Maintenance of diversity in a hierarchical host-parasite model with balancing selection and reinfection

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Abstract: Motivated by observations in DNA data of the human cytomegalovirus, we study the dynamics and the maintenance of diversity in a hierarchical model of a two-type parasite population distributed over its hosts. The parasite is assumed to be capable to persist in its host and to reinfect other hosts, and balancing selection is assumed to maintain diversity within hosts. For a suitable parameter regime in which parasite reproduction is faster than reinfection and reinfection is faster than host replacement, we show that in the limit of large host and parasite populations the system is driven by a dynamical system with a globally stable equilibrium, guaranteeing that both types are maintained in the parasite population for a long time on the host time scale.

Keywords and phrases: hierarchical host-parasite system, balancing selection, mean-field limit, random genealogies
AMS classification: primary: 60K35, secondary: 92D15, 92D25.

1. Introduction

Diversity is essential for the survival of species, see [1]. This applies in particular to parasites. An interesting example is the human cytomegalovirus (HCMV), an old herpesvirus, which is carried by a substantial fraction of mankind [2] and in general leads to an asymptomatic infection in the immunocompetent host [3, 4]. In DNA data of HCMV a high genetic diversity is observed in coding regions, see [5]. This diversity can be helpful to resist the defense of the host. Furthermore, for guaranteeing its long term survival, HCMV seems to have developed elaborate mechanisms which allow it to persist lifelong in its host and to establish reinfections in already infected hosts.

We propose a model to study the effects of these mechanisms on the maintenance of diversity in a parasite population. A central issue hereby is that the diversity of the (surrounding) parasite population can be introduced into single hosts.

In our model we assume for the sake of simplicity that each infected host carries a constant number $N$ of parasites until its death, and that only two types of parasites exist, type $A$ and type $B$. We consider only the population of infected hosts and assume that its size $M$ is constant. The evolution of the frequency of type $A$ in each of the $M$ hosts is driven by three factors: a) parasite reproduction, b) host replacement, and c) reinfection. Within hosts, parasites reproduce subject to balancing selection with a drift to an equilibrium frequency of the two types. Whenever a host dies, it is replaced by a new, so far uninfected host, which instantly suffers a primary infection from a randomly chosen infected host. At such a primary infection the host is infected with a single type chosen randomly according to the type frequencies in the infecting host; the type $A$-frequency in the primary infected host is then instantly set to either 1 or 0. At reinfection a single parasite in the reinfected host is replaced by a randomly chosen parasite transmitted from the infecting host.

This scenario can be interpreted in classical population genetics terms as a population distributed over $M$ islands and migration between islands. Within each island reproduction is panmictic and driven by balancing selection or alternatively (in a diploid setting) by a model of overdominance, i.e. heterozygote advantage, see [6].
Host replacement events (which model the death of a host and its replacement by a primary infected host) can be interpreted as extinction-recolonization events; the role of such events on the reduction of neutral diversity was studied e.g. in [7]. Since in our model a host after primary infection carries either only type $A$ or type $B$-parasites, host replacement leads to a reduction of polymorphic hosts, i.e. of hosts that simultaneously carry both types of parasites. Furthermore, host replacement produces fluctuations in the host type frequency which eventually leads to the extinction of one parasite type.

The role of balancing selection in evolution is still a matter of debate. It has been proposed that host-parasite coevolution is one of the main forces driving immune genes to evolve under balancing selection, see e.g. [8]. The host defense system, e.g. the major histocompatibility complex (MHC) of vertebrates, exhibits a large diversity and MHC genes show patterns of balancing selection, see [9].

In our hierarchical model for the evolution of the parasite population we study the effect of balancing selection on the diversity in parasite populations and on the spread of this diversity in the host population; hereby effects on the level of the host population and on the level of the parasite population are taken into account. Related hierarchical models have been studied from a mathematical perspective e.g. by [10, 11]. In these papers an emphasis on models for selection on two scales is made and phase transitions (in the mean-field limit) are studied at which particularly the higher level of selection (group selection) can drive the evolution of the population. In our model, balancing selection is only acting on the lower level (within-host parasite populations), but we focus on parameter regimes in which balancing selection is also lifted to the higher level, such that both parasite types are maintained in the host population for a long time, in which hosts carrying a single parasite type only, as well as hosts carrying both types of parasites are present in the population. (This corresponds to a scenario observed in samples of HCMV hosts).

It turns out that for large parasite and large host populations this scenario applies if
- the effective reinfection rate, that is the rate at which in so far single-type infected hosts a second type is established, acts on the same time scale than host replacement,
- balancing selection is strong enough to keep host type frequencies close to the equilibrium frequency, once a host was effectively reinfected, and
- parasite reproduction is (much) faster than host replacement, with a mild upper bound on its rate.

Then we show that on the (microscopic, within-host) parasite time scale balancing selection maintains diversity in the host population also on the (macroscopic) host time scale. The evolution of type frequencies within a typical host can be separated into two alternating phases: 1) A host infected with a single type waits for a successful reinfection event or the next host replacement event, and 2) a host carrying both types close to the equilibrium frequency waits for a replacement event converting the host to a pure-type host again. We will identify the limiting random genealogies of typical hosts by using graphical representations of these and approximate random genealogies of hosts in the model with a finite (but large) number of parasites. Furthermore, we obtain also a limit law for the hosts’ type dynamics as the number of hosts becomes large, and identify the deterministic dynamical system that governs the host type frequencies.

Essential quantities to show the concentration on the two pure frequencies and the equilibrium frequency are the probability of balance, i.e. the probability with which a reinfection event leads to the establishment of the second type in a so far single-type infected host, and the time to balance, i.e. the time needed to reach (a small neighborhood of) the equilibrium frequency $\eta$ after reinfection. These quantities determine the parameter regimes in which we can observe the described scenario. Similar to the the case of positive selection (see e.g. [12, 13, 14]), branching process approximations as well as approximations by deterministic ODE’s can be used to estimate these probabilities and times. A notable difference compared to the situation studied e.g. in [13] is a modification in Haldane’s formula: the probability to balance (when starting from frequency 0) differs from the fixation probability in the case of positive selection by the factor $\eta$ (which is the equilibrium frequency), see Lemma 3.6. Furthermore the time to balance is longer than the time of a selective sweep in the corresponding setting. This is due to the fact that random fluctuations close to the equilibrium are larger than fluctuations close to the boundary.
2. Model and Results

2.1. Model

Let $M, N \in \mathbb{N}$. We model the evolution of the parasite population distributed over $M$ hosts by a $\{0, \frac{1}{N}, \ldots, 1\}^M$-valued Markovian jump process $X^{N,M} = (X_{1}^{N,M}(t), \ldots, X_{M}^{N,M}(t))_{t \geq 0}$, where $X_{i}^{N,M}(t), 1 \leq i \leq M$, represents the relative frequency of type $A$-parasites in host $i$ at time $t$. (As long as there is no ambiguity, we suppress the superscripts $N,M$).

Reproduction of parasites within hosts follows a Moran dynamic with balancing selection towards an equilibrium frequency $\eta$, for some fixed $\eta \in (0,1)$. The reproduction rate of parasites is assumed to be $g_{N}$ times larger than the rate of host replacement (to be defined below). More specifically, in host $i$ parasites of type $A$, when having relative frequency $x_{i}$, reproduce at rate $g_{N}(1 + s_{N}(\eta - x_{i}))$ and those of type $B$ at rate $g_{N}(1 + s_{N}(\eta - x_{i}))$, where $s_{N}$ is a small positive number. Thus the rate of reproduction of type $A$-parasites is larger (smaller) than that of type $B$-parasites, if the frequency of type $A$ is below (above) the equilibrium frequency $\eta$, at which type $A$ and type $B$ are balanced. At a reproduction event a parasite splits into two and replaces a randomly chosen parasite from the same host. A change in frequency only occurs if the type of the reproducing parasite differs from the type of the parasite which is replaced. Reinfection events occur at rate $r_{N}$ per host; then a single parasite in the reinfecting host (both of which are randomly chosen) is copied and transmitted to the reininfected host. At the same time a randomly chosen parasite is instantly removed from this host; in this way the parasite population size in each of the hosts is kept constant. A reinfection event leads to a change in frequency in the reinfected host only if the type of the replaced parasite differs from the transmitted one. Hence, if $X^{N,M} = (x_{1}, \ldots, x_{M})$, then the frequency of type $A$ in host $i$ changes due to reinfection at rate $r_{N} \frac{1}{M} \sum_{j=1}^{M} x_{j}(1-x_{j})$ by an amount of $+1/N$, and at rate $r_{N} \frac{1}{M} \sum_{j=1}^{M} (1-x_{j})x_{j}$ by an amount $-1/N$. If an infected host dies it is replaced by a so far uninfected host, which instantly is infected by a randomly chosen infected host. Then only a single type is transmitted, leading to jumps of the type $A$-frequency to $0$ and $1$ at rate $(1-x)$ and $x$, respectively, for each host.

To summarize, jumps from state $x = (x_{1}, \ldots, x_{M}) \in \{0, \frac{1}{N}, \ldots, 1\}^{M}$ occur for $i = 1, \ldots, M$

- to $x + \frac{1}{N}e_{i}$ at rate $g_{N}(1 + s_{N}(\eta - x_{i}))N x_{i}(1-x_{i}) + r_{N} \frac{1}{M} \sum_{j=1}^{M} x_{j}(1-x_{j})$
- to $x - \frac{1}{N}e_{i}$ at rate $g_{N}(1 + s_{N}(\eta - x_{i}))N x_{i}(1-x_{i}) + r_{N} \frac{1}{M} \sum_{j=1}^{M} (1-x_{j})x_{i} n$
- to $x + (1-x_{i})e_{i}$ at rate $x$, and
- to $x - x_{i}e_{i}$ at rate $(1-x)$,

with $\bar{x} := \frac{1}{M} \sum_{j=1}^{M} x_{j}$ and $e_{i} = (0, \ldots, 1, \ldots, 0)$ the $i$-th unit vector of length $M$.

Remark 2.1. The biological relevance and the generalizations of this model are discussed in detail in the biological counterpart [15] of this manuscript. Briefly summarized: When analyzing DNA samples of the human cytomegalovirus it is striking that many coding regions cluster into a few, phylogenetically distant haplotypes, see [5] and the references therein. Given that these haplotypes lie in coding regions and hence the fitness landscape should be sharply peaked, it seems that genetic drift should erase haplotype diversity before it is repaired by mutation. In light of the contrary observation, one might suppose that haplotypes are actively maintained in the viral population, as we do in our model.

The major motivation for the above described model thus comes from observations of DNA samples of HCMV. However, as simultaneous infections by several genotypes or even by several species appear to be the rule rather than the exception, see [16, 17], the scenario discussed here is (perhaps in suitable generalisations) likely to be relevant also for other host-parasite systems.

Next we will make assumptions on the strength of selection and intensity of reinfection and parasite reproduction relative to host replacement. For strong enough selection we show that, in the limit of an infinitely large parasite population per host, only three states of typical hosts exist, those infected only with one of the types $A$ or $B$ and those infected with both types, where $A$ is
These three host states will also be called the pure states (if the frequency of type A in a host is 0 or 1) and the mixed state (if the frequency of type A in a host is \( \eta \)).

Only reinfection events can change a host state from a pure to the mixed state. In most cases reinfection events are not effective, in the sense that these events cause only a short excursion from the boundary frequencies 0 and 1. We will see that if the selection strength and reinfection rate are appropriately scaled, the effective reinfection rate acts on the same time scale as host replacement. Furthermore, if selection is of moderate strength and parasite reproduction is fast enough (but not too fast), transitions of the boundary frequencies to the equilibrium frequency \( \eta \) will appear as jumps on the host time scale and transitions between the host states 0, \( \eta \) and 1 are only caused by host replacement and effective reinfection events. See also Figure 1 for an illustration of the type A-frequency path in a typical host for large \( N \).

We will see in Theorem 3 that if the effective reinfection rate is larger than a certain bound depending on \( \eta \) then there exists in the limit \( N \to \infty \) and \( M \to \infty \) a stable equilibrium of the relative frequencies of hosts of type 0, \( \eta \) and 1, at which both types of parasites are present in the entire parasite population at a non-trivial frequency.

The precise assumptions on the parameters are as follows:

**Assumptions (A):**

1. (moderate selection)
   \[ s_N = N^{-\epsilon} \]
   for some \( 0 < \epsilon < 1/5 \).
2. (frequent reinfection)
   \[ \lim_{N \to \infty} r_N s_N = r \]
   for some \( r > 0 \).
3. (fast parasite reproduction)
   \[ 1/g_N = o(N^{-5r}) \]
   \[ g_N = O(\exp(N^{1/5})) \]

**Remark 2.2.**

- Assumption (A1) implies that
  \[ \lim_{N \to \infty} s_N = 0 \]
  and
  \[ \lim_{N \to \infty} s_N N = \infty. \]

- For large \( N \)
  \[ 1 \ll r_N \ll g_N, \]
  that is hosts experience frequent reinfections during their lifetime and between two reinfection events many parasite reproduction events happen. Thus the scaling seems realistic; see [15] for additional discussion.

In the following will analyze the cases “\( N \to \infty \) with \( M \) fixed” (Theorem 1), “first \( N \to \infty \), then \( M \to \infty \)” (Corollary 2.5) and ”\( N \to \infty \), \( M \to \infty \) jointly” (Theorem 2).

### 2.2. Large parasite population, finite host population

Let \( M \in \mathbb{N} \). We prepare our first main result by defining the \( \{0, 1, \eta\}^M \)-valued Markovian jump process \( Y^M = (Y^M_t, ..., Y^M_{t+1})_{t \geq 0} \), which will turn out to be the process of type A-frequencies in
hosts $1, \ldots, M$ in the limit $N \to \infty$. From the state $y = (y_1, \ldots, y_M)$, the process $Y^M$ jumps by flipping for $i \in \{1, \ldots, M\}$ the component $y_i$

from 0 or $\eta$ to 1 at rate $\frac{1}{M} \sum_{j=1}^{M} y_j$,

from 1 or $\eta$ to 0 at rate $\frac{1}{M} \sum_{j=1}^{M} (1 - y_j)$,

from 0 to $\eta$ at rate $\frac{2r\eta}{M} \sum_{j=1}^{M} y_j$,

from 1 to $\eta$ at rate $\frac{2r(1 - \eta)}{M} \sum_{j=1}^{M} (1 - y_j)$.

**Remark 2.3** (Graphical representation of $Y^M$). The process $Y^M$ has a graphical representation which explains the jump rates in terms of the underlying hierarchical structure and will also be instrumental in the proof of Theorem 1. This representation has two main ingredients:

1) the replacement arrows: for each pair $i, j \in \{1, \ldots, M\}$ there is a Poisson process of rate $1/M$ on the time axis. At such a time point, if host $j$ is in state 0 or 1, then host $i$ instantly adopts that state; if, however, host $j$ is in state $\eta$, then host $i$ instantly jumps to state 1 with probability $\eta$ and to state 0 with probability $1 - \eta$.

2) the potential effective reinfection arrows: for each pair $i, j \in \{1, \ldots, M\}$ there is a Poisson process of rate $2r/M$ on the time axis. At such a time point,

a) if host $j$ is in state 1 and host $i$ is in state 0, then host $i$ instantly changes to state $\eta$ with probability $\eta$, and remains in state 0 with probability $1 - \eta$,

b) if host $j$ is in state 0 and host $i$ is in state 1, then host $i$ instantly changes to state $\eta$ with probability $1 - \eta$, and remains in state 1 with probability $\eta$,

c) if host $j$ is in state $\eta$ and host $i$ is in state 0, then host $i$ instantly changes to state $\eta$ with probability $2\eta^2$, and stays in state 0 with probability $1 - \eta^2$,

b) if host $j$ in state 1 and host $i$ is in state 0, then host $j$ instantly changes to state $\eta$ with probability $(1 - \eta)^2$ and stays in state 1 with probability $1 - (1 - \eta)^2$, and

e) in the remaining cases nothing changes.

