



HAL
open science

Timing of pathogen adaptation to a multicomponent treatment

Romain Bourget, Loïc Chaumont, Natalia Sapoukhina

► **To cite this version:**

Romain Bourget, Loïc Chaumont, Natalia Sapoukhina. Timing of pathogen adaptation to a multicomponent treatment. 2012. hal-00700540v1

HAL Id: hal-00700540

<https://hal.science/hal-00700540v1>

Preprint submitted on 23 May 2012 (v1), last revised 19 Aug 2013 (v2)

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Timing of pathogen adaptation to a multicomponent treatment

R. Bourget^{1,2,*}, L. Chaumont¹, N. Sapoukhina²

¹ LAREMA, Département de Mathématiques, Université d'Angers, 2, Blvd Lavoisier
Angers Cedex 01, 49045, France

² INRA, IRHS, PRES UNAM, SFR QUASAV, Rue G. Morel F-49071 Beaucouze , France

² Université d'Angers, IRHS, PRES UNAM, SFR QUASAV, Blvd Lavoisier F-49071
Angers, France

² Agrocampus Ouest, IRHS, PRES UNAM, SFR QUASAV, Rue Le Nôtre F-40045
Angers, France

* E-mail: bourget@math.univ-angers.fr

Abstract

The rational use of multicomponent treatments such as multidrug therapies, combination vaccines/chemicals, and plants carrying multigenic resistance requires an understanding of pathogen adaptive dynamics. Here, we studied the rate of pathogen adaptation to a host population which was subjected to a multicomponent treatment. To describe the adaptive dynamics of a pathogen population spreading through a host population diversified by the treatment, we formulated and analyzed a stochastic model of pathogen dynamics based on a birth and death processes with mutations and migrations of individual pathogens. Our main finding is that stochastic migration process plays a key role in the estimation of the pathogen adaptation rate. In particular, taking the stochastic migration process into consideration in modelling pathogen adaptive dynamics alters the criteria for the critical proportion of the host treated in order to impede pathogen adaptation. Moreover, our results show that we should avoid identifying treatment durability with mutation cost, since its impact on the adaptation rate depends on the structure of the treatment-diversified host population and the pathogen migration rate. We also found that a multicomponent treatment can be durable, if it is not combined with intermediate treatments including only some of the components. Our model helps to elucidate the interplay between the treatment strategy used and the processes underlying pathogen adaptive dynamics. The model can be used for designing durable multicomponent treatment strategies that impede the evolution of harmful populations.

Author Summary

Multicomponent treatments are thought to be more durable, since pathogens have to accumulate numerous mutations to overcome them. A treatment deployment strategy can prolong the durability of the multicomponent treatment, since it can reduce the chances that a mutant pathogen will survive. To estimate treatment durability and to derive guidelines for designing sustainable deployment strategies for multicomponent treatments, we developed a mathematical model describing the dynamics of a mutant pathogen in a heterogeneous host population split into various types by the treatment strategy. We found that to be durable the treatment strategy must take pathogen growth and migration rates into account. We also show that pure, multicomponent treatment is the most effective strategy for impeding pathogen adaptation, but if we cannot guarantee the absence of hosts carrying some of the components of the treatment, it is better to apply a diversified treatment that splits the host population into numerous types. Our results provide a basic understanding of how the life-cycle parameters of the pathogen population and controllable parameters of a treatment strategy affect the rate of pathogen adaptation to a multicomponent treatment.

1 Introduction

The emergence of pathogen mutants able to overcome the total immunity of a host population, induced by a multicomponent treatment, becomes a real problem in medicine, agriculture and forestry [1, 2, 3, 4, 5, 6]. Even if adapting a multicomponent treatment that eradicates the disease involves multiple mutations, and therefore the cost of multiple mutation, several phenomena, such as genetic drift, migration, recombination and the selective pressure exerted by the treatment, make it possible for an escape mutant to emerge.

The estimation of the emergence time for an escape mutant overcoming multicomponent treatment is a way to predict treatment durability. Two processes are generally considered to determine the time before an escape mutant *appears* within a resident population through an adaptive mutation and its *establishment*: the treatment-induced mutant has to build up an initial population. However, if the host population is split by a treatment strategy into totally immune and untreated hosts, we have to take a new process into consideration - the *migration* of a mutant from an untreated host into a treated host [7]. If the basic reproductive number of a new pathogen type is greater than one, it is almost certain to be established, since there is no competition for the treated hosts. Therefore, we define *the emergence time* of an escape mutant as the time taken for it to migrate from an untreated into a treated host.

To estimate the durability of a treatment strategy we need a model that can take into account the mutation and migration processes that are affected by the properties of the treatment strategy. The theory of adaptation demonstrates that the size of the population, the genetic drift, the mutation probability, the probability distribution of mutational effects [8] and recombination events [9] have a dramatic effect on the speed of population change. However, this theory ignores the properties that result from the treatment strategy, e.g. the structure of a diversified host population. Models linking pathogen adaptive dynamics with treatment strategies are widespread in medicine. Vaccination theory studying the dynamics of escape mutants in response to a vaccination campaign highlights strategies that could lead to the emergence of a vaccine-resistant strain [10, 11] or to the emergence of virulence [12]. However, models based on vaccination theory are deterministic and do not explicitly describe the emergence of an escape mutant within a pathogen population, and so cannot be used to estimate the durability of treatment. Modelling is also used to investigate different aspects of the adaptive dynamics of cancers to drug treatments, immune responses to tumours and age-specific acceleration of cancer. All these aspects include rare mutations and their fixation in a random process [13, 14]. Models have shown that the waiting time before the emergence of an escape mutant depends on the mutation rate and on the mutation cost [15, 16]. Since these models focus on the micro-scale processes of adaptive dynamics, they do not take migration into consideration. Another group of models that link pathogen-adaptive dynamics to treatment strategies is used in theoretical epidemiology. Deterministic epidemiological models have shown that adaptive dynamics are influenced by the treatment dose [17, 18], i.e. by the proportion of hosts treated, and by compensatory mutations [19]. However, deterministic models that account for stochastic mutations and migrations in an implicit way cannot be used to estimate the durability of complex treatment strategies including using several treatments and the splitting of the host population into numerous types. There is therefore a lack of methods that can account for the impact of both the mutation and migration processes on the timing of pathogen adaptation to multicomponent treatments [7].

