An extended Moran process that captures the struggle for fitness

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Abstract

When a new type of individual appears in a stable population, the newcomer is typically not advantageous. Due to stochasticity, the new type can grow in numbers, but the newcomers can only become advantageous if they manage to change the environment in such a way that they increase their fitness. This dynamics is observed in several situations in which a relatively stable population is invaded by an alternative strategy, for instance the evolution of cooperation among bacteria, the invasion of cancer in a multicellular organism and the evolution of ideas that contradict social norms. These examples also show that, by generating different versions of itself, the new type increases the probability of winning the struggle for fitness. Our model captures the imposed cooperation whereby the first generation of newcomers dies while changing the environment such that the next generations become more advantageous.

Keywords: `Evolutionary dynamics, Nonlinear dynamics, Mathematical modelling, Game theory, Cooperation`

1. Introduction

When unconditional cooperators appear in a large group of defectors, they are exploited until they become extinct. The best possible scenario for this type of cooperators is to change the environment such that another type of cooperators that are regulated and only cooperate under certain conditions becomes advantageous. Furthermore, when defectors appear in a regulated cooperation, the first generation of defectors typically dies while changing the environment such that the next generations become more advantageous; hence, cooperation

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is imposed on the defectors. In this paper, we propose a model that captures this dynamics. More specifically, we introduce an extension of the Moran process whereby individuals can change the fitness landscape of the population by modifying the environment.

1.1. The Moran process

The Moran process represents the simplest possible stochastic model that captures the three basic building blocks of evolution – replication, mutation and selection – in a finite population [1],[2]. The process assumes that the population size is constant and that each type of individual has constant fitness. In each time step, a random individual is selected to reproduce and a random individual is selected to die. In one implementation of the Moran process, all individuals are initially of the same type, denoted the *wild type*. When a wild-type individual reproduces, a mutation that creates a new type of individuals, denoted the *mutant type*, occurs with probability u. It is assumed that no other mutation can occur. The wild type has reproductive rate 1, whereas the mutant type has reproductive rate r, where r is a non-negative constant. All individuals are selected to die at the same rate. Hence, the mutant type is advantageous if $r > 1$, neutral if $r = 1$ and disadvantageous if $r < 1$. In each time step, the number of mutants can increase by one, decrease by one or remain constant. The probabilities for these three events are

$$\mathrm{P}(i+1|i) = \frac{u(N-i)+ri}{N-i+ir}\frac{N-i}{N}, \tag{1}$$

$$\mathrm{P}(i-1|i) = \frac{(1-u)(N-i)}{N-i+ir}\frac{i}{N}, \tag{2}$$

$$\mathrm{P}(i|i) = 1 - P(i+1|i) - P(i-1|i), \tag{3}$$

respectively, where N is the population size and i is the number of mutants. The model is discussed more thoroughly in Appendix A.

If the timescale of the mutants' fixation is much shorter than the timescale of mutation, then a lineage of mutants is likely to take over the whole population or become extinct before another lineage of mutants is created from the wild type. In this case, the probability that i mutants will eventually invade the whole population is

$$\rho_i = \frac{r^{N-i}\left(1-r^i\right)}{1-r^N} \tag{4}$$

if $r \neq 1$ and

$$\rho_i = \frac{i}{N} \tag{5}$$

if it is a neutral Moran process, that is, $r = 1$ [3].

The Moran process can also capture the competition dynamics between three types of individuals [3]–[6]. As discussed more thoroughly in Subsections 1.2

and 1.3, a mutant created in a stable population has in general low fitness, because it is attacked by defence mechanisms that protect the stability of the population. However, the first type of mutants, denoted *intermediate mutants*, typically has a higher mutation rate than the wild type and can produce a new type of mutants that avoids most of these attacks. This type of mutants is denoted *resistant mutants*. The reproductive rates of the wild type, intermediate mutants and resistant mutants are 1, r and r_1, respectively, where $r \leq 1 < r_1$.

As discussed more thoroughly by Wodarz and Komarova [3], Nowak et al. [7] and Breivik [8], the ability to create new variants is important when a mutant type invades a population. However, as discussed more thoroughly in the next subsection, no individual has anything to gain from changing only its strategy in an *evolutionarily stable population*, and this indicates that the mutants must also change their environment to become advantageous.

In the extended Moran model presented in this paper, the fitness is not constant. Similar to the model presented by Wodarz and Komarova [3], the model presented in this paper considers three types of individuals, namely the wild type, intermediate mutants and resistant mutants, but, in contrast to the previous model, the resistant mutants become advantageous only if the mutants manage to change the environment. However, changing the environment reduces the fitness of the intermediate mutants; thus, there is a cost for the mutants. In particular, there is a chance that the mutants will not produce a resistant type; in this case, the mutants actually reduce their own fitness. To analyse this dynamics, we use the results from evolutionary game theory, which is presented in the next subsection.

1.2. Evolutionary game theory

Evolutionary game theory is the generic approach to evolutionary dynamics [9],[10]. In these games, the fitness depends on the frequencies of the different types in the population [2]. In contrast to traditional game theory, evolutionary game theory does not rely on rationality [11]. Instead it considers a population of individuals with fixed strategies that interact randomly. When two individuals interact, each receives a payoff that depends on the strategy of both individuals. The payoff is interpreted as fitness [12].

Table 1 shows the payoffs in a well-known game called the *prisoner's dilemma* [2]. This game has two strategies: cooperation and defection. A group of cooperators has higher fitness than a group of defectors. However, if a defector and a cooperator meet, the defector receives a higher payoff than the cooperator, and, what is more, the defectors are fitter than the cooperators in a mixed group.

In an evolutionary game, a mutation can change the strategy of an individual. In some cases, the mutation increases the fitness of the individual. For instance, consider a group of cooperators with interactions that are captured by the prisoner's dilemma. If a mutation causes an individual to change strategy to defection, the individual increases its payoff. This means that cooperation is an unstable strategy. On the contrary, a strategy is a *Nash equilibrium* if no individual can deviate from this strategy and increase its payoff [13]. Defection

in the prisoner's dilemma is a Nash equilibrium because, if a defector mutates into a cooperator, it decreases its payoff.

A Nash equilibrium is also an *evolutionarily stable strategy* if selection opposes the invasion of an alternative strategy [9]. That is, if a sufficiently large population adopts an evolutionarily stable strategy, it cannot be invaded by any alternative strategy that is initially rare. For the prisoner's dilemma, defection is an evolutionarily stable strategy. Hence, cooperators cannot invade a large population of defectors of which interaction is captured by the prisoner's dilemma. However, as discussed more thoroughly in Section 4, a relatively small group of defectors can be invaded by cooperators.

The prisoner's dilemma illustrates why a well-functioning cooperation, such as a multicellular organism or society, must have control mechanisms that stabilise the cooperation and protect against defective individuals. Even though cooperations are not stable in general [2], the control mechanisms make them behave similarly to an evolutionarily stable population within relatively short timescales.

In the next subsection, we discuss some of the mechanisms that regulate cooperation in a multicellular organism, whereas the regulation of human interaction is examined in Subsection 4.3.

1.3. Regulation of cooperation in a multicellular organism

In a large multicellular organism, such as a human being, millions of cells must cooperate [3],[14]. This cooperation is maintained by a very complex network of signals and cellular checkpoints, and the immune system is an important component of this network. The immune system must detect mutant cells that have stopped cooperating as well as foreign agents, from viruses to parasitic worms, and distinguish them from the organism's own healthy tissue [15].

Mutated cells can be detected and killed by T cells, which are a type of white blood cells [16]. The exact details of how the T cells are regulated and activated are still uncertain [17]. In a nutshell, a type of T cells, called antigen-presenting cells (APCs), circulates with the blood. If an APC recognises a foreign protein, called an antigen, on a cell, then it makes a copy of the antigen and transports it to the lymph nodes. When the lymph nodes receive the antigen, the production of a type of T cells called cytoxic T lymphocytes (CTLs) is activated. A CTL is programmed to find and kill the cells that display the type of antigen brought to the lymph nodes by the APCs [18].

The body can also prevent the growth of mutated cells by limiting the blood supply. As discussed more thoroughly in Section 4, this can lead to acidification of the microenvironment, which increases the death rate of both mutant cells and healthy cells. However, a new type of mutant that is resistant to the acidic environment, might be created [19]–[24]. This competition dynamics is captured by the extended Moran process, presented in the next section.

2. Extended Moran process with non-constant fitness

In this section, we present an extension of the Moran process with non-constant fitness. The model assumes that the population has constant size, N, and that it consists of three types of individuals, namely the wild type, intermediate mutants and resistant mutants. During reproduction, a wild-type individual can mutate into an intermediate mutant with probability u and an intermediate mutant can mutate into a resistant mutant with probability u_1. It is assumed that no other mutation can occur.

The environment is described by a parameter called the *fitness parameter*. As long as the fitness parameter is below the *fitness threshold*, Υ, all individuals have the same fitness. The mutants increase the fitness parameter, and, when the fitness parameter reaches Υ, the fitness of the non-resistant individuals decreases, whereas the resistant mutants become advantageous.

In each time step, the following four events occur:

1. A random individual is selected to reproduce and a random individual is selected to die.
2. If the fitness parameter is higher than Υ, a random individual is selected. If the selected individual is not resistant, it dies, and a random individual reproduces, whereas, if the selected individual is resistant, nothing occurs in this event.
3. A random individual is selected. If it is a mutant, then $1/N$ is added to the fitness parameter.
4. The fitness parameter is reduced by $F \times 100$ per cent, where $0 \leq F \leq 1$.

Similar to the original Moran process, it is assumed that all individuals are selected simultaneously and randomly in events 1–3. Hence, if there are i mutants at the beginning of the time step, the probability of selecting a mutant in event 3 is i/N. In events 1 and 2, the probability of selecting a mutant for reproduction is also constant. However, the same individual cannot die twice; hence, if the same individual is selected to die in events 1 and event 2, a new random individual must be selected to die. Nevertheless, as shown in Subsection 2.2, for sufficiently large population sizes, the probability of selecting a mutant is approximately i/N in both events 1 and 2.

Initially, all the cells are the wild type and the fitness parameter equals zero. Eventually, a mutant is created, and it is assumed that the timescale of the mutants' fixation is much shorter than the timescale of mutation. Hence, a lineage of mutants is likely to take over the whole population or become extinct before another lineage of mutants is created from the wild type.

2.1. Event 1

Let i and j denote the numbers of intermediate mutants and resistant mutants, respectively, at the beginning of a given time step. Since the population size is constant, N, the number of wild-type individuals is $N - i - j$.

All individuals are selected to die and reproduce at the same constant rate. It is assumed that the same individual can be selected to reproduce and to die and that a new individual cannot be selected to die in the same time step in which it is produced. Thus, by ignoring further mutations, the probabilities that an intermediate mutant, a resistant mutant and a wild-type individual is selected to reproduce or to die are

$$P_{im} = \frac{i}{N}, \tag{6}$$

$$P_{rm} = \frac{j}{N}, \tag{7}$$

$$P_w = \frac{N-i-j}{N}, \tag{8}$$

respectively. Hence, we obtain the following transition probabilities for event 1:

$$\begin{aligned}
\mathrm{P}^1(i+1,j|i,j) &= \frac{i}{N}\frac{N-i-j}{N},\\
\mathrm{P}^1(i+1,j-1|i,j) &= \frac{i}{N}\frac{j}{N},\\
\mathrm{P}^1(i,j+1|i,j) &= \frac{j}{N}\frac{N-i-j}{N},\\
\mathrm{P}^1(i-1,j+1|i,j) &= \frac{i}{N}\frac{j}{N},\\
\mathrm{P}^1(i-1,j|i,j) &= \frac{i}{N}\frac{N-i-j}{N},\\
\mathrm{P}^1(i,j-1|i,j) &= \frac{j}{N}\frac{N-i-j}{N},\\
\mathrm{P}^1(i,j|i,j) &= 1-2\frac{i}{N}\frac{N-i-j}{N}-2\frac{i}{N}\frac{j}{N}-2\frac{j}{N}\frac{N-i-j}{N}.
\end{aligned}$$

2.2. Event 2

If the fitness parameter is below Υ, then nothing occurs in event 2. On the other hand, if the fitness parameter is higher than Υ, then a non-resistant individual can be selected to die.

To obtain a simplistic model, we want the probability of selecting a given type of individual to be constant throughout the time step. As discussed in Appendix A, this is the case for the standard Moran process.

By assuming that a new individual cannot be selected to reproduce or die in the same time step in which it was produced, and that the same individual can be selected to reproduce several times and to die in the same time step, the probabilities that an individual selected to reproduce in event 2 is an intermediate mutant, a resistant mutant and a wild type are given in (6), (7) and (8), respectively.

On the other hand, the same individual cannot die several times. That is, the probability that an intermediate mutant will be selected to die in event 1

is i/N, and, in this case, the probability of selecting an intermediate mutant to die in event 2 is $(i-1)/(N-1)$. The probability that the individual selected to die in event 1 is not an intermediate mutant, is $1-i/N$, and, in this case, the probability of selecting an intermediate mutant to die in event 2 is $i/(N-1)$. Thus, it follows by the rule of total probability that the probability that an intermediate mutant is selected to die in event 2, given that the fitness parameter is higher than Υ, is

$$P^2_{-im} = \frac{i}{N}\frac{i-1}{N-1} + \left(1-\frac{i}{N}\right)\frac{i}{N-1} = \frac{i}{N-1} - \frac{1}{N(N-1)}.$$

For large population sizes, $1/(N-1) \approx 1/N$ and $1/N >> 1/N^2$. Hence, P^2_{-im} tends to

$$P^2_{-im} = \frac{i}{N}.$$

For similar reasons, if the fitness parameter is higher than Υ, then the probability that a wild-type individual is selected to die in event 2 tends to

$$P^2_{-w} = \frac{N-i-j}{N}$$

for large population sizes, and consequently the transition probabilities for event 2 are

$$\mathrm{P}^2(i-1, j|i, j) = \frac{i}{N}\frac{N-i-j}{N}, \tag{9}$$

$$\mathrm{P}^2(i, j-1|i, j) = \frac{j}{N}\frac{N-i-j}{N}, \tag{10}$$

$$\mathrm{P}^2(i-1, j+1|i, j) = \frac{i}{N}\frac{j}{N}, \tag{11}$$

$$\mathrm{P}^2(i+1, j-1|i, j) = \frac{i}{N}\frac{j}{N}, \tag{12}$$

$$\mathrm{P}^2(i, j|i, j) = 1 - \frac{i}{N}\frac{N-i-j}{N} - 2\frac{i}{N}\frac{j}{N} - \frac{j}{N}\frac{N-i-j}{N}. \tag{13}$$

2.3. Events 3 and 4

Event 3 captures the assumption that the mutants raise the fitness parameter. The main reason why the fitness parameter is raised by $1/N$ in this event is that the growth environment is subdivided into N sites in Section 3.

Event 4 captures the diffusion of the fitness parameter. If $F = 0$, then the population is in an isolated growth environment, whereas, if $F = 1$, the fitness parameter decreases to zero at the end of every time step.

2.4. Expected functions

When the fitness parameter is lower than the fitness threshold Υ, the competition dynamics between the mutants and the wild type is identical to an

ordinary neutral Moran process. Thus, we are interested in how long it takes for the mutants to change the competition dynamics by increasing the fitness parameter to a level higher than Υ. In this subsection, we derive the expected time until the fitness parameter reaches this limit.

We expect that the number of mutants must reach a certain limit, ν, before the fitness parameter approaches Υ. Since the population dynamics is identical to a neutral Moran process when the fitness parameter is below Υ, we can use the following theorem to find the probability that the number of mutants will reach ν.

Theorem 2.1. *The probability that the neutral Moran process will reach the state in which there are ν mutants, given that the present number of mutants is i, is*

$$P(\text{reach } \nu \mid i\ ) = \frac{i}{\nu},$$

where $0 \leq i \leq \nu$.

Theorem 2.1 is a standard result in Markov chain analysis [25]; hence, the proof is left to Appendix B.

It follows from Theorem 2.1 that most lineages of mutant cells become extinct before they reach the state ν if $\nu > 2$. We are interested in investigating the lineages that survive long enough for the fitness parameter to reach the threshold Υ.

