_0 in $\frac{K}{K+\sqrt{3}z_0}$ times.

Let us show that the allelic frequencies, p_s and p_r, do not change with time. From equality $\begin{pmatrix} N_{ss} \\ N_{rs} \\ N_{rr} \\ 1 \end{pmatrix} = \mathbf{T}*\mathbf{S}* \begin{pmatrix} x \\ y \\ z \\ 1 \end{pmatrix}$ we have:

$$\begin{aligned} N_{ss} &= \frac{1}{\sqrt{2}}x-\frac{1}{\sqrt{6}}y+\frac{1}{\sqrt{3}}z+\frac{K}{2}; \\ N_{rs} &= \frac{2}{\sqrt{6}}y+\frac{1}{\sqrt{3}}z; \\ N_{rr} &= -\frac{1}{\sqrt{2}}x-\frac{1}{\sqrt{6}}y+\frac{1}{\sqrt{3}}z+\frac{K}{2}. \end{aligned}$$

Then the allelic frequencies are:

$$p_s = \frac{N_{ss} + \frac{1}{2}N_{rs}}{N} = \frac{1}{2} + \frac{x}{\sqrt{2}\left(\sqrt{3}z + K\right)};$$
$$p_r = \frac{N_{rr} + \frac{1}{2}N_{rs}}{N} = \frac{1}{2} - \frac{x}{\sqrt{2}\left(\sqrt{3}z + K\right)}. \qquad (2.14)$$

Substituting the initial point $\left(N_{ss}^0, N_{rs}^0, N_{rr}^0\right)$ with coordinates in new basis $\left(x_0, y_0, z_0\right)$ and limit point $\left(N_{ss}^*, N_{rs}^*, N_{rr}^*\right)$ with coordinates $\left(\frac{x_0 K}{K + \sqrt{3}z_0}, y, 0\right)$ into expressions for the allelic frequencies (2.14), we obtain:

$$p_s^0 = \frac{1}{2} + \frac{x_0}{\sqrt{2}\left(\sqrt{3}z_0 + K\right)} = p_s^*;$$
$$p_r^0 = \frac{1}{2} - \frac{x_0}{\sqrt{2}\left(\sqrt{3}z_0 + K\right)} = p_r^*.$$

Moreover, for the arbitrary initial point $\left(x_0, y_0, z_0\right)$ the ratio of the allelic frequencies is constant at any instant of time t. Denoting $\eta = -\sqrt{3}z_0 + e^{(b-\mu)t}\left(K + \sqrt{3}z_0\right)$, let us substitute expressions for $x(t)$ and $z(t)$ into (2.14):

$$p_s = \frac{1}{2} + \frac{x}{\sqrt{2}\left(\sqrt{3}z + K\right)} = \frac{1}{2} + \frac{1}{\sqrt{2}}\left(\frac{x_0 K e^{(b-\mu)t}}{\eta} \cdot \frac{1}{\frac{\sqrt{3}z_0 K}{\eta} + K}\right) =$$
$$= \frac{1}{2} + \frac{1}{\sqrt{2}}\left(\frac{x_0 e^{(b-\mu)t}}{\sqrt{3}z_0 + \eta}\right) = \frac{1}{2} + \frac{x_0}{\sqrt{2}\left(\sqrt{3}z_0 + K\right)}.$$

Similarly, $p_r = \frac{1}{2} - \frac{x_0}{\sqrt{2}\left(\sqrt{3}z_0 + K\right)}$, $\forall\, t \geq 0$.

This completes the proof ■

From Theorem 1, the deviation from the equilibrium point $\left(x^*, y^*, 0\right)$ lying on the parabola in the *x*-direction leads the system to the new equilibrium point

$\left(x^* + \Delta x^*, y^* + \Delta y^*, 0\right)$. The deviation from the equilibrium point $\left(x^*, y^*, 0\right)$ in the *y*-direction leads the system to the same point $\left(x^*, y^*, 0\right)$. According to Theorem 2, the deviation from the equilibrium point $\left(x^*, y^*, 0\right)$ in the *z*-direction leads the system to the new equilibrium point $\left(\frac{x^* K}{K + \sqrt{3}\Delta z^*}, y^* + \Delta y^*, 0\right)$.

Thus, due to the absence of the Bt-modified plants in the pest habitat there is no Bt-toxin selection and co-existence of all three pest genotypes is possible, i.e., the polymorphism exists for all points of parabola excepting end-points A and C. However, here the matter concerns Lyapunov stability rather than asymptotic stability. Note that moving along the parabola from the point A to the point C corresponds to the variation of the allelic frequencies in the pest population from the complete absence of the Bt-resistant genotype *rr* (the extreme case of *r* allele absence corresponds to the point A) to the complete elimination of Bt-susceptible genotype ss (the extreme case of complete dominance of *r* allele corresponds to the point C).

Theorems of invariability of the allelic frequencies p_s and p_r in model (2.11) in the case of homogeneous non-Bt habitat may be proved by another way.

Lemma 1. The point demo-genetic model (2.11) in the frequency notation coincides with the Fisher-Haldane-Wright model (1.2) (where $d(N) = \mu + \alpha N$). However, in the general case, the genetic structure of a population does not necessarily evolve to the Hardy-Weinberg equilibrium (1.1).

Proof. Summing all equations of system (2.11) and denoting the frequency of each genotype $u_{ij}(t) = \frac{N_{ij}(t)}{N(t)}$, we obtain an equation describing the dynamics of the total population density *N*:

$$\frac{dN}{dt} = N(bW - (\mu + \alpha N)), \tag{2.15}$$

where

$$W(u_{ss},u_{rs},u_{rr}) = W_{ss}\left(u_{ss}+\frac{u_{rs}}{2}\right)^2 + 2W_{rs}\left(u_{ss}+\frac{u_{rs}}{2}\right)\left(\frac{u_{rs}}{2}+u_{rr}\right) + W_{rr}\left(\frac{u_{rs}}{2}+u_{rr}\right)^2.$$

Let us pass to the frequency form of demo-genetic model (2.11) according to the method proposed by Svirezhev & Pasekov (1982). Expressing the density of each genotype via its frequency and total population density of the pest $N_{ij} = u_{ij}N$, the original system (2.11) can be rewritten as follows:

$$\begin{aligned}
N\frac{du_{ss}}{dt} + u_{ss}\frac{dN}{dt} &= W_{ss}bN\left(u_{ss}+\frac{u_{rs}}{2}\right)^2 - \alpha u_{ss}N^2 - \mu u_{ss}N;\\
N\frac{du_{rs}}{dt} + u_{rs}\frac{dN}{dt} &= 2W_{rs}bN\left(u_{ss}+\frac{u_{rs}}{2}\right)\left(\frac{u_{rs}}{2}+u_{rr}\right) - \alpha u_{rs}N^2 - \mu u_{rs}N;\\
N\frac{du_{rr}}{dt} + u_{rr}\frac{dN}{dt} &= W_{rr}bN\left(\frac{u_{rs}}{2}+u_{rr}\right)^2 - \alpha u_{rr}N^2 - \mu u_{rr}N,
\end{aligned} \qquad (2.16)$$

where $u_{ss}+u_{rs}+u_{rr}=1$.

Let us denote the reproduction function of each genotype by f_{ij}:

$$\begin{aligned}
f_{ss}(u_{ss},u_{rs},u_{rr}) &= W_{ss}bN\left(u_{ss}+\frac{u_{rs}}{2}\right)^2;\\
f_{rs}(u_{ss},u_{rs},u_{rr}) &= 2W_{rs}bN\left(u_{ss}+\frac{u_{rs}}{2}\right)\left(\frac{u_{rs}}{2}+u_{rr}\right);\\
f_{rr}(u_{ss},u_{rs},u_{rr}) &= W_{rr}bN\left(\frac{u_{rs}}{2}+u_{rr}\right)^2.
\end{aligned} \qquad (2.17)$$

Then system (2.16) can be rewritten as:

$$N\frac{du_{ij}}{dt} + u_{ij}\frac{dN}{dt} = f_{ij} - \alpha u_{ij}N^2 - \mu u_{ij}N, \qquad (2.18)$$

Substituting in (2.18) the expression for the derivative of the total pest density (2.15), we have:

$$\frac{du_{ij}}{dt} = \frac{1}{N}f_{ij} - u_{ij}bW. \qquad (2.19)$$

Let us pass from (2.19) to the equations for the allelic frequencies $p_r = u_{rr} + \frac{1}{2}u_{rs}$, $p_s = u_{ss} + \frac{1}{2}u_{rs}$. Due to $p_r + p_s = 1$, it is quite enough to consider solely the equation for the Bt-resistance allele p_r:

$$\frac{dp_r}{dt} = \frac{du_{rr}}{dt} + \frac{1}{2}\frac{du_{rs}}{dt} = \frac{1}{N}\left(f_{rr} + \frac{1}{2}f_{rs}\right) - p_r bW\,. \tag{2.20}$$

Taking into account equation (2.15) and the fact that $f_{rr} + \frac{1}{2}f_{rs} = p_r bN\left(W_{rr}p_r + W_{rs}p_s\right)$, we obtain the following system of equations:

$$\begin{aligned} &\frac{dp_r}{dt} = bp_r\left(W_r - W\right); \\ &\frac{dN}{dt} = N\left(bW - \left(\mu + \alpha N\right)\right); \\ &p_s + p_r = 1, \end{aligned} \tag{2.21}$$

where $W_r = W_{rs}p_s + W_{rr}p_r$ is the mean fitness of the Bt-resistance allele. W can be interpreted as the mean population fitness and be written via allelic frequencies as $W = W_{ss}p_s^2 + 2W_{rs}p_s p_r + W_{rr}p_r^2$.

Note that in the general case, system (2.21) does not necessarily evolve to the Hardy-Weinberg equilibrium (1.1): $u_{ss}^* = p_s^2$, $u_{rs}^* = 2p_s p_r$, $u_{rr}^* = p_r^2$. Introducing the additional variable $\xi = u_{ss}u_{rr} - \frac{u_{rs}^2}{4}$ to quantify the deviation of system (2.21) from Hardy-Weinberg equilibrium (see Svirezhev & Pasekov 1982) and expressing the genotype frequencies as $u_{ss} = p_s^2 + \xi$, $u_{rs} = 2p_s p_r - 2\xi$, $u_{rr} = p_r^2 + \xi$, we obtain an differential equation describing the spatio-temporal dynamics of the deviation ξ:

$$\begin{aligned} \frac{d\xi}{dt} &= \frac{du_{rr}}{dt} - 2p_r\frac{dp_r}{dt} = bW_{rr}p_r^2 - bW\left(p_r^2 + \xi\right) - 2b\left(W_r - W\right)p_r^2 = \\ &= b\left(p_s^2 p_r^2\left(W_{ss} + W_{rr} - 2W_{rs}\right) - \xi W\right). \end{aligned} \tag{2.22}$$

We can see that, for genotypes differing in fitness, the deviation ξ tends to zero (i.e., system (2.21) tends to the Hardy-Weinberg equilibrium) only if the frequency of one of the two alleles –*r* or *s* – tends to zero. Otherwise, in a general polymorphic case, e.g., if W_{rs} exceeds W_{ss} and W_{rr}, system (2.21) evolves beyond the Hardy-Weinberg equilibrium.

Lemma 1 is proved ▲

Let us come back to the question of the invariability of the allelic frequencies when there is no Bt-toxin selection in the crop field. In this case, $W_{ss} = W_{rs} = W_{rr} = 1$. According to Lemma 1, we find: $\frac{dp_s}{dt} = 0$, $\frac{dp_r}{dt} = 0$, $\frac{d\xi}{dt} = -\xi b$. Then $p_s = 1 - p_r = const$ and the deviation of system (2.11) from Hardy-Weinberg equilibrium exponentially decays.

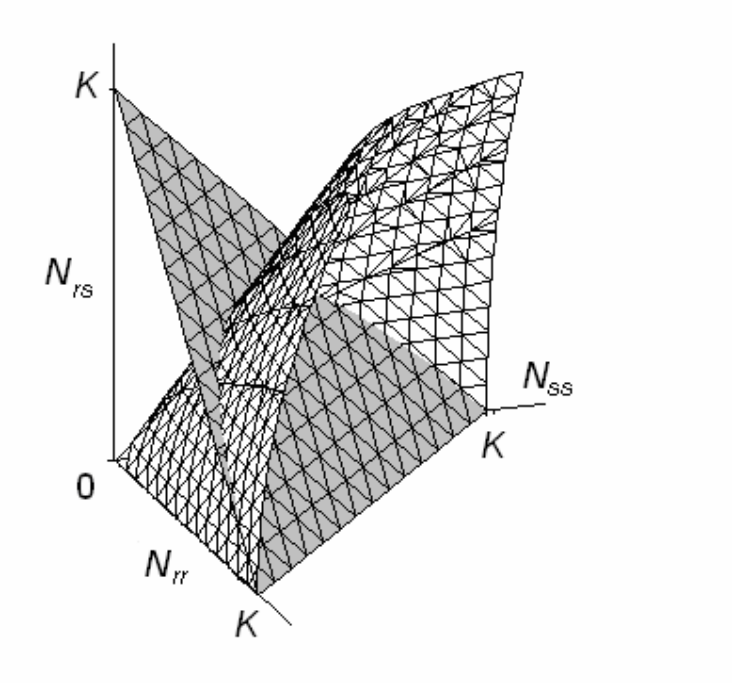


Fig. 2.3. The Hardy-Weinberg equilibrium $u_{ss}u_{rr} = \frac{u_{rs}^2}{4}$ in three-dimensional space of phase variables (N_{ss}, N_{rs}, N_{rr}) defines the surface of cone (marked in white), where $u_{ij} = \frac{N_{ij}}{N}$, $N = N_{ss} + N_{rs} + N_{rr} = K$ (the grey plane), N_{ss}, N_{rs}, N_{rr} are the densities of corresponding genotypes.

Note that Kostitzin model (2.11) can evolve in the whole phase space of variables $N_{ij} \geq 0$, i.e., it has more degrees of freedom than the Fisher-Haldane-Wright model (1.2), according to which the system never leaves the surface defined by the equation of the Hardy-Weinberg equilibrium $u_{ss}u_{rr} = \frac{u_{rs}^2}{4}$ (white cone in Fig. 2.3).

Theorem 3. All equilibrium states of point demo-genetic model (2.11) satisfy Hardy-Weinberg equilibrium (1.1) if $W_{ij} = 1$ ($i, j = r$ or s).

Proof. Let $W_{ij} = 1$ (i, j = r or s) and u_{ss}, u_{rs}, u_{rr} be the frequencies of corresponding genotypes. Taking into account that $u_{ij} = \frac{N_{ij}}{N}$ and $p_i = u_{ii} + \frac{1}{2}u_{ij}$, we transform system (2.11) to the frequency form and find the equilibrium states of modified model:

$$\begin{aligned} & b\,p_s^2 - u_{ss}(\mu + \alpha K) = 0; \\ & 2b\,p_s p_r - u_{rs}(\mu + \alpha K) = 0; \\ & b\,p_r^2 - u_{rr}(\mu + \alpha K) = 0. \end{aligned} \qquad (2.23)$$

Note that $\mu + \alpha K = b$. Then system (2.23) gives the Hardy-Weinberg equilibrium condition (1.1):

$$\begin{aligned} u_{ss} &= p_s^2; \\ u_{rs} &= 2p_s p_r; \\ u_{rr} &= p_r^2. \end{aligned}$$

So, the proof is complete ■

II. *Let us consider now the subcase when the pest habitat consists solely of toxic Bt-crop.* According to the concept of the HDR strategy, we will consider the extreme case: the offspring of the Bt-resistant genotypes *ss* and *rs* dies on Bt-plants while *rr* insects are entirely resistant to Bt-toxin. Then fitness of the Bt-susceptible insects $W_{ss} = 0$ and $W_{rs} = 0$ and Bt-resistant insects $W_{rr} = 1$. Let us show that in this case, selection favours the fixation of Bt-resistance allele *r* and the complete

elimination of Bt-susceptible genotypes *ss* and *rs*, i.e., point C in Fig. 2.2 is the unique and stable equilibrium of system (2.11).

Modified system (2.11) is:

$$\begin{aligned}
\frac{dN_{ss}}{dt} &= -\alpha N_{ss} N - \mu N_{ss};\\
\frac{dN_{rs}}{dt} &= -\alpha N_{rs} N - \mu N_{rs};\\
\frac{dN_{rr}}{dt} &= \frac{b}{N}\left(\frac{N_{rs}}{2} + N_{rr}\right)^2 - \alpha N_{rr} N - \mu N_{rr}.
\end{aligned} \tag{2.24}$$

According to system (2.24), the Bt-susceptible genotypes become extinct and *s* allele is entirely eliminated with time. It is clear that point $(0, 0, K)$ is a unique stable equilibrium of system (2.24). The equilibrium densities of genotypes are: $N_{ss}^* = 0$, $N_{rs}^* = 0$, $N_{rr}^* = K$. There are no other equilibrium states in system (2.24).

The total extinction of the Bt-susceptible insects in the Bt-area corresponds to the extreme case and is not always justified in practice. For instance, in the ECB population about 0.01% of susceptibles can survive on some Bt-maize hybrids. Moreover, if the genotype possessing the Bt-resistance gene has to 'pay' for the advantage in the toxic Bt-fields, the proportion of genotypic fitnesses W_{ij} will determine the dynamics of the allelic frequencies in the biological system, according to the Fisher's Fundamental Theorem of natural selection (Fisher, 1930).

Indeed, system (2.21) under constant selection has three equilibrium states of the allelic frequencies which are also the equilibriums of the Fisher-Haldane-Wright model (Ginzburg & Golenberg 1985):

(i) $p_r^* = 1,\ p_s^* = 0;$

(ii) $p_r^* = 0,\ p_s^* = 1;$

(iii) $p_r^* = \dfrac{W_{rs} - W_{ss}}{2W_{rs} - W_{ss} - W_{rr}},\ p_s^* = 1 - p_r^*.$

It follows from (2.22) that in the stationary state the deviation of the system from the Hardy-Weinberg equilibrium ξ is:

$$\xi^* = -\frac{p_s^2 p_r^2 (2W_{rs} - W_{ss} - W_{rr})}{W_{ss} p_s^2 + 2W_{rs} p_s p_r + W_{rr} p_r^2} \le 0.$$

Let us determine the stability of each equilibrium depending on the proportion of fitnesses that are, in fact, the survival coefficients of genotypes in our biological system. If $W_{rr} > W_{rs} > W_{ss}$, equilibrium (i) is stable, i.e., the population consists solely of homozygotes *rr*. Case $W_{rr} < W_{rs} < W_{ss}$ is similar to the previous one and equilibrium (ii) is stable. Moreover, for both cases the equilibrium deviation from the Hardy-Weinberg equilibrium $\xi^* = 0$. If the heterozygous genotype has the maximum fitness in the population, i.e., $W_{rr} < W_{rs} > W_{ss}$, the system evolves to the polymorphic state (iii) and $\xi^* < 0$. Otherwise, if $W_{rr} > W_{rs} < W_{ss}$, system (2.21) reaches the equilibrium which satisfies the Hardy-Weinberg equilibrium (i.e., $\xi^* = 0$) at (i) or (ii) depending on the initial allelic frequencies.

By accepting the hypothesis of weak selection, i.e., of small difference between genotypic fitnesses:

$$W_{ss} = A + \varepsilon \tilde{W}_{ss},\ W_{rs} = A + \varepsilon \tilde{W}_{rs},\ W_{rr} = A + \varepsilon \tilde{W}_{rr},$$

where $\varepsilon << 1$, system (2.21), (2.22) can be written as:

$$\begin{aligned} \frac{dp_r}{dt} &= \varepsilon b p_r (\tilde{W}_r - \tilde{W}); \\ \frac{dN}{dt} &= N(bA - \mu - \alpha N) + \varepsilon b N \tilde{W}; \\ \frac{d\xi}{dt} &= \varepsilon b \left(p_s^2 p_r^2 (\tilde{W}_{ss} + \tilde{W}_{rr} - 2\tilde{W}_{rs}) - \xi \tilde{W} \right) - \xi b A. \end{aligned} \qquad (2.25)$$

In (2.25) we use $\tilde{W}_{ij}$ instead of W_{ij} in all expressions with tildes. Under weak selection and small ε the dynamics of system (2.25) quickly reaches the

neighborhood of plane $\xi = 0$ and the total population density also quickly becomes close to 'carrying capacity' $K = N^* = \frac{bA - \mu}{\alpha}$. Then in the neighborhood of $\xi = 0$ the allelic frequencies slowly evolve and the total population density N is retained in the neighborhood of equilibrium N^*, approaching it monotonically.

2.2.2 *Heterogeneous pest habitat.*

In this case, the dynamics of studied biological system is entirely described by the spatial demo-genetic model (2.6).

Theorem 4. In the frequency form the spatial demo-genetic model is descibed by the following system of equations:

$$\frac{\partial p_r}{\partial t} = bp_r(W_r - W) + \delta\Delta p_r + 2\delta\nabla p_r \cdot \nabla \ln N;$$
$$\frac{\partial N}{\partial t} = N(bW - (\mu + \alpha N)) + \delta\Delta N;$$
$$\nabla p_r \cdot \mathbf{n} = \nabla N \cdot \mathbf{n} = 0, \quad \mathbf{x} \in \partial\Omega.$$

Proof. Using Lemma 1, in (2.6) the functions of local kinetics in terms of frequencies will be defined by the right-hand parts of equations (2.21).

Eliminating the local kinetics from (2.6), let us consider reduced system:

$$\frac{\partial N_{ij}}{\partial t} = \delta\Delta N_{ij}, \tag{2.26}$$

where $i, j = r$ or s.

Summing all equations of system (2.26) and denoting the frequency of each genotype $u_{ij}(x,t) = \frac{N_{ij}(x,t)}{N(x,t)}$, we obtain $\frac{\partial N}{\partial t} = \delta\Delta N$. Then the dynamics of the total population density N is described by the following differential equation:

$$\frac{\partial N}{\partial t} = N(bW - (\mu + \alpha N)) + \delta\Delta N, \tag{2.27}$$

where the mean population fitness $W = W_{ss}p_s^2 + 2W_{rs}p_s p_r + W_{rr}p_r^2$.

Transforming (2.26) to the frequency form in the same way as in Lemma 1, we get:

$$\frac{\partial u_{ij}}{\partial t} = \frac{1}{N}\frac{\partial N_{ij}}{\partial t} - \frac{u_{ij}}{N}\frac{\partial N}{\partial t} = \frac{1}{N}\delta\Delta\left(u_{ij}N\right) - \frac{u_{ij}}{N}\delta\Delta N = \\ = \delta\left(\Delta u_{ij} + 2\frac{\partial u_{ij}}{\partial x}\frac{\partial \ln N}{\partial x} + 2\frac{\partial u_{ij}}{\partial y}\frac{\partial \ln N}{\partial y}\right), \tag{2.28}$$

where $u_{ss} + u_{rs} + u_{rr} = 1$.

Then, taking into account expression (2.28) and the equality $p_r = 1 - p_s = u_{rr} + \frac{1}{2}u_{rs}$, we have:

$$\frac{\partial p_r}{\partial t} = \frac{\partial u_{rr}}{\partial t} + \frac{1}{2}\frac{\partial u_{rs}}{\partial t} = \delta\left(\Delta p_r + 2\frac{\partial p_r}{\partial x}\frac{\partial \ln N}{\partial x} + 2\frac{\partial p_r}{\partial y}\frac{\partial \ln N}{\partial y}\right) = \\ = \delta\Delta p_r + 2\delta\nabla p_r \cdot \nabla \ln N. \tag{2.29}$$

Adding the local kinetics of system (2.21) into (2.29), we obtain the equation describing the spatio-temporal dynamics of the frequency of the Bt-resistance allele p_r in spatial demo-genetic model (2.6):

$$\frac{\partial p_r}{\partial t} = bp_r\left(W_r - W\right) + \delta\Delta p_r + 2\delta\nabla p_r \cdot \nabla \ln N, \tag{2.30}$$

where the mean fitness of the Bt-resistance allele $W_r = W_{rs}p_s + W_{rr}p_r$.

Equations (2.27), (2.30) with the boundary conditions

$$\nabla p_r \cdot \mathbf{n} = \nabla N \cdot \mathbf{n} = 0, \quad \mathbf{x} \in \partial\Omega, \tag{2.31}$$

where $\mathbf{n}$ is the external normal to the boundary $\partial\Omega$, entirely describe the evolution of the frequency of the Bt-resistance allele and the dynamics of the total population density.

So, in the frequency form the spatial demo-genetic model (2.6) is:

$$\begin{aligned}
&\frac{\partial p_r}{\partial t} = bp_r(W_r - W) + \delta\Delta p_r + 2\delta\nabla p_r \cdot \nabla \ln N;\\
&\frac{\partial N}{\partial t} = N(bW - (\mu + \alpha N)) + \delta\Delta N; \qquad (2.32)\\
&\nabla p_r \cdot \mathbf{n} = \nabla N \cdot \mathbf{n} = 0, \quad \mathbf{x} \in \partial\Omega.
\end{aligned}$$

Model (2.32) differs from the classical population genetics model (1.2) coupled with diffusion (the spatial Fisher-Haldane-Wright model) only by the term $2\delta\nabla p_r \cdot \nabla \ln N$, which, together with the diffusion term, describes the dispersal of the resistance allele. Clearly, this term can be interpreted as an 'advective' term describing a directed flow of the allelic frequency p_r with velocity $-2\delta\nabla \ln N$. This advection, which is never taken into account in spatial Fisher-Haldane-Wright models, results from the heterogeneity of the spatial distribution of N and p_r and disappears if either N or p_r is uniformly distributed.

Theorem 4 is proved ■

Consequence. Diffusion Fisher-Haldane-Wright model correctly describes spatial gene dispersal in a diploid population only in the idealistic and unrealistic case of homogeneous distribution of the total population density throughout the entire farming area Ω.

Theorem 5. The deviation of spatial demo-genetic system (2.6) from the Hardy-Weinberg equilibrium (1.1) is given by the differential equation:

$$\frac{\partial \xi}{\partial t} = b\left(p_s^2 p_r^2 (W_{ss} + W_{rr} - 2W_{rs}) - \xi W\right) + \delta\Delta\xi + 2\delta\nabla \ln N \cdot \nabla\xi + 2\delta\left|\nabla p_r\right|^2. \quad (2.33)$$

Proof. As in Lemma 1, let us introduce the additional variable $\xi = u_{ss}u_{rr} - \frac{u_{rs}^2}{4}$ to quantify the deviation of system (2.6) from the Hardy-Weinberg equilibrium (1.1) and express the genotypic frequencies via the deviation ξ and the allelic frequencies: $u_{ss} = p_s^2 + \xi$, $u_{rs} = 2p_s p_r - 2\xi$, $u_{rr} = p_r^2 + \xi$. Then the differential equation of spatio-temporal dynamics of deviation ξ can be written as (2.33).

As well as in the point model, system (2.6) tends to Hardy-Weinberg equilibrium (1.1) ($\xi \to 0$, $t \to \infty$) only if the frequency of one of the two alleles – r or s – tends to zero. Otherwise, if W_{rs} exceeds W_{ss} and W_{rr}, system (2.6) evolves beyond the Hardy-Weinberg equilibrium to the polymorphic state. Moreover, the deviation ξ increases due to the spatial heterogeneity of allelic frequencies.