The objective of this paper is to estimate the rate of pathogen adaptation in a host population which is subjected to a multicomponent treatment, and to provide some general guidance about durable strategies for multicomponent treatments. In order to describe pathogen adaptive dynamics in a diversified host population receiving a multicomponent treatment, we formulated and analyzed a stochastic model based on a multitype birth-and-death process. This allowed us to account for pathogen mutation and migration processes, as well as for the structure of an invaded host population diversified by the treatment. In numerical simulations we varied the values of pathogen growth and migration rates, and we determined the time till the emergence of a mutant pathogen in a host carrying a multicomponent treatment. We

first explored the impact of the proportion of the hosts treated on treatment durability, and then the impact of the mutation cost. We also investigated the durability of various different multicomponent treatment deployment strategies. We discuss the application of the results obtained to multidrug therapies, combination vaccination/chemicals, and to the use of multigene resistance in plant breeding and in cultivar mixtures.

2 Results

2.1 Model overview

We constructed a stochastic population model based on a multitype birth-and-death process, describing pathogen adaptation to a treated host population. We assume that there are N different treatment components that can be combined in various ways to devise a treatment strategy. A treatment including all N components is designated a multicomponent treatment, treatments with one component are designated monocomponent treatments, and other treatments, with from 2 to $N - 1$ components, are designated intermediate treatments. Thus, the host population diversified by a treatment strategy can contain up to 2^N types: one untreated and several different treated types receiving different combinations of the treatment components. Since our model is non-spatial, it assumes that an applied treatment strategy will result in a well-mixed, heterogeneous host population.

The initial composition of the pathogen population includes a resident pathogen type infecting untreated hosts, and can include some pathogen types that have already adapted to hosts that have received monocomponent treatments. Our model describes the dynamics of any pathogen type i infecting a particular host type j , driven by birth and death, mutation and migration processes (see the Methods section). Like the host population, the pathogen population can contain up to 2^N pathogen types. The model exhibits the process of the progressive adaptation of a resident pathogen population to all types of the treatment-diversified host population. The pathogen dynamics depend on the mutation cost β_j associated with adapting to host type j , the growth rate r , the mutation rate ν , the migration rate D , and the total carrying capacity K of the host population (Table 1).

To investigate the impact of the treatment strategy on its durability, we considered five distinct multicomponent treatment strategies, Str1, . . . , Str5, that split the host population into different proportions of various types, ξ_j (Figure 3A). The first treatment strategy, Str1, splits the host population into equal proportions of a maximum number of types, 2^N . In other words, the number of hosts receiving multicomponent treatment is reduced to $1/2^N$, and they are mixed with untreated hosts and hosts receiving monocomponent and intermediate treatments. We then progressively modified the conditions under which the multicomponent treatment is used in the treatment strategy. First of all, in Str2 we increased the number of hosts treated with multicomponent treatment to $1/2$ of the host population. Next, in Str3, we assumed that monocomponent treatments had already been overcome by the pathogen. In Str4, we eliminated intermediate treatments in order to analyze their effect on the pathogen adaptation rate. Finally, in Str5, we left only untreated hosts and hosts receiving a multicomponent treatment in a 1:1 proportion.

By numerical simulations we estimated the waiting time for the first emergence of a mutant pathogen individual on the host receiving the multicomponent treatment. We varied the treatment strategy (Figure 3A) and the values of pathogen life-cycle parameters, such as pathogen growth rate, migration rate and mutation cost, and studied the response of the mean emergence waiting time, S (see the Methods section for explicit expression), henceforth termed the "emergence time" for the sake of simplicity.

2.2 Emergence time as a U-shaped function of the proportion of the host treated

Numerical simulations show that in the context of a two-type host population including treated and untreated individuals, the emergence time is a U-shaped function of the proportion of the hosts treated, ξ (Figure 1A). We see that at the fixed value of r , the highest values of the emergence time function can correspond to both low and high ξ values (Figure 1A). The impact of the proportion of the host treated on the emergence time depends on the migration, D , and the growth, r , rates of the pathogen population. Figure 1B summarizes the response of the emergence time to the variation of r , D and ξ . At most combinations of r and D , the emergence time is longer when either low proportions of the hosts were treated, $\xi < 0.3$, or high proportions, $\xi > 0.7$. However, when D had a medium or high value, $D > 0.1$, and r is low, $r < 0.5$, the emergence of an escape mutant can be impeded only by treating high proportions of the host. For low $D < 0.1$, and high $r > 1$ values, small proportions provide a better control of emergence, whereas for high $D > 0.2$, coupled with high $r > 1$, at any proportion the emergence time is short and we cannot therefore impede swift pathogen adaptation. If treated hosts are subjected to a multicomponent treatment, the emergence time keeps its U-shape versus ξ , but the increase in the component number prolongs the emergence time. In contrast to the impact of migration and growth rates on the emergence time, the carrying capacity, K , of the host population affects only the values of the emergence time function but not its shape. An increase in K slows pathogen adaptation.

Our model also demonstrates how mutation and migration processes drive the emergence time (Figure 1C). The proportion of hosts treated, ξ , determines the importance of each process in pathogen adaptation. When ξ is small, the time to mutation is short and the time to migration is long. As ξ increases, mutation time grows, while migration time decreases. If small proportions of the hosts are treated, the emergence time is the sum of the mutation time and the migration time, whereas for high proportions, the emergence time is greater than this sum.

2.3 Impact of the mutation cost on the emergence time

The model shows that an increase in the mutation cost increases the time to emergence, but that the intensity of the impact of the mutation cost depends on the migration rate (Figure 2A). Indeed, the higher migration rate, the slower the increase in the emergence time with the increase in mutation cost. It is easy to see from Figure 2A that the effect of an increase in the migration rate becomes more pronounced with an increase in the number of treatment components. For a monocomponent treatment, the mutation cost has almost no effect on the emergence time at high values of the migration rate (not illustrated). However, this can be altered by the deployment strategy of the multicomponent treatment. Figure 2B demonstrates that we can observe a delay in the emergence time at high migration rates, if the deployment strategy divides the host population in many types, e.g. as Str2 (Figure 3A). As before, the effect of an increasing migration rate intensifies with the number of treatment components.