Theorem 2.2. *Conditioning on the fact that the neutral Moran process eventually reaches the state in which there are ν mutants, the transition probabilities for $0 < i < \nu$ are*

$$P_\nu(i+1|i) = \frac{i+1}{N}\left(1 - \frac{i}{N}\right) \tag{14}$$

$$P_\nu(i-1|i) = \frac{i-1}{N}\left(1 - \frac{i}{N}\right) \tag{15}$$

$$P_\nu(i|i) = 1 - 2\frac{i}{N}\left(1 - \frac{i}{N}\right) \tag{16}$$

where i is the present number of mutants.

Proof. We have four events:

- A_1: the next time step moves to state $i+1$.
- A_2: the next time step moves to state $i-1$.
- B: the process is currently in state i.
- C: the process will reach state ν.

For $k \in 1, 2$, we want to determine the conditional probability

$$\mathrm{P}(A_k|B \cap C) = \frac{A_k \cap B \cap C}{B \cap C}.$$

It follows from Theorem 2.1 that

$$\begin{aligned}
\mathrm{P}(\text{reach } \nu|i) &= \mathrm{P}(C|B) = \frac{\mathrm{P}(B \cap C)}{\mathrm{P}(B)} = \frac{i}{\nu}, \\
\mathrm{P}(\text{reach } \nu|i+1) &= \mathrm{P}(C|A_1 \cap B) = \frac{\mathrm{P}(A_1 \cap B \cap C)}{\mathrm{P}(A_1 \cap B)} = \frac{i+1}{\nu}, \\
\mathrm{P}(\text{reach } \nu|i-1) &= \mathrm{P}(C|A_2 \cap B) = \frac{\mathrm{P}(A_2 \cap B \cap C)}{\mathrm{P}(A_2 \cap B)} = \frac{i-1}{\nu},
\end{aligned}$$

and it follows from the transition probabilities given in (1)–(3), with $u = 0$ and $r = 1$, that

$$\begin{aligned}
\mathrm{P}(i+1|i) &= \mathrm{P}(A_1|B) = \frac{\mathrm{P}(A_1 \cap B)}{\mathrm{P}(B)} = \frac{i}{N}\left(1 - \frac{i}{N}\right), \\
\mathrm{P}(i-1|i) &= \mathrm{P}(A_2|B) = \frac{\mathrm{P}(A_2 \cap B)}{\mathrm{P}(B)} = \frac{i}{N}\left(1 - \frac{i}{N}\right).
\end{aligned}$$

Thus, we obtain the following equality:

$$\begin{aligned}
\mathrm{P}(A_k|B \cap C) &= \frac{\mathrm{P}(A_k \cap B \cap C)}{\mathrm{P}(B \cap C)} \\
&= \frac{\mathrm{P}(A_k \cap B \cap C)}{\mathrm{P}(B \cap C)} \left(\frac{\mathrm{P}(A_k \cap B)}{\mathrm{P}(A_k \cap B)}\right) \left(\frac{\mathrm{P}(B)}{\mathrm{P}(B)}\right) \\
&= \left(\frac{\mathrm{P}(A_k \cap B \cap C)}{\mathrm{P}(A_k \cap B)}\right) \left(\frac{\mathrm{P}(A_k \cap B)}{\mathrm{P}(B)}\right) \left(\frac{\mathrm{P}(B \cap C)}{\mathrm{P}(B)}\right)^{-1} \\
&= \frac{\mathrm{P}(C|A_k \cap B)\mathrm{P}(A_k|B)}{\mathrm{P}(C|B)}.
\end{aligned}$$

Hence,

$$\begin{aligned}
\mathrm{P}(A_1|B \cap C) &= \frac{\mathrm{P}(C|A_1 \cap B)\mathrm{P}(A_1|B)}{\mathrm{P}(C|B)} = \frac{\frac{i+1}{\nu}\frac{i}{N}\left(1 - \frac{i}{N}\right)}{\frac{i}{\nu}} = \frac{i+1}{N}\left(1 - \frac{i}{N}\right), \\
\mathrm{P}(A_2|B \cap C) &= \frac{\mathrm{P}(C|A_2 \cap B)\mathrm{P}(A_2|B)}{\mathrm{P}(C|B)} = \frac{\frac{i-1}{\nu}\frac{i}{N}\left(1 - \frac{i}{N}\right)}{\frac{i}{\nu}} = \frac{i-1}{N}\left(1 - \frac{i}{N}\right).
\end{aligned}$$

□

Proposition 2.3. *Conditioning on the fact that the neutral Moran process eventually reaches the state in which there are ν mutants, the expected number of mutants before the process reaches ν is approximately*

$$\mu(t) = N - (N-1)\exp(-2t/N) \tag{17}$$

in generation t, where one generation is N time steps and the first mutant is generated at $t = 0$.

Proof. It follows from the transition probabilities given in Equations (14)–(16) that the expected number of mutant cells, $\mu(t)$, must satisfy

$$\begin{aligned}\mu(t+1/N) &= \mu(t) + \frac{\mu(t)+1}{N}\left(1-\frac{\mu(t)}{N}\right) - \frac{\mu(t)-1}{N}\left(1-\frac{\mu(t)}{N}\right) \\ &= \mu(t) + \frac{2}{N}\left(1-\frac{\mu(t)}{N}\right).\end{aligned}$$

We use the following approximation:

$$\frac{\mathrm{d}\mu}{\mathrm{d}t}(t) \approx \frac{\mu(t+1/N)-\mu(t)}{1/N} = 2\left(1-\frac{\mu(t)}{N}\right).$$

The differential equation has general solutions of the following form:

$$\mu(t) = N + \alpha\exp(-2t/N),$$

where α is a constant. Since the first mutant was generated at $t=0$, that is, $\mu(0)=1$, we obtain the solution

$$\mu(t) = N - (N-1)\exp(-2t/N).$$

□

We finally arrive at an expression for the expected fitness parameter given that the mutants survive long enough to change the competition dynamics.

Proposition 2.4. *Conditioning on the fact that the extended Moran process with non-constant fitness eventually reaches the state in which there are ν mutants, given that the fitness parameter is below Υ, the expected fitness parameter in generation t is approximately*

$$\begin{aligned}\Gamma(t) = \frac{1-F}{FN} &- \exp(-2t/N)\left(\frac{(1-F)(N-1)}{N^2F-2}\right) \\ &+ \exp(-NFt)\left(\Gamma(0) + \frac{1-F}{FN} - \frac{(1-F)(N-1)}{N^2F-2}\right)\end{aligned}$$

for $F \neq 0$ and

$$\Gamma(t) = t + \frac{N-1}{2}(\exp(-2t/N)-1) + \Gamma(0)$$

for $F \approx 0$, where the first mutant is generated at $t=0$ and $\Gamma(0)$ is the fitness parameter when the first mutant in the lineage is generated.

Proof. It follows from events 3 and 4, given at the beginning of Section 2, that the fitness parameter, $\Gamma(t)$, must satisfy

$$\Gamma(t+1/N) = (\Gamma(t) + \mu(t)/N^2)(1-F),$$

where $\mu(t)$ is the expected number of mutant cells given in Equation (17). By using the approximation

$$\frac{\mathrm{d}\Gamma}{\mathrm{d}t}(t) \approx \frac{\Gamma(t+1/N) - \Gamma(t)}{1/N},$$

we obtain the differential equation

$$\frac{\mathrm{d}\Gamma}{\mathrm{d}t} + NF\Gamma = \frac{1-F}{N}\mu.$$

For $F = 0$, we have general solutions of the form

$$\begin{aligned}\Gamma(t) &= 1/N \int \mu(t)dt \\ &= 1/N \int N - (N-1)\exp(-2t/N)dt \\ &= t + \frac{N-1}{2}\exp(-2t/N) + \alpha,\end{aligned}$$

where α is a constant. Thus, we obtain

$$\Gamma(t) = t + \frac{N-1}{2}(\exp(-2t/N) - 1) + \Gamma(0),$$

where $\Gamma(0)$ is the fitness parameter when the first mutant is generated. For $F \neq 0$, we have

$$\Gamma(t) = \exp(-NFt)\left(\Gamma(0) + \frac{1-F}{N}\int_0^t \exp(NFy)\mu(y)\mathrm{d}y\right).$$

Since

$$\begin{aligned}&\int_0^t \exp(NFy)(N - (N-1)\exp(-2y/N))\mathrm{d}y \\ &= \frac{\exp\left(-\frac{2t}{N}\right)\left(\left(\left(FN^2-2\right)\exp\left(\frac{2t}{N}\right) - FN^2 + FN\right)\exp\left(FNt\right) + (2-FN)\exp\left(\frac{2t}{N}\right)\right)}{F\left(FN^2-2\right)},\end{aligned}$$

we obtain

$$\begin{aligned}\Gamma(t) = \frac{1-F}{FN} &- \exp(-2t/N)\left(\frac{(1-F)(N-1)}{N^2F-2}\right) \\ &+ \exp(-NFt)\left(\Gamma(0) + \frac{1-F}{FN} - \frac{(1-F)(N-1)}{N^2F-2}\right).\end{aligned}$$

□

2.4.1. Expected functions and numerical simulations

Figure 1 displays the expected functions and numerical simulations of the extended Moran process. In all cases, the fitness parameter remains below the fitness threshold; hence, the growth of the mutant population is only driven by stochasticity. Consequently, the population dynamics is characterised by great variation. Figures 1(a)–(f) display the expected functions and simulations of mutant populations that reach population size $\nu = 10^3$, starting with a single mutant. It follows from Theorem 2.1 that the probability that a single mutant will generate a lineage of mutants that reaches population size $\nu = 10^3$ is $\rho = 10^{-3}$, regardless of the total population size. Indeed, for all three population sizes, $N = 10^3$, $N = 10^4$ and $N = 10^6$, we performed on average a thousand simulations to obtain one simulation in which the mutant population size reached $\nu = 10^3$, starting with a single mutant.

Note that the transition probabilities given in (14)–(16) and the expected number of mutants given in (17) do not contain the term ν. It is shown in the respective proofs that the terms with ν cancel out. However, a more intuitive explanation is as follows. The expected functions plotted in Figure 1 condition on the fact that the mutant populations reach the size $\nu = 10^3$. However, suppose that we stopped the simulations when the mutant populations reached the size $\nu_0 = 10^2$. Should this change the expected function? Clearly not. This is also compatible with the fact that neither the transition probabilities given in (14)–(16) nor the expected number of mutants depend on the size of ν.

In Figures 1(a)–(d), the diffusion rate of the fitness parameter, F, equals the inverse of the total population size, $1/N$. On these terms, it is expected that the fitness parameter is approximately F times the number of mutants. In point of fact, the simulations of the fitness parameter are close to F times the simulations of the number of mutants. In Figures 1(e)–(h), the diffusion rate of the fitness parameter, F, equals zero. In this case, the fitness parameter cannot decrease but is expected to increase as long as there are mutant individuals in the population. Figures 1(e) and 1(f) display the expected function and simulation of a mutant population that reaches the population size $\nu = 1500$, starting with a single mutant, and the corresponding fitness parameter, respectively. As illustrated in Figure 1(e), the mutant population size decreases in some time intervals for the simulation. However, as displayed in Figure 1(f), the fitness parameter does not decrease. In the simulation displayed in Figure 1(g), the mutant population size fluctuates before the mutant type becomes extinct around generation $t = 1600$. Even though the number of mutants remains below $\nu = 750$, the fitness parameter reaches 54. On the other hand, in the simulation displayed in Figures 1(e) and 1(f), the population size is close to $\nu = 1500$ when the fitness parameter is approximately 54. Thus, the simulation displayed in Figures 1(g) and 1(h) illustrates that, when F is equal to or relatively close to zero, then the mutant population can raise the fitness parameter to relatively high levels by delaying extinction.

2.5. The fitness parameter reaches the fitness threshold

In this subsection, we consider the case in which the fitness parameter reaches the fitness threshold, Υ, which means that the death rate of both the intermediate mutants and the wild-type individuals decrease whereas the resistant mutants become advantageous.

Let ν be the number of mutants. If no resistant mutant has been generated, the competition between the wild-type individuals and the intermediate mutants can be captured by a neutral Moran process; hence, it follows from Equation (5) that the probability that the intermediate mutants will invade the whole population is ν/N, given that no resistant mutant is generated before the intermediate mutants reach fixation.

On the other hand, if at least one resistant mutant has been generated, this lineage has a great advantage, because these cells survive when the fitness parameter is high. Thus, when the fitness parameter is higher than Υ, the resistant mutants are expected to invade the whole population.

If the timescale of fixation of the resistant mutants is much shorter than the timescale of mutation from the intermediate to the resistant type, then a lineage of resistant mutants is likely to take over the whole population or become extinct before another resistant mutant is created from the intermediate type. In this case, the expected number of resistant mutants in generation t, denoted $\chi(t)$, can be approximated as follows. In event 1 of the time step described at the beginning of Section 2, all the cells are expected to reproduce and die at the same rate; thus, $\chi(t)$ remains constant. On the other hand, if a cell that is not resistant is selected in event 2, then the selected cell dies, and a random cell is selected to reproduce. As derived in Subsection 2.2, the number of resistant mutants can either increase by one with probability $\pi(j) = \frac{j}{N}\left(1 - \frac{j}{N}\right)$ or remain constant with probability $1 - \pi(j)$, where j is the number of resistant mutants. Consequently, the expected number of resistant mutants in generation t must satisfy the equality

$$\chi(t + 1/N) = \chi(t) + \pi(\chi(t)).$$

We use the approximation

$$\frac{\mathrm{d}\chi}{\mathrm{d}t}(t) \approx \frac{\chi(t + 1/N) - \chi(t)}{1/N}$$

and obtain the differential equation

$$\frac{\mathrm{d}\chi}{\mathrm{d}t} = \chi\left(1 - \frac{\chi}{N}\right)$$

which has the solution

$$\chi(t) = \frac{N\chi(0)\exp(t)}{\chi(0)(\exp(t) - 1) + N}, \tag{18}$$

where $\chi(0)$ is the number of resistant mutants when the fitness parameter reaches the threshold Υ. Clearly $\chi(t)$ converges to N, which means that the

resistant mutants are expected to invade the whole population. The expected number of individuals that are not resistant is $N - \chi(t)$. Since intermediate mutants and wild-type individuals are neutral variants, the relation

$$\frac{\text{expected number of intermediate mutants}}{\text{expected number of wild-type individuals}}$$

remains constant. Thus, the expected number of intermediate mutants is approximately

$$\phi(t) = \frac{\nu - \chi(0)}{N - \chi(0)}(N - \chi(t))$$

and the expected number of wild-type individuals is approximately

$$\zeta(t) = \frac{N - \nu}{N - \chi(0)}(N - \chi(t)),$$

where ν is the total number of mutants when the fitness parameter reaches the threshold, Υ. Clearly, both the wild-type individuals and the intermediate mutants are expected to become extinct.

2.5.1. Expected functions and numerical simulations

Figures 2–4 display the expected functions and numerical simulations of the extended Moran process. In all cases, a mutant is generated in generation $t = 0$, and, since the mutants and the wild type are neutral variants as long as the fitness parameter is below Υ, the mutant population grows due to stochasticity and the population dynamics is characterised by great variation.

For the simulation illustrated in Figures 2 and 4, the fitness parameter reaches the fitness threshold, Υ. This means that the death rate of both the intermediate mutants and the wild-type individuals increases, whereas the resistant mutants become advantageous. If there is no resistant mutant in the population when the fitness parameter is above Υ, the probability that the intermediate mutants will invade the whole population is i/N, where i is the number of mutants and N is the total population size. For the simulation illustrated in Figure 3, the number of intermediate mutants is approximately $i = 10^3$ when the fitness parameter reaches the fitness threshold $\Upsilon = 0.1$. The mutation rate, μ_1, is relatively low; hence, no resistant mutant has been generated. Since the total population size is $N = 10^5$, the probability that the intermediate mutants will invade the whole population, given that no resistant mutant is generated, is $P_{inv} = 10^{-2}$. Due to stochasticity, the mutant population size nearly doubles before it starts decreasing. Since the diffusion rate of the fitness parameter, F, is relatively high, the fitness parameter decreases to a level below Υ soon after the number of mutants decreases to $i = 10^3$, and ultimately the mutant population becomes extinct.