Theorem 5 is proved ■

In the pest population the intensity of density fluxes providing a connection between Bt-domains and refuges is determined by the value of diffusion coefficient δ. Let us consider two extreme cases: the complete panmixia ($\delta = \infty$) and the complete isolation ($\delta = 0$) of insects dwelling in the farming area Ω that consists of two continuous disjoint domains of Bt-crop Ω_{Bt} and refuge Ω_{ref}. Let the fraction of the refuge be P_{ref}: $0 \le P_{ref} \le 1$. Then the fraction of domain planted with Bt-crop is $1 - P_{ref}$.

I. *The pest population is panmictic* ($\delta = \infty$). This means that the diffusion between Bt-domain and refuge is infinitely large. Then the population is uniformly distributed in the whole area Ω, and from (2.5) we have the spatially averaged genotypic fitness:

$$\begin{aligned} W_{rr} &= 1 - c; \\ W_{rs} &= P_{ref}(1 - h_c c) + (1 - P_{ref})(1 - \sigma + h_\sigma(\sigma - c)); \\ W_{ss} &= P_{ref} + (1 - P_{ref})(1 - \sigma). \end{aligned} \qquad (2.34)$$

It follows from Theorem 4-5 that with infinite diffusion, the dynamics of the spatial demo-genetic model (2.6) coincides with the dynamics of the non-spatial system (2.21) that is also the Fisher-Haldane-Wright model. Without loss of generality, let *b* in (2.21) be 1. Then

$$\frac{dp_r}{dt} = p_r(W_r - W) = f(p_r), \qquad (2.35)$$

where

$$W_r = W_{rr}p_r + W_{rs}(1-p_r);$$
$$W = W_{rr}p_r^2 + 2W_{rs}p_r(1-p_r) + W_{ss}(1-p_r)^2.$$

Note that the right-hand part of equation (2.35) $f(p_r)$ is a cubic polynomial: $f(p_r) = p_r(1-p_r)g(p_r)$, where $g(p_r)$ is the linear function of p_r. Then equation $f(\overline{p}_r) = 0$ has 3 real roots that give the equilibrium states of system (2.35):

$$\overline{p}_r^0 = 0;$$
$$\overline{p}_r^1 = 1; \qquad (2.36)$$
$$\overline{p}_r^2 = \frac{h_\sigma(c-\sigma)(1-P_{ref}) + P_{ref}h_c c}{2\left(h_\sigma(c-\sigma)(1-P_{ref}) + P_{ref}h_c c\right) + \sigma(1-P_{ref}) - c},$$

where the value of $\overline{p}_r^2$ depends on 5 parameters: $\overline{p}_r^2 = \overline{p}_r^2(\sigma, h_\sigma, c, h_c, P_{ref})$. Note that the allelic frequency makes sense only on segment $[0,1]$. Let us fix 4 of 5 parameters. Following Vacher et al. (2003), we assume that the intensity of the Bt-toxin selection is 100% ($\sigma = 1$) and the Bt-resistance cost is small ($c = 0.2$ with the dominance level $h_c = 0.2$). Let us show that the dominance level associated with the Bt-toxin selection, h_σ, that is called also the effective dominance (Tabashnik et al., 2004) and defined by Lenormand & Raymond (1998) and Vacher et al. (2003, 2004) as the quantity $1-h_\sigma$, stipulates qualitatively different behaviour of system (2.35) when varying parameter P_{ref}.

Let us consider two subcases:

(a) *low dominance level* $h_\sigma = 0.05$.

It follows from (2.36) that depending on the values of P_{ref} for the given genetic parameters, $\overline{p}_r^2$ may be negative, positive or be equal to zero. Let the range of P_{ref} such that $\overline{p}_r^2 = \overline{p}_r^2(P_{ref}) \in [0,1]$, i.e., $\overline{p}_r^2$ has the physical sense, be $\left[P_{ref}^1, P_{ref}^2\right]$. Note that if $P_{ref}^2 < P_{ref} < 1$, the critical case of $\overline{p}_r^2 = \pm\infty$ appears. We will use symbol P_{ref}^∞ to denote such refuge fraction. The value of $\overline{p}_r^2$ becomes

negative if $P_{ref} < P_{ref}^1$ or $P_{ref} > P_{ref}^\infty$, positive if $P_{ref} \in \left(P_{ref}^1, P_{ref}^\infty\right)$ and zero if $P_{ref} = P_{ref}^1$.

Let us draw a diagram of the right-hand part of equation (2.35) $f(p_r)$ for the following values of the refuge fraction P_{ref} (Fig. 2.4): $P_{ref} = P_{ref}^1$, $P_{ref} \in \left(P_{ref}^1, P_{ref}^2\right)$ and $P_{ref} > P_{ref}^2$. We will study the stability of the equilibrium states (2.36) of system (2.35), using the graphic method (e.g., Rubin 2004).

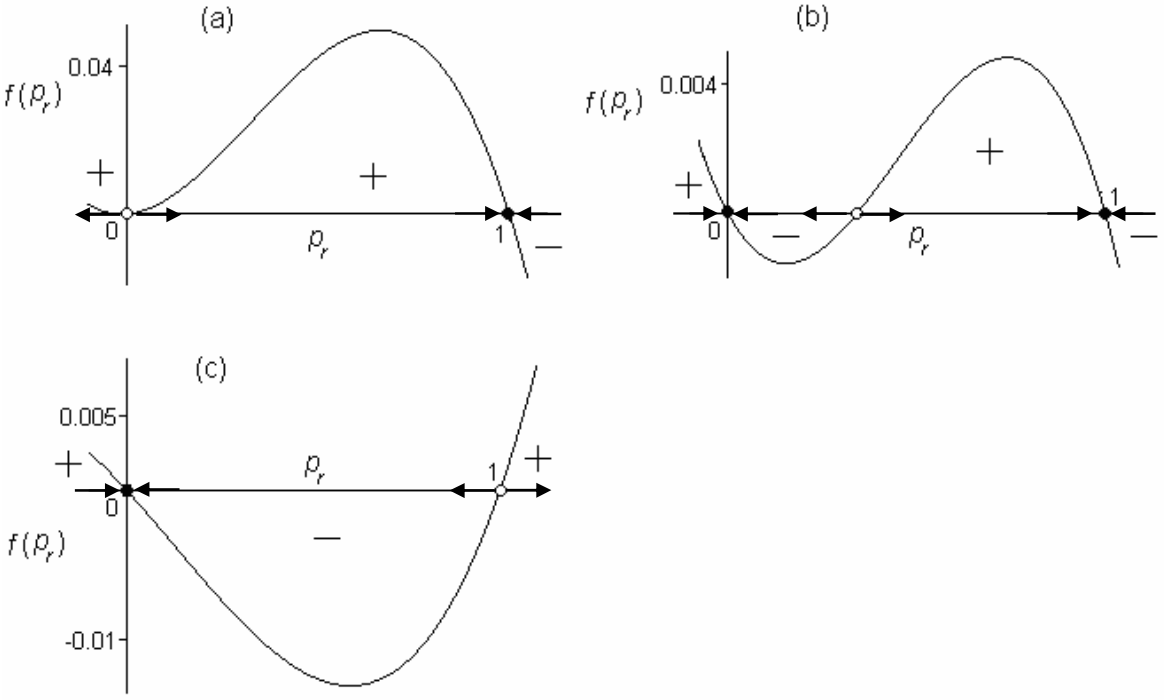


Fig. 2.4. Right-hand part of equation (2.35) $f(p_r)$ as a function of the frequency of the Bt-resistance allele, p_r, for various refuge fractions P_{ref}: (a) $P_{ref} = P_{ref}^1$; (b) $P_{ref} \in \left(P_{ref}^1, P_{ref}^2\right)$; (c) $P_{ref} > P_{ref}^2$. The stable equilibriums of system (2.35) are marked with black circles and the unstable equilibriums are marked with white circles. The given set of genetic parameters ($\sigma = 1$, $c = 0.2$, $h_c = 0.2$) corresponds to the HDR strategy with low dominance level of the Bt-toxin selection $h_\sigma = 0.05$.

Let $P_{ref} \in \left(P_{ref}^1, P_{ref}^2\right)$ (Fig. 2.4b). Then with growth of argument p_r, at points $\overline{p}_r^0 = 0$ and $\overline{p}_r^1 = 1$ function $f(p_r)$ changes its sign from plus to minus, i.e., both equilibriums $\overline{p}_r^0 = 0$ and $\overline{p}_r^1 = 1$ are stable, and vice versa, at point $\overline{p}_r^2 \in (0,1)$

function $f(p_r)$ changes sign from minus to plus, and, hence, equilibrium $\overline{p}_r^2$ is unstable. In this case, the evolution of the system is defined by the initial value of the allelic frequency p_r: if $p_r(t=0)$ is below the critical value $p_r^{cr} = \overline{p}_r^2$, the Bt-resistance allele is eliminated with time, otherwise, it forces out the Bt-susceptible allele. Therefore, if $P_{ref} \in \left(P_{ref}^1, P_{ref}^2\right)$, it means only the local stability of equilibriums $\overline{p}_r^0 = 0$ and $\overline{p}_r^1 = 1$. In other cases, if $P_{ref} \notin \left(P_{ref}^1, P_{ref}^2\right)$ (Fig. 2.4a, c), the evolution of the genetic structure is determined by the stability of equilibriums $\overline{p}_r^0 = 0$ and $\overline{p}_r^1 = 1$. Note that when varying parameter P_{ref} from 0 to 1, equilibrium $\overline{p}_r^2$ changes its sign and nature of the stability: when crossing the point P_{ref}^1 the negative equilibrium $\overline{p}_r^2$ that has no meaning in population genetics, loses its stability and becomes positive. Besides, within segment $\left[P_{ref}^1, P_{ref}^2\right]$ the condition $\overline{p}_r^2 \in [0,1]$ is satisfied. When crossing the point P_{ref}^2 the unstable equilibrium $\overline{p}_r^2$ becomes stable again but its value exceeds 1 (it is not illustrated). And, finally, at bifurcating point P_{ref}^{∞} the equilibrium $\overline{p}_r^2$ loses its stability and its value becomes negative (Fig. 2.4c). Case (a) in Fig. 2.4 shows that independently of the initial values of allelic frequencies p_s and p_r, the refuge fraction P_{ref} is too small ($P_{ref} \le P_{ref}^1$) and the selection favours the fixation of the Bt-resistance allele *r* and the elimination of the Bt-susceptible allele *s*. In that case, the equilibrium $\overline{p}_r^1 = 1$ is stable while $\overline{p}_r^0 = 0$ is unstable. If the refuge fraction is large enough ($P_{ref} \ge P_{ref}^2$), the equilibrium $\overline{p}_r^1 = 1$ becomes unstable and with time the *s* allele entirely sweeps out the *r* allele (Fig. 2.4c).

With given set of genetic parameters ($\sigma = 1$, $h_\sigma = 0.05$, $c = 0.2$, $h_c = 0.2$), for any refuge fraction $P_{ref} \in [0,1]$ the fitness of heterozygous insects *rs* is lower than fitness of both homozygotes *ss* and/or *rr* (Fig. 2.5a): $W_{ss} < W_{rs} < W_{rr}$ if

$P_{ref} \in \left[0, P_{ref}^1\right)$, $W_{rs} \le W_{ss} < W_{rr}$ if $P_{ref} \in \left[P_{ref}^1, P_{ref}^3\right)$, $W_{rs} < W_{rr} \le W_{ss}$ if $P_{ref} \in \left[P_{ref}^3, P_{ref}^2\right)$ and $W_{rr} \le W_{rs} < W_{ss}$ if $P_{ref} \in \left[P_{ref}^2, 1\right]$. It means that for any refuge size, the heterozygous genotype has no advantage compared to homozygous genotypes. Therefore, following the Fisher's Fundamental Theorem (Fisher 1930), in such population the stable polymorphism can not exist.

The bifurcation diagram (Fig. 2.5b) shows the equilibrium states of system (2.35) as functions of parameter P_{ref}, and equalities $W_{ss} = W_{rs}$ and $W_{rs} = W_{rr}$ determine the bifurcation values of P_{ref}: $P_{ref} = P_{ref}^1$ and $P_{ref} = P_{ref}^2$ at which equilibriums collide and exchange their stability.

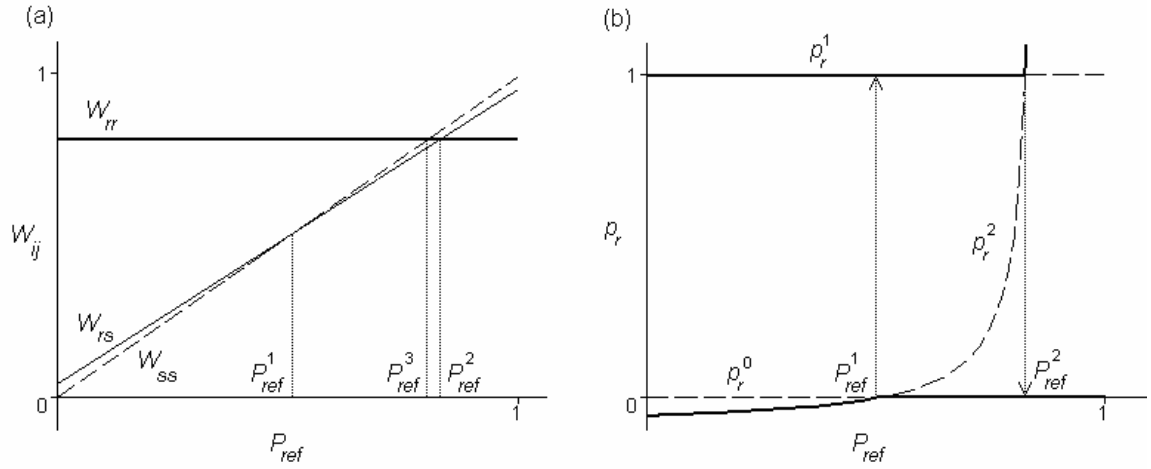


Fig. 2.5. (a) Spatially averaged genotypic fitness W_{ij} as a function of the refuge fraction P_{ref}. Dotted line corresponds to the fitness of *ss* genotype; thin solid line – to the fitness of *rs* genotype; thick solid line – to the fitness of *rr* genotype. (b) Frequency of the Bt-resistance allele p_r as a function of the refuge fraction P_{ref}. The stable equilibrium branches of system (2.35) are marked by thick solid line, unstable equilibrium branches are marked by dotted line. P_{ref}^1 and P_{ref}^2 are the bifurcation values of parameter P_{ref}. Given set of genetic parameters ($\sigma = 1$, $c = 0.2$, $h_c = 0.2$) corresponds to the HDR strategy with low dominance level of Bt-toxin selection $h_\sigma = 0.05$.

Assume that for the certain value of $P_{ref} \in \left[0, P_{ref}^2\right)$, the system is at point corresponding to the upper stable branch $\overline{p}_r^1 = 1$, i.e., the refuge fraction is small to

suppress the Bt-resistance allele (Fig. 2.5b). When increasing parameter P_{ref}, the system moves along the branch of stable equilibrium $\overline{p}_r^1 = 1$ up to the bifurcation point $P_{ref} = P_{ref}^2$, and then the stiff step-wise transition of the system to the bottom stable branch $\overline{p}_r^0 = 0$ occurs. Being the system at equilibrium $\overline{p}_r^0 = 0$ means that sufficiently large size of the refuge provides the elimination of the *r* allele. When decreasing parameter P_{ref}, the system moves to the left along the branch $\overline{p}_r^0 = 0$ up to the bifurcation point $P_{ref} = P_{ref}^1 < P_{ref}^2$, after that it returns step-wise to the starting branch $\overline{p}_r^1 = 1$. Thus, in varying parameter P_{ref}, the closed hysteresis cycle is implemented in the system.

So, with low dominance levels of Bt-toxin selection h_σ, the bifurcation in system (2.35) occurs stiffly. Smooth adaptive control of the system by the small variations of the refuge size is impossible due to the presence of hysteresis: when as a result of decrease of the refuge percentage $P_{ref} < P_{ref}^1$ the Bt-resistance allele *r* entirely sweeps out the Bt-susceptible allele *s*, the Bt-resistance gene can be suppressed again only if the refuge fraction will exceed P_{ref}^2, i.e., P_{ref} become large enough. Actually, it may be a question of the total stop of the Bt-crop using.

If $P_{ref} \in \left(P_{ref}^1, P_{ref}^2\right)$, the branch of unstable equilibriums of system (2.35) $0 < \overline{p}_r^2 = \overline{p}_r\left(P_{ref}\right) < 1$ corresponding to the polymorphism in the pest population divides the domain of the initial values of the allelic frequency p_r into the basins of attractions of equilibriums $\overline{p}_r^0 = 0$ and $\overline{p}_r^1 = 1$, respectively. In this case, both equilibriums $\overline{p}_r^0$ and $\overline{p}_r^1$ are locally stable if $0 < \overline{p}_r^2 < 1$. Therefore, with any given refuge fraction $P_{ref} \in \left(P_{ref}^1, P_{ref}^2\right)$, the success of the HDR strategy use depends on the initial frequency of the *r* allele: if $0 < p_r(t=0) < \overline{p}_r^2$, the *r* allele is eliminated with time. If the refuge fraction P_{ref} exceeds P_{ref}^2, the elimination of the *r* allele

occurs at any initial frequency $p_r(t=0)$. Note that the branch of the stable equilibrium $\overline{p}_r^2 \notin [0,1]$ has no biological sense; in this case, in the system the stable equilibrium $\overline{p}_r^1 = 1$ is stabilized if the refuge fraction does not exceed P_{ref}^1.

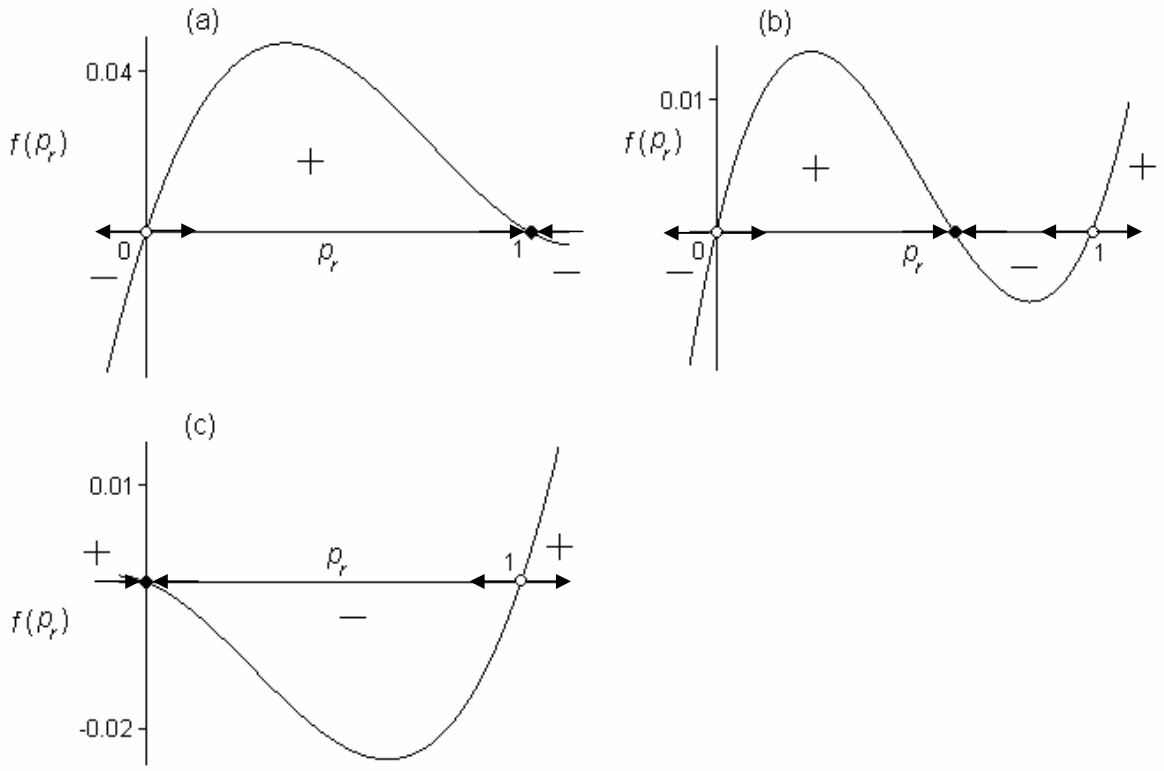


Fig. 2.6. Right-hand part of equation (2.35) $f(p_r)$ as a function of the frequency of the Bt-resistance allele, p_r, for various refuge fractions P_{ref}: (a) $P_{ref} < P_{ref}^1$; (b) $P_{ref} \in (P_{ref}^1, P_{ref}^2)$; (c) $P_{ref} > P_{ref}^2$. The stable equilibriums of system (2.35) are marked with black circles and the unstable equilibriums are marked with white circles. Given set of genetic parameters ($\sigma = 1$, $c = 0.2$, $h_c = 0.2$) corresponds to the HDR strategy with high dominance level of the Bt-toxin selection $h_\sigma = 0.7$.

(b) *high dominance level* $h_\sigma = 0.7$.

Let the other genetic parameters be the same as in the subcase (a): $\sigma = 1$, $c = 0.2$, $h_c = 0.2$. Denoting the range of the refuge fraction $[P_{ref}^1, P_{ref}^2]$, for which the allelic frequency $\overline{p}_r^2 = \overline{p}_r^2(P_{ref}) \in [0,1]$, from formulas (2.36) we obtain that the

value of $\overline{p}_r^2$ becomes negative if $P_{ref} \in \left(P_{ref}^2, 1\right]$, zero if $P_{ref} = P_{ref}^2$ and positive if $P_{ref} \in \left[0, P_{ref}^2\right)$.

Let us analyse the stability of equilibriums of system (2.35) with high dominance level of the Bt-toxin selection. Let $P_{ref} \in \left(P_{ref}^1, P_{ref}^2\right)$. Then with growth of argument p_r, at points $\overline{p}_r^0 = 0$ and $\overline{p}_r^1 = 1$ function $f(p_r)$ changes its sign from minus to plus, i.e., both equilibriums $\overline{p}_r^0 = 0$ and $\overline{p}_r^1 = 1$ are unstable; and vice versa, at point $\overline{p}_r^2 \in (0,1)$ function $f(p_r)$ changes sign from plus to minus, and, hence, $\overline{p}_r^2$ is the stable equilibrium (Fig. 2.6b).

The stability of equilibrium $\overline{p}_r^2$ means the existence of the stable polymorphism in the pest population. Such case is possible only if the heterozygous genotype *rs* has the advantage. Indeed, as shown in Fig 2.7a, if $P_{ref} \in \left(P_{ref}^1, P_{ref}^2\right)$ the fitness of heterozygotes *rs* is higher than those of homozygotes *ss* and *rr*. In other cases, if $P_{ref} \notin \left(P_{ref}^1, P_{ref}^2\right)$, homozygotes have higher fitness than heterozygotes do, and, moreover, selection favours the elimination of the *s* allele if $P_{ref} \le P_{ref}^1$ (Fig. 2.6a) and the elimination of the *r* allele if $P_{ref} \ge P_{ref}^2$ (Fig. 2.6c).

In contrast to the stiff bifurcation appearing with the low dominance level of the Bt-toxin selection (e.g., $h_\sigma = 0.05$ in Fig. 2.5b), with high dominance level (e.g., $h_\sigma = 0.7$ in Fig. 2.7b), bifurcation of the system that moves along the branches of stable equilibriums $\overline{p}_r^0 = 0$, $\overline{p}_r^1 = 1$ and $\overline{p}_r^2 = \overline{p}_r\left(P_{ref}\right)$, occurs softly at the critical points P_{ref}^1 and P_{ref}^2. Such behaviour of the system seems more preferential because varying the refuge fraction P_{ref}, one can safely manage the HDR strategy, gradually decreasing the frequency of the Bt-resistant homozygotes *rr* up to the reasonable level.

Note that in both cases (low and high dominance of selection), increase in cost of resistance c reduces the interval $\left[0, P_{ref}^1\right)$ in which the selection favours the fixation of the Bt-resistance allele r and the complete elimination of the Bt-susceptible allele s.

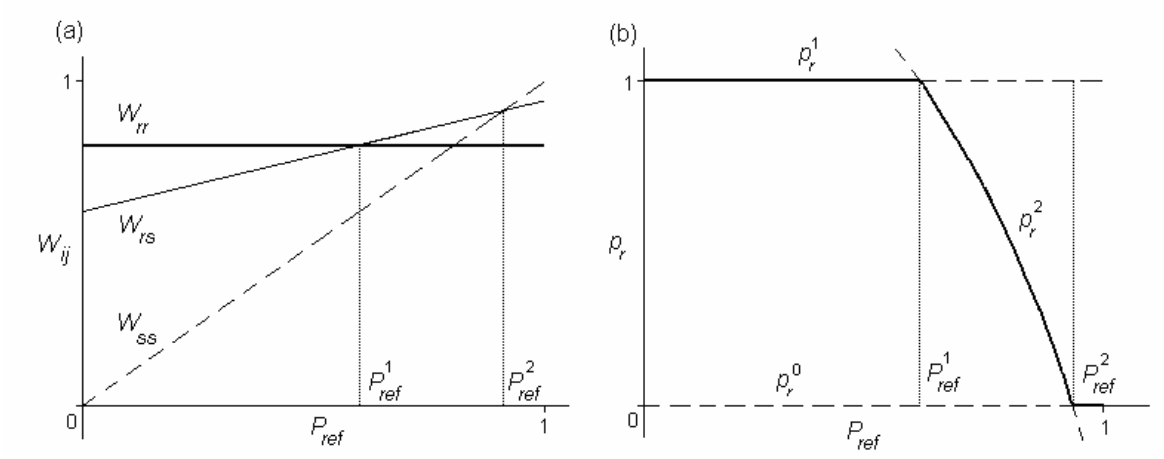


Fig. 2.7. (a) Spatially averaged genotypic fitness W_{ij} as a function of the refuge fraction P_{ref}. Dotted line corresponds to the fitness of *ss* genotype; thin solid line – to the fitness of *rs* genotype; thick solid line – to the fitness of *rr* genotype. (b) Frequency of the Bt-resistance allele p_r as a function of the refuge fraction P_{ref}. The stable equilibrium branches of system (2.35) are marked by thick solid line, unstable equilibrium branches are marked by dotted line. P_{ref}^1 and P_{ref}^2 are the bifurcation values of parameter P_{ref}. Given set of genetic parameters ($\sigma = 1$, $c = 0.2$, $h_c = 0.2$) corresponds to the HDR strategy with high dominance level of Bt-toxin selection $h_\sigma = 0.7$.

II. *Insects dwelling in Bt-field are entirely isolated from insects dwelling in refuge* ($\delta = 0$). In this case, there is no diffusion flux between Bt-field and refuge, i.e., pest population consists of two territorially independent panmictic subpopulations. Such isolation barriers may often appear in spatially distributed populations, for instance, due to the geographical obstacles or isolation by a distance. Since we assume that each subpopulation is panmictic, in each of domains Ω_{Bt} and Ω_{ref} the evolution of the genetic structure of the pest is described by system (2.35).