2.4 The effect of multicomponent treatment deployment strategies on its durability

Figure 3 shows that the emergence time increases with the number of components in a treatment. Interestingly, the deployment strategy of a multicomponent treatment also has an important impact on the rate of the pathogen adaptation. We assume that this treatment can either be deployed alone or used simultaneously with other treatments involving various combinations of the same components (Figure 3A). Thus, a treatment strategy can deploy a multicomponent treatment including all N components with monocomponent treatments with only one component, and various intermediate treatments with combinations of 2 to $N - 1$ components. As the proportion of the hosts carrying multicomponent treatment increases, the emergence time of an escape mutant increases progressively from Str1 to Str2. Nevertheless,

the emergence time decreases if the pathogen has already adapted to hosts receiving mono-component treatments, as in Str3. When there are no hosts receiving intermediate treatments, Str4, the emergence time increases, if the number of components is equal to or more than 3. Treatment strategy Str5, which only divides the host population into two-types: untreated hosts and treated hosts receiving multicomponent treatment, is the most durable. The increase in the growth rate raises the probability of mutation, and thus shortens the emergence time in any strategy, especially if the pathogen has accumulated several mutations on the same hosts (Figure 3D). Figure 3C shows that the migration rate has a more complicated impact on the emergence time than the growth rate: the increase in the migration rate prolongs the emergence time, if the degree of host diversification is high, as in strategies Str1, Str2 and Str3.

3 Discussion

In this article, we have developed a mathematical framework for estimating the rate of pathogen adaptation in response to selection pressure from a multicomponent treatment of a host population, such as multidrugs, combination vaccines/chemicals and cultivars carrying multiple resistance genes. To describe the emergence of an escape mutant in a pathogen population, we used a multi-type birth and death process. We showed that the durability of the multicomponent treatment depends on how it is deployed. Our model provides a basic understanding of how life-cycle parameters of the pathogen population and controllable parameters of a treatment strategy affect the rate of pathogen adaptation to a multicomponent treatment. Our results have direct practical applications for the management of pathogen adaptive dynamics by complex multicomponent treatment strategies.

Multi-type birth and death processes are a powerful tool for modelling adaptive pathogen dynamics, since it can easily be adapted to many biological situations by adjusting the transition rates [20, 21]. This approach makes possible to monitor the stochastic dynamics of small populations, such as an escape mutant. Moreover, this approach makes it possible to derive an analytical estimation of the emergence time [22] to study the durability of the treatment strategies. Note that the model results can be affected by transition functions. However, the comparative analysis of the impact of various transition functions on the model dynamics was outside the scope of our study. It is also known that a spatial structure of the host population can have an impact on the rate of pathogen adaptation [7, 23]. Since our model is non-spatial, it can only be applied when a treatment-diversified host population is well-mixed and its spatial structure can be ignored. To preserve the simplicity of the model and the coherence of the results, we did not consider either compensatory mutations or recombinations that could accelerate the emergence of mutants escaping a multicomponent treatment [19, 24, 25]. However, the advantage of our approach is that it can be easily extended to the description of progressive pathogen adaptation, such as the erosion of imperfect vaccines or of partial cultivar resistance. Due to its simple structure, the model can be modified to fit the interactions between treatment components in order to study their effects on the rate of pathogen adaptation. We propose to explore this in our future work.

3.1 The role of the proportion of the host treated in pathogen adaptation

Our model shows that the optimum proportion of hosts treated in order to impede the adaptation of the pathogen population depends on the interplay between the intensity of pathogen reproduction and migration processes. If both processes have high rates, then durable control is impossible, and the treatment will soon be overcome. This finding is consistent with empirical results showing that plant pathogens, such as rust and mildew, which have a high gene flow and large population size, have a long history of defeating major resistance genes and their pyramids [26]. If the migration rate prevails over the pathogen growth rate, then the proportion of hosts treated should be high enough to reduce

the size of the resident pathogen population on the untreated hosts, and thus to reduce the probability of mutation. Conversely, when growth rate dominates over migration rate, the proportion of the host treated should be low in order to reduce the probability of migration. Overall, the proportion of hosts treated should be adjusted to control the recessive process: mutation or migration. If the two processes are equivalent, the rate of pathogen adaptation to treatment can be slowed down by treating either small or high proportions of the host. This conclusion is the same as that based on the fundamentally different model of van den Bosch & Gilligan [17], which is deterministic and it does not take the mutation cost into account. However, the extension of our model to a multicomponent treatment showed that the result can be applied generally: when the number of treatment components increases, the emergence time function keeps its U-shaped form. In the context of adaptation to multicomponent treatment, an individual pathogen has to cope with more than one mutation, which makes the emergence of an escape mutant on the untreated hosts a rare event, especially when the size of the untreated host subpopulation is small. Because of the additive mutation cost, mutants do not live for long on the untreated hosts, which reduces the probability of the successive migrations onto the treated host, especially when the frequency of treated hosts is low.

Epidemiological models that ignore pathogen migration and the stochasticity of pathogen dynamics show that the optimal vaccination coverage that prevents the emergence of a drug resistant pathogen strain is about $1 - 1/R_0$ [11], where R_0 is the basic reproductive number. Note that this estimation includes intermediate proportions of treated hosts that, according to our results, can accelerate pathogen adaptation and thereby reduce the durability of the vaccination strategy. In plant epidemiology, Ohtsuki and Sasaki [27] concluded that if there is a high risk of the development of virulent pathogen that can infect the resistant host, the fraction of resistant crop should never exceed about twenty five percent for any pathogen having $R_0 > 1$. Comparing these findings with our results, we can conclude that accounting for the stochastic migration process in modelling pathogen adaptive dynamics alters extant criteria for the critical proportion of treated hosts that could impede pathogen adaptation. This conclusion confirms the recent finding of Débarre et al. [18] who have shown, using a deterministic model in which migration consists of diffusion, that pathogen dispersal ranges should be included in the estimation of a critical size of the treated area, below which the drug-resistant strain cannot persist.

To be sustainable, a treatment strategy has to control not only the spread of the epidemic, but also the adaptive dynamics of the pathogen [18]. Theoretical studies of epidemiology and biological invasions focusing on the control of population spread demonstrate that there is a lower limit for the proportion of treated hosts that can minimize this population expansion, which is claimed to be about seventy percent [28, 29, 27, 30]. Our results suggest that this proportion does not offer a durable control strategy for a pathogen population with high reproduction and low migration rates, since it would simply accelerate its adaptation. We show that there is also an upper limit below which the values of treated host proportion can lead to efficient control of the evolutionary dynamics of epidemics. Superimposing our results over epidemiology criteria can suggest the conditions for the optimum proportion of the treated hosts leading to the control of both the evolutionary and invasive dynamics of the epidemics. Taking the evolutionary dimension of epidemics into consideration can lead to essential changes in the criteria for epidemic and invasion control. Fabre et al. [31] recently linked the characteristics of plant resistance level with epidemic dynamics in their theoretical study of sustainable strategies of the plant resistance, have shown that low cropping ratios of a resistant plant can prolong its durability, whatever its resistance level, but they do not provide optimum epidemic control, while high cropping ratios can provide both durable resistance and optimum control, if the level of resistance is high and the epidemic intensity is intermediate.