The simulation illustrated in Figure 2 has the same low mutation rate as the simulation illustrated in Figure 3, and therefore there is no resistant mutant in the population when the fitness parameter reaches Υ. However, due to stochasticity, the fitness parameter remains above the fitness threshold Υ, and,

after approximately $t = 200$ generations, a resistant mutant is generated. This type is expected to invade the population, because it survives when the fitness parameter is high, and this makes it a very advantageous type. In point of fact, the growth of resistant mutants lies close to the expected function given in (18), as illustrated in Figure 2d.

The simulation displayed in Figure 4 has a relatively high mutation rate, and thus there are resistant mutants present in the population when the fitness parameter reaches the fitness threshold, Υ. The resistant type invades the population, but, as illustrated in Figures 2d and 4d, for the simulations with high mutation rates, the growth of the mutants does not lie as close to the expected function as the simulations with a low mutation rate. The reason for this is that the expected function given in (18) assumes that $\mu_1 \approx 0$, and this assumption does not hold when μ_1 is high.

3. Extended Moran process with cooperation entities

In this section, *cooperation entities* that can kill mutants, are included in the extended Moran process. Cooperation entities can represent regulation mechanisms that defend a cooperation, for instance T-cells in a multicellular organism. This is discussed in greater detail in Subsection 4.2. However, cooperation entities can also represent the cost of cooperation, for instance when cooperators invade a group of defectors, as discussed in Subsection 4.1.

The population still consists of N individuals, which are subdivided into three types, namely the wild type, intermediate mutants and resistant mutants. However, in events 5–8, the intermediate mutants and the resistant mutants behave identically; consequently, we simply refer to them as mutants.

In addition, there are up to N cooperation entities. The growth environment in which the population is located is subdivided into N sites. Each site contains exactly one individual; furthermore, each site can contain exactly one cooperation entity or no cooperation entity. At the beginning of each time step, the process passes through events 1–4, which are described in Section 2. Afterwards, the following events occur:

5. A random site is selected. If the site contains both a mutant and a cooperation entity, the mutant dies and a random individual is selected to reproduce.

6. A random site is selected, and, if this site contains a cooperation entity, it reproduces. The new cooperation entity is placed in a random site that does not already contain a cooperation entity at the end of the time step.

7. A random site is selected, and, if the site contains a cooperation entity, it dies.

8. A random site is selected. If the site contains a mutant and no cooperation entity, then, with probability P_d, a cooperation entity is activated and placed in the selected site.

At the end of each time step, all the individuals of the population are mixed and placed in random sites. As discussed in Section 2, it is assumed that, in all the events for each time step, the individuals are selected simultaneously. This assumption also holds for the cooperation entities. That is, if there are k cooperation entities at the beginning of a time step, then the probability that the selected site will contain a cooperation entity is k/N in both event 6 and event 7.

3.1. Event 5

If the selected site contains a wild-type individual, then nothing occurs at event 5. On the other hand, if the selected site contains both a cooperation entity and a mutant, then the mutant dies.

Since the population is mixed at the end of each time step, the probability that the selected site will contain both a mutant and a cooperation entity is

$$P_{de\ m} = \frac{k}{N}\frac{i}{N},$$

where k is the number of cooperation entities and i is the number of mutants.

As discussed in Subsections 2.1 and 2.2 and in Appendix A, we want the probability of selecting a given type of individual to be constant throughout the time step to keep the model as simplistic as possible. In Subsection 2.2, we show that the probability of selecting an individual to reproduce or die is approximately constant in events 1 and 2 for large population sizes. Since the same argument holds for event 5, the probabilities that the number of mutants decrease by one and remain constant in event 5 are

$$\mathrm{P}^5(i-1|i) = \frac{k}{N}\frac{i}{N}\left(1-\frac{i}{N}\right), \tag{19}$$

$$\mathrm{P}^5(i|i) = 1-\frac{k}{N}\frac{i}{N}\left(1-\frac{i}{N}\right), \tag{20}$$

respectively, where k and i are the number of cooperation entities and the number of mutants at the beginning of the time step, respectively.

3.2. Events 6–8

The cooperation entities are activated by the mutants. In addition, the cooperation entities can reproduce and die. We assume that the same cooperation entity can be selected to reproduce and die in the same time step and that a new cooperation entity cannot be selected to die in the time step in which it is produced. These are similar to the assumptions made in the Moran process, discussed in Appendix A.

Let k and i denote the numbers of cooperation entities and mutants at the beginning of the time step, respectively. The probability that a cooperation entity will be selected to reproduce and to die in events 6 and 7, respectively, is

$$P_{ce} = \frac{k}{N},$$

whereas the probability that a cooperation entity will be activated by a mutant in event 8 is

$$P_{ac\ ce} = P_d \frac{i}{N} \left(1 - \frac{k}{N}\right). \tag{21}$$

3.3. Implications of cooperation entities

As discussed more thoroughly in Subsection 4.1, cooperation entities can represent cooperation. Moreover, they can represent T cells. As discussed in Subsection 1.3, if an APC recognises an antigen on a mutated cell, the production of CTLs is activated. This activation is captured by event 8. The CTLs are programmed to find and kill mutated cells, which is captured by event 5. The exact details of how the T cells are regulated and activated are uncertain. For instance, it is still unknown why APCs do not always recognise antigens on mutated cells. One hypothesis is that APCs only activate CTLs if healthy tissue is being injured [26]. In our model, healthy tissue, which is represented by the wild type, is not injured as long as the fitness parameter is below Υ. Hence, in some examples, the cooperation entities are not activated until the fitness parameter reaches this limit, whereas, in other examples, the cooperation entities are activated earlier.

In Section 2, the intermediate mutants and the wild type are neutral variants. However, when the cooperation entities are included, there is much more at stake for the mutants. If the activation of cooperation entities only depends on the presence of mutated cells, the mutants are disadvantageous when the fitness parameter is below Υ. Hence, the survival of the mutants depends on how fast they raise the fitness parameter, because resistant mutants become advantageous when the fitness parameter is higher than Υ. On the other hand, if the cooperation entities are not activated until the fitness parameter reaches Υ, the mutants and the wild type are neutral variants when the fitness parameter is below Υ, whereas the fitness of the mutants depends on whether a resistant mutant has been generated when the fitness parameter reaches Υ. That is, if all the mutants are of the intermediate type, then these cells are disadvantageous, whereas, if resistant mutants have been generated, these cells become advantageous. Hence, the probability of mutant invasion increases if the fitness parameter remains below Υ until a resistant mutant has been generated.

3.4. The cooperation entities are activated before the fitness parameter reaches the fitness threshold

When the activation of cooperation entities only depends on the presence of mutant cells, the mutants are disadvantageous when the fitness parameter is below Υ. That is, all individuals have the same probability of being selected to die and reproduce in event 1. However, in event 5, mutants can be selected to die if they are located in a site with a cooperation entity, whereas wild-type individuals can only be selected to reproduce in this event.

In event 5, the number of mutants either decreases by one or remains constant with probabilities given in (19) and (20), respectively. Hence, the expected number of mutants in generation t, $\phi(t)$, must satisfy

$$\phi(t+1/N) = \phi(t) - \frac{\kappa(t)}{N}\frac{\phi(t)}{N}\left(1 - \frac{\phi(t)}{N}\right),$$

where $\kappa(t)$ is the expected number of cooperation entities in generation t. By using the approximation

$$\frac{\mathrm{d}\phi}{\mathrm{d}t}(t) \approx \frac{\phi(t+1/N) - \phi(t)}{1/N},$$

we obtain the following differential equation:

$$\frac{\mathrm{d}\phi}{\mathrm{d}t} = -\kappa\frac{\phi}{N}\left(1 - \frac{\phi}{N}\right). \tag{22}$$

As discussed in Subsection 3.2, the probability that a cooperation entity will reproduce equals the probability that a cooperation entity will die in events 6 and 7, respectively; hence, the number of cooperation entities is expected to remain constant after these two events. In event 8, a cooperation entity is activated by a mutant with probability $P_{ac\ ce}$, given in (21). Otherwise, the number of cooperation entities remains constant. Hence, the expected number of cooperation entities must satisfy the difference equation

$$\kappa(t+1/N) = \kappa(t) + P_d\frac{\phi(t)}{N}\left(1 - \frac{\kappa(t)}{N}\right).$$

By using the approximation

$$\frac{\mathrm{d}\kappa}{\mathrm{d}t}(t) \approx \frac{\kappa(t+1/N), -\kappa(t)}{1/N}$$

we obtain the following differential equation:

$$\frac{\mathrm{d}\kappa}{\mathrm{d}t} = P_d\phi\left(1 - \frac{\kappa}{N}\right). \tag{23}$$

3.4.1. Numerical simulations

Figures 5–7 display numerical simulations of the extended Moran process with cooperation entities. In all the cases, the activation of cooperation entities depends only on the presence of the mutant cells. Hence, the mutants are disadvantageous when the fitness parameter is below Υ. On the other hand, the resistant mutants become advantageous if the fitness parameter reaches the fitness threshold Υ. Thus, the survival of the mutants depends on how fast they raise the fitness parameter.

When the fitness parameter is below Υ, it follows from the differential equation given in (22) that, if there is at least one cooperation entity in the system,

it is expected that the number of mutants will decrease until the mutants are extinct. However, the extinction can be delayed due to stochasticity, and, given that the diffusion rates of both the fitness parameter, F, and the fitness threshold, Υ, are relatively low, it is possible that the mutants will survive long enough to raise the fitness parameter above Υ. Due to stochasticity, the mutants become extinct before the fitness parameter reaches the fitness threshold, $\Upsilon = 2.5$, in the simulation illustrated in Figure 5, whereas, in the simulation displayed in Figure 6, the mutants survive long enough for the fitness parameter to reach the fitness threshold. Furthermore, if the mutant population produces at least one resistant mutant, this type of cells becomes advantageous when the fitness parameter is above Υ and is expected to invade the whole population.

It follows from the differential equation given in (23) that, if there is at least one mutant in the system, the number of cooperation entities is expected to grow until it reaches N. However, if the activation rate, P_d, is relatively low, then the activation of the cooperation entities can be delayed due to stochasticity. In this case, the mutants and the wild type are initially neutral variants, and the mutants can grow in number due to stochasticity. On these terms, the fitness parameter can reach the fitness threshold, Υ, even when it is relatively high. Moreover, the probability that the mutant population will produce a resistant type increases as the number of mutants increases. This scenario is illustrated in Figure 7.

3.5. The fitness parameter reaches the fitness threshold

When the fitness parameter reaches the fitness threshold, Υ, the intermediate mutants and the wild-type individuals have the same probability of being selected to die and reproduce in events 1 and 2. However, in event 5, the intermediate mutants can be selected to die if they are located in a site with a cooperation entity, whereas the wild-type individuals can only be selected to reproduce in this event. Hence, the wild-type individuals are more advantageous than the intermediate mutants.

If the mutants produce a resistant lineage, these mutants will be more advantageous than the wild-type individuals when the fitness parameter is higher than Υ and there are relatively few cooperation entities. That is, in event 1, the resistant mutants and the wild-type individuals have the same probability of being selected to die and to reproduce, whereas each wild-type individual has a probability $1/N$ of being selected to die in event 2, and each resistant mutant has a probability k/N^2 of being selected to die in event 5, where k is the number of cooperation entities. Thus, if each site contains a cooperation entity, the competition dynamics between the resistant mutants and the wild-type individuals is neutral, and the resistant mutants are increasingly advantageous with a decreasing number of cooperation entities.

Let i, j and k denote the number of intermediate mutants, resistant mutants and cooperation entities, respectively. Since the total number of individuals in the population is constant, N, the number of wild-type individuals is $N - i - j$.

It follows from the transition probabilities given in (9)–(13) that the probabilities that the number of intermediate mutants will decrease by one, remain

constant and increase by one in event 2 are

$$q^2_{-1}(j,i,k) = \pi(i), \tag{24}$$

$$q^2_0(j,i,k) = 1 - 2\pi(i) - \frac{ij}{N^2}, \tag{25}$$

$$q^2_1(j,i,k) = \pi(i) - \frac{ij}{N^2}, \tag{26}$$

respectively, where $\pi(i) = i/N(1 - i/N)$. Moreover, since the intermediate mutants and the resistant mutants are neutral variants in event 5, it follows from Subsection 3.1 that the probabilities that the number of intermediate mutants will decrease by one, remain constant and increase by one in event 5 are

$$\begin{aligned}
q^5_{-1}(j,i,k) &= \frac{k}{N}\pi(i), \\
q^5_0(j,i,k) &= 1 - \frac{k}{N}\left(\pi(i) + \frac{ij}{N^2}\right), \\
q^6_1(j,i,k) &= \frac{k}{N}\frac{ij}{N^2},
\end{aligned}$$

respectively. Thus, the probabilities that the number of intermediate mutants will decrease by two, decrease by one, increase by one and increase by two after events 2 and 5 are

$$\begin{aligned}
Q^{2,5}_{-2}(j,i,k) &= \frac{k}{N}\pi(i)^2, \\
Q^{2,5}_{-1}(j,i,k) &= \pi(i)\left(1 + \frac{k}{N}(1 - 3\pi(i)\right), \\
Q^{2,5}_{1}(j,i,k) &= \pi(i)\left(1 - \frac{k}{N}\left(\pi(i) + \frac{ij}{N^2}\right)\right) + \frac{ij}{N^2}\left(-1 + \frac{k}{N}\left(1 - \pi(i) + 2\frac{ij}{N^2}\right)\right), \\
Q^{2,5}_{2}(j,i,k) &= \frac{k}{N}\frac{ij}{N^2}\left(\pi(i) - \frac{ij}{N^2}\right),
\end{aligned}$$

respectively; hence, the expected number of intermediate mutants in generation t, $\phi(t)$, must satisfy

$$\begin{aligned}
\phi(t + 1/N) = \phi(t) &- 2Q^{2,5}_{-2}(\chi(t),\phi(t),\kappa(t)) - Q^{2,5}_{-1}(\chi(t),\phi(t),\kappa(t)) \\
&+ Q^{2,5}_{1}(\chi(t),\phi(t),\kappa(t)) + 2Q^{2,5}_{2}(\chi(t),\phi(t),\kappa(t)),
\end{aligned}$$

where $\chi(t)$ and $\kappa(t)$ are the expected numbers of resistant mutants and cooperation entities, respectively, in generation t. By using the approximation

$$\frac{\mathrm{d}\phi}{\mathrm{d}t}(t) \approx \frac{\phi(t + 1/N) - \phi(t)}{1/N},$$

we obtain the following differential equation:

$$\frac{\mathrm{d}\phi}{\mathrm{d}t} = -\phi\left(\left(1 - \frac{\phi}{N}\right)\frac{\kappa}{N} + \frac{\chi}{N}\left(1 - \frac{\kappa}{N}\right)\right). \tag{27}$$

Since $\phi, \kappa \leq N$, it follows that the expected number of intermediate mutants decreases towards zero.