We assume that in the Bt-field the fitness of the Bt-resistant genotype *rr* is higher than the fitness of the Bt-susceptible genotypes *ss* and *rs* and in the refuge the Bt-susceptible genotype *ss* has the maximum fitness. Due to the isolation, the homozygotization occurs in each subpopulation: in the Bt-field the genetic structure of the population is presented only by *rr* homozygote insects, in the refuge – only by *ss* homozygotes. Then with time, the frequency of the Bt-resistance allele in the whole population reaches the following value (Fig. 2.8):

$$p_r = \frac{N_{rr}\left(1-P_{ref}\right)}{N_{ss}P_{ref} + N_{rr}\left(1-P_{ref}\right)}. \tag{2.37}$$

If the genotypic fitness is calculated by formulas (2.5), then (2.37) is modified to:

$$p_r = \frac{\left(bW_{rr}^{Bt} - \mu\right)\left(1-P_{ref}\right)}{\left(bW_{ss}^{ref} - \mu\right)P_{ref} + \left(bW_{rr}^{Bt} - \mu\right)\left(1-P_{ref}\right)}, \tag{2.38}$$

where $W_{ss}^{ref} = W_{ss}(x)\big|_{x\in\Omega_{ref}}$, $W_{rr}^{Bt} = W_{rr}(x)\big|_{x\in\Omega_{Bt}}$.

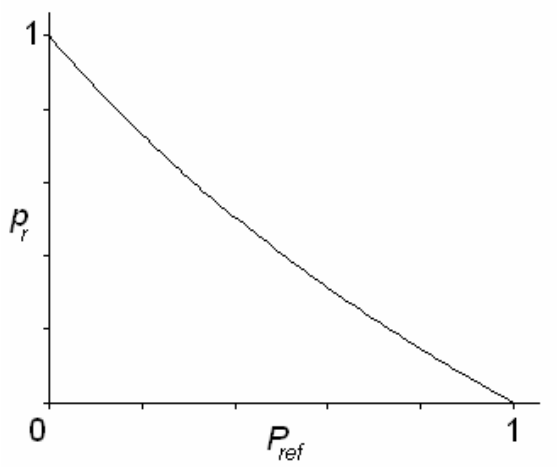


Fig. 2.8. The frequency of the Bt-resistance allele p_r as a function of the refuge fraction P_{ref}: case of the complete isolation of panmictic subpopulations in Ω_{Bt} and Ω_{ref} domains. Here $W_{ss}^{ref} = 1$, $W_{rr}^{Bt} = 0.9$, $b = 1$, $\mu = 0.69$.

Thus, we investigated two opposite extreme cases – infinitely large and zero diffusion density fluxes between Bt-field and refuge or, in other words, panmixia

and isolation in the ECB population. The question naturally arises: how will the genetic structure of the pest evolve in the heterogeneous habitat with intermediate values of diffusion $\delta \in (0, \infty)$? In order to find an answer, it is required to study qualitatively the behaviour of the spatial demo-genetic model (2.6).

Let the whole pest habitat be a rectangle $\Omega = [0, L_x] \times [0, L_y]$. This is the simplest two-dimensional (2D) configuration of Ω. Without loss of generality, we will consider a one-dimensional (1D) case of system (2.6). The use of a 1D model essentially simplifies the mathematical notations. In particular, such 1D habitat corresponds to a single-strip pattern for the refuge (Fig. 2.9).

If initially all genotypes are uniformly distributed along the side L_y of this refuge pattern, there are no density fluxes in this direction. Therefore, the dynamics of system (2.6) does not depend on the size L_y, and it is entirely described by the 1D model.

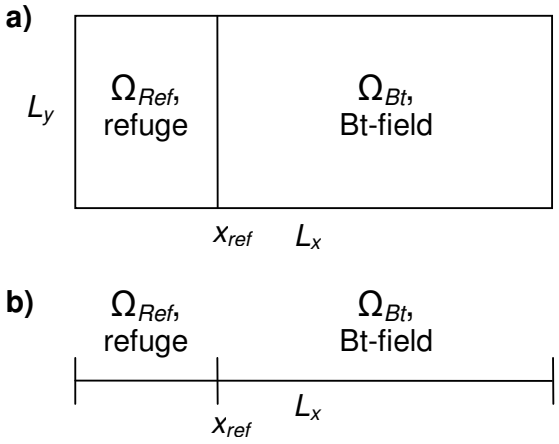


Fig. 2.9. (a) Border single-strip refuge pattern for the rectangular habitat Ω. (b) Its 1D simplification in the absence of the density fluxes of the pest genotypes along the side L_y.

In order to find stationary states of system (2.6) from condition $\frac{\partial N_{ij}}{\partial t} = 0$ (i, j = *r* or *s*), in fact, we must solve the following boundary-value problem:

$$
\begin{aligned}
&\frac{d^2N_{ss}}{dx^2} = -\frac{1}{\delta}\left(W_{ss}\,\frac{b}{N}\left(N_{ss} + \frac{N_{rs}}{2}\right)^2 - \alpha N_{ss}N - \mu N_{ss}\right);\\
&\frac{d^2N_{rs}}{dx^2} = -\frac{1}{\delta}\left(W_{rs}\,\frac{2b}{N}\left(N_{ss} + \frac{N_{rs}}{2}\right)\left(\frac{N_{rs}}{2} + N_{rr}\right) - \alpha N_{rs}N - \mu N_{rs}\right);\\
&\frac{d^2N_{rr}}{dx^2} = -\frac{1}{\delta}\left(W_{rr}\,\frac{b}{N}\left(\frac{N_{rs}}{2} + N_{rr}\right)^2 - \alpha N_{rr}N - \mu N_{rr}\right);\\
&\left.\frac{dN_{ss}}{dx}\right|_{x=0,L_x} = \left.\frac{dN_{rs}}{dx}\right|_{x=0,L_x} = \left.\frac{dN_{rr}}{dx}\right|_{x=0,L_x} = 0, \quad x\in[0,L_x].
\end{aligned}
\tag{2.39}
$$

Let us find the conditions under which the solutions of boundary-value problem (2.39) exist.

Theorem 6. Spatially homogeneous stationary solutions of system (2.6) such that $N_{ss}^*(x)=0$, $N_{rs}^*(x)=0$, $N_{rr}^*(x)=\dfrac{bW_{rr}-\mu}{\alpha}$, $\forall\, x\in[0,L_x]$, where $W_{rr}=1-c$ from formulas (2.5), always exist.

Proof. Indeed, as a result of substitution of $\left(N_{ss}^*, N_{rs}^*, N_{rr}^*\right)$ into system (2.39) each equation of (2.39) becomes identical.
Theorem 6 is proved ■

Theorem 7. If such spatially heterogeneous stationary solutions of system (2.6) that $\forall\, x\in[0,L_x]$ $N_{ss}^*(x)\in(0,K)$ and $N_{rs}^*(x)=N_{rr}^*(x)=0$, exist for the habitat configuration presented in Fig. 2.9 and if $W_{ss}(x)=0$ for $x\in\Omega_{Bt}$ and $W_{ss}(x)=1$ for $x\in\Omega_{ref}$, then the following condition holds:

$$
N_0^2\left(K-\frac{2}{3}N_0\right) < N_{ref}^2\,\frac{b}{\alpha},
$$

where $N_{ref}<N_0$, $N_0=N(0)$, $N_{ref}=N\left(x_{ref}\right)$ ($x_{ref}\in(0,L_x)$ is the boundary point between Bt-field and refuge).

Note that Theorem 7 gives only the necessary condition for existence of such solutions but not sufficient. In Theorem 7 the matter concerns the genetic structure of the pest population which consists only of insects of the *ss* genotype while the *rs* and *rr* genotypes possessing the Bt-resistance gene *r* are absent. The proof of Theorem 7 will also provide the method of construction of such solutions.

Proof. If the HDR strategy provides a 100% efficiency of the Bt-toxin selection ($\sigma = 1$), from formulas (2.5) we get the fitness of *ss* genotype:

$$W_{ss} = \begin{cases} 0, & x \in \Omega_{Bt}; \\ 1, & x \in \Omega_{ref}. \end{cases} \tag{2.40}$$

According to the condition of the theorem, such a solution of boundary-value problem (2.39) that the pest population consists only of individuals of the *ss* genotype exists. If in (2.39) the densities of *rs* and *rr* genotypes are set to zero for any $x \in [0, L_x]$, the problem (2.39) reduces to:

$$\begin{aligned} &\ddot{N} = \frac{\alpha}{\delta} N\left(N - \frac{W_{ss} b - \mu}{\alpha} \right), \\ &\dot{N}(0) = \dot{N}(L_x) = 0, \end{aligned} \tag{2.41}$$

where $N(x)$ is the total density of the population consisting only of homozygotes *ss*. Hereinafter, the operator of differentiation by *x* is denoted as a dot above the variable.

Note that the solution of (2.41) will define some density distribution of the *ss* genotype on the segment $[0, L_x]$. Such distribution coupled with the zero distributions of *rs* and *rr* genotypes will be the sought-for solution of the stationary boundary-value problem (2.39).

Since the fitness W_{ss} in (2.41) determines the qualitative difference in the dynamics in the Bt-field and refuge, we will consider problem (2.41) for each of these domains separately. Recall that in the initial problem (2.6) there are no boundary conditions between Bt-field and refuge. Therefore, in each domain the solving of (2.41) reduces, in fact, to the Cauchy problem (with additionally given

initial conditions that define the population density at the boundaries of habitat Ω). However, constructing the solution of (2.41) in the whole habitat Ω, we should choose the initial and terminal densities $N(0)$ and $N(L_x)$ so that at the interface between Bt-field and refuge such solution and its spatial gradient have no discontinuity and the values of $N(x) \in (0, K)\ \forall x \in [0, L_x]$.

Let us consider problem (2.41) for the refuge ($W_{ss} = 1$), reducing the second order equation to the normal system of differential equations:

$$\begin{cases} \dot{N}_1 = Y_1; \\ \dot{Y}_1 = \dfrac{\alpha}{\delta} N_1 (N_1 - K), \\ Y_1(0) = 0, \quad x \in [0, x_{ref}], \end{cases} \tag{2.42}$$

where $N_1(x)$ is the population density in the refuge, $Y_1(x)$ is its spatial gradient, $x_{ref} \in (0, L_x)$ is the interface point between Bt-field and refuge (Fig. 2.9).

We find the stationary states of system (2.42). There always exist two of them:

(i) $N_1^* = 0$, $Y_1^* \left(= \dot{N}_1^*\right) = 0$;

(ii) $N_1^* = K$, $Y_1^* \left(= \dot{N}_1^*\right) = 0$.

The characteristic equation of (2.42) is:

$$\lambda^2 - \frac{\alpha}{\delta}(2N - K) = 0. \tag{2.43}$$

Then from (2.43) equilibrium (i) is a centre ($\lambda_{1,2} = \pm i\sqrt{K\dfrac{\alpha}{\delta}}$), and equilibrium (ii) is a saddle ($\lambda_{1,2} = \pm\sqrt{K\dfrac{\alpha}{\delta}}$). Phase portrait of system (2.42) is shown in Fig. 2.10a.

As evident from Fig. 2.10a, if we complete the Cauchy problem (2.42) by the initial condition for the population density N_1 such that $0 < N_0 = N_1(0) < K$, the generating point will be describing the closed phase trajectory as long as the condition $x \in [0, x_{ref}]$ holds, i.e., while system remains in the refuge. With a given

initial condition $N_0 \in (0, K)$ and $Y_1(0) = 0$, the population density $N_1(x)$ and its derivative $Y_1(x)$ are decreasing monotonically as long as $N_1(x) > 0$ (i.e., while the population density makes biological sense), derivative $Y_1(x)$ is negative at that. In general, with any given $N_0 \in (0, K)$, the density $N_1^{ref} = N_1(x_{ref})$ at some point $x_{ref} \in (0, L_x)$ may be not only positive but also zero and even be negative. However, the condition of the theorem supposes the existence of such solution of stationary problem (2.39) that makes physical sense. Then $\forall\, x \in [0, x_{ref}]$ $N_1(x) \in (0, K)$, and $\forall\, x_{ref} \in (0, L_x)$ $\exists\, N_1^{ref} \in (0, K)$. Thus, on the phase plane for the point lying above the separatrix and having coordinates (N_1^{ref}, Y_1^{ref}): $N_1^{ref} \in (0, K)$ and $Y_1^{ref} = Y_1(x_{ref}) < 0$ one can always find $N_0 \in (N_1^{ref}, K)$: $Y_1(0) = 0$ $(\dot{N}_0 = 0)$.

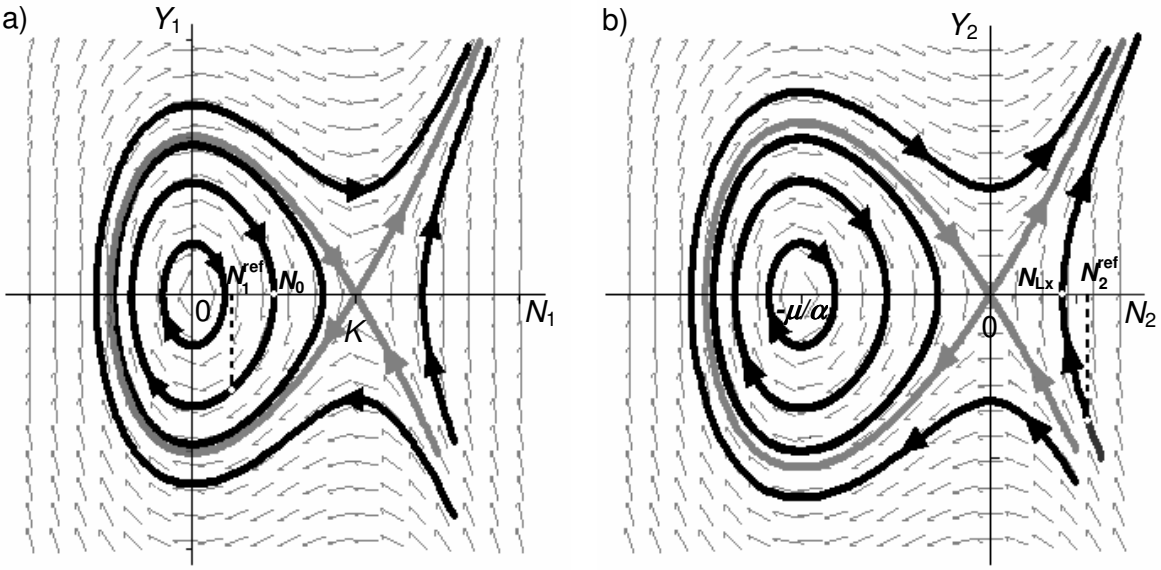


Fig. 2.10. Phase portraits of the stationary system for the population consisting solely of insects of ss genotype dwelling in the refuge (a) and in the Bt-field (b). Some phase trajectories are marked with thick lines; separatrices are marked with grey thick lines. Arrows define the directional field of the system.

Since the function $N_1(x) \in (0, K)$ on the whole half-open interval $[0, x_{ref})$, it follows from (2.42) that its second derivative $\dot{Y}_1(x) = \ddot{N}_1(x) < 0$ on $[0, x_{ref})$. Then $N_1(x)$ is a decreasing and concave (convex upwards) function on $[0, x_{ref})$.

Let us consider now the problem (2.41) for the Bt-field ($W_{ss} = 0$):

$$\begin{cases} \dot{N}_2 = Y_2; \\ \dot{Y}_2 = \dfrac{\alpha}{\delta} N_2 \left(N_2 + \dfrac{\mu}{\alpha} \right), \\ Y_2(L_x) = 0, \quad x \in [x_{ref}, L_x], \end{cases} \tag{2.44}$$

where $N_2(x)$ is the population density in the Bt-field, $Y_2(x)$ is its spatial gradient. Such system has two equilibriums:

(iii) $N_2^* = 0$, $Y_2^* \left(= \dot{N}_2^*\right) = 0$;

(iv) $N_2^* = -\dfrac{\mu}{\alpha}$, $Y_2^* \left(= \dot{N}_2^*\right) = 0$.

It follows from the characteristic equation of (2.44) $\lambda^2 - \dfrac{\alpha}{\delta}\left(2N + \dfrac{\mu}{\alpha} \right) = 0$ that equilibrium (iii) is a saddle ($\lambda_{1,2} = \pm\sqrt{\dfrac{\mu}{\delta}}$), and equilibrium (iv) is a centre ($\lambda_{1,2} = \pm i\sqrt{\dfrac{\mu}{\delta}}$).

Phase portrait of system (2.44) is shown in Fig. 2.10b.

If we complete the problem (2.44) by the condition for the population density on the right end of segment $[x_{ref}, L_x]$ such that $N_{Lx} = N_2(L_x) > 0$, the system will draw an unclosed trajectory of hyperbolic type (Fig. 2.10b) as long as $x \in [x_{ref}, L_x]$, i.e., while system remains in the Bt-field. Moreover, for $N_{Lx} > 0$ the condition $N_2(x) > 0$ holds. For any $N_{Lx} > 0$: $Y_2(L_x) = 0$ the population density in the Bt-field $N_2(x)$ decreases monotonically with growth of x but its derivative

$Y_2(x)$ increases monotonically, $N_2(x)>0$ and $Y_2(x)<0$ at that. Then for $\forall\, N_{Lx}>0$: $Y_2(L_x)=0$ $\left(\dot{N}_{Lx}=0\right)$ and $\forall\, x_{ref}\in(0, L_x)$ $\exists\, N_2^{ref}=N_2(x_{ref})>N_{Lx}$: $Y_2(x_{ref})<0$ $\left(\dot{N}_2^{ref}<0\right)$. Note that with any given $N_{Lx}\in(0, K)$: $Y_2(L_x)=0$ the density N_2^{ref} does not necessarily belong to $(0, K)$. It follows from the condition of the theorem that $\forall\, x\in[x_{ref}, L_x]$ $N_2(x)\in(0, K)$ and $\forall\, x_{ref}\in(0, L_x)$ $\exists\, N_2^{ref}\in(0, K)$. Thus, on the phase plane for the point lying above the separatrix and having coordinates (N_2^{ref}, Y_2^{ref}): $N_2^{ref}\in(0, K)$ and $Y_2^{ref}=Y_2(x_{ref})<0$, one can always find $N_{Lx}\in(0, N_2^{ref})$: $Y_2(L_x)=0$.

For any function $N_2(x)>0$, $x\in(x_{ref}, L_x]$ its second derivative $\dot{Y}_2(x)=\ddot{N}_2(x)>0$ for all $x\in(x_{ref}, L_x]$. Then $N_2(x)>0$ is decreasing and convex (convex downwards) function on $(x_{ref}, L_x]$.

If $N_1^{ref}=N_2^{ref}=N_{ref}>0$ and $\dot{N}_1^{ref}=\dot{N}_2^{ref}=\dot{N}_{ref}<0$, point $x_{ref}\in(0, L_x)$ is the point of inflection of function $N(x)$ in (2.41), as this function is concave on $[0, x_{ref})$ and convex on $(x_{ref}, L_x]$ (Fig. 2.11).

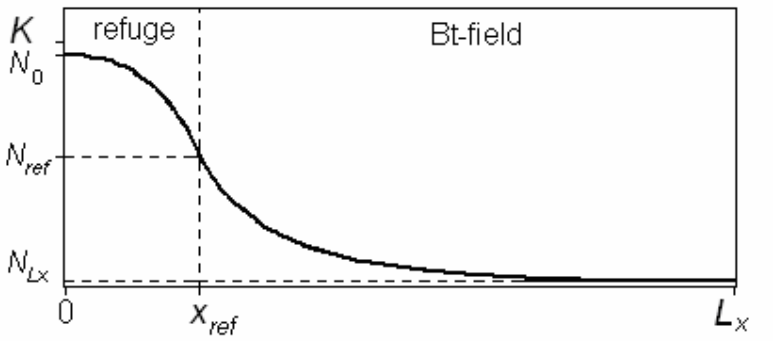


Fig. 2.11. Stationary solution of system (2.6) such that the genetic structure of the pest population consists only of individuals of *ss* genotype while *rs* and *rr* genotypes possessing Bt-resistance gene are absent. x_{ref} is the interface point between Bt-field (80%) and refuge (20%).

Let us find the necessary condition under which the solution $N(x)$ of the boundary-value problem (2.41) is continuous and continuously differentiable at point $x_{ref} \in (0, L_x)$. To construct a solution, we choose such initial and terminal densities N_0 and N_{Lx} from interval $(0, K)$ that at point $x_{ref} \in (0, L_x)$ the solution of system (2.42) coincides with the solution of system (2.44), i.e., $N_1^{ref} = N_2^{ref} = N_{ref}$ and $\dot{N}_1^{ref} = \dot{N}_2^{ref} = \dot{N}_{ref}$, and, moreover, $N_{ref} \in (0, K)$, $\dot{N}_{ref} < 0$. Then solution of (2.41) will be continuous and continuously differentiable on the whole 1D habitat Ω.

We will analyse the dynamics of system (2.41) on the phase plane. Starting from the initial point with coordinates $(N_0, 0)$: $N_0 \in (0, K)$ (Fig. 2.10a, point A in Fig. 2.12), system (2.41) will draw an appropriate closed trajectory of system (2.42) as long as $x \le x_{ref}$, i.e., up to point with coordinates $(N_{ref}, \dot{N}_{ref})$, then at point $(N_{ref}, \dot{N}_{ref})$, system (2.41) will proceed to some phase trajectory of system (2.44) and continue moving as long as $x \le L_x$. If point with coordinates $(N_{ref}, \dot{N}_{ref})$: $N_{ref} \in (0, K)$, $\dot{N}_{ref} < 0$ (point B in Fig. 2.12) lies above incoming separatrix of the saddle of system (2.44) in the fourth quadrant of the phase plane (grey dotted line in Fig. 2.12), after the transiting from the refuge to the Bt-field, system (2.41) will continue drawing a non-closed trajectory of hyperbolic type up to point $(N_{Lx}, 0)$: $N_{Lx} \in (0, K)$ (point C in Fig. 2.12). The solution constructed in such a way will be continuous and continuously differentiable on whole domain $[0, L_x]$ and, in addition, all its values on $[0, L_x]$ will lie in interval $(0, K)$.

We will find the phase trajectories of (2.42) in an explicit form, using the first integral of equation

$$\ddot{N}_1 = \frac{\alpha}{\delta} N_1 (N_1 - K) = F(N_1). \qquad (2.45)$$

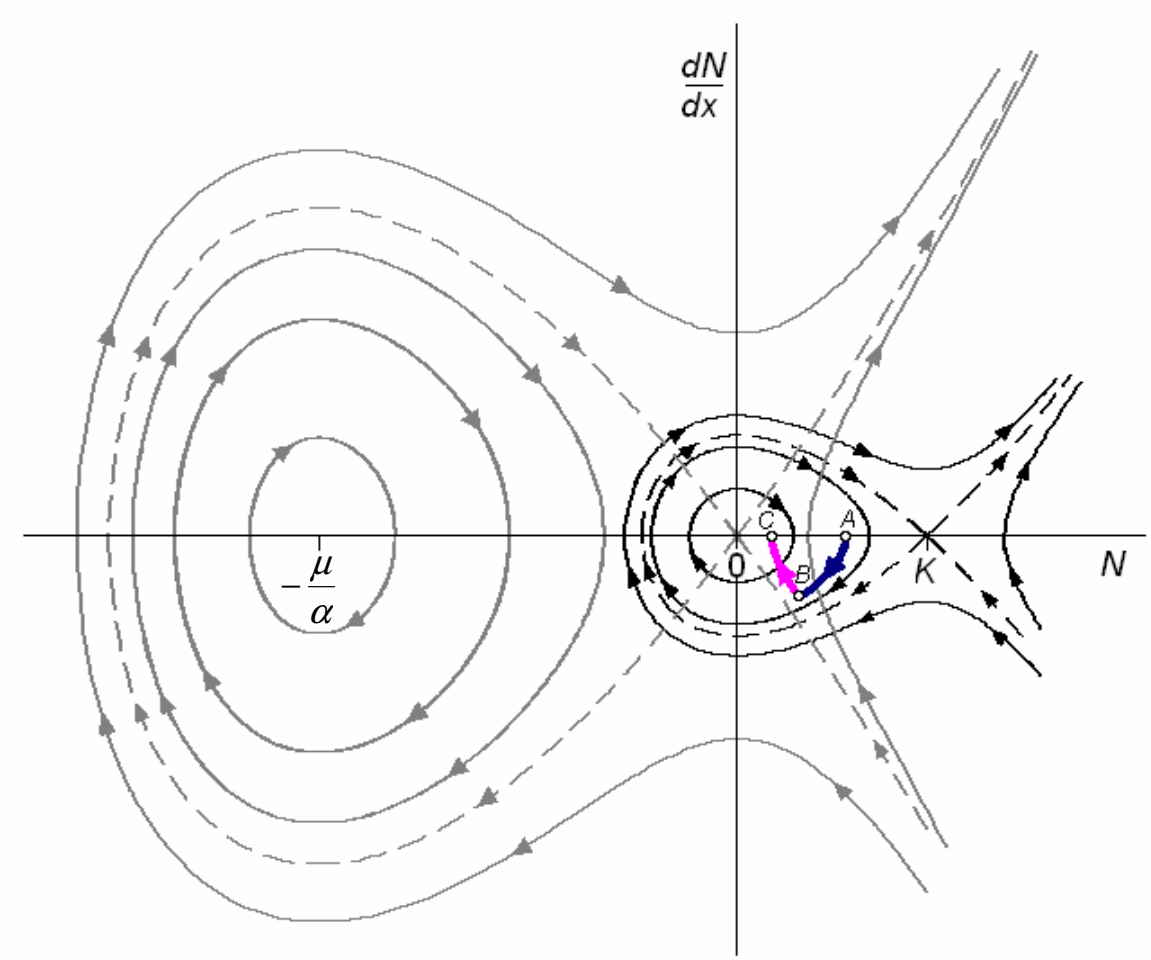


Fig. 2.12. Phase portrait of system (2.41). Phase trajectories of system are marked with black lines in the refuge Ω_{ref} and with grey lines in the Bt-field Ω_{Bt}. Separatrices are marked with dotted lines. Arc *AB* corresponds to the section of the closed phase trajectory which is generated by system within the refuge. Arc *BC* corresponds to the section of the non-closed phase trajectory of hyperbolic type, which is generated by system within the Bt-field.

Denoting $V(N_1)=\int_0^{N_1}\left(\frac{\alpha}{\delta}\eta(\eta-K)\right)d\eta$, we obtain $F(N_1)=\dot{V}(N_1)$ and can rewrite equation (2.45) as:

$$\ddot{N}_1-\dot{V}(N_1)=0. \qquad (2.46)$$

We multiply equation (2.46) by $\dot{N}_1$ and rewrite its left-hand part as the total derivative:

$$\frac{d}{dx}\left(\frac{\dot{N}_1^2}{2}-V(N_1)\right)=0.$$

The expression under the sign of first derivative must be constant:

$$\frac{\dot{N}_1^2}{2}-V(N_1)=C_1. \tag{2.47}$$

At each value of constant C_1 this equation determines some trajectory on the phase plane for system (2.42).

