Analysis of a stochastic predator–prey model with applications to intrahost HIV genetic diversity

Sivan Leviyang

Received: 14 August 2009 / Revised: 19 November 2011 / Published online: 4 December 2011
© Springer-Verlag 2011

Abstract  During an infection, HIV experiences strong selection by immune system T cells. Recent experimental work has shown that MHC escape mutations form an important pathway for HIV to avoid such selection. In this paper, we study a model of MHC escape mutation. The model is a predator–prey model with two prey, composed of two HIV variants, and one predator, the immune system CD8 cells. We assume that one HIV variant is visible to CD8 cells and one is not. The model takes the form of a system of stochastic differential equations. Motivated by well-known results concerning the short life-cycle of HIV intrahost, we assume that HIV population dynamics occur on a faster time scale then CD8 population dynamics. This separation of time scales allows us to analyze our model using an asymptotic approach. Using this model we study the impact of an MHC escape mutation on the population dynamics and genetic evolution of the intrahost HIV population. From the perspective of population dynamics, we show that the competition between the visible and invisible HIV variants can reach steady states in which either a single variant exists or in which coexistence occurs depending on the parameter regime. We show that in some parameter regimes the end state of the system is stochastic. From a genetics perspective, we study the impact of the population dynamics on the lineages of an HIV sample taken after an escape mutation occurs. We show that the lineages go through severe bottlenecks and that in certain parameter regimes the lineage distribution can be characterized by a Kingman coalescent. Our results depend on methods from diffusion theory and coalescent theory.

Keywords  HIV · Predator–prey · Genetic diversity · Coalescent

S. Leviyang (✉)
Department of Mathematics, Georgetown University, Washington, DC, USA
e-mail: sr286@georgetown.edu
1 Introduction

During HIV infection, HIV and the immune system T cell populations form a complex and dynamic, coupled system. Many authors have modeled and analyzed this interaction (e.g. Nowak and May 2000; Perelson 2002). In such work, authors usually consider the interaction of HIV, CD4 T cells, and CD8 T cells through deterministic predator–prey ODE models. In this paper, our biological motivation is to consider the effect of MHC escape mutations (described biologically below) on the genetic diversity and population dynamics of the infecting HIV population. Mathematically, in order to examine these biological issues, we extend the typical ODE models by including stochastic effects in the population dynamics and considering lineages of infected HIV cells as one looks backward in time. More specifically, we change the typical ODE models to stochastic differential equations (SDE) and consider a coalescent process of HIV evolution on top of the population dynamics.

We consider a model of HIV–CD8 interaction that focuses on so-called MHC escape mutations. Roughly speaking, when HIV enters a CD4 cell certain mechanisms within the cell cut up HIV proteins into small pieces (usually 8–11 amino acids long) and present these pieces on the surface of the cell. This presentation is accomplished by the binding of the viral pieces to so-called MHC I molecules to form a peptide–MHC complex (pMHC) (DeFranco et al. 2007). For our purposes and to simplify the explanation, the pMHC complex can be thought of as representing a certain short nucleotide sequence in the HIV genome. CD8 cells are equipped with T cell receptors (TCRs) that can bind to a pMHC complex and then destroy the presenting cell. Critically, each TCR binds to a limited pattern of nucleotide sequences (DeFranco et al. 2007). In this sense, since each CD8 cell has only one type of TCR, we can think of each CD8 as targeting some short segment of the viral genome.

Recently, there has been much experimental and statistical work on mutations in HIV that avoid MHC I presentation (e.g. Althaus and de Boer 2008; Delport et al. 2008; Frahm et al. 2006; Ngumbela et al. 2008; Rousseau et al. 2008) and many authors have suggested that such mutations play a key role in HIV dynamics (Goulder and Watkins 2008; Leslie et al. 2005; Bhattacharya et al. 2007). The MHC I molecule cannot present every type of nucleotide sequence (DeFranco et al. 2007), and it is possible for the virus to mutate and evade MHC presentation. In such a case, a mutation (or series of mutations) will render the virus invisible to the CD8 cell that was previously able to attack virus infected cells.

We consider a simplified model of such an MHC escape mutation. We assume that initially all HIV infected cells are subject to attack by a collection of CD8 cells with a common TCR. We refer to CD4 cells infected by HIV variants that are visible to these CD8 cells as wild type cells. Then, we assume that a single infected cell changes in its HIV genetic state and becomes invisible to the CD8 cell attack, we refer to this new type of infected cell as the mutant type.

Our motivation centers on understanding the population dynamics and genetic evolution caused by escape mutations that occur during the chronic stage of HIV when
CD8 and HIV population sizes are relatively stable (Emini 2002). In terms of population dynamics, we are interested in whether the mutant type survives, the wild type survives, or both. From a genetics perspective, the escape mutation reflects a change in the HIV genome at a given location, but we are interested in the effect of the resultant population dynamics on other parts of the genome. As an analogy, strong selective sweeps, for example, may be caused by mutations at a given point in the genome, but genetic diversity at other areas of the genome are affected by the sweep (Hartl and Clark 1997). Similarly, we would like to understand the impact of an MHC escape mutation and the resultant dynamics on intrahost HIV genetic diversity. In this paper we will ignore recombination.

We specify birth and death rates for the CD8, wild type, and mutant type cells and consider the associated coupled birth–death processes. However, rather than consider the birth–death processes directly, we analyze an associated SDE system. A critical feature of our analysis is a separation of time scales. HIV has been shown to evolve on a time scale of hours to days, while the CD8 cells evolve on a time scale of days to weeks (Ho et al. 1995). Technically, this means that the CD8 cells’ birth–death process has much lower rates than the wild and mutant type birth–death processes. We use this separation of time scale to apply an asymptotic analysis to the associated SDE system. More precisely, we introduce a parameter \( \varepsilon \), defined below, which is a ratio of CD8 cell birth rates to HIV cell death rates. Biologically, \( \varepsilon \) can be thought of as a measure of immune system speed, a large \( \varepsilon \) means the number of CD8 cells quickly expands and equilibrates in response to changes in the number of HIV infected CD4 cells. Letting \( V \) represent the order of the infected CD4 cell population size (we do not assume fixed population size), we analyze our SDE in a large population-slow immune system limit: \( V \to \infty \) and \( \varepsilon \to 0 \). Since the number of HIV infected cells has been estimated as high as \( 10^9 \) (Emini 2002) while \( \varepsilon \) is small due to the small generation time of HIV, the \( V \to \infty \) and \( \varepsilon \to 0 \) limit is biologically significant. Indeed, we use computer simulations to demonstrate the applicability of our asymptotic results to finite populations in parameter regimes relevant to HIV. From a mathematical perspective, we develop asymptotic expansions in \( \varepsilon \) in order to analyze our SDE.

Our results show that the rate at which we take \( \varepsilon \to 0 \) relative to \( V \to \infty \) changes the dynamics and genetics of the HIV population. In other words, we demonstrate the existence of different scaling limits for the SDE. Further, by considering the range of biologically reasonable parameter values for HIV infection, we show that HIV dynamics and genetics can fall into different scaling regimes depending on the specific parameters chosen.

The fitness of the mutant type relative to the wild type plays a central role in our analysis and the scaling limits we derive. We consider a mutant which is less fit than the wild type when CD8 attack is ignored but more fit than the wild type given the level of CD8 attack present when the initial mutant type is introduced (other situations are less interesting and are discussed below). Since initially we assume a single mutated cell, there is always some probability that the mutant population dies out early on, before the number of mutant cells can grow to an appreciable level. If this situation does not occur and the mutant does initially rise to appreciable level, our results demonstrate three regimes for the resultant HIV dynamics depending on the scaling chosen for \( \varepsilon \) relative to \( V \). Roughly, when the immune system is slow, i.e. \( \varepsilon \) is relatively small, the
mutant will push the wild type to extinction. On the other hand, when the immune system is fast, i.e., $\varepsilon$ is relatively large, the mutant and wild type will coexist. For intermediate values of immune system speed, the wild type can die out, the mutant type can die out, or the two types can coexist and each of these three outcomes occurs with a probability strictly between zero and one.

The modeling of viral and immune system dynamics is usually accomplished through deterministic ODEs (Nowak and May 2000; Perelson 2002). As we explain in Sect. 2, if one considers our SDE system in the large population limit $V \to \infty$ while keeping all the SDE parameters, including $\varepsilon$, constant, a deterministic ODE is recovered. However, while an MHC mutation can lead to mutant loss, wild type loss, or coexistence under our SDE model, under the associated deterministic ODE model an MHC mutation always results in coexistence between the mutant and wild type populations. In this way, our results suggest that by using deterministic ODEs to model viral and immune system dynamics, important stochastic effects that can fundamentally change the dynamics are being ignored.

The impact of the MHC mutation on HIV genetic diversity depends on the population dynamics. We consider questions of genetics diversity by considering the lineages of a sample of infected cells taken after the escape mutation occurs. We consider the fate of the lineages as we trace back from the sample time to the time of the initial MHC mutation. When the immune system is slow and hence the wild type is pushed to extinction, all lineages trace back to the initial mutant. As a result, a genetic bottleneck occurs and diversity is reduced. On the other hand, when the immune system is fast and hence the mutant and wild types coexist, mutant cells in the sample still trace back to the initial mutant, but wild type cells in the sample do not coalesce during the time considered. Put another way, if we consider only wild type lineages, then the lineages do not coalesce. The result is a partial genetic bottleneck and a less severe reduction in diversity than the case in which a mutant fixes. For intermediate immune system speeds, we show that lineages of wild type cells from the sample can be described by a Kingman coalescent run for a stochastic period of time. Such a case creates an intermediate loss in diversity because some wild type lineages will coalesce but not all, while all mutant lineages still coalesce as in the two previous cases.

An open question that has received considerable attention is the effective population size of HIV during infection. Effective population size is a way of baselining the genetic evolution of a population by comparing it to the genetic evolution of classical Wright–Fisher populations (Durrett 2002). One way to define effective population size is as the expected time needed for two lineages to coalesce. Following from the comments of the previous paragraphs, our results demonstrate that the time needed for two HIV lineages to coalesce is heavily influenced by MHC mutations and immune system speed. From this perspective, a single intrahost HIV effective population size may not be applicable across different patients or even during the course of a single HIV infection.

2 The model

We let $v(t), v^*(t), p(t)$ be the number of wild type infected cells, mutant type infected cells, and CD8 cells targeting the wild type infected cells, respectively (here $p$ stands
for predator). We assume the dynamics of these populations are given by a birth–death process with the following rates.

| Type | Birth rate per cell | Death rate per cell |
|------|---------------------|---------------------|
| $v$  | $k/2 + \Delta k/2$  | $k/2 - \Delta k/2 + c(v + v^*) + ap$ |
| $v^*$| $k^*/2 + \Delta k^*/2$| $k^*/2 - \Delta k^*/2 + c(v + v^*)$ |
| $p$  | $h/2 + bv$          | $h/2 + dp$          |

The parameters $k, k^*, \Delta k, \Delta k^*, h$ represent baseline birth and death rates for each of the cell types when interaction between the cell types can be ignored. Note that we set the birth and death rates of $p$ equal because CD8 cells require antigenic stimulation to expand in number, on the other hand we can assume that the HIV birth rate exceeds the HIV death rate for both mutant and wild type cells. The parameter $a$ measures the rate of CD8 cell killing of wild type cells, $c$ is a logistic growth factor representing competition between infected cells for uninfected cells. Finally $b$ represents the rate of CD8 expansion in the presence of wild type antigen, while $d$ represents a logistic growth factor corresponding to competition between CD8 cells for stimulation from helper T cells and other immune system mechanisms.

By using a birth–death process as our underlying model we have implicitly assumed that all HIV infected cells produce a modest number of offspring infected cells. Indeed, the birth–death process requires the offspring number of each infected cell to be roughly Poisson distributed. It may be that a small percentage of HIV infected cells produce an enormous number of offspring infected cells, while the majority of HIV infected cells produce no offspring. In such a situation the model we have considered would need to be modified.

### 2.1 The approximating SDE

Kurtz (1981) described a connection between birth–death processes and SDEs. The approximation of birth–death processes by SDEs improves in accuracy as population size rises. For HIV, $v, v^*$ and $p$ are all of enormous order. With this in mind, if we rescale the SDE associated with our CD8-HIV birth–death process, we can remove several of the parameters and make the time scale $O(1)$. Doing this, we arrive at the following SDE system. In (2.1), $\mathbb{V}$ is the order of the infected cell population size and $v, v^*$ and $p$ represent the now rescaled population variables (see the Appendix for a precise description of the rescaling).

\[
\begin{align*}
    dv &= v(1 - (v + v^*) - p)dt + \sqrt{v(k + (v + v^*) + p)/\mathbb{V}} dB_1(t), \\
    dv^* &= v^*(f - (v + v^*))dt + \sqrt{v^*(k^* + (v + v^*))/\mathbb{V}} dB_2(t), \\
    dp &= \varepsilon p(v - \alpha p)dt,
\end{align*}
\]  

(2.1)

where $\varepsilon = b/c, \alpha = dc/ab$. We set $u(t) = (v(t), v^*(t), p(t))$. Equation (2.1) is taken in the sense of Ito and hence $u(t)$ is Markovian (Karatzas and Shreve 1991).
In (2.1), \( \epsilon \) is the time scale of the CD8 dynamics while HIV infected cell dynamics occur on an \( O(1) \) time scale. Informally then, we refer to \( \epsilon \) as immune system speed. To provide a biological interpretation for \( \alpha \), notice that we can decompose the dynamics of CD8 cells in (2.1) into birth events which occur at rate \( \epsilon v \) per CD8 cell and death events which occur at rate \( \epsilon \alpha p \) per CD8 cell. Put another way, conditioning on the occurrence of a birth–death event, birth and death events occur with probability \( v/(v + \alpha p) \) and \( \alpha p/(v + \alpha p) \), respectively. Notice that these conditional probabilities do not depend on \( \epsilon \). Indeed, \( \epsilon \) affects the rate at which events occur, but not whether the events are births or deaths. Biologically, \( \alpha \) is a measure of a CD8 cell’s need for stimulation in order to proliferate. If \( \alpha \) is relatively small, then with high probability a CD8 cell needs little antigenic stimulation, as measured by \( v \), in order to proliferate many times before it dies.

SDE systems studied by Kurtz such as (2.1) become deterministic as the scaling factor, our \( \bar{V} \), goes to infinity. However, our system is not exactly of Kurtz’s form as \( \epsilon \) will be scaled with \( \bar{V} \), i.e. \( \epsilon \) will be taken \( O(1/\log(\bar{V})) \). From this point on we take (2.1) as our description of the evolution of \( u \) and no longer consider the birth–death processes. Although this is an approximation, we believe that our results will hold for the birth–death processes as well. Finally, notice that there is no stochastic term in the \( p \) equation. There should be one, but we have dropped it. This will have no effect on our results and simplifies the explanation (see Sect. 5 for a more precise justification).

We assume that the escape mutation arises at time \( t = 0 \), and that previously \( v^* = 0 \) and the system (2.1), restricted to \( v, p \), is in equilibrium. This assumption of equilibrium corresponds to our interest in the chronic stage of HIV infection. More precisely, we take

\[
v(0) = \frac{\alpha}{1 + \alpha}, \quad v^*(0) = \frac{1}{\bar{V}}, \quad p(0) = \frac{1}{1 + \alpha}
\]

In (2.1) the absolute fitness of \( v \), in the absence of CD8 cell effects, is 1 while the fitness of \( v^* \) is \( f \). \( f \) is the ratio of mutant to wild type fitness prior to rescaling (see the Appendix for details). Typically, in order to avoid immune system attack, escape mutants are less fit than the original wild type and so we take \( f < 1 \). We contrast absolute fitness with CD8 influenced fitness. If CD8 cell attack is considered, the fitness of \( v \) and \( v^* \) are \( 1 - p \) and \( f \), respectively. If \( 1 - p(0) > f \) then the mutant is initially less fit than the wild type and the dynamics are not interesting, indeed the mutant will simply quickly die out. As mentioned in the introduction, we restrict our attention to the interesting case of \( 1 - p(0) < f \). Using (2.2) this translates to \( f - \alpha(1 - f) > 0 \) and we will assume this condition throughout the rest of this paper.

We will consider (2.1) in the limit \( \bar{V} \to \infty \) with \( \epsilon = O(1/\log(\bar{V})) \) over a time interval \([0, O(1/\epsilon^2)]\). The \( \epsilon \) scaling will be shown to be the correct scaling to see \( O(1) \) stochastic effects, and the time interval scaling is the length of time the system needs to be guaranteed to return to an equilibrium after the escape mutation arises.

Associated with (2.1) is the deterministic analogue in which the stochastic terms are simply dropped.

\[
\frac{d\bar{v}}{dr} = \bar{v}(1 - \bar{p} - \bar{v} - \bar{v}^*)
\]
Analysis of a stochastic predator–prey model

Fig. 1 Solution of (2.3) for $\varepsilon = .01, \alpha = 1, f = .8$ up to time $O(1/\varepsilon^2)$

\[
\begin{align*}
\frac{d\bar{v}^*}{dt} &= \bar{v}^* (f - \bar{v} - \bar{v}^*) \\
\frac{d\bar{p}}{dt} &= \varepsilon \bar{p} (\bar{v} - \alpha \bar{p})
\end{align*}
\] (2.3)

with,

\[
\bar{v}(0) = \frac{\alpha}{1 + \alpha}, \quad \bar{v}^*(0) = \frac{1}{\sqrt{f}}, \quad \bar{p}(0) = \frac{1}{1 + \alpha}.
\] (2.4)

We set $\bar{u}(t) = (\bar{v}(t), \bar{v}^*(t), \bar{p}(t))$. Throughout this paper, we use a bar to distinguish a variable associated with the deterministic system (2.3) from the corresponding variable associated with the stochastic system (2.1).