We will now derive an approximation for the expected number of resistant mutants. It follows from the transition probabilities given in (9)–(13) that the probabilities that the number of resistant mutants will remain constant and increase by one in event 2 are

$$\begin{aligned} p_0^2(j,i,k) &= 1-\pi(j), \\ p_1^2(j,i,k) &= \pi(j), \end{aligned}$$

respectively, where $\pi(j) = j/N(1-j/N)$. Since the mutants are neutral variants in event 5, it follows from Subsection 3.1 that the probabilities that the number of resistant mutants will decrease by one, remain constant and increase by one in event 5 are

$$\begin{aligned} p_{-1}^5(j,i,k) &= \frac{k}{N}\pi(j), \\ p_0^5(j,i,k) &= 1-\frac{k}{N}\left(\pi(j)+\frac{ij}{N^2}\right), \\ p_1^5(j,i,k) &= \frac{k}{N}\frac{ij}{N^2}, \end{aligned}$$

respectively. Thus, the probabilities that the number of resistant mutants will decrease by one, increase by one and increase by two after events 2 and 5 are

$$\begin{aligned} P_{-1}^{2,5}(j,i,k) &= \frac{k}{N}\pi(j)(1-\pi(j)), \\ P_1^{2,5}(j,i,k) &= \pi(j)\left(1-\frac{k}{N}\left(\pi(j)+\frac{ij}{N^2}\right)\right)+\frac{k}{N}\frac{ij}{N^2}(1-\pi(j)), \\ P_2^{2,5}(j,i,k) &= \frac{k}{N}\frac{ij}{N^2}\pi(j), \end{aligned}$$

respectively; hence, the expected number of resistant mutants must satisfy

$$\begin{aligned} \chi(t+1/N) = \chi(t) &- P_{-1}^{2,5}(\chi(t),\phi(t),\kappa(t)) \\ &+ P_1^{2,5}(\chi(t),\phi(t),\kappa(t)) + 2P_2^{2,5}(\chi(t),\phi(t),\kappa(t)). \end{aligned}$$

By using the approximation

$$\frac{\mathrm{d}\chi}{\mathrm{d}t}(t) \approx \frac{\chi(t+1/N)-\chi(t)}{1/N},$$

we obtain the differential equation

$$\frac{\mathrm{d}\chi}{\mathrm{d}t} = \chi\left(\left(1-\frac{\chi}{N}\right)\left(1-\frac{\kappa}{N}\right)+\frac{\phi}{N}\frac{\kappa}{N}\right).$$

Since

$$N = \chi(t) + \phi(t) + \zeta(t),$$

where $\zeta(t)$ is the expected number of healthy cells, it follows that

$$\frac{\mathrm{d}\zeta}{\mathrm{d}t} = -\frac{\mathrm{d}\chi}{\mathrm{d}t} - \frac{\mathrm{d}\phi}{\mathrm{d}t} = \zeta\left(\left(1 - \frac{\zeta}{N}\right)\frac{\kappa}{N} - \frac{\chi}{N}\right).$$

The expected number of cooperation entities is described by the differential equation given in (23). Hence, the expected numbers of resistant mutants, wild-type individuals and cooperation entities are described by the following system of differential equations:

$$\frac{\mathrm{d}\chi}{\mathrm{d}t} = \chi\left(1 - \frac{\chi}{N} - \frac{\zeta}{N}\frac{\kappa}{N}\right), \tag{28}$$

$$\frac{\mathrm{d}\zeta}{\mathrm{d}t} = \zeta\left(\left(1 - \frac{\zeta}{N}\right)\frac{\kappa}{N} - \frac{\chi}{N}\right), \tag{29}$$

$$\frac{\mathrm{d}\kappa}{\mathrm{d}t} = P_d N\left(1 - \frac{\zeta}{N}\right)\left(1 - \frac{\kappa}{N}\right), \tag{30}$$

respectively. The system is in equilibrium on the line

$$\mathcal{L}^* = \{\kappa = N, \zeta + \chi = N\},$$

and the point

$$(\chi^*, \zeta^*, \kappa^*) = (0, 0, N).$$

The domain

$$\mathcal{D} = \{0 \leq \kappa, \zeta + \chi \leq N | 0 \leq \zeta, \chi\}$$

is bounded by the following five planes:

$$\begin{aligned}
\mathcal{P}^1 &= \{\kappa = N | 0 \leq \chi, \zeta \ ; \ \zeta + \chi \leq N\}, \\
\mathcal{P}^2 &= \{\chi + \zeta = N | 0 \leq \chi, \zeta \ ; \ 0 \leq \kappa \leq N\}, \\
\mathcal{P}^3 &= \{\chi = 0 | 0 \leq \kappa, \zeta \leq N\}, \\
\mathcal{P}^4 &= \{\zeta = 0 | 0 \leq \kappa, \chi \leq N\}, \\
\mathcal{P}^5 &= \{\kappa = 0 | 0 < \chi, \zeta \ ; \ \zeta + \chi < N\}.
\end{aligned}$$

Clearly, a solution of the system of differential equations given in (28)–(30) cannot leave the domain $\mathcal{D}$. Moreover, it follows from the differential equations given in (28) and (30) that both χ and κ grow in the interior of $\mathcal{D}$, denoted $\mathcal{D}^*$. Hence, any solution with initial values in $\mathcal{D}^*$ will grow towards the equilibrium line, $\mathcal{L}^*$.

3.6. $\mathcal{P}^1$: N cooperation entities

When all the sites contain a cooperation entity, the resistant mutants and the wild-type individuals are neutral variants, whereas the intermediate mutants are disadvantageous. Substituting $\kappa = N$ into the differential equation given in (27), we obtain

$$\frac{\mathrm{d}\phi}{\mathrm{d}t} = -\phi\left(1 - \frac{\phi}{N}\right).$$

By scaling the generations such that $t = 0$ is the generation when the number of cooperation entities reaches N, we obtain

$$\phi(t) = \frac{N\phi(0)\exp(-t)}{\phi(0)(\exp(-t) - 1) + N}.$$

Clearly, $\phi(t)$ converges to zero. Since the resistant mutants and the wild-type individuals are neutral variants, the expected number of resistant mutants is

$$\chi(t) = \frac{\chi(0)}{N - \phi(0)}\left(N - \phi(t)\right)$$

and the expected number of wild-type individuals is

$$\zeta(t) = \frac{\zeta(0)}{N - \phi(0)}\left(N - \phi(t)\right).$$

Thus, $\chi(t)$ converges to $\frac{\chi(0)N}{N-\phi(0)}$, whereas $\zeta(t)$ converges to $\frac{\zeta(0)N}{N-\phi(0)} = N - \frac{\chi(0)N}{N-\phi(0)}$.

Figure 9 displays a numerical simulation of the extended Moran process with N cooperation entities. In this case, the resistant mutants and the wild type are neutral variants, whereas the intermediate mutants are disadvantageous. Hence, the ratio of resistant mutants and wild-type individuals is expected to remain constant, whereas the intermediate mutants are expected to become extinct. Since the resistant mutants and the wild type are neutral variants, their competition dynamics is characterised by great variation, whereas the simulation of the intermediate mutants lies close to the expected function, as illustrated by Figure 9.

3.7. $\mathcal{P}^2$: The intermediate mutants become extinct

In this subsection, we consider the case in which all the intermediate mutants become extinct. By substituting $\zeta = N - \chi$ into the differential equations given in (28) and (30), we obtain

$$\frac{\mathrm{d}\chi}{\mathrm{d}t} = \chi\left(1 - \frac{\chi}{N}\right)\left(1 - \frac{\kappa}{N}\right) \tag{31}$$

$$\frac{\mathrm{d}\kappa}{\mathrm{d}t} = P_d\chi\left(1 - \frac{\kappa}{N}\right). \tag{32}$$

It follows from the differential equations above that κ grows until $\kappa = N$, whereas χ grows as longs as $\chi < N$ and $\kappa < N$. Since $\frac{\mathrm{d}\zeta}{\mathrm{d}t} = -\frac{\mathrm{d}\chi}{\mathrm{d}t}$, it follows that ζ decreases as long as $\chi < N$ and $\kappa < N$. The case in which χ reaches N before κ corresponds to the invasion of resistant mutants and the extinction of wild-type individuals, whereas the case in which κ reaches N before κ corresponds to the survival of both the wild type and the resistant type, as described in Subsection 3.6

It follows from the differential equations given in (31) and (32) that

$$\frac{\frac{\mathrm{d}\kappa}{\mathrm{d}t}}{\frac{\mathrm{d}\chi}{\mathrm{d}t}} = \frac{\mathrm{d}\kappa}{\mathrm{d}\chi} = \frac{P_{APC}}{1 - \frac{\chi}{N}}$$

for $0 < \chi < N$ and $\kappa < N$. Thus,

$$\int \mathrm{d}\kappa = NP_d \int \frac{\mathrm{d}\chi}{(N - \chi)}.$$

Hence, a solution of the system given in 31 and 32, $\Omega(t) = (\chi(t), N - \chi(t), \kappa(t)) \in \mathcal{P}^1$, with initial value $\Omega(0) = (\chi(0), N - \chi(0), \kappa(0)) \in \mathcal{P}^1$, where $0 < \chi(0) < N$ and $\kappa(0) < N$, must satisfy

$$\begin{aligned}
\kappa(t) &= \kappa(0) + NP_d \ln\left(\frac{N - \chi(0)}{N - \chi(t)}\right) \\
\zeta(t) &= N - \chi(t),
\end{aligned}$$

as long as $\chi(t) < N$ and $\kappa(t) < N$. We are interested in investigating whether the cooperation entities or the resistant mutants reach the population size N first. To achieve this, we make use of the fact that the process is discrete and investigate which population is expected to reach the population size $N-1$ first. For sufficiently large population sizes, this is equivalent to reaching N. We have

$$\kappa(t) = \kappa(0) + NP_d \ln\left(\frac{N - \chi(0)}{N - \chi(t)}\right) = N - 1$$

for

$$\chi(t) = N - \frac{N - \chi(0)}{\exp\left(\frac{N - (\kappa(0)+1)}{NP_d}\right)}.$$

Hence, $\kappa(t)$ reaches $N - 1$ before $\chi(t)$ if

$$1 < \frac{N - \chi(0)}{\exp\left(\frac{N - (\kappa(0)+1)}{NP_d}\right)}.$$

The above inequality can be expressed as

$$\frac{N - (\kappa(0) + 1)}{N \ln(N - \chi(0)} < P_d. \tag{33}$$

3.7.1. Numerical simulations

Figures 10–13 display simulations in which the fitness parameter reaches the fitness threshold, Υ, and there is a race between the resistant mutants and the cooperation entities to reach population size N. The inequality given in (33) is derived under the assumption that the intermediate mutants are extinct, and this is not the case when the first resistant mutant appears in the simulations illustrated in Figures 10–13. However, since the intermediate mutants become very disadvantageous, their population size decreases rapidly, and therefore the inequality in (33) gives a good indication of whether the cooperation entities win the race to reach population size N.

The activation rate of the cooperation entities is very high in the example illustrated in Figure 11. Consequently, the left side, which equals 0.1, is less than the right side, which equals 1, in the inequality given in (33), and this indicates that the cooperation entities will win the race. In point of fact, the number of cooperation entities reaches N when the number of resistant mutants is approximately 4×10^4. The example illustrated in Figure 10 has a moderate activation rate of the cooperation entities, and both sides of the inequality given in (33) are approximately 0.1. Indeed, the number of cooperation entities grows more slowly towards N than the number of resistant mutants.

If there are no resistant mutants in the population when the fitness parameter reaches Υ, it is possible that the cooperation entities will win the race towards N even though the cooperation entities are activated at a moderate rate. That is, the examples given in Figures 10 and 13 have the same activation rate. However, in the example illustrated in Figure 13, there are approximately 7×10^3 cooperation entities in the system when the first resistant mutant is produced. Thus, the left side, which equals 0.08, is less than the right side, which equals 0.1, in the inequality given in (33). In fact, the number of cooperation entities reaches N when the number of resistant mutants is approximately 8×10^4.

However, if the activation rate of the cooperation entities is sufficiently low, the resistant mutants can invade the system even though the production of the first resistant mutant is delayed. In the example given in Figure 12, there are approximately 7×10^3 cooperation entities in the system when the first resistant mutant is produced. However, the left side, which equals 0.08, is higher than the right side, which equals 0.01, in the inequality given in (33). Indeed, the resistant mutants reach the population size N first.

4. Discussion

Several other models and texts describe situations in which relatively stable populations are invaded by an alternative strategy. Examples are the evolution of cooperation among bacteria and multicellularity [14],[27]–[29], the invasion of cancer [19]–[24] and the evolution of ideas that contradict social norms [30],[31]. These models and texts are more detailed and sophisticated than the model described in this paper. However, by keeping our model simplistic, it applies to different situations, as illustrated by the examples below. Hence, our model gives

a more general description of the dynamics that occur when a stable population is invaded by an alternative strategy.

4.1. Evolution of cooperation among bacteria and multicellularity

When life started to evolve about four billion years ago, the first life forms adopted the most basic strategy, which is to outcompete other individuals by dividing as fast as possible [2]. However, proliferation requires resources, such as space and nutrient molecules, and different individuals can have access to some resources and no access to other resources. In these situations, cooperation can be beneficial [10],[14],[27].

A simplified example of cooperation among single-celled organisms is that one cell has access to enough nutrient molecules for two cell divisions but no space, whereas another cell has access to enough space for two cell divisions but no nutrient molecules. Thus, if the two cells share their resources, that is, mutual cooperation, they will both reproduce. On the contrary, if the two cells do not share their resources, that is, mutual defection, neither of the cells will reproduce. However, if only one cell shares its resources and the other does not share, then the cooperator does not reproduce and loses its resources whereas the defector reproduces twice.

This simple example illustrates the dilemma of cooperation: even though mutual cooperation leads to a higher payoff than mutual defection, a defector has a higher payoff than a cooperator when they meet. Indeed, it is a version of the prisoner's dilemma, which is discussed in Subsection 1.2.

Moreover, a group of cooperating cells is vulnerable to intruders and mutants that stop cooperating, because these cells can invade the colony by exploiting the cooperating cells [32]. Hence, a group of cooperators can only survive in the long term if it develops regulation mechanisms that control the cooperation, for instance by modifying the microenvironment such that the defectors lose their advantages. Indeed, the evolution of multicellular organisms was driven by increasingly advanced regulation mechanisms among cooperating cells [14].

A small group of cooperators can invade a large population of defectors if they manage to change the environment such that defection becomes a disadvantageous strategy. This is illustrated by Figure 6. In the context of the evolution of cooperation among cells, the wild-type individuals represent defectors and the intermediate mutants represent unconditional cooperators. Cooperation is captured by the cooperation entities.

The fitness parameter represents the evolution of regulation mechanisms, whereas the resistant mutants represents conditional cooperators. In a nutshell, the conditional cooperators cooperate with cells that are of the same type and create a microenvironment that kills cells that are of a different type. As illustrated by Figure 5 and 6, the cooperators are disadvantageous when the fitness parameter is below Υ. Indeed, in the example given in Figure 5, the cooperators become extinct. On the other hand, due to stochasticity, the cooperators survive long enough to raise the fitness parameter above Υ in the example illustrated by Figure 5, and then the conditional cooperators invade the whole population.

4.2. The invasion of cancer

As discussed in Subsections 1.3 and 4.1, the human body has an advanced defence system that attacks mutant cells that have stopped cooperating. Hence, mutant cells are in general disadvantageous when they first appear in the body, and, what is more, mutant cells that progress into cancer typically change their microenvironment and create new variants that are advantageous in the new microenvironment [19]–[24]. This dynamics is captured by the model presented in this paper. In this context, the cooperation entities represent the immune response, such as T cells, whereas the wild type and the mutant type represent the healthy cells and the mutant cells, respectively.

Figures 5–7 illustrate the case in which T cells detect and kill mutant cells before they cause any harm, whereas Figures 8 and 10–13 illustrate the case in which T cells are only activated if they harm healthy tissue. In the first case, the healthy cells are initially advantageous, whereas, in the latter case, the competition dynamics is neutral. Given that mutants can evolve into cancer cells, it might seem that the best strategy is to kill them once they appear in the body. However, too aggressive an immune system poses a greater risk to the body than mutant cells with minor genetic errors [26],[33].

The body can limit the blood flow to mutant cells. Hence, these cells must break down the end product of glycolysis anaerobically, and this leads to an acidic microenvironment [20]. In the model, the acid level is represented by the fitness parameter. When the acid level reaches the limit Υ, the death rate of the cells that are not acid resistant increases. Moreover, since the mutants are harming the healthy cells, the T cells are activated. Thus, the non-resistant mutants become less advantageous than the healthy cells, and, as illustrated in Figure 8, they are expected to become extinct if they do not produce an acid-resistant variant. On the other hand, if the mutant cells survive long enough such that they produce a variant that is acid resistant, this cell type has a great advantage, because they can kill other cells by increasing the acid level, as illustrated in Figures 10–13.

As illustrated by the examples given in Figures 10–13, there is a race between the acid-resistant mutants and the T cells. If the T cells respond quickly, such that there is a T cell at every site in the microenvironment before the normal cells become extinct, the acid-resistant mutants are neutralised. In this case, the mutant cells are vulnerable to new attacks from the body's defence mechanisms.