3.2 Mutation cost and treatment durability

Our model confirms the fact that mutation cost increases the emergence time [24, 32, 33, 34] and that it is not the only parameter controlling the emergence of an escape mutant [35]. Moreover, our model

shows that a high migration rate can mitigate the impact of the mutation cost on the emergence time. Indeed, the mutation cost essentially determines the intensity of the competition between resident and mutant pathogen types on the untreated hosts. When the migration rate is high, mutants escape easier the lot to be outcompeted by resident individuals. When the migration rate is low, the probability that the mutant will become extinct on the untreated hosts is high, and a mutant has to be able to create an abundant population to produce a migration event, and thereby for an emergence to be statistically probable. Interestingly, treatments that split up the host population into numerous types can enhance the impact of the mutation cost on the pathogen adaptation rate, even if the pathogen has a high migration rate. In the treatment-diversified host population, the number of suitable hosts for intermediate mutants is greatly reduced, and high migration rates increase the probability of migrating onto unsuitable hosts resulting in extinction, thereby increasing the emergence time. We conclude that we should abandon the general idea that mutation cost determines treatment durability, since, as we have seen, the biological context can greatly alter its impact on the adaptation rate.

3.3 Multicomponent treatment strategies

It is commonly thought that the number of components deployed in a treatment strategy has a significant impact on the rate of pathogen adaptation [16, 33, 36, 37, 23]. Our model shows that in fact the adaptation rate depends on the deployment strategy of the multicomponent treatment, i.e. on the proportion of hosts treated, and on the presence of hosts receiving intermediate treatment. Intermediate treatment, including only some of the components, make it possible for an escape mutant to establish an abundant population and to accumulate the number of mutations required to overcome a multicomponent treatment. Our results demonstrate that a purely multicomponent treatment is the most effective strategy for impeding pathogen adaptation, but if we cannot guarantee the absence of hosts receiving intermediate treatments, it is better to apply a diversified treatment that will split the host population into numerous types.

Our model suggests that if a multicomponent treatment is deployed simultaneously with treatments that have already been overcome, the adaptation rate increases greatly. Indeed, fewer mutations are needed to create an escape mutant able to invade hosts receiving the multicomponent treatment. However, deploying treatments involving three or more defeated components and their combinations can still be effective, if they have been overcome independently and if there are no hosts receiving intermediate treatments. The absence of intermediate treatments slows down pathogen adaptation, since the pathogen has to accumulate all the necessary mutations and then migrate successfully, whereas if some hosts receive the defeated monocomponent treatment, this limits the emergence of an escape mutant.

Our results explain the empirical observations of the swift pathogen adaptation stimulated by the use of intermediate treatments. Despite the fact that our results correspond to instantaneous host diversification in response to treatment, we can draw an analogy with situations in which various treatments are deployed successively, thus diversifying the host population over time. For instance, to control *Bremia lactucae*, breeders add a new resistance gene to the lettuce cultivar after each rather rapid breakdown of lettuce resistance by the pathogen [38]. In other words, a new lettuce cultivar carrying several defeated and one non-defeated resistance genes is deployed just after a cultivar has lost its resistance. This can be viewed as corresponding to intermediate treatment and it allows the pathogen to overcome a new resistant cultivar by a just single mutation. Our model links pathogen adaptive dynamics to controllable parameters of treatment strategies, and it can be applied to the design of sustainable strategies for the selection and deployment of new multigene resistant plants, even if they carry defeated resistance genes.

3.4 Conclusions

Migration and mutation are two evolutionary forces that drive pathogen adaptation. Our results show that the durability of multicomponent treatments intended to control pathogen dynamics depends on the

balance between these two forces (Figure 1C). Since our model is appropriate for a large class of organisms, it can be used to design sustainable strategies of such multicomponent treatments as multidrugs, multicomponent vaccines/chemicals and cultivars carrying multigene resistance, that could help to prevent rapid disease adaptation. The model is also promising for deriving strategies for the deployment of defeated treatments. The model constructed to include an all-or-nothing qualitative pathogen response is currently appropriate for the management of partial treatments, such as imperfect vaccines and cultivars carrying quantitative trait loci.

4 Methods

4.1 Stochastic pathogen population model

A multitype birth-and-death process (also known as a competition process) $(X, \{\mathbb{P}_x : x \in \mathbb{N}_0^d\})$ is a continuous, time-homogeneous, Markov chain with a state space \mathbb{N}_0^d , for $d \geq 1$, whose transition matrix only allows transitions to certain nearest neighbours [39]. Let us call $X_t^{(i,j)}$ the population size at time t of pathogen type i on host type j ; $(i, j) \in [1, 2^N]^2$. If pathogen type i is not able to infect host type j , then for all t , $X_t^{(i,j)} = 0$. Each pathogen type $X^{(i,j)}$ corresponds to one dimension in the multi-type birth-and-death process, in particular the dimension of the state space of the Markov chain X is $d = 2^{2N}$.

We are interested in the emergence time of a mutant pathogen that occurred on a host receiving multicomponent treatment. We assume that the escape mutant will invade this host type since it has a positive growth rate and there is no competition. Thus, the emergence time S represents the time during which the multicomponent treatment is efficient:

$$S = \inf\{t \geq 0 : X_t^{(2^N, 2^N)} > 0\}, \quad (1)$$

where $X^{(2^N, 2^N)}$ is pathogen type with N mutations able to invade hosts carrying N -component treatment.

Furthermore, we define stochastic birth and death, migration and mutation events that drive pathogen adaptive dynamics.

Birth event.

An individual pathogen can duplicate itself to produce a new individual belonging to the same pathogen type. We define the birth transition rate of pathogen type i on host type j as a product between the growth rate of the pathogen type, its fitness β_i , the pathogen type size $X_t^{(i,j)}$ and the probability that it will not mutate:

$$\lambda_t^{ij} = r\beta_i(1 - p_i)X_t^{(i,j)}, \quad (2)$$

where r is the growth rate of pathogen type i , and p_i is the probability that it will mutate. We assume that mutations lead to a decrease in pathogen fitness as a result of the additional mutation cost. We define a cost C_z ($z \in [1, N]$) for each mutation, such that the final fitness of a pathogen type i results in $\beta_i = 1 - \sum_{z=1}^N C_z \mathbb{1}_{\{\text{The individual } i \text{ carried the mutation } z\}}$ ($\beta_i \in [0, 1]$) [40, 41].