With the just described rules, and the help of up to two coin tosses with success probability $\eta$ per arrow, from the initial host state configuration $(Y^M(0))$ the (random) host state configuration $(Y^M(t))$ is determined. See Figure 2 for an illustration.

**Theorem 1.** Let $M \in \mathbb{N}$. Under conditions (A), assume that the law of $X^{N,M}(0)$ converges weakly as $N \to \infty$ to a distribution $\rho$ concentrated on $\{(0) \cup [\alpha, 1 - \alpha] \cup \{1\}\}^M$ for some $\alpha > 0$.

Then for any $t > 0$ and any $0 < \delta < t$ the process $X^{N,M}$ converges on every time interval $[\delta, t]$ in distribution with respect to the Skorokhod topology to the process $Y^M$, with the initial distribution of $Y^M$ being the image of $\rho$ under the mapping $0 \mapsto 0$, $1 \mapsto 1$, $[\alpha, 1 - \alpha] \ni x \mapsto \eta$.

We postpone the proof of Theorem 1 to Section 3.3, but give here a
Fig 2. An illustration of the graphical representation of $Y^M$. Solid arrows indicate host replacement events and dashed arrows stand for potential effective reinfection events. If at a host replacement event the incoming line is of type $\eta$, then a coin toss decides which parasite type (A or B) is transmitted. The host that suffers such a primary infection then instantly takes the state 1 or 0. The outcome of the coin toss (A or B) is annotated by the letter next to the tail of the arrow. If at a reinfection event the incoming line is of type $\eta$, two coin tosses are necessary, one to decide which type is transmitted (the letter (A or B) next to the tail of the arrow indicates the result of this coin toss) and one coin toss to decide if the transmitted type may establish itself in the infected host (the digit 1 stand for "yes" and 0 for "no"). At time $0$ lines are randomly typed with 0, $\eta$ and 1 according to some initial distribution. At time $t$ the propagated types are displayed. In this example, for two of the arrows (the ones without letters/digits at their tails) no coin tosses are necessary to decide the state of the continuing line.

Sketch of the proof: In the following we will need the sets $U^{\eta.N} := (\eta - s_N, \eta + s_N)$ and $D^{\eta.N} := [\eta - s_{3/2}^N, \eta + s_{3/2}^N]$. Note that $D^{\eta,N} \subset U^{\eta.N}$.

The proof of Theorem 1 is based on the following properties of Moran processes subject to balancing selection of moderate strength:

a) (Concentration on the states $\{0, 1\} \cup U^{\eta,N}$ as $N \to \infty$)
   i) With high probability, i.e. with a probability tending to 1 as $N \to \infty$, every host is at any time point, at which she is involved in a reinfection or host replacement event, in a state that belongs to the set $\{0, 1\} \cup U^{\eta,N}$, see Lemma 3.12.
   ii) With high probability, the interval $U^{\eta,N}$ is left because of a host replacement event, and not because of the fluctuations that go along with the random reproduction of parasites, see Lemma 3.11.

b) (Probability of balance) The probability that in a host in state 0 (i.e. a pure type B-host), after a reinfection with a single parasite of type A, the equilibrium frequency $\eta$ is hit before returning to the boundary frequency 0 is $2\eta s_N + o(s_N)$. Likewise, the probability that in a pure type A-host, after a reinfection with a single parasite of type B, the equilibrium frequency $\eta$ is hit before returning to the boundary frequency 1 is $2(1 - \eta)s_N + o(s_N)$, see Lemma 3.6.

c) (Time to balance) The time needed to reach $D^{\eta.N}$ after an effective reinfection is with high probability of order $O(N^{\epsilon_N + \delta}/g_N)$, see Proposition 3.8.

The assumptions of Theorem 1 imply that the parasite frequency in each host is with high probability contained in $\{0, 1\} \cup D^{\eta,N}$ after a short time. A host in state 1 or 0 remains in her state until she is (replaced or) hit by a reinfection event. As soon as this host is hit by a reinfection, an excursion of type A-parasite frequencies within this host starts which eventually returns to the starting point or reaches $D^{\eta,N}$ before the next reinfection or host replacement event hits this host, according to property a)i). If $D^{\eta,N}$ is reached before the return to the starting point, we call the reinfection event effective and otherwise ineffective. If at some reinfection event the proportion of hosts in state $\ell \in \{0, 1\}$ is $x^{\ell,N}$, and $x^{\eta,N}$ is the proportion of hosts whose state is in $U^{\eta,N}$, then it follows from property b) and property a)i) that the effective reinfection rate of a host in state 0 is...
In view of Remark 2.3 and Proposition 3.3, we define for a given \( \eta \) the following time-inhomogeneous Markovian jump process \( V = (V_s)_{0 \leq s \leq t} \) with state space \( \{0, 1, \eta\} \): At time \( s \) the process \( V \) jumps from any state to state 

\[
\begin{align*}
0 & \text{ at rate } v_0^\eta + (1-\eta)v_0^\eta \\
1 & \text{ at rate } v_1^\eta + \eta v_1^\eta,
\end{align*}
\]

from state 0 to state \( \eta \) at rate \( 2\eta v_1^\eta + \eta v_1^\eta \), and from state 1 to state \( \eta \) at rate \( 2r(1-\eta)(v_0^\eta + (1-\eta)v_0^\eta) \).

where \( \mathbf{v} = (\mathbf{v}_s) = (v_0^\eta, v_1^\eta, v_s^\eta)_{0 \leq s \leq t} \) is the solution of the dynamical system (1) starting from \( \mathbf{v}_0 \).
Proposition 2.5 (Propagation of chaos). Assume
\[ \frac{1}{M} \sum_{i=1}^{M} \delta_{Y_i^M(0)} \to \nu_0^0 \delta_0 + \nu_0^1 \delta_1 \]
as \( M \to \infty \) for some \( \nu^0 = (\nu_0^0, \nu_0^1, \nu_1^1) \in \Delta^3 \). Moreover, assume that the initial states \( Y_1^M(0), \ldots, Y_M^M(0) \) are exchangeable, i.e. arise through a drawing without replacement from their empirical distribution (given the latter). Then, for each \( t > 0 \) the random paths \( Y_t^M = (Y_t^M(s))_{0 \leq s \leq t}, \ i = 1, \ldots, M, \) of the host type frequencies are exchangeable, and for each \( k \in \mathbb{N}, \)
\[ (Y_t^M, \ldots, Y_k^M) \to (V_1, \ldots, V_k), \]
in distribution with respect to the Skorokhod-topology as \( M \to \infty, \) where \( (V_1, \ldots, V_k) \) are i.i.d. copies of the process \( V = (V(s))_{0 \leq s \leq t} \) specified in Definition 2.4.

This proposition as well as the subsequent corollary will be proved in Section 3.1.

Let \( S \) be a Polish space, and denote by \( D([0, t]; S) \) the space of càdlàg paths on the time interval \([0, t]\) with state space \( S \) and by \( M_1(D([0, t]; S)) \) the set of probability measures on the Borel \( \sigma \)-Algebra on \( D([0, t]; S) \) endowed with the Skorokhod distance.

Corollary 2.6 (Empirical distribution of host states as \( M \to \infty \)). In the situation of Proposition 2.5 the sequence of \( M_1(D([0, t]; \{0, \eta, 1\})) \)-valued random variables \( \nu^M := \frac{1}{M} \sum_{i=1}^{M} \delta_{Y_i^M} \) converges (w.r.t. the weak topology) to \( \mathcal{L}(V) \).

Moreover, the \( \Delta^3 \)-valued process
\[ (Z_t^M(s))_{0 \leq s \leq t} := \left( Z_0^M(s), Z_{\eta}^M(s), Z_1^M(s) \right)_{0 \leq s \leq t} \]
of proportions of hosts in states 0, \( \eta \) and 1, i.e.
\[ Z_t^M(s) = \frac{\# \{ \ell \in \{0, \ldots, M\} | Y_t^M(s) = \ell \} }{M} = \frac{1}{M} \sum_{i=1}^{M} \delta_{Y_i^M(s)}(\ell), \quad \ell = 0, \eta, 1, \]
converges (w.r.t. the Skorokhod-topology) to \( (\nu_s)_{0 \leq s \leq t}, \) the solution of the dynamical system (1).

Remark 2.7. The process \( Z^M \) is a Markovian jump process with jumps from \( z = (z^0, z^\eta, z^1) \) to
\[ z + \left( \frac{1}{M}, -\frac{1}{M}, 0 \right) \quad \text{at rate} \quad Mz^\eta(z^0 + (1-\eta)z^\eta) \]
\[ z + \left( -\frac{1}{M}, 0, \frac{1}{M} \right) \quad \text{at rate} \quad M(z^\eta(1-\eta)z^1 + z^0z^1) \]
\[ z + (-\frac{1}{M}, 0, \frac{1}{M}) \quad \text{at rate} \quad M(z^1z^0 + z^0z^\eta) \]
\[ z + \left( 0, \frac{1}{M}, -\frac{1}{M} \right) \quad \text{at rate} \quad 2\tau M(\eta z^1 + \eta^2 z^\eta)z^0 \]
\[ z + (0, -\frac{1}{M}, \frac{1}{M}) \quad \text{at rate} \quad 2\tau M((1-\eta)z^0 + (1-\eta)^2 z^\eta)z^1 \]
\[ z + (0, -\frac{1}{M}, \frac{1}{M}) \quad \text{at rate} \quad Mz^\eta(z^1 + \eta z^\eta). \]

One easily checks by direct calculations that the generator of \( Z^M \) converges to the generator of the solution \( \nu \) of (1), which for any continuously differentiable function \( f : \Delta^3 \to \mathbb{R} \) is of the form
\[ Gf(v^0, v^\eta, v^1) = \sum_{\ell \in \{0, \eta, 1\}} v^\ell \frac{\partial f}{\partial v^\ell}(v^0, v^\eta, v^1). \]

2.4. Joint limit: \( M = M_N \to \infty \) for \( N \to \infty \)

In analogy to Proposition 2.5 a propagation of chaos can be shown also in the case of a joint limit of \( N \) and \( M \) to \( \infty, \) i.e. \( M = M_N \) and \( M_N \to \infty \) for \( N \to \infty. \) This is the topic of the next theorem.

Here and the following we write
\[ \mu_N := \frac{1}{M_N} \sum_{i=1}^{M_N} \delta_{X_i^N(0)}; \quad \mu_s = \frac{1}{M_N} \sum_{i=1}^{M_N} \delta_{X_i^N(s)} \]
(2)
for the empirical distributions of the system of trajectories $X^{N,M_N}$ and their evaluation at some time $s \geq 0$.

**Theorem 2** (Propagation of chaos). Let Assumptions ($A$) be valid. For $M = M_N \to \infty$ as $N \to \infty$, assume that $\mu_N$ converges weakly as $N \to \infty$ to a distribution $\pi$ on $\{0\} \cup [\alpha,1-\alpha] \cup \{1\}$ for some $\alpha > 0$. Moreover, assume that for any $N$ the initial states $X^{N,M_N}_1(0), \ldots, X^{N,M_N}_M(0)$ are exchangeable (i.e. arise as drawings without replacement from their empirical distribution $\mu_N$).

Then, for any $t > 0$, any $0 < \delta < t$ and $k \in \mathbb{N}$, the processes $X^{N,M_N}_1, \ldots, X^{N,M_N}_k$ converge, as $N \to \infty$, in distribution with respect to the Skorokhod topology, jointly on the time interval $[\delta, t]$ to $k$ i.i.d. copies of the process $V$ specified in Definition 2.4, where the distribution of $V(0)$ has the weights $\pi(\{0\}), \pi([\alpha,1-\alpha]), \pi(\{1\})$.

We postpone the proof of this theorem and its subsequent corollary to Section 3.3.

**Corollary 2.8.** In the situation of Theorem 2, $\mu^N \to \mathcal{L}(V)$ in distribution as $N \to \infty$.

### 2.5. Properties of the dynamical system $v$

The following result will be proved in Section 3.2.

**Proposition 2.9** (Equilibria).

A. i) The dynamical system $v$ has the three equilibrium points $(1,0,0)$, $(0,0,1)$ and $u = (u^0, u^v, u^1)$ with

$$
u^0 = \frac{2\eta(1-\eta)^2 - (2\eta - 1)}{2\eta^2 + 4\eta^2(1-\eta)}$$

$$
u^v = \frac{4\eta^2(1-\eta)^3 - (2\eta - 1)^2(2\eta(1-\eta) + 1)}{2\eta^2(1-\eta)^2(1 + 2\eta(1-\eta))}$$

$$
u^1 = \frac{2(1-\eta)(1-\eta)\eta^3 + 2\eta - 1}{2(1-\eta)^2 + 4\eta(1-\eta)^3}.$$

ii) $u \in \Delta^3$ iff $r \geq \max\{\frac{2\eta - 1}{2\eta(1-\eta)^2}, \frac{1-2\eta}{2(1-\eta)^2}\}$. At equality, for $\eta > 1/2$ the point $u$ equals $(0,0,1)$ and for $\eta < 1/2$ the point $u$ equals $(1,0,0)$.

B. i) If

$$r > \max\{\frac{2\eta - 1}{2\eta(1-\eta)^2}, \frac{1-2\eta}{2(1-\eta)^2}\},$$

then

a) the equilibria $(0,0,1)$ and $(1,0,0)$ are saddle points, and

b) the equilibrium $u$ is globally stable on $\Delta^3 \setminus \{(0,0,1) \cup (1,0,0)\}$.

ii) For $r \leq \max\{\frac{2\eta - 1}{2\eta(1-\eta)^2}, \frac{1-2\eta}{2(1-\eta)^2}\}$ in the case $\eta > 0.5$ the equilibrium $(0,0,1)$ is globally stable on $\Delta^3 \setminus \{(0,0,0) \cup (1,0,0)\}$ is a saddle point, in the case $\eta < 0.5$ the equilibrium $(1,0,0)$ is globally stable on $\Delta^3 \setminus (0,0,1)$ and $(0,0,1)$ is a saddle point.

**Remark 2.10.**

- The existence of a stable equilibrium $u$ in the case $r > \max\{\frac{2\eta - 1}{2\eta(1-\eta)^2}, \frac{1-2\eta}{2(1-\eta)^2}\}$ guarantees the coexistence of both types in the parasite population for any time $t > 0$ in the limit $N \to \infty, M \to \infty$, when initially both types were present at a non-trivial amount. In Sec 2.2.6 we give an estimate on the time for which both types are maintained in the population for large $N$ and $M$.

- See also Figure 3 for an illustration of the system.

- We have $w^N \to 1$, i.e. in the limit $r \to \infty$ there are only hosts in state $\eta$.

- If $r = 0$ eventually one parasite type will be lost.

- For $\eta = \frac{1}{2}$
only hosts in state 0
only hosts in state $\eta$
only hosts in state 1

Fig 3. Position of the coordinates $(u^0, u^1)$ of the stable equilibrium $u$ in $\mathbb{A}^2 = \{(x, y) : x, y \geq 0, x + y \leq 1\}$: for $\eta < 0.5$, $(u^0, u^1)$ is in the upper-left subtriangle of $\mathbb{A}^2$, for $\eta < 0.5$, $(u^0, u^1)$ is on the line separating the two subtriangles, and wanders downwards as $r$ increases.