Evaluating $V(N_1)$ and substituting it into (2.47), we find the first integral describing the trajectories of system (2.42) on the phase plane:

$$\dot{N}_1=\pm\sqrt{C_1+\frac{\alpha}{\delta}N_1^2\left(\frac{2N_1}{3}-K\right)}. \tag{2.48}$$

Among all phase trajectories given by equation (2.48), let us choose such trajectory that satisfies the boundary condition of problem (2.42), i.e., it passes through point $(N_0,0)$: $N_0\in(0,K)$. Then in (2.48) $C_1=-\frac{\alpha}{\delta}N_0^2\left(\frac{2N_0}{3}-K\right)$ and the phase trajectory of the system within the refuge domain is closed (Fig. 2.10a, 2.12).

Substituting $N_1=N_{ref}$ into (2.48), we evaluate derivative $\dot{N}_{ref}$ at point $x=x_{ref}$:

$$\dot{N}_{ref}=\pm\sqrt{\frac{\alpha}{\delta}\left(N_{ref}^2\left(\frac{2N_{ref}}{3}-K\right)-N_0^2\left(\frac{2N_0}{3}-K\right)\right)}. \tag{2.49}$$

The expression under the square-root sign is non-negative if $N_{ref}<N_0$. Indeed,

$$N_{ref}^2\left(2N_{ref}/3-K\right)-N_0^2\left(2N_0/3-K\right)=$$
$$\left(N_0-N_{ref}\right)\left(K\left(N_{ref}+N_0\right)-2\left(N_{ref}^2+N_0N_{ref}+N_0^2\right)/3\right)\overset{N_0>N_{ref}}{>}$$
$$\left(N_0-N_{ref}\right)\left(N_0\left(N_{ref}+N_0\right)-2\left(N_{ref}^2+N_0N_{ref}+N_0^2\right)/3\right)=$$
$$\left(N_0-N_{ref}\right)\left(N_0^2+N_0N_{ref}-2N_{ref}^2\right)/3=\left(N_0-N_{ref}\right)^2\left(N_0+2N_{ref}\right)/3>0.$$

Let us choose $N_0\in\left(0,K\right)$ such that at the interface between the refuge and the Bt-field $N_{ref}>0$ and $\dot{N}_{ref}<0$.

In order that the point with coordinates $\left(N_{ref},\dot{N}_{ref}\right)$ lies above incoming separatrix of the saddle of system (2.44) in the fourth quadrant of the phase plane, it is necessary for the ordinate of this point $\dot{N}_{ref}$ to be less than the ordinate of the point belonging to the separatrix and having the same abscissa N_{ref}. We will find the equation of the separatrix of system (2.44), using its first integral. We multiply equation $\ddot{N}_2=\frac{\alpha}{\delta}N_2\left(N_2+\frac{\mu}{\alpha}\right)$ by $\dot{N}_2$, transfer all terms into the left-hand part and rewrite it as the total derivative. Taking into account that the expression under the sign of the first derivative must be constant, we obtain the first integral describing the move of system (2.44) on the phase plane:

$$\dot{N}_2=\pm\sqrt{C_2+\frac{\alpha}{\delta}N_2^2\left(\frac{2N_2}{3}+\frac{\mu}{\alpha}\right)},\qquad(2.50)$$

where $C_2=const$.

Equation (2.50) defines the family of phase trajectories of system (2.44). We substitute $C_2=0$ into (2.50). Then equation

$$\dot{N}_2=\pm\sqrt{\frac{\alpha}{\delta}N_2^2\left(\frac{2N_2}{3}+\frac{\mu}{\alpha}\right)}\qquad(2.51)$$

defines the curve consisting of a couple of incoming separatrices and a couple of outgoing separatrices and, in addition, the saddle point. However, the separatrix of system (2.44) does not include the saddle point $\left(0,0\right)$ but converges asymptotically

to it if $x \to \infty$ (Fig. 2.10b, 2.12). We are interested only in the separatrix located in the fourth quadrant of the phase plane. Substituting $N_2 = N_{ref} \in (0, N_0)$ into (2.51), and discarding the positive value of appropriate derivative, we obtain:

$$\dot{N}_{ref}^{sep} = -\sqrt{\frac{\alpha}{\delta} N_{ref}^2 \left(\frac{2N_{ref}}{3} + \frac{\mu}{\alpha} \right)}. \tag{2.52}$$

Then in order that solution $N(x)$ of system (2.41) be continuous and continuously differentiable in $[0, L_x]$, and all its values belong to the interval $(0, K)$, it is necessary that $\dot{N}_{ref} > \dot{N}_{ref}^{sep}$, i.e.

$$-\sqrt{\frac{\alpha}{\delta}\left(N_{ref}^2 \left(\frac{2N_{ref}}{3} - K \right) - N_0^2 \left(\frac{2N_0}{3} - K \right) \right)} > -\sqrt{\frac{\alpha}{\delta} N_{ref}^2 \left(\frac{2N_{ref}}{3} + \frac{\mu}{\alpha} \right)}$$

or

$$N_{ref}^2 \frac{b}{\alpha} > N_0^2 \left(K - \frac{2}{3} N_0 \right). \tag{2.53}$$

Thus, we construct spatially heterogeneous stationary solution of system (2.6) for the habitat configuration presented in Fig. 2.9 such that the genetic structure of the pest consists solely of insects of *ss* genotype. Such solution is continuous and continuously differentiable in the whole segment $[0, L_x]$, and its values belong to the interval $(0, K)$ and, moreover, zero-flux boundary conditions hold.

Theorem 7 is completely proved ■

Remark: In the proof of Theorem 7 we require not only the continuity of function $N_{ss}(x)$ at point x_{ref} but also the continuity of its first derivative because the density flux $-\delta \frac{\partial N_{ss}}{\partial x}$ through this point must be constant. However, the second derivative of this function at point x_{ref} cannot be continuous because the function

of local kinetics of system (2.6) is not continuous at the interface between the refuge and the Bt-field.

A more general theorem is true:

Theorem 8. If the spatially heterogeneous stationary solutions of system (2.6), such that $\forall\, x\in[0, L_x]\;\; N^*_{ss}(x)\in\left(0, \dfrac{W^{ref}_{ss}b-\mu}{\alpha}\right)$ and $N^*_{rs}(x)=N^*_{rr}(x)=0$, exist for the habitat configuration presented in Fig. 2.9 and if $W^{ref}_{ss}>W^{Bt}_{ss}$ and $W^{ref}_{ss}>\dfrac{\mu}{b}$ ($W^{ref}_{ss}=W_{ss}(x)\big|_{x\in\Omega_{ref}}$, $W^{Bt}_{ss}=W_{ss}(x)\big|_{x\in\Omega_{Bt}}$), then the following condition holds:

$$N_0^2\left(\frac{W^{ref}_{ss}b-\mu}{\alpha}-\frac{2}{3}N_0\right)<N^2_{ref}\,\frac{b\left(W^{ref}_{ss}-W^{Bt}_{ss}\right)}{\alpha},$$

where $N_{ref}<N_0$, $N_0=N(0)$, $N_{ref}=N\left(x_{ref}\right)$ ($x_{ref}\in(0, L_x)$ is the interface point between Bt-field and refuge).

Proof. As in Theorem 7, let in (2.39) the densities of *rs* and *rr* genotypes be zero for all $x\in[0, L_x]$. Then the boundary-value problem (2.39) reduces to (2.41). Note that here we do not suppose that the genotypic fitness $W_{ij}\in[0,1]$ satisfies formulas (2.5). Let us analyse the singular points of system (2.41) in the refuge Ω_{ref} and in the Bt-field Ω_{Bt}:

$$\begin{cases}\dot N_j=Y_j;\\ \dot Y_j=\dfrac{\alpha}{\delta}N_j\left(N_j-\dfrac{W^j_{ss}b-\mu}{\alpha}\right),\end{cases}\qquad(2.54)$$
$$\dot Y_{ref}(0)=0,\quad \dot Y_{Bt}(L_x)=0,\quad j=ref \text{ or } Bt.$$

System (2.54) has four singular points:

$$N^*_j=0,\; Y^*_j=0;$$

$$N_j^* = \frac{W_{ss}^j b - \mu}{\alpha},\ Y_j^* = 0.$$

The characteristic equation for (2.54) is $\lambda_j^2 - \frac{\alpha}{\delta}\left(2N_j - \frac{W_{ss}^j b - \mu}{\alpha}\right) = 0$.

Let us consider three cases:

a) $W_{ss}^{ref} > \frac{\mu}{b}$, $W_{ss}^{Bt} < \frac{\mu}{b}$. Then $N_{ref}^* = 0$, $Y_{ref}^* = 0$ is a centre; $N_{Bt}^* = 0$, $Y_{Bt}^* = 0$ is a saddle; $N_{ref}^* = \frac{W_{ss}^{ref} b - \mu}{\alpha} > 0$, $Y_{ref}^* = 0$ is a saddle; $N_{Bt}^* = \frac{W_{ss}^{Bt} b - \mu}{\alpha} < 0$, $Y_{Bt}^* = 0$ is a centre (Fig. 2.13a). This case is similar to considered one in Theorem 7. Repeating the scheme of constructing the stationary solution of Theorem 7, we obtain the necessary condition for existence of the solution of Theorem 8:

$$N_0^2\left(\frac{W_{ss}^{ref} b - \mu}{\alpha} - \frac{2}{3}N_0\right) < N_{ref}^2 \frac{b\left(W_{ss}^{ref} - W_{ss}^{Bt}\right)}{\alpha}, \qquad (2.55)$$

where $N_{ref} < N_0$, $N_0 = N(0)$, $N_{ref} = N(x_{ref})$ ($x_{ref} \in (0, L_x)$is the boundary point between Bt-field and refuge).

b) $W_{ss}^{ref} > \frac{\mu}{b}$, $W_{ss}^{Bt} > \frac{\mu}{b}$. Then $N_{ref}^* = 0$, $Y_{ref}^* = 0$ is a centre; $N_{Bt}^* = 0$, $Y_{Bt}^* = 0$ is a centre; $N_{ref}^* = \frac{W_{ss}^{ref} b - \mu}{\alpha} > 0$, $Y_{ref}^* = 0$ is a saddle; $N_{Bt}^* = \frac{W_{ss}^{Bt} b - \mu}{\alpha} > 0$, $Y_{Bt}^* = 0$ is a saddle (Fig. 2.13b). One can see from Fig. 2.13b that in this case, the necessary condition for existence of the solution of Theorem 8 is also defined by condition (2.55).

c) $W_{ss}^{Bt} < W_{ss}^{ref} < \frac{\mu}{b}$. Then $N_{ref}^* = 0$, $Y_{ref}^* = 0$ is a saddle; $N_{Bt}^* = 0$, $Y_{Bt}^* = 0$ is a saddle; $N_{ref}^* = \frac{W_{ss}^{ref} b - \mu}{\alpha} < 0$, $Y_{ref}^* = 0$ is a centre; $N_{Bt}^* = \frac{W_{ss}^{Bt} b - \mu}{\alpha} < 0$, $Y_{Bt}^* = 0$ is a centre (Fig. 2.13c). In this case, the stationary solution of system (2.6) is as follows: $N_{ss}^*(x) = N_{rs}^*(x) = N_{rr}^*(x) = 0\ \ \forall\, x \in [0, L_x]$, that corresponds to the saddle

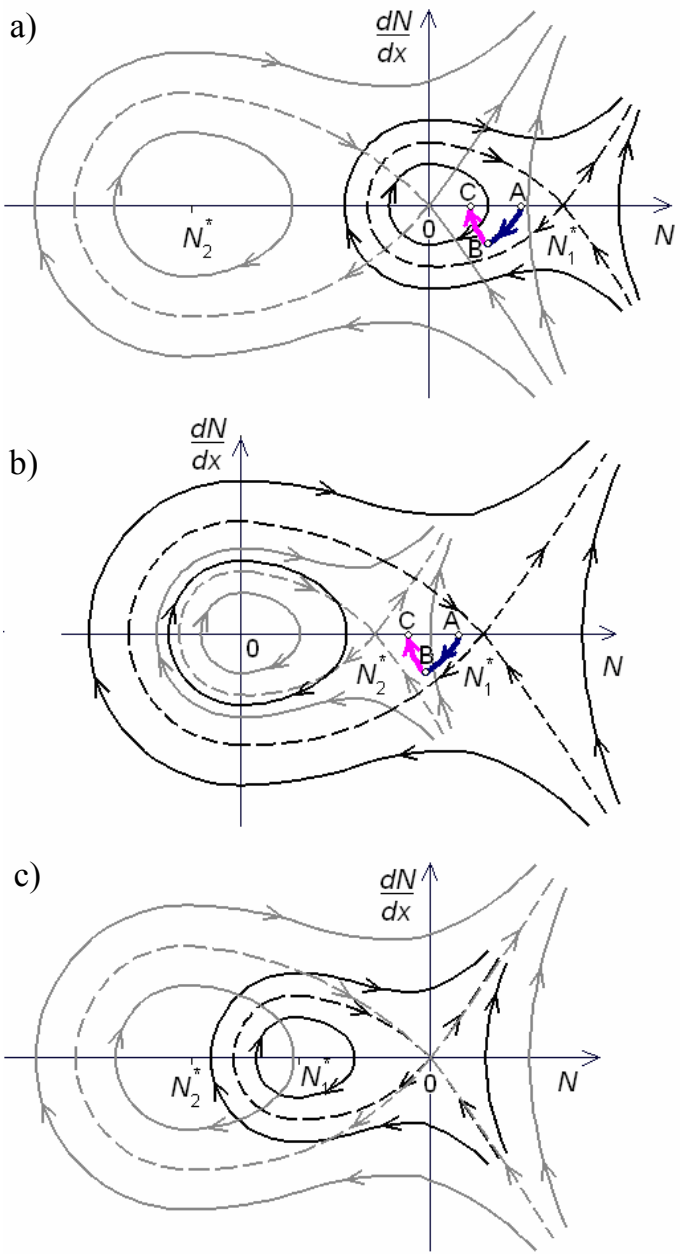


Fig. 2.13. Phase portraits of system (2.41) in the case of $W_{ss}^{Bt} < W_{ss}^{ref}$. Here $N_1^* = \left(W_{ss}^{ref} b - \mu\right)/\alpha$, $N_2^* = \left(W_{ss}^{Bt} b - \mu\right)/\alpha$. (a) $W_{ss}^{ref} > \mu/b$, $W_{ss}^{Bt} < \mu/b$; (b) $W_{ss}^{ref} > \mu/b$, $W_{ss}^{Bt} > \mu/b$; (c) $W_{ss}^{Bt} < W_{ss}^{ref} < \mu/b$. Phase trajectories of system are marked with black lines in the refuge Ω_{ref} and with grey lines in the Bt-field Ω_{Bt}. Separatrices are marked with dotted lines. Arc AB corresponds to the section of the closed phase trajectory of the system within the refuge. Arc BC corresponds to the section of the non-closed phase trajectory of hyperbolic type that is generated by system within the Bt-field. Point A corresponds to the left boundary condition of problem (2.41), point C – to the right-hand one. Point B is the point of sewing together the solutions in the refuge and in the Bt-field.

point (0, 0) on the phase plane (Fig. 2.13c), i.e., to the unstable equilibrium.
Theorem 8 is completely proved ■

2.3 Simulation results

To investigate the spatio-temporal dynamics of the genetic structure of the ECB population when using different scenarios of management strategies (the HDR strategy, biocontrol and their combination), simulation models were constructed in the integrated development environment Delphi 7.0. These models allow varying all considered characteristics of plant resource, pest and its parasitoid, defining their initial distributions in space, fixing different sizes of the ECB habitat, various sizes, arrangement and configuration of refuges. The bi-trophic models "pest – parasitoid" and "plant resource – pest" and the appropriate simulation results will be described in details in the third chapter.

For carrying out numerical simulations, we discretized in space the original continuous diffusion models (demo-genetic models in the density form (2.6) and in the frequency form (2.32) and also Fisher-Haldane-Wright model which is actually model (2.32) less the advective term) with a regular grid along the spatial coordinates x, y, approximating the spatial derivatives with the central difference in each node (see Appendix 2). The obtained system of ordinary differential equations with the preset initial conditions was integrated by the Runge-Kutta method of the fourth order with automatic time step selection. The accuracy of calculations was checked on the doubled spatial grid.

In all our simulations, the initial total density of the pest was taken as 2% of the carrying capacity $K = 147.4 \cdot 10^6$ ind/km^2 (see § 2.1.5), corresponding to $N^0 = 2.948 \times 10^6$ ind/km^2 (or 0.44 ind/plant). We assume that as a result of recurrent mutations, the Bt-resistance allele already exists in the pest population at an initial frequency of $p_r^0 = 0.0015$, which is somewhat higher than the estimate of $p_r < 10^{-3}$ for the ECB population in the US Corn Belt (Andow et al. 2000; Bourguet et al. 2003). Such initial conditions correspond to a pessimistic scenario

leading to more cautious forecasts for resistance development in the pest population. We also assume that, before planting the Bt maize, there were no resistant homozygous individuals *rr* and only a small number of heterozygotes *rs* possessing one copy of the Bt-resistance allele. These assumptions are consistent with the results of field investigations in natural ECB populations (Andow et al. 2000; Bourguet et al. 2003). If we assume that the initial genotype densities are uniformly distributed in space, given that $p_r = \frac{N_{rr} + 0.5N_{rs}}{N}$, we obtain the following initial densities of pest genotypes: $N_{ss}^0 = 2939156$ ind/km^2 (0.439 ind/plant), $N_{rs}^0 = 8844$ ind/km^2 (0.001 ind/plant), $N_{rr}^0 = 0$.

2.3.1 *Stability analysis of the homogeneous and heterogeneous spatial states of the model*

Varying the size of the single-strip refuge (Fig. 2.9b) in a one-dimensional habitat 16 km long, we investigated the stability of stationary states of model (2.32) and Fisherian diffusion model under the assumption that the insects possessing the Bt-resistance gene 'pays' 10% of the fitness W_{rr} ($c = 0.1$) for the advantage in the toxic Bt-fields. The genetic parameters of the model corresponds to the HDR strategy (see Fig. 2.14), the ecological parameters – to the modelled pest species *Ostrinia nubilalis* (§ 2.1.5). As the large-scale diffusion coefficient δ of insect species is difficult to estimate from a small number of field observations, we will vary this coefficient from 0 to ∞, with irregular increments.

Note that spatially homogeneous stationary state of system (2.6): $N_{ss}^*(x) = 0$, $N_{rs}^*(x) = 0$, $N_{rr}^*(x) = \frac{b(1-c)-\mu}{\alpha}$ $\forall\, x \in [0, L_x]$, the existence of which was proved in Theorem 6, corresponds to the spatially homogeneous stationary state $\overline{p}_r = 1$ of system (2.32). The spatially heterogeneous stationary solutions of model (2.6) such that $N_{ss}^*(x) \in (0, K)$, $N_{rs}^*(x) = N_{rr}^*(x) = 0$ $\forall\, x \in [0, L_x]$, correspond to the equilibrium $\overline{p}_r = 0$ in model (2.32). For constructing such solutions, we used a

shooting method modified according to Theorem 7 so that to sew together solutions obtained for two qualitatively different domains of pest habitat: Bt field and refuge (Appendix 3A). Then, using Matlab 7.0, we found numerically the bifurcation values of the refuge percentage at which the equilibriums $\overline{p}_r = 0$, $\overline{p}_r = 1$ lose their stability in model (2.32) (Appendix 3B). The location of eigenvalues of Jacobian of system (2.6) on the complex plane characterises the occurring bifurcations. When varying the bifurcation parameter (refuge percentage), the equilibriums $\overline{p}_r = 0$ and $\overline{p}_r = 1$ lose their stability monotonically because only one eigenvalue crosses the imaginary axis from the left-hand to the right-hand of the complex plane while the imaginary part of this eigenvalue remains zero. Each branch of stable non-trivial equilibrium $\overline{p}_r \in (0,1)$ of model (2.32) that corresponds to the stable polymorphic stationary state of system (2.6) $N^*_{ss}(x),\ N^*_{rs}(x),\ N^*_{rr}(x) \in (0, K)\ \forall\, x \in [0, L_x]$, is constructed by means of numerical simulations. We supplemented the bifurcation diagram with the branches of equilibriums arising from the extreme cases – panmixia ($\delta = \infty$) and isolation ($\delta = 0$) between Bt-field and refuge – considered in details in § 2.2.2. With sufficiently high diffusion coefficient δ (for instance, with $\delta = 1$ km^{2}yr^{-1} and higher, up to $\delta = \infty$), the branch corresponding to the polymorphic state of the population ($\overline{p}_r \in (0,1)$) becomes unstable and the hysteresis cycle appears in the system (Fig. 2.14a).

We also constructed the bifurcation diagram for the Fisher-Haldane-Wright model (Fig. 2.14b), using the same method for the determination of the bifurcation values of the refuge percentage as in demo-genetic model (2.32). Note that according to Lemma 1 and Consequence of Theorem 4, spatially homogeneous stationary state of demo-genetic model (2.32) $\overline{p}_r = 1$ is also an equilibrium of the Fisher-Haldane-Wright model. Therefore, the bifurcation values of the refuge percentage at which such equilibrium loses its stability coincide for both models.

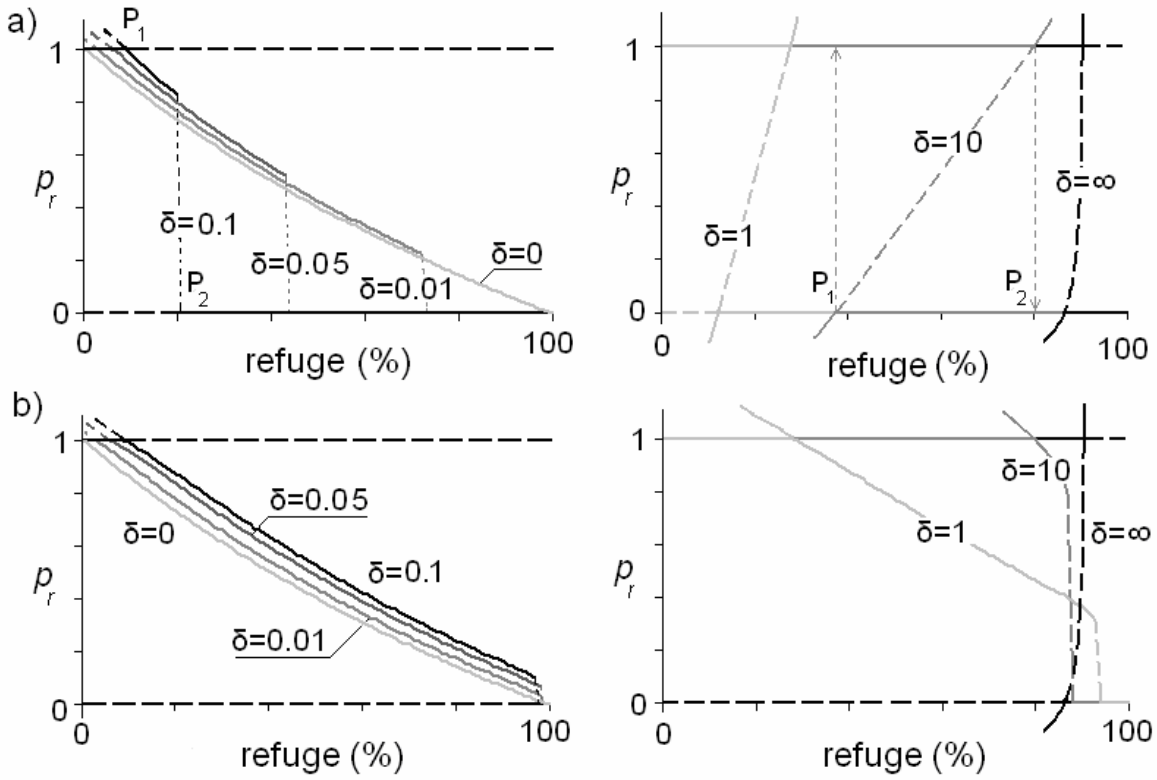


Fig. 2.14. Frequency of the Bt-resistance allele p_r as a function of refuge percentage for (a) the demo-genetic model (2.6) and (b) the Fisher-Haldane-Wright model. The branches of stable equilibriums are marked with solid lines. The branches of unstable equilibriums are marked with dotted lines. A given set of genetic parameters corresponds to the HDR strategy: $\sigma = 1$, $c = 0.1$, $h_\sigma = 0.14$, $h_c = 0.2$.

It is noteworthy that with a cost of Bt-resistance, the HDR strategy allows not only delaying as in case of $c = 0$ but also entirely preventing the pest adaptation to the Bt-modified crop. Let us compare the stationary regimes emerging in both diffusion models – demo-genetic model and Fisherian – depending on the possibility to solve this applied problem.

Bifurcation analysis of the demo-genetic model (2.32) has shown that with small-to-high diffusion coefficient δ, the stiff bifurcation in (2.32) occurs (Fig. 2.14a). With high pest dispersal ($\delta \geq 1$ km^{2}yr^{-1}), there exists a closed hysteresis cycle which does not allow to manage system (2.32) smoothly via the small variation of the refuge percentage. For instance, with $\delta = 10$ km^{2}yr^{-1}, if the

refuge size becomes less than P_1, the Bt-resistance allele *r* entirely sweeps out the Bt-susceptible allele *s* (all population will consist solely of the Bt-resistant insects of *rr* genotype) and the Bt-resistance gene can be suppressed again only owing to the excessive increase of the refuge percentage ($>P_2$), i.e., here this is a question of the really large refuges. In this case, it is most likely that growers will have to stop the Bt-crop using in fields, thereby losing profit.

With low pest dispersal ($\delta < 0.1$ km^{2}yr^{-1}), we may smoothly manage the system, adaptively varying the refuge size, despite the gaps in the critical points in motion along the stable branch $\overline{p}_r = 0$. For instance, with $\delta = 0.1$ km^{2}yr^{-1}, crossing the critical point P_2 with decrease of the refuge size, one can always return to the stable regime $p_r = 0$ when in the population there is no Bt-resistance gene, just slightly having increased the refuge size. Thus, the pest dispersal plays an important role in ensuring the efficiency of the HDR strategy.

Bifurcation analysis of the Fisher-Haldane-Wright model has shown (Fig. 2.14b) that only in cases of zero and of infinitely large pest mobility ($\delta = 0$ and ∞) this model gives the same prognosis as the demo-genetic model (2.32). In other cases, the Fisherian model predicts that the effective use of the HDR strategy aimed at preventing the pest adaptation to Bt-maize ($p_r = 0$) will require too large refuges close to 100% (98% of the whole cultivated area Ω with $\delta = 0.1$ km^{2}yr^{-1}) while in the demo-genetic model (2.32) one may entirely prevent the Bt-resistance evolution in the ECB population with much less refuge sizes (21% of the whole cultivated area Ω with $\delta = 0.1$ km^{2}yr^{-1}).