Death event.

We assume that the number of individual pathogens can decrease as a result of death and of migration into unsuitable treated hosts. To include the negative effect of intra-competition on the dynamics of the pathogen, the death transition rate of pathogen type i in host type j is based on the Lotka-Volterra equation,

$$\mu_t^{ij} = \frac{r\beta_i(1 - p_i)}{\xi_j K} \left(\sum_{l=1}^{2^N} \frac{\beta_l}{\beta_i} X_t^{(l,j)} - 1 \right) + X_t^{(i,j)} \sum_{m=1}^{2^N} \xi_m (D - D_{im}), \quad (3)$$

where K is the carrying capacity of the host population, ξ_j is the proportion of host type j , such as $\sum_{j=1}^{2^N} \xi_j = 1$ and the size of host type j is $\xi_j K$. Parameter D is the pathogen dispersal rate. If pathogen

type i can infect the host m , then $D_{im} = D$, else $D_{im} = 0$.

Mutation event.

A mutation occurs during reproduction, and this is why it is considered as the spontaneous birth of a type i pathogen on host type j . The mutation rate is equal to the sum of all the mutations of the potential ancestor k ,

$$\Lambda_t^{ij} = \sum_{k \in j} p_{ki} r \beta_k X_t^{(k,j)}, \quad (4)$$

where p_{ki} is the probability that pathogen type k will mutate into pathogen type i . We assume that the pathogen population undergoes one mutation per reproduction. Thus, if pathogen type i can be attained only by means of several mutations, then $p_{ki} = 0$. We have $\sum_{i \in j, i \neq k} p_{ki} = p_k$, where $i \in j$ means that pathogen type i inhabits host type j .

Migration event.

A migration is the transfer of an individual pathogen from host type j into another type k host. This event is equivalent to the death of pathogen type i on host type j , and the birth of pathogen type i on host type k :

$$\gamma_t^{ijk} = \xi_k D_{ik} X_t^{(i,j)}, \quad (5)$$

where γ_t^{ijk} is the migration rate. Since the model is not spatially explicit, the migration rate depends solely on the size of the host type. Hereinafter, in numerical simulations, we use the dispersal rate, D , as the principle descriptor of the migration process. Thus, for the sake of simplicity we designate parameter D as the migration rate.

Interevent time.

We define the probability of each event as its transition rate divided by the sum of all transition rates. As in other stochastic epidemic models [42], the interevent time is the time between transitions, and it follows an exponential distribution with parameter:

$$\frac{1}{\sum_{ijk} \lambda_t^{ij} + \mu_t^{ij} + \Lambda_t^{ij} + \gamma_t^{ijk}}. \quad (6)$$

4.2 The parameters and implementation of the model

To perform numerical simulations, we used a range of biologically-relevant parameter values corresponding to various diseases (Table 1). We applied the Gillespie algorithm [43] to track the exact trajectories of the birth and death process. Since the algorithm is computationally expensive for large populations, we used a Gillespie method up to a certain population size and then, when population size attained high values and approached its equilibrium, we used its deterministic equilibrium calculated from the corresponding system of differential equations. Indeed, it has been shown that a birth and death process converges to a differential equation when the population size is high [44]. To test our algorithm, we compared it with some exact trajectories using Student's t- test. Each simulation was run until an escape mutant emerged on a host receiving the N -component treatment. For each set of parameters, 1000 simulations were run to estimate the mean emergence time. The estimation of confident intervals of the means showed that they were significantly different. The model was implemented in C++ using Code Blocks and GNU GCC compiler.

Acknowledgments

The authors would like to thank Frédéric Fabre for helpful discussions. Funding for this research was provided by Région Pays de la Loire (MODEMAVE project) and by SPE Department of INRA.

References

1. Anderson RM, May RM (1991) *Infectious diseases of humans : dynamics and control*. Oxford : Oxford University Press.
2. McLean AR (1995) Vaccination, evolution and changes in the efficacy of vaccines: A theoretical framework. *P Roy Soc Lond B Bio* 261: 389-393.
3. Rybicki EP, Pietersen G (1999) Plant virus disease problems in the developing world. Academic Press, volume 53 of *Advances in Virus Research*. pp. 127 - 175.
4. Nowak MA, Michor F, Komarova NL, Iwasa Y (2004) Evolutionary dynamics of tumor suppressor gene inactivation. *P Natl Aca Sci USA* 101: 10635-10638.
5. Michor F, Iwasa Y, Nowak MA (2004) Dynamics of cancer progression. *Nat Rev Cancer* 4: 197–205.
6. Anderson PK, Cunningham AA, Patel NG, Morales FJ, Epstein PR, et al. (2004) Emerging infectious diseases of plants: pathogen pollution, climate change and agrotechnology drivers. *Trends Ecol Evol* 19: 535 - 544.
7. Consortium R (2010) The skill and style to model the evolution of resistance to pesticides and drugs. *Evol Appl* 3: 375–390.
8. Park SC, Simon D, Krug J (2010) The speed of evolution in large asexual populations. *J Stat Phys* 138: 381–410.
9. Rouzine IM, Coffin JM (2010) Multi-site adaptation in the presence of infrequent recombination. *Theor Popul Biol* 77: 189 - 204.
10. McLean AR (1995) Vaccination, evolution and changes in the efficacy of vaccines: A theoretical framework. *P Roy Soc Lond B Bio* 261: 389–393.
11. Scherer A, McLean A (2002) Mathematical models of vaccination. *Brit Med Bull* 62: 187-199.
12. Gandon S, Day T (2007) The evolutionary epidemiology of vaccination. *J R Soc Interface* 4: 803–817.
13. Iwasa Y, Michor F, Komarova NL, Nowak MA (2005) Population genetics of tumor suppressor genes. *J Theor Biol* 233: 15 - 23.
14. Serra MC, Haccou P (2007) Dynamics of escape mutants. *Theor Popul Biol* 72: 167 - 178.
15. Komarova N (2006) Stochastic modeling of drug resistance in cancer. *J Theor Biol* 239: 351 - 366.
16. Arora P, Dixit NM (2009) Timing the emergence of resistance to anti-HIV drugs with large genetic barriers. *PLoS Comput Biol* 5: e1000305.
17. van den Bosch F, Gilligan C (2003) Measures of durability of resistance. *Phytopathology* 93: 616-25.