2.2 Decomposition of oscillations

The deterministic system (2.3) produces oscillatory dynamics as the system moves from the original equilibrium of $\bar{u} = (\alpha/(1 + \alpha), 0, 1/(1 + \alpha))$ to the new equilibrium of $\bar{u} = (\alpha(1 - f), f - \alpha(1 - f), 1 - f)$. Figure 1 shows an explicit solution of (2.3) for $\varepsilon = .01, \alpha = 1, f = .8$.

The oscillatory dynamics result from the time scale separation. Figure 2 provides a zoom in of the first oscillation in the dynamics of $\bar{u}$. Immediately after the escape mutation arises, at $t = 0$, there is an initial stage of the dynamics in which $\bar{v}, \bar{p}$ are held relatively fixed while $\bar{v}^*$ rises. This initial stage, which in Fig. 2 ends at $t = T_0$, occurs only immediately after $t = 0$ and is not repeated. After the initial stage ends at time $T_0$, we separate the oscillation into four stages which form a full cycle: stage I delimited by $[T_0, T_I]$, stage II delimited by $[T_I, T_{II}]$, stage III delimited by $[T_{II}, T_{III}]$, and stage IV delimited by $[T_{III}, T_{IV}]$.
and stage IV delimited by \([T_{III}, T_{IV}]\). In stage I, \(\bar{v}\) collapses to \(o(1)\) levels while \(\bar{v}^*\) rises to \(O(1)\) levels. This occurs because the CD8 influenced fitness of \(\bar{v}\), given by \(1 - \bar{p}\), is less than \(f\) during stage I. In stage II \(\bar{v}\) stays at \(o(1)\) levels, but \(\bar{p}\) drops until \(\bar{v}\) becomes more fit than \(\bar{v}^*\). When \(\bar{p} = 1 - f\), \(\bar{v}\) and \(\bar{v}^*\) are equally fit, indeed at this point \(\bar{v}\) reaches its minimum. After that time \(\bar{v}\) rises until \(\bar{v}(T_{II}) = \bar{v}(T_I)\). In stage III, \(\bar{v}^*\) is less fit than \(\bar{v}\) and \(\bar{v}^*\) collapses to \(o(1)\) levels. In stage IV, \(\bar{p}\) rises until \(\bar{v}\) becomes more fit than \(\bar{v}\) which causes \(\bar{v}^*\) to rise until \(\bar{v}^*(T_{IV}) = \bar{v}^*(T_{III})\). At the end of stage IV the system has returned to the situation of time \(T_s\) and the cycle repeats. We refer to the stages I–IV as a cycle, and so the dynamics of \(\bar{u}\) and \(\bar{v}\) are formed by a sequence of cycles. As Fig. 1 shows, with each cycle the strength of the oscillations is damped. The stochastic system (2.1) has identical stages with \(T_I, T_{II}, T_{III}, T_{IV}\) defined analogously to \(\bar{T}_I, \bar{T}_{II}, \bar{T}_{III}, \bar{T}_{IV}\). \(T_s\) is used for both (2.1) and (2.3). The definitions of \(T_s, \bar{T}_I, \bar{T}_{II}, \bar{T}_{III}, \bar{T}_{IV}\) will be made precise in Sect. 5, for now we simply provide the reader with an intuition for the dynamics.

We will show that (2.1) behaves essentially as (2.3). The exception will be during times in a small subinterval in each of stages II and IV during which \(v\) and \(v^*\) are at a minimum. If \(\varepsilon\) is too small, then at these subintervals \(v\) or \(v^*\) will be driven to zero by the stochastic terms in (2.1). If \(\varepsilon\) is too large, then at these subintervals, (2.1) will behave as (2.3) and stochastic effects can be ignored. However, if \(\varepsilon\) is at the appropriate scaling, namely \(O(1/\log(V))\), then we will show that \(v\), in stage II, and \(v^*\), in stage IV, behave like Feller diffusions.

The damping of the oscillations will be crucial to our analysis. Stochastic effects play an important role when \(v\) and \(v^*\) are at their minima. The damping of the oscillations means that the minima become less extreme with each passing cycle. Consequently, as we shall show, if \(v\) or \(v^*\) are not lost during the first cycle, then (2.1) will reduce to (2.3) and stochastic effects can be ignored for the rest of the considered time interval.
From a genetic perspective, the behavior of $v$ and $v^*$ during stages II and IV correspond to severe bottlenecks. We will explore the effects of these bottlenecks on the lineages of a sample of infected cells taken at a time $O(1/\varepsilon^2)$ time units after the escape mutation occurs.

3 Results

We are interested in determining the probability of wild type loss, mutant type loss, or coexistence. If the wild type is lost, then the steady state of (2.1) is given by $u_M = (0, f, 0)$. If the mutant is lost then the steady state is $u_W = (\alpha/(1 + \alpha), 0, 1/(1 + \alpha))$. And finally if coexistence occurs then the steady state is $u_C = (\alpha(1 - f), f - \alpha(1 - f), 1 - f)$.

We further discern between two types of mutant loss. The mutant may be lost immediately after the initial mutation occurs, that is before the mutant population reaches a significant proportion of the virus population (the term significant proportion will be made precise shortly). This type of mutant loss occurs in any stochastic system in which individuals (in our case cells) have a non-zero probability of dying before producing offspring and has nothing to do with the interaction between the different infected cell types and CD8s. We refer to this type of mutant loss as failed mutant dynamics. Alternatively, the mutant may rise to significant population levels but then subsequently be lost. We refer to these type of dynamics as lost mutant dynamics. Our results focus on lost mutant dynamics since these type of dynamics reflect the HIV and CD8 dynamics we wish to explore, but to make things precise we must also consider failed mutant dynamics.

To frame our results, we consider two extreme cases. If $\varepsilon = 0$, a frozen immune system, then when $f > 1 - p(0)$ the mutant is initially, and hence always since $\tilde{p}(t)$ is fixed, fitter than the wild type. Consequently, if the mutant is not lost due to early stochastic effects (the case of failed mutant dynamic) then in the $V \to \infty$ limit the wild type will be lost with probability 1. In the other extreme when $\varepsilon = \infty$, a hyper-reactive immune system, the wild type will be lost with probability 0 as long as $f < 1$. Indeed since $\varepsilon = \infty$, the $p$ equation in (2.1) will always be in steady state and (2.1) can be reduced to a two equation system. Since no parameters of the reduced SDE depend on $V$ and $v(0)$ does not depend on $V$, as well, as $V \to \infty$ the SDE approaches a deterministic system for which the wild type is always of order 1. We are led to ask: what happens when $\varepsilon$ falls between these two extremes?

To answer this question, we take $V \to \infty$ and let $\varepsilon \to 0$ in a way that depends on $V$. In Theorem 1 we set

$$\varepsilon = \frac{\beta}{\log(V)},$$

where $\beta$ is held constant as $V \to \infty$. $\beta$ can be thought of as a scaled immune system speed. Figure 3 shows the results of Theorem 1 graphically for fixed $f, \alpha$. $\phi_{\lim}$ and $\psi_{\lim}$, defined below, are functions of $f$ and $\alpha$. The upper portion of the figure considers $f, \alpha$ for which $\phi_{\lim} < \psi_{\lim}$, while the lower portion considers $f, \alpha$ for which $\phi_{\lim} > \psi_{\lim}$. When $\phi_{\lim} < \psi_{\lim}$ the wild type is lost, mutant is lost, and coexistence
Fig. 3 Predictions of Theorem 1 as $\beta$ ranges from 0 to $\infty$. In the case $\phi_{\text{lim}} < \psi_{\text{lim}}$, the upper portion of the figure shows that for small, intermediate, and large $\beta$ the wild type is lost, mutant is lost, and coexistence occurs, respectively. As $\beta$ increases, immune system speed increases. The upper and lower portions of the figure correspond to relatively small and large $f$, respectively, as seen through Fig. 4.

occurs when $\beta < \psi_{\text{lim}}$, $\psi_{\text{lim}} < \beta < \phi_{\text{lim}}$, and $\phi_{\text{lim}} < \beta$, respectively. Similarly, the lower portion of the figure gives the system outcome when $\phi_{\text{lim}} > \psi_{\text{lim}}$. While Theorem 1 is asymptotic, we can conclude, for example, that for large $V$ and $f$, $\alpha$ such that $\phi_{\text{lim}} > \psi_{\text{lim}}$, the condition $\varepsilon \gg \phi_{\text{lim}}/\log(V)$ implies coexistence.

Figure 4 graphically displays the results of Theorem 1 for a range of $f$ values given $\alpha = 1$ (the case of a failed mutant is ignored). The relationship between $\phi_{\text{lim}}$ and $\psi_{\text{lim}}$ seen in Fig. 4 is general with $\phi_{\text{lim}}$ always increasing and diverging at $f = 1$ and $\psi_{\text{lim}}$ always possessing a single maximum and equaling zero at the two possible endpoints of $f: \alpha/(1 + \alpha)$ and 1. When $f < \alpha/(1 + \alpha)$, we will have a failed mutant while when $f > 1$ the mutant will push the wild type to loss regardless of $\varepsilon$. The upper portion and lower portions of Fig. 3 correspond to one-dimensional slices of Fig. 4 for, say, $f = .55$ and $f = .65$, respectively.

Theorem 1 does not allow us to predict system behavior in cases for which $|\varepsilon - \phi_{\text{lim}}/\log(V)| \to 0$ or $|\varepsilon - \psi_{\text{lim}}/\log(V)| \to 0$ as $V \to \infty$. These are interesting cases as they include the boundaries between the different $\beta$ regimes shown in Figs. 3 and 4. To deal with such cases, we scale $\varepsilon$ as follows,

$$\varepsilon = \phi_{\text{lim}} \left( \frac{1}{\log V} + \frac{1}{2} \frac{\log \log V}{(\log V)^2} - \frac{\log \left( \sqrt{\phi_{\text{lim}}} \kappa \right)}{(\log V)^2} \right),$$

(3.2)

where $\kappa$ is a fixed constant as $V \to \infty$ analogous to $\beta$ but under this new scaling. As with $\beta$, immune system speed increases with $\kappa$. Figure 5 graphically displays the relationship of this new scaling and the results of Theorem 2 to the $\beta$ scaling of (3.1) and the results of Theorem 1. Figure 5 considers the case $\psi_{\text{lim}} < \phi_{\text{lim}}$, but the connection between $\kappa$ and $\beta$ is the same regardless of $\psi_{\text{lim}}$’s relation to $\phi_{\text{lim}}$. Notice that we scale
Fig. 4 Graph of $\phi_{\text{lim}}$ (dashed line) and $\psi_{\text{lim}}$ (solid line) along with results from the table in Theorem 1. $\phi_{\text{lim}}$ is cut off to allow for presentable scales. $\alpha = 1$. $f$ is the fitness of the mutant for the rescaled SDE (2.1). Under our rescaling the wild type has fitness 1. When $f < .5$ the mutant will simply be immediately pushed out by the wild type, a case we refer to as a failed mutant.

Fig. 5 Predictions of Theorem 2 as $\kappa$ ranges from 0 to $\infty$ in relation to the predictions of Theorem 1 and the $\beta$ scaling. Here we consider the case $\psi_{\text{lim}} < \phi_{\text{lim}}$, but the case $\phi_{\text{lim}} \geq \psi_{\text{lim}}$ is similar.

$\varepsilon$ so that $|\varepsilon - \phi_{\text{lim}} / \log(V)| \to 0$ as $V \to \infty$. There is also an analogous scaling for $|\varepsilon - \psi_{\text{lim}} / \log(V)| \to 0$ and then a result analogous to Theorem 2, however to avoid redundancy we do not state this result.

Theorem 2 gives an explicit formula for the probability of wild type loss as a function of $\kappa$, $f$, $k$, $k^*$, and $\alpha$. All these variables are assumed fixed as $V \to \infty$. For small $\kappa$ the probability of wild type loss approaches 1 while for large $\kappa$ the
probability approaches 0, as suggested by Fig. 5. For intermediate values of \( \kappa \), the probability is strictly between 0 and 1. Similarly, Theorem 2 gives a characterization for the probability of mutant loss.

To state Theorem 1 we need some notation. We consider the system up to time \( t_f \) such that \( t_f = O(1/\varepsilon^2) \) and we show that by time \( t_f \) the system is arbitrarily close to a steady state. Below, when we write \( P(u \rightsquigarrow (u_1, u_2, u_3)) = p \) we mean that for any fixed constant \( c \), we have \( \lim_{V \to \infty} P(\|u(t_f) - (u_1, u_2, u_3)\|_\infty < c) = p \). Define,

\[
\phi_{\lim}(\alpha, f) = \frac{-1}{\alpha} \left[ f - \alpha(1 - f) + \log((1 + \alpha)(1 - f)) \right].
\]

(3.3)

\[
\psi_{\lim}(\alpha, f) = \frac{-1}{1 + \alpha} \log\left(\frac{\alpha H_{II}}{(1 + \alpha(H_{II} + 1))(f - \alpha(1 - f))}\right) + (1 - f) \log\left(\frac{(1 - f)\alpha H_{II}}{f - \alpha(1 - f)}\right).
\]

(3.4)

where \( H_{II} \) solves the following equality,

\[
(1 - f)H_{II} = \frac{1}{\alpha} \log\left(1 + \frac{\alpha}{1 + \alpha} H_{II}\right).
\]

(3.5)

Notice that \( H_{II} \) is a function of \( f \) and \( \alpha \) although we do not make this dependence explicit. Since we assume \( f - \alpha(1 - f) > 0 \), Taylor expansion arguments guarantee \( \phi_{\lim}, \psi_{\lim} > 0 \).

**Theorem 1** Set \( \varepsilon = \beta/\log(\forall) \) and \( t_f = t/\varepsilon^2 \) where \( \beta \) and \( t \) are held fixed. By a failed mutant we will mean, \( \sup_{t' \leq t_f} v^*(t') < \varepsilon \).

| If | Then |
|----|------|
| \( \frac{\phi_{\lim}(\alpha, f)}{\beta} \geq 1 \) | \( P(u \rightsquigarrow u_M) = 1 - p_{\text{failed}} \) |
| \( \frac{\phi_{\lim}(\alpha, f)}{\beta} < 1 \) and \( \frac{\psi_{\lim}(\alpha, f)}{\beta} \geq 1 \) | \( P(u \rightsquigarrow u_W) = p_{\text{failed}} \) |
| \( \frac{\phi_{\lim}(\alpha, f)}{\beta} < 1 \) and \( \frac{\psi_{\lim}(\alpha, f)}{\beta} < 1 \) | \( P(u \rightsquigarrow u_W, \text{failed mutant}) = p_{\text{failed}} \) |
| \( P(u \rightsquigarrow u_W, \text{lost mutant}) = 1 - p_{\text{failed}} \) | \( P(u \rightsquigarrow u_C) = 1 - p_{\text{failed}} \) |
| \( P(u \rightsquigarrow u_W) = p_{\text{failed}} \) | \( P(u \rightsquigarrow u_W) = p_{\text{failed}} \) |

where,

\[
p_{\text{failed}} = \exp\left[-\frac{4(f - \alpha(1 - f))}{(k^* + 1)(\alpha + 1)}\right]
\]

(3.6)

We emphasize that in the scaling of Theorem 1, the end state of (2.1) is completely deterministic. In order to state Theorem 2, we define \( w(t) \) to be the solution of the following Feller diffusion at time \( t \):

\[
dw = \sqrt{w}dB.
\]

(3.7)

\( w(0) = 1. \)
**Theorem 2** Set $\varepsilon$ according to (3.2) and $t_f = t/\varepsilon^2$. Define,

\[
T_{\text{wild}} = \sqrt{2\pi} (k + 1) \gamma_1,
\]

\[
T_{\text{mutant}} = \sqrt{2\pi} (k^* + f) \gamma_2.
\]

where

\[
\gamma_1 = \sqrt{\frac{1}{\alpha(1-f)^2}} \exp \left[ \left( \frac{f - \alpha(1-f)}{\alpha} \right) J_I \right] \left( \frac{1 + \alpha}{\alpha f} \right)^{\frac{1}{\kappa}}
\]

\[
\gamma_2 = \sqrt{\frac{1}{(f - \alpha(1-f))}} \exp \left[ \frac{(f - \alpha(1-f))(J_I + J_{III}) + \alpha(1-f)J_{III}H_{II}}{\alpha H_{II}} \right] \left( \frac{1 + \alpha(1 + H_{II})}{(1 + \alpha)\alpha(1 + H_{II})} \right)^{\frac{1}{\eta_{III}}} \left( \frac{1}{\kappa} \right)^{\frac{1}{\eta_{III}}}.
\]

Above, $J_I$ and $J_{III}$ are constants defined in Sect. 7, while $\eta_{III}$ is a random variable with distribution,

\[
\eta_{III} = w[T_{\text{wild}}].
\]

Further set,

\[
\rho_W = P(w[T_{\text{wild}}] = 0),
\]

\[
\rho_M = P(w[T_{\text{mutant}}] = 0)
\]

Then,

\[
P(u \sim u_W, \text{failed mutant}) = p_{\text{failed}}
\]

\[
P(u \sim u_W, \text{mutant lost}) = (1 - p_{\text{failed}})(1 - \rho_W) \rho_M
\]

\[
P(u \sim u_M) = (1 - p_{\text{failed}})\rho_W
\]

\[
P(u \sim u_C) = (1 - p_{\text{failed}})(1 - \rho_W)(1 - \rho_M)
\]

Notice that in Theorem 2, the end state of (2.1) is stochastic. Theorem 2 shows that the boundaries formed by $\phi_{\text{lim}}$ or $\psi_{\text{lim}}$ between the deterministic regions of Theorem 1 are stochastic with width of scale $O(1/(\log V)^2)$. The probability of wild type and mutant loss are expressed in terms of the probability that a Feller diffusion is lost through (3.13). However, standard arguments show $P(w[T_{\text{wild}}] = 0) = \exp[-2/T_{\text{wild}}]$ so that our results lead to explicit formulas. We state the results of Theorem 2 in terms of a Feller diffusion to provide context and intuition. The stochasticity of Theorem 2 comes from the stochasticity of the oscillations produced by (2.1).