2.3.2 *Analysis of the efficiency of the "high dose-refuge" strategy for 1D and 2D habitats*

For solving the posed problem, we have carried out a series of simulations with the demo-genetic model (2.32) under the assumption that there is no Bt-resistance cost which is paid by the insects possessing the Bt-resistance gene for their advantage in toxic Bt-plants ($c = 0$). It is evident that without cost of

resistance, it is impossible to prevent the pest adaptation to the Bt-crop. In this case, the HDR strategy may only delay the Bt-resistance development in the pest population, i.e., spatially homogeneous distribution $N_{ss}(x) = N_{rs}(x) = 0$, $N_{rr}(x) = K \ \ \forall x \in \Omega$ is a unique stable stationary state of model (2.6), or $p_r(x) = 1$, $N(x) = N_{rr}(x) = K$, $\xi(x) = 0 \ \ \forall x \in \Omega$ in model (2.32).

The proposed model (2.32) was used for three purposes:

- to investigate the spatio-temporal patterns of Bt-resistance development in the ECB population;
- to study the influence of refuge size and ECB dispersal on delaying Bt-resistance;
- to compare the effectiveness of refuge configurations.

Let us consider the simplest case of the pest habitat $\Omega = [0, L_x] \times [0, L_y]$ where $L_x = 16$ km, $L_y = 16$ km, i.e., we fix the modelled field Ω as a square.

We used two criteria for assessing the efficiency of Bt-resistance management and pest control strategies:

1) time taken to develop Bt-resistance, evaluated as the time T_{10} required for the frequency of the resistance allele to reach 10% over the total ECB population;

2) spatially averaged ECB density: $< N >= \frac{1}{L_x} \int_0^{L_x} N(x,t)dx$ for the 1D habitat and $< N >= \frac{1}{L_x L_y} \int_0^{L_y} \int_0^{L_x} N(x,y,t)dxdy$ for the rectangle 2D habitat.

In all simulations, we assumed the partial Bt-resistance of the heterozygous genotype, having determined the “high dose” as ability of Bt-toxin to kill 100% of Bt-susceptible homozygous insects and 95% of heterozygous insects ($\sigma = 1$, $h_\sigma = 0.05$). According to formulas (2.5), in the absence of the Bt-resistance cost ($c = 0$) the fitness of each genotype in the ECB population is defined as:

$$W_{rr} \equiv 1, \quad \text{everywhere in } \Omega; \quad W_{rs}(x,y) = \begin{cases} 1, & \mathbf{x} \in \Omega_{Ref}; \\ 0.05, & \mathbf{x} \in \Omega_{Bt}; \end{cases} \quad W_{ss}(x,y) = \begin{cases} 1, & \mathbf{x} \in \Omega_{Ref}; \\ 0, & \mathbf{x} \in \Omega_{Bt}. \end{cases}$$

(a) *spatio-temporal patterns of Bt-resistance development*

Using a fixed refuge percentage (20% of Ω) and a fixed diffusion coefficient $\delta = 0.1$ km^{2}yr^{-1}, we analysed the genotypic dynamics and the rate of Bt-resistance invasion in the ECB population, using a single-strip pattern for the refuge (Fig. 2.9a).

Simulations with the demo-genetic model (2.32) indicated that the HDR strategy has an immediate effect, disrupting the initial homogeneity of genotype densities. However, the frequency of the Bt-resistance allele p_r slowly increases, reaching 0.002 only after 11 years (Fig. 2.15a). At this stage, pest density in the refuge reaches levels slightly below the carrying capacity whereas the pest is virtually absent from the Bt area. In the refuge and also in the cultivated area as a whole, the pest population consists principally of insects of the *ss* genotype (about 99%). With given set of model parameters, this distribution persists for almost 560 years. Nevertheless, the *rr* genotype has a high coefficient of survival on Bt plants and, despite the influx of large numbers of Bt-susceptible potential mates from the refuge, the frequency of the Bt-resistance allele p_r slowly but steadily increases. As a result, the system tends ultimately to spatially homogeneous state corresponding to complete invasion with the resistant *rr* genotype in the whole cultivated area Ω (Fig. 2.15e).). Once the frequency of the Bt-resistance gene reaches some critical value ($p_r \approx 10\%$), complete invasion of the Bt area by the *rr* genotype takes only five years (Fig. 2.15d), the Bt-susceptible genotypes from the refuge being completely replaced by the resistant genotype within 36 years (Fig. 2.15e).

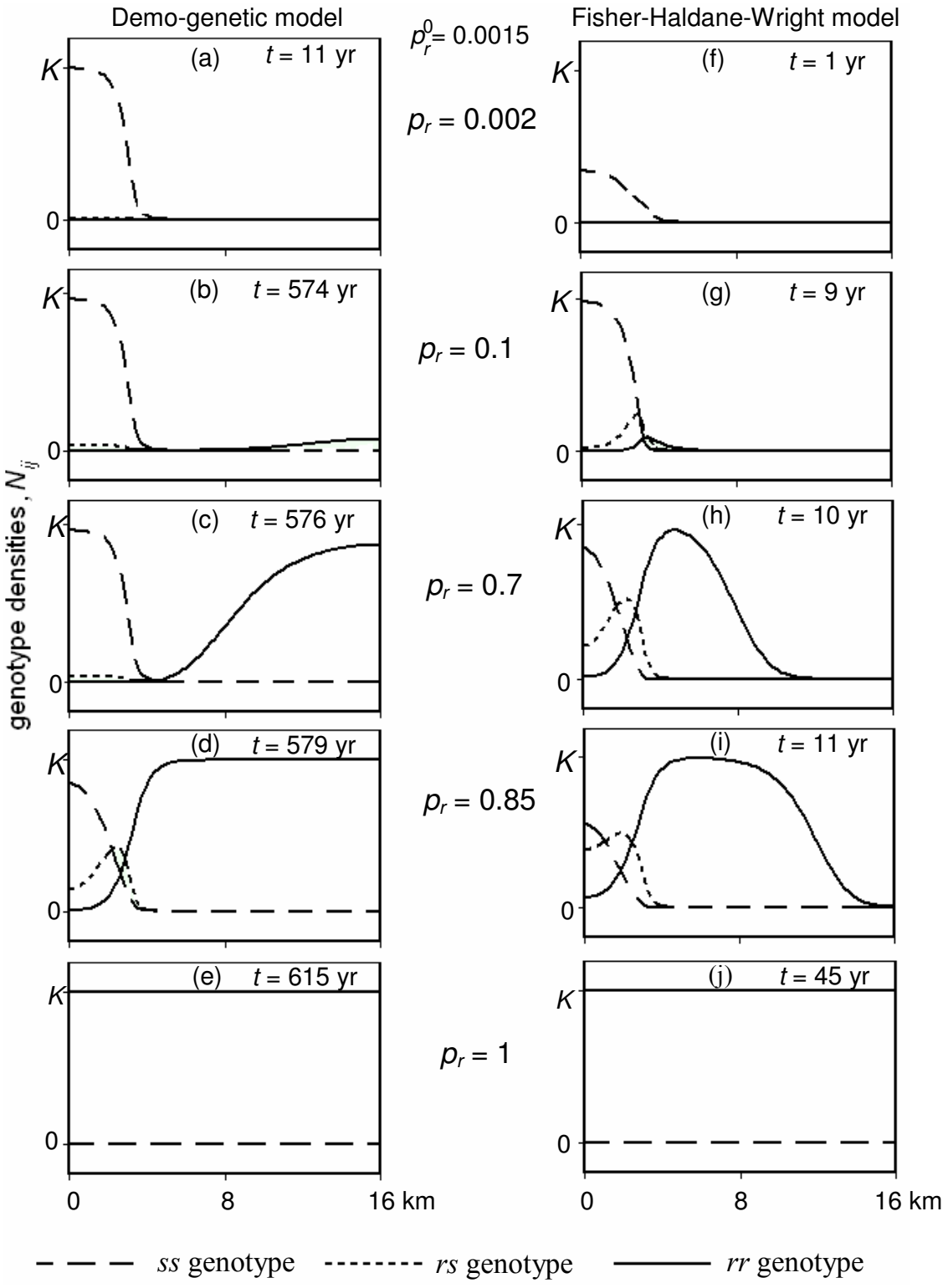


Fig. 2.15. Density distribution of ECB genotypes in a one-dimensional area 16 km long at the time (years) at which the frequency of the resistance allele p_r sequentially reaches 0.002, 0.1, 0.7, 0.85 and 1, for a 20% refuge area, in both diffusion models: demo-genetic and Fisherian.

We carried out similar simulations with the Fisher-Haldane-Wright diffusion model. In contrast to what was observed with the demo-genetic model (2.32), when p_r reaches 0.2% in the Fisherian model, Bt-susceptible genotypes occupy only 30% of the carrying capacity of the refuge (Fig. 2.15f). However, the spatially heterogeneous distribution of Bt-susceptible genotypes (as in Fig. 2.15a) emerges very rapidly (within 4 years) but persists for only five years (contrary to 560 years in the demo-genetic model). Complete invasion by the Bt-resistant genotype *rr* requires a further 36 years (Fig. 2.15j).

The difference between two modelling approaches – demo-genetic and Fisherian – lies in both the duration of the process of the pest adaptation to Bt-crop and the nature of the spatio-temporal dynamics. In the demo-genetic diffusion model (2.32), the conditions favouring the appearance of *rr* individuals are at the extreme right-hand side of the Bt domain (Fig. 2.15b). In the Fisherian diffusion model, these conditions occur near the border between the refuge and the Bt field areas (Fig. 2.15g).

(b) *influence of refuge size and ECB dispersal*

We determined the period of time T_{10} during which the frequency of the resistance allele remained below 10% in a series of simulations with the demo-genetic diffusion model and Fisherian diffusion model, varying the size of the single-strip refuge (Fig. 2.9b) and the diffusion coefficient δ. The results are reported in Table 2.1.

The data for the demo-genetic model showed that in cases of low pest dispersal ($\delta \leq 0.01$ km^2 yr^{-1}) or panmixia ($\delta = \infty$), the increasing of the size of the refuge has little effect despite the monotonic increase of time T_{10}, as it does not delay the development of Bt resistance (Bt resistance develops within 7 to 26 years). For intermediate values of diffusion coefficient δ (0.01 to 1 km^2 yr^{-1}), T_{10} steeply increases with increasing of refuge size in the demo-genetic model (2.32), and may even reach several hundreds and thousands of years, providing strong

Table 2.1. Time T_{10} (years) in the demo-genetic and Fisherian diffusion models, for various combinations of refuge size and diffusion coefficient, with a single-strip border refuge as in Fig. 2.9b.

Diffusion, δ (km^2 yr^{-1})	Refuge percentage (%)									
	5	10	15	20	25	30	35	40	45	50
	Demo-genetic diffusion model									
0	24	24	24	24	24	24	24	25	25	25
0.01	24	24	24	24	25	25	25	25	25	26
0.02	24	24	24	25	25	25	26	2034	2483	2968
0.03	24	25	25	25	992	1294	1627	1988	2376	2791
0.04	24	25	485	720	979	1262	1567	1894	2242	2610
0.05	92	266	473	700	947	1213	1496	1798	2116	2451
0.1	67	205	382	574	776	988	1208	1437	1675	1920
0.5	20	69	140	229	329	435	545	657	771	881
1	13	37	78	130	192	261	335	410	487	564
2	10	21	43	72	106	146	191	239	289	341
3	9	16	30	51	75	103	135	170	207	246
4	8	14	24	39	59	80	105	132	161	192
5	8	12	20	32	48	66	86	108	132	156
10	7	9	13	18	26	35	46	57	69	80
20	7	8	10	12	15	19	24	29	35	41
…	…	…	…	…	…	…	…	…	…	…
∞	7	7	8	8	9	9	10	11	12	13
	Fisher-Haldane-Wright diffusion model									
0	24	24	24	24	24	24	24	25	25	25
0.01	8	9	9	9	9	9	9	10	10	10
0.02	8	9	9	9	9	9	9	9	9	9
0.03	8	8	9	9	9	9	9	9	9	9
0.04	8	8	9	9	9	9	9	9	9	9
0.05	8	8	9	9	9	9	9	9	9	9
0.1	8	8	8	9	9	9	9	9	9	9
0.5	7	8	8	8	8	8	9	9	9	9
1	7	7	8	8	8	8	9	9	9	9
2	7	7	8	8	8	8	9	9	9	9
3	7	7	8	8	8	9	9	9	10	10
4	5	7	8	8	8	9	9	10	10	11
5	5	7	8	8	8	9	9	10	11	12
10	5	6	8	8	9	9	10	10	11	12
20	4	5	6	8	9	9	10	11	12	13
…	…	…	…	…	…	…	…	…	…	…
∞	7	7	8	8	9	9	10	11	12	13

evidence that the HDR strategy is efficient. However, for a given refuge size, T_{10} increases considerably at a particular value of the diffusion coefficient, then decreases monotonically with further increases in δ. At high levels of pest dispersal ($\delta > 1$ km^2 yr^{-1}), T_{10} increases only weakly with refuge size. Note that the monotonic dependence of T_{10} on the refuge percentage holds at any δ.

Demo-genetic model (2.32) also indicates that in the total absence of a refuge in the toxic Bt-field ($\Omega = \Omega_{Bt}$) the Bt-resistance develops within 7 years at any ECB mobility.

For comparison, we performed the same simulations at the same parameters in the conventional frequency-based model (Table 2.1). One can see that throughout the range of δ variation the time T_{10} monotonically (but slightly) increases with the refuge size. On the other hand, the increasing pest mobility at fixed refuge size violates the monotony: the delay time first declines with increasing mobility and then tends to rise again. However, all the T_{10} values thus obtained are too low to support the HDR strategy: mostly less than 10 years, and within 25 years at any combinations.

(c) *effectiveness of refuge configurations*

We investigated the effects of refuge shape and their spatial arrangement relative to the Bt-field on the efficiency of the HDR strategy with different fixed values of refuge percentage and pest dispersal δ (Fig. 2.16, 2.17). Simulations with the demo-genetic model (2.32) showed that for a field size of 16 km by 16 km, the single-strip border refuge (Fig. 2.16a) was the most effective of the refuge forms tested (Figs. 2.16a-f). Locating the single-strip refuge in the middle of the maize field (Fig. 2.16b) approximately halved T_{10}, resulting in significantly higher levels of ECB infestation in the Bt area than with the refuge at the border, as in Fig. 2.16a. Note that the efficiency of this pattern is similar to the efficiency evaluated with two refuge strips located along the opposite sides of the Bt-field (Fig. 2.16c). Splitting a one-strip refuge into several strips located within the Bt-field even

greater decreased the efficiency of the refuge (Figs. 2.16d,e). However, four strips planted with conventional maize in the frame refuge pattern (Fig. 2.16 f) almost in 10 times are more effective in the delay time T_{10} than pattern (e) in Fig. 2.16.

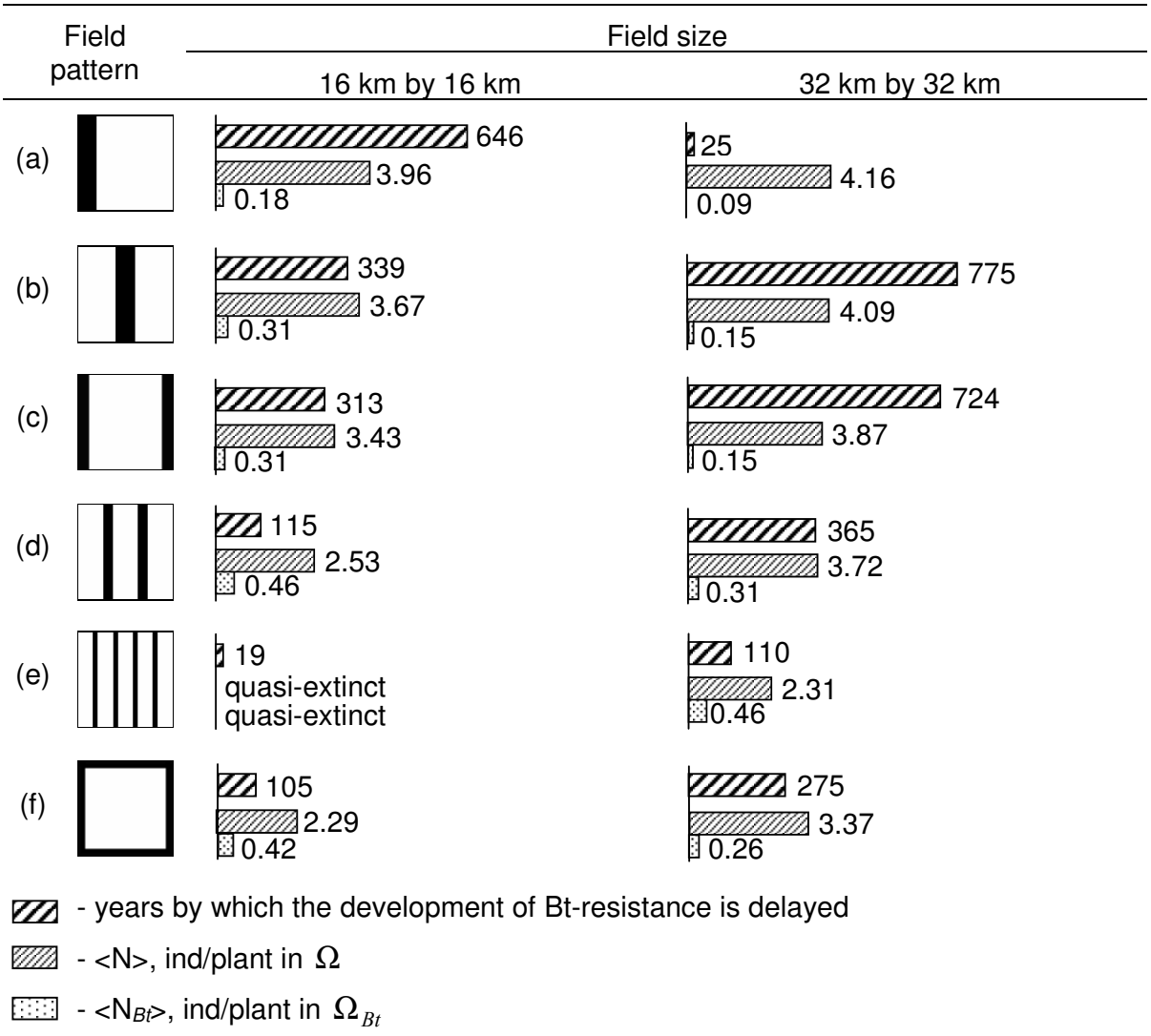


Fig. 2.16. Time T_{10} (years) required for the frequency of the resistance allele to reach 10% over the whole farming area Ω and the levels of ECB invasion (ind/plant) of the whole maize area and the Bt area, with $p_r < 0.1$ (during T_{10}), in the demo-genetic diffusion model. The refuge area is shown in black and the Bt area is shown in white. Refuges account for 20% of total area for all patterns. Pest dispersal $\delta = 0.07\,\mathrm{km^2 yr^{-1}}$.

Simulations with square refuge structures also indicated that, for the same field size of 16 km by 16 km and the same proportion (20%) of refuge, increasing the number of refuge patches by decreasing their size greatly decreased the

efficiency of the HDR strategy (Fig. 2.17). Note that as with strip refuges (Fig. 2.16), the aggregation of square refuges along the border of habitat Ω, in particular, in one of its corners (Fig. 2.17a) allows much longer to suppress the Bt-resistance development in the ECB population and provide lower infestation level of the Bt-field by the pest than the refuge located in the middle of the Bt-field

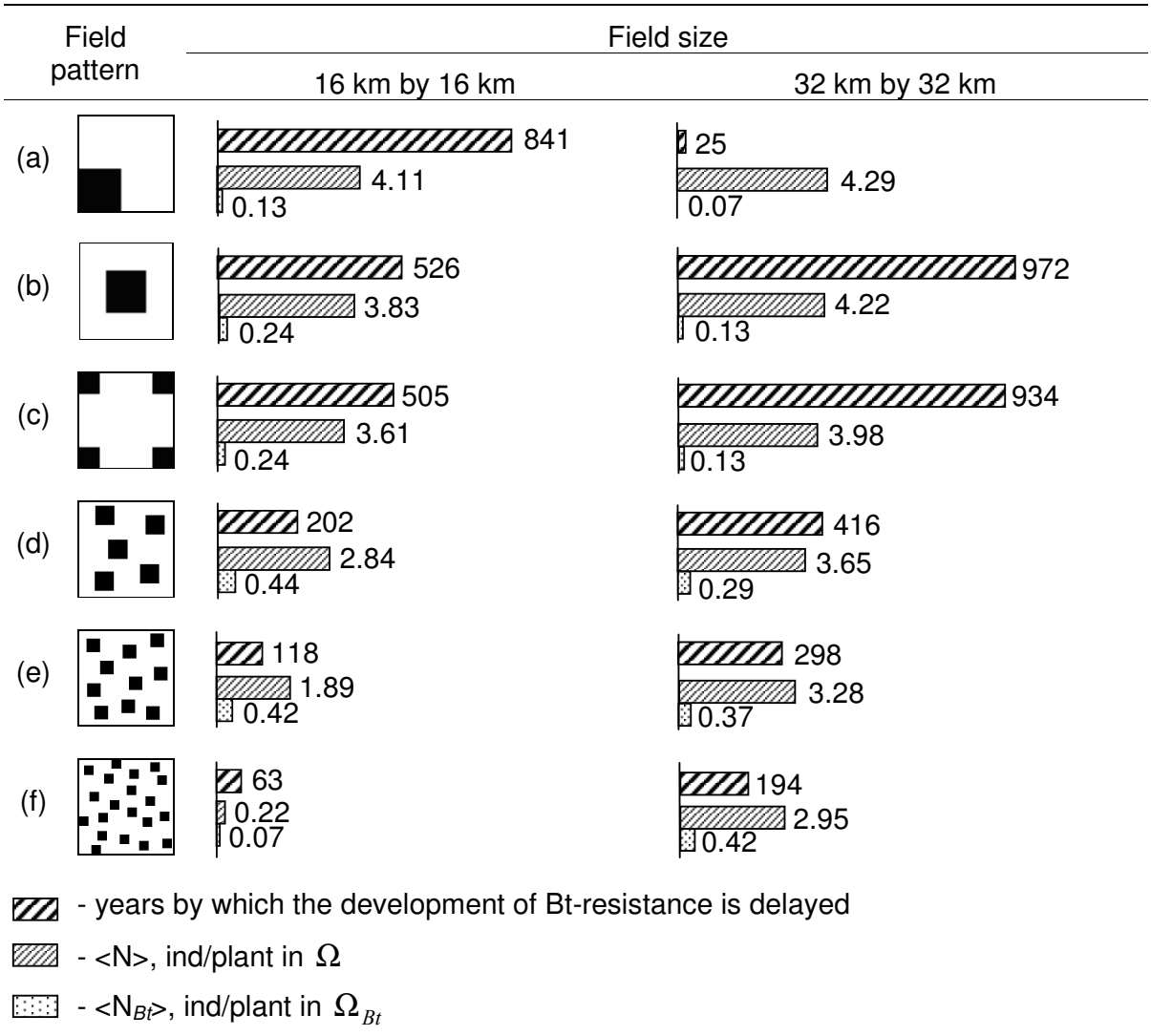


Fig. 2.17. Time T_{10} (years) required for the frequency of the resistance allele to reach 10% over the whole farming area Ω and the levels of ECB invasion (ind/plant) of the whole maize area and the Bt area, with $p_r < 0.1$ (during T_{10}), in the demo-genetic diffusion model. The refuge area is shown in black and the Bt area is shown in white. Refuges account for 20% of total area for all patterns. Pest dispersal $\delta = 0.07\,\mathrm{km^2 yr^{-1}}$.

(Fig. 2.17b). In addition, the efficiency of patterns (b) and (c) in Fig. 2.17 virtually coincides.

Note that pest dispersal and field area are interrelated quantities. The diffusion coefficient δ can be normalised with respect to field size, if a decrease in δ is considered equivalent to an increase in field size. Thus, our conclusions concerning the maximal efficiency of aggregated refuges (Figs. 2.16a and 2.17a) depend on the fixed value of δ and/or field size. For analysing this dependence, we enlarged the total area of modelled habitat Ω in 4 times (see second columns in Figs. 2.16-17), keeping the proportion between refuge and Bt-field as 20% and 80%, respectively. In this case, those refuge patterns that were more effective with smaller field area (16 km by 16 km) demonstrate the significant reduction of time required for the Bt-adaptation of the ECB: from 646 and 841 to 23 and 24 years, respectively, for patterns in Figs. 2.16a and 2.17a. However, regarding time T_{10} the efficiency of other spatial refuge structures doubled and even tripled (Figs. 2.16 b-d,f and 2.17b-f) and for four-strip pattern (e) in Fig. 2.16 T_{10} increased almost in 10 times. At the same time, the level of ECB infestation decreased: for some patterns this characteristic became nearly two times less (Figs. 2.16 b,c,f and 2.17 b,c). Moreover, with the ECB habitat of 32 km by 32 km as well as with the habitat of 16 km by 16 km, model (2.32) predicts virtually the same efficiency of strip refuge patterns (b) and (c) in Fig. 2.16, which virtually coincides with the efficiency of pattern (a) for the habitat of 16 km by 16 km (Fig. 2.16). We also obtain the similar result with the square refuges (compare patterns (b) and (c) for the habitat of 32 km by 32 km and pattern (a) for the habitat of 16 km by 16 km in Fig. 2.17). Such fact of results congruence is not surprising and for the refuge patterns (b) and (c) in Figs. 2.16 and 2.17 it is entirely explained by the equivalence of location of these patterns within the Bt-field in regard to the same number and direction of diffusive density fluxes connecting a refuge and Bt-field in the habitat with reflective boundaries. Besides, refuge patterns (b) and (c) for the habitat of 32 km by 32 km virtually implement fourfold iteration of pattern (a) for

the habitat of 16 km by 16 km, since the intensity of the diffusion flux δ remained constant in all simulations.

It is evident that with larger farming area, at the regional scale for example, (or with a lower pest dispersal) the refuge patches (e.g., Figs. 2.16e,f and 2.17e,f) may delay Bt-resistance in the ECB population more efficiently than aggregated refuges (e.g., Figs. 2.16b-d and 2.17b-d).

In all simulations, the pest population was much smaller within the Bt area, but the density of the pest over the entire area of cultivated maize remained high, essentially due to high levels of ECB infestation in the refuge.

2.3.3 *Calculation of profit when using the "high dose-refuge" strategy for 1D habitat*

It follows from the above-considered problems (§ 2.3.2) that two introduced criteria evaluating the efficiency of the HDR strategy (time T_{10} taken to develop Bt-resistance and spatially averaged ECB density $\langle N \rangle$) are not enough to find optimal parameters of the best strategy. As shown in Table 2.1, it is impossible to simultaneously maximize the time T_{10} and minimize $\langle N \rangle$ because these goals are mutually exclusive: maximizing time T_{10} owing to the extension of the refuge, we enlarge the favourable region for the reproduction and development of the pest and thereby we enhance the total pest density within the whole farming area. The natural necessity to introduce the additional criterion appears. As such criterion we have chosen a profit on a sale of a harvest which could be reaped from the whole area over some period of time. The profit is evaluated as the total difference between proceeds from crop sale and costs including only purchase of seeds. Such formula is very simple as it does not take into account a list of other costs (for instance, technological expenses for field cultivation) and, thus, it may be considered as the first approximation to constructing the more complex function of profit (see, e.g., Hurley et al. 1999, 2001).