18. Débarre F, Lenormand T, Gandon S (2009) Evolutionary epidemiology of drug-resistance in space. *PLoS Comput Biol* 5: e1000337.
19. Handel A, Regoes RR, Antia R (2006) The role of compensatory mutations in the emergence of drug resistance. *PLoS Comput Biol* 2: e137.
20. Iwasa Y, Michor F, Nowak MA (2004) Evolutionary dynamics of invasion and escape. *J Theor Biol* 226: 205 - 214.
21. Novozhilov AS, Karev GP, Koonin EV (2006) Biological applications of the theory of birth-and-death processes. *Briefings in Bioinformatics* 7: 70-85.
22. Bourget R, Chaumont L, Sapoukhina N (2012) Exponentiality of first passage times and quasi stationary distributions. Under revision .
23. Sapoukhina N, Durel CE, Le Cam B (2009) Spatial deployment of gene-for-gene resistance governs evolution and spread of pathogen populations. *Theor Ecol* 2: 229-238.
24. MacLean RC, Hall AR, Perron GG, Buckling A (2010) The population genetics of antibiotic resistance: integrating molecular mechanisms and treatment contexts. *Nature Reviews Genetics* 11: 405–414.
25. Rhodes TD, Nikolaitchik O, Chen J, Powell D, Hu WS (2005) Genetic recombination of human immunodeficiency virus type 1 in one round of viral replication: Effects of genetic distance, target cells, accessory genes, and lack of high negative interference in crossover events. *J Virol* 79: 1666-1677.
26. McDonald BA, Linde C (2002) Pathogen population genetics, evolutionary potential, and durable resistance. *Annu Rev Phytopathol* 40: 349-379.
27. Ohtsuki A, Sasaki A (2006) Epidemiology and disease-control under gene-for-gene plant-pathogen interaction. *J Theor Biol* 238: 780 - 794.
28. Collingham YC, Huntley B (2000) Impacts of habitat fragmentation and patch size upon migration rates. *Ecol Appl* 10: 131–144.
29. Otten W, Bailey DJ, Gilligan CA (2004) Empirical evidence of spatial thresholds to control invasion of fungal parasites and saprotrophs. *New Phytol* 163: 125–132.
30. Suzuki SU, Sasaki A (2011) How does the resistance threshold in spatially explicit epidemic dynamics depend on the basic reproductive ratio and spatial correlation of crop genotypes? *J Theor Biol* 276: 117 - 125.
31. Fabre F, Rousseau E, Mailleret L, Moury B (2012) Durable strategies to deploy plant resistance in agricultural landscapes. *New Phytol* 193: 1064–1075.
32. Demon I, Haccou P, van den Bosch F (2007) Introgression of resistance genes between populations: A model study of insecticide resistance in *bemisia tabaci*. *Theor Popul Biol* 72: 292 - 304.
33. Fabre F, Bruchou C, Palloix A, Moury B (2009) Key determinants of resistance durability to plant viruses: Insights from a model linking within- and between-host dynamics. *Virus Res* 141: 140 - 149.
34. Aviran S, Shah PS, Schaffer DV, Arkin AP (2010) Computational models of HIV-1 resistance to gene therapy elucidate therapy design principles. *PLoS Comput Biol* 6: e1000883.

35. Lannou C, Mundt CC (1997) Evolution of a pathogen population in host mixtures: rate of emergence of complex races. *Theor Appl Genet* 94: 991-999.
36. Antia R, Regoes RR, Koella JC, Bergstrom CT (2003) The role of evolution in the emergence of infectious diseases. *Nature* 426: 658 - 661.
37. Lion S, Baalen Mv (2008) Self-structuring in spatial evolutionary ecology. *Ecol Lett* 11: 277-295.
38. Michelmore R, Wong J (2008) Classical and molecular genetics of *bremia lactuca*, cause of lettuce downy mildew. *Eur J Plant Pathol* 122: 19-30.
39. Reuter GEH (1961) Competition processes. Univ. California Press, volume II of *Proc. 4th Berkeley Sympos. Math. Statist. and Prob.* pp. 421 - 430.
40. Phillips PC (2008) Epistasis the essential role of gene interactions in the structure and evolution of genetic systems. *Nat Rev Genet* 9: 855-867.
41. Trindade S, Sousa A, Xavier KB, Dionisio F, Ferreira MG, et al. (2009) Positive epistasis drives the acquisition of multidrug resistance. *PLoS Genet* 5: e1000578.
42. Nath M, Woolliams JA, Bishop SC (2008) Assessment of the dynamics of microparasite infections in genetically homogeneous and heterogeneous populations using a stochastic epidemic model. *J Anim Sci* 86: 1747-1757.
43. Gillespie DT (1977) Exact stochastic simulation of coupled chemical reactions. *J Phys Chem-US* 81: 2340-2361.
44. Ethier SN, Kurtz TG (2005) Markov processes: characterization and convergence. Wiley series in probability and statistics; Wiley-Interscience paperback series.
45. Cuevas JM, Moya A, Sanjun R (2005) Following the very initial growth of biological rna viral clones. *J Genl Virol* 86: 435-443.
46. Ayme V, Souche S, Caranta C, Jacquemond M, Chadoeuf J, et al. (2006) Different mutations in the genome-linked protein vpg of potato virus y confer virulence on the pvr23 resistance in pepper. *Mol Plant-Microbe Interact* 19: 557-563.
47. Carrasco P, Dars J, Agudelo-Romero P, Elena S (2007) A real-time rt-pcr assay for quantifying the fitness of tobacco etch virus in competition experiments. *J Virol Methods* 139: 181 - 188.
48. Labbé P, Sidos N, Raymond M, Lenormand T (May 2009) Resistance gene replacement in the mosquito culex pipiens: Fitness estimation from long-term cline series. *Genetics* 182: 303-312.
49. Kimura M (1968) Evolutionary rate at the molecular level. *Nature* 217: 624-626.
50. Sanjun R, Nebot MR, Chirico N, Mansky LM, Belshaw R (October 1, 2010) Viral mutation rates. *J Virol* 84: 9733-9748.