On the other hand, if the normal cells become extinct before there is a T cell at every site, the resistant mutants are expected to take over the microenvironment. This represents the onset of a more aggressive form of cancer. Indeed, many observations reveal that cancer cells exhibit glucose fermentation even when there is enough oxygen present. This is called the Warburg effect and has been described in several other papers.

The model by Robertson-Tessi et al. includes several other mechanisms of immune evasion that tumours use, including immunosuppressive surface markers such as PD-L1, the down-regulation of antigen presentation machinery, the recruitment of immunosuppressive immune cells and the secretion of immuno-

suppressive factors such as TGF-beta [22]. Moreover, several other models indicate that tissue architecture and signals between different microenvironments play major roles in population dynamics and the progression of cancer [34]–[36].

It is possible to include these mechanisms in our model. However, the main scope of this paper is to give a general characterisation of the dynamics that occur when a stable population is invaded; therefore, we keep the model as simple as possible.

4.3. Evolution of ideas that contradict social norms

Game and evolutionary theory can also be used to study human behaviour and society [37]. For instance, the founders of Marxism, Karl Marx and Friedrich Engels, were inspired by Charles Darwin [38].

The model can also capture the dynamics of political changes that are less dramatic than revolutions and dictatorships, for instance when politicians use populist rhetoric or, depending on who has the power of definition, speak freely. Sylvi Listhaug is a Norwegian politician for the Progress Party who was Minister of Migration from December 2015 to March 2018. Listhaug has been called the Trump of Norway, both as a compliment and as a criticism [39],[40].

The consensus of the Norwegian political elite is to address problems related to immigration and integration in a polite and indirect way. Hence, Listhaug's direct and confrontational style has created waves of reactions. Her critics claim that her aggressive style creates conflicts with people who could become allies and that she should rather focus on building a broad and inclusive alliance. A paper by Pinker et al. [41], in which the authors apply ideas from evolutionary biology and game theory to illuminate possible advantages of indirect speech, lend some support to Listhaug's critics. Pinker et al. argue that most human communication involves a mixture of cooperation and conflict and that indirect speech is used to negotiate the type of relationship holding between the speaker and the hearer. Moreover, indirectness in speech appears to be nearly universal [42].

However, when it comes to integration, indirect speech might promote parallel societies, because it can create misunderstandings about what is socially acceptable and make the majority society seem very complex and unmanageable.

Regardless of whether indirect speech is an advantage, breaking an unwritten law is associated with social stigmatisation. Thus, Listhaug must pay a cost for bringing up unpleasant issues related to migration and integration in a direct and, perhaps, populistic way [31]. Listhaug's statements are almost automatically considered to be controversial, as philosopher Lars Kolbeinstveit, from the liberal think tank Civita, writes in a text about Listhaug and the media [43].

In point of fact, after Listhaug claimed that the Labour Party puts the rights of terrorists above the security of the nation in a Facebook post, the reactions were so strong that Listhaug announced her resignation from the Government to avoid a vote of confidence [44].

Even though Listhaug reduced her political influence, at least on the short term, after she resigned as Minister of Immigration, her political party, the

Progress Party, gained support after her fall [45]. Moreover, there has been an increased use of words regarding anti-elitism as well as a more heated immigration debate on the Internet [46].

5. Conclusion

In this paper, an extension of the Moran process with non-constant fitness is presented. The model captures not only the competition between different types of individuals but also the struggle for fitness. That is, the type of individuals that manage to change the environment such that they become advantageous is expected to outcompete other types of individuals.

The model captures the dynamics that occurs when a relatively stable population is invaded by a new type of individuals and can reproduce the following events:

1. When a new type of individual appears in a relatively stable population, the newcomer is not advantageous.

2. Due to stochasticity, the new type grows in number and generates different versions of itself.

3. The new type becomes advantageous if it manages to change the environment such that at least one of its variants increases its fitness.

These events occur in different examples in which a relatively stable population is invaded by a new type of individuals, for instance the evolution of cooperation among bacteria and multicellularity, the invasion of cancer and the evolution of ideas that contradict existing social norms. Several models have already been proposed to describe these situations; however, none of them generalise the phenomena. Indeed, to our knowledge, the model presented in this paper is the first general model of competition dynamics in relatively stable populations that captures events 1–3.

Appendix A.

In this subsection, we summarise the way in which Wodarz and Komarova [3] obtain the transition probabilities for the Moran process given in (1)–(3).

The Moran process assumes that the population has A constant size, N, and consists of two types of individuals, denoted the wild type and the mutant type. The individuals can reproduce, mutate and die.

When a wild-type individual reproduces, the probability that it will produce a wild-type individual is $1-u$, and the probability that it will produce a mutant is u, where $0 \leq u \leq 1$. It is assumed that when a mutant individual reproduces, it always produces a new mutant. Moreover, the wild-type individuals have reproductive rate 1 and the mutants have reproductive rate r, where $r > 0$. Both types are selected to die at the same rate. In each time step, one individual

reproduces and one individual dies. It is assumed that the same individual can be selected both to reproduce and to die.

Let i denote the number of mutants at the beginning of a given time step. Thus, the number of wild-type individuals at the beginning of the time step is $N-i$. The probability that a wild-type individual will reproduce is proportional to its frequency and the reproductive rate and is given by $(N-i)/(N-i+ri)$. Similarly, the probability that a mutant will reproduce is $ri/(N-i+ri)$. Thus, the probabilities that the new individual will be a wild type and a mutant type are

$$P_{+w} = (1-u)\frac{N-i}{N-i+ri},$$
$$P_{+m} = u\frac{N-i}{N-i+ri} + \frac{ri}{N-i+ri},$$

respectively.

The Moran process assumes that the new individual cannot be selected to die in the time step in which it was produced. Hence, the probability that a type of individual will be selected to die depends on its abundance at the beginning of the time step. That is, the probabilities that the individual selected to die is a wild-type individual and a mutant are

$$P_{-w} = \frac{N-i}{N}, \tag{A.1}$$
$$P_{-m} = \frac{i}{N}, \tag{A.2}$$

respectively.

Note that, if the new individual could be selected to die in the same time step in which it was produced, then the probability that an individual of a certain type will be selected to die would depend on which type the new individual is. Moreover, the population size would be $N+1$ before the selected individual dies. Thus, the conditional probabilities that the individual selected to die is of a certain type would be

$$\mathrm{P}(A|B) = \frac{N+1-i}{N+1}, \tag{A.3}$$
$$\mathrm{P}(A|C) = \frac{N-i}{N+1}, \tag{A.4}$$
$$\mathrm{P}(D|B) = \frac{i}{N+1}, \tag{A.5}$$
$$\mathrm{P}(D|C) = \frac{i+1}{N+1}, \tag{A.6}$$

where the events A–D are as follows:

- A: a wild-type individual is selected to die.
- B: the new individual is wild type.

- C: the new individual is a mutant.
- D: a mutant is selected to die.

Hence, if the new individual could be selected to die in the same time step in which it was produced, the probabilities associated with each time step would be more complex; consequently, it would become more complicated to compute the absorption time and the probabilities of being absorbed. Furthermore, for a sufficiently large population size, N, the probability given in (A.1) is a reasonable approximation of the probabilities given in (A.3) and (A.4); likewise, (A.2) is a tolerable approximation of (A.5) and (A.6). These approximations are very good when i is close to $N/2$. However, for $i = 1$

$$\mathrm{P}(D|C) = 2\mathrm{P}(D|B),$$

and for $i = N - 1$

$$\mathrm{P}(A|B) = 2\mathrm{P}(A|C).$$

690 Even though the approximations are not very precise when i is either very small or close to N, the request for simplicity weighs more in the Moran model.

In each time step of the Moran process, the number of mutants can increase by one, decrease by one or remain constant. By assuming that the new individual cannot be selected to die in the time step in which it was produced, the probabilities of these three events are given by

$$\begin{aligned}
\mathrm{P}(i+1|i) &= P_{+m}P_{-w} = \frac{u(N-i)+ri}{N-i+ir}\frac{N-i}{N}, \\
\mathrm{P}(i-1|i) &= P_{+w}P_{-m} = \frac{(1-u)(N-i)}{N-i+ir}\frac{i}{N}, \\
\mathrm{P}(i|i) &= 1 - P(i+1|i) - P(i-1|i),
\end{aligned}$$

respectively.

Appendix B.

Given that the present number of mutants is i, there are $i-1$, i or $i+1$ mutants after the next time step. The probabilities for these events are given in Equations (1)–(3), respectively, with $r = 1$ and $u = 0$. Thus, the conditional probability of reaching state ν, $\mathrm{P}(\text{reach } \nu \mid i\ )$, must satisfy

$$\begin{aligned}
\mathrm{P}(\text{reach } \nu \mid i\ ) = \mathrm{P}(\text{reach } \nu \mid i-1\ )\frac{i}{N}\left(1-\frac{i}{N}\right) + \mathrm{P}(\text{reach } \nu \mid i\ )\left(1-2\frac{i}{N}\right) \\
+ \mathrm{P}(\text{reach } \nu \mid i+1\ )\frac{i}{N}\left(1-\frac{i}{N}\right).
\end{aligned}$$

This equation can be reduced to the following second-order difference equation with constant coefficients:

$$\mathrm{P}(\text{reach } \nu \mid i-1\ ) = 2\mathrm{P}(\text{reach } \nu \mid i\ ) - \mathrm{P}(\text{reach } \nu \mid i+1\ ).$$

Since the corresponding quadratic equation

$$r^2 - 2r + 1 = 0$$

has only one root, namely $r = 1$, the solutions of the difference equation have the form

$$\mathrm{P}(\text{reach } \nu \mid i\ ) = \alpha i + \beta$$

where α and β are constants. Note that the system has exactly two absorbing states, namely $i = 0$ and $i = \nu$, with corresponding transition probabilities $\mathrm{P}(\text{reach } \nu \mid 0\ ) = 0$ and $\mathrm{P}(\text{reach } \nu \mid \nu\ ) = 1$. Thus, we have the following boundary conditions:

$$0 = 2\mathrm{P}(\text{absorbed in } \nu \mid 1\ ) - \mathrm{P}(\text{absorbed in } \nu \mid 2\ )$$

$$\mathrm{P}(\text{absorbed in } \nu \mid \nu - 2\ ) = 2\mathrm{P}(\text{absorbed in } \nu \mid \nu - 1\ ) - 1.$$

We obtain $\alpha = 1/\nu$ and $\beta = 0$. Hence, the conditional probability for reaching ν is

$$\mathrm{P}(\text{reach } \nu \mid i\ ) = \frac{i}{\nu}.$$

Appendix C.

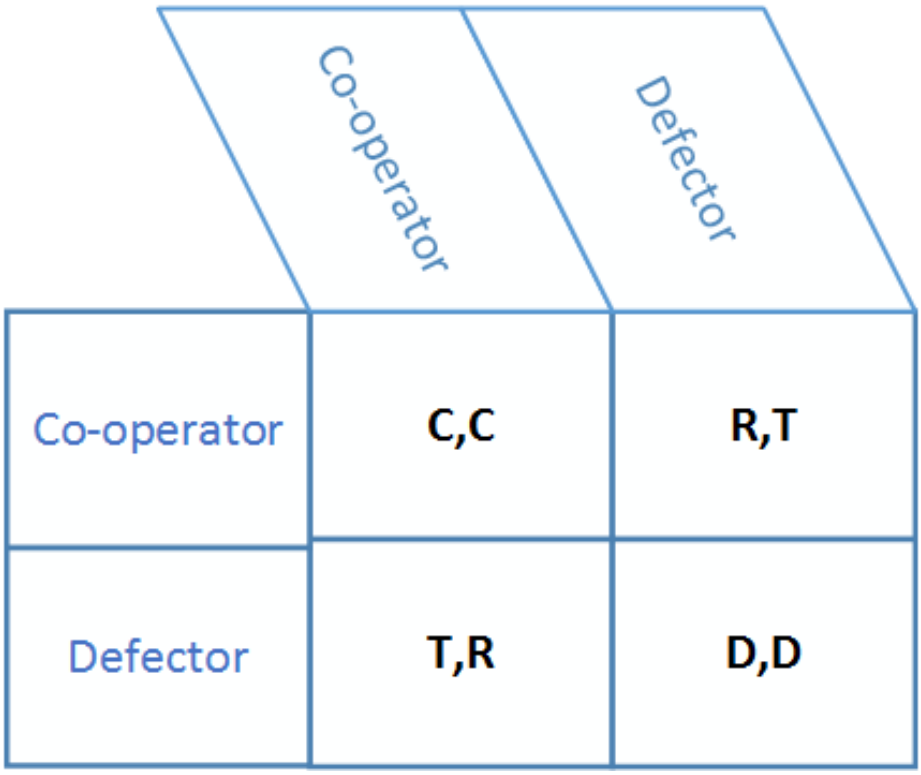

Table 1 Payoff matrix for prisoner's dilemma
This Table display the payoff matrix for a 2×2 game with two strategies, namely cooperation and defection. If the following inequalities $T > C > D > R$ hold, then the game is a version of the prisoner's dilemma.

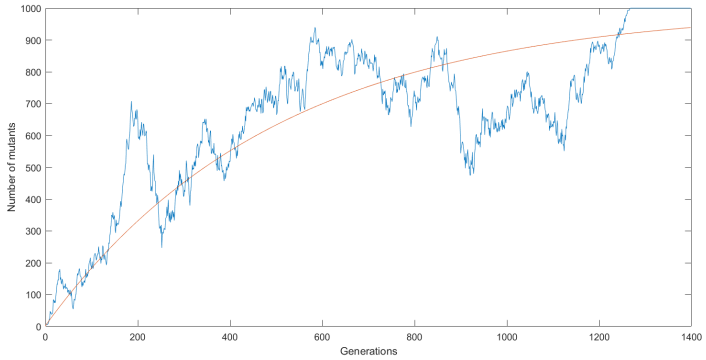

Figure 1a displays the number of mutants for $N = 10^3$ and $F = 10^{-3}$

Figure 1 Population dynamics when the fitness parameter is below Υ
When the fitness parameter is below Υ, the population dynamics is identical to a neutral Moran process. Moreover, starting with one mutant at generation $t = 0$, the probability that this lineage reaches population size $i = 10^3$ is 10^{-3}. The growth of the fitness parameter, depends on the diffusion rate, F. In Figure 1(a)(d), F equals the inverse of the total population size. On these terms, it is expected that the fitness parameter is approximately F times the number of mutants. And in point of fact, the fitness parameter is close to F times the number of mutants in the simulations displayed in (a)(d). On the other hand, in Figure 1(e)(h), F equals zero. In this case, the fitness parameter cannot decrease, but is expected to increase as long as there are mutants in the population. And indeed, the simulation displayed in Figure 1(e) and (f) illustrates that given that the number of mutants reaches $i = 1.5 \times 10^3$, it follows that the fitness parameter grows exponentially, whereas the simulation displayed in Figure 1(g) and (h) illuminates that the fitness parameter grows until the mutants are extinct.

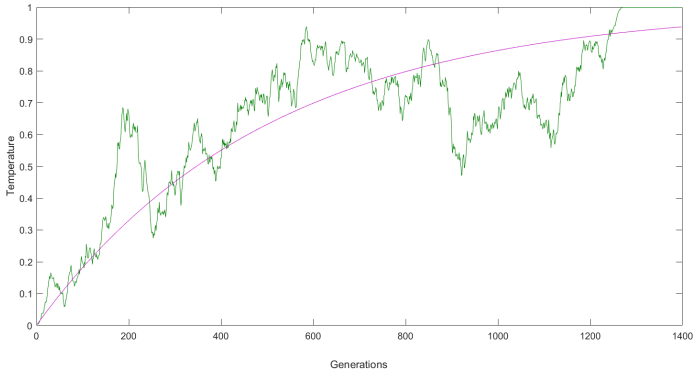

Figure 1b displays the fitness parameter for $N = 10^3$ and $F = 10^{-3}$.