We express our genetic results within the context of population sampling. To make things somewhat concrete, we assume that a sample of $n$ infected cells is taken at time $t_f$. The genetic composition of this sample across the HIV genome can be determined.
if one knows the lineages formed by the \( n \) cells in the sample and the mutations that occur on these lineages. The lineages and mutations associated with a sample are not deterministic and hence must be specified through a probability distribution.

In this work, we do not determine the full distribution of the lineages and mutations associated with the \( n \) cells in the sample (although our methods should allow for this). Rather, we characterize the state of the lineages formed by the \( n \) cells of the sample at time 0. To explain this precisely, let \( y_1, y_2, \ldots, y_n \) be labels for the \( n \) infected cells sampled at time \( t_f \). At time 0 these \( n \) cells will have some number of ancestors, say \( n_0 \), and we can arbitrarily label these ancestors \( z_1, z_2, \ldots, z_{n_0} \). Each \( z_i \) will be the ancestor of a certain number of the \( n \) sampled cells, let this number be \( B_i \). Then we have \( B_1 + B_2 + \cdots + B_{n_0} = n \) since every sampled cell \( y_i \) must be descendant from some \( z_j \). Our results specify the distribution of \( (n_0, B_1, B_2, \ldots, B_{n_0}) \).

The Kingman coalescent, which can be derived from a Wright–Fisher population model, is a specific probability distribution for the lineages of a sample (Durrett 2002). For any time \( t \), we let \( \Pi(t; n) \) be the lineage distribution specified by the Kingman coalescent run for time \( t \) and assuming \( n \) sampled individuals. Our results will show that the distribution of \( (n_0, B_1, B_2, \ldots, B_{n_0}) \) is the same as that specified by the Kingman coalescent run for some time \( T_{\text{genetic}} \). In this way, we show that our viral population run for time \( t_f \) will have a similar level of genetic diversity as a Wright-Fisher population run for time \( T_{\text{genetic}} \).

Our results will actually split into cases depending on whether the wild type is lost, mutant type is lost, or coexistence occurs. In the case of one type surviving, we will be able to characterize the genetic diversity by a single Kingman coalescent started with \( n \) individuals. However, when the types coexist, we need two Kingman coalescents to characterize the resultant distribution.

The genetic results follow the same scaling regimes as specified in Theorems 1 and 2. We state the results associated with the parameter regime given in Theorem 2. The following theorem shows that the distribution of \( (n_0, B_1, B_2, \ldots, B_n) \) is a function of four random variables defined in the theorem: \( w_1, w_2, \xi, \zeta \).

**Theorem 3** Let \( f, \varepsilon, T_{\text{wild}}, T_{\text{mutant}}, p_{\text{failed}} \) be as in Theorem 2. Let \( w_1, w_2 \) be versions of the Feller process \( w \) specified in (3.7) and let the Feller process in the definition of \( \eta_{11}, (3.12) \), be \( w_1 \). Let \( \xi \) be a uniform random variable on \([0, 1]\) and let \( \zeta \) be a binomial random variable with \( n \) trails and success probability \( \frac{\alpha(1-f)}{f} \) and let \( \xi \) be a binomial random variable with \( n \) trials and success probability \( \frac{\alpha(1-f)}{f} \). Assume \( w_1, w_2, \xi, \zeta \) are independent. Define the times \( T_{\text{genetic},1}, T_{\text{genetic},2} \) according to the following table (in the cases where the entry for \( T_{\text{genetic},2} \) is a \( - \), only \( T_{\text{genetic},1} \) is defined.)

| If | \( T_{\text{genetic},1}, T_{\text{genetic},2} \) |
|----|---------------------------------------------|
| \( \zeta < p_{\text{failed}} \) | \( 0, - \) |
| \( \zeta > p_{\text{failed}}, \quad w_1[T_{\text{wild}}] = 0 \) | \( \infty, - \) |
| \( \zeta > p_{\text{failed}}, \quad w_1[T_{\text{wild}}] \neq 0, \quad w_2[T_{\text{mutant}}] = 0 \) | \( \int_0^{T_{\text{wild}}} ds \left( \frac{k+\varepsilon}{k+1} \right)^{\frac{1}{w_1[s]}}, - \) |
| \( \zeta > p_{\text{failed}}, \quad w_1[T_{\text{wild}}] \neq 0, \quad w_2[T_{\text{mutant}}] \neq 0 \) | \( \int_0^{T_{\text{wild}}} ds \left( \frac{k+\varepsilon}{k+1} \right)^{\frac{1}{w_1[s]}}, \infty \) |
In the cases where \( T_{\text{genetic},2} \) is not defined then,
\[
\lim_{V \to \infty} (n_0, B_1, B_2, \ldots, B_{n_0}) = \Pi(T_{\text{genetic},1}; n) \tag{3.15}
\]

In the case where \( T_{\text{genetic},2} \) is defined then,
\[
\lim_{V \to \infty} (n_0, B_1, B_2, \ldots, B_{n_0}) = (\Pi_1(T_{\text{genetic},1}; \xi), \Pi_2(T_{\text{genetic},2}, n - \xi)), \tag{3.16}
\]

where \( \Pi_1, \Pi_2 \) are independent versions of \( \Pi \). Both of the above limits are meant in the sense of convergence in distribution.

4 Discussion

In this section, we explore the implications of the asymptotic results described in Theorems 1–3. We also investigate the accuracy of these results for finite \( V \), i.e. without taking \( V \to \infty \). Throughout we consider \( V = 10^8 \), recall that \( V \) represents the number of HIV infected cells. Estimates for \( V \) lie in the range \( 10^6-10^8 \) (Crandal 1999). We take the extreme end, but the results described below are essentially the same for \( V = 10^6 \). First, we consider the role of \( \epsilon \) and \( \alpha \) in determining wild and mutant type survival probabilities.
Figure 6 shows $\phi_{\text{lim}}/\log(V)$ and $\psi_{\text{lim}}/\log(V)$ versus $f$ for $\alpha = .1, 1, 5$ with $f \in [\alpha/(1 + \alpha), 1]$. For $f$ values lower and greater than this range the mutant type and wild type, respectively, will be lost regardless of $\varepsilon$. Recall, $f$ is the ratio of mutant fitness to wild type fitness. As Fig. 4 shows, $\phi_{\text{lim}}$ and $\psi_{\text{lim}}$ always intersect at some value which we label as $\hat{f}$. We find $\hat{f} = .14, .61, .89$ for Fig. 6a–c, respectively. According to Theorem 1, given an $f$ for which $f > \hat{f}$, values of $\varepsilon$ ‘significantly’ above and below the dotted line in the figures will lead to coexistence and wild type loss, respectively. We examine what is meant by ‘significantly’ in a moment. Taking the case $\alpha = 1$ as a base case, we see from Fig. 6b that $\varepsilon = .1$ assures coexistence for all but the most fit mutants.

Recall that $\alpha$ measures the degree to which CD8 cells require antigenic stimulation to proliferate rather than die out. As $\alpha$ rises the relative amount of CD8 proliferation drops. Accordingly, we expect wild type survival probabilities to rise with $\alpha$. Indeed, Fig. 6 shows when $f = .9$, $\varepsilon$ must be significantly greater than .75, .05, .0025 to ensure wild type survival in the cases $\alpha = .1, 1, 5$, respectively. At the early stages of chronic infection, we do not expect the CD8 cell time scale to be .0025 slower than the HIV time scale. So, in such a setting, when $f = .9, \alpha = 5$ the wild type will survive. On the other hand, the CD8 cell time scale is probably <.75 of the HIV time scale, so when $f = .9, \alpha = .1$ the wild type will be lost.

To understand the effect of HIV disease progression on $\varepsilon$ and $\alpha$ we note in the notation of our birth–death model, $\varepsilon = b/c, \alpha = dc/ab$. $c$ reflects competition between HIV virions for host cells while $d$ reflects, among many things, competition between CD8 cells for helper T cell stimulation. As disease progresses and helper T cell counts drop, we expect this competition to increase and consequently $c$ and $d$ should rise over time. $a$ represents the kill rate of HIV infected cells by a CD8 cell while $b$ represents the rate of CD8 cell stimulation by an antigen. We might expect $a$ and $b$ to stay
roughly constant or drop with disease progression. Putting these observations together, we expect $\varepsilon$ to decrease and $\alpha$ to increase with disease progression. These comments connect with our intuitive expectation. As HIV infection progresses, the loss of helper T cells should lead to slower immune response and less CD8 cell proliferation.

The rate of change in $\alpha$ relative to $\varepsilon$ will have a profound impact on HIV diversity. Indeed, suppose initially $\varepsilon = .1, \alpha = .1$. If a mutant arises with, say, $f = .95$, the wild type will not survive as seen through Fig. 6a. Now imagine that disease progresses so that $\varepsilon = .025, \alpha = 1$. Examining Fig. 6b shows that as before a mutant with $f = .95$ will drive out the wild type. However, if disease progresses so that $\varepsilon = .025, \alpha = 5$, then Fig. 6c shows that coexistence will occur. While our assumptions on $a, b, c, d$ may not hold, the preceding observations demonstrate that immune system speed and HIV diversity may not be related in a simple way as disease progresses. Although, for fixed $\alpha$, decreasing $\varepsilon$ raises the probability of coexistence.

Referring to Fig. 6a, we now focus on the case $f = .5, \alpha = .1$. Imagine starting at the point $(.5, 0)$ on the Cartesian axes given in Fig. 6a and moving vertically upwards, letting $\varepsilon$ be our y coordinate. We start with $\varepsilon = 0$ and so we expect to be in a regime of wild type loss until $\varepsilon \approx \phi_{\text{lim}}/\log(V)$ after which we will be in a coexistence regime. Figure 7 shows numerical results along with the theoretical predictions of Theorem 2 for the probability of wild type survival versus $\varepsilon$. Numerical results were produced by integrating (2.1) 1,000 times for each $\varepsilon$ value.

Theorem 2 gives the probability of wild type loss as $P(w[T_{\text{wild}}] = 0)$ (see 3.13), where we are ignoring the possibility of a failed mutant. Standard results give $P(w[T_{\text{wild}}] = 0) = 1 - \exp[-2/T_{\text{wild}}]$. We distinguish between three ways to compute $T_{\text{wild}}$. We can set $T_{\text{wild}}$ according to (3.8). (3.8) results from taking $V \to \infty$ and so we refer to this as the limit formula. We also have a formula for $T_{\text{wild}}$ for finite $V$, (given in Sect. 7 by (7.53)). This formula, which we refer to as the pre-limit
Wild type survival probability. For each \( \varepsilon \) the bars from left to right are approximations given by numerical integration of (2.1), integral formula, limit formula, and pre-limit formula. \( \alpha = 1, f = .8, V = 10^8 \)

formula, can be numerically evaluated (the function \( \phi \) must be numerically integrated) and depends only on the deterministic system (2.3) through the value of \( \tilde{p}(t) \). Finally we have \( T_{\text{wild}} \approx \int_{T_{\text{II}}}^{T_{\text{I}}} ds (k + 1)/(V \tilde{v}(s)) \), we refer to this expression as the integral formula (see the proof of Lemma 7.4 in Sect. 7 for details). Notice that the integral depends only on the deterministic system through \( \tilde{v}(t) \).

For a given \( \varepsilon \) there are four bars in Fig. 7 which represent the probability of wild type survival as approximated by, from left to right, the numerical results, integral formula, limit formula, and pre-limit formula. When \( \varepsilon < .08 \) or \( \varepsilon > .15 \), all four approximation methods predict that the wild type will survive with probability very near 0 or 1, respectively. For intermediate values of \( \varepsilon \) all four approximations show a gradual increase in survival probability. Taking the numerical results as an accurate approximation of the true value, the integral formula gives close to correct results while the limit and pre-limit formulas give the correct trend but are not very precise. Notice that the pre-limit formula is more accurate than the limit formula. Both formulas are correct up to \( O(\varepsilon|\log \varepsilon|) \) with \( \varepsilon = O(1/\log(V)) \). For \( V = 10^8 \), we have \( \varepsilon|\log \varepsilon| \approx .15 \) and so we expect \( O(1) \) relative error. We have consider the case \( V = 10^{12} \), an unrealistic value for HIV, and in this setting our formulas relative error becomes <10% (results not shown).

Figure 7 confirms that the scaling of \( \varepsilon \) in terms of \( \kappa \) given in (3.2) is the appropriate scaling for the transition between deterministic wild type loss and deterministic wild type survival. Notice that the range of values for which wild type survival is stochastic centers roughly around the dotted line in Fig. 6a where it intersects the vertical line of \( f = .5 \). As predicted by Theorem 2, this stochastic region is \( O(1/(\log(V))^2) \). A similar analysis for the case \( \alpha = 1, f = .8 \) is shown in Fig. 8.

In the preceding discussion we have considered \( f > \hat{f} \), which puts us in the regime of coexistence or wild type loss. In other words, the mutant is fit enough to survive
with probability near 1. When we consider \( f < \hat{f} \), then according to Fig. 4 all three regimes of coexistence, wild type loss, and mutant loss are possible. Figure 9 is a zoom-in of Fig. 6b on the values \( f \in [\alpha/(1 + \alpha), \hat{f}] \). Given an \( f \) value in this range, if \( \varepsilon \) is less than the height of the dashed line, between the dashed line and solid line, and above the solid line then Theorem 1 guarantees that, at least asymptotically, the wild type is lost, mutant type is lost, and coexistence occurs, respectively. In Fig. 10 we compare simulation results approximating survival probabilities to the theoretical predictions in Theorem 2. We set \( f = .58 \), note \( f < \hat{f} \), and \( \alpha = 1 \). Since the preceding discussion demonstrated the superiority of the integral formula to the limit and pre-limit formulas, we use the integral formula to generate the theoretical predictions. Results for the limit and pre-limit formulas are similar to Fig. 7 in that they are correct to \( O(1) \), but there is significant relative error. For the mutant type the integral formula is given by \[
\int_{T_{II}}^{T_{IV}} ds \frac{(k^* + f)}{(Vv^*(s))}.
\]

We now consider genetic diversity as explored through Theorem 3. Since we assume that all mutants descend from a single initial mutation at time zero, genetic diversity in our model reduces to understanding the coalescence of wild type lineages. These lineages coalesce with significant probability only when \( Vv(t) \), the number of wild types, is small. In the deterministic case, \( \bar{v}(t) \) reaches a minimum during stage II and stays near that minimum for \( O(1/\sqrt{\varepsilon}) \). To see this, let \( t^* \) be the time at which \( \bar{v}(t) \) is minimum (in our proofs we use the notation \( s_{II}/\varepsilon \) for \( t^* \)). When \( \bar{v}(t) \) is small we have

\[
\frac{d\bar{v}(t)}{dt} \approx \bar{v}(1 - f - \bar{p}(t)),
\]

\[
\frac{d\bar{p}(t)}{dt} \approx -\varepsilon\alpha \bar{p}^2(t).
\]

For \( \bar{v}(t^*) \) to be a minimum we require \( \bar{p}(t^*) \approx 1 - f \). Integrating (4.17) to first order in \( \varepsilon \) leads to \( \bar{p}(t) = (1 - f) - \varepsilon\alpha(1 - f)^2(t - t^*) \). In turn \( \bar{v}(t) \approx \bar{v}(t^*) \)
exp[εα(1 − f)^2(t − t^*)^2/2] and from this expression we see that \( \bar{v}(t) = O(\bar{v}(t^*)) \)
for \( O(1/\sqrt{\varepsilon}) \).

Consider now wild type lineages taken from the sample at time \( t_f \) and traced backwards in time. Except for time near \( t^* \) the wild type population is large and with high probability no coalescent events occur. However, near \( t^* \) the wild type population is of size \( O(\kappa/\sqrt{\varepsilon}) \), this is shown through the asymptotic expansions of Sect. 6, and it stays at this order for time \( O(1/\sqrt{\varepsilon}) \). The Kingman coalescent is formed by considering a Wright–Fisher population of size \( N \) evolved for time of order \( N \) and then taking \( N \to \infty \). The wild type lineages are connected to the Kingman coalescent through similar arguments, except that \( 1/\sqrt{\varepsilon} \) plays the role of \( N \). Indeed, in Theorem 3 we take \( V \to \infty \) and so implicitly \( \varepsilon \to 0 \) thereby making the connection to the Kingman coalescent exact. When we consider the stochastic wild type dynamics, the situation is similar except that we have \( v(t) \approx \bar{v}(t)w(\tau(t)) \) where \( \tau(t) \) is a time rescaling described in Sect. 7 and \( w \) is a Feller diffusion run for time \( T_{\text{wild}} \) and conditioned on \( w(T_{\text{wild}}) \neq 0 \).