Figure Legends

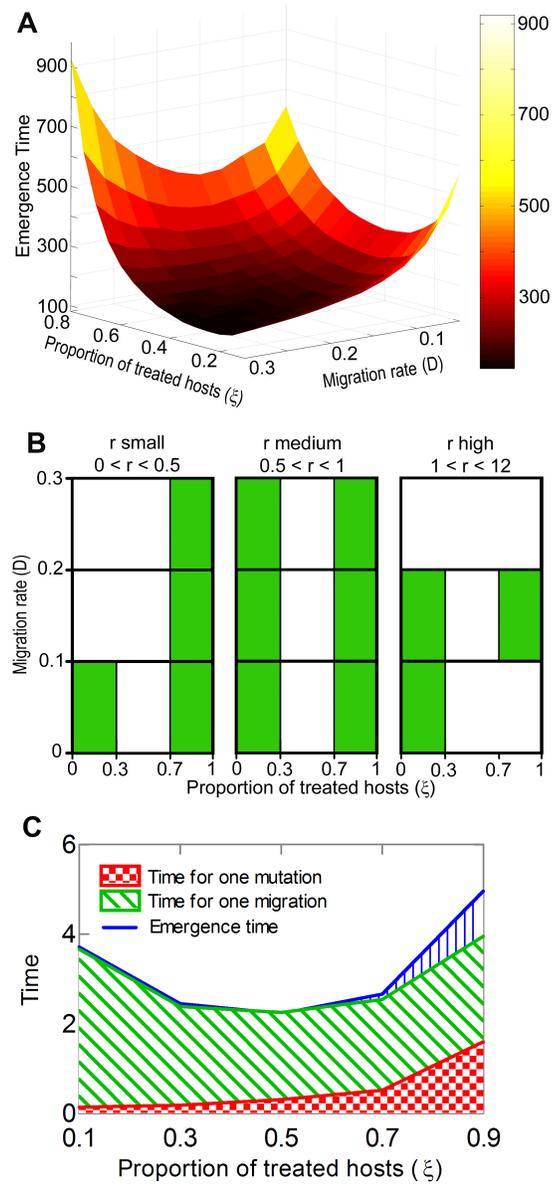


Figure 1. Model predictions of emergence time dynamics. We assume a treatment that would divide the host population into untreated and treated individuals, so that the proportion of treated hosts is ξ . The emergence time of an escape mutant is the time before it migrates from an untreated into a treated host. (A) Emergence time as a function of the migration rate, D , and the proportion of hosts treated, ξ . The results are based on a simulation of model Eq. (2-6) in Methods with the following parameter values: $r = 0.3$, $\nu = 10^{-5}$, $C = 0.2$, $K = 10000$. (B) A simplified decision diagram to assist with developing treatment strategies in order to achieve durable pathogen control. The decision diagram sums up the emergence time functions obtained as in (A), but with a tuning growth rate, r , from 0 to 12. All the other parameter values are identical to those in Figure 1A. For any pair of pathogen parameters (r , D), the diagram depicts in green the proportions of treated hosts, ξ , that could inhibit pathogen adaptation. For instance, a pathogen with high growth and dispersal rates adapts swiftly at any proportion of the host treated, while the adaptation of a pathogen with intermediate growth and migration rates can be inhibited by either low or high proportions. (C) Emergence time decomposition. Mean times of mutation, mutant migration and mutant emergence on a treated host as functions of the proportion of the host treated, ξ . The mutation time is the time the first pathogen mutation occurred on an untreated host. The migration time is the time of the first migration of the pathogen mutant from an untreated to a treated host. To reduce the calculation time, simulations were performed with the following parameter values: $r = 0.8$, $D = 0.2$, $\nu = 10^{-3}$, $C = 0.1$, $K = 10000$.

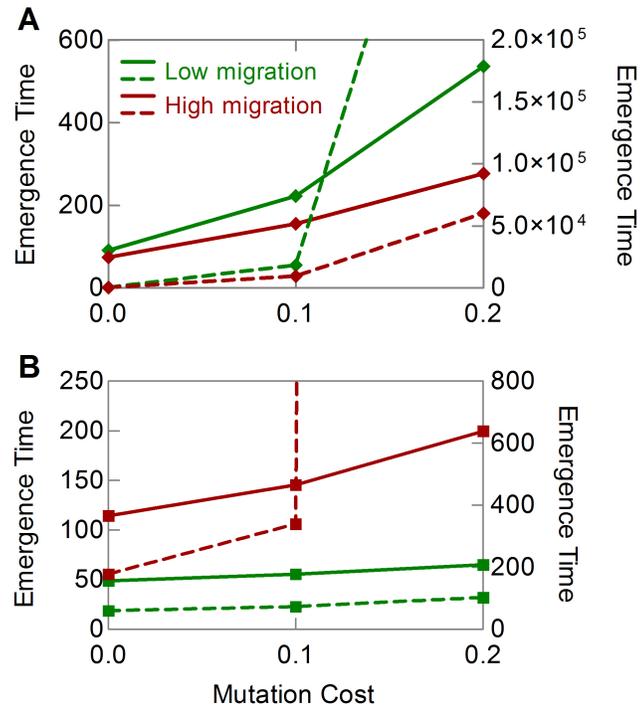


Figure 2. Emergence time as a function of the mutation cost. The emergence time is plotted for a two-component treatment (solid line, left axis) and a three-component treatment (dotted line, right axis) at low (green) and high (red) migration rates. (A) The treatment strategy splits the host population into a mixture of untreated hosts and receiving multicomponent treatment in a 1:1 proportion (Str5, Figure 3A). (B) Multicomponent treatment is deployed with other treatments involving different combinations of the $N - 1$ components, so that the host type carrying the multicomponent treatment is 50% and the other host types are present in equal proportions (Str2, Figure 3A). In (A) and (B), we let $r = 0.3$, $D_{low} = 0.05$, $D_{high} = 0.25$, $\nu = 10^{-3}$ and $K = 10000$.