$u^0 = u^1 = \frac{1}{2+r}$

Furthermore, in equilibrium the probability to draw from the parasite population a parasite of type $A$ is $\frac{1}{2+r} + \frac{r}{2+r} \frac{1}{2} = \frac{1}{2} = \eta$, that is the population mean equals the equilibrium frequency $\eta$. In general, this is not the case. Otherwise it should hold, that $u^0 \eta + u^1 = \eta$, that is $u^1 = \eta(1-u^0) = \eta(u^0 + u^1) \Leftrightarrow u^1 = \frac{\eta}{1-\eta}u_0$. One checks, that this relationship is only valid for $\eta = \frac{1}{2}$. 

2.6. Maintenance of a polymorphic state

Let Assumptions (A) be fulfilled and assume that the reinfection rate $r$ is not only larger than $\max\{\frac{2\eta-1}{2(1-\eta)^2}, \frac{1-2\eta}{2(1-\eta)^2}\}$ (see Proposition 2.9 ii)), but even fulfills $r > \max\{\frac{\eta}{2(1-\eta)^2}, \frac{1-\eta}{2\eta}\}$. Furthermore, we consider the setting of a joint limit of $M$ and $N$, i.e. $M = M_N$ and $M_N \to \infty$ as $N \to \infty$. Since the equilibrium $u$ of the dynamical system (1) is stable, then – once a state close to $u$ is reached – both types are maintained in the parasite population for a long time. However, for finite $N$ eventually one of the types will get lost and the population enters a monomorphic state with all hosts being infected either only with type $A$ or only with type $B$. In the next proposition we will give an asymptotic lower bound for this time.

Let us add mutation to the Markov process $X^{N,M}$ by allowing each parasite to mutate at rate $u_N$ to the types $A$ and $B$, respectively, per parasite generation. We abbreviate

$$\theta_N := u_N M_N g_N,$$

this is the total rate at which parasite mutate in the total host population on the host time scale. If $\theta_N = o(r_N)$, then (as we will see in the proof of Theorem 3) the rate at which a type is transmitted by reinfections is much larger than the mutation rate to that type, even if that type is retained only in a single host (around the equilibrium frequency). In this case the dynamical system which arises as the limiting evolution of $X^{N,M}$ as $N \to \infty$ is not perturbed by mutations.

However, mutation eventually turns a monomorphic host population into a polymorphic one. In Theorem 3 we will give an upper bound on the time at which with high probability, i.e. with a probability that tends to 1 as $N \to \infty$, from a monomorphic state a state in a small neighborhood of $u$ is reached.

Together with the lower bound on the time for which a polymorphic state is maintained, we arrive at a lower bound on the mutation rate, such that the proportion of time during which the population is in a monomorphic state is negligible relative to the time during which the
population is in a polymorphic state. We will see that this lower bound is exponentially small in the host population size, see Remark 2.11. From a perspective regarding application it seems important that the lower bound is this small. Indeed, the polymorphicity we are modeling is found in coding regions. Type $A$ and type $B$ represent different genotypes/alleles of the same gene (e.g. in HCMV there exist for the region UL 75 two genotypes; these genotypes are separated by one deletion (removing an amino acid) and 4 non-synonymous point mutations). Since no "intermediate genotypes" are found in samples it is likely that a deep fitness valley lies between these two genotypes. Consequently, the mutation rate from type $A$ to type $B$ is likely to be very small. (The averaged mutation rate in HCMV is estimated to be $2 \cdot 10^{-7}$, see [18]). Under the assumption that the deletion rate is of the same order and that "intermediate" genotypes lead to non-reproducible virus, the deletion and the mutations would have to occur simultaneously, this would lead to an estimate of $u_N = 3 \cdot 10^{-34}$. If the fitness landscape is less extreme, the waiting time for a successful mutant might be shorter, see [19] for related results, and [15] for more discussion.

For $x \in [0, 1]^M$ denote by $\mu^x = \frac{1}{M} \sum_{i=1}^{M} \delta_{x_i}$ the empirical distribution of $x$ and for $\delta > 0$ define

$$V^\delta,N = \{ x \in [0, 1]^M | \mu^x(\{\ell\}) \in [u^\ell - \delta, u^\ell + \delta] \text{ for } \ell = 1, 2; \mu^x(U^\eta,N) \in [u^\eta - \delta, u^\eta + \delta] \}. \quad (4)$$

Furthermore, let

$$\tau^N_\delta = \inf \{ t > 0 | X^{N,M}(t) \in V^\delta,N \}$$

be the first time at which the process $X^{N,M}$ enters $V^\delta,N$, and let

$$\tau^N_0 = \inf \{ t > 0 | \mu^N(\{0\}) = 1 \text{ or } \mu^N(\{1\}) = 1 \}$$

be the first time at which the population becomes monomorphic.

**Theorem 3.** Assume $\theta_N = o(r^N)$, $r > \max\{\frac{\eta}{2(1-\eta)^2}, \frac{1-\eta}{2r}\}$ and let Assumptions (A) be fulfilled. Choose $\gamma > 0$ arbitrarily small. Then

(i) for any $\delta > 0$

$$\lim_{N \to \infty} \mathbb{P}_\theta(\tau^N_\delta < \frac{1}{\theta_N s_N} + M^N_N) = 1 \quad (5)$$

with $\Theta \in \{(0, 0, 1), (1, 0, 0)\}$

(ii) for any $\delta < \frac{1}{2} \min\{u^0, u^0, u^1\}$ and any sequence $(x_N)_n \in \mathbb{N}$ with the properties $x_N \in V^\delta,N$ and $\lim_{N \to \infty} \mu^N(\{0, 1\} \cup U^\eta,N) = 1$ one has

$$\lim_{N \to \infty} \mathbb{P}_{x_N}(\tau^N_0 > \exp(M^{-1}\gamma)) = 1.$$  

We postpone the proof to Section 3.4.

**Remark 2.11.** From the Theorem 3 it follows that if $\theta_N^{-1} = o(\exp(M^{-1}\gamma)s_N)$ for some $\gamma > 0$ (or in other words, if $\theta_N \gg \frac{1}{\exp(M^{-1}\gamma)s_N}$) then most of the time both parasite types coexist in the entire parasite population in a non-negligible amount.

### 3. Proofs

In the following we will use the phrase with high probability as $N \to \infty$ or simply whp as a synonym for with probability converging to 1 as $N \to \infty$. Recall also the definitions of the sets $U^\eta,N$ and $D^\eta,N$ from the sketch of the proof of Theorem 1:

$$U^\eta,N = (\eta - s_N, \eta + s_N) \quad (6)$$

$$D^\eta,N = (\eta - s_N^{3/2}, \eta + s_N^{3/2}). \quad (7)$$

As already mentioned in the sketch of the proof of Theorem 1 we distinguish between effective and ineffective reinfection events. Assume host $i$ is reinfected at time $s > 0$, and $X_i^N(s \rightarrow)$ is in state 0 or 1, then $X_i^N$ either returns to that state before it reaches $D^\eta,N$, or it reaches $D^\eta,N$ before returning. In the former case we call the reinfection event ineffective and in the latter effective.
3.1. Propagation of chaos: Proof of Proposition 2.5

With a view to Remark 2.3, we now give a graphical representation for \(v = (v_t)_{t \geq 0}\), the solution of the dynamical system (1). This representation (proved in Lemma 3.3) will be in terms of a family of nested trees \((T_s)_{s \geq 0}\) whose branches are labeled by the states \(\{0, \eta, 1\}\), and will then be used to prove the “propagation of chaos” result Proposition 2.5 for the process \(Y^M\) in the limit \(M \to \infty\).

**Definition 3.1** (The labeled random tree \(T_t\)). For \(t \geq 0\) we construct a tree \(T_t\) with root at time \(t\) and leaves at time 0 as follows: A single (distinguished) line starts from the root backwards in time. The growth of the tree backwards in time is then as follows: Each line is hit by HR-events at rate 1 and PER-events at rate 2r. (HR and PER stand for host replacement and potential effective reinfection.) At each such event, the line splits into two branches, the continuing and the incoming one (where “incoming” refers to the direction from the leaves to the root). Whenever the distinguished line is hit by an HR-event, we keep both branches in the tree and designate the continuing branch as the continuation of the distinguished line. Whenever a line other than the distinguished one is hit by a HR-event, we discard the continuing branch and keep only the incoming one in the tree. At a PER-event (irrespective of whether the line is the distinguished one or not) we keep both the incoming and the continuing branch in the tree.

Now assign to the leaves at time 0 independently the states 0, 1 or \(\eta\) according to the distribution with weights \(v^0_0, v^1_0, v^\eta_0\), and let the states propagate from the leaves up to the root according to the following rule:

At an HR-event (occurring at time \(\tau\), say), if the incoming branch at time \(\tau-\) is in state 0 or 1, then the continuing branch takes the state of the incoming branch. If the incoming branch at time \(\tau-\) is in state \(\eta\), then the state of the continuing branch at time \(\tau\) is decided by a coin toss: it is 1 with probability \(\eta\), and 0 with probability \(1 - \eta\).

At a PER-event (occurring at time \(\tau\), say),

a) if the incoming branch is in state 1 and the continuing branch is in state 0 at time \(\tau-\), then at time \(\tau\) the state of the continuing branch changes to \(\eta\) with probability \(\eta\), and remains in 1 with probability \(1 - \eta\),

b) if the incoming branch is in state 0 at time \(\tau-\) and the continuing branch is in state 1 at time \(\tau-\), then at time \(\tau\) the state of the continuing branch changes to \(\eta\) with probability \(1 - \eta\), and remains in 0 with probability \(\eta\),

c) if the incoming branch is in state \(\eta\) and the continuing branch is in state 0 at time \(\tau-\), then at time \(\tau\) the state of the continuing branch changes to \(\eta\) with probability \(\eta^2\), and remains in 0 with probability \(1 - \eta^2\), and

d) if the incoming branch is in state \(\eta\) and the continuing branch is in state 1 at time \(\tau-\), then at time \(\tau\) the type of the continuing branch changes to \(\eta\) with probability \((1 - \eta)^2\), and remains in 0 with probability \(1 - (1 - \eta)^2\),

e) in the other cases the continuing branch does not change its state.

**Remark 3.2.**

(i) The construction of \(T_t\) proceeds as follows: First we construct backwards from time \(t\) an ancestry with host replacement events occurring at rate 1 and potential effective reinfection events occurring at rate 2r, second we mark the leaves of the tree according to the initial distribution \(v_0 \in \Delta^3\) at time 0. Then states are propagated (forwards) until HR or PER arrows are hit. At an arrow independent coin tosses decide which type is transmitted from hosts in state \(\eta\), and whether a potential effective reinfection becomes effective. Note that the additional coin toss at a PER event scales the rate 2r of potential effective reinfection events down to the host-state dependent rate of effective reinfection events.

(ii) By choosing at time \(s\) the distinguished line as a root, we obtain nested Galton-Watson trees \(T_s, 0 \leq s \leq t\), see Figure 4.

**Lemma 3.3** (Probabilistic representation of the dynamical system (1)). Let \((T_s)_{s \geq 0}\) be as in Remark 3.2 (ii), and \(C_s\) be the state of the root of the tree \(T_s\), as specified in Definition 3.1. The
Fig 4. An example of a tree as specified in Definition 3.1. If the distinguished line is hit by an HR event (solid arrows), then both lines are followed backwards, the incoming (with arrow) and the continuing branch. If another line (different from the distinguished one) is hit by an HR event, then only the incoming branch is followed further (and a dot is drawn to indicate that an HR event happened). Next to the arrows and dots the incoming types and the results of the coin tosses are recorded. Next to a PER event (dashed arrows) the letter gives the transmitted type and the digit indicates the result of the second coin toss, which decides if the “possible effective reinfection event” is realized or not, see Remark 3.2(ii). At an HR event the letter gives the transmitted type. At time 0 the lines are typed according to \( v_0 \). The type of the distinguished line is displayed between times 0 and \( t \).
solution \( \mathbf{v} \) of the dynamical system (1) then has the probabilistic representation

\[
v^\ell_s = \mathbb{P}(C_s = \ell), \quad s \geq 0, \quad \ell \in \{0, 1, \eta\}.
\]

Proof. We abbreviate \( f(s) := (f^0(s), f^\eta(s), f^1(s)) := (\mathbb{P}(C_s = 0), \mathbb{P}(C_s = \eta), \mathbb{P}(C_s = 1)) \). Then, by construction, \( f(0) = v_0 \). It thus remains to show that \( f \) solves the differential equation (1).

We check only the equation for the first component, i.e. show that

\[
\partial f^0(s) \partial s = (1 - \eta)f^\eta(s) - 2r \eta f^0(s)(f^1(s) + \eta f^\eta(s)), \quad s \in [0, t).
\]

(The remaining cases are checked analogously.)

Write

\[
\mathbb{P}(C_{s+\delta} = 0) = \mathbb{P}(C_{s+\delta} = 0|C_s = 0)\mathbb{P}(C_s = 0) + \mathbb{P}(C_{s+\delta} = 0|C_s = \eta)\mathbb{P}(C_s = \eta) + \mathbb{P}(C_{s+\delta} = 0|C_s = 1)\mathbb{P}(C_s = 1)
\]

and calculate

\[
\mathbb{P}(C_{s+\delta} = 0|C_s = 0) = 1 - (2r + 1)\delta + \delta(f^0(s) + (1 - \eta)f^\eta(s)) + 2r \delta(f^0(s) + f^1(s)(1 - \eta) + f^\eta(s)((1 - \eta) + \eta(1 - \eta))) + \mathcal{O}(\delta^2)
\]

To see the latter equality we note first that in the time interval \([s, s + \delta]\) the distinguished line is hit by no more than one (HR or PER) arrow up to an event of probability \(\mathcal{O}(\delta^2)\). Then, given \( C_s = 0 \), the root of \( T_{s+\delta} \) is in state 0 if the distinguished line is not hit by a PER or HR event between times \( s \) and \( s + \delta \), or if an HR event happens but the incoming line is also of type 0 or the incoming line is of type \( \eta \) and transmits type 0, or if a PER event happens but it is not becoming effective, see Remark 3.2 (ii).

Similarly we obtain

\[
\mathbb{P}(C_{s+\delta} = 0|C_s = \eta) = \delta(f^0(s) + (1 - \eta)f^\eta(s)) + \mathcal{O}(\delta^2)
\]

and

\[
\mathbb{P}(C_{s+\delta} = 0|C_s = 1) = \delta(f^0(s) + (1 - \eta)f^\eta(s)) + \mathcal{O}(\delta^2).
\]

This leads to

\[
\lim_{\delta \to 0} \frac{\mathbb{P}(C_{s+\delta} = 0) - \mathbb{P}(C_s = 0)}{\delta} = (1 - \eta)f^\eta(s) - 2r \eta f^0(s)(f^1(s) + \eta f^\eta(s)).
\]

The following corollary is now immediate from Lemma 3.3 and Definition 2.4.

**Corollary 3.4** (Tree representation of the process \( V \)). Let \( (T_s)_{s \geq 0} \) and \( (C_s)_{s \geq 0} \) be as in Lemma 3.3, with all the leaves of the nested trees \( T_s \) marked independently according to \( v_0 \in \Delta^1 \). Then \( (C_s)_{s \geq 0} \) has the same distribution as the process \( V \) specified in Definition 2.4. In particular, for \( s \geq 0 \) the law of \( V_s \) equals \( v^0_0 \delta_0 + v^\eta_0 \delta_\eta + v^1_0 \delta_1 \), where \( \mathbf{v} = (v^0, v^\eta, v^1) \) is the solution of the dynamical system (1) with initial condition \( v_0 \).