For \( V \) finite, the results of Theorem 3 will be accurate if \( \kappa/\sqrt{\varepsilon} \gg 1 \). Put another way, the larger the minimum wild type population size the more accurate the Kingman coalescent approximation becomes. More precisely, if we have \( n \) lineages, then the Kingman approximation improves as \( n^2/\min(v(t)) \) gets smaller. If we take \( n = 10 \), i.e. we sample 10 infected cells at time \( t_f \), then a reasonably good approximation occurs for \( \min(v(t)) > 1,000 \). Figure 11 examines the minimum number of wild types under \( \alpha = 1 \) for \( f = .6, .8, .95 \) over a range of \( \varepsilon \) values. The figure is generated from the deterministic system, but results for the stochastic system are similar. For the case \( f = .8 \), Fig. 11b, we find that \( \varepsilon \geq .03 \) gives a Kingman coalescent approximation with small error when \( n = 10 \). When \( \varepsilon = .03 \), Fig. 8 shows that the wild type survives with probability near 1. Further, solving (3.2) gives \( \kappa \approx 20,000 \). Here we see that for
$\varepsilon$ in the parameter regime considered, the asymptotic results given by Theorem 3 only apply for very large $\kappa$ which in turns means that we are out of the stochastic end stage regime. In cases where $\kappa$ is more modest, the finiteness of the population will create situations in which multiple lineages can coalesce at once and the Kingman coalescent cannot apply. Other descriptions through the $\Lambda$ coalescent may be possible, but we have not pursued this issue.

Several authors have explored the issue of intrahost HIV effective population size (Leigh-Brown 1997; Rouzine and Coffin 1999; Kouyos et al. 2006) with the general result that the effective population size is of order 1,000. This is surprising when compared to a census size expected to be in the millions. From our discussion above, a Wright–Fisher population of size $O(\kappa/\varepsilon)$ evolved for $O(1/\sqrt{\varepsilon})$ will produce the same level diversity as the dynamics given through (2.1). As a result we will have $N_e = O(\kappa/\sqrt{\varepsilon})$. Figure 12 gives $N_e$ values over the range of $\varepsilon$ given in Fig. 11. Specific $N_e$ values were produced by assuming that the time span of the wild type bottleneck is $1/(\sqrt{\varepsilon} \alpha(1 - f))$ and then computing the required Wright–Fisher population size that would produce the same diversity as predicted by Theorem 3. Since the order of the wild type population size during the bottleneck is determined by the minimum $v(t)$ value, the similarity of Figs. 11 and 12 is expected. Examining Fig. 12c, we see that a mutant with $f = .95$ will produce an effective HIV population size of order 1,000 when $\varepsilon \approx .15$. Such an $\varepsilon$ value reflects CD8 cell dynamics on the time scale of a week if we take HIV dynamics to occur on the order of a day.

Our CD8–HIV dynamics model is certainly overly simplified. Among the many factors we ignore, we have not considered CD8 cell attack at multiple epitopes, nor have we considered the effect of helper T cell depletion. However, our analysis suggests that stochasticity plays an important role in HIV evolution in two ways. As we
have shown, in certain parameter regimes that seem plausible for HIV, stochasticity plays a role in the survival of specific HIV variants. Further, the genetic diversity of HIV may be significantly affected by bottlenecks created by CD8 cell attack. Such bottlenecks may explain the low effective population size of HIV.

5 Proofs of theorems

In this section we prove Theorems 1–3. We analyze the stochastic system (2.1) by comparing it to the deterministic system (2.3). More precisely, in Sect. 6 we consider the deterministic system in stages I–IV. For each stage, we determine an asymptotic expansion in $\varepsilon$ of $u$ at the end of the stage. So, for example, in stage II we take $\bar{u}(\bar{T}_I)$ as given and determine an expansion for $\tilde{u}(\tilde{T}_{II})$. In Sect. 7 we consider the stochastic system through stage I–IV. Roughly, the idea will be that in stage I and III, $u$ and $\bar{u}$ behave, with high probability, almost identically while in stage II and IV, $u$ and $\bar{u}$ differ due to stochastic effects.

The main technical ideas needed to prove our theorems are contained in the lemmas of Sects. 6 and 7. In this section we put these lemmas together to prove the theorems. By doing so, we hope to provide the reader with an underlying intuition for the more technical lemmas found in Sects. 6 and 7. Before beginning in this task, we need to precisely define stage I–IV and the initial stage. We set for the deterministic system,

$$
\bar{T}_I = \inf\{t > 0 : \bar{v}(t) = \varepsilon^q\},
\bar{T}_{II} = \inf\{t > \bar{T}_I : \bar{v}(t) = \varepsilon^q\},
\bar{T}_{III} = \inf\{t > \bar{T}_{II} : \bar{v}^*(t) = \varepsilon^q\},
\bar{T}_{IV} = \inf\{t > \bar{T}_{III} : \bar{v}^*(t) = \varepsilon^q\},
$$

Fig. 12 Effective population size as a function of $\varepsilon$. The subfigures have the same parameters as those in Fig. 11. The effective population size is computed as described in the text. The log is base 10.
\[ \bar{T}_{IV} = \inf\{t > \bar{T}_{III} : \bar{v}^*(t) = \varepsilon^q\}, \]

and similarly for the stochastic system,

\[ T_I = \inf\{t > 0 : \bar{v}(t) = \varepsilon^q\}, \]
\[ T_{II} = \inf\{t > T_I : v(t) = \varepsilon^q\}, \]
\[ T_{III} = \inf\{t > T_{II} : v^*(t) = \varepsilon^q\}, \]
\[ T_{IV} = \inf\{t > T_{III} : v^*(t) = \varepsilon^q\}, \]

(5.2)

where \( q = 4 \). In Sect. 2 we stated that in stage I, \( v \) collapses to \( o(1) \) levels. What we meant, as seen from the definitions above, is that \( v \) collapses to the value of \( \varepsilon^q \). Essentially, \( q \) is chosen so that when a variable falls below \( \varepsilon^q \), its effect will not be felt in the \( V \to \infty \) limit. For example, in stage II, \( v \leq \varepsilon^q \) and the result is that the dynamics of \( p \), given by \( \dot{p} = \varepsilon p(v - \alpha p) \) can be reduced to the integrable \( \dot{p} = -\varepsilon \alpha p^2 \). Set,

\[ T_s = \inf\{t : v^* \notin (0, \varepsilon^q)\} \]

(5.3)

\( T_s \) is considered only in the stochastic system and so \( \bar{T}_s = T_s \). Indeed, we will simply start the deterministic system at time \( T_s \) by setting \( \bar{u}(T_s) = u(T_s) \).

We now proceed to prove Theorems 1–3. Theorems 1 and 2 have similar proofs, so we prove Theorem 2 and within that proof we comment on the connections to the Proof of Theorem 1

Proof of Theorem 2 To help the reader parse our arguments, we decompose this proof according to which stage we consider. At the end of the proof we consider a full cycle.

5.1 Initial stage

We start by considering the initial stage. From (5.3) we have three possibilities. \( v(T_s) = \varepsilon^q \), \( v(T_s) = 0 \) or \( T_s = \infty \). Lemma 7.1 shows that \( P(T_s = \infty) = 0 \) and \( \lim_{V \to \infty} P(v(T_s) = 0) = p_{\text{failed}} \). So with probability \( p_{\text{failed}} \) the stochastic system never exceeds \( \varepsilon^q \) and we have a failed mutant. Lemma 7.1 also shows that \( v, p \) do not deviate beyond \( O(\varepsilon^q) \) from \( v(0), p(0) \) by time \( T_s \), so if a failed mutant occurs, the system returns to state \( u_W \).

Stage I

If the mutant does not fail, then stage I starts. We take \( \bar{u}(T_s) = u(T_s) \). Lemma 7.2 gives for stage I,

\[ P\left( \sup_{T_s \leq t \leq T_I} \|u(t) - \bar{u}(t)\|_\infty \geq \frac{1}{\sqrt{V}} \right) \leq O\left( \frac{(\log \log V)^2 (\log V)^2}{\sqrt{V}} \right) \]

(5.4)

and Lemma 6.1 gives the asymptotic of \( \bar{u} \), up to \( O(\varepsilon) \), at the end of stage I.
Stage II

Lemma 6.2 shows that the deterministic system $v$ reaches an absolute minimum in stage II. In Sect. 7 we label that minimum as $s_{II}^{\epsilon}$, and we are able to asymptotically compute its value as a function of $p(T_I)$. To emphasize this we write, $s_{II}^{\epsilon}(p(T_I))$. In Lemmas 7.3–7.5 we define an interval $[t_0, t_1]$ centered about $s_{II}^{\epsilon}(p(T_I))$ and of width $\frac{2}{\sqrt{\epsilon}}$. For our proofs to work, $m$ can be taken as any value between $\frac{1}{2}$ and $\frac{2}{3}$, but intuitively what matters is that the width of $[t_0, t_1]$ be much greater than $\frac{2}{\sqrt{\epsilon}}$. Lemma 7.3 shows that on $[T_I, t_0]$, $|u - \bar{u}|$ is bounded by $O(\epsilon^{q+1})$ with probability $O(\epsilon^2)$. Lemma 7.5 shows the identical conclusion for the interval $[T_I, T_{II}]$. Lemma 7.4 shows that inside the interval $[t_0, t_1]$ stochastic effects matter and $u$ may deviate from $\bar{u}$. Indeed, Lemma 7.4 gives,

$$
\lim_{\mathbb{V} \to \infty} P(v \text{ is lost in } [t_0, t_1]) = \lim_{\mathbb{V} \to \infty} P\left( w\left[ \sqrt{2\pi (k+1)} \Xi_{II} \right] = 0 \right), \quad (5.5)
$$

where

$$
\Xi_{II} = \frac{1}{\sqrt{\alpha(1-f)^2}} \left( \exp\left[ -\phi \left( \frac{s_{II}(p(T_I))}{\epsilon} \right) \right] \right). \quad (5.6)
$$

The function $\phi$ in (5.6) is defined in Sect. 7. We caution the reader that $\phi_{\lim}$ is not $\phi$, essentially $\phi$ is $\log \left( \frac{v(t)}{v(T_I)} \right)$ although we define $\phi$ somewhat differently for technical reasons. The connection between $\phi$ and $\phi_{\lim}$ is given by the following relation which is justified in Lemma 7.4.

$$
-\phi \left( \frac{s_{II}}{\epsilon} \right) = \frac{\phi_{\lim}}{\epsilon} - q |\log \epsilon| + z + O \left( \epsilon^{3/2} |\log \epsilon| \right), \quad (5.7)
$$

where

$$
z = \frac{f - \alpha(1-f)}{\alpha} J_I + \log \left( \frac{1+\alpha}{\alpha f} \right) - \log(\kappa). \quad (5.8)
$$

(5.7) leads to,

$$
\exp\left[ -\phi \left( \frac{s_{II}(p(T_I))}{\epsilon} \right) \right] = \exp\left[ \frac{\phi_{\lim}}{\epsilon} \right] \epsilon^q \exp[z] \left( 1 + O(\epsilon^{3/2} |\log \epsilon|) \right). \quad (5.9)
$$

Plugging (5.9) into (5.6) and using the scaling of $\epsilon$ in Theorem 2 gives,

$$
\lim_{\mathbb{V} \to \infty} \Xi_{II} = \Upsilon_1. \quad (5.10)
$$

Plugging (5.10) into (5.5) gives

$$
\lim_{\mathbb{V} \to \infty} P(v \text{ is lost in } [t_0, t_1]) = P(w[T_{\text{wild}}] = 0) \quad (5.11)
$$
We note that in Theorem 1 the scaling will force the following duality in $\Xi_{II}$,

$$\lim_{V \to \infty} \Xi_{II} = \begin{cases} \infty & \text{if } \frac{\phi}{\beta} \geq 1, \\ 0 & \text{if } \frac{\phi}{\beta} < 1. \end{cases}$$  \tag{5.12}$$

Since $w[\infty] = 0$ and $w[0] = 1$ we have,

$$P(\nu \text{ is lost in } [t_0, t_1]) = \begin{cases} 1 & \text{if } \frac{\phi}{\beta} \geq 1, \\ 0 & \text{if } \frac{\phi}{\beta} < 1. \end{cases}$$  \tag{5.13}$$

and this is the essential difference between the results in Theorems 1 and 2. If $\nu$ is lost during stage II, it is straightforward to show that the system must go to $u_M$.

**Stage III**

If the wild type is not lost in stage II, then by the same arguments used in Lemma 7.2 to show that $u \approx \bar{u}$ in stage I, we can show that $u \approx \bar{u}$ in stage III (with the precise statement being identical to that found in (5.4)).

**Stage IV**

The arguments of stage IV are almost identical to stage II, except that $v^*$ is now what collapses rather than $v$. We define a function $\psi$ in Sect. 7 that plays the role $\phi$ did in stage II. And the relationship between $\psi$ and $\psi_{lim}$ is completely analogous to the relationship between $\phi$ and $\phi_{lim}$. If the mutant is lost then the system goes to $u_W$.

### 5.2 Behavior over a full cycle

If both the mutant and the wild type survive the first cycle of stages I–IV then our claim is that the system gets arbitrarily close, at least to $O(1)$, to $u_C$. This is a result of the damped oscillations seen in Fig. 1. To demonstrate the damping of the oscillations and their impact on the probability of losing $v$ or $v^*$ in a given cycle, we first note that by Lemmas 6.1 and 6.3, $\tilde{p}$ changes by only $O(\varepsilon \log \varepsilon)$ during stages I and III. And since $u$ and $\bar{u}$ are linked during those stages through (5.4) the same will be true of $p$ and $\tilde{p}$. In stage II, since $v$ is $O(\varepsilon^q)$ we will have $dp(t)/dt = -\varepsilon \alpha p^2 + O(\varepsilon^{q+1})$. In stage IV we will show that since $v^* \leq O(\varepsilon^q)$ we have $v - (1 - p) = O(\varepsilon)$. From this we have $dp(t)/dt = \varepsilon p(1 - (1 + \alpha)p) + O(\varepsilon^2)$. Both stages II and IV can be shown to be of duration $O(\frac{1}{\varepsilon})$ and so we can explicitly integrate $p$ through the cycle with an error term $O(\varepsilon)$. We find $0 < p(T_{IIV}) - (1 - f) < p(T_s) - (1 - f)$ and so the starting value of $p(t)$ in subsequent cycles is damped towards $(1 - f)$.

To connect to the probability of loss, consider the impact of this damping on $\phi_{lim}$. $\phi_{lim}$ can be thought of as a function of $p(T_s)$ since $\phi \left( \frac{s(T_s)}{\varepsilon} \right)$ is, through this con-
connection we can consider how \(\phi_{\lim}\) changes with \(p(T_s)\). Explicit differentiation gives,

\[
\frac{\partial \phi_{\lim}(p(T_s))}{\partial p(T_s)} = \frac{p(T_s) - (1 - f)}{p^2(T_s)} < 0
\]  

(5.14)

So with each progressive cycle, \(\phi_{\lim}\) will be \(O(1)\) smaller. The same can be said for \(\psi_{\lim}\). To see the effect of this, let \(\phi_{\lim}^{(1)}\) be the value of \(\phi_{\lim}\) corresponding to the first cycle, i.e. exactly \(\phi_{\lim}\), and \(\phi_{\lim}^{(2)}\) be the value of \(\phi_{\lim}\) corresponding to the second cycle. Then we have,

\[
\exp\left[\frac{\phi_{\lim}^{(2)}}{\varepsilon}\right] = \exp\left[\frac{\phi_{\lim}^{(1)}}{\varepsilon}\right]\left(\exp[-O\left(\frac{1}{\varepsilon}\right)]\right) = \exp\left[\frac{\phi_{\lim}^{(1)}}{\varepsilon}\right]\left(\exp[-O(\log \Psi)]\right).
\]  

(5.15)

If we follow the arguments that led to (5.13) we see that if \(v\) is not lost in the first stage II it will not be lost in subsequent stages, and similarly for \(v^*\).

Now note that we set \(t_f = O\left(\frac{1}{\varepsilon^2}\right)\). We show in Sects. 6 and 7 that a full cycle takes \(O\left(\frac{1}{\varepsilon}\right)\), so if \(v\) and \(v^*\) are not lost we are considering \(O\left(\frac{1}{\varepsilon}\right)\) cycles. Since we have shown that \(p(T_{IV}) - (1 - f) < p(T_s) - (1 - f)\) we see that with every cycle the next \(p(T_s)\) gets \(O(1)\) closer to \(1 - f\). This implies that by the time interval \([O\left(\frac{1}{\varepsilon^2}\right), t_f]\), \(p - (1 - f)\) will be \(o(1)\). It is then easy to show that \(v\) and \(v^*\) get within \(o(1)\) to their values in \(u_C\). And so \(u\) gets within \(o(1)\) of \(u_C\).