According to the common formula for calculation of Net Present Value (NPV), we propose a formula of profit evaluation as applied to our problem:

$$\Pi = \sum_{t=0}^{T} \left(V_Y Y - \left(V_{Bt} \Omega_{Bt} + V_{ref} \Omega_{ref} \right) \right) \frac{1}{(1+\rho)^t}, \tag{2.56}$$

where $Y = Y(N)$ is the function of maize yield harvested from the whole area Ω, N is the total density of pest population, V_Y is the market price of grain yield, V_{Bt} is the market price of Bt-seeds, V_{ref} is the market price of conventional (non-transgenic) seeds, Ω_{Bt} is the total area planted with Bt-crop, Ω_{ref} is the total area planted with conventional crop, ρ is the discount rate, T is the time period.

Using the simple logistic equation for the growth of plant resource consumed by pest with the Lotka–Volterra linear trophic function, we obtain a formula for evaluation of the yield Y:

$$R = b_R R \left(1 - \frac{R}{K_R} \right) - aNR \tag{2.57}$$

where R is the biomass of plant resource, b_R is the growth rate of plant biomass, K_R is the "carrying capacity" of plant resource; a is the searching efficiency of the pest.

Nontrivial equilibrium value of the plant biomass $R^* = K_R \left(1 - \frac{a}{b_R} N^* \right)$.

Without loss of generality, let coefficients a and b_R be 1. Then the yield function Y is:

$$Y = K_R (1 - N). \tag{2.58}$$

We estimated parameters in (2.56), (2.58). According to Benbrook (2001), average retail price of conventional seeds and Bt-seeds was 31.21 $ per acre and 40.76 $ per acre, respectively, in 2000, i.e., $V_{ref} = 7705.26\,\$/\mathrm{km}^2$, $V_{Bt} = 10063.02\,\$/\mathrm{km}^2$. The average market price of maize was 2.10 $ per bushel (Benbrook, 2001). Then $V_Y = 82.67\,\$/\text{tonne}$.

The potential grain yield of maize can reach 12.6 tonne/ha if the density of maize population is 6.7 plants/m^2 (Jacobs & Pearson 1991). In our measure units the carrying capacity of plant resource $K_R = 1260$ tonne km^{-2}.

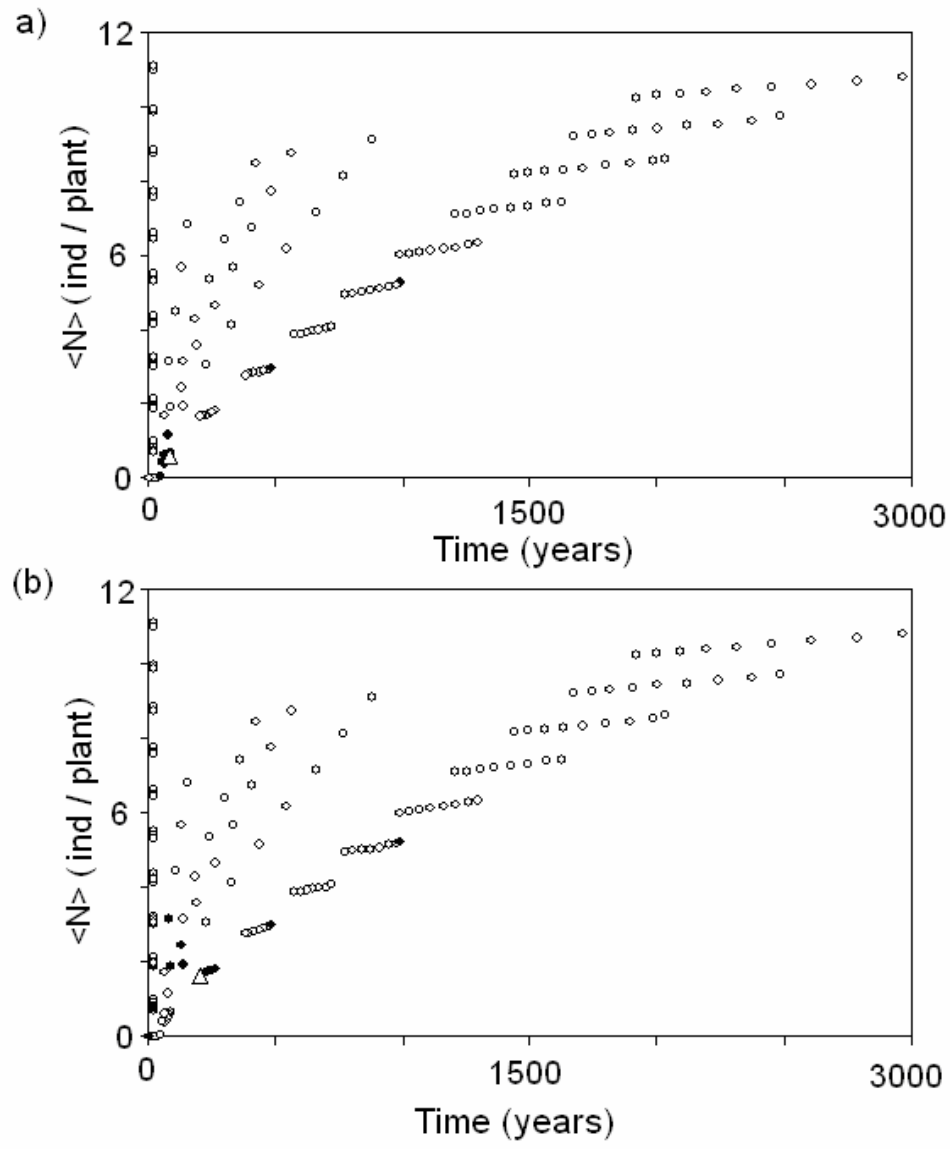


Fig. 2.18. A Pareto diagram for two criteria: time T_{10} (years) required for the frequency of the resistance allele to reach 10% over the whole farming area Ω and the levels of ECB invasion (ind/plant) of the whole maize area, with $p_r < 0.1$ (during T_{10}). (a) $\rho = 5.75\%$; (b) $\rho = 0$. The optimal refuge sizes Ω_{ref} which provide the maximum of profit Π with different fixed habitat sizes Ω are marked with black circles. The optimal parameters (Ω, Ω_{ref}) with respect to three criteria (T_{10}, <*N*>, Π) are marked with triangles.

The discount rate ρ on 28.03.2006 was 5.75% (Federal Reserve Bank of San Fransisco, http://www.frbsf.org/banking/data/discount/index.html).

Let $T = 100$ years. We fix one-strip refuge pattern presented in Fig. 2.19.

Let us consider three-criterial search problem of optimal combination of the pest habitat area and refuge percentage (Ω, Ω_{ref}). Note that the use of this optimising criteria maximizes the delay time of Bt-resistance development T_{10} and profit on a sale of maize yield Π and simultaneously minimizes the ECB infestation level <*N*> of the whole habitat Ω.

The result of multi-criterial analysis is presented in Pareto diagram (Fig. 2.18). Each point of the diagram is a result of the implementation of the HDR strategy with given refuge percentage and pest dispersal δ (in the previous section we discussed the correlation of δ with habitat size in details, see also Table 2.1). Refuge percentage varied from 0 to 30% with step 5%; the pest dispersal – from 0.001 to 5 km^2yr^{-1} with irregular step. The tradeoff between three criteria $(T_{10}, <N>, \Pi)$ is achieved at $\Omega = 15\,km \times 15\,km$ and $\Omega_{ref} = 5\%\Omega$ for $T_{10} = 86$ yr, $< N >= 0.58$ ind/plant and $\Pi = 15815\,\$/ha$ if $\rho = 0$ (triangle in Fig. 2.18a); at $\Omega = 61\,km \times 61\,km$ and $\Omega_{ref} = 10\%\Omega$ for $T_{10} = 205$ yr, $< N >= 1.64$ ind/plant and $\Pi = 86570\,\$/ha$ if $\rho = 5.75\%$ (triangle in Fig. 2.18b).

Discussion

In this section we have demonstrated that formal addition of a diffusion term into a classical population genetics model (Fisher-Haldane-Wright model) may lead to serious errors in forecasting the evolution of the genetic structure of a spatially distributed population. The source of this fallacy is clear. The Fisherian concept initially concerned species with an ecologically autonomous haplophase (Abrosov & Bogolyubov 1988). Application of such a model to population dynamics of diploid organisms implies a number of auxiliary conditions that would ensure panmictic reproduction, specifically, uniform spatial distribution of the population and absence of density fluxes. Nonetheless, the approach relying on

Fisherian diffusional models remains quite popular, and it has been used to describe the spatiotemporal dynamics of the Bt-resistance allele in pest populations (Lenormand & Raymond 1998; Vacher et al 2003; Cerda & Wright 2004; Tabashnik et al. 2004, 2005).

An alternative is the demo-genetic approach put forward by V.A. Kostitzin (1883–1963), a disciple of V.I. Vernadsky and an outstanding Russian mathematician, astrophysicist, and biophysicist. He was the first to recognize that the competition theory developed by Volterra for interaction between species can also be applied to interaction between genotypes in a diploid population (Kostitzin 1936, 1937, 1938a,b,c). This approach allows explicit description of the evolutionary selection of the fittest genotype as an immediate result of intraspecific competition. Regretfully, Kostizin's works (which were highly commended by Volterra, see preface in (Kostitzin 1937), p. 6-7) and, particularly, his criticism of the unjustified used of Fisherian frequency models, are now known into few (Bogolyubov 2002; Scudo & Ziegler 1976), though in Russia his demo-genetic approach was furthered by some authors (Svirezhev & Pasekov 1982 and also Abrosov & Bogolyubov 1988).

By contrast to the Fisherian frequency-based models, the Kostitzin model describes the population dynamics at the level of genotype densities and thus can most naturally be used in spatial reaction–diffusion modelling. We hope that this circumstance will attract the attention of researchers; which should be spurred by the currently growing interest in studies on spatially distributed ecosystems.

Local interaction of pest genotypes in the demo-genetic model (2.6) is described by Kostitzin equations that are somewhat modified according to the specific features of the modelled system; namely, genotype fitness is considered here in terms of larvae survival instead of genotype fertility (see details in § 2.1.2).

It should once again be stressed that the use of differential equations makes model (2.6) a continuous approximation of the processes of pest reproduction and succession of generations, which under clearly seasonal conditions are actually

discrete rather than continuous. However, since the model is intended exclusively for long-term forecasting, its continuity is a natural simplification that should be taken into account when interpreting the results.

An accurate transition of the initial density form (2.6) into the frequency form (2.32) reveals its basic distinction from the diffusional version of the Fisher-Haldane-Wright model: along with the diffusive propagation of allele frequency, the demo-genetic model considers a directed gene flux induced by the heterogeneity of the pest density distribution. This means that a Fisherian diffusional model would adequately describe the spatial gene dispersal in a diploid population only in the idealistic and unrealistic case of homogeneous total population density distribution throughout the entire farming area Ω that is heterogeneous owing to the HDR strategy application.

How large can be the influence of the advective term $2\delta\nabla p_r \cdot \nabla \ln N$ in (2.32) becomes obvious upon comparison of the simulation results obtained with the two models (Tables 2.1). With certain combinations of the refuge size and pest mobility, the HDR strategy modelled with coefficients of genotype fitness in (2.5) can delay the spread of Bt-resistance by hundreds and even thousands of years — an effect not nearly attainable with the diffusional version of Fisherian model (Table 2.1). The delays predicted by the demo-genetic model can easily explain why, despite the broad cultivation of transgenic maize over a decade in the USA and some other countries, no Bt-resistant homozygous ECB has yet been detected.

Thus, our quite simple demo-genetic model (2.6), unlike Fisherian, can reproduce and substantiate the efficacy of the refuge in delaying the evolution of pest resistance to the Bt crop.

Note that in all simulations, we used the initial frequency of the Bt-resistance gene in the ECB population $p_r^0 = 1.5\times10^{-3}$. This value is, at least, an order more than the observed value in the natural ECB populations (see Andow et al. 2000; Bourguet et al. 2003). With given p_r^0 and intermediate values of the diffusion coefficient, the Fisherian model predicts the Bt-resistance delay for 8-9

years (unlike several hundreds years in the demo-genetic model). However, the simple simulation test with two diffusional models (demo-genetic and Fisherian) with much lower initial frequency of the Bt-resistance allele $p_r^0 = 1.5\times10^{-6}$ also indicated the weak efficiency of the HDR strategy in the Fisher-Haldane-Wright model: $T_{10} = 23$ years with 20% refuge and $\delta = 0.1$ km^{2}yr^{-1} compared to 2221 years in the demo-genetic model. Thus, even with very low initial frequency of the Bt-resistance gene in the pest population and sufficiently large refuge, the diffusional Fisherian model cannot give the realistic prognosis regarding the rate of the Bt-resistance evolution.

The success of the HDR strategy is determined not just by the existence of a refuge for susceptible insects but by the intensity of their flux from the refuge onto the Bt-field, which provides for mating between Bt-resistant insects migrating from the Bt-field and the Bt-susceptible insects from the refuge, thereby decreasing the frequency of the resistance allele in every next generation. It is this flux that allows the system (2.6) to persist for a long time in the vicinity of an unstable spatially heterogeneous steady state corresponding to the absence of *rr* and *rs* genotypes (Fig. 2.15a) before transition to a stable homogeneous steady state $N_{ss}(x) = 0$; $N_{rs}(x) = 0$; $N_{rr}(x) = K$ (Fig. 2e). It is important that over this time throughout the field the spatial gradients of total density $N(x)$ and resistance gene frequency $p_r(x)$ are opposite (Fig. 2.19a), so the advective flux counteracts the growth of p_r because $2\delta\nabla p_r \cdot \nabla \ln N < 0$. As the ecological characteristics of all ECB genotypes are identical, in the refuge proper the *rr* genotype is simply outnumbered by the susceptible ones and thus completely displaced by competition. In the Bt area, especially at the refuge border, *rr* is suppressed by *ss* and *sr* coming from the refuge. Remarkably, as soon as the number of resistant homozygotes in the Bt area becomes large enough (Fig. 2.15b), the advective flux of gene frequency theretofore opposing its diffusive flow reverses its direction

(Fig. 2.19b) and promotes the spatial spread of the resistance allele (Fig. 2c-e) in the final stage of the transition process.

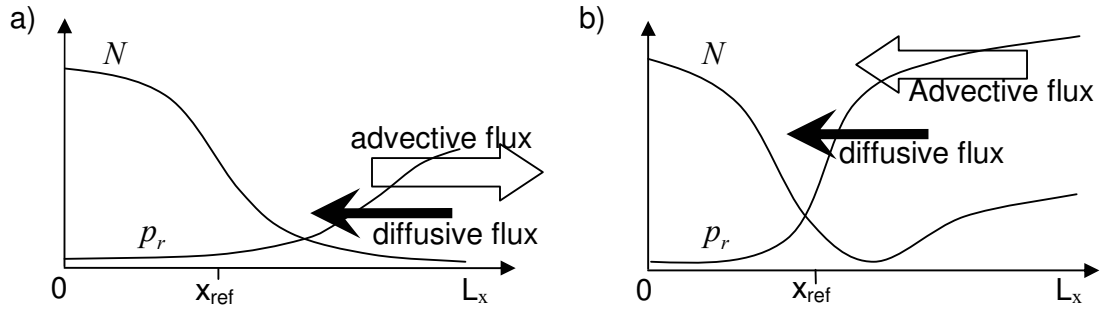


Fig. 2.19. Scheme of spatial distribution of frequency p_r and total density N in the demo-genetic model (2.32) in 1D habitat when (a) the density of resistant insects in the Bt-field is very low (≈ 0) and (b) the density of resistant insects in the Bt-field increased due to the spatial dispersal of the Bt-resistance gene in the pest population.

Thus, one of the key factors determining effectiveness of the refuge as a source of susceptible insects is the pest mobility. As already noted in analysis of Table 2.1, very low mobility does not ensure an efflux of susceptible genotypes that would be sufficient to overwhelm the resistant genotype in the Bt area. In this case, such weak diffusion simply subtracts from the *ss* density in the refuge, increasing the chances of its replacement by *rr* immigrants from the Bt area and thus *speeding up* the spread of resistance. Interestingly, refuge efficacy also declines when the pest mobility (i.e., diffusion exchange between refuge and Bt area) is infinitely high, resulting in system homogenization and panmixia. One can see that in both extreme cases the demo-genetic and the Fisherian models give similar prognoses (Table 2.1).

Another key factor determining the efficiency of the refuge is the refuge size. If refuges are too small, they are unable to delay the development of resistance for very long. The intensity of the diffusive density flux due to the spatial heterogeneity of the habitat acts as a negative force, resulting in sweeping out all susceptible individuals from the small refuge, increasing the probability of their replacement by Bt-resistant individuals invading from the Bt area. The results

presented in Table 2.1 with a 5% refuge, and also in Figs. 2.16 and 2.17 for $\Omega = 16$ km by 16 km illustrate our conclusions. The inefficiency of small refuges is related to the classical problem of a critical habitat size, below which populations spreading by diffusion cannot persist.

Although we consider here the demo-genetic processes occurring in the ECB population, the proposed model (2.6) and its frequency version (2.32) are universal and could be applied for explaining the evolutionary and spatial phenomena in any diploid population. The theoretical value of the model lies in its ability to reveal the role of spatial heterogeneity in maintaining genetic diversity in dispersing populations. The practical use of the results obtained with conceptual model offered here requires field observations and identification of the parameters for a particular agro-ecosystem. A most important factor determining the success of the HDR strategy is the diffusion coefficient δ, which is hard to specify. Evaluation of this parameter requires monitoring of large-scale movements of the pest density spots rather than rapid motion of adult moths; there are examples of such field studies (Sharov et al. 1995; Winder et al. 2005). Although we cannot really manipulate pest dispersal to increase the efficiency of the HDR strategy, our results suggest that the same goal could be achieved by controlling the size, proportion and spatial arrangement of Bt areas and refuges (Table 2.1, Figs. 2.16 and 2.17).

CHAPTER 3

BI-TROPHIC DEMO-GENETIC MODELS

3.1 Model "pest – parasitoid"

As reported above (see Introduction), some natural enemies of the European corn borer, for example, larval parasitoids *Macrocentrus grandii*, *Lydella thompsoni* and other, are the effective biological control agents of this pest. They are successfully used in many Integrated Pest Management programs (Charlet et al. 2002). However, the ability of parasitoids to control the ECB density in Bt-fields is a controversial point as their efficiency may be reduced due to the mass death of pest larvae which are the main feed of parasitoid larvae. This fact is supported by some laboratory studies (Bourguet et al. 2002; Venditti & Steffey 2003; Losey et al. 2004). In this case, refuges can be necessary not only for the struggle against the pest adaptation to Bt-toxin but also for maintaining the parasitoid population at the required level in the Bt-field owing to its migration from the refuge. Additionally, this strategy should lower the pest density throughout the entire farming area and is likely to delay the Bt-resistance development in the pest population longer than the autonomous use of the HDR strategy. For studying the effectiveness of combination of the HDR strategy and biocontrol by means of natural ECB parasitoid we developed a bi-trophic spatial demo-genetic model "pest – parasitoid".

3.1.1 *The model*

Let the trophic interaction between pest and its parasitoid be described by the simplest linear Lotka-Volterra function; the local kinetics of competing pest genotypes is given by the modified Kostitzin's model (see equations (2.2)). We also assume that both insects' species can move randomly within the modelled pest habitat Ω with reflective boundaries. Then the model is as follows:

$$
\begin{aligned}
&\frac{\partial N_{ss}}{\partial t} = W_{ss} f_{ss}(N_{ss}, N_{rs}, N_{rr}) - \frac{N_{ss}}{N} g(N)P + \delta \Delta N_{ss};\\
&\frac{\partial N_{rs}}{\partial t} = W_{rs} f_{rs}(N_{ss}, N_{rs}, N_{rr}) - \frac{N_{rs}}{N} g(N)P + \delta \Delta N_{rs};\\
&\frac{\partial N_{rr}}{\partial t} = W_{rr} f_{rr}(N_{ss}, N_{rs}, N_{rr}) - \frac{N_{rr}}{N} g(N)P + \delta \Delta N_{rr};\\
&\frac{\partial P}{\partial t} = eg(N)P - \mu_p P + \delta_p \Delta P,\\
&\nabla N_{ss} \cdot \mathbf{n} = \nabla N_{rs} \cdot \mathbf{n} = \nabla N_{rr} \cdot \mathbf{n} = \nabla P \cdot \mathbf{n} = 0, \quad \mathbf{x} \in \partial\Omega,
\end{aligned}
\tag{3.1}
$$

where $P = P(\mathbf{x}, t)$ is the parasitoid density at position $\mathbf{x} \in \Omega$ at time t; the functional response $g(N) = aN$ is considered as a Lotka-Volterra trophic function; a is the searching efficiency of parasitoid; e is the parasitoid conversion efficiency; μ_P и δ_P are the mortality rate and diffusion coefficient of parasitoid, respectively. The other parameters and variables in (3.1) are similar to those in (2.6). The reproduction function f_{ij} ($i, j = r$ or s) sets the proportions of progeny distribution over the three genotypes according to formulas (2.2). The HDR strategy is modelled by genotypic fitness W_{ij} defining the survival of larvae depending on the spatial localization (see formulas (2.5)).

Transiting to the frequency form, we get (see also the proofs of Lemma 1 and Theorem 4):

$$
\begin{aligned}
&\frac{\partial p_r}{\partial t} = bp_r(W_r - W) + \delta \Delta p_r + 2\delta \nabla \ln N \cdot \nabla p_r;\\
&\frac{\partial N}{\partial t} = N(bW - (\mu + \alpha N)) - g(N)P + \delta \Delta N;\\
&\frac{\partial P}{\partial t} = eg(N)P - \mu_p P + \delta_p \Delta P;\\
&p_s + p_r = 1,\\
&\nabla p_r \cdot \mathbf{n} = \nabla N \cdot \mathbf{n} = \nabla P \cdot \mathbf{n} = 0, \quad \mathbf{x} \in \partial\Omega,
\end{aligned}
\tag{3.2}
$$

where $W_r = W_{rs} p_s + W_{rr} p_r$, $W = W_{ss} p_s^2 + 2W_{rs} p_s p_r + W_{rr} p_r^2$. Meaning of parameters and variables in (3.2) is interpreted as in the frequency version of one-

level demo-genetic model (2.32). Note that the deviation of system from the Hardy-Weinberg equilibrium (1.1) is described by equation (2.33).

As in model (2.6), besides diffusion here we have directed fluxes of p_r with the advection velocity $-2\delta\nabla\ln N$ that are induced due to spatial heterogeneity of the total pest density N and allelic frequency p_r. Note also "conventional" bi-trophic Fisher-Haldane-Wright model is given by model (3.2) less the advective term $2\delta\nabla\ln N\cdot\nabla p_r$ in the balance equation for the allele frequency p_r.

3.1.2 *Estimation of demographic model parameters for the larval parasitoid Macrocentrus grandii*

For bi-trophic models (demo-denetic (2.32) and Fisherian) we additionally estimated parameters corresponding to the parasitoid species *Macrocentrus grandii* Goidanich. This polyembryonic wasp is a larval parasitoid of ECB.

The life history of the parasitoid *M. grandii* is characterized by 3 essential phases: internal, external and adult. The survival during the first 2 stages depends significantly on the daily temperature. According to Onstad & Kornkven (1999), the survival in the internal phase is 0.33 if the temperature is below 20°C and 1 otherwise; for the external phase, it is 0.90 if the temperature fluctuates from 18 to 25°C and 0.50 otherwise. All adults survive independently of temperature.

It is assumed that *M. grandii* as well as its host has two generations that are well synchronized with two generations of the ECB, i.e., the adult stage of this parasitoid concurs the preferential larval stages of the ECB. Such assumption does not contradict field observations (Orr & Pleasants 1995; Sked & Calvin2005). The development of the first parasitoid generation is considered to take place in the favourable temperature period 18-25°C while the second generation develops in colder period as it overwinters in the ECB diapausing larvae. Applying the same technique for estimating the model parameters in (2.32) as in model (2.6) (see § 2.1.5), we obtain the average instantaneous mortality rate of the parasitoid *M. grandii*: $\mu_P=\mu_{1P}\tau_{1P}+\mu_{2P}\tau_{2P}=1.91\,\mathrm{yr}^{-1}$, where $\mu_{1P}=\dfrac{-\ln(0.9)}{\tau_{1P}}$ is the mortality

of the first parasitoid generation, $\mu_{2P} = \dfrac{-\ln(0.33 \cdot 0.5)}{\tau_{2P}}$ is the mortality of the second parasitoid generation (see formulas (2.9), (2.10)).

In the USA the mean number of *Macrocentrus cingulum* Brichke (formerly *Macrocentrus grandii* Giodanich) per brood emerged from a single host is 16.4 individuals (Sked & Calvin 2005). Then the conversion coefficient is estimated as $e = 16.4\,\text{ind}^{-1}$.

As the efficiency of *M. grandii* significantly depends on the geographical location: in the northern France the level of parasitism does not exceed 5% (Bourguet et al. 2003; Agusti et al. 2005) but in the USA it can reach 45% with peak 61% (Sked and Calvin, 2005), we vary the percentage of parasitism from 0 to 75%.

In the ECB population the level of parasitism is defined via coefficient of searching efficiency of parasitoid, *a*. In order to set 25% parasitism level in model (2.32), the equilibrium value of the total ECB density N^* is set to 75% of the carrying capacity *K*: $N^* = 0.75K$. We obtain the equilibrium N^* from the simple Lotka-Volterra host-parasitoid model with the logistic growth of the host:

$$\frac{dN}{dt} = N(b - (\mu + \alpha N)) - g(N)P;$$
$$\frac{dP}{dt} = eg(N)P - \mu_p P.$$

Note that this model is a result of summation of the first three equations in (3.2) under the assumption that the entire pest habitat is a refuge, i.e., $\Omega = \Omega_{ref}$ (see also § 2.2.1).

Then $N^* = \dfrac{\mu_P}{ea} = 0.75K$ and $a = 1.05 \times 10^{-9}$ yr^{-1}km^2. We also set $a = 1.58 \times 10^{-9}$ yr^{-1}km^2 and $a = 3.16 \times 10^{-9}$ yr^{-1}km^2 that correspond to 50% and 75% levels of parasitism in the ECB population, respectively.

In simulations, we have been varying the diffusion coefficient of parasitoid δ_P under the assumption that parasitoid dispersal cannot be less than pest dispersal.

The other model parameters were estimated earlier (§ 2.1.5).

3.1.3 *Results of numerical simulations*

In order to investigate the efficiency of biocontrol in the ECB population whose density is controlled by transgenic maize, and adaptation to Bt-toxin is governed by the HDR strategy, we have carried out a series of simulations with bi-trophic demo-genetic model (3.2).

As in one-level model (2.32), the efficiency of the strategies combination is estimated by two criteria: (*i*) the time taken to develop Bt-resistance, evaluated as the time T_{10} required for the frequency of the resistance allele to reach 10% over the total ECB population; (*ii*) the spatially averaged ECB density <*N*>.