**Proof of Proposition 2.5.** Consider the graphical representation of the processes \( Y^M_1, \ldots, Y^M_k \) described in Remark 2.3. In this representation we can follow backwards the ancestry of the hosts determining the state of \( Y^M_1 \) at time \( t \) for all \( s \leq t \) (where \( t > 0 \) was fixed), in analogy to the procedure described in Definition 3.1.

Let \( E_M \) be the event that the \( k \) graphs constructed in this manner are collision-free, in the sense that the graphical representations of \( Y^M_1, \ldots, Y^M_k \) do not share any lines and that each of these \( k \) graphs is a tree. The probability of the event \( E_M \) converges to 1 as \( M \to \infty \). Conditioned
on $E_M$ the graphical representation can be coupled with that of $k$ i.i.d. copies of the tree $T_i$ specified in Definition 3.1. On the event $E_M$, the random marking of the leaves of the forest results through random draws (without replacement) from the type frequencies of $Y^M(0)$. These converge by assumption to $W^k$. Thus, the convergence of the finite dimensional distributions follows from Corollary 3.4. Tightness is immediate, as the process has only “large” jumps.

**Proof of Corollary 2.6.** Since a finite number of draws (with replacement) from a large urn produces no collision with high probability, we observe for all $k \in \mathbb{N}$ and each bounded continuous function $f$ defined on $D([0, t]; \{0, \eta, 1\})$ that

$$\left| \mathbb{E}\left[ \int \cdots \int f(y_1) \cdots f(y_k) \nu^M(dy_1) \cdots \nu^M(dy_k) \right] - \mathbb{E}[f(Y^M_1) \cdots f(Y^M_k)] \right| \to 0$$

as $M \to \infty$. By Proposition 2.5 the r.h.s converges to $(\mathbb{E}[f(V)])^k$, hence $\mathbb{E}((\int f(y)\nu^M(dy))^k) \to (\mathbb{E}[f(V)])^k$, which suffices to conclude the convergence of $\nu_M$ to $\mathcal{L}(V)$ in the weak topology.

The latter convergence together with Corollary 3.4 implies that for each $s \in [0, t]$

$$\frac{1}{M} \sum_{i=1}^{M} \delta_{Y^M_i(s)} \to \mathcal{L}(V_s) = v_s^0 \delta_0 + v_s^\eta \delta_\eta + v_s^1 \delta_1$$

in distribution as $M \to \infty$. In other words, writing

$$\frac{1}{M} \sum_{i=1}^{M} \delta_{Y^M_i(s)} = Z_0^M(s) \delta_0 + Z_\eta^M(s) \delta_\eta + Z_1^M(s) \delta_1,$$

we obtain for the host type frequencies $Z^M(s) = (Z_0^M(s), Z_\eta^M(s), Z_1^M(s))$ that

$$Z^M(s) \to v_s$$

in distribution as $M \to \infty$.

The tightness of $(Z^M)_{M \in \mathbb{N}} := (Z^M(s))_{0 \leq s \leq t}$ with respect to the Skorokhod topology can be seen as follows: According to the criterion of Theorem 3.7.2 in [20] it suffices to show that for any $\delta_1 > 0$ there exists a $\delta_2 > 0$ such that

$$\sup_{M \in \mathbb{N}} \mathbb{P}(\omega(Z^M, \delta_2) > \delta_1) < \delta_1,$$

where $\omega(Z^M, \delta_2)$ denotes the modulus of continuity of $Z^M$ with resolution $\delta_2$ on the time interval $[0, t]$.

Whenever a host is effectively reinfected or a host replacement occurs, this leads to a jump of size $1/M$ in $Z^M$. The rate at which these events occur can be estimated by a constant $c > 0$. Consequently, the maximal jump size between two time points of distance $\leq \delta_2$ is at most

$$c\delta_2 + \frac{1}{M^{1/4}}$$

with probability $1 - \frac{c\delta_2}{M^{1/4}}$. Consequently the probability, that in all $t/\delta_2$ intervals of length $\delta_2$ the jump size is smaller than $c\delta_2 + \frac{1}{M^{1/4}}$ can be estimated by $\left(1 - \frac{c\delta_2}{M^{1/4}}\right)^{t/\delta_2}$. For $\delta_2$ small enough and $M \geq M_0$ with $M_0$ large enough we can achieve that $c\delta_2 + \frac{1}{M^{1/4}} < \delta_1$ and $\left(1 - \frac{c\delta_2}{M^{1/4}}\right)^{t/\delta_2} > 1 - \delta_1$.

On the other hand, for $M \leq M_0$ the number of the events happening in the time interval $[0, t]$ can be estimated by a sufficiently large number $K_0$ with probability $p$ arbitrarily close to 1. By choosing $\delta_2$ small enough it is guaranteed that all these event belong to different time intervals of length $\delta_2$ with probability $1 - \delta_1$. Altogether this shows (8) and proves the claimed tightness. \qed
3.2. Proof of Proposition 2.9

A (i) It is obvious from (1) that (0,0,1) and (1,0,0) are equilibrium points. Further, we calculate from \( \dot{u}^0 = 0 \) and \( \dot{u}^1 = 0 \), that

\[
\dot{u}^0 = \frac{2r\eta u^0 v^0}{1 - \eta - 2r\eta^2 v^0}
\]

and

\[
\dot{u}^1 = \frac{2\eta + 2r\eta^2 (1 - \eta) u^0}{2r(1 - \eta)^2 \eta}
\]

\( \dot{u}^0 = 0 \) does not increase information, since \( \dot{u}^1 + \dot{u}^0 = \dot{u}^0 \). Using \( u^0 + u^1 + u^1 = 1 \) we obtain that

\[
u^0 = \frac{2r(1 - \eta)^2 (2\eta - 1)}{2r(1 - \eta)^2 + 4r^2 \eta(1 - \eta)^3}
\]

hence

\[
u^1 = \frac{2\eta + 2r\eta^2 (1 - \eta) u^0}{2r(1 - \eta)^2 \eta} = \frac{2r(1 - \eta)^2 (2\eta - 1)}{2r(1 - \eta)^2 + 4r^2 \eta(1 - \eta)^3}
\]

and

\[
u^0 = \frac{2r\eta u^0 v^0}{1 - \eta - 2r\eta^2 v^0} = \frac{u^0(2\eta - 1 + 2r\eta^2 (1 - \eta) u^0)}{(1 - \eta)^2 (1 - \eta - 2r\eta^2 v^0)}
\]

\[
= \frac{2r\eta^3 (1 - \eta)^3 - (2\eta - 1)^2 (2r\eta (1 - \eta) + 1)}{2r\eta^2 (1 - \eta)^2 (1 + 2r\eta (1 - \eta))}.
\]

(ii) If \( r = \frac{2\eta - 1}{2\eta(1 - \eta)} \), one calculates, that \( u^0 = u^0 = 0 \) and \( u^1 = 0 \). For \( r < \frac{2\eta - 1}{2\eta(1 - \eta)} \) the equilibrium \( u \notin \Delta^3 \).

If \( r > \max\{\frac{2\eta - 1}{2\eta(1 - \eta)}, \frac{1 - 2\eta}{2\eta(1 - \eta)}\} \), the equilibrium point \( u \) lies in the interior of \( \Delta^3 \). This can be seen as follows: First for \( r > \max\{\frac{2\eta - 1}{2\eta(1 - \eta)}, \frac{1 - 2\eta}{2\eta(1 - \eta)}\} \) \( u^0 \) as well as \( u^1 \) are strictly positive. For \( \eta < \frac{1}{2} \) and \( r = \frac{1 - 2\eta}{2\eta(1 - \eta)} \), we have \( u^1 = 0 \) and \( u^0 = 1 \). For \( r \to \infty \) both \( u^0 \to 0 \) and \( u^1 \to 0 \). We calculate that \( \frac{\partial^2 \lambda}{\partial r^2} = -8r^2 \eta^4 (1 - \eta)^3 + 8r\eta^3 (1 - \eta)(2\eta - 1) + 2r\eta (2\eta - 1) \). For \( r > 0 \) this derivative is negative, as it is negative for \( r \to \infty \) and both roots have negative real parts according to the Routh-Hurwitz criterion, see [21], §15.715, p. 1076. Consequently \( u^0 \) is strictly monotonically decreasing from 1 to 0. Analogously one argues for \( u^1 \) and \( u^0 \).

B (Stability) To analyze the stability of the dynamical system \( v \) we project the system onto \( \Delta^2 = \{(x,y)|x,y \in [0,1], x+y \leq 1\} \) by considering only the coordinates \( v^0 \) and \( v^1 \). The three fixed points correspond in this projection to the points (0,1), (1,0) and \( (u^0, u^1) \).

We recall that an equilibrium point is asymptotically stable if all real parts of the eigenvalues of the Jacobian are strictly negative.

The Jacobian \( \mathcal{J}_v \) of the dynamical system \( v \) is

\[
\mathcal{J}_v = \begin{pmatrix}
-\eta - 2r(\eta - (1 - \eta)^2) + 4r\eta^2 v^0 & -\eta - 2r(\eta - (1 - \eta)^2) + 4r(1 - \eta)^2 v^1 \\
-\eta - 2r(\eta - (1 - \eta)^2) + 4r\eta^2 v^1 & -\eta - 2r(\eta - (1 - \eta)^2) + 4r(1 - \eta)^2 v^0
\end{pmatrix}
\]

(i) Case \( r > \max\{\frac{2\eta - 1}{2\eta(1 - \eta)}, \frac{1 - 2\eta}{2\eta(1 - \eta)}\} \):

a) (Equilibrium points at the boundary)

For \( v^0 = 0 \) and \( v^1 = 1 \) the Jacobian equals

\[
\begin{pmatrix}
\eta - 1 - 2r\eta & \eta - 1 \\
\eta - 2r(1 - \eta)\eta & \eta - 2r(1 - \eta)^2
\end{pmatrix}
\]

In this case the eigenvalues solve

\[
\lambda^2 + \lambda(1 + 2r(\eta - (1 - \eta)^2)) + 2r(\eta^2 - (1 - \eta)^3 - (1 - \eta)^2) - 4r^2\eta(1 - \eta)^2 = 0.
\]
The second coefficient is $< 0$ iff $r > \frac{2n-1}{2n(1-\eta)^2}$. (Analogously for $r^0 = 1$ and $v^1 = 0$ the second coefficient is $< 0$ iff $r > \frac{2n}{2n(1-\eta)^2}$.) Hence, $(0,1)$ is for $r > \max\{\frac{2n-1}{2n}, \frac{1-2n}{2n}\}$ a saddle point. Analogously, one argues that $(1,0)$ is a saddle point.

According to Corollary 2.6 the dynamical system $u$ is the deterministic limit of the Markov process $Z^M$, whose state space is a subset of $\Delta^3$. Consequently, in the points $(0,1)$ and $(1,0)$ one eigenvector (appropriately oriented) is pointing into the interior of $\Delta^3$ and one pointing in a direction outside of $\Delta^3$.

b) (Equilibrium point in the interior)

The fixed point $u$ is globally stable in $\Delta^3\setminus\{(0,1), (1,0)\}$, if all trajectories starting in a point of $\Delta^3\setminus\{(0,1), (1,0)\}$ converge to $u$. By the Poincaré-Bendixson-Theorem, see e.g. Theorem 1.8.1 in [22], in a 2-dimensional differential dynamical system each compact $\omega$-limit set, containing only finitely many fixed points, is either a fixed point, a periodic orbit or a connected set, consisting of homoclinic and heteroclinic orbits connecting a finite set of fixed points. We can exclude heteroclinic orbits, because the vector field corresponding to the dynamical system $v$ is pointing into the interior of $\Delta^3$. So if we can show that no periodic orbits exist in the interior of $\Delta^3$, then the limit set has to be a fixed point, the point $u$. We check, that the partial derivatives fulfill $\frac{\partial v^i}{\partial \eta} \leq 0$ for $i, j \in \{0, 1\}$, $i \neq j$ and $v^i, v^j \in \Delta^2$. Hence, the dynamical system is competitive and we can apply Theorem 2.3 of [23] stating that all trajectories starting in $\Delta^3\setminus\{(0,1), (1,0)\}$ converge to some point in $\Delta^3$. This point can only be the fixed point $u$.

ii) Case $r < \max\{\frac{2n-1}{2n(1-\eta)^2}, \frac{1-2n}{2n}\}$:

In this case $u$ does not belong to $\Delta^3$. To assess the stability of the other fixed points consider first the case $\eta > \frac{1}{2}$. Then $\max\{\frac{2n-1}{2n(1-\eta)^2}, \frac{1-2n}{2n}\} = \frac{2n-1}{\eta(1-\eta)^2}$ and since $r > 0$, we obtain that $r > \frac{1-2n}{\eta(1-\eta)^2}$. Consequently, $(1,0)$ is a saddle point.

As $r < \frac{2n-1}{\eta}$, the second coefficient of (9) is $> 0$. To assess the stability of $(0,1)$ we analyze the first coefficient. For $\eta > \frac{1-\sqrt{5}}{2}$ the first coefficient is $> 0$. Consequently, both eigenvalues are strictly negative and hence $(0,1)$ is an asymptotically stable equilibrium point.

Since no other equilibrium point is contained in $\Delta^3$, the point $(0,1)$ must also be a globally stable equilibrium point on $\Delta^3\setminus\{(1,0)\}$.

For $\eta < \frac{1}{2}$ one argues analogously.

Case $r = \max\{\frac{2n-1}{2n(1-\eta)^2}, \frac{1-2n}{2n}\}$:

The claim follows by continuity. Consider the case $\eta > \frac{1}{2}$: For $r < \max\{\frac{2n-1}{2n(1-\eta)^2}, \frac{1-2n}{2n}\}$ the point $(1,0)$ is a saddle point and $(0,1)$ is globally stable on $\Delta^3\setminus\{(1,0)\}$. On the other hand, for $r > \max\{\frac{2n-1}{2n(1-\eta)^2}, \frac{1-2n}{2n}\}$ the point $(1,0)$ is a saddle point, $u$ is globally stable on $\Delta^3\setminus\{(0,1)\}$ and $u \to (0,1)$ as $r \downarrow \max\{\frac{2n-1}{2n(1-\eta)^2}, \frac{1-2n}{2n}\}$.

One argues analogously for $\eta < \frac{1}{2}$.

**3.3. Proofs of Theorem 1 and Theorem 2**

The proofs of Theorems 1 and 2 are based on several lemmata; these we state next. Basically these lemmata make statements about hitting probabilities and hitting times of the path of the frequency of type $A$ in a single host.