Finally, our analysis of the different stages contained expansions with error terms \(o(\varepsilon)\) and excluded sets with probability \(O(\varepsilon^2)\). Since by time \(t_f\) we have gone through at most \(O\left(\frac{1}{\varepsilon}\right)\) cycles, if we now take \(\Psi \to \infty\) which takes \(\varepsilon \to 0\) our arguments become true with probability approaching one. \(\square\)

Before finishing with Theorems 1 and 2 we return to an issue raised in Sect. 2. In that section, we stated that the stochastic terms involving \(p\) had been dropped in (2.1) but that our results would be unaffected. Indeed, \(v\) and \(v^*\) are only affected by stochastic terms when they drop to low levels in stages II and IV. \(p\) never experiences such bottlenecks, so the stochastic terms in the \(p\) equation will have no effect. If we included them we would need a lemma similar to Lemma 7.2. But this would just add technicalities to our discussion.

We now prove Theorem 3. Before proceeding we explain how we build sample lineages on the population process \(w(t)\). These justifications are similar to arguments found in Wakeley and Sargsyan (2009). Take two times \(t\) and \(t + \Delta t\). Suppose at time \(t + \Delta t\) we have \(n'\) sample lineages of wild type. If a birth event happens in the underlying birth–death process during \([t, t + \Delta t]\) then the number of lineages may drop from \(n'\) to \(n' - 1\). Indeed, if the parent and child associated with the birth event are both part of the \(n'\) sampled cells at time \(t + \Delta t\) then we have a coalescent event and at time \(t\) there will be \(n' - 1\) lineages. By symmetry, given a birth event there is a probability \(\frac{n'(n' - 1)}{2^n'(t) \bar{v}_W(t) - 1}\) that a coalescent event will occur (recall that \(\bar{v}_W(t)\) is the number of wild type cells at time \(t\)).
To compute the probability of a coalescent event, we need to know the probability of a birth event in \([t, t + \Delta t]\) conditioned on the value of \(u(t + \Delta t)\). Set \(u(t + \Delta t) = \hat{u} = (\hat{v}, \hat{\nu}^*, \hat{\rho})\). Then an application of Bayes rule gives

\[
P(\text{birth} \mid u(t + \Delta t) = \hat{u}) = \frac{P(\text{birth} \mid u(t) = (\hat{v} - \frac{1}{\sqrt{v}}, \hat{\nu}^*, \hat{\rho})) P(u(t) = (\hat{v} - \frac{1}{\sqrt{v}}, \hat{\nu}^*, \hat{\rho}))}{P(u(t + \Delta t) = \hat{u}) + O(\Delta t^2)}.
\]

In the rescaling that gave us (2.1), the birth rate of wild types is \(k + \frac{1}{2}\) (see the Appendix for details of the rescaling that justify this comment). This gives,

\[
P \left( \text{birth} | u(t) = \left( \hat{v} - \frac{1}{\sqrt{v}}, \hat{\nu}^*, \hat{\rho} \right) \right) = \left( k + \frac{1}{2} \right) \left( \sqrt{v} - 1 \right) \Delta t + O(\Delta t^2). \quad (5.17)
\]

Now we wish to show,

\[
P \left( u(t + \Delta t) = \left( \hat{v} - \frac{1}{\sqrt{v}}, \hat{\nu}^*, \hat{\rho} \right) \right) = P(u(t + \Delta t) = \hat{u}) + O \left( \frac{1}{\sqrt{\nu}(t)} \right). \quad (5.18)
\]

To see this, assume \(\sqrt{\nu}(t)\) to be large and consider \(u(t - \tau)\) such that \(\tau \gg \frac{1}{\sqrt{\nu}(t)}\) but \(\tau \ll 1\). Since \(\tau\) is small, we can take \(u(t - \tau) \approx u(t)\). Then, on \([t - \tau, t + \Delta t]\) the number of birth events will be approximately Poisson distributed with mean \((k + \frac{1}{2})\sqrt{\nu}(t)(\tau + \Delta t)\).

Conditioned on \(u(t - \tau)\), the difference between the cases \(u(t + \Delta t) = (\hat{v} - \frac{1}{\sqrt{v}}, \hat{\nu}^*, \hat{\rho})\) and \(u(t + \Delta t) = \hat{u}\) is that the number of birth events or death events during \([t - \tau, t + \Delta t]\) differs by 1. For the birth events, simple arguments involving the Poisson distribution then give (5.18). Similar arguments apply to the death events. To ignore the \(O \left( \frac{1}{\sqrt{\nu}(t)} \right)\) term in (5.18), we require \(\sqrt{\nu}(t) \to \infty\) as \(\nu \to \infty\). This will not be true if for some \(t, \sqrt{\nu}(t) = O(1)\). However, we only consider wild type lineages when wild types are not lost. And by the computations of Lemma 7.4, in such settings we always have \(\sqrt{\nu} \geq O \left( \frac{1}{\sqrt{v}} \right)\). And so \(\sqrt{\nu} \to \infty\) as \(\nu \to \infty\). Combining the arguments above, we find the rate of a coalescent event at time \(t\) to be \((k + \frac{1}{2})\frac{n'(\nu') - 1}{\sqrt[4]{\nu'(s)}}\) \(\sqrt{\nu}(s)\).

Finally, before proceeding to the Proof of Theorem 3 we connect our lineage distribution to the Kingman coalescent. A well-known result in coalescent theory states that if lineages coalesce at rate, say, \(r(t)\) over an interval \([0, T]\), then the lineages at time zero of this time varying coalescent process will have the same distribution as the Kingman coalescent run for time \(\int_0^T ds r(s)\) (Tavare 2001). Essentially, in the Kingman coalescent lineages coalesce at rate 1, so by a time rescaling one can produce coalescent events at the correct rate, \(r(t)\). For us, the consequence of this observation is that the distribution of wild type lineages will be given by a Kingman coalescent run for time \(\int_0^t ds \frac{k + \frac{1}{2}}{\sqrt{\nu(s)}}\). Hence, in the Proof of Theorem 3 we focus on the quantity \(\int_0^t ds \frac{1}{\sqrt{\nu(s)}}\).
Proof of Theorem 3 We recall the notation $\Pi(t, n)$, introduced in Sect. 3, representing the number of lineages left at time zero from $n$ sampled cells at time $t$ according to the Kingman coalescent distribution. Also in Sect. 3, we introduced the variables $(n_0, B_1, B_2, \ldots, B_n)$ to describe the number of lineages left at $t = 0$ from $n$ sampled cells taken at $t = t_f$. We first consider the following cases: mutant fails, wild type loss, and mutant loss.

If the mutant fails then Lemma 7.1 shows that $v(t) = \frac{\alpha}{1 + \alpha} + O(\epsilon^q)$ for all $t \in [0, t_f]$. Then we have,

$$\lim_{V \to \infty} \int_0^{t_f} ds \frac{1}{V v(s)} = \lim_{V \to \infty} O \left( \frac{1}{\epsilon^2 V} \right) = 0 \quad (5.19)$$

If the wild type is lost then, since there is only a single mutant at time 0, $n_0 = 1$ and $B_1 = n$. This is the same distribution at $\Pi_1(\infty; n)$.

Now we consider the case of the mutant type being lost. First we claim,

$$\lim_{V \to \infty} \int_0^{t_f} ds \frac{1}{V v(s)} = \lim_{V \to \infty} \int_{t_0}^{t_1} ds \frac{1}{V v(s)} \quad (5.20)$$

where recall that $[t_0, t_1]$ is a subinterval in stage II during the first cycle. To see (5.20), first note that in stages I, III, and IV and in the initial stage we have $v \geq \epsilon^q$. So since the duration of these stages is $O\left(\frac{1}{\epsilon}\right)$ we have,

$$\lim_{V \to \infty} \int_{[0, T_I] \cup [T_{II}, T_{IV}]} ds \frac{1}{V v(s)} = \lim_{V \to \infty} O \left( \frac{1}{\epsilon q + 1/V} \right) = 0. \quad (5.21)$$

On $[T_{IV}, t_f]$ the mutant is already lost and $v(t) = O(1)$, so $\lim_{V \to \infty} \int_{[T_{IV}, t_f]} ds \frac{1}{V v(s)} = 0$. We are left to consider $[T_I, T_{II}]$ during the first cycle. The key relation is (7.67) in Lemma 7.4 which allows us to compute $v(t)$ for $t \in [t_0, t_1]$. By plugging in $t = \frac{s_{II}}{\epsilon}$ in (7.67) we arrive at,

$$v(t_0) = \bar{v} \left( \frac{s_{II}}{\epsilon} \right) \exp \left[ \alpha (1 - f)^2 \frac{1}{\epsilon^{2m-1}} \right] \quad (5.22)$$

We now wish to demonstrate the following bound,

$$\lim_{V \to \infty} \int_{T_I}^{T_{II}} ds \frac{1}{V v(s)} = \lim_{V \to \infty} \int_{t_0}^{t_1} ds \frac{1}{V v(s)} \quad (5.23)$$
To see this first note that $\dot{v}$ is always bounded by 1. So at least for one time unit, $v(t)$ is of order $v(\frac{t_1}{\epsilon})$. We have then,

$$\int_{t_0}^{t_1} ds \frac{1}{\sqrt{v(s)}} \geq O\left(\frac{1}{\sqrt{v(\frac{t_1}{\epsilon})}}\right).$$  \hspace{1cm} (5.24)

From the Proof of Theorem 1, $v$ is well approximated by $\bar{v}$ in stage II outside of $[t_0, t_1]$. Further, $\bar{v}$ is strictly decreasing on $[\bar{T}_I, t_0]$ and strictly increasing on $[t_1, \bar{T}_{II}]$. Since stage II is of duration $O\left(\frac{1}{\epsilon}\right)$ we must have,

$$\int_{[T_I, t_0] \cup [T_{II}, t_1]} ds \frac{1}{\sqrt{v(s)}} \leq \frac{1}{\epsilon \sqrt{v(t_0)}} = \frac{1}{\epsilon \sqrt{v(\frac{t_1}{\epsilon})}} \exp[\alpha(1 - f)^2 \frac{1}{\epsilon^{3m-1}}].$$  \hspace{1cm} (5.25)

From the above bound and (5.24), (5.23) follows. Summarizing, we have shown,

$$\lim_{V \to \infty} \int_{t_0}^{t_f} ds \frac{1}{\sqrt{v(s)}} = \lim_{V \to \infty} \int_{t_0}^{t_1} ds \frac{1}{\sqrt{v(s)}}.$$

Finally, Lemma 7.4 shows $\int_{t_0}^{t_1} ds \frac{1}{\sqrt{v(s)}} \to \frac{1}{k+1} \int_{0}^{\bar{T}_{wild}} ds \frac{1}{\sqrt{1+s}}$.

We have left the case of the wild type and mutant type both surviving. In this case, the computations are simply a combination of the wild type loss and mutant type loss case after we split the sample into wild and mutant samples. We have $v(t_f) = \alpha(1 - f)$ and $v^*(t_f) = \bar{f} - \alpha(1 - \bar{f})$. So the probability of drawing a wild type is, as $V \to \infty$, exactly $\frac{\alpha(1-f)}{f}$ and the number of wild types out of $n$ sampled cells is binomial with $n$ trials and success probability $\frac{\alpha(1-f)}{f}$.

\hfill \Box

6 The deterministic system

In this section we consider the deterministic system (2.3). Our goal will be to find asymptotic expansions for $\tilde{u}$ at the end of each of stages I–IV and to develop estimate of the $\tilde{u}$ dynamics during the stages as well. We define $\delta(t) = \tilde{p}(t) - (1 - f)$.

6.1 Stage I

Recall that stage I is given by the interval $[T_s, \bar{T}_I]$. In this subsection, for notational convenience, we set $\delta = \delta(T_s)$. We assume $\tilde{v}^*(T_s) = \epsilon^q$, $\tilde{v}(T_s) - (1 - \tilde{p}(T_s)) \leq O(\epsilon)$ (this assumption will connect to Lemma 7.1 found in Sect. 7).
Lemma 6.1 \( \tilde{T}_I - T_s = O\left(\frac{\log \varepsilon}{\delta}\right) \) and,

\[
|f - \tilde{v}^*(\tilde{T}_I)| = O(\varepsilon^q),
\]

\[
\tilde{p}(\tilde{T}_I) = \tilde{p}(T_s) - \frac{q \varepsilon \log(\varepsilon)}{\delta} \Delta \tilde{p}_{I,1} + \frac{\varepsilon}{\delta} \Delta \tilde{p}_{I,2} + O(\varepsilon^2 |\log \varepsilon|^3)
\]

where,

\[
\Delta \tilde{p}_{I,1} = \tilde{p}(T_s)(1 - (1 + 2\alpha)\tilde{p}(T_s)),
\]

\[
\Delta \tilde{p}_{I,2} = \tilde{p}(T_s)(\delta J_1 - \alpha \tilde{p}(T_s) \log(f(1 - \tilde{p}(T_s)))).
\]

\( J_1 \) is defined by,

\[
J_I = \lim_{\xi \to 0} \left( \int_0^\infty ds r_I(s) - \frac{(1 - \tilde{p}(0))}{\delta} |\log \xi| \right)
\]

where \( r_I(0) = 1 - \tilde{p}(0) \) and

\[
\frac{dr_I(t)}{dt} = r_I \left( 1 - \tilde{p}(0) - r_I - \frac{\xi}{1 - \tilde{p}(0) \exp[\delta t]} \right)
\]

Proof Before starting on the proof, we provide some intuition. Roughly, the slow time scale of \( \bar{p} \) allows us to estimate \( \bar{p} \) to within \( O(\varepsilon) \). This in turn allows us to estimate \( \bar{v}, \bar{v}^* \) with small error. Which then in turn, allows us to derive an asymptotic expansion for \( \bar{p} \).

To make these comments precise, we first note the bound \( |\tilde{p}(t) - \tilde{p}(T_s)| \leq \varepsilon(t - T_s) \), and in turn

\[
\tilde{p}(\tilde{T}_I) = \tilde{p}(T_s) + \varepsilon \int_{T_s}^{\tilde{T}_I} ds \tilde{p}(T_s)(\bar{v}(s) - \alpha \tilde{p}(T_s)) + O(\varepsilon^2 (\tilde{T}_I - T_s)^2).
\]

Using (6.6), we can expand \( \tilde{p}(\tilde{T}_I) \) if we have expansions for \( (\tilde{T}_I - T_s) \) and \( \int_{T_s}^{\tilde{T}_I} ds \bar{v}(s) \).

We first consider \( (\tilde{T}_I - T_s) \). Differentiating \( \log(\bar{v}) - \log(\bar{v}^*) \) and integrating the result leads to

\[
\frac{\bar{v}(t)}{\bar{v}^*(t)} = \frac{\bar{v}(T_s)}{\bar{v}^*(T_s)} \exp[-\delta(t - T_s) + O(\varepsilon(t - T_s))].
\]

Set \( t = \tilde{T}_I \) in the above relation. Then using the facts \( \bar{v}(\tilde{T}_I) = \varepsilon^q \) and \( \bar{v}^*(T_s) = \varepsilon^q \), we can derive the following asymptotic expansion for \( (\tilde{T}_I - T_s) \),

\[
\tilde{T}_I - T_s = \frac{2q}{\delta} |\log(\varepsilon)| + \frac{1}{\delta} \log(f(1 - p(T_s))) + O(\varepsilon|\log(\varepsilon)|).
\]
Now we consider $\int_{T_s}^{\bar{T}_I} ds \tilde{v}(s)$. To do this, we split $[T_s, \bar{T}_I]$ into three time periods. Define

$$T_A = \inf \{ t : \tilde{v}^*(t) = \gamma \}, \quad T_B = \inf \{ t : \tilde{v}(t) = \gamma \},$$

(6.9)

where $\gamma > 0$ is $O(1)$ but taken to be small. Using (6.7), we can show

$$T_A - T_s = \frac{q}{\delta} |\log \varepsilon| + O(|\log \gamma|),$$

$$T_B - T_A = O(|\log \gamma|),$$

(6.10)

$$\bar{T}_I - T_B = \frac{q}{\delta} |\log \varepsilon| + O(|\log \gamma|).$$

Consider $\int_{T_s}^{T_A} ds \tilde{v}(s)$. Intuitively, on $[T_s, T_A]$, we have $\tilde{v} \approx 1 - \bar{p}(T_s)$. And so we expect $\int_{T_s}^{T_A} ds \tilde{v}(s) \approx (1 - \bar{p}(T_s)) \frac{q}{\delta} |\log \varepsilon| + O(1)$. To demonstrate this, we first use (6.7) to find,

$$\tilde{v}^*(t) = \tilde{v}(t) g(t),$$

(6.11)

where

$$g(t) = \frac{e^q}{\tilde{v}(T_s)} \exp[\delta t + O(\varepsilon t)].$$

(6.12)

Now let $x(t) = \tilde{v} - (1 - \bar{p}(T_s))$. Then,

$$\frac{dx(t)}{dt} = -\tilde{v}(x + \tilde{v}g).$$

(6.13)

An integrating factor gives,

$$x(t) = x(T_s) \exp \left[ -\int_{T_s}^{t} ds \tilde{v}(s) \right] - \int_{T_s}^{t} ds \tilde{v}(s) g(s) \exp \left[ -\int_{T_s}^{s} ds \tilde{v}(s) \right].$$

(6.14)