It is assumed that the initial densities of the pest $N^0 = 2.948\times10^6$ ind/km^2 and its parasitoid $P^0 = N^0/2$ are uniformly distributed in space. We set the initial frequency of the Bt-resistance allele $p_r^0 = 0.0015$. Let 0.3% of the initial pest population be Bt-susceptible heterozygotes *rs* and there are no Bt-resistant *rr* insects in the pest population.

Simulations indicated that with a single-strip refuge (Fig. 2.9b) in 1D area 16 km long, the biocontrol by means of parasitoids can increase the efficiency of refuges, additionally delaying the ECB adaptation to Bt-maize only if the pest is mobile enough (0.07, 1 km^{2}yr^{-1}) (Fig. 3.1c-f). With $\delta = 0.07$ km^{2}yr^{-1} and small refuges (less than 10% with $\delta_P = 2\delta$ and <18% with $\delta_P = 6\delta$), the higher the level of parasitism, the more effective the combination of two strategies, and, vice versa, when increasing the refuge size, the refuge efficiency decreases with growth of parasitism level (Fig. 3.1c,d). However, if the refuge is small, biocontrol very slightly increases the delay time T_{10} whereas with large refuge, the harmful effect of parasitoids lowering the ability of refuge to produce the Bt-susceptible insects

leads to the significant shortening of T_{10}. Note that in the absence of parasitoid in system (3.2) the autonomous application of the HDR strategy demonstrates a tendency: the higher the pest dispersal, the faster the Bt-resistance development in the ECB population (thick solid line in Fig. 3.1, see also Table 2.1).

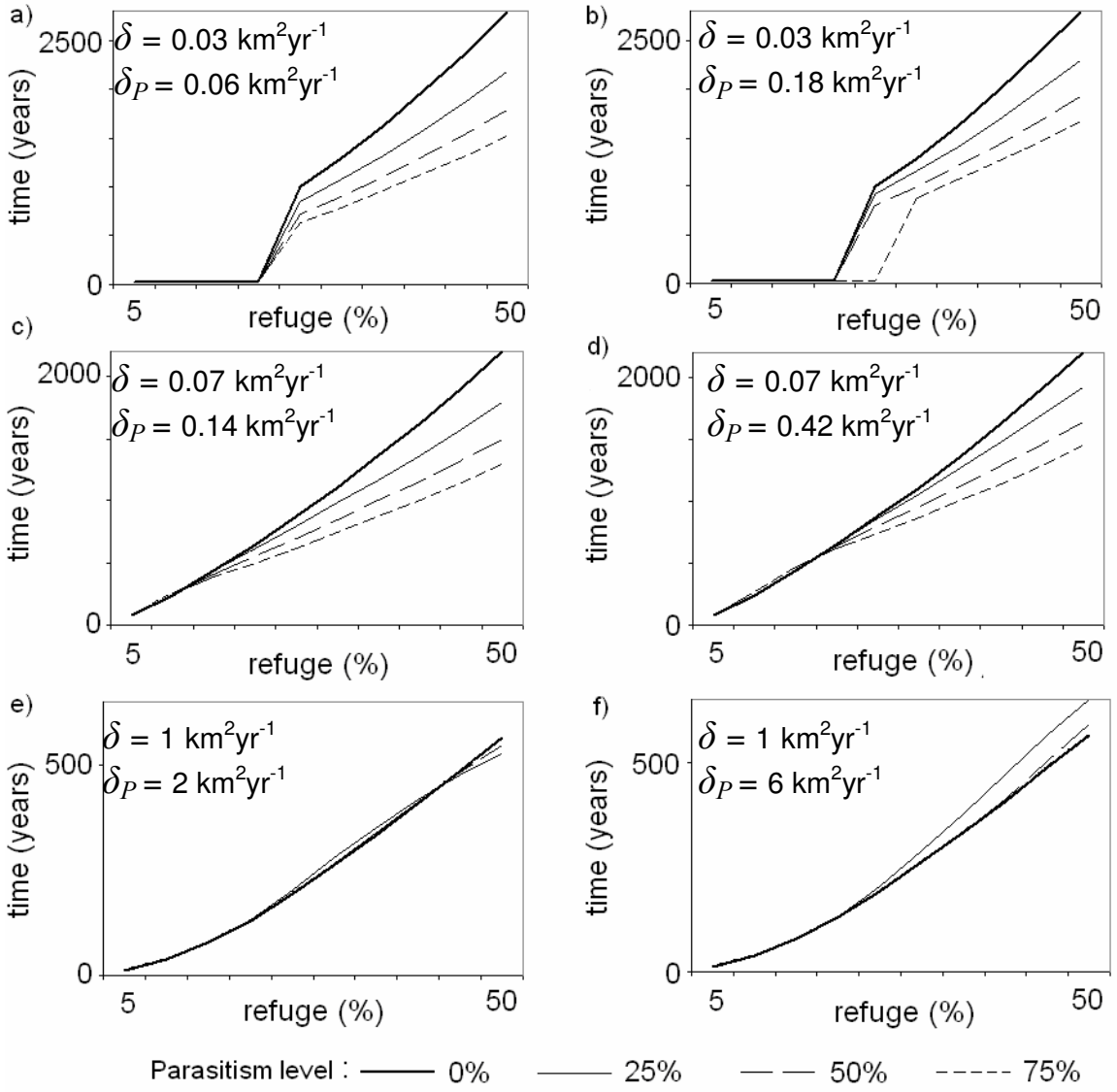


Fig. 3.1. Time T_{10} (years) required for the frequency of the resistance allele to reach 10% over the entire farming area Ω in the demo-genetic model (3.2) with different dispersals of pest δ and its parasitoid δ_P.

If the pest dispersal is high ($\delta = 1$ km^{2}yr^{-1}) for the given habitat size Ω, the presence of highly mobile parasitoid ($\delta_P = 6\delta$) in the biological system can significantly increase the refuge efficiency (Fig. 3.1f) provided that the refuge size

exceeds 20%. If $\delta = 1$ km^{2}yr^{-1} and the refuge size is small (less than 20%), the refuge efficiency does not depend on the parasitism level in the ECB population (Fig. 3.1e,f).

With very low pest mobility ($\delta = 0.03$ km^{2}yr^{-1}), the higher the level of parasitism, the faster the Bt-resistance adaptation of the ECB to Bt-maize (Fig. 3.1a,b). The maximum refuge efficiency is reached in the absence of parasitoid in system (3.2).

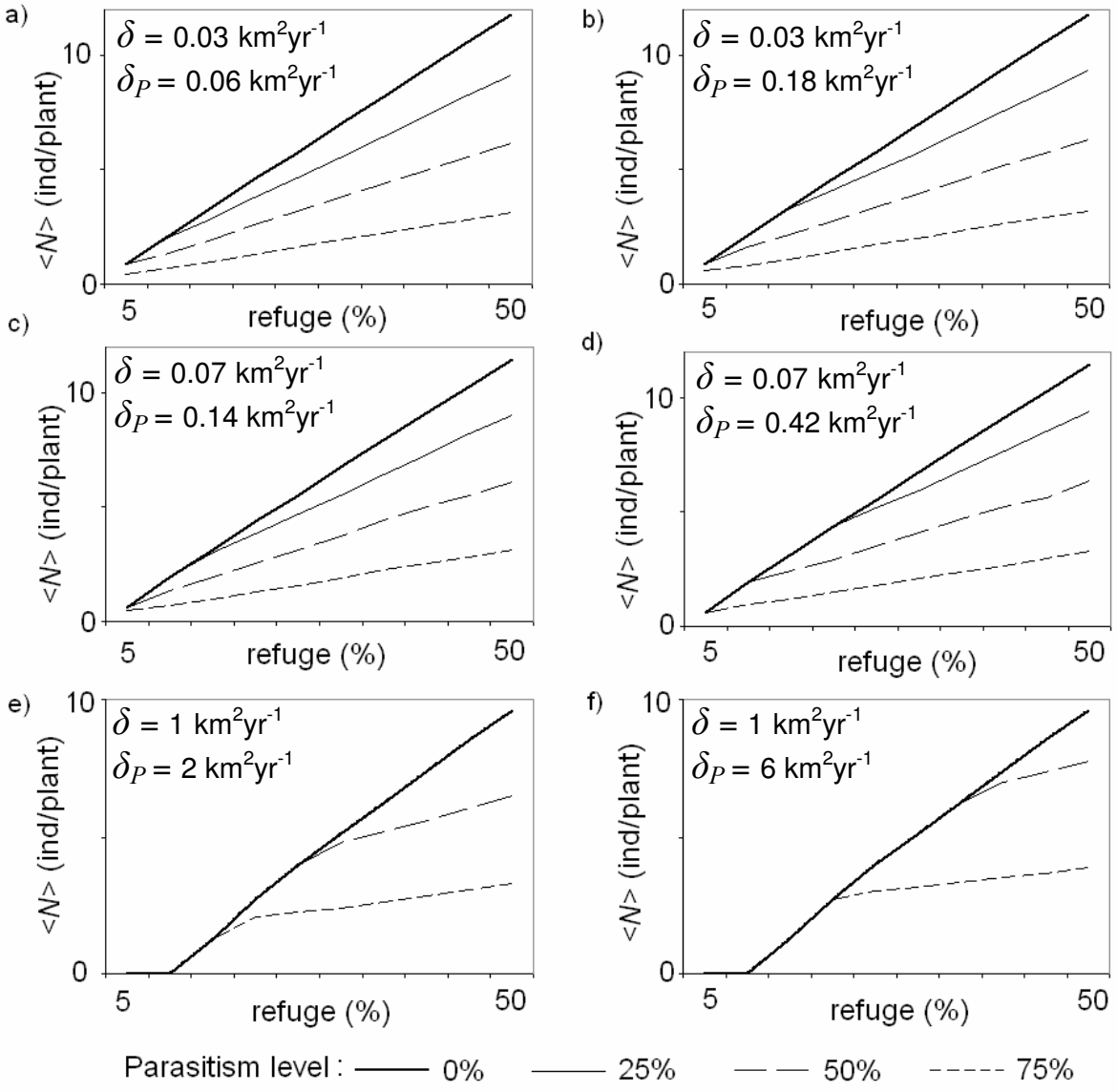


Fig. 3.2. Spatially averaged pest density, maintained in the ECB population throughout the entire habitat Ω as long as $p_r < 10\%$ in the demo-genetic model (3.2) with different dispersals of pest δ and its parasitoid δ_P.

According to the second criterion (spatially averaged pest density <*N*>), the high pest dispersal ($\delta = 1$ km^{2}yr^{-1}) influences negatively the efficiency of the combination of the HDR strategy with biocontrol by means of parasitoids (Fig. 3.2e,f): the low parasitism levels (less than 25%) cannot control the population of mobile insects while the high levels of parasitism provides a higher ECB invasion <*N*> than with less mobile pest ($\delta = 0.07$, 0.03 km^{2}yr^{-1}). Note that with $\delta = 0.03$ km^{2}yr^{-1} and $\delta = 0.07$ km^{2}yr^{-1}, one can see almost linear growth of <*N*> when increasing the refuge size (Fig. 3.2a-d). Nevertheless, with 75% level of parasitism, the combination of two management strategies decreases the mean density of the pest on average in 4 times as compared with results obtained with autonomous use of the HDR strategy and on average in 7 time regarding the carrying capacity (22 ind/plant). It is noteworthy that in each simulation the mean pest number per plant, in fact, signifies the mean invasion level of the refuge by the ECB since the values of <*N*> are close to zero in the Bt-field (in Ω_{Bt} the population density is strongly reduced due to the Bt-toxin and consumption of pests by parasitoid).

3.2 Model "crop – pest"

3.2.1 *The model*

Model (2.6) as well its equivalent (2.32), allows one to solve purposeful problems related to efficient and long-term pest control. Accounting for the spatio-temporal dynamics of the plant resource expands the applicability of the model and brings it closer to real agro-ecosystems.

Let the growth of plant (maize) biomass $R = R(\mathbf{x}, t)$ at position $\mathbf{x}$ at time t obey the logistic law. Also let the consumption of the biomass by the pest (ECB) be described by a trophic function $g(R)$ defining the individual rations. In the simplest case, $g(R) = aR$ is the Lotka–Volterra linear trophic function. Considering the genetic heterogeneity of the ECB population arising through selection pressure for Bt-resistance as well as the possibility of active diffusional

movements of the pest within the 1D habitat, we obtain a two-level demo-genetic model describing the dynamic processes of resource – pest interactions:

$$\begin{aligned}
&\frac{\partial R}{\partial t} = r_R R(1 - R/K_R) - aRN;\\
&\frac{\partial N_{ij}}{\partial t} = eaRf_{ij} - \mu N_{ij} + \delta \Delta N_{ij},\\
&\nabla N_{ij} \cdot \mathbf{n} = 0, \quad \mathbf{x} \in \Omega,
\end{aligned} \tag{3.3}$$

where $N = \sum N_{ij}$ $(i, j = r \text{ or } s)$; r_R is the Maltusian coefficient for plant biomass growth; K_R is the "carrying capacity" of the plant resource; a is the coefficient of the pest searching efficiency; e is the coefficient of the pest conversion efficiency; function f_{ij} sets the proportions of progeny distribution over the three genotypes and the survival of larvae depending on the spatial localization, as above in model (2.6):

$$\begin{aligned}
&f_{ss}(N_{ss}, N_{rs}, N_{rr}) = W_{ss} \frac{1}{N}\left(N_{ss} + \frac{N_{rs}}{2}\right)^2;\\
&f_{rs}(N_{ss}, N_{rs}, N_{rr}) = W_{rs} \frac{2}{N}\left(N_{ss} + \frac{N_{rs}}{2}\right)\left(\frac{N_{rs}}{2} + N_{rr}\right);\\
&f_{rr}(N_{ss}, N_{rs}, N_{rr}) = W_{rr} \frac{1}{N}\left(\frac{N_{rs}}{2} + N_{rr}\right)^2.
\end{aligned} \tag{3.4}$$

The other parameters and variables in (3.3) are similar to those in (2.6).

In the frequency form, we get:

$$\begin{aligned}
&\partial_t R = r_R R(1 - R/K_R) - aRN;\\
&\partial_t p_r = eaRp_r(W_r - W) + \delta \Delta p_r + 2\delta \nabla p_r \cdot \nabla \ln N;\\
&\partial_t N = N(eaRW - \mu) + \delta \Delta N;\\
&p_s + p_r = 1,\\
&\nabla p_r \cdot \mathbf{n} = \nabla N \cdot \mathbf{n} = 0, \quad \mathbf{x} \in \partial\Omega,
\end{aligned} \tag{3.5}$$

where $W_r = W_{rs} p_s + W_{rr} p_r$, $W = W_{ss} p_s^2 + 2W_{rs} p_s p_r + W_{rr} p_r^2$.

Note that the local kinetics term in the balance equation for the allele frequency p_r differs from the continuous form of the Fisherian equation in that the pest birth rate is not constant but depends on the individual rations $g(R) = aR$, increasing with the resource density as specified by the Lotka–Volterra function. In the absence of feed, the pest does not reproduce, and the local variations in p_r are caused solely by spatial flows. The deviation of (3.3) from the Hardy-Weinberg equilibrium is described by equation (2.33) where $b = eaR$.

As in model (2.6), besides diffusion here we have directed fluxes of allelic frequency p_r at the advection rate $-2\delta \nabla \ln N$ due to spatial heterogeneity of pest density and allelic frequency.

3.2.2 *Estimation of demographic model parameters for the maize*

For the two-level resource – pest model (3.3) we additionally estimated the biomass growth coefficient r_R, assuming for maize a biomass-doubling time of 10 days: $r_R = \frac{365}{10} \ln 2 = 25.3$ yr^{-1}, which agrees with the generalized literature data on the growth of dry above-ground plant mass and the average values observed for cereals (Kovalev 2003).

The yield of dry above-ground mass for maize may exceed 400 q/ha (quintal of 100 kg) (Kovalev 2003), we assumed a maximum of 500 q/ha. In our units of measurement, the carrying capacity in the plant resource is $K_R = 5 \cdot 10^4$ q km^{-2}.

We fit other model parameters so that the equilibrium value of plant biomass would be 60% of the capacity, $R^* = 0.6 K_R$.

The complete development of ECB larvae takes about one month. In this time the larvae can eat 10 times the pupal weight (ca. 5 g), i.e., nearly 50 g. Hence the conversion efficiency coefficient can be estimated at $e = 5$ q^{-1}.

The searching efficiency coefficient a is chosen so as to allow collation of models (2.6) and (3.3); namely, in (3.3) the pest growth eaR at functions f_{ij} in the

pest density equation should correspond to the birth rate b in (2.6). With $R^* = 0.6K_R$, we get $b = eaR^* = 0.6\,eaK_R$ or

$$a = \frac{b}{0.6eK_R} = \frac{9.94}{0.6 \cdot 5 \cdot 5 \cdot 10^4} = 66.27 \cdot 10^{-6} \text{ km}^2 \text{ yr}^{-1}.$$

3.2.3 *Results of numerical simulations*

For the resource – pest model, the initial density of the plant dry biomass was taken to be $R^0 = 1500$ q km^{-2}, also assuming uniform space distribution.

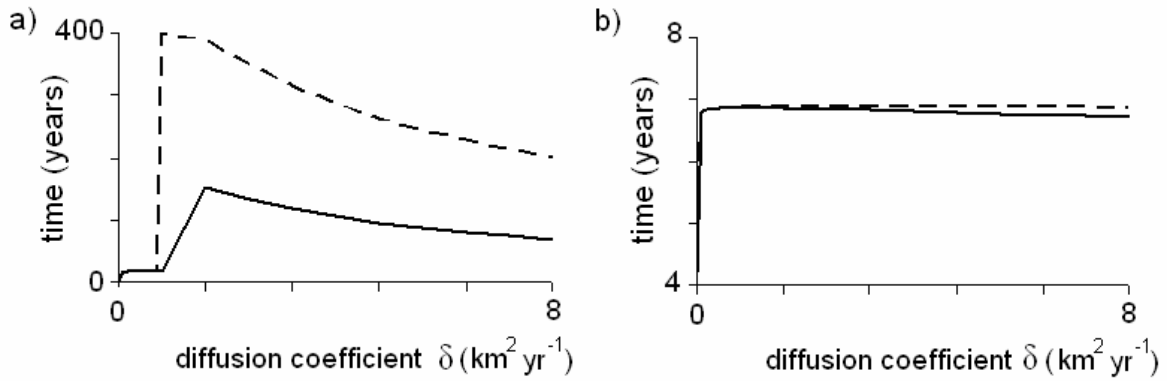


Fig. 3.3 Time T_{10} (years) required for the frequency of the resistance allele to reach 10% as a function of pest mobility δ predicted by (A): the bi-trophic demo-genetic model "resource – pest" (3.5) and (B) the diffusional model based on the Fisherian equations (model (3.5) without the advective term in equation for p_r) with 10% (solid line) and 20% (dashed line) single-strip refuge.

To assess the influence of the plant resource, we compared the delays predicted by our two-level demo-genetic model (3.5) and a two-level Fisher-Haldane-Wright diffusional model (corresponding to (3.5) without the advective term $2\delta \nabla p_r \nabla \ln N$, see above) with 10% and 20% refuge. Just as in simulations without the resource, the demo-genetic model predicts far longer times to Bt resistance evolution than the Fisherian model, as well as a dramatic jump of T_{10} followed by a monotonic decline with increasing pest mobility δ (Fig. 3.3). For complete mixing between the Bt and refuge areas, the two models give a similar outcome: quite quick (within 10 yr) spreading of the *rr* genotype in the pest population (not shown).

Discussion

Incorporation of an explicit description for the spatio-temporal dynamics of maize biomass in the demo-genetic model (3.3) allows account of the dependence of pest reproduction on the state of the plant resource, thereby making the model more realistic. The results of numerical simulations with (3.3) qualitatively agree with those for the basic model (2.6). This confirms the importance of considering the directed gene flux in the frequency form (3.5). Comparing Fig. 3.3 with the corresponding columns in Table 2.1, one can see that Bt-resistance in the two-level model (3.5) emerges somewhat faster than in (2.6). Indeed, in the Bt-field where infestation is largely suppressed by the Bt-toxin the density of maize biomass exceeds the equilibrium $R^* = 0.6K$. This raises the pest feeding rations so that its reproduction rate in (3.3) becomes higher than in (2.6). Recall that in (3.3) the pest reproduction intensity determines the rate of evolution of the population genetic structure, see (3.5). Probably the use of a more realistic trophic function accounting for saturation of the pest rations with increasing the available resource, e.g., a Holling type II function $g(R) = aR/(1 + ahR)$, would extend the delay T_{10}.

To bring the model closer to reality, one should perhaps also consider the seasonal events in the system, in particular, regular replanting and harvesting (see. e.g., Medvinsky et al. 2004). How can this influence the T_{10} estimates? On the one hand, any events resulting in periodic reduction of plant biomass and pest density, especially in the beginning of the crop year, should additionally delay the evolution of Bt-resistance. On the other hand, periodical homogenization of the system is likely to accelerate the spreading of the Bt-resistance gene. A definite answer awaits further studies.

Two-level model (3.1) and its equivalent (3.2) proposed in this chapter allow investigating another linear trophic chain “pest – parasitoid”. By means of simulations, we showed the dual effect of biocontrol in the ECB population whose density is controlled by transgenic maize, and adaptation to Bt-toxin is governed by the HDR strategy (Fig. 3.1 and 3.2). On the one hand, parasitoid can

significantly reduce the pest density throughout the entire habitat, thereby decreasing the damage of the maize crop (Fig. 3.2). On the other hand, due to the high toxicity of Bt-maize, almost zero density of the ECB in Bt-fields results in that the refuges rich in insects become the main feeding area of parasitoids and with time, cannot reproduce the sufficient number of Bt-susceptible insects to suppress the Bt-resistant subpopulation of the ECB in Bt-fields, thereby accelerating the ECB adaptation to Bt-maize (Fig. 3.1 a-d). It is clear that this situation will appear in those cases when the long-term application (>100 years) of the HDR strategy occurs, i.e., with moderate pest mobility. If the pest is highly mobile, the Bt-resistant insects shortly emerge in Bt-fields even with the HDR strategy application but they are attacked by parasitoids. Then if the subpopulation of Bt-susceptibles persists by that time at the level required to suppress the Bt-resistance gene in Bt-field, the combination of the HDR strategy and biocontrol delays Bt-adaptation of the ECB more efficiently than the HDR strategy applied separately.

Note that we did not investigate the efficiency of the two-level Fisherian model “pest – parasitoid” as in this model due to the absence of advective term $2\delta \nabla p_r \nabla \ln N$ the equation for p_r does not depend on the variable N the value of which is controlled by parasitoid. Therefore, the presence of parasitoid in the biological system will not influence the time of Bt-resistance development in the pest population.

CONCLUSIONS

1. Spatial demo-genetic model of resistance evolution to transgenic maize in the European corn borer population is developed. The mechanism of the “high dose – refuge” strategy is modelled;
2. The stability of stationary solutions for the demo-genetic model is investigated for one-dimensional habitat. It is proved analytically that spatial heterogeneity caused by refuges induces the advective flux of Bt-resistance genes, and this flux delays the diffusion dispersal of Bt-resistance genes in pest population;
3. The model dynamics is investigated numerically for various scenarios of the HDR strategy. It is examined the efficiency of the HDR strategy depending on the size and configuration of refuge and pest mobility;
4. Two-level demo-genetic model “plant resource – pest” that explicitly takes into account the dynamics of the plant biomass is developed. The long-term efficiency of the HDR strategy is studied numerically;
5. Two-level demo-genetic model “pest – parasitoid” that allows combining the HDR strategy with biological control by means of pest parasitoid is developed. It is investigated how the efficiency of combination of two strategies depends on the ECB dispersal and parasitism level.

APPENDIX 1

ABRIDGED DICTIONARY OF MAIN GENETIC TERMS

ALLELE (from Greek αλληλος each other) is one of the alternative forms of a gene occupying a given locus (position) on a chromosome. New alleles arise from existing ones by mutation. Diploid organisms have paired homologous chromosomes in their somatic cells, and these contain two copies of each gene. In a diploid organism two alleles make up the individual's genotype.

AUTOSOMAL is a non-sex.

CHROMOSOME is a threadlike linear strand of DNA and associated proteins in the nucleus of animal and plant cells; it carries the genes and functions in the transmission of hereditary information.

DIPLOID is having two sets of chromosomes or the double haploid number of chromosomes in the germ cell, with one member of each chromosome pair derived from the maternal gamete and one from the paternal gamete. A diploid individual is HOMOZYGOUS if the same allele is present twice, or HETEROZYGOUS if two different alleles are present.

DNA is a deoxyribonucleic acid. It is a nucleic acid that carries the genetic information in the cell and is capable of self-replication and synthesis of RNA (ribonucleic acid).

DOMINANCE is an expression of a trait in both the homozygous and the heterozygous condition.

DOMINANT ALLELE is a member of a pair of alleles which is phenotypically indistinguishable in both the homozygous and heterozygous condition.

GAMETE is a specialized germ cell that fuses with another gamete during fertilization (conception) in multicellular organisms that reproduce sexually. Gametes of a diploid organism are haploid cells; that is, they contain one complete set of chromosomes. When two gametes fuse (in animals typically involving a

sperm and an egg), they form a zygote — a cell that has two complete sets of chromosomes and therefore is diploid.

GENE is a hereditary unit consisting of a sequence of DNA that occupies a specific location on a chromosome and determines a particular characteristic in an organism. Genes undergo mutation when their DNA sequence changes.

GENETICS is the science of genes, heredity, and the variation of organisms.

GENOTYPE is a combination of alleles located on homologous chromosomes that determines a specific characteristic or trait.

HAPLOID is a term denoting an organism (e.g., virus or bacterium) or a cell (e.g., gametic) with haploid set of chromosomes.

HARDY-WEINBERG LAW (principle, equilibrium) is the equation that describes genetic balance within a population. It may be stated as follows: In a large, random-mating population, the proportion of dominant and recessive genes (*see* dominance and recessiveness) tends to remain constant from generation to generation unless outside forces act to change it. Forces that can disturb this natural balance are selection, mutation, gene flow, and natural selection.

HETEROZYGOTE is an organism that has different alleles at a particular gene locus on homologous chromosomes.

HOMOZYGOTE is an organism that has the same alleles at a particular gene locus on homologous chromosomes.

LOCUS is a position that a given gene occupies on a chromosome.

MEIOSIS is the process of cell division in sexually reproducing organisms that reduces the number of chromosomes in reproductive cells from diploid to haploid, leading to the production of gametes in animals and spores in plants

MENDELIAN INHERITANCE (or Mendelian genetics or Mendelism) is a set of primary tenets relating to the transmission of hereditary characteristics from parent organisms to their children.

MUTATIONS are the changes to the genetic material (either DNA or RNA). Mutations create variation in the gene pool, and the less favorable (or deleterious)

mutations are removed from the gene pool by natural selection, while more favorable (beneficial or advantageous) ones tend to accumulate, resulting in evolutionary change.

PANMIXIA is random mating within a breeding population. In a closed population this results in a high degree of uniformity. Complete panmixia is possible only in ideal, infinitely large and well mixed homogeneous populations.