The following lemma is elementary and well-known:

**Lemma 3.5** (Ruin probabilities). Let $W$ be a random walk on $\mathbb{Z}$ starting in 0, with increment distribution $p\delta_1 + q\delta_{-1}$, $p + q = 1$. Then, for $N_1$ and $N_2 \in \mathbb{N}$, the probability that $W$ hits $N_1$ before it hits $-N_2$ is

$$
\frac{(p/q)^{N_2} - 1}{(p/q)^{N_1+N_2} - 1} = \frac{(q/p)^{N_1} - 1}{(q/p)^{N_1+N_2} - 1}.
$$

**Lemma 3.6** (Probability to balance). Let Assumptions (A) be fulfilled.

Let $\xi^N = (\xi_i^N)_{i \geq 0}$ be a Markov process on $\{0, 1/N, \ldots, 1\}$ with jumps from $i/N$ to
according to (14). Hence, we can couple for some \( r'_{N,1}, r'_{N,2} \) which may change in time but satisfy
\[
0 \leq r'_{N,1}, r'_{N,2} \leq r_N/g_N. \tag{11}
\]

For \( x \in \{0, \frac{1}{N}, \ldots, \frac{N-1}{N}, 1\} \) let
\[
\tau_x = \inf\{t \geq 0 | \xi^N_t = x\}.
\]

Then
\[
\lim_{N \to \infty} \frac{\mathbb{P}_1(\tau_{[\eta N]/N} < \tau_0)}{2sN\eta} = 1 \tag{12}
\]
and
\[
\lim_{N \to \infty} \frac{\mathbb{P}_{\eta N}(\tau_{[\eta N]} < \tau_N)}{2sN(1-\eta)} = 1, \tag{13}
\]
where the subscript of \( \mathbb{P} \) denotes the initial state of \( \xi^N \).

Proof. First we remark that from Assumption (11) we obtain
\[
r'_{N,k} \leq \frac{r_N}{g_N} = \frac{r}{sNg_N} = o(s_N), \quad k = 1, 2. \tag{14}
\]

We prove only statement (12); the second statement (13) follows analogously.

In order to tie in with Lemma 3.5 we can also consider the process \( \xi'_{N} = N\xi^N \) and show instead of (12) the convergence
\[
\lim_{N \to \infty} \frac{\mathbb{P}_1(\tau'_{[\eta N]/N} < \tau'_0)}{2sN\eta} = 1 \tag{15}
\]
with \( \tau'_x = \inf\{t \geq 0 | \xi'^N_t = xN\} \) for \( x \in \{0, \frac{1}{N}, \ldots, \frac{N-1}{N}, 1\} \).

To prove an upper bound on the probability in the numerator of (15) note that as long as \( 1 \leq i \leq \eta N \) the probability that the next event is a birth is
\[
\frac{i(N-i)(1+s_{N}\eta)+r'_{N,1}+r'_{N,2}}{2(1-s_{N}\eta+o(s_N)}
\]
according to (14). Hence, we can couple \( \xi'^N \) with an (asymmetric) random walk \( (R_n^{(1)})_{n \geq 0} \), which makes jumps of size one upwards with probability \( \frac{1+s_{N}\eta+o(s_N)}{2} \) and downwards with probability \( \frac{1-s_{N}\eta+o(s_N)}{2} \), and is absorbed at 0, such that
\[
\mathbb{P}_1(\tau'_{[\eta N]/N} < \tau'_0) \leq \mathbb{P}_1(\exists k \geq 0 : R_k^{(1)} \geq \delta N).
\]

For the random walk \( (R_n^{(1)})_{n \geq 0} \) we have
\[
\mathbb{P}_1(R_\infty^{(1)} = \infty) = 1 - \mathbb{P}_1(R_\infty^{(1)} = 0)
\]
and by Lemma 3.5 we have
\[
\phi_N := \mathbb{P}_1(R_\infty^{(1)} = \infty) = 2sN\eta + o(s_N).
\]

Furthermore using \( s_N N \to \infty \) we have
\[
\lim_{N \to \infty} \frac{\mathbb{P}_1(\exists k \geq 0 : R_k^{(1)} \geq \delta N)}{\mathbb{P}_1(R_\infty^{(1)} = \infty)} = 1,
\]
since \( \mathbb{P}(R_\infty^{(1)} = \infty | \exists k \geq 0 : R_k^{(1)} \geq \delta N) \geq 1 - (1 - \phi_N)^\delta N = 1 - (1 - 2sN\eta + o(s_N))^{\delta N} \to 1. \)
To obtain a lower bound on the probability in the numerator of (15), we fix an arbitrary $\delta < \eta$ and note that we can couple $\xi^N$ with a random walk $(R_{n}^{(2)})_{n \geq 0}$ which makes jumps of size one upwards with probability $\frac{1+\sin(\eta-\delta)+o(\sin \delta)}{1-s_N(\eta-\delta)+o(s_N)}$ and downwards with probability $\frac{1-s_N(\eta-\delta)+o(s_N)}{1+\sin(\eta-\delta)+o(\sin \delta)}$, and is absorbed 0, such that

$$\mathbb{P}_1(R_{\infty}^{(2)} = \infty) \leq \mathbb{P}_1(\tau_{\lfloor \frac{\delta N}{N} \rfloor}^{\prime} < \tau_0).$$

We have (again by Lemma 3.5)

$$\mathbb{P}_1(R_{\infty}^{(2)} = \infty) = 2s_N(\eta - \delta) + o(s_N).$$

To finish, we show that the probability $p_0^N$ that $\xi^N$ hits $\lfloor \frac{\delta N}{N} \rfloor$ before 0 (when starting in $\lfloor \frac{\delta N}{N} \rfloor$) also tends to 1 for $N \to \infty$. Since $\delta > 0$ was arbitrary this concludes the proof. To do so we calculate first the probability $\tilde{p}_0^N$ that $\xi^N$ hits $\lfloor \frac{(\eta-\delta)N}{N} \rfloor$ before 0, when starting in $\lfloor \frac{\delta N}{N} \rfloor$. This can be estimated by the the hitting probability (10) with $p = \frac{1+\sin \delta}{2} + o(s_N)$, $N_1 = \lfloor N(\eta - \delta) \rfloor$ and $N_2 = \lfloor N\delta \rfloor$. Then

$$\tilde{p}_0^N \geq 1 - \frac{\lfloor N(\eta-\delta) \rfloor - 1}{\lfloor 2s_N(\eta - \delta) + o(s_N) \rfloor} - 1 \xrightarrow{N \to \infty} 1.$$

For $\delta$ small enough, the probability to hit $\lfloor \frac{\delta N}{N} \rfloor$ before $\lfloor \frac{(\eta-\delta)N}{N} \rfloor$ when starting in $\lfloor \frac{(\eta-\delta)N}{N} \rfloor$, can be estimated from below by below by $\frac{1}{2}$. Hence we arrive at

$$p_0^N \geq \sum_{k=0}^{\infty} \left(\frac{1}{2}\right)^{k+1} \tilde{p}_0^N = \frac{1}{2} \frac{1}{1-\tilde{p}_0^N/2} \xrightarrow{N \to \infty} 1. \tag{16}$$

In the following we will speak of a non-effective excursion from $x$ when a path starting in state $x \in [0, 1]$ returns to $x$ before it hits the frequency $\frac{\lfloor \frac{\delta N}{N} \rfloor}{N}$.

**Remark 3.7.** In the proof of Lemma 3.6 we showed that $\lim_{N \to \infty} \mathbb{P}_N(\tau_{\lfloor \frac{\delta N}{N} \rfloor} < \tau | \tau_{\lfloor \frac{\delta N}{N} \rfloor} | < \tau_0) = 1$, for any $\delta > 0$. This implies that there exists a sequence $\delta_N$ converging to 0 sufficiently slowly such that

$$\lim_{N \to \infty} \mathbb{P}_N(\tau_{\lfloor \frac{\delta N}{N} \rfloor} < \tau_0 | \tau_{\lfloor \frac{\delta N}{N} \rfloor} < \tau_0) = 1.$$ 

We can interpret the last statement also as a bound on the height of a non-effective excursion from 0. Specifically, we have

$$\lim_{N \to \infty} \mathbb{P}_N(\max_{0 \leq t < \tau_0} \xi_t^N < \frac{\lfloor \frac{\delta N}{N} \rfloor}{N} | \tau_{\lfloor \frac{\delta N}{N} \rfloor} < \tau_0) = 1.$$

For the proofs of Theorem 1 and Theorem 2 we need an estimate on the time that a type $A$-frequency path needs to reach the interval $D \eta N$, see Equation 7, when starting from $\frac{1}{N}$ or $1 - \frac{1}{N}$, respectively. This as well as an estimate on the asymptotic time to eventually reach the equilibrium frequency $\eta$ will be handled in the next proposition.

**Proposition 3.8** (Time to balance). *Let Assumptions (A) be fulfilled. Let $\xi^N$ be a Markov process as in Lemma 3.6. For any $\delta > 0$ we have as $N \to \infty$

$$\mathbb{P}_N(\tau_{\lfloor \frac{\delta N}{N} \rfloor} < \frac{N(\frac{3\delta}{2}+\delta)}{g_N} | \tau_{\lfloor \frac{\delta N}{N} \rfloor} < \infty) \to 1, \tag{17}$$

$$\mathbb{P}_N(\tau_{\lfloor \frac{\delta N}{N} \rfloor} < \frac{N(2+\delta)}{g_N} | \tau_{\lfloor \frac{\delta N}{N} \rfloor} < \infty) \to 1. \tag{18}$$

Analogous statements hold when the process is started in $\frac{N-1}{N}$. 

To prepare the proof we give estimates on the time a random walk needs to exit a neighborhood of size $h_N$.

**Lemma 3.9.** Let $h_N > \frac{1}{N}$ and $(W_t^{(N)})_{t \geq 0} = \frac{S_{(t+1)}}{N}$ be a rescaled, symmetric random walk with $S_j = \sum_{k=1}^j \zeta_k$ for iid $(\zeta_k)_{k \geq 1}$ with $P(\zeta_1 = 1) = P(\zeta_1 = -1) = \frac{1}{2}$. Let

$$T_{h_N} = \inf \{ t \geq 0 | |W_t^{(N)}| \geq h_N \}.$$

Then

$$E[T_{h_N}] = h_N^2$$

as well as

$$E[T_{h_N}^2] = \frac{5}{3} h_N^4 - \frac{2 h_N^2}{3 N^2},$$

from which follows

$$\mathbb{V}[T_{h_N}] = \frac{2}{3} (h_N^4 - \frac{h_N^2}{N^2}).$$

**Proof.** For the unscaled random walk $(S_j)_{j \geq 1}$ it is well-known that the expected hitting time of the set $\{h_N N, -h_N N\}$ is $(h_N N)^2$. The second moment of this hitting time can be calculated by considering the martingale

$$M_j := S_j^2 - 6 j S_j^2 + 3j^2 + 2j, \quad j = 0, 1, \ldots$$

Rescaling proves the claim. \hfill \Box

**Proof of Proposition 3.8.** We have $\{\tau_{\frac{[nN]}{N}} < \infty \} \subset \{\tau_{\frac{(\eta-x^2)N}{N}} < \infty \}$ and

$$\lim_{N \to \infty} \frac{\mathbb{P}_1(\tau_{\frac{(\eta-x^2)N}{N}} < \infty)}{\mathbb{P}_1(\tau_{\frac{[nN]}{N}} < \infty)} = 1.$$

Hence, for proving (17) it suffices to condition on the event $\{\tau_{\frac{[nN]}{N}} < \infty \}$.

We separate the time to reach the frequency $\frac{[nN]}{N}$ starting from the frequency $\frac{1}{N}$ into four phases:

1. Reaching a (fixed) frequency $\frac{[hN]}{N} > 0$, for some $h > 0$,
2. Climbing from $\frac{[hN]}{N}$ to $\frac{([\eta-h]N)}{N}$,
3. Climbing from $\frac{([\eta-h]N)}{N}$ to $\frac{([\eta-hN]N)}{N}$ for some appropriate sequence $h_N$ with $h_N \to 0$,
4. Reaching $\frac{[\eta N]}{N}$ from $\frac{([\eta-hN]N)}{N}$.

For the proof of (17) only the first three phases are relevant.

For a stochastic process $L = (L_t)_{t \geq 0}$ with state space $\subset [0, 1]$ denote by

$$T_{h_N}^L = \inf \{ t \geq 0 | L_t \geq \frac{[hN]}{N} \}$$

and for an $L$ with state space $\subset \{0, \ldots, N\}$ put

$$T_{h_N}^L = \inf \{ t \geq 0 | L_t \geq [hN] \}.$$

In phase 1, we consider as in the proof of Lemma 3.6 the process $\xi^t = N \xi$ instead of $\xi$. The process $\xi^t$ is a birth-death process with birth rate $\lambda_t = i \frac{N-1}{N} g_N (1 + s_N (\eta - \frac{i}{N}) + o(s_N))$ and death rate $\mu_t = i \frac{N-1}{N} g_N (1 - s_N (\eta - \frac{i}{N}) + o(s_N))$ according to (14).

Note that $\lambda_t \geq i \frac{N-1}{N} g_N (1 + s_N (\eta - h) + o(s_N))$ and $\mu_t \leq i \frac{N-1}{N} g_N (1 - s_N (\eta - h) + o(s_N))$ as long as $i < h$. Consequently, in phase 1 we have

$$\frac{\lambda_t}{\mu_t + \lambda_t} \geq \frac{1 + s_N (\eta - h) + o(s_N)}{2}$$

and

$$\frac{\mu_t}{\mu_t + \lambda_t} \leq \frac{1 - s_N (\eta - h) + o(s_N)}{2}.$$
As long as \( \frac{N-1}{N} \geq 1 - h \) we can couple \( \xi' \) with a continuous time binary Galton-Watson process \( W \) with individual birth rate \( g_N(1 + s_N(\eta - h) + o(s_N))(1 - h) \) and individual death rate \( g_N(1 - s_N(\eta - h) + o(s_N))(1 - h) \), such that \( T_h^\xi \leq T_h^W \) almost surely.

The probability that a single line in \( W \) will not be immortal is the solution of the equation
\[
1 - s_N(\eta - h) + o(s_N) + \frac{1}{1 + s_N(\eta - h) + o(s_N)}z^2 = z,
\]
which is smaller than 1, see (Athreya and Ney, 1972, Chapter I.5).

So when an immortal line splits, the new line has a chance \( 1 - \frac{1 - s_N(\eta - h) + o(s_N)}{1 + s_N(\eta - h) + o(s_N)} \leq 2s_N(\eta - h) + o(s_N) \) to be immortal. Therefore we can couple \( W \) conditioned to hit \( h \) with a pure-birth process \( G \) with birth rate \( 2s_Ng_N(\eta - h)(1 - h) + o(s_N) \), such that \( T_h^G \leq T_h^W \) almost surely.

Because of
\[
\mathbb{E}[T_h^G] = \sum_{i=1}^{hN-1} \frac{1}{2i(1 - h)g_Ns_N(\eta - h)} = \frac{\log(hN)}{(s_N + o(s_N))g_N} + \mathcal{O}\left(\frac{1}{s_Ng_N}\right)
\]
we can estimate for any \( \delta > 0 \)
\[
\mathbb{P}\left(T_h^G > \frac{1}{s_N^{1+\delta}g_N}\bigg| T_h^\xi < \infty\right) = \mathbb{P}\left(T_h^\xi > \frac{1}{s_N^{1+\delta}g_N}\bigg| T_h^\xi < \infty\right) \leq \mathbb{P}\left(T_h^G > \frac{1}{s_N^{1+\delta}g_N}\right) \leq \frac{1/\delta}{1/(s_N^{2(\delta+1)}/g_N)} \rightarrow 0.
\]

In phase 2 we rescale time in the process \( \xi \) by a factor \( 1/(g_Ns_N) \) and denote the corresponding process by \( V' \). Then the infinitesimal mean of the time rescaled process \( V' \) equals \( 2V'(1 - V')(\eta - V') \) in state \( V' \) and the infinitesimal variance equals \( \frac{1}{s_N}V'(1 - V') + o\left(\frac{1}{s_N}\right) \). Since \( s_NN \rightarrow \infty \), also \( \frac{1}{s_N}V'(1 - V') \rightarrow 0 \). Consequently, \( V' \) converges to the solution of the differential equation \( \dot{x} = \frac{1}{2x(1 - x)(\eta - x)} \) with initial condition \( x(0) = h \). The level \( \eta - h \) is reached after time \( \mathcal{O}(1) \) and consequently, when rescaling time back the second phase can be estimated by \( \mathcal{O}(N^2/g_N) \) time units whp.