Using (6.14), we now bound $\int_{T_s}^{T_A} ds x(s)$. On $[T_s, T_A]$, $\tilde{v}(s) = O(1)$. So considering the first term to the right of the equality in (6.14), we have

$$\int_{T_s}^{T_A} ds x(T_s) \exp \left[ -\int_{T_s}^{s} ds' \tilde{v}(s') \right] \leq O(1).$$

(6.15)
For the second term in (6.14), notice \( \int_{T_s}^{T} ds \tilde{v}(s) \exp[-\int_{s}^{T} ds \tilde{v}(s)] = 1 \). We can think of \( \tilde{v}(s) \exp[-\int_{s}^{T} ds \tilde{v}(s)] \) as a weighting function and since \( g(t) \) is exponentially increasing with \( g(T_A) = O(1) \) we have,

\[
\left| \int_{T_s}^{T} ds \int_{T_s}^{s} ds' \tilde{v}^2(s')g(s') \left[ -\int_{s'}^{s} ds'' \tilde{v}(s'') \right] \right| \leq \int_{T_s}^{T} ds g(s) = O(1). \tag{6.16}
\]

We have arrived at \( \int_{T_s}^{T} ds x(s) = O(1) \). And so we have,

\[
\int_{T_s}^{T} ds \tilde{v}(s) = (1 - \tilde{p}(0))(T_A - T_s) + O(1). \tag{6.17}
\]

Since \( T_B - T_A = O(1) \), we trivially have \( \int_{T_A}^{T_B} ds \tilde{v}(s) = O(1) \). Finally, on \([T_B, \tilde{T}_I]\), \( d\tilde{v}/dt < \tilde{v}(-d+\gamma) \). So \( \tilde{v} \) is exponentially decreasing and we have \( \int_{T_B}^{\tilde{T}_I} ds \tilde{v}(s) = O(1) \). Putting all these integral bounds together gives the expansion,

\[
\int_{T_s}^{\tilde{T}_I} ds \tilde{v}(s) = \frac{q(1 - \tilde{p}(T_s))}{\delta} |\log \varepsilon| + J_I + O(\varepsilon |\log \varepsilon|), \tag{6.18}
\]

where \( J_I \) is a constant. We have,

\[
J_I = \lim_{\varepsilon \to 0} \left( \int_{T_s}^{\tilde{T}_I} ds \tilde{v}(s) - \frac{q(1 - \tilde{p}(0))}{\delta} |\log \varepsilon| \right), \tag{6.19}
\]

Dropping \( o(1) \) terms that will disappear in the limit directly above, we have

\[
\frac{d\tilde{v}(t)}{dt} = \tilde{v} \left( 1 - \tilde{p}(T_s) - \frac{q(1 - \tilde{p}(0))}{1 - \tilde{p}(0)} \exp[\delta t] \right) \tag{6.20}
\]

with \( \tilde{v}(T_s) = 1 - \tilde{p}(0) \). Substituting \( \xi = \varepsilon q \) gives the characterization of \( J_I \) in (6.4) where the replacement of \( \tilde{T}_I \) in (6.19) by \( \infty \) in (6.4) does not change the limit because \( r_I(t) \) exponentially collapses as \( t \to \infty \). (6.2) now follows by plugging (6.8) and (6.18) into (6.6).

(6.1) follows by similar methods. Essentially, on \([T_B, \tilde{T}_I]\) we have \( d\tilde{v}^*/dt \approx \tilde{v}^*(f - \tilde{v}^*) \) since the contribution of \( \tilde{v} \) is small. Integrating this relation gives (6.1) with error terms controlled by methods similar to those used above. \( \square \)
6.2 Stage II

From Lemma 6.1 we can assume $\delta(\bar{T}_I) > 0$, $\bar{v}(\bar{T}_I) = \varepsilon^q$, and $|\bar{v}^*(\bar{T}_I) - f| = O(\varepsilon^q)$.

**Lemma 6.2** Let $H_{II}$ be the solution of $(1 - f)H_{II} = \frac{1}{\alpha} \log(1 + \alpha p(\bar{T}_I)H_{II})$. Then,

$$
\left| (T_{II} - T_I) \frac{H_{II}}{\varepsilon} \right| = O(\varepsilon^q - 1) \quad (6.21)
$$

$$
\bar{p}(T_{II}) = \frac{\bar{p}(T_I)}{1 + \alpha \bar{p}(T_I)H_{II}} + O(\varepsilon). \quad (6.22)
$$

For $t \in [T_I, T_{II}]$ we have,

$$
\sup_t |\bar{v}^*(t) - f| \leq O(\varepsilon^q)
$$

$$
\bar{v}(t) = \bar{v}(T_I) \exp \left( (1 - f)(t - T_I) - \frac{1}{\alpha \varepsilon} \log(1 + \varepsilon \alpha \bar{p}(T_I)(t - T_I)) + O(\varepsilon^q) \right) \quad (6.23)
$$

**Proof** We first show that on $[\bar{T}_I, \bar{T}_{II}]$, $\bar{p}$ has simple dynamics. Indeed, for all $t \in [\bar{T}_I, \bar{T}_{II}]$,

$$
\dot{\bar{p}} = -\varepsilon \alpha \bar{p}^2 + C \varepsilon^{1+q}, \quad (6.24)
$$

From this we have,

$$
\bar{p}(t) = \frac{\bar{p}(T_I)}{1 + \varepsilon \alpha \bar{p}(T_I)(t - T_I)} + O(\varepsilon^q) \quad (6.25)
$$

Now consider $\bar{v}^*$ for $t \in [T_I, T_{II}]$.

$$
\bar{v}(t) = \bar{v}(T_I) \exp \left[ (1 - f)(t - T_I) - \frac{1}{\alpha \varepsilon} \log(1 + \varepsilon \alpha \bar{p}(T_I)(t - T_I)) + O(\varepsilon^q) \right] \quad (6.28)
$$

where $C \leq 1$. Since $|f - \bar{v}^*(T_I)| = O(\varepsilon^q)$, from (6.26) we can conclude that $|f - \bar{v}^*| \leq O(\varepsilon^q)$ on $[T_I, T_{II}]$.

Now we bound $T_{II}$. We have for $t \in [T_I, T_{II}]$,

$$
\dot{\bar{v}} = \bar{v}(1 - f - \bar{p} + O(\varepsilon^q)) \quad (6.27)
$$

Plugging (6.25) into the relation directly above leads to

$$
\bar{v}(t) = \bar{v}(T_I) \exp \left[ (1 - f)(t - T_I) - \frac{1}{\alpha \varepsilon} \log(1 + \varepsilon \alpha \bar{p}(T_I)(t - T_I)) + O(\varepsilon^q) \right] \quad (6.28)
$$
Since \( \tilde{p}(T_I) > 1 - f \), a simple Taylor series argument shows,

\[
v \left( T_I + \frac{H_{II}}{\varepsilon} - O(\varepsilon^{q-1}) \right) < \varepsilon^q < v \left( T_I + \frac{H_{II}}{\varepsilon} + O(\varepsilon^{q-1}) \right).
\] (6.29)

So we can conclude that \( T_I + \frac{H_{II}}{\varepsilon} - O(\varepsilon^{q-1}) < T_{II} < T_I + \frac{H_{II}}{\varepsilon} + O(\varepsilon^{q-1}) \) and the lemma follows. \( \square \)

6.3 Stage III

From Lemma 6.2 we can assume \( \delta(T_{II}) < 0 \), \( \tilde{v}(T_{II}) = \varepsilon^q \), and \( |\tilde{v}^*(T_{II}) - f| \leq O(\varepsilon^q) \). For convenience in this section set \( \delta = \delta(T_{II}) \).

**Lemma 6.3**  
\( \bar{T}_{III} - \bar{T}_{II} = O \left( \frac{|\log \varepsilon|}{|\delta|} \right) \),

\[
|\bar{v}(T_{III}) - (1 - \bar{p}(T_{III}))| = O(\varepsilon),
\] (6.30)

\[
\bar{p}(T_{III}) = \bar{p}(\bar{T}_{II}) + \frac{q \varepsilon \log(\varepsilon)}{\delta} \Delta \bar{p}_{III,1} - \frac{\varepsilon}{|\delta|} \Delta \bar{p}_{III,2} + O \left( \varepsilon^2 |\log \varepsilon|^2 \right) \) (6.31)

where,

\[
\Delta \bar{p}_{III,1} = \bar{p}(\bar{T}_{II})(1 - (1 + 2\alpha) \bar{p}(\bar{T}_{II})),
\] (6.32)

\[
\Delta \bar{p}_{III,2} = \bar{p}(\bar{T}_{II})(-\delta J_{III} - \alpha \bar{p}(\bar{T}_{II}) \log(f(1 - \bar{p}(\bar{T}_{II})))).
\]

\( J_{III} \) is defined by

\[
J_{III} = \lim_{\xi \to 0} \left( \frac{1}{|\xi| |\log \xi|} \int_0^\xi ds r_{III}(s) - \frac{(1 - \bar{p}(0))}{|\delta|} |\log \xi| \right),
\] (6.33)

where \( r_{III}(0) = \xi \) and

\[
\frac{dr_{III}(t)}{dt} = r_{III} \left( 1 - \bar{p}(0) - r_{III} - \frac{f}{\xi} \exp[\delta t] \right).
\] (6.34)

**Proof**  The proof of the lemma is almost identical to that of Lemma 6.1. The only slight difference involves the proof of (6.30). Set \( \Delta \tilde{v} = \tilde{v} - (1 - \bar{p}) \). Then direct computation gives

\[
\dot{\Delta} \tilde{v} = -\tilde{v} \Delta \tilde{v} - \tilde{v} \tilde{v}^* + \varepsilon \bar{p}(\bar{v} - \alpha \bar{p}).
\] (6.35)

Using an integrating factor of \( \int_{\bar{T}_{II}}^t ds \tilde{v}(s) \), we can integrate (6.35). We then use the arguments used to analyze (6.14) to demonstrate (6.30). \( \square \)
6.4 Stage IV

From the results of Lemma 6.3 we can assume \( \delta(\overline{T}_{III}) < 0 \), \(|\overline{v}(\overline{T}_{III}) - (1 - p(\overline{T}_{III}))| = O(\varepsilon) \), and \( \overline{v}^* = \varepsilon q \).

**Lemma 6.4** Define \( H_{IV} \) as the solution of the following equation,

\[
(1 - f)H_{IV} = \frac{1}{1 + \alpha} \log \left( 1 + (1 + \alpha)\bar{p}(\overline{T}_{III})(\exp[H_{IV}] - 1) \right). \tag{6.36}
\]

Then \( |(\overline{T}_{IV} - \overline{T}_{III}) - \frac{H_{IV}}{\varepsilon}| = O(\varepsilon) \) and

\[
\bar{p}(\overline{T}_{IV}) = \frac{\bar{p}(\overline{T}_{III}) \exp[H_{IV}]}{1 + (1 + \alpha)\bar{p}(\overline{T}_{III})(\exp[H_{IV}] - 1)} + O(\varepsilon). \tag{6.37}
\]

For \( t \in [\overline{T}_{III}, \overline{T}_{IV}] \) we have,

\[
|\bar{v}(t) - (1 - \bar{p}(t))| \leq O(\varepsilon) \tag{6.38}
\]

\[
\bar{v}^*(t) = \bar{v}^*(\overline{T}_{III}) \exp[g(t) + O(\varepsilon)] \tag{6.39}
\]

where,

\[
g(t) = -(1 - f)(t - \overline{T}_{III}) + \frac{1}{(1 + \alpha)\varepsilon} \log \left( 1 + (1 + \alpha)\bar{p}(\overline{T}_{III})(\exp[\varepsilon(t - \overline{T}_{III})] - 1) \right) \tag{6.40}
\]

**Proof** We start by considering \( \bar{v} - (1 - \bar{p}) \). Recall the definition of \( \Delta \bar{v} \) from Lemma 6.3. By the comments in Lemma 6.3 we have \( \Delta \bar{v} = O(\varepsilon) \) and hence \( \bar{v} = (1 - \bar{p}) + O(\varepsilon) \). However, to compute \( \bar{v}^* \) to \( O(\varepsilon) \) we need \( \bar{v} \) to one higher order. To see why, suppose we have \( \bar{v} = 1 - p + O(\varepsilon) \). Then we would have the estimate \( \frac{d\bar{v}^*(t)}{dt} = \bar{v}^*(\bar{p} - (1 - f) + O(\varepsilon)) \) and integrating this expression for \( O(1) \) time units leads to \( O(1) \) error terms. To estimate \( \bar{v}^* \) to \( O(\varepsilon) \) we consider integrating \( \Delta \bar{v} \). We have,

\[
\int_{\overline{T}_{III}}^{t} ds \Delta \bar{v}(s) = \int_{\overline{T}_{III}}^{t} ds I_1(s) + \int_{\overline{T}_{III}}^{t} ds I_2(s) + O(\varepsilon^2) \tag{6.41}
\]

where

\[
I_1(t) = \Delta \bar{v}(\overline{T}_{III}) \exp \left[ - \int_{\overline{T}_{III}}^{t} ds(1 - \bar{p}(s)) \right],
\]

\[
I_2(t) = \varepsilon \int_{\overline{T}_{III}}^{t} ds \exp \left[ - \int_{s}^{t} ds'(1 - \bar{p}(s')) \right] \bar{p}(s)(1 - (1 + \alpha)\bar{p}(s)) \tag{6.42}
\]
Since $\Delta \tilde{v} (\tilde{T}_{III}) = O(\varepsilon)$ we will have $\int_{\tilde{T}_{III}}^{t} ds I_1(s) = O(\varepsilon)$. Surprisingly, the same is true for $\int_{\tilde{T}_{III}}^{t} ds I_2(s)$. To see this, we first note the following expansion,

$$I_2(t) = \varepsilon \frac{\tilde{p}(1 - (1 + \alpha) \tilde{p}(s))}{1 - \tilde{p}(t)} + O(\varepsilon^2)$$

$$= \varepsilon \frac{d \tilde{p}(t)}{1 - \tilde{p}(t)} + O(\varepsilon^2)$$

$$= \varepsilon \frac{d \log(1 - \tilde{p})(t)}{dt} + O(\varepsilon^2). \quad (6.43)$$

Since $I_2(t)$ is to first order a derivative, it’s integral will be $O(\varepsilon)$. We have then

$$\tilde{v}^*(t) = \tilde{v}^*(\tilde{T}_{III}) \exp \left[ - \int_{\tilde{T}_{III}}^{t} ds (1 - f) - \tilde{p}(s) \right] + O(\varepsilon) \quad (6.44)$$

We now consider $\tilde{p}$. First note that in stage IV we have,

$$\dot{\tilde{p}} = \varepsilon \tilde{p}(1 - (1 + \alpha) \tilde{p}) + O(\varepsilon^2). \quad (6.45)$$

Solving for $\tilde{p}$ gives,

$$\tilde{p}(t) = \frac{\tilde{p}(\tilde{T}_{III}) \exp[\varepsilon(t - \tilde{T}_{III})]}{(1 + (1 + \alpha) p(\tilde{T}_{III}) (\exp[\varepsilon(t - \tilde{T}_{III})] - 1)} + O(\varepsilon^2)(t - \tilde{T}_{III}) \quad (6.46)$$

Plugging (6.46) into (6.44) gives (6.38). Recall that $\tilde{T}_{IV}$ is defined by $\tilde{v}^*(\tilde{T}_{IV}) = \varepsilon^g$. Considering $g(t)$ and the definition of $H_{IV}$, a Taylor expansion gives,

$$\tilde{T}_{IV} - \tilde{T}_{III} = \frac{H_{IV}}{\varepsilon} + O(\varepsilon). \quad (6.47)$$

\[\Box\]

### 7 The stochastic system

In this section we consider the stochastic system (2.1). Similarly to Sect. 6, our goal will be to find asymptotic expansions for $u$ at the end of each of stages I–IV and develop estimates for the dynamics of $\tilde{u}$ within the stages. In this section we also consider the initial stage. We recall from Sect. 6 that $\delta(t) = \tilde{p}(t) - (1 - f)$ and we emphasize that $\delta$ depends on the deterministic system (2.3) and not the stochastic system (2.1). Finally, in this section we will assume that $\varepsilon$ obeys the scaling of Theorem 2. The arguments in the case of Theorem 1 scaling are similar, and in fact simpler.
7.1 Initial stage

Recall that at \( t = 0 \) we have,

\[
v(0) = \frac{\alpha}{1 + \alpha}, \quad p(0) = \frac{1}{1 + \alpha}, \quad v^*(0) = \frac{1}{V}.
\]  (7.1)

Set \( \Delta v = v - v(0) \), \( \Delta v^* = v^* - v^*(0) \) and \( \Delta p = p - p(0) \). Then define \( T \) by

\[
T = \inf \{ t : v^* \notin (0, \varepsilon^q), \ |\Delta v| = \varepsilon^q \text{ or } |\Delta p| = \varepsilon^q \} \]  (7.2)

Note that \( T \) is not quite \( T_s \), but the lemma below will show that the two are equivalent in the \( V \to \infty \) limit.

We have the following lemma.