POLYMORPHISM is a simultaneous coexistence of more than one genotype with non-zero frequency in a population.

RECESSIVENESS is a failure of one of a pair of genes (alleles) presented in an individual to express itself in an observable manner because of the greater influence, or dominance, of its opposite-acting partner. Both alleles affect the same inherited characteristic, but the presence of the recessive gene cannot be determined by observation of the organism; that is, though present in the organism's genotype (gene makeup), the recessive trait is not evident in its phenotype (observable characteristics).

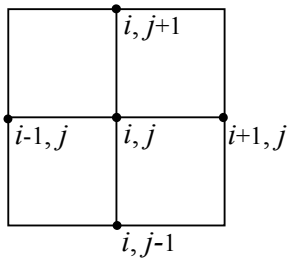
RECESSIVE GENE is a gene that is phenotypically expressed in the homozygous state but masked in the presence of a dominant gene.

ZIGOTE is a cell that is the result of fertilization (including the organism that develops from that cell). That is, two haploid cells (gametes)—usually (but not always) an ovum from a female and a sperm cell from a male—merge into a single diploid cell called the zygote.

APPENDIX 2

NUMERICAL SOLUTIONS OF THE DEMO-GENETIC MODEL IN THE DENSITY FORM (2.6) AND IN THE FREQUENCY FORM (2.32) FOR 2D HABITAT

We construct the differential-difference scheme for integration of systems (2.6) and (2.32) in the 2D case of area Ω, passing on to the grid approximation of models in space. Let the pest habitat be rectangle $\Omega = [0, L_x] \times [0, L_y]$. In area Ω we introduce the regular grid of intersecting lines $x_i = (i-1)h_x \quad (1 \le i \le n_x)$ and $y_j = (j-1)h_y \quad (1 \le j \le n_y)$, where $h_x = \dfrac{L_x}{n_x - 1}$ and $h_y = \dfrac{L_y}{n_y - 1}$ are the grid steps in the *x*- and *y*-directions, respectively. We use the conventional five-point stencil.



Each spatial derivative was approximated by the appropriate second-order central difference for each node. For some function $u = u(x, y, t)$ we adduce formulas that were applied for approximating the spatial derivatives in models (2.6) and (2.32):

(a) approximation of the first derivative in the internal points of Ω:

$$\frac{\partial u}{\partial x} = \frac{u^{i+1,j} - u^{i-1,j}}{2h_x}, \quad \frac{\partial u}{\partial y} = \frac{u^{i,j+1} - u^{i,j-1}}{2h_y}, \quad (1 < i < n_x, \quad 1 < j < n_y);$$

at the boundary ($i = 1$, $i = n_x$, $j = 1$, $j = n_y$): $\dfrac{\partial u}{\partial x} = \dfrac{\partial u}{\partial y} = 0$.

(b) approximation of the second derivative in the internal points of Ω:

$$\frac{\partial^2 u}{\partial x^2} = \frac{u^{i+1,j} - 2u^{i,j} + u^{i-1,j}}{h_x^2}, \quad \frac{\partial^2 u}{\partial y^2} = \frac{u^{i,j+1} - 2u^{i,j} + u^{i,j-1}}{h_y^2}, \quad (1 < i < n_x, \quad 1 < j < n_y),$$

at the boundary of ∂Ω:

$$i=1: \quad \frac{\partial^2 u}{\partial x^2}=\frac{2\left(u^{2,j}-u^{1,j}\right)}{h_x^2}; \qquad i=n_x: \quad \frac{\partial^2 u}{\partial x^2}=\frac{2\left(u^{n_x-1,j}-u^{n_x,j}\right)}{h_x^2};$$

$$j=1: \quad \frac{\partial^2 u}{\partial y^2}=\frac{2\left(u^{i,2}-u^{i,1}\right)}{h_y^2}; \qquad j=n_y: \quad \frac{\partial^2 u}{\partial y^2}=\frac{2\left(u^{i,n_y-1}-u^{i,n_y}\right)}{h_y^2}.$$

Thus, at the boundary of area Ω we used the method of the fictive point in the formulas of central difference: $u^{n_x+1,j}=u^{n_x-1,j}$, $u^{i,n_y+1}=u^{i,n_y-1}$.

Let us denote the values of functions in system (2.6) at grid nodes as $N_{ss}^{i,j}(t)=N_{ss}\left(x_i,y_j,t\right)$, $N_{rs}^{i,j}(t)=N_{rs}\left(x_i,y_j,t\right)$, $N_{rr}^{i,j}(t)=N_{rr}\left(x_i,y_j,t\right)$ and in system (2.32) $p_r^{i,j}(t)=p_r\left(x_i,y_j,t\right)$, $N^{i,j}(t)=N\left(x_i,y_j,t\right)$, $\xi^{i,j}(t)=\xi\left(x_i,y_j,t\right)$.

According to the approximation formulas adduced above, we obtain a differential-difference scheme for integration of system (2.6) for *ss* genotype, that is a system of ordinary differential equations:

$$\frac{dN_{ss}^{i,j}}{dt}=W_{ss}f_{ss}^{i,j}-\alpha N_{ss}^{i,j}N^{i,j}-\mu N_{ss}^{i,j}+$$
$$+\delta\left(\frac{N_{ss}^{i+1,j}-2N_{ss}^{i,j}+N_{ss}^{i-1,j}}{h_x^2}+\frac{N_{ss}^{i,j+1}-2N_{ss}^{i,j}+N_{ss}^{i,j-1}}{h_y^2}\right), \quad (A2.1)$$

$1<i<n_x, \quad 1<j<n_y,$

where $f_{ss}^{i,j}=f_{ss}\left(N_{ss}^{i,j},N_{rs}^{i,j},N_{rr}^{i,j}\right)$ (see formulas 2.2). Similarly, we can get the difference equations for *rs* and *rr* genotypes. At the boundary points of Ω we substitute the appropriate difference approximations.

Differential-difference scheme for integration of system (2.32) in the internal grid nodes ($1<i<n_x, \quad 1<j<n_y$) is:

$$\frac{dp_r^{i,j}}{dt} = bp_r^{i,j}\left(W_r^{i,j} - W^{i,j}\right) +$$
$$+ \delta\left(\frac{p_r^{i+1,j} - 2p_r^{i,j} + p_r^{i-1,j}}{h_x^2} + \frac{p_r^{i,j+1} - 2p_r^{i,j} + p_r^{i,j-1}}{h_y^2}\right)$$
$$+ 2\delta\frac{1}{N^{i,j}}\left(\frac{p_r^{i+1,j} - p_r^{i-1,j}}{2h_x}\frac{N^{i+1,j} - N^{i-1,j}}{2h_x} + \frac{p_r^{i,j+1} - p_r^{i,j-1}}{2h_y}\frac{N^{i,j+1} - N^{i,j-1}}{2h_y}\right);$$

$$\frac{dN^{i,j}}{dt} = N^{i,j}\left(bW^{i,j} - \left(\mu + \alpha N^{i,j}\right)\right)$$
$$+ \delta\left(\frac{N^{i+1,j} - 2N^{i,j} + N^{i-1,j}}{h_x^2} + \frac{N^{i,j+1} - 2N^{i,j} + N^{i,j-1}}{h_y^2}\right);$$

$$\frac{\partial\xi^{i,j}}{\partial t} = b\left(\left(1 - p_r^{i,j}\right)^2\left(p_r^{i,j}\right)^2\left(W_{ss} + W_{rr} - 2W_{rs}\right) - \xi^{i,j}W^{i,j}\right) +$$
$$+ \delta\left(\frac{\xi^{i+1,j} - 2\xi^{i,j} + \xi^{i-1,j}}{h_x^2} + \frac{\xi^{i,j+1} - 2\xi^{i,j} + \xi^{i,j-1}}{h_y^2}\right)$$
$$+ 2\delta\frac{1}{N^{i,j}}\left(\frac{\xi^{i+1,j} - \xi^{i-1,j}}{2h_x}\frac{N^{i+1,j} - N^{i-1,j}}{2h_x} + \frac{\xi^{i,j+1} - \xi^{i,j-1}}{2h_y}\frac{N^{i,j+1} - N^{i,j-1}}{2h_y}\right) \quad \text{(A2.2)}$$
$$+ 2\delta\left(\left(\frac{p_r^{i+1,j} - p_r^{i-1,j}}{2h_x}\right)^2 + \left(\frac{p_r^{i,j+1} - p_r^{i,j-1}}{2h_y}\right)^2\right),$$

where $W_r^{i,j} = W_{rs}\left(1 - p_r^{i,j}\right) + W_{rr}p_r^{i,j}$,

$W^{i,j} = W_{ss}\left(1 - p_r^{i,j}\right)^2 + 2W_{rs}\left(1 - p_r^{i,j}\right)p_r^{i,j} + W_{rr}\left(p_r^{i,j}\right)^2$.

At the boundary points of Ω we substitute the appropriate difference approximations.

The obtained systems of ordinary differential equations (ODEs) was then integrated by the fourth-order Runge-Kutta method with automatic time step and accuracy control (see Kalitkin 1978). Note that excluding the advective term in scheme (A2.2) in the equation for p_r, we obtain the differential-difference scheme for integration of system in Fisher-Haldane-Wright model.

APPENDIX 3

A) NUMERICAL METHOD FOR FINDING THE SPATIALLY HETEROGENEOUS STATIONARY SOLUTIONS OF PROBLEM (2.6) IN 1D AREA

In order to find spatially heterogeneous stationary solutions of (2.6) in 1D habitat $\Omega = [0, L_x]$ consisting of two segments: refuge $[0, x_{ref}]$ and Bt-field $[x_{ref}, L_x]$ (Fig. 2.9b), the appropriate stationary boundary-value problem (2.39) was solved numerically. For solving (2.39) we used the shooting method, applying the same constructing scheme of solutions (2.39) as in proof of Theorem 7. Taking into account the sewing together of solutions at point x_{ref} (Fig. 2.11), we modified the shooting method in the following way. As the shooting parameters we took the genotype densities at the ends of habitat segment: $\beta_1^0 = N_{ss}(0)$, $\beta_2^0 = N_{rs}(0)$, $\beta_3^0 = N_{rr}(0)$, $\beta_1^{L_x} = N_{ss}(L_x)$, $\beta_2^{L_x} = N_{rs}(L_x)$, $\beta_3^{L_x} = N_{rr}(L_x)$, obtained by the simulation model at that moment when the spatially heterogeneous close to stationary regime was set at large *t*. Let us pass to the normal form of system (2.39):

$$
\begin{aligned}
&\dot{u}_1 = u_4;\\
&\dot{u}_2 = u_5;\\
&\dot{u}_3 = u_6;\\
&\dot{u}_4 = -\frac{1}{\delta}\left(W_{ss}\frac{b}{u}\left(u_1 + \frac{u_2}{2}\right)^2 - \alpha u_1 u - \mu u_1 \right);\\
&\dot{u}_5 = -\frac{1}{\delta}\left(W_{rs}\frac{2b}{u}\left(u_1 + \frac{u_2}{2}\right)\left(\frac{u_2}{2} + u_3\right) - \alpha u_2 u - \mu u_2 \right);\\
&\dot{u}_6 = -\frac{1}{\delta}\left(W_{rr}\frac{b}{u}\left(\frac{u_2}{2} + u_3\right)^2 - \alpha u_3 u - \mu u_3 \right),
\end{aligned}
\qquad \text{(A3.1)}
$$

where $\dot{u}_i = \dfrac{du_i}{dx}$, $u_1 = N_{ss}$, $u_2 = N_{rs}$, $u_3 = N_{rr}$, $u_4 = \dfrac{dN_{ss}}{dx}$, $u_5 = \dfrac{dN_{rs}}{dx}$, $u_6 = \dfrac{dN_{rr}}{dx}$, $u = u_1 + u_2 + u_3$.

Taking into account the boundary conditions (zero flux of genotype densities at the habitat boundary Ω) of (2.39), we expand the set of shooting parameters for (A3.1): $\beta_4^0 = \beta_5^0 = \beta_6^0 = 0$, $\beta_4^{L_x} = \beta_5^{L_x} = \beta_6^{L_x} = 0$. Note that this parameter values are strictly fixed. Using shooting method, we select only 6 parameters: β_1^0, β_2^0, β_3^0, $\beta_1^{L_x}$, $\beta_2^{L_x}$, $\beta_3^{L_x}$.

According to the constructing scheme of solutions (2.39) described in the proof of Theorem 7, we considered problem (A3.1) on each segment, $[0, x_{ref}]$ and $[x_{ref}, L_x]$, separately. Thus, the boundary-value problem (2.39) was reduced to two Cauchy problems for the system of differential equations (A3.1) with initial conditions β_i^0 on $[0, x_{ref}]$ and $\beta_i^{L_x}$ on $[x_{ref}, L_x]$ ($i = 1,...,6$). Then each of the Cauchy problems was integrated by the fourth-order Runge-Kutta method with automatic step in x-direction with consideration of integration direction (positive direction on $[0, x_{ref}]$ and negative one on $[x_{ref}, L_x]$). The values of shooting parameters were chosen so that to satisfy the boundary conditions of problem (2.39). However, it is not sufficient in order to the solutions of Cauchy problems for (A3.1) coincided at point x_{ref}, i.e., in general, $u_i^*(\boldsymbol{\beta}^0)\big|_{x=x_{ref}} \neq u_i^*(\boldsymbol{\beta}^{L_x})\big|_{x=x_{ref}}$ ($i = 1,...,6$). Using Newton's method, we have been changing the shooting parameters on each of the segment ends $[0, L_x]$ until we got values for which $u_i^*(\boldsymbol{\beta}^0)\big|_{x=x_{ref}} - u_i^*(\boldsymbol{\beta}^{L_x})\big|_{x=x_{ref}} \approx 0$ with prescribed accuracy.

In fact, we need to solve a system of 6 nonlinear equations with 6 unknown β_i^0 and $\beta_i^{L_x}$ ($i = 1,...,3$):

$$\mathbf{F}(\boldsymbol{\beta}) = 0, \qquad \text{(A3.2)}$$

where vector $F_i(\boldsymbol{\beta}) = u_i^*(\boldsymbol{\beta}^0) - u_i^*(\boldsymbol{\beta}^{L_x})$ $(i = 1,...,6)$,

$\boldsymbol{\beta} = (\beta_1^0, \beta_2^0, \beta_3^0, 0, 0, 0, \beta_1^{L_x}, \beta_2^{L_x}, \beta_3^{L_x}, 0, 0, 0)$.

We find the solution of system (A3.2) by the Newton's method. For this purpose, we estimate the next approximation of shooting parameters at each *k*-th iteration, solving the auxiliary linear problem by Gauss method: $\mathbf{F}'(\boldsymbol{\beta}^k)(\boldsymbol{\beta}^{k+1} - \boldsymbol{\beta}^k) = -\mathbf{F}(\boldsymbol{\beta}^k)$, where $\mathbf{F}'(\boldsymbol{\beta}) = \left\| \frac{\partial F_i}{\partial \beta_j} \right\|$. The exit condition of iterative process is $\left\| \boldsymbol{\beta}^{k+1} - \boldsymbol{\beta}^k \right\| < \varepsilon$.

Such method allows finding the spatially heterogeneous stationary solutions of problem (2.6) in one-dimensional area $\Omega = [0, L_x]$ (Fig. 2.9b) with fixed refuge percentage (i.e., with fixed segment length $[0, x_{ref}]$). In order to construct such solutions for the whole range of refuge percentage (0 to 100%), we use one-parameter continuation method:

Step 1: Using shooting method, we find the solution of system (2.39) with some arbitrary refuge percentage. At this step, the initial shooting parameters $\boldsymbol{\beta}$ were obtained by simulation model when the spatial close to stationary regime was set ($t >> 1$).

Step 2: Varying the refuge percentage (increasing or decreasing) with a small step (e.g., 1%), we find the solution of system (2.39) with new value of the refuge percentage, using the shooting method. However, here the initial shooting parameters are the values of $\boldsymbol{\beta}$ obtained as the solution of system (A3.2) at the previous Step.

We continue the process (Step 2) until we find all existing spatially heterogeneous stationary solitions of (2.39) in $\Omega = [0, L_x]$.

B) STABILITY ANALYSIS FOR STATIONARY STATES OF DEMO-GENETIC MODEL (2.6) IN 1D AREA

Numerical stability analysis of stationary states of model (2.6) in one-dimensional area $\Omega = [0, L_x]$ the part of which is refuge (Fig. 2.9b) has been carried out by programms written in Matlab 7.0 and allowing to find numerically the eigenvalues of Jacobian of system (2.6) and to show their location on the complex plane.

Let $\mathbf{u}$ be a vector with $3n_x$ elements: $u_i = N_{ss}(x_i)$ $(i = 1,...,n_x)$, $u_i = N_{rs}(x_i)$ $(i = n_x + 1,...,2n_x)$ and $u_i = N_{rr}(x_i)$ $(i = 2n_x + 1,...,3n_x)$. n_x is the number of points of a regular partition of segment $[0, L_x]$. Jacobian of system (2.6) in 1D area is calculated by the differential-difference scheme (A2.1), rewritten in new variables u_i for segment $[0, L_x]$. Without loss of generality, for $n_x = 4$ Jacobian is:

$$
\left(\begin{array}{cccc|cccc|cccc}
f_{1,1}+d_{1,1} & d_{1,2} & & & f_{1,5} & & & & f_{1,9} & & & \\
d_{2,1} & f_{2,2}+d_{2,2} & d_{2,3} & & & f_{2,6} & & & & f_{2,10} & & \\
 & d_{3,2} & f_{3,3}+d_{3,3} & d_{3,4} & & & f_{3,7} & & & & f_{3,11} & \\
 & & d_{4,3} & f_{4,4}+d_{4,4} & & & & f_{4,8} & & & & f_{4,12} \\
\hline
f_{5,1} & & & & f_{5,5}+d_{5,5} & d_{5,6} & & & f_{5,9} & & & \\
 & f_{6,2} & & & d_{6,5} & f_{6,6}+d_{6,6} & d_{6,7} & & & f_{6,10} & & \\
 & & f_{7,3} & & & d_{7,6} & f_{7,7}+d_{7,7} & d_{7,8} & & & f_{7,11} & \\
 & & & f_{8,4} & & & d_{8,7} & f_{8,8}+d_{8,8} & & & & f_{8,12} \\
\hline
f_{9,1} & & & & f_{9,5} & & & & f_{9,9}+d_{9,9} & d_{9,10} & & \\
 & f_{10,2} & & & & f_{10,6} & & & d_{10,9} & f_{10,10}+d_{10,10} & d_{10,11} & \\
 & & f_{11,3} & & & & f_{11,7} & & & d_{11,10} & f_{11,11}+d_{11,11} & d_{11,12} \\
 & & & f_{12,4} & & & & f_{12,8} & & & d_{12,11} & f_{12,12}+d_{12,12}
\end{array}\right) \qquad \text{(A3.3)}
$$

where $f_{i,j} = \dfrac{\partial f_i}{\partial u_j}$ $(i, j = 1,...,3n_x)$:

$$f_k = W_{ss}\frac{b}{U}\left(u_k + \frac{u_{k+n_x}}{2}\right)^2 - \alpha u_k U - \mu u_k;$$

$$f_{k+n_x} = W_{rs}\frac{2b}{U}\left(u_k + \frac{u_{k+n_x}}{2}\right)\left(\frac{u_{k+n_x}}{2} + u_{k+2n_x}\right) - \alpha u_{k+n_x} U - \mu u_{k+n_x};$$

$$f_{k+2n_x} = W_{rr}\frac{b}{U}\left(\frac{u_{k+n_x}}{2} + u_{k+2n_x}\right)^2 - \alpha u_{k+2n_x} U - \mu u_{k+2n_x};$$

$$U = u_k + u_{k+n_x} + u_{k+2n_x}, \quad k = 1,...,n_x;$$

$d_{i,j} = \dfrac{\partial d_i}{\partial u_j}$, d_i is the approximation of diffusion terms in (2.6) by the central differences $(i, j = 1,...,3n_x)$;

$$d_{k,k} = d_{k+n_x,k+n_x} = d_{k+2n_x,k+2n_x} = -2\frac{\delta}{h_x^2}; \quad 1 \le k \le n_x$$

$$d_{1,2} = d_{1+n_x,2+n_x} = d_{1+2n_x,2+2n_x} = d_{n_x,n_x-1} = d_{2n_x,2n_x-1} = d_{3n_x,3n_x-1} = 2\frac{\delta}{h_x^2};$$

$$d_{k,k+1} = d_{k+n_x,k+1+n_x} = d_{k+2n_x,k+1+2n_x} =$$

$$= d_{k,k-1} = d_{k+n_x,k-1+n_x} = d_{k+2n_x,k-1+2n_x} = \frac{\delta}{h_x^2}; \quad 1 < k < n_x.$$

Substituting the stationary solutions of system (2.6) into Jacobian (A3.3), we find its eigenvalues for each solution. Note that the spatially heterogeneous stationary solutions of (2.6), the finding algorithm of which is described in details in Appendix 3A, were obtained by the fourth-order Runge-Kutta method with automatic step in x-direction, i.e., with irregular step by x. For the correct substitution of such stationary solution into Jacobian, we interpolated it by the cubic spline, using the regular grid with n_x nodes.

For analysing the stability of spatially heterogeneous stationary solutions of (2.6) such that $N_{ss}(x)=N_{rs}(x)=0$, $N_{rr}(x)=\frac{bW_{rr}-\mu}{\alpha}$ the following Matlab 7.0 script has been used:

```
clear all;
b=1, delta=0.001; mu=0.688129, alpha=0.311871;
survBt=[0 0.09 0.9], survRef=[1 0.98 0.9],
N=100; L=50, h=L/(N-1),step=10; k=1;


% spatially homogeneous stationary solution
for i=1:N,
    u(i)=0;
    u(i+N)=0;
    u(i+2*N)=(b*0.9-mu)/alpha;
end

% cycle by diffusion
while delta<=100,
    g=zeros(N*3);
    % segment boundary j=1
    for i=1:3,
        g(1+(i-1)*N,1+(i-1)*N)=-2*delta/h^2;
        g(1+(i-1)*N,2+(i-1)*N)=2*delta/h^2;
    end
    % segment boundary j=N
    for i=1:3,
        g(N+(i-1)*N,N+(i-1)*N)=-2*delta/h^2;
        g(N+(i-1)*N, N-1+(i-1)*N)=2*delta/h^2;
    end
    % internal points of segment 1<j<N
    for i=2:N-1,
     for j=1:3,
       g(i+(j-1)*N,i+1+(j-1)*N)=delta/h^2;
       g(i+(j-1)*N,i+(j-1)*N)=-2*delta/h^2;
       g(i+(j-1)*N,i-1+(j-1)*N)=delta/h^2;
     end
    end

    % cycle by refuge percentage iRef
    for iRef=0:100,
        flag=0;
        for i=1:3, W(i)=survRef(i); end
        Pref=iRef*N/100;
        f=g;

        % fill in the Jacobian matrix
        for i=1:N,
           if (flag==0)
             if (Pref<i) for j=1:3, W(j)=survBt(j); flag=1; end
             end
           end

            f(i,i)=f(i,i)+2*W(1)*b*(u(i)+1/2*u(i+N))/(u(i)+u(i+N)+u(i+2*N))-
                   W(1)*b*(u(i)+1/2*u(i+N))^2/(u(i)+u(i+N)+u(i+2*N))^2-mu-
                   alpha*(u(i)+u(i+N)+u(i+2*N))-alpha*u(i);

            f(i,i+N)=f(i,i+N)+W(1)*b*(u(i)+1/2*u(i+N))/(u(i)+u(i+N)+u(i+2*N))-
```

```
                W(1)*b*(u(i)+1/2*u(i+N))^2/(u(i)+u(i+N)+u(i+2*N))^2-alpha*u(i);

            f(i,i+2*N)=f(i,i+2*N)-W(1)*b*(u(i)+1/2*u(i+N))^2/
                       (u(i)+u(i+N)+u(i+2*N))^2-alpha*u(i);

            f(i+N,i)=f(i+N,i)+2*W(2)*b*(1/2*u(i+N)+u(i+2*N))/(u(i)+u(i+N)+u(i+2*N))-
                     2*W(2)*b*(u(i)+1/2*u(i+N))*(1/2*u(i+N)+u(i+2*N))/
                     (u(i)+u(i+N)+u(i+2*N))^2-alpha*u(i+N);

            f(i+N,i+N)=f(i+N,i+N)+W(2)*b*(1/2*u(i+N)+u(i+2*N))/(u(i)+u(i+N)+u(i+2*N))+
                       W(2)*b*(u(i)+1/2*u(i+N))/(u(i)+u(i+N)+u(i+2*N))-
                       2*W(2)*b*(u(i)+1/2*u(i+N))*(1/2*u(i+N)+u(i+2*N))/
                       (u(i)+u(i+N)+u(i+2*N))^2-mu
                       -alpha*(u(i)+u(i+N)+u(i+2*N))-alpha*u(i+N);

            f(i+N,i+2*N)=f(i+N,i+2*N)+2*W(2)*b*(u(i)+1/2*u(i+N))/(u(i)+u(i+N)+u(i+2*N)
                         )-2*W(2)*b*(u(i)+1/2*u(i+N))*(1/2*u(i+N)+u(i+2*N))/
                         (u(i)+u(i+N)+u(i+2*N))^2-alpha*u(i+N);

            f(i+2*N,i)=f(i+2*N,i)-W(3)*b*(1/2*u(i+N)+u(i+2*N))^2/
                       (u(i)+u(i+N)+u(i+2*N))^2-alpha*u(i+2*N);

            f(i+2*N,i+N)=f(i+2*N,i+N)+W(3)*b*(1/2*u(i+N)+u(i+2*N))/(u(i)+u(i+N)+u(i+2*
                         N))-W(3)*b*(1/2*u(i+N)+u(i+2*N))^2/(u(i)+u(i+N)+u(i+2*N))^2-
                         alpha*u(i+2*N);

            f(i+2*N,i+2*N)=f(i+2*N,i+2*N)+2*W(3)*b*(1/2*u(i+N)+u(i+2*N))/(u(i)+u(i+N)+
                           u(i+2*N))-W(3)*b*(1/2*u(i+N)+u(i+2*N))^2/
                           (u(i)+u(i+N)+u(i+2*N))^2-mu
                           -alpha*(u(i)+u(i+N)+u(i+2*N))-alpha*u(i+2*N);

        end % end for

        E=eig(f);

        maxEV(k,iRef+1)=max(E);
        minEV(k,iRef+1)=min(E);

    end % end of cycle by iRef

    k=k+1;
    delta=delta*step;

end; % end of cycle by diffusion

x=0:100;
% results (maximum eigenvalues for each stationary solution)
for i=0:100,
    EV1(i+1)=maxEV(1,i+1);
    EV2(i+1)=maxEV(2,i+1);
    EV3(i+1)=maxEV(3,i+1);
    EV4(i+1)=maxEV(4,i+1);
    EV5(i+1)=maxEV(5,i+1);
    EV6(i+1)=maxEV(6,i+1);
    EV7(i+1)=0;
end

plot(x,EV1,'-',x,EV2,'-',x,EV3,'-',x,EV4,'-',x,EV5,'-',x,EV6,'-',x,EV7),
```

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