In phase 3 we refine the argument of phase 2. Instead of rescaling time by \( \frac{1}{s_Ng_N} \) we rescale by a larger factor \( k_N/g_N \), so that \( N/k_N \) still converges to \( \infty \). In this manner the time to reach a level \( \eta - h_N \) can be estimated by \( \mathcal{O}(k_N^{1+\delta}/g_N) \) whp, if \( kNh_Ns_N - \frac{N}{N} \rightarrow 1 \) for any \( \delta > 0 \).

In order to show (17) we choose \( h_N = s_N^{3/2} \) and consequently arrive at \( k_N = N^\beta/2 \).

For showing (18) we choose \( k_N = N^{(1+2\epsilon)/3} \) and \( h_N = N^{-(1-\epsilon)/3} \).

In the last phase 4 we set \( s_N = 0 \) and \( r_{N,1} = r_{N,2} = 0 \). This gives an upper bound on the time \( T_4 = T_{\eta}^\xi - T_{\eta-h_N}^\xi \) to reach the level \( \frac{[\eta + h_N]}{N} \) from \( \frac{[\eta-h_N]}{N} \). Rescale time by \( N/(\eta(1-\eta))g_N \). For \( i \) close to \( N/\eta \) we can estimate \( i(N-i)/(\eta(1-\eta)) \) by \( N^2 \) and hence by ignoring balancing selection we arrive at a random walk with increments \( \pm \frac{1}{\sqrt{x}} \) occurring at rate \( N^2 \).

Until finally the level \( \frac{[\eta-h_N]}{N} \) is hit the process may return to the level \( \frac{[\eta-h_N]}{N} \) several times. Since below level \( \frac{[\eta-h_N]}{N} \), the approximation of phase 3 holds, we can approximate the path by the excursions of a rescaled random walk to the levels \( \frac{[\eta]}{N} \) and \( \frac{[\eta-2h_N]}{N} \). If the random walk hits the level \( \frac{[\eta-2h_N]}{N} \) it returns to the level \( \frac{[\eta-h_N]}{N} \) within a time \( \mathcal{O}(k_N^{1+\delta}) \) (using phase 3). Hence, we can estimate the time \( T_4 \) by \( T_4 \leq (\sum_{i=0}^{R}(\frac{N}{\eta(1-\eta)} + L_i) + S)/g_N \), where \( R \) is geometrically distributed with parameter \( 1/2 \) (it counts the number of hits of the level \( \frac{[\eta-2h_N]}{N} \) before the level \( \frac{[\eta-h_N]}{N} \) is hit) and \( K_i \sim T_{h_N} \) of Lemma 3.9. \( L_i \) are the lengths of the transitions starting from \( \frac{[\eta-2h_N]}{N} \) to \( \frac{[\eta-h_N]}{N} \) and finally \( S \) is the length of the last transition from \( \frac{[\eta-h_N]}{N} \) to \( \frac{[\eta]}{N} \) (which does not hit the level \( \frac{[\eta-2h_N]}{N} \)).

Choosing \( h_N = N^{-(1-\epsilon)/3} \) yields \( k_N = Nh_N^2 \) and hence with Lemma 3.9 we can estimate
\[
\mathbb{E}[T_4] \leq (\mathbb{E}[R])\mathbb{E}[cNK_1 + L_1] + \mathbb{E}[S])/g_N \leq c_2(h_N^2N + \mathcal{O}(k_N^{1+\delta}))/g_N
\]
for appropriate constants \( c_1, c_2 > 0 \) which are needed due to rescaling of time and by adding the different summands. Furthermore,

\[
V[g_N T_4] \leq E[(\sum_{i=0}^{R} (NK_i + L_i) + S)^2]
\]

\[
\leq \sum_{j=0}^{\infty} \mathbb{P}(R = j)E[(\sum_{i=0}^{j} (K_i + L_i) + S)^2]
\]

\[
\leq (O(k_N^{2+\delta}) + O(h_N N^2)) \sum_{j=0}^{\infty} \frac{1}{2} (j^2 + 6j + 1).
\]

and since \( h_N^{-1} N^2 = O(k_N^{2+\delta}) \) we obtain

\[
\mathbb{P}(T_4 < k_N^{1+\delta}/g_N) \xrightarrow{N \to \infty} 0
\]

for any \( \delta > 0. \)

**Lemma 3.10** (Length of ineffective excursions). Let Assumptions (A) be fulfilled and let \( \xi^N \) be the same process as in Lemma 3.6. Assume \( \xi^N(0) = 1/N. \) Let \( \tau^N_0 = \inf\{ t > 0 | \xi(t) = 0 \} \) and let \( \tau^N_\eta = \inf\{ t > 0 | \xi(t) = \frac{\eta}{N} \}. \)

Then

\[
\lim_{N \to \infty} \mathbb{P}(\tau^N_0 < N^{3+\delta}/g_N | \tau^N_0 < \tau^N_\eta) = 1
\]

for any \( \delta > 0. \)

**Proof.** Because of Remark 3.7 we may replace the event \( \{ \tau^N_0 < \tau^N_\eta \} \) in (19) by \( \{ \tau^N_0 < \tau^N_{\delta_N} \} \) for a sequence \( \delta_N \) converging to 0 sufficiently slowly.

In the following we rescale time by \( 1/g_N \) and space by \( N \) and denote the corresponding process by \( \xi^N(t) = N \xi^N(t/g_N) \). Let \( W := W^N = (W^N)_t \geq 0 \) be a birth-death process starting in \( W^N_0 = 1 \) with individual birth rate \( (1 - \delta_N)(1 + s_N \eta + o(s_N)) \) and individual death rate \( (1 - \delta_N)(1 - s_N(\eta - \delta_N) + o(s_N)) \). We can couple the process \( \xi^N(t) \) with \( W \) as long as \( \xi^N(t) < \delta_N N \), such that the hitting time of 0 of \( W \) is stochastically larger than that of \( \xi^N(t) \) and that

\[
\lim_{N \to \infty} \frac{\mathbb{P}(\tau^W_0 < \tau^W_{\delta_N})}{\mathbb{P}(\tau^N_0 < \tau^N_{\delta_N})} = 1
\]

with \( \tau^W_{\delta_N} = \inf\{ t > 0 | W^N_t = \lfloor xN \rfloor \}. \)

In order to prove (19) it thus suffices to show

\[
\lim_{N \to \infty} \mathbb{P}(\tau^W_0 < N^{3+\delta} | \tau^N_0 < \tau^W_{\delta_N}) = 1.
\]

We can interpret the process \( W \) also as a time-continuous binary branching process with individual reproduction rate \( (1 - \delta_N)(2 - s_N \delta_N + o(s_N)) \) and with offspring distribution weights

\[
p_0 = \frac{1-s_N(\eta - \delta_N) + o(s_N)}{2s_N(\eta - \delta_N) + o(s_N)} \quad \text{and} \quad p_2 = \frac{1+s_N+o(s_N)}{2s_N+o(s_N)}.
\]

Denote by \( E \) the event “\( W \) goes extinct”. It suffices to show

\[
\lim_{N \to \infty} \mathbb{P}(\tau^W_0 < N^{3+\delta} | E) = 1,
\]

because then we can argue as follows.

We have \( \mathbb{P}(E) = \mathbb{P}(E, \tau^W_0 < \tau^W_{\delta_N}) + \mathbb{P}(E, \tau^W_0 > \tau^W_{\delta_N}) \) and

\[
\mathbb{P}(E, \tau^W_0 > \tau^W_{\delta_N}) \leq \mathbb{P}(E, W^N_0 = \lfloor \delta_N N \rfloor) \leq (1 - 2s_N \eta + o(s_N))^{\eta N} = O(\exp(-N^{1-\epsilon})).
\]
Consequently,
\[ \mathbb{P}(\tau_0^W < N^{\epsilon + \delta} | E) = \frac{\mathbb{P}(\tau_0^W < N^{\epsilon + \delta}, E)}{\mathbb{P}(E)} \leq \frac{\mathbb{P}(\tau_0^W < \tau_{\delta_N}^W) + \mathcal{O}(\exp(-N^{1-\epsilon}))}{\mathbb{P}(\tau_0^W < N^{\epsilon + \delta} \cap \tau_0^W < \tau_{\delta_N}^W)} \leq \frac{\mathbb{P}(\tau_0^W < \tau_{\delta_N}^W) + \mathcal{O}(\exp(-N^{1-\epsilon}))}{\mathbb{P}(\tau_0^W < N^{\epsilon + \delta} \cap \tau_0^W < \tau_{\delta_N}^W)} = \frac{\mathbb{P}(\tau_0^W < \tau_{\delta_N}^W)(1 + \mathcal{O}(\exp(-N^{1-\epsilon})))}{\mathbb{P}(\tau_0^W < N^{\epsilon + \delta} \cap \tau_0^W < \tau_{\delta_N}^W)} = \mathbb{P}(\tau_0^W < N^{\epsilon + \delta} | \tau_0^W < \tau_{\delta_N}^W)(1 + o(1)), \]

since \( \mathbb{P}(\tau_0^W < \tau_{\delta_N}^W) = 2q^s + o(s_N) \).

To show (20) recall that as in the discrete case the offspring distribution of the branching process conditioned on extinction is given by \( \mathbb{E}[\xi] \) and \( p_2q \) where \( q = 1 - 2s_N\eta + o(s_N) \) denotes the probability of extinction.

So the generating function of the conditioned process, \( F(s, t) = \mathbb{E}[s^W | E] \), solves the differential equation
\[
\frac{\partial F(s, t)}{\partial t} = (1 - \delta_N)(1 - s_N(\eta - \delta_N) + o(s_N)) - (1 - \delta_N)\left(\frac{1 - s_N(\eta - \delta_N) + o(s_N)}{q}\right)F(s, t) + (1 - \delta_N)(1 + s_N\eta + o(s_N))qF(s, t)^2
\]
with initial condition \( F(s, 0) = s \).

\[ M_t := \mathbb{E}[W_t | E] = \frac{\partial F(0, t)}{\partial s} \text{ solves } \frac{dM_t}{dt} = (1 - \delta_N)((1 + s_N\eta + o(s_N))q - \frac{1 - s_N(\eta - \delta_N) + o(s_N)}{q})M_t \]
with \( M_0 = 1 \), hence \( M_t = e^{(1-\delta_N)((1+s_N\eta+o(s_N))q-\frac{1-s_N(\eta-\delta_N)+o(s_N)}{q})t} \).

Since \( q = 1 - 2s_N\eta + o(s_N) \) we arrive at \( M_t = e^{-2(s_N\eta + o(s_N))t} \).

Consequently, for any \( \delta > 0 \)
\[ \mathbb{P}(\tau_0^W > N^{\epsilon + \delta} | E) = \mathbb{P}(W_{N^{\epsilon + \delta}} > 0 | E) \leq \mathbb{E}[W_{N^{\epsilon + \delta}} | E] \leq e^{-(2s_N\eta + o(s_N))N^{\epsilon + \delta}}, \]
which yields (20) \( \square \)

**Lemma 3.11** (Time to leave balance). *Let Assumptions (A) be fulfilled. Consider a Markov process \( \xi^N = (\xi^N_t)_{t \geq 0} \) on \( \{0, 1/N, ..., 1\} \) with the same transition rates as in Lemma 3.6.*

*Start \( \xi_0 \) in \( \frac{[N(\eta \pm s_N^{1/2})]}{N} \) and let*
\[ \tau_{s_N} = \inf\{t \geq 0 | \xi_t = \frac{[N(\eta \pm s_N)]}{N}\}. \]

*Then whp*
\[ \tau_{s_N}^{-1} = \mathcal{O}(g_N \exp(-N^{1-7\epsilon/2-\delta})) \]
*for any \( \delta > 0 \).*

**Proof.** We consider as in the proof of Lemma 3.6 the process \( \xi^N = N\xi^N \).

It suffices to estimate the time to reach from \( a = \lfloor N(\eta + s_N^{1/2}) \rfloor \) the level \( b = \lfloor (\eta + s_N)N \rfloor \). Consider first the probability \( p_d \) to reach from \( a \) the level \( a-1 \) before \( b \). We estimate this probability
from below by putting in Lemma 3.5 $N_1 := 1, N_2 := N(s_N - s_N^{3/2})$ and $p := \frac{1}{2}(1 - s_N^{5/2} + o(s_N^{5/2}))$. Hence

$$p_d \geq \frac{(1 - s_N^{5/2} + o(s_N^{5/2}))^{N(s_N - s_N^{3/2})}}{(1 + s_N^{5/2} + o(s_N^{5/2}))^{N(s_N - s_N^{3/2}) + 1}} - 1$$

$$\geq 1 - 2\exp(-N^{1-7\epsilon/2}) + o(\exp(-N^{1-7\epsilon/2}))$$

Now couple $\xi_i$ with a Markov process $W$ with state space $\{a - 1, a, b\}$, such that $\tau_{\xi_i}^W < \tau_s^W = \inf\{t \geq 0|W_t = b\}$. When $W = a$ it makes jumps at rate $g_N$ to state $a - \frac{1}{2}$ with probability $p_d$ and to $b$ with probability $1 - p_d$. Assume for state $a - \frac{1}{2}$ the process $W$ returns instantly to state $a$ with probability 1. Hence the number of trials needed to enter from state $a$ state $b$ is geometrically distributed with mean $\frac{1}{1 - p_d}$, which gives the desired estimate.

**Lemma 3.12** (Typical host states as $N \to \infty$). Let $t > 0$. In the situation of Theorem 1 for each $i \in \{1, \ldots, M\}$, and in the situation of Theorem 2 for each $i \in \{1, \ldots, k\}$ the following is true: At any reinfection event and at any host replacement event in which host $i$ is involved in the time interval $[0, t]$, this host is whp in a state in $\{0, 1\} \cup U^{0, N}$.

**Proof.** First of all note that the total rate of reinfection events at which host $i$ is infecting another host or host $i$ is infected by another host, is $2r/s_N$ and the total rate of host replacement events is $2$.

- (whp no reinfections and no host replacements occur during ineffective excursions) The length of an ineffective excursion can be bounded from above by $N^{c+\delta}/g_N$ with probability $1 - \exp(-cN^c)$ for an appropriate constant $c > 0$ and $\delta > 0$, see the proof of Lemma 3.10. The probability that neither another reinfection event nor a host replacement event happens during an ineffective excursion can be estimated from below by

$$1 - \exp(-cN^c))\left(\frac{2r}{s_N} + 2\frac{N^{c+\delta}}{g_N}\right)$$

$$\sim (1 - \exp(-cN^c))(1 - \frac{N^{2c+\delta}}{g_N}),$$

since $g_N \gg N^{5\epsilon}$. The number of reinfection events at which host $i$ is reinfection within the time frame $[0, t]$ can be estimated from above by $2N^c/r$ for some probability $p_N$ with $p_N \to 1$. Hence, the probability that during none of the ineffective excursions occurring within the time interval $[0, t]$ a reinfection event happens can be estimated from below by

$$p_N(1 - \exp(-cN^c))^{2N^c/r}(1 - \frac{N^{2c+\delta}}{g_N})^{2N^c/r} \to 1$$

for $\delta < 1$.