**Lemma 7.1**

\[
\lim_{V \to \infty} P(v^*(T) = \varepsilon^q \text{ or } v^*(T) = 0) = 1. \]  (7.3)

\[
\lim_{V \to \infty} P(v^*(T) = 0) = \exp \left[ -\frac{4(f - \alpha(1 - f))}{(k^* + 1)(1 + \alpha)} \right]. \]  (7.4)

\[
\lim_{V \to \infty} P \left( T \leq \frac{2 \log V}{f - v(0)} \right) = 1. \]  (7.5)

**Proof** Define two stopping times,

\[
T_\Delta = \inf \{ t : |\Delta v| = \varepsilon^q \text{ or } |\Delta p| = \varepsilon^q \} \]

\[
T_* = \inf \{ t : v^* \notin (0, \varepsilon^q) \} \]  (7.6)

Then clearly \( T = \min\{T_\Delta, T_*\} \). We now consider the following stochastic system. Essentially this system is (2.1) except that \( v^*, v \) and \( p \) become fixed once \( v^* \) exits \( (0, \varepsilon^q) \), \( |\Delta v| \geq \varepsilon^q \), and \( |\Delta p| \geq \varepsilon^q \), respectively. \( \chi \) is the indicator function.

\[
d\tilde{v} = \chi(|\tilde{v} - v(0)| \leq \varepsilon^q) \tilde{v}(1 - (\tilde{v} + \tilde{v}^*) - \tilde{p})dt + \chi(|\tilde{v} - v(0)| \leq \varepsilon^q) \sqrt{\tilde{v}(k + (\tilde{v} + \tilde{v}^*) + \tilde{p})} dB_1(t), \]

\[
d\tilde{v}^* = \chi(\tilde{v}^* \leq \varepsilon^q) \tilde{v}^*(f - (\tilde{v} + \tilde{v}^*))dt + \chi(\tilde{v}^* \leq \varepsilon^q) \sqrt{\tilde{v}^*(k^* + (\tilde{v} + \tilde{v}^*))} dB_2(t), \]

\[
d\tilde{p} = \chi(|\tilde{p} - p(0)| \leq \varepsilon^q) \varepsilon \tilde{p} (\tilde{v} - \tilde{p})dt \]  (7.7)

Notice that in the system (7.7) we are guaranteed \(|\tilde{v} - v(0)| \leq \varepsilon^q\), \(|\tilde{p} - p(0)| \leq \varepsilon^q\), and \( \tilde{v}^* \leq \varepsilon^q \) for all time. Define \( \tilde{T}_\Delta \) and \( \tilde{T}_* \) analogously to \( T_\Delta, T_* \) and notice that \( T = \min\{\tilde{T}_\Delta, \tilde{T}_*\} \) since up to time \( T \) the systems (2.1) and (7.7) evolve identically.
We now consider $\tilde{T}_s$. To control $\tilde{v}^*$ we bound it from above and below by two diffusions that are simpler to analyze. Set,

$$
\begin{align*}
\frac{d\tilde{v}^*_A(t)}{dt} &= \tilde{v}^*_A(f - v(0) + \varepsilon^q)dt + \sqrt{\frac{\tilde{v}^*_A(k^* + \tilde{v}^*_A + \tilde{v})}{\mathbb{V}}} dB_2(t), \\
\frac{d\tilde{v}^*_B(t)}{dt} &= \tilde{v}^*_B(f - v(0) - 2\varepsilon^q)dt + \sqrt{\frac{\tilde{v}^*_A(k^* + \tilde{v}^*_B + \tilde{v})}{\mathbb{V}}} dB_2(t),
\end{align*}
$$

(7.8)

and notice that the drift term in $\tilde{v}^*$ is less than and greater than the drift terms of $\tilde{v}^*_A$ and $\tilde{v}^*_B$, respectively (the $A$ and $B$ in $\tilde{v}^*_A$ and $\tilde{v}^*_B$ stand for above and below, respectively).

By pathwise uniqueness of solution we have $\tilde{v}^*_B \leq \tilde{v}^* \leq \tilde{v}^*_A$ pointwise for all $t \leq \tilde{T}_s$ on the probability space of the two Brownian motions $B_1, B_2$ (Karatzas and Shreve 1991). For any $t$ we have the following bound,

$$
P(\tilde{T}_s < t) \geq P(\tilde{v}^*_A(t) = 0) + P(\tilde{v}^*_B(t) \geq \varepsilon^q).
$$

(7.9)

We would like to run $\tilde{v}^*_A$ and $\tilde{v}^*_B$ long enough to ensure that either these diffusions will be absorbed or reach $\varepsilon^q$. If we ignore the variance terms in (7.8) we would find that $\tilde{v}^*_A(t) = \varepsilon^q$ for $t \approx \frac{1}{f - \nu(0)} \log \mathbb{V}$. With this in mind, we set $\hat{\tau} = \frac{2}{f - \nu(0)} \log \mathbb{V}$ and proceed to examine $\tilde{v}^*_A(\hat{\tau})$ and $\tilde{v}^*_B(\hat{\tau})$. We consider first $P(\tilde{v}^*_A(\hat{\tau}) = 0)$. Set $x_A = \mathbb{V} \exp[-(f - \nu(0) + \varepsilon^q)\hat{\tau}]\tilde{v}^*_A$, then

$$
\frac{dx_A}{dt} = \sqrt{x_A(k^* + \nu(0) + O(\varepsilon^q))} \exp[-(f - \nu(0) + \varepsilon^q)\hat{\tau}] dB_2(t).
$$

(7.10)

We now perform a time change, $w_A(\tau(t)) = x_A(t)$ with

$$
\tau_A'(t) = (k^* + \nu(0) + O(\varepsilon^q)) \exp[-(f - \nu(0) + \varepsilon^q)t].
$$

(7.11)

This leads to,

$$
\frac{dw_A}{dt} = \sqrt{w_A} dB_2,
$$

(7.12)

with $w_A(0) = 1$. Note that $w_A$ is a weak solution to (7.12) since $w_A$ is not $B_2$ measurable due to its dependence on $B_1$. However, we only care about the distribution of $w_A(\hat{\tau})$, and by weak uniqueness $w_A(\hat{\tau})$ will have the same distribution as the strong solution of (7.12) (Karatzas and Shreve 1991).

Recall we are interested in $P(\tilde{v}^*_A(\hat{\tau}) = 0)$. Let $t_A = \tau_A(\hat{\tau})$. Then,

$$
P(\tilde{v}^*_A(\hat{\tau}) = 0) = P(x_A(\hat{\tau}) = 0) = P(w_A(t_A) = 0).
$$

(7.13)

Explicit integration gives

$$
t_A = \frac{1}{2} \left( \frac{k^* + 1}{f - \nu(0)} \right) + O \left( \frac{\varepsilon^q}{f - \nu(0)} \right)
$$

(7.14)
Then standard results (see Athreya and Ney 1972, p. 260), give

\[ P(\tilde{v}_A^*(\hat{t}) = 0) = P(w[t_A] = 0) = \exp\left( -\frac{2}{t_A} \right) = \exp\left( -\frac{4(f - v(0))}{k^* + 1} \right) + O(\varepsilon^q). \] (7.15)

Now we consider \( P(\tilde{v}_B^*(\hat{t}) \geq \varepsilon^q) \). We perform the same series of transforms as we did for \( \tilde{v}_A^* \) except that now we have,

\[ x_B = \mathbb{V} \exp[-(f - v(0) - 2\varepsilon^q)t]\tilde{v}_B^*, \]
\[ \tau_B(t) = (k^* + v(0) + O(\varepsilon^q)) \exp[(f - v(0) - 2\varepsilon^q)t]. \] (7.16)

Setting \( t_B = \tau_B(\hat{t}) \) we can compute,

\[ t_B = t_A \left( 1 + O\left( \frac{\varepsilon^q}{f - v(0)} \right) \right). \] (7.17)

We can follow our transforms, defining \( w_B \) analogously to \( w_A \), to find the following,

\[ P(\tilde{v}_B^*(\hat{t}) \geq \varepsilon^q) = P(w[t_B] \geq \gamma) \] (7.18)

where \( \gamma = \frac{\varepsilon^q}{\exp[(f - v(0) - O(\varepsilon^q))t]} \). Plugging in our scaling for \( \varepsilon \) gives \( \gamma = O\left( \frac{1}{\mathbb{V} \log \mathbb{V}^q} \right) \) and so \( \lim_{\mathbb{V} \to \infty} \gamma = 0 \). Further, from (7.17) and since \( w_A \) are described by the same diffusion, we have

\[ \lim_{\mathbb{V} \to \infty} P(w_B[t_B] \geq \gamma) = \lim_{\mathbb{V} \to \infty} P(w_A[t_A] \neq 0). \] (7.19)

If we now examine the dynamics of \( \tilde{v} \) and \( \tilde{p} \), the same type of methods that we applied to \( v^* \) show that \( \mathbb{T}_\Delta > O(\log \mathbb{V}) \) with probability approaching one and (7.4) follows. To see (7.5) notice that,

\[ \lim_{\mathbb{V} \to \infty} P(T < \hat{t}) = \lim_{\mathbb{V} \to \infty} P(w_A[t_A] = 0) + \lim_{\mathbb{V} \to \infty} P(w_A[t_A] \neq 0) = 1 \] (7.20)

\[ \square \]

7.2 Stage I and III

We assume that \( \tilde{u}(T_s) = u(T_s) \) and that \( \tilde{u}(T_s) \) satisfies the conclusion of Lemma 7.1. Then we have the following result which covers stage I behavior. An identical analogous result exists for stage III behavior.

**Lemma 7.2**

\[ P\left( \sup_{T_s \leq t \leq T_s} \|u(t) - \tilde{u}(t)\|_\infty \geq \frac{1}{\mathbb{V}^q} \right) \leq O\left( \frac{(\log \log \mathbb{V})^2 (\log \mathbb{V})^2}{\sqrt{\mathbb{V}}} \right) \] (7.21)
Proof Set \( D = \frac{1}{\sqrt{\pi t}} \) and define
\[
E = \frac{u - \bar{u}}{D}
\]
(7.22)
We have,
\[
dE = \frac{a(u) - a(\bar{u})}{D} dt + \frac{\sigma(u)}{\sqrt{\pi D}} dB
\]
(7.23)
where
\[
a(\bar{u}) = \begin{pmatrix}
\bar{v}(1 - \bar{v} - \bar{v}^* - \bar{p}) \\
v^*(f - \bar{v} - \bar{v}^*) \\
\varepsilon \bar{p}(\bar{v} - \bar{p})
\end{pmatrix},
\sigma(\bar{u}) = \begin{pmatrix}
\sqrt{v(k + (\bar{v} + \bar{v}^*) + \bar{p})} \\
\sqrt{v^*(k^* + (\bar{v} + \bar{v}^*))}
\end{pmatrix}
\]
(7.24)
Let \( T \) be a stopping time defined as \( T = \min\{t > T_s : \|E(t)\| > 1\} \) and \( E^T(t) = E(t \wedge T) \). We will show that \( T \gg |\log \varepsilon| \) with high probability and this will lead to \( T \gg T_1 \) with high probability. Employing a Taylor expansion, we have for all \( T_s \leq t < T \),
\[
dE^T(t) = (\nabla a(\bar{u})) E^T + O(D) dt + \frac{\sigma(\bar{u} + DE^T)}{\sqrt{\pi D}} dB
\]
(7.25)
Using the integrating factor \( \exp[- \int_0^t ds \nabla a(\bar{u})] \) we can arrive at
\[
E^T(t) = \int_0^{t \wedge T} ds \exp \left[ \int_s^t ds' \nabla a(\bar{u}(s')) \right] O(D)
\]
\[
+ \int_0^{t \wedge T} dB(s) \exp \left[ \int_s^t ds' \nabla a(\bar{u}(s')) \right] \frac{\sigma(\bar{u} + DE^T)}{\sqrt{\pi D}}
\]
(7.26)
Simple computation gives
\[
\nabla a(\bar{u}) = \begin{pmatrix}
(1 - \bar{v} - \bar{v}^* - \bar{p}) - \bar{v} - \bar{v} \\
-v^*(f - \bar{v} - \bar{v}^*) - \bar{v}^* - \bar{v} \\
\varepsilon \bar{p}(\bar{v} - \bar{p})
\end{pmatrix}
\]
(7.27)
Since \( \bar{v}, \bar{v}^*, \bar{p} \) are bounded we have \( \|\nabla a(\bar{u})\| \leq 1 \). Using this bound in (7.26) along with a standard martingale argument gives,
\[
E \left[ \sup_{t \leq C |\log \varepsilon|} E^2(t \wedge T) \right] \leq O(D^2(|\log \varepsilon|)^2 \exp[2 |\log \varepsilon|]) + |\log \varepsilon| \frac{\exp[2 |\log \varepsilon|]}{\sqrt{\pi D^2}}
\]
(7.28)
Recalling that $\varepsilon = O\left(\frac{1}{\log V}\right)$ gives,

$$E\left[\sup_{t \leq C|\log \varepsilon|} E^2(t \wedge T)\right] = O\left(\frac{(\log \log V)^2(\log V)^2}{\sqrt{V}}\right).$$  \hfill (7.29)

A simple Chebyshev argument now gives,

$$P\left(\sup_{t \leq C|\log \varepsilon|} \|u - \bar{u}\|(t \wedge T)\|_\infty \geq D\right) \leq O\left(\frac{(\log \log V)^2(\log V)^2}{\sqrt{V}}\right).$$  \hfill (7.30)

But then by the definition of $T$ we may replace $t \wedge T$ by $t$ in the expression directly above. Finally we note that $T_I = O(|\log \varepsilon|)$ and $\bar{v}(t) = O(\varepsilon^q)$ in time $O(|\log \varepsilon|)$. Since $T_I$ is defined by $v(T_I) = \varepsilon^q$, from (7.30) we see that $T_I = O(|\log \varepsilon|)$ and so we may replace the term $\sup_{t \leq C|\log \varepsilon|}$ in (7.30) by $\sup_{t \leq T_I}$.

7.3 Stage II

Now we consider the time interval $[T_I, T_{II}]$. This interval is where stochastic effects become important and $v$ diverges from $\bar{v}$. By Lemmas 6.1 and 7.2, $|f - v^*(T_I)| \leq O(\varepsilon^q)$ outside a set of probability $O\left(\frac{1}{\sqrt{V}}\right)$. On $[T_I, T_{II}]$ we have $dv/dt \approx v(1 - f - p)$ since $v^* \approx f$ and $v \leq \varepsilon^q$. Setting $\phi(t) = \int_{T_I}^t ds(1 - f) - \bar{p}(s)$ we will have $v(t) \approx v(T_I) \exp[\phi(t)]$. Notice that $\phi$ depends on $\bar{p}(T_I)$ although we mostly suppress this dependence. By the results of Lemma 6.2 we can integrate $\bar{p}$ to find,

$$\bar{p}(t) = \frac{\bar{p}(T_I)}{1 + \varepsilon\alpha \bar{p}(T_I)(t - T_I)} + O(\varepsilon^q),$$  \hfill (7.31)

and this allows us to explicitly form $\phi(t)$,

$$\phi(t) = (1 - f)(t - T_I) - \frac{1}{\alpha\varepsilon} \log(1 + \varepsilon\alpha \bar{p}(T_I)(t - T_I)) + O(\varepsilon^q).$$  \hfill (7.32)

Since $\bar{p}$ is strictly decreasing in stage II, $\phi$ has a single critical point which we set as $s_{II}$ (as mentioned in Sect. 5). We have $\phi'(\frac{s_{II}}{\varepsilon}) = (1 - f) - \bar{p}(\frac{s_{II}}{\varepsilon}) = 0$. Through (7.31), we can solve for $s_{II}$. In fact,

$$s_{II} = \varepsilon T_I + \frac{\delta(T_I)}{\alpha(1 - f)\bar{p}(T_I)} + O(\varepsilon^q),$$

$$\phi\left(\frac{s_{II}}{\varepsilon}\right) = -\frac{1}{\alpha\varepsilon} \left[ -\frac{\delta(T_I)}{\bar{p}(T_I)} + \log\left(1 + \frac{\delta(T_I)}{1 - f}\right) \right] + O(\varepsilon^q),$$

$$\phi''\left(\frac{s_{II}}{\varepsilon}\right) = \varepsilon\alpha(1 - f)^2 + O(\varepsilon^q),$$

$$\phi'''\left(\frac{s_{II}}{\varepsilon}\right) = O(\varepsilon^2).$$  \hfill (7.33)
We split the interval \([T_I, T_{II}]\) into three pieces using the times
\[ t_0 = s_{II} - \frac{1}{m}, \quad t_1 = s_{II} + \frac{1}{m}, \]
where \(m\) can take any value between \(\frac{1}{2}\) and \(\frac{2}{3}\). A consequence of our arguments will be \(T_I < t_0 < t_1 < T_{II}\). The following lemma shows that in the time
interval \([T_I, t_0]\), \(u\) stays close to \(\bar{u}\).

**Lemma 7.3** Outside of a set \(\Omega\) such that \(P(\Omega) \leq \varepsilon^{q-2}\) we have for any \(t \in [T_I, t_0]\),

\[
|v(t) - \bar{v}(t)| \leq \varepsilon \bar{v}(t),
\]

|\(v^*(t) - \bar{v}^*(t)| \leq \varepsilon^{\frac{q+1}{2}}
\]

|\(p(t) - \bar{p}(t)| \leq \varepsilon^{\frac{q+1}{2}}.
\]

**Proof** From Lemmas 6.1 and 7.2 we see that (7.34)–(7.36) hold for \(t = T_I\). In Lemma 7.2 we were able to scale \(u - \bar{u}\) by a constant \(D\). Here, things are not so simple because \(\bar{v}\) and \(v\) may drop to values below \(D\). Set \(r = \frac{q+1}{2}\) and define,

\[
E = \begin{pmatrix}
\frac{v - \bar{v}}{h(t)} \\
\frac{v^* - \bar{v}^*}{\varepsilon r} \\
\frac{p - \bar{p}}{\varepsilon^r}
\end{pmatrix}
\]

where \(h(t) = \bar{v}(\bar{T}_I) \exp[\phi(t)]\). Note \(h(t) = \bar{v}(t)(1 + O(\varepsilon^{q-1}))\).