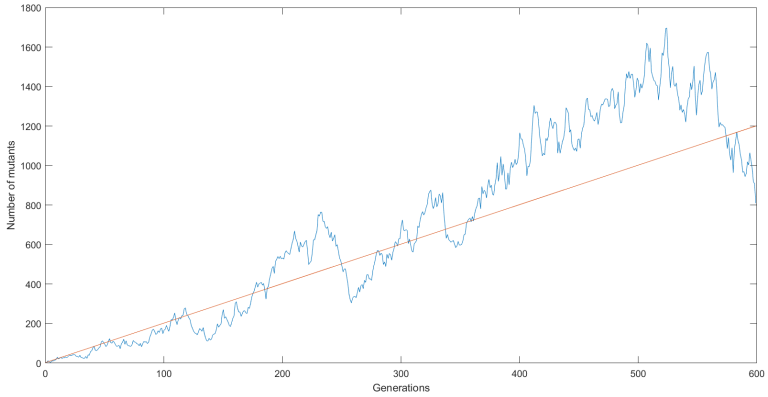

Figure 1c displays the number of mutants for $N = 10^6$ and $F = 10^{-6}$

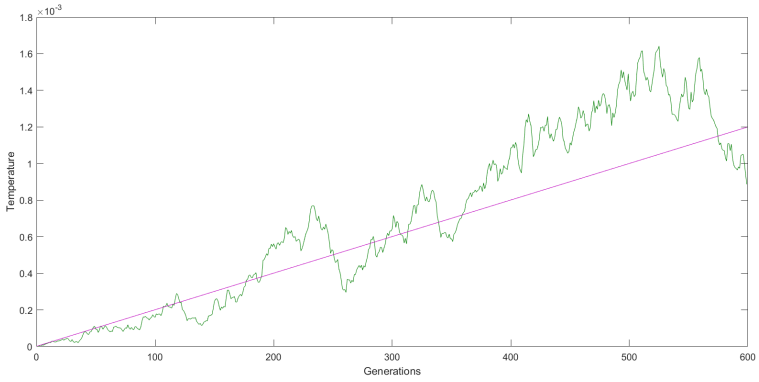

Figure 1d displays the fitness parameter for $N = 10^6$ and $F = 10^{-6}$

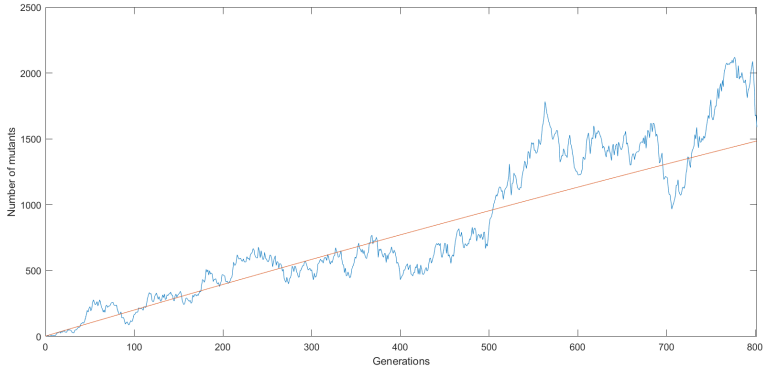

Figure 1e displays the number of mutants for $N = 10^4$ and $F = 0$

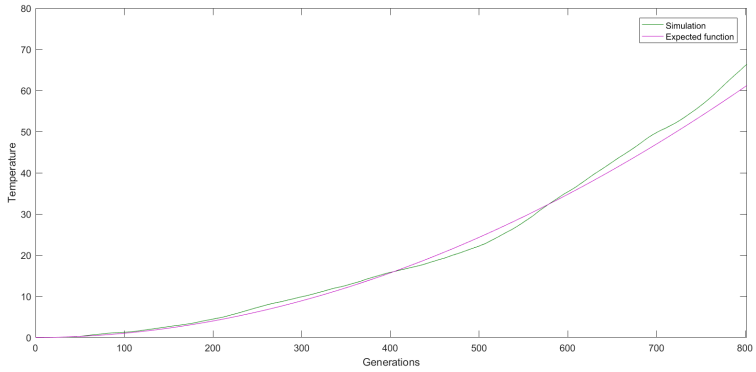

Figure 1f displays the fitness parameter for $N = 10^4$ and $F = 0$

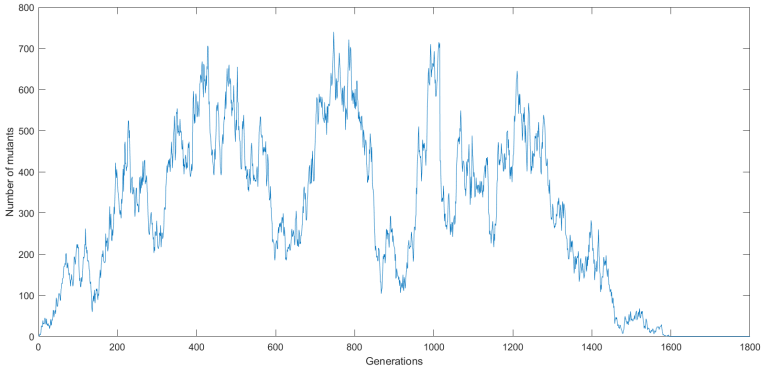

Figure 1g displays the number of mutants for $N = 10^4$ and $F = 0$

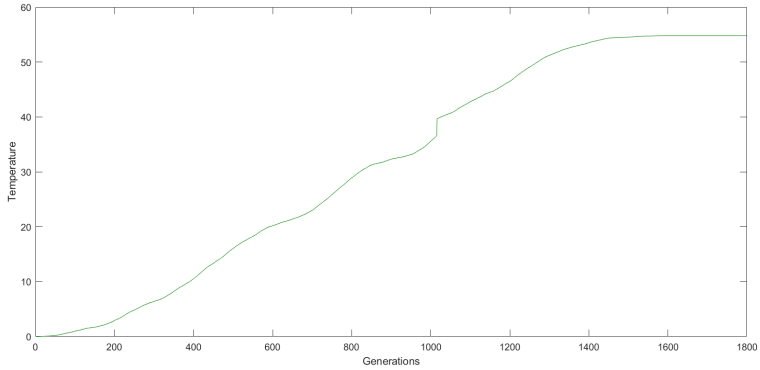

Figure 1h displays the fitness parameter for $N = 10^4$ and $F = 0$

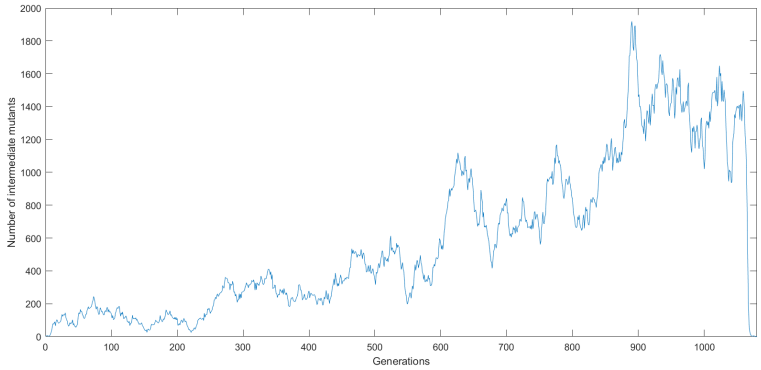

Figure 2a displays the number of intermediate mutants

Figure 2 Low mutation rate and high diffusion rate: Invasion of mutants
The first mutant is generated at generation $t = 0$, and due to stochasticity, the mutant population grows in number and the fitness parameter reaches the limit Υ at generation $t = 854$. Since both the mutant population size and the mutation rate, μ_1, are relatively small, no resistant individual is present in the population when the fitness parameter reaches the limit. However, at generation $t = 1058$, a resistant mutant is generated, and since this type of individual is very advantageous, it is expected to invade the whole population. And indeed, as illustrated in Figure 2(d), the growth of resistant mutants lies close to the expected function.
The parameter sizes are: $N = 10^5$, $\Upsilon = 0.1$, $\mu = 10^{-5}$ and $F = 10^{-6}$.

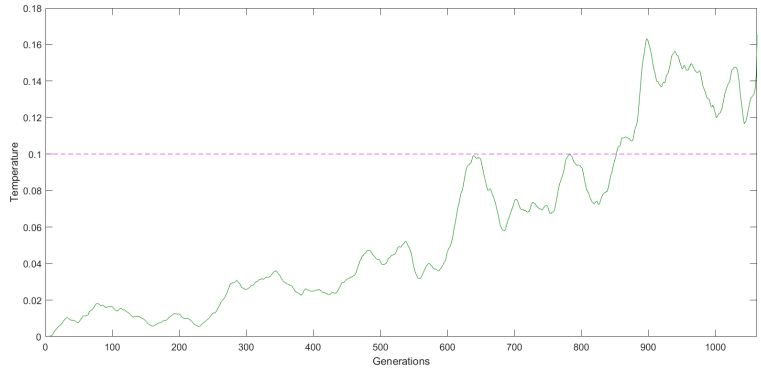

Figure 2b displays the fitness parameter and the pink dashed line marks the limit Υ

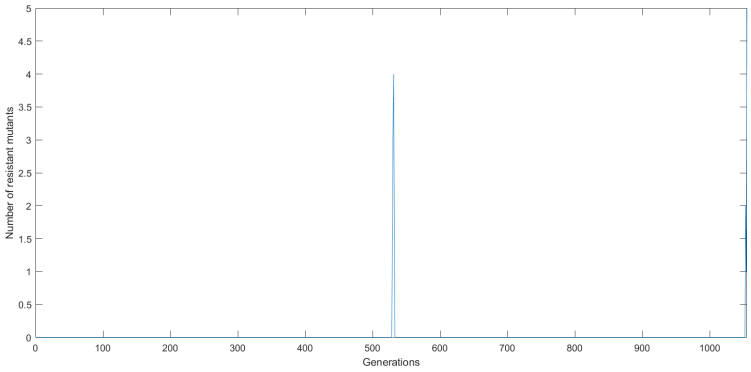

Figure 2c displays the number of resistant mutants before the invasion

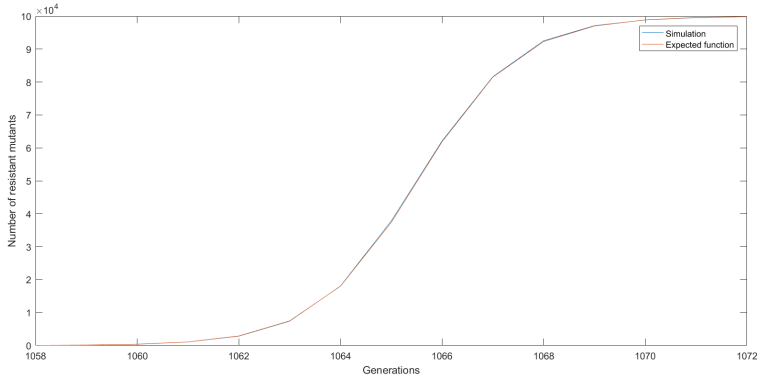

Figure 2d displays the invasion of resistant mutants, both the simulation and the expected function

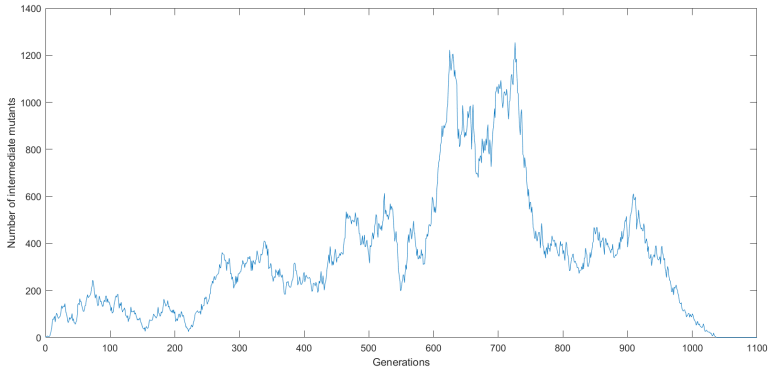

Figure 3a displays the number of intermediate mutants

Figure 3 Low mutation rate and high diffusion rate: Extinction of mutants
The first mutant is generated at generation $t = 0$, and due to stochasticity, the mutant population grows in number and the fitness parameter reaches the limit Υ at generation $t = 630$. Since both the mutant population size and the mutation rate, μ_1, are relatively small, no resistant individual is present in the population when the fitness parameter reaches the limit. Moreover, since the diffusion rate of the fitness parameter, F, is relatively high, the fitness parameter starts to decrease when the number of mutants decreases. Hence, the mutant population goes extinct.

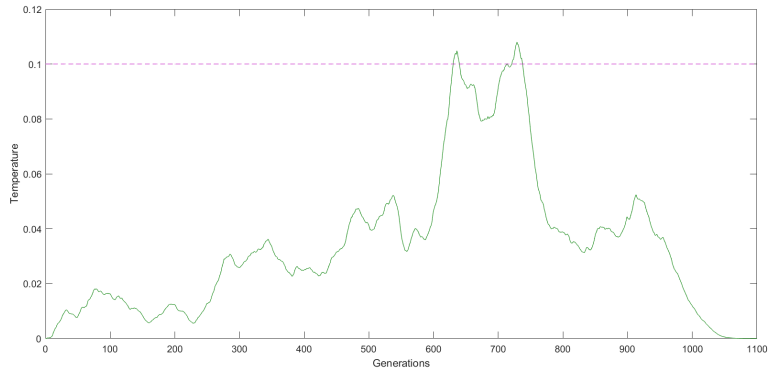

Figure 3b displays the fitness parameter and the pink dashed line marks the limit Υ

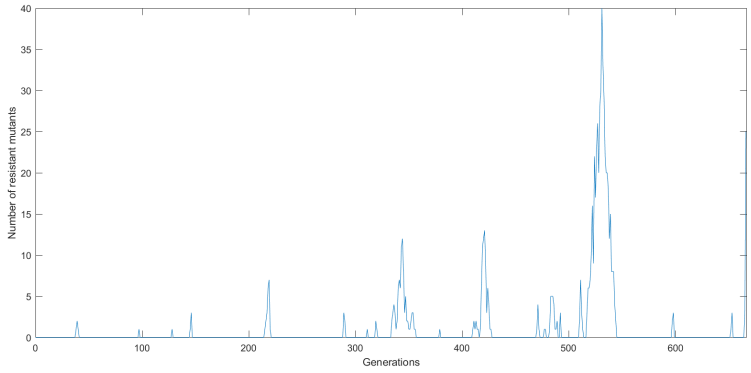

Figure 3c displays the number of resistant mutants

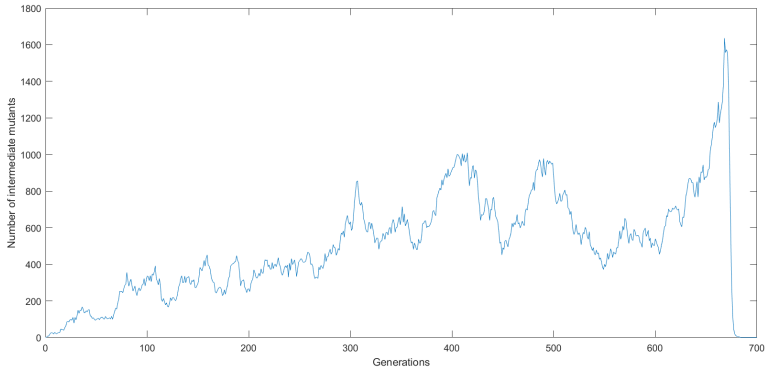

Figure 4a displays the number of intermediate mutants

High mutation rate: Invasion of mutants
The first mutant is generated at generation $t = 0$, and due to stochasticity, the mutant population grows in number and the fitness parameter reaches the limit Υ at generation $t = 662$. Since the mutation rate, μ_1, is relatively large, resistant individuals are present in the population when the fitness parameter reaches Υ. Moreover, since this type of individual is very advantageous, it is expected to invade the whole population. And indeed, as illustrated in Figure 3(d), the resistant mutants invade the population.
The parameter sizes are: $N = 10^5$, $\Upsilon = 0.1$, $\mu = 10^{-4}$ and $F = 10^{-6}$