- (whp no reinfections and no host replacements during transitions from a boundary state to $D^{0, N}$) Consider the event $E_N$ that the duration of a transition from state 0 or 1 to $D^{0, N}$ is smaller than $N^{3\epsilon}/g_N$. By Proposition 3.8 there is a sequence $\delta_N \to 0$ such that

$$\mathbb{P}(E_N) \geq 1 - \delta_N.$$

Since the probability that a reinfection event is effective is proportional to $s_N$, the probability $g_N$ that the number of effective reinfection events is larger than $k_N$ converges to 0 as $N \to \infty$, where $k_N$ is an arbitrary sequence with $k_N \to \infty$. 

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The probability that within a time interval of length \([0, N^{3\epsilon}/g_N]\) a reinfection event or a host replacement event happens in which host \(i\) is involved can be estimated from above by

\[
1 - \exp\left(-\frac{2rN^{4\epsilon}}{g_N}\right) \sim \frac{2rN^{4\epsilon}}{g_N}.
\]

Consequently, we estimate the probability that no reinfection and no host replacement event happens during a transition from the boundary to \(D_{n,N}\) by

\[
q_N(1 - \delta_N)^{k_N}(1 - \frac{N^{4\epsilon}}{g_N})^{k_N}.
\]

This converges to 1 if we choose \(k_N \leq \min\{\frac{r}{\sqrt{g_N}}, \frac{\sqrt{N}}{\sqrt{g_N}}\}\).

- (remaining time) If a host is started in state 0 or 1, then she alternates only between phases in a pure state and ineffective excursions, until she is effectively reinfected. The same applies to the time immediately after a host replacement. If a host starts in some state in \(D_{n,N}\) or has reached \(D_{n,N}\) after an effective reinfection, then she remains within \(U_{n,N}\) whp until the next host replacement event. Indeed, without host replacement, starting from a frequency in \(D_{n,N}\), it follows from Lemma 3.11 that the type \(A\)-frequency remains whp within the set \(U_{n,N}\) for at least \(\exp(N^{\frac{3\epsilon}{4}})/g_N\) time units. Consequently, due to Assumption (A3), the set \(U_{n,N}\) is whp left only because of a host replacement. As the number of times a host reenters the interval \(U_{n,N}\) can whp be bounded by any sequence \(k_N\) with \(k_N \to \infty\), we conclude that whp in any phase between a successful reinfection and a host replacement event the host’s type \(A\)-frequency remains in the interval \(U_{n,N}\).

\[\square\]

**Proof of Theorem 1.** Since \(M\) is fixed, we will briefly write \(X_N\) instead of \(X_{N,M}\). Let \(\alpha > 0\) be as in the theorem’s assumption.

To prove the convergence of \(X_N\) to \(Y^M\), we will construct a process \(\hat{X}^{N,M}\), also denoted by \(\hat{X}^N\) for short, in a similar graphical way as \(Y^M\) and then will couple \(X_N\) and \(\hat{X}^N\).

To this purpose, let \(\hat{\xi}^N\) be the process defined in Lemma 3.6 with \(r'_{N,1} = r'_{N,2} = 0\), and abbreviate its “probabilities to balance” by

\[
p^0_N := \mathbb{P}_X^n(\tau_{[\eta - s^{3/2}, n]} < \tau_0); \quad p^1_N := \mathbb{P}_{\eta - s^{3/2}}(\tau_{[\eta + s^{3/2}]} < \tau_N).
\]

Construct \(\hat{X}^N\) on the time interval \([0, t]\) as follows:

(i) Between each pair \((i, j)\), with \(i, j \in \{1, ..., M\}\) draw HR arrows at rate \(1/M\) and PER arrows at rate \(r_N s_N/M\).

(ii) At time 0 initialize hosts 1, ..., \(M\) according to the initial distribution of \(X^N\).

(iii) Then let the intra-host Moran processes evolve within each host until a PER or HR arrow hits this host at some time \(s\). If at that time an HR event is shot from host \(i\) to host \(j\), then toss a 0-1-coin whose outcome is 1 with probability \(\hat{X}_i(s-)\), and set \(\hat{X}_j(s)\) equal to the result of the coin toss. If at time \(s\) a PER arrow is shot from host \(i\) to host \(j\), then check if host \(j\) is in state 0 or 1. If that is the case, ignore the arrow. If that is the case, then toss a 0-1-coin whose outcome is 1 with probability \(\hat{X}_i(s-)\). The outcome of this coin toss gives the type being transmitted at the reinfection event. If \(\hat{X}_j(s-)\) coincides with the outcome of the coin toss, then ignore the arrow. If \(\hat{X}_j(s-)\) does not coincide with the outcome of the coin toss, then toss a second 0-1-coin now with success probability \(p^0_N X_{s_0}^N / s_N\). If the result of the second coin toss is 0, then ignore the arrow. If the result of the second coin toss is 1, then start in host \(j\) a type \(A\)-frequency path according to the process \(\xi^N\) from Lemma 3.6 with \(r'_{N,1} = r'_{N,2} = 0\), starting in 1/N and conditioned to reach the state \(\frac{[(\eta - s^{3/2})N]}{N}\) if \(\hat{X}_j(s-) = 0\), and starting in \((N - 1)/N\) and conditioned to reach the state \(\frac{[(\eta + s^{3/2})N]}{N}\) if \(\hat{X}_j(s-) = 1\). Afterwards perform an (unconditioned) walk according to the process \(\xi^N\) with \(r'_{N,1} = r'_{N,2} = 0\).
Next we show that

1) the finite dimensional distributions of the process $\hat{X}_i^N$ converge to those of $Y^M$.

2) $X^N$ and $\hat{X}^N$ can be coupled such that for all $\delta_1 > 0$ and $s \in [0, t]$,

$$\lim_{N \to \infty} \mathbb{P}(\max_{i = 1, \ldots, M} |X_i^N(s) - \hat{X}_i^N(s)| > \delta_1) = 0,$$

(21)

(which implies that the finite dimensional distributions of $X^N$ and $\hat{X}^N$ have the same limiting distributions).

3) the sequence $X^N$ is tight with respect to the Skorokhod topology on every time interval $[\delta, t]$.

Proofs of claims 1)-3):

1) If $\hat{X}_i^N(0) \in [\alpha, 1 - \alpha]$, then we know from Proposition 3.8 that $\hat{X}_i^N$ reaches whp the interval $D^\eta N$, see (7), before host $i$ is affected by a reinfection or a host replacement, since $N^{3r}/g_N \ll r_N$. Each component of $X^N$ starting in state 0 or 1 remains in that state until an effective reinfection event happens, which then results in a transition to $D^\eta N$. Due to the assumption of the theorem and because of Proposition 3.8 the duration of the transition converges to 0 on the host time scale as $N \to \infty$. Furthermore the intervals $D^\eta N$ shrink to $\{\eta\}$ as $N \to \infty$, and hence in the limit an effective reinfection event leads to a jump from 0 or 1 to $\eta$. After an effective reinfection event the set $U^\eta N$ can be left because of random fluctuations or due to a host replacement event. According to Lemma 3.11 whp the exit from $U^\eta N$, see (6), is caused by an HR event. Since $p_N^0 s_N \to 2r\eta$ and $p_N^1 s_N \to 2r(1 - \eta)$, we conclude that the rates at which transitions from state 0 or 1 to $D^\eta N$ occur converges as $N \to \infty$ to the jump rates of the process $Y^M$ from states 0 or 1 to $\eta$.

Altogether we observe that the limiting process of $X^N$ is concentrated on $\{0, \eta, 1\}$ and the rates at which transitions occur between the states converge to those of $Y^M$. This proves 1).

2) In order to obtain the desired coupling of $X^N$ and $\hat{X}^N$, we condition on the event $E$ that that in any host excursions from the states 0 and 1 (caused by reinfection) are non-overlapping and that during transitions from state 0, resp. state 1, to a state in $D^\eta N$ in a host no further reinfection arrows hit this host. Since by Lemma 3.12 $E$ is an event of high probability it suffices to show (21) conditioned on $E$. Hence, in the following we tacitly condition on $E$.

Then the probability that in $X^N$ a reinfection hitting a a host in state 0 and coming from a host in state 1 becomes effective is is $p_N^0$. If a host is in state 0 and is hit by a reinfection arrow that is shot by a host whose state is in $U^\eta N$, then the probability at which the reinfection becomes effective is bounded from below by $(\eta - s_N) p_N^0$ and from above by $(\eta + s_N) p_N^0$. (A similar reasoning applies for hosts that are in state 1 when suffering a reinfection.) Furthermore the distributions of a transition path from 0 to $\eta - s_N^{3/2}$ and from 1 to $\eta + s_N^{3/2}$, resp., in $X^N$ and $\hat{X}^N$ coincide. Whenever host $i$ is effectively reinfeected it performs whp in $X^N$ as well as in $\hat{X}^N$ random fluctuations within $U^\eta N$ until a HR event turns host $i$ into a state in 0 or 1 again according to Lemma 3.11. To couple $X^N$ and $\hat{X}^N$ we can assume that these random fluctuations are performed in $X^N$ and $\hat{X}^N$ independently. At the times $s$ of host replacements, independent uniform random variables $U_s$ are drawn from $[0, 1]$. If $U \leq X_i^N(s-)$, then the replaced host in $X_N$ jumps to state 1. Similarly, If $U \leq \hat{X}_i^N(s-)$, then the replaced host in $X_N$ jumps to state 0. Since $|X_i^N(s-) - \hat{X}_i^N(s-)| \leq 2s_N$ whp, the same type is transmitted to the replaced host whp.

Due to assumptions (A) and because the total number $M$ of hosts does not depend on $N$, the total number of effective reinfection events as well as the total number of host replacement events in $[0, t]$ is less than $k_N$ for any sequence $k_N$ with $k_N \to \infty$ as $N \to \infty$. Thus, for each $s \in [0, t]$ it follows that whp the distance of each pair of components $(X_i^N(s), \hat{X}_i^N(s))$ of $X^N(s)$ and $\hat{X}^N(s)$ has distance $\leq 2s_N$. This implies (21).  

3) For the tightness of the sequence $(X^N)_{N \geq 1} = ((X_1^N, \ldots, X_M^N))_{N \geq 1}$ in the Skorokhod topology on every interval $[\delta, t]$ according to Theorem 3.7.2 in [20] it suffices to show for all $\delta_2 > 0$ there exists a $\delta_3 > 0$, such that

$$\sup_{N \in \mathbb{N}} \mathbb{P}(w^{(3)}(X^N, \delta_3) > \delta_2) < \delta_2,$$

(22)

where $w^{(3)}(X^N, \delta_3)$ denotes the modulus of continuity of $X^N$ with resolution $\delta_3$ on the time interval $[\delta, t]$. Here is a sketch how to see (22). Reinfection events cause small jumps and lead
to ineffective excursions or stepwise transitions to $[\eta N^1]/N$. The total number of effective reinfection events that occur in the time interval $[0, t]$ can whp be bounded by any sequence $k_N$ with $k_N \to \infty$. Hence, for any sequence $\delta_N$ with $\delta_N \to 0$ for $N \to \infty$, whp transitions that result from distinct effective reinfection events can be sorted into different time intervals of length $\delta_N$. Ineffective reinfection events happen more often, their number can whp be estimated by $k_N \delta_N \eta N^1$. Consequently, there exists a sequence $\delta_N$ with $\delta_N \to 0$ for $N \to \infty$, such that the probability $p_N$ to return from frequency $\delta_N$ to 0 is so small that $(1 - p_N)^{\delta_N \eta N^1} \to 1$ for $N \to \infty$. Hence whp the heights all ineffective excursions from 0 do not exceed $\delta_N$ as $N \to \infty$. Analogously one argues for ineffective excursions from 1. Altogether this implies (22), and shows the claimed tightness.

Proof of Theorem 2. We argue similarly as in the proof of Theorem 1. Let $\hat{X}^N := \hat{X}^{N,M_N}$ be the same process as in the proof of Theorem 1. We claim that for all $k \in \mathbb{N}$ and $t > 0$ and $0 < \delta < t$

1) the finite dimensional distributions of $(\hat{X}^N_1, ..., \hat{X}^N_k)$ converge to those of $(V_1, ..., V_k)$,

2) we can couple $X^N$ and $\hat{X}^N$ such that for all $\delta > 0$ and $s \in [0, t]$

$$\lim_{N \to \infty} \mathbb{P} (\max_{i=1,...,k} |X^N_i(s) - \hat{X}^N_i(s)| > \delta) = 0,$$

(which implies that finite dimensional distributions of $(X^N_1, ..., X^N_k)$ and $(\hat{X}^N_1, ..., \hat{X}^N_k)$ have the same limiting distributions),

3) the sequence $(X^N_1, ..., X^N_k)$ is tight with respect to the Skorokhod topology on $[0, t]$.

The proof of these claims follows along the same lines as the proof of Theorem 1. Again we construct the HR and PER-arrows between pairs of hosts, where the latter arise as a thinning (with retransmission probability $s_N$) of the reinfection arrows. However, now we keep track only of those arrows which contribute to the “history” of hosts $1, ..., k$. More specifically, we follow back also the lineages of the “primary” hosts that shot the HR and the PER-arrows hitting hosts $1, ..., k$, and the lineages of the “secondary” hosts that shot the HR and PER-arrows hitting the “primary” hosts, etc. An essential point is that the number of all hosts that are involved in this “influence graph” (of hosts $1, ..., k$ along the time interval $[0, t]$) remains tight as $N \to \infty$. Therefore the arguments from the proof of Theorem 1 apply for proving the claim 2).

The other important point is that, due to the assumption $M_N \to \infty$ as $N \to \infty$, with high probability all the replacement and potential effective reinfection arrows that are involved in the history of hosts $1, ..., k$ back from time $t$, are shot by pairwise different hosts. Consequently, the sequence of influence graphs of hosts $1, ..., k$ in the time interval $[0, t]$ converges, as $N \to \infty$, to a forest of $k$ trees, which are i.i.d. copies of the tree $T_k$ specified in Definition 3.1. Claim 1) then follows because of Corollary 3.4.

Finally, claim 3) is shown in complete analogy to the corresponding claim 3) in Theorem 1.

Proof of Corollary 3.13. This is inferred from Theorem 2 by the very same arguments which served to conclude the first part of Corollary 2.6 from Proposition 2.5.

3.4. Proof of Theorem 3

We first derive a corollary from Theorem 2 together with Proposition 2.9.

Corollary 3.13. Let Assumptions (A) and (3) be valid and suppose $M_N \to \infty$ as $N \to \infty$. Let $\mu^N$ be the empirical distribution of $X^{N,M_N}(0)$ as defined in (2), and assume as in Theorem 2 that the initial states $X^{N,M_N}_1(0), ..., X^{N,M_N}_M(0)$ are exchangeable. For some $\alpha > 0$ and $\delta' > 0$ assume that $\mu^N_0(\{0\} \cup (\alpha, 1 - \alpha) \cup \{1\}) \to 1$ as $N \to \infty$, and that $\mu^N_0(\{0\} \cup (\alpha, 1 - \alpha)) \geq \delta'$ as well as $\mu^N_0((\alpha, 1 - \alpha) \cup \{1\}) \geq \delta'$ for all sufficiently large $N$. Then for each $\delta > 0$ there exists a (sufficiently large) $t > 0$ such that

$$\mathbb{P}((\mu^N_0(\{0\}), \mu^N_0(U^{\eta,N}), \mu^N_0(\{1\})) \in V^{\delta,t}) \to 1$$

as $N \to \infty$. 

where \( V^{\delta,u} := (u^0 - \delta, u^0 + \delta) \times (u^n - \delta, u^n + \delta) \times (u^1 - \delta, u^1 + \delta). \)

**Proof of Corollary 3.13.** a) Let \( (v_t) \) be the solution of (1). For given \( \delta \) and \( \delta' \) in \((0,1/2)\) let \( t \) be so large that \( v_t \in V^{\delta'/2,u} \) for each initial condition \( v_0 \) such that \( v_0^0 + v_0^n \geq \delta' \) as well as \( v_0^0 + v_0^1 \geq \delta'. \)

b) Define \( v_0(N) \) as the (possibly random) element of \( \Delta^3 \) whose components are the weights of the image of the (possibly random) measure \( \mu_0^N \) under the mapping \( \phi : 0 \to 0, (0,1) \ni x \to \eta, 1 \to 1 \).