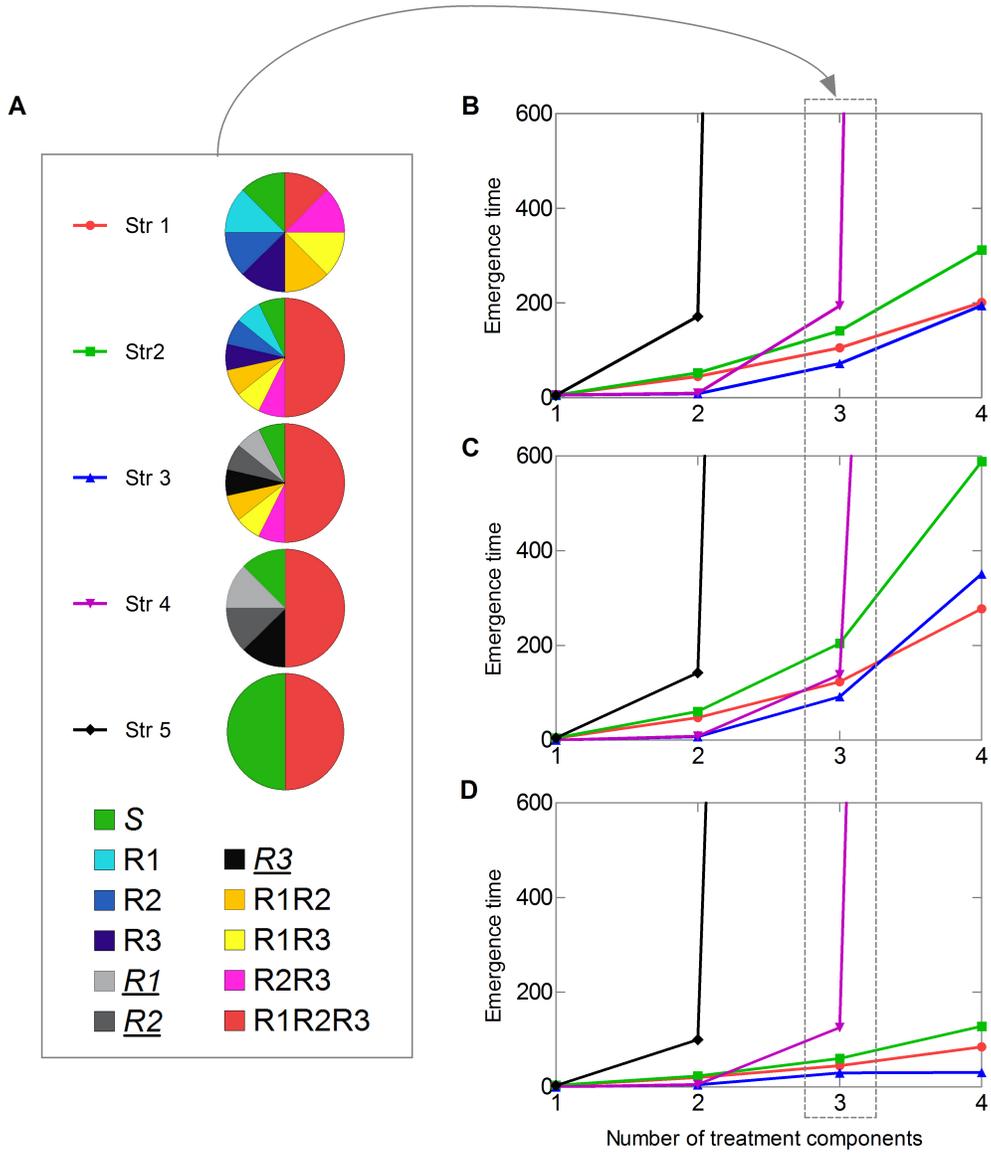


Figure 3. Emergence time as a function of the number of treatment components for five different treatment strategies, Str1, . . . , Str5. Pie charts (A) depict the composition of the treatment-diversified host population for a three-component treatment: each colour corresponds to a host type listed below, and the proportion of each sector is illustrated. Host type S includes untreated hosts, types R1, R2, R3 and R1, R2, R3 - hosts receiving different monocomponent treatments, host types R1R2, R1R3, R2R3 receiving different intermediate treatments, and type R1R2R3 consists of hosts receiving multicomponent treatment. Host types with *italic and underline* names are receiving treatments that have already been overcome. We used the same deployment principle for the N -component treatment. The first strategy, Str1, diversifies the host population into all possible $2^N - 1$ treated types carrying different combinations of the treatment components and the untreated one in equal proportions. The composition of the host population subjected by the second treatment strategy, Str2, is similar to Str1, but the proportions of the different types are different: the hosts receiving multicomponent treatment is 50% of the host population, the proportions of the other $2^N - 1$ host types are equal. The third strategy, Str3, is similar to the second one, but we assume that all mono-component treatments have already been overcome. Str3 results in the fourth strategy, Str4, by retaining only mono-component treatments and multicomponent treatments, and eliminating intermediate treatments. The use of the last strategy, Str5, results in 1:1 two-type host population: untreated hosts and treated hosts receiving multicomponent treatment. In (B), the pathogen has low growth and migration rates, $r = 0.3$ and $D = 0.1$. For Str4, in the case of 4-component treatment, the emergence time has a value of 13764.3, and for Str5, in the context of a 3-component treatment, the emergence time has a value of 12372.7. In (C), the pathogen has a low growth rate and a medium migration rate, $r = 0.3$ and $D = 0.2$. For Str4, in the context of a 4-component treatment, the emergence time attains a value of 4721.4, and for Str5, in the context of a 3-component treatment, the emergence time value is 9440.18. In (D), the pathogen has a high growth rate and a low migration rate, $r = 0.8$ and $D = 0.1$. For Str4, in the context of 4-component treatment, the emergence time attains a value of 9863.58, and for Str5, in the context of 3-component treatment, the emergence time value is 8451.13. In (A-C), the other parameters are $\beta = 0.1$, $\nu = 10^{-3}$, $K = 10000$ and $\forall z, C_z = 0.1$.

Tables

Table 1. Definition and values of the parameters used to model pathogen adaptive dynamics.

| Name | Value | Description | References |
|-------------|-----------------|--|--------------|
| $X^{(i,j)}$ | - | Number of individuals of type i on the environment j | - |
| r | [0.3; 12] | Growth rate | [45, 33] |
| D | [0; 0.3] | Migration rate | - |
| C_z | [0; 0.8] | Mutation cost of the mutation z | [46, 47, 48] |
| β_i | - | Fitness of a pathogen type i | - |
| p_{ki} | [0; 10^{-3}] | Probability for a pathogen type k to mutate in a pathogen type i | [49, 33, 50] |
| p_i | - | Mutation probability for a pathogen type i | - |
| ξ_j | [0; 1] | Proportion of host type j | - |
| K | 10000 | Total carrying capacity | - |
| S | - | Emergence time | - |