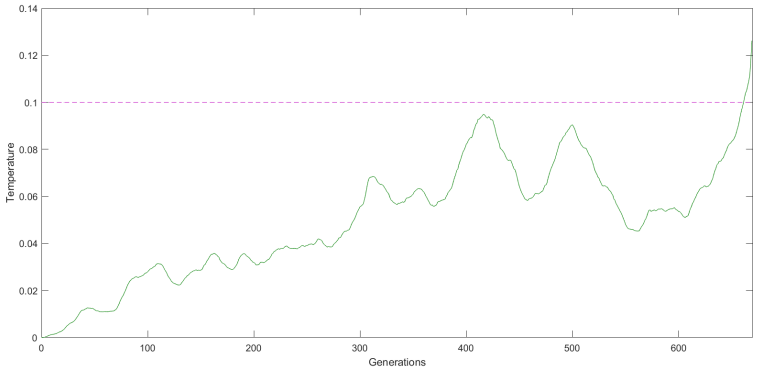

Figure 4b displays the fitness parameter and the pink dashed line marks the limit Υ

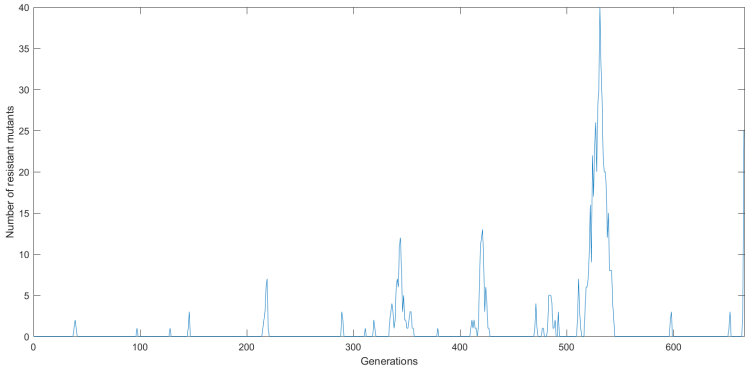

Figure 4b displays the number of resistant mutants before the invasion

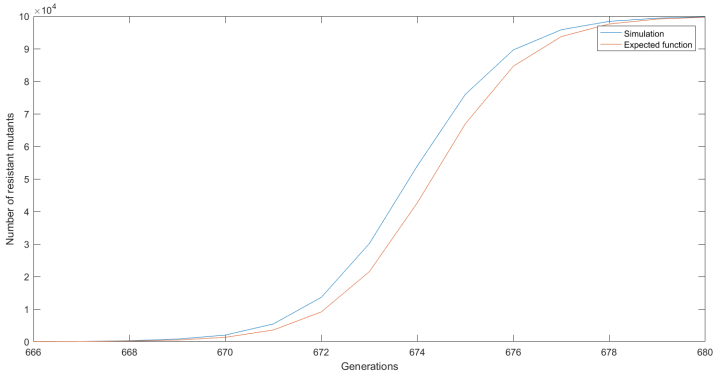

Figure 4c displays the invasion of resistant mutants, both the simulation and the expected function

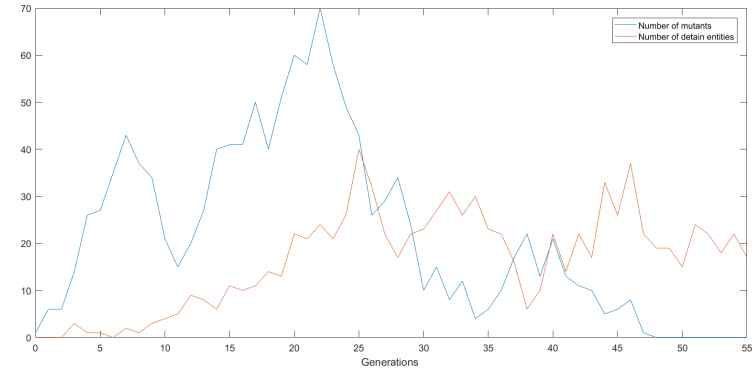

Figure 5a displays the number of mutants and the number of cooperation entities

The cooperation entities make the mutants disadvantageous
The first mutant is generated at generation $t = 0$, and almost immediately after, a cooperation entity is activated. The population of cooperation entities grows in number, whereas the mutant population gets extinct before the fitness parameter reaches the limit Υ.
The parameter sizes are: $N = 10^3$, $\Upsilon = 2.5$, $\mu = 10^{-3}$, $P = 0.01$, $F = 10^{-5}$.

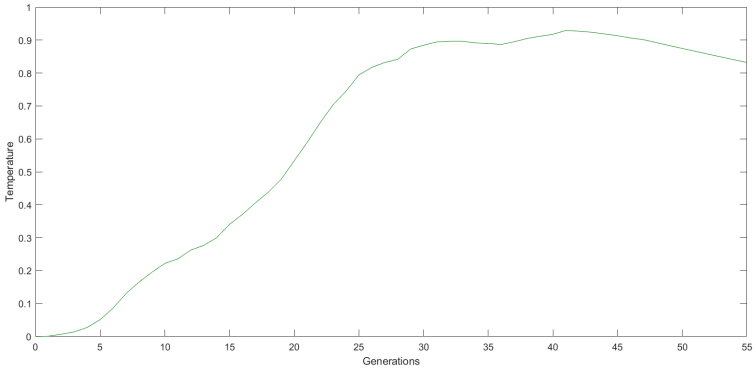

Figure 5b displays the fitness parameter and the pink dashed line marks the limit Υ

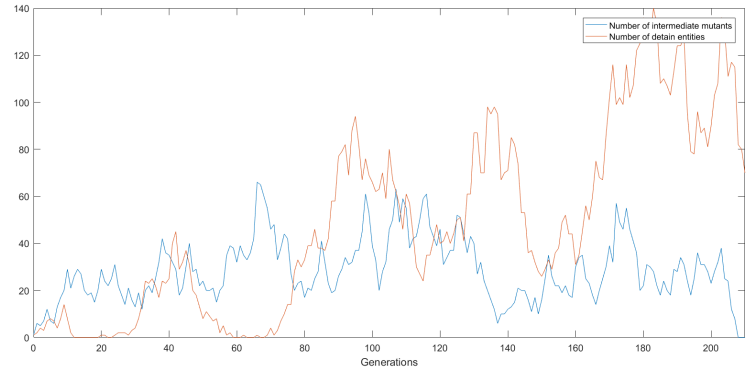

Figure 6a displays the number of intermediate mutants and the number of cooperation entities before the resistant mutants invade the whole population

Figure 6 The mutants lay low before they invade
The first mutant is generated at generation $t = 0$, and immediately after, a cooperaion entity is activated. The population of cooperation entities grows in number and prevent the mutant population from expansion. However, the mutants avoid extinction, and survive long enough to raise the fitness parameter above Υ. Since both the mutation rate, μ, and the mutant population size are relatively small, the mutant population contains no resistant when the fitness parameter reaches Υ. However, after 75 generations, a resistant mutant is generated, and since the resistant mutants are advantageous when the number of cooperation entities is less N and the fitness parameter is above Υ, the resistant mutants invade the whole population.
The parameter sizes are: $N = 10^3$, $\Upsilon = 2.5$, $\mu = 10^{-3}$, $P = 0.01$, $F = 10{-}5$.

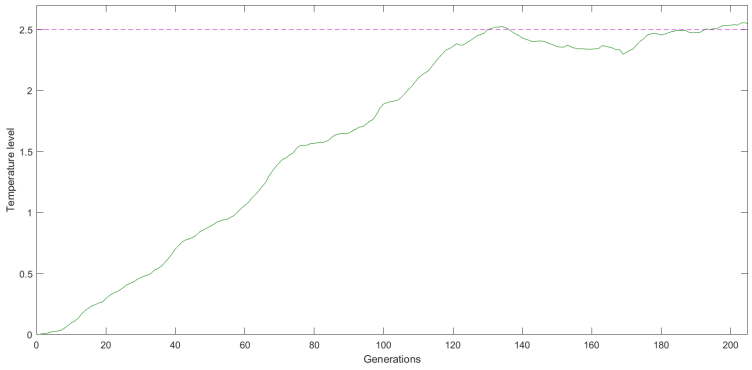

Figure 6b displays the fitness parameter and the pink dashed line marks the limit Υ

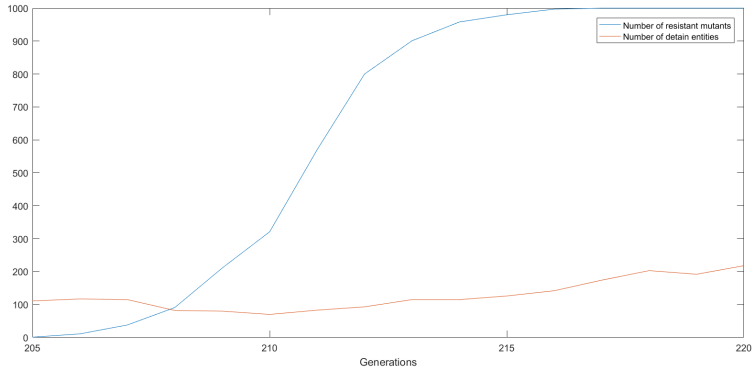

Figure 6c displays the number of resistant mutants and the number of cooperation entities as the resistant mutants invade the whole population

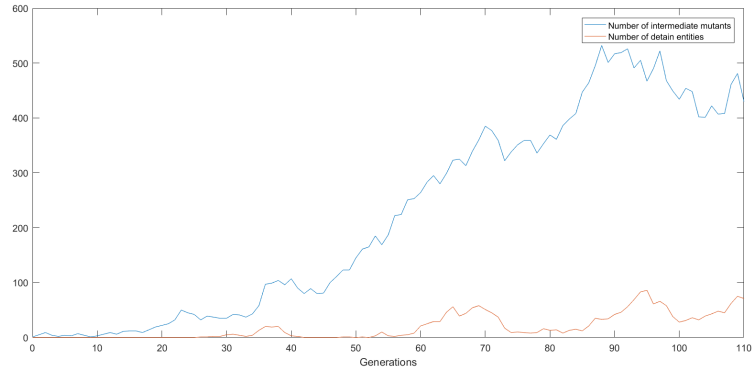

Figure 7a displays the number of intermediate mutants and the number of cooperation entities before the resistant mutants invade the whole population

Figure 7 The mutants grow faster than the cooperation entities and invade the whole population
The first mutant is generated at generation $t = 0$, and due to stochasticity, the mutant population grows fast whereas the growth of the cooperation entities is delayed. Consequently, the fitness parameter reaches the limit Υ. Since the population size is relatively large, there have already been generated resistant mutants, and since the resistant mutants are advantageous when the number of cooperation entities is less N and the fitness parameter is above Υ, the resistant mutants invade the whole population.
The parameter sizes are: $N = 10^3$, $\Upsilon = 20$, $\mu = 10^{-3}$, $P = 0.01$ and $F = 10^{-5}$.

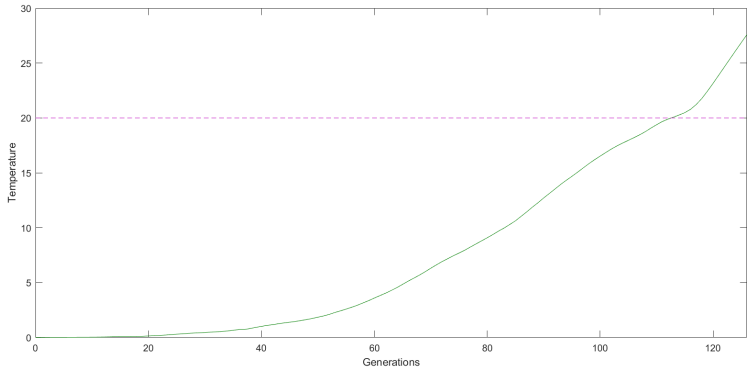

Figure 7b displays the fitness parameter and the pink dashed line marks the limit Υ.

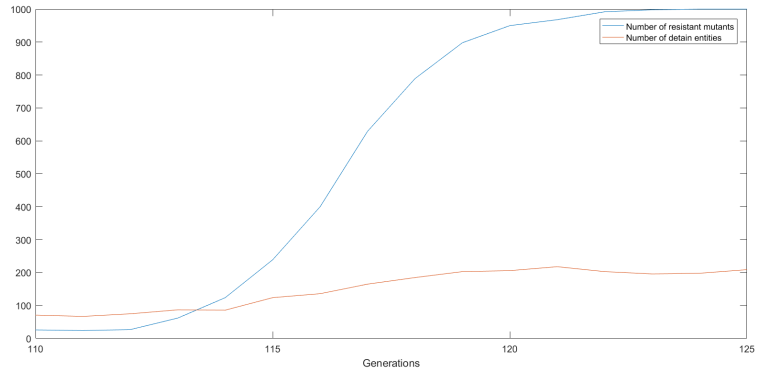

Figure 7c displays the number of resistant mutants and the number of cooperation entities as the resistant mutants invade the whole population

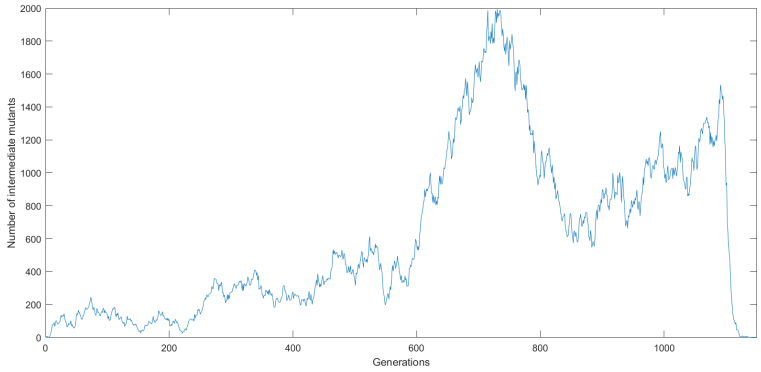

Figure 8a display the number of intermediate mutants

Figure 8 High activation rate of the cooperation entities: The mutants get extinct
A mutant appears in the population at generation $t = 0$ and generates a lineage of mutants that survives long enough such that the fitness parameter reaches the limit Υ at generation $t = 1092$. The mutation rate, μ_1 is relatively low and when the fitness parameter reaches Υ, there are no resistant mutants in the population. Moreover, the activation rate of the cooperation entities is very high, and hence, the number of cooperation entities grows rapidly, whereas the mutants become increasingly disadvantageous and decrease fast towards zero.
The parameter sizes are: $N = 10^5$, $\Upsilon = 5$, $\mu = 10^(-5)$, $P = 1$ and $F = 10^(-8)$.