The graphical construction in the proof of Theorem 2 then shows that for large \( N \) and given \( v_0(N) \), the distribution of \( \phi(X^1_1(t)) \) is close to \( v_t \), where \( (v_t) \) is the solution of (1) with initial condition \( v_0(N) \). Due to our assumption on \( \mu_0^N \), the initial condition \( v_0(N) \) satisfies the requirement in step a) of the proof, hence the weights of the distribution of \( \phi(X^1_1(t)) \) belong to \( V^{\delta,N} \) for \( N \) large enough. The same reasoning as in the proof of Corollary 2.8 then shows the claimed assertion. \( \Box \)

We are now prepared for the

**Proof of Theorem 3.** We first discuss the consequences of the assumption \( \theta_N = o(r_N) \). In a population with all hosts being in state 0 except one whose state is in \( \cup_{\eta \leq \eta} N \), the population mutation rate to type \( A \) is \( u_N, N g_N M = \theta_N \), whereas the rate at which type \( A \) is transmitted into the population is \( \sim r_N \eta \). Thus, under the assumption \( \theta_N = o(r_N) \), even in this extremal case mutation is dominated by reinfection, and thus the assertions of Theorem (2) remain valid.

Let \( p_N \) be the probability that a monomorphic population consisting of pure type \( A \)-hosts only, after experiencing in one single parasite a mutation to type \( B \), turns into a polymorphic one, with \( X^{N,M} \) reaching the set \( V^{\delta,N} \) (defined in (4)). Also, let \( T \) be the time at which \( X^{N,M} \) takes to reach the set \( V^{\delta,N} \) after a successful mutant occurred.

(i) To arrive at (5) we show that

a) \( p_N = c s_N + o(s_N) \) for some constant \( c = c(\eta,r) \) not depending on \( N \),

b) the time \( T \) which \( X^{N,M} \) takes to reach the set \( V^{\delta,N} \) (defined in (4)) after a successful mutant occurred can be estimated by \( T \leq (M_N)^\gamma \) whp.

From this and a) it follows that the waiting time to reach a polymorphic state from a monomorphic one can whp be estimated from above by the sum of \( T \) and an exponentially distributed random variable with parameter \( \theta_N p_N \).

We now carry out this program.

a) Assume that initially every host is carrying only type \( A \) parasites, and that a mutation to type \( B \) happens in a single parasite in a randomly chosen host.

1. By Lemma 3.6 the probability that the frequency of type \( A \) parasites in this host declines from 1 to \( \eta \) is \( 2(1-\eta)s_N + o(s_N) \).

2. We show next that the probability of a propagation of type \( B \) such that the configuration of host states \( X^{N,M} \) reaches \( V^{\delta,N} \) can be estimated from below by a constant \( \tilde{c} = \tilde{c}(\eta,r) > 0 \) for all sufficiently large \( N \in \mathbb{N} \).

To this purpose we first set out to estimate the probability to reach a (small) frequency \( \delta_2 \) of hosts with states in \( \{0\} \cup U^{n,N} \). We will couple this number with a supercritical branching process. For this, start with a single host whose state is in \( U^{n,N} \) and assume all other hosts carry only parasites of type \( A \).

Now consider the following modification \( \bar{X}^N \) of \( X^{N,M} \):

- Ignore all ineffective reinfection events that affect hosts in state 1.
- If a host in state 0 appears (due to some host replacement event), then switch its type instantly to a state in \( D^{\eta,N} = [\eta - s_N^{3/2}, \eta + s_N^{3/2}] \).
- If a host reaches a state \( (0,1) \setminus (\eta - s_N, \eta + s_N) \), then switch its state instantly to state 1.

For each sequence \( x_N \in D^{\eta,N} \), the rate at which the state of a host starting from \( x_N \) leaves \( U^{n,N} \) by random fluctuations, converges to 0 as \( N \to \infty \) by Lemma 3.11. For each \( N \) let \( t_N \) be an upper bounded of this rate with \( t_N \to 0 \) as \( N \to \infty \).
Write $\tilde{Z}_{t}^{\eta,N} := |\{i : \tilde{X}_{i}^{N} \in U^{\eta,N}, 1 \leq i \leq M_{N}\}|$. The rate at which the process $\tilde{Z}_{t}^{\eta,N}$ jumps from $k$ to $k + 1$ is

$$2r(1 + o(1))(1 - \eta)(1 - \eta + O(s_{N}))(k + \frac{k}{M}(M - k) + \frac{k}{M}(1 - \eta + O(s_{N}))(M - k))$$

and the rate at which the process $\tilde{Z}_{t}^{\eta,N}$ jumps from $k$ to $k - 1$ is not larger than

$$\frac{k}{M}(M - k + (\eta + O(s_{N}))k + l_{N}).$$

To see (24), note that the number of hosts with state in $U^{\eta,N}$ increases by 1 if a host with state in $U^{\eta,N}$ reinfects effectively a host in state 1 and transmits type $B$, or a host with state in $U^{\eta,N}$ replaces a host in state 0 and transmits type $B$ (since in this case immediately the host state is changed from 0 to type $U^{\eta,N}$). Similarly (25) can be explained.

When $X^{N,M_{N}}$ and $\tilde{X}^{N}$ start in the same configuration, then the process $\tilde{Z}_{t}^{\eta,N}$ is (asymptotically as $N \to \infty$) stochastically smaller than the process $M_{N}\mu^{N}({\{0\} \cup U^{\eta,N}})$ as long as both processes are between 0 and $M_{N}\delta'$ for $\delta'$ small enough – the reason being that in this case the average increase of hosts in states 0 or $U^{\eta,N}$ is lowest if all host states are in $U^{\eta,N}$. This asymptotic statement can be read off from (1): if $\delta' > 0$ is small enough, then for all $0 \leq x < \delta'$ with $v_{0} + v_{1} = x$ we have $v_{0}(v_{0}, v_{1}, 1 - x) + v_{1}(v_{0}, v_{1}, 1 - x) \geq \delta'(0, x, 1 - x) + \delta'(0, x, 1 - x)$.

Now let $\varsigma_{N}$ be a Markovian jump process on the natural numbers which jumps from $k$ to $k + 1$ at rate $k(2r(1 - \eta)^2(1 - \delta') + (1 - \delta')(1 - \eta) + o(1))$ and from $k$ to $k - 1$ at rate $k(1 + o(1))$.

The form of the jump rates of $\tilde{Z}_{t}^{\eta,N}$ allows to couple $\tilde{Z}_{t}^{\eta,N}$ and $\varsigma_{N}$ such that $\tilde{Z}_{t}^{\eta,N} \geq \varsigma_{N}$ with high probability provided both processes have the same starting point, and as long as both processes are smaller than $M_{N}\delta'$. From the just derived rates one checks (using the assumption in Theorem 3 that $\mu^{N}({\{0\} \cup U^{\eta,N}})$ reaches the level $\delta'$ can be estimated by the survival probability $\tilde{c}(\delta')$ of the branching process $\varsigma$.

3. Combining 1. and 2. we have proved that the probability to reach from a single parasite mutation (to type $B$) a frequency $\delta'$ of hosts with states in $\{0\} \cup U^{\eta,N}$ is not less than $2(1 - \eta)\varsigma_{N} + o(\varsigma_{N})\tilde{c}(\delta') = c_{\varsigma_{N}} + o(\varsigma_{N})$. The fact that this is also the (asymptotic) probability that $X^{N,M_{N}}$ reaches the set $V^{\delta,N}$ is now a direct consequence of Corollary 3.13.

b) The supercritical branching process $\varsigma$ can also be used to estimate the time which the process $\mu^{N}({\{0\} \cup U^{\eta,N}})$ needs to reach the level $\delta'$. For this we thin $\varsigma$ (conditioned to non-extinction) by considering only the immortal lines. This amounts to decreasing the birth rate by the positive factor $\tilde{c}(\delta')$. The thinned process is a Yule process with a positive rate. Hence, the time until $\varsigma$ (conditioned to non-extinction) reaches the level $\delta'M_{N}$ can be estimated from above by $(M_{N})^\gamma$ whp. Also, recall from the arguments given in the proof of Theorem 1 that the time it takes for the frequency of the successful mutant’s offspring (in the host that was affected by the mutation) to rise from 1/N to $(1 - \eta) - s_{N}^{3/2}$ is asymptotically negligible on the host time scale as $N \to \infty$.

(ii) For $\mu^{N}(\{1\})$ to hit 1, when $X^{N,M_{N}}$ starts from $V^{\delta,N}$, the process $M_{N}\mu^{N}({\{0\} \cup U^{\eta,N}})$ has to visit some $[\delta'M_{N}]$, with a small enough $\delta' > 0$. Starting from then, we compare the process $M_{N}\mu^{N}({\{0\} \cup U^{\eta,N}})$ with the defined process $\varsigma_{N}$, see part i) a) 2. of the proof. Because of the comparison arguments given there, it will be helpful to compute

$$p_{\delta'} := \Pr_{[M_{N}]}(\varsigma_{N} \text{ hits } [M_{N}\delta'/4] \text{ before it hits } [M_{N}3\delta'/4]).$$

An inspection of the jump rates of $\varsigma_{N}$ given in part i) a) 2. of the proof (and using the assumption $r > \frac{\eta}{2(1 - \eta)^2}$ stated in Theorem 3) shows that for $\delta'$ small enough there exists a
Lemma 3.5 therefore gives the existence of a $c > 1$ such that

$$p^{\delta'} \leq \frac{c^{[M_N\delta'/4]} - 1}{c^{[M_N\delta'/2]} - 1} \sim \exp(-(\log c)M_N\delta'/4).$$

Hence the time $\tau^N$ which $\mu^N(\{1\})$ needs to hit 1, when $X^{N,M_N}$ starts from $V^{\delta,N}$, can whp be estimated from below by $\sum_{j=1}^G H_j$ where $G$ is a geometrically distributed variable with success probability $\exp(-(\log c)M_N\delta'/4)$ and $H_j$ are independent copies of the time which $\zeta^N$ needs to reach $\{[M_N\delta'/4], [M_N3\delta'/4]\}$ when starting in $[M_N\delta'/2]$. From this it follows that whp

$$\tau^N > \exp((M_N)^{1-\gamma}).$$

Analogously, one arrives at an estimate for the time which $\mu^N(\{0\})$ needs to hit 1. Hence the claim follows.

\bigskip

Acknowledgements

This research was supported by the DFG priority programme 1590, in particular through grant WA-947/4-2 to AW. We thank Josef Hofbauer for help concerning the stability of the dynamical system (1).

References

[1] R. Frankham, Genetics and extinction, Biological Conservation 126(2) (2005) 131–140.
[2] M. Cannon, D. Schmid, T. Hyde, Review of cytomegalovirus seroprevalence and demographic characteristics associated with infection, Reviews in Medical Virology 20 (2010) 202–213.
[3] P. Griffiths, C. Baboonian, A prospective study of primary cytomegalovirus infection during pregnancy: final report, BJOG 91(4) (1984) 307–315.
[4] F. Zanghellini, S. Boppna, V. Emery, P. Griffiths, R. Pass, Asymptomatic primary cytomegalovirus infection: virologic and immunologic features, J. Infect. Dis. 180(3) (1999) 702–707.
[5] E. Puchhammer-Stöckl, I. Görzer, Human cytomegalovirus: an enormous variety of strains and their possible clinical significance in the human host, Future Medicine 6(2) (2011) 259–271.
[6] J. Gillespie, Population Genetics: A Concise Guide, Second Edition, The Johns Hopkins University Press, 2004.
[7] J. Pannell, B. Charlesworth, Neutral genetic diversity in a metapopulation with recurrent local extinction and recolonization, Evolution 53(3) (1999) 664–676.
[8] M. Croze, D. Zivkovic, W. Stephan, S. Hutter, Balancing selection on immunity genes: review of the current literature and new analysis in drosophila melanogaster, Zoology 119(4) (2016) 322–329.
[9] E. Leffler, Z. Gao, S. Pfeifer, L. Segurel, A. Auton, O. Venn, R. Bowden, R. Bontrop, J. Wall, G. Sella, P. Donnelly, G. McVean, M. Przeworski, Multiple instances of ancient balancing selection shared between humans and chimpanzees, Science 339 (2013) (2013) 1578–1582.
[10] D. Dawson, Multilevel mutation-selection systems and set-valued duals, J.Math.Biol. 76 (2018) 295–378.
[11] S. Luo, C. Mattingly, Scaling limits of a model for selection at two scales, Nonlinearity 30(4).
[12] N. Champagnat, A microscopic interpretation for adaptive dynamics trait substitution sequence models, Stochastic Process. Appl. 116 (2006) 1127–1160.
[13] A. Gonzáles Casanova, N. Kurt, A. Wakolbinger, L. Yuan, An individual-based model for the lenski experiment, and the deceleration of the relative fitness, Stoch. Processes Appl. 126 (2017) 2211–2252.
[14] C. Pokalyuk, P. Pfaffelhuber, The ancestral selection graph under strong directional selection, Theoretical Population Biology 87 (2013) 25–33.
[15] C. Pokalyuk, On the role of reinfection for parasite populations, in preparation (2018+).
[16] T. Petney, R. Andrews, Multiparasite communities in animals and humans: frequency, structure and pathogenic significance, International Journal of Parasitology 28 (1998) 337–393.
[17] C. Lord, B. Barnard, K. Day, J. Hargrove, J. McNamara, R. Paul, K. Trenholme, M. Woolhouse, Aggregation and distribution of strains in micro-parasites, Transactions of the Royal Society B: Biological Sciences 354 (1999) 799–807.
[18] N. Renzette, C. Pokalyuk, L. Gibson, B. Bhattacharjee, M. Schleiss, K. Hamprecht, A. Yamamoto, M. Mussi-Pinhata, W. Britt, J. Jensen, T. Kowalik, The limits and patterns of human cytomegalovirus genetic diversity in humans, PNAS (2015) E4120–E4128.
[19] A. Bovier, L. Coquille, C. Smadi, Crossing a fitness valley as a metastable transition in a stochastic population model, https://arxiv.org/abs/1801.06473 (2018).
[20] S. Ethier, T. Kurtz, Markov Processes: Characterization and Convergence, John Wiley & Sons, Inc., 1986.
[21] I. Gradshteyn, I. Ryzhik, Tables of Integrals, Series, and Products, Academic Press, 2000.
[22] J. Guckenheimer, P. Holmes, Nonlinear oscillations, dynamical systems, and bifurcations of vector fields, Springer, 1986.
[23] M. Hirsch, Systems of differential equations which are competitive or cooperative. i: Limit sets, SIAM J. Math. Anal. 13(2) (1982) 167–179.