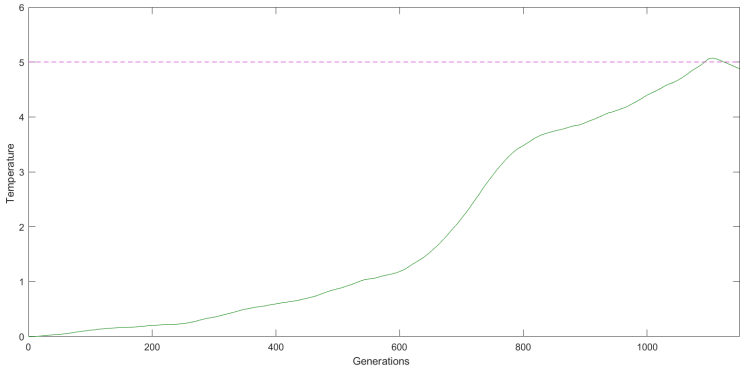

Figure 8b displays the fitness and the pink dotted line marks the limit Υ

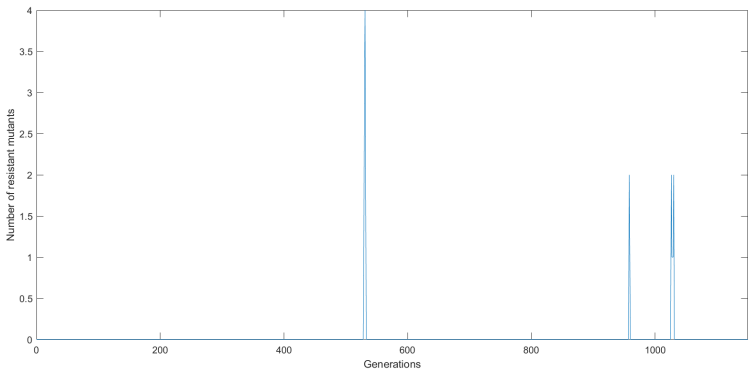

Figure 8c displays the number of resistant mutants

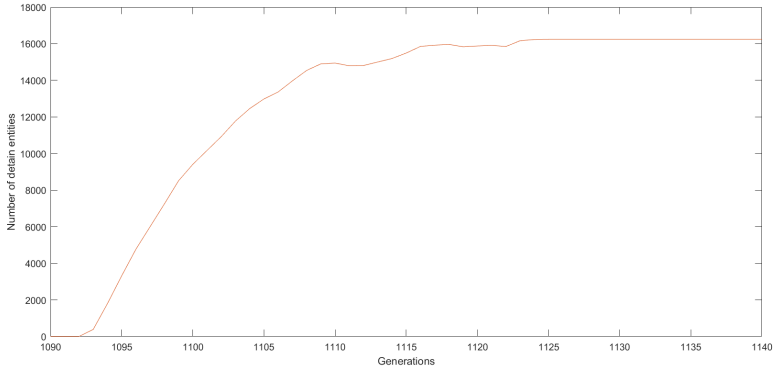

Figure 8d displays the number of cooperation entities

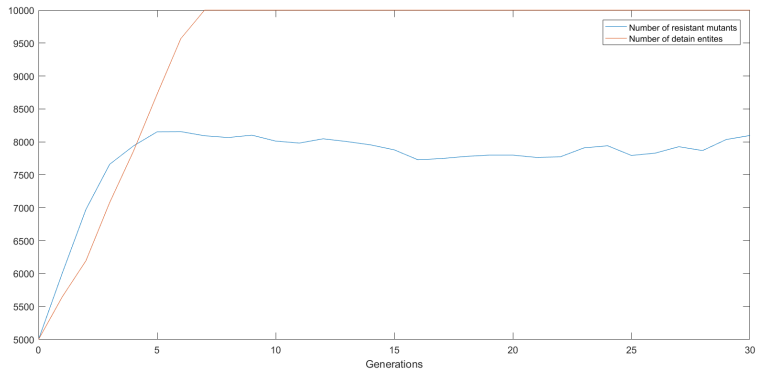

Figure 9 N **cooperation entities**
This Figure shows the case when the initial number of cooperation entities is $N = 10^4$, whereas the initial number of wild-type individuals, resistant mutants and intermediate mutants are 10, 10 and $N - 20$, respectively. Since the intermediate mutants are disadvantageous whereas the wild-type individuals and the resistant mutants are neutral variants, it is expected that the intermediate mutants get extinct while the wild-type individuals and the resistant mutants both grow towards $N/2$. The competition dynamics between the wild type and the resistant mutants is characterised by great variance whereas the number of intermediate mutants follows the expected function closely.

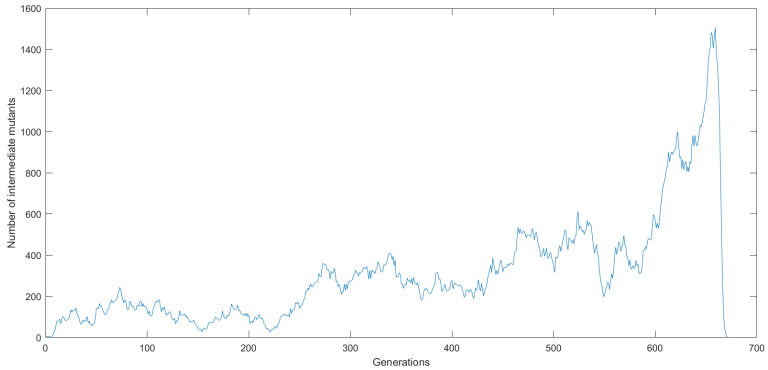

Figure 10a displays the number of intermediate mutants

Figure 10 Moderate activation rate of cooperation entities and invasion of resistant mutants
A mutant appears in the population at generation $t = 0$ and generates a lineage of mutants that survive long enough such that the fitness parameter reaches the limit Υ. When the fitness parameter reaches this limit, the population of mutants has already generated four resistant individuals, which are advantageous as long as the number of cooperation entities are lower than the population size, N. Even though the number of cooperation entities grows quit quickly, the number of resistant mutants reaches N first.
The parameter sizes are: $N = 10^5$, $\Upsilon = 0.1$, $\mu = 10^{-5}$, $P = 0.1$ and $F = 10^{-6}$.

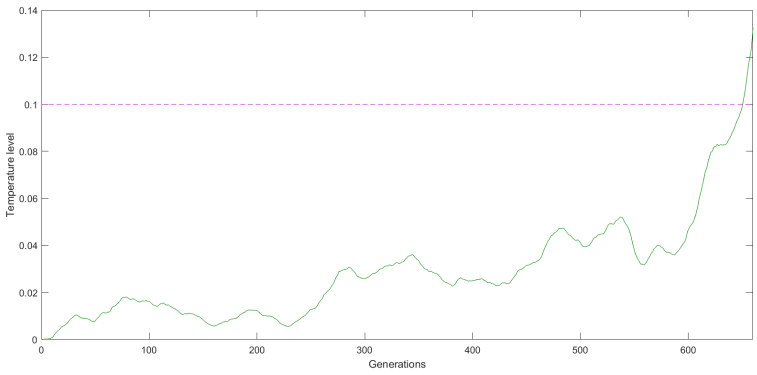

Figure 10b displays the fitness parameter and the pink dashed line marks the limit Υ

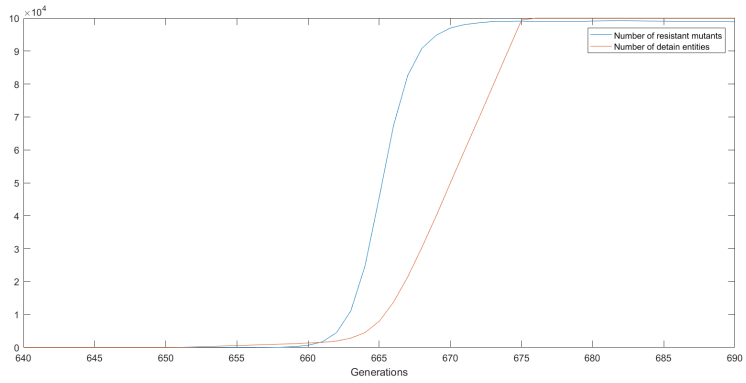

Figure 10c displays the number of resistant mutants and the number of cooperation entities

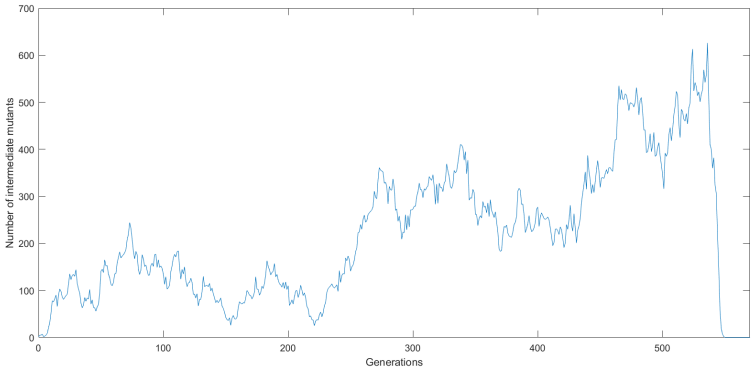

Figure 11a displays the number of intermediate mutants

Figure 11 High activation rate of cooperation entities and coexistence of resistant mutants and wild-type individuals
A mutant appears in the population at generation $t = 0$ and generates a lineage of mutants that survive long enough such that the fitness parameter reaches the limit Υ. When the fitness parameter reaches this limit, the population of mutants has already generated four resistant individuals, which are advantageous as long as the number of cooperation entities are lower than the population size, N. However, since the activation rate of the cooperation entities is very high, the number of cooperation entities reaches N when the number of resistant mutants is approximately 4×10^4. Since the wild-type individuals and resistant mutants become neutral variants, the number of each type is expected to remain constant. The parameter sizes are: $N = 10^5$, $\Upsilon = 1$, $\mu = 10^{-5}$, $P = 1$ and $F = 10^{-8}$.

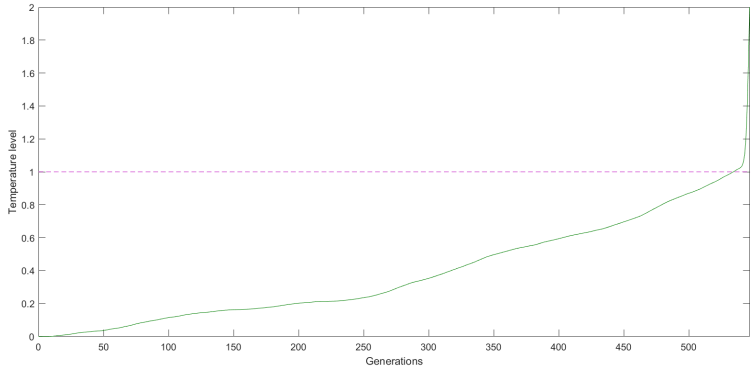

Figure 11b displays the fitness parameter and the pink dashed line marks the limit Υ

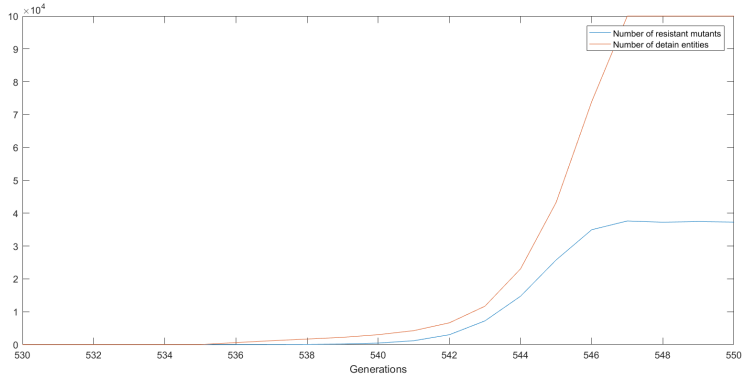

Figure 11c displays the number of resistant mutants and the number of cooperation entities

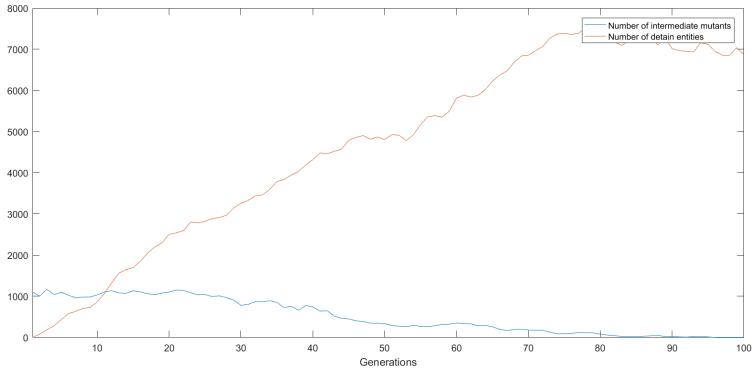

Figure 12a displays the number of intermediate mutants and the number of cooperation entities before the resistant mutants invade the population

Figure 12 Low activation rate of cooperation entities and delayed invasion of resistant mutants
The fitness parameter reaches the limit Υ at generation $t = 0$, and all the mutants are non-resistant from generation $t = 0$ to generation $t = 432$. Thus, these mutants become increasingly disadvantageous as the number of cooperation entities grows. Since the diffusion rate, F, equals zero, the fitness parameter remains above Υ even though the number of mutants decreases towards zero. A resistant mutant is generated at generation $t = 433$, and as long as the number cooperation entities is less than the population size, N, the resistant mutants are advantageous and grow exponentially. Since the activation rate is relatively low, the population of resistant mutants beats the cooperation entities in the race towards N. The initial number of intermediate mutants is $i = 558$. The other parameter sizes are: $N = 10^5$, $\mu = 10^{-5}$, $P = 0.01$ and $F = 0$.

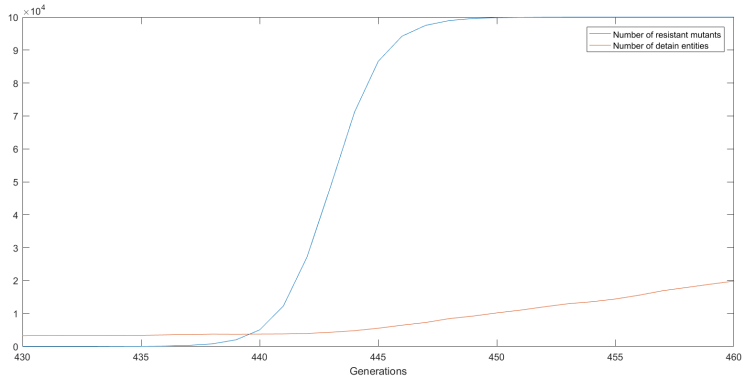

Figure 12b displays the number of resistant mutants and the number of cooperation entities as the resistant mutants invade the whole population

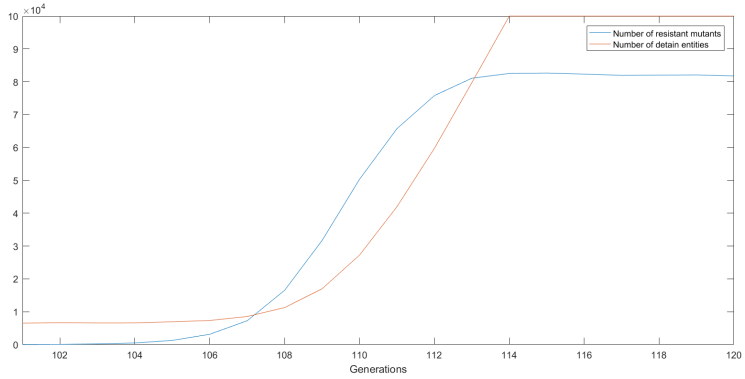

Figure 13a displays the number of intermediate mutants and the number of cooperation entities before the first resistant mutant is generated

Figure 13 Moderate activation rate of cooperation entities and co-existence of resistant mutants and wild-type individuals
The fitness parameter reaches the limit Υ at generation $t = 0$, and all the mutants are non-resistant from generation $t = 0$ to generation $t = 101$. Thus, these mutants become increasingly disadvantageous as the number of cooperation entities grows. Since the diffusion rate, F, equals zero, the fitness parameter remains above Υ even though the number of mutants decreases towards zero. A resistant mutant is generated at generation $t = 101$, and as long as the number cooperation entities is less than the population size, N, the resistant mutants are advantageous and grow exponentially. However, since the activation rate of the cooperation entities is sufficiently high, the number of cooperation entities reaches N when the number of resistant mutants is approximately 8×10^4. Since the wild-type individuals and resistant mutants become neutral variants, the number of each type is expected to remain constant. The initial number of intermediate mutants is $i = 1107$. The other parameter sizes are: $N = 10^5$, $\Upsilon = 0.1$, $\mu = 10^{-4}$, $P = 0.25$ and $F = 0$.

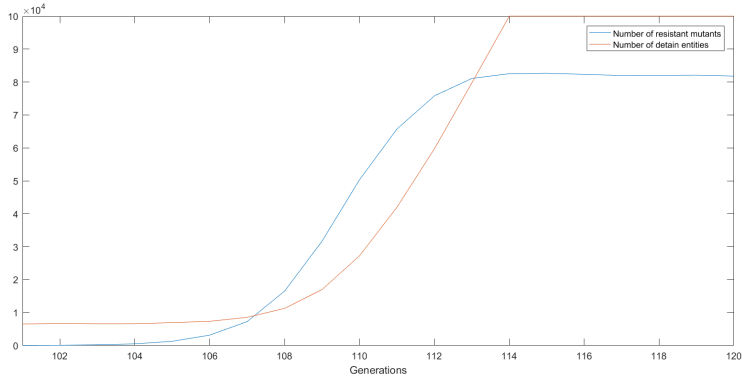

Figure 13 b displays the number of resistant mutants and the number of cooperation entities

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