We write \(E = (E_1, E_2, E_3)\) and set \(T = \inf\{t : \|E(t)\|_\infty > \varepsilon, t < t_0\}\). Now, notice that the coordinates of \(a\) given in (7.24) are all second order polynomials and so an exact second order Taylor expansion exists for \(a\). Using this Taylor expansion gives at time \(t \leq T\),

\[
de_1 = g_1(t)E_1 + O(\varepsilon^r) + \frac{\sigma_1(u)}{h(t)} dB_1
\]

\[
de_2 = g_2(t)E_2 + O(\varepsilon^r) + \frac{\sigma_2(u)}{\varepsilon q} dB_2
\]

\[
de_3 = g_3(t)E_3 + O(\varepsilon^r).
\]

where

\[
g(t) = \begin{pmatrix}
-\phi'(t) + (1 - \bar{v}^* - \bar{v} - \bar{p}) \\
f - \bar{v} - \bar{v}^* \\
\varepsilon(\bar{v} - \bar{p})
\end{pmatrix}
\]

We would now like to use \(g(t)\) as an integrating factor. Notice first,

\[
g(t) = \begin{pmatrix}
O(\varepsilon^q) \\
O(\varepsilon^q) \\
O(\varepsilon)
\end{pmatrix}
\]
Set $G_i(s, t) = \exp[\int_s^t ds' g_i(s')]$. Then we can integrate (7.38) using $G$ and arrive at,

\[
E_1(t \wedge T) = \int_{T_I}^{t \wedge T} ds G_1(s, t \wedge T) O(\varepsilon^r) + \int_{T_I}^{t \wedge T} dB_1(s) G_1(s, t \wedge T) \frac{\sigma_1(u)}{h(s) \sqrt{\nu}}
\]

(7.43)

\[
E_2(t \wedge T) = \int_{T_I}^{t \wedge T} ds G_2(s, t \wedge T) O(\varepsilon^r) + \int_{T_I}^{t \wedge T} dB_2(s) G_2(s, t \wedge T) \frac{\sigma_2(u)}{\varepsilon^q \sqrt{\nu}}
\]

(7.44)

\[
E_3(t \wedge T) = \int_{T_I}^{t \wedge T} ds G_3(s, t \wedge T) O(\varepsilon^r).
\]

(7.45)

Initial condition terms involving $E(T_I)$ that should appear in the expressions directly above are of lower order, so we have suppressed them for simplicity. From the above relations we find directly $E_3(t \wedge T) = O(\varepsilon^{r-1})$. To bound $E_1$ we consider second moments.

\[
E \left[ \sup_{T_I \leq t' \leq t} E_1^2(t' \wedge T) \right] \leq O(\varepsilon^{2(r-1)}) + E \left[ \left( \int_{T_I}^{t \wedge T} dB(s) \sqrt{\frac{v(1 - v - v^* - p)}{h^2(t) \nu}} \right)^2 \right]
\]

(7.46)

where we have used the fact that $G_1(s, t \wedge T) = O(1)$. For $t \leq T$, we have $\bar{v} = O(h(t))$. Using this observation and standard Martingale arguments gives,

\[
E \left[ \sup_{T_I \leq t' \leq t} E_1^2(t' \wedge T) \right] \leq O(\varepsilon^{q-1}) + O \left( \frac{1}{\bar{v}(T_I)} \int_{T_I}^{t \wedge T} ds \exp[-\phi(s)] \right)
\]

(7.47)

The situation is simpler for $E_2$. We use $\sigma_2(u) \leq 1$ and arrive at,

\[
E \left[ \sup_{t' \leq t} E_2^2(t' \wedge T) \right] \leq O(\varepsilon^{2r}) + O \left( \frac{1}{\varepsilon^{2q} \sqrt{\nu}} \right).
\]

(7.48)

Using our moment bounds on $E_1$, $E_2$ and pointwise bound on $E_3$ we now bound $E(t)$ and hence remove our restriction of $t \leq T$ outside a set of small probability. Indeed first consider $E_1$. By a Chebyshev bound,

\[
P \left( \sup_{T_I \leq t' \leq t_0 \wedge T} |E_1(t')| \geq \frac{\varepsilon}{2} \right) = O(\varepsilon^{q-2}) + I
\]

(7.49)
where

\[ I = \int_{T_I}^{T} ds \frac{\exp[-\phi(s)]}{\tilde{v}(T_I)\varepsilon^2\sqrt{\nu}} \]  

(7.50)

Recall that \( \tilde{v}(T_I) = \varepsilon^{q} \). We consider \( I \) by performing a Taylor series expansion of \( \phi \) about \( \frac{S_{II}}{\varepsilon} \).

\[
I \leq \frac{1}{\sqrt{\varepsilon q + 2}} \int_{T_I}^{t_0} ds \exp[-\phi(s)]
= \frac{1}{\sqrt{\varepsilon q + 3}} \int_{T_I}^{s_{II} - \varepsilon^{-1-m}} ds \exp\left[-\phi\left(\frac{s}{\varepsilon}\right)\right]
= \frac{1}{\sqrt{\varepsilon q + 3}} \int_{T_I}^{s_{II} - \varepsilon^{-1-m}} ds \exp\left[-\phi\left(\frac{s_{II}}{\varepsilon}\right)\right] O\left(\exp\left[-\alpha(1-f)\frac{2\varepsilon}{2} \left(\frac{s}{\varepsilon} - \frac{s_{II}}{\varepsilon}\right)^2\right]\right)
= \frac{\exp[-\phi(\frac{s_{II}}{\varepsilon})]}{\sqrt{\varepsilon q + 2}} O\left(\exp\left[-O\left(\frac{1}{\varepsilon^{2m-1}}\right)\right]\right).
\]

(7.51)

Now, \( \phi \) is a function of \( p(T_I) \) for which we have an explicit asymptotic expression. Using the expansions of Lemma 6.1 we can express \( p(T_I) \) in terms of \( p(T_s) \) (the difference is \( O(\varepsilon |\log \varepsilon|) \)). Applying a Taylor series argument for \( \phi \), we can then compute \( \phi(\frac{s_{II}}{\varepsilon}) \) in terms of \( p(T_s) \). Recalling that \( p(T_s) = \frac{1}{1+\alpha} + O(\varepsilon^q) \) we can arrive at the relation between \( \phi_{lim} \) and \( \phi \) given in (5.7). Plugging this into (7.51) and using the scaling of Theorem 2 gives \( I = O(\frac{1}{\varepsilon^2} \exp[-O(\frac{1}{\varepsilon^{2m-1}})]) \). Bounds for \( E_2, E_3 \) are straightforward and we can conclude \( P(T < t_0) \leq O(\varepsilon^{q-2}) \). \( \Box \)

Now we consider the interval \( [t_0, t_1] \). This interval is where stochastic effects become important and \( v \) diverges from \( \tilde{v} \).

\textbf{Lemma 7.4} If \( \frac{1}{2} < m < \frac{2}{3} \) then outside of a set \( \Omega \) with \( P(\Omega) \leq O(\varepsilon^2) \) we have,

\[
\sup_{t \in [t_0, t_1]} |p(t) - \tilde{p}(t)| < O\left(\varepsilon^{\frac{q+1}{2}}\right)
\]
\[
\sup_{t \in [t_0, t_1]} |v^*(t) - \tilde{v}^*(t)| > O\left(\varepsilon^{\frac{q+1}{2}}\right)
\]

(7.52)

Set,

\[
\Xi_{II} = \sqrt{\frac{1}{\alpha(1-f)^2}} \left(\frac{\exp[-\phi(\frac{s_{II}}{\varepsilon})]}{\sqrt{\nu(T_I)\sqrt{\varepsilon}}}\right)
\]

(7.53)
Then,

$$\Upsilon_1 = \lim_{V \to \infty} \Xi_{11} = \sqrt{\frac{1}{\alpha(1-f)^2}} \exp \left[ \frac{f - \alpha(1-f)}{\alpha} J_I \right] \left( \frac{1 + \alpha}{\alpha f} \right) \frac{1}{k},$$  \hspace{1cm} (7.54)$$

$$v(t_1) = w \left[ \sqrt{2\pi (k+1) \Xi_{11}} \right] \tilde{v}(t_0) (1 + O(\varepsilon^{2-3m})), \hspace{1cm} (7.55)$$

and,

$$\int_{t_0}^{t_1} ds \frac{k+1}{\sqrt{Vv(s)}} = \int_{0}^{t_1} ds \frac{1}{w[s]} (1 + O(\varepsilon^{2-3m})) \hspace{1cm} (7.56)$$

$$\lim_{V \to \infty} \int_{t_0}^{t_1} ds \frac{k+1}{\sqrt{v(s)}} = \int_{0}^{T_{wild}} ds \frac{1}{w[s]} \hspace{1cm} (7.57)$$

**Proof** We first define a stopping time \( T \) as follows,

$$T = t_1 \land \inf \{ t > t_0 : v(t) > \varepsilon^q \text{ or } |v^*(t) - f| \geq \varepsilon^q \}.$$  \hspace{1cm} (7.58)

Let \( z(t) = \frac{p - \bar{p}}{\varepsilon} \) and recall from Lemma 7.3 that \( r = \frac{q+1}{2} \). Then \( dz(t \land T)/dt = -\varepsilon(p + \bar{p})z + O(\varepsilon^r) \) and we have \( z(0) \leq O(\varepsilon^r) \). We can conclude \( |p - \bar{p}| = O(\varepsilon^r) \) for \( t \in [t_0, T] \). A similar argument shows \( |v^* - \bar{v}^*| = O(\varepsilon^r) \) on \([t_0, T]\).

Now we turn to the dynamics of \( v(t \land T) \).

$$dv = v(\phi'(t) + O(\varepsilon^r))dt + \sqrt{\frac{v(k + f + p(t) + O(\varepsilon^q))}{\sqrt{V}}} dB_1 \hspace{1cm} (7.59)$$

Next, we linearize \( \phi'(t) \) and \( \bar{p}(t) \) about \( \frac{5L}{\varepsilon} \). Recall \( \phi'(\frac{5L}{\varepsilon}) = 0 \) and \( \bar{p}(\frac{5L}{\varepsilon}) = (1 - f) \).

$$dv = v \left( \phi'' \left( \frac{5L}{\varepsilon} \right) \left( t - \frac{5L}{\varepsilon} \right) + O \left( \varepsilon^{2(1-m)} \right) \right) dt + \sqrt{\frac{v(k + 1 + O(\varepsilon^{1-m}))}{\sqrt{V}}} dB_1 \hspace{1cm} (7.60)$$

Now we control \( v \) with the same techniques used in Lemma 7.1. Define diffusions \( v_A, v_B \) on the Brownian motion space produced by \( B_1, B_2 \) as follows,

$$dv_A = v \left( \phi'' \left( \frac{5L}{\varepsilon} \right) \left( t - \frac{5L}{\varepsilon} \right) + C \varepsilon^{2(1-m)} \right) dt + \sqrt{\frac{v(k + 1 + O(\varepsilon^{1-m}))}{\sqrt{V}}} dB_1 \hspace{1cm} (7.61)$$
and

\[ dv_B = v \left( \phi'' \left( \frac{SII}{\varepsilon} \right) \left( t - \frac{SII}{\varepsilon} \right) - Ce^{2(1-m)} \right) dt + \sqrt{\frac{v(k+1) + O(\varepsilon^{1-m})}{\mathcal{V}} \, dB_1} \]

(7.62)

where C is an O(1) constant. Then up to time T, \( v_B < v < v_A \). We will show that \( v_B(T) \to v_A(T) \) in distribution and this characterizes \( v(T) \). Consider \( v_A \). We proceed as in Lemma 7.1. First we define,

\[ x_A(t) = \frac{v_A(t)}{\bar{v}(t_0)} \exp \left[ -\phi'' \left( \frac{SII}{\varepsilon} \right) \int_{t_0}^{t} ds \left( s - \frac{SII}{\varepsilon} \right) + Ce^{2(1-m)} \right]. \]  

(7.63)

Then define

\[ w_A(\tau_A(t)) = x_A(t) \]  

(7.64)

with \( \tau_A(t_0) = 0 \) and

\[ \tau'_A(t) = \frac{k + 1 + O(\varepsilon^{1-m})}{\sqrt{\mathcal{V}} \bar{v}(t_0)} \exp \left[ -\phi'' \left( \frac{SII}{\varepsilon} \right) \int_{t_0}^{t} ds \left( s - \frac{SII}{\varepsilon} \right) + Ce^{2(1-m)} \right]. \]  

(7.65)

Under these transformations, \( w_A \) is a weak solution of the following Feller diffusion,

\[ dw_A = \sqrt{w_A} dB_1 \]  

with \( w_A(0) = 1 \). Using (7.63) and (7.64), we find

\[ v_A(t) = w[\tau_A(t)]\bar{v}(t) \left( 1 + O(\varepsilon^{2-3m}) \right), \]  

(7.66)

where we have applied the following relation which follows by Taylor expansion of \( \phi(t) \) about \( \frac{SII}{\varepsilon} \),

\[ \bar{v}_A(t) = \bar{v}(t_0) \exp[\phi(t) - \phi(t_0) + O(\varepsilon^q t)] \]

\[ = \bar{v}(t_0) \exp \left[ \phi'' \left( \frac{SII}{\varepsilon} \right) \int_{t_0}^{t} ds \left( s - \frac{SII}{\varepsilon} \right) + O(\varepsilon^{2-3m}) \right]. \]  

(7.67)

Notice that plugging (7.67) into (7.65) gives

\[ \tau'_A(t) = \frac{k + 1 + O(\varepsilon^{2-3m})}{\sqrt{\mathcal{V}} \bar{v}(t)}, \]  

(7.68)
showing that $\tau_A(t)$ rescales time according to the deterministic population size $\mathcal{V}\bar{v}(t)$. The results for $v_B$ are identical and so we can conclude $v(t \land T) = v_A(t \land T)(1 + O(\varepsilon^{2-3m}))$.

To demonstrate (7.56) we first note

$$
\int_{t_0}^{t_1} ds \frac{k + 1}{\mathcal{V}\bar{v}(s)} = \int_{t_0}^{t_1} ds \frac{(k + 1)(1 + O(\varepsilon^{2-3m}))}{\mathcal{V}w[\tau_A(s)]\bar{v}(s)} = \int_{t_0}^{\tau_A(t_1)} \frac{1 + O(\varepsilon^{2-3m})}{w[s]} ds, \quad (7.69)
$$

where the first equality follows from (7.66) and the second equality follows from applying the transform $s \rightarrow \tau(s)$ and noting (7.68). We have left the task of determining $\tau_A(t_1)$ and $\tau_A(t_0)$. Trivially $\tau_A(t_0) = 0$. Integrating (7.65) and applying (7.67) with $t$ set to $T$ gives the following,

$$
\tau_A(t_1) = \left( \frac{k + 1}{\mathcal{V}\bar{v}(T)} \right) \int_{t_0}^{t_1} ds \exp \left[ - \phi'' \left( \frac{3II}{\varepsilon} \right) \int ds' \left( \frac{I}{\varepsilon} + O(\varepsilon^{2-3m}) \right) \right]
$$

$$
= \left( \frac{k + 1}{\mathcal{V}\bar{v}(T)} \right) \sqrt{\varepsilon(1-f)^2} \left( t_1 - \frac{3II}{\varepsilon} \right) \int_{t_0}^{t_1} ds \exp \left[ - \frac{s^2}{2} \right] \left( 1 + O(\varepsilon^{2-3m}) \right).
$$

$$
= \sqrt{\frac{2\pi}{\mathcal{V}\bar{v}(T)}} \sqrt{\varepsilon(1-f)^2} \left( t_1 - \frac{3II}{\varepsilon} \right) \left( 1 + O(\varepsilon^{2-3m}) \right). \quad (7.70)
$$

where the last equality is achieved by noting that $\sqrt{\varepsilon(t_1 - 3II/\varepsilon)} = O\left( \frac{1}{\sqrt{\varepsilon}} \right)$ and similarly for $\sqrt{\varepsilon(t_0 - 3II/\varepsilon)}$. Plugging (7.70) into (7.69) and applying a straightforward rescaling gives (7.56). Equation (7.57) now follows by noting $\lim_{\mathcal{V} \rightarrow \infty} \sqrt{2\pi}(k + 1)\mathcal{Z}_{III} = T_{\text{wild}}$. Equation (7.55) follows from (7.70) and (7.66).

As described in the proof of Lemma 7.3, a Taylor series argument on $\phi$ using the expansions for $\tilde{p}$ developed in Lemma 6.1 allows us to derive (5.7). Using this formula and our scaling for $\varepsilon$ gives (7.54).

Now we eliminate the $T$ dependence of our result. Through a Chebyshev inequality we have

$$
P\left( \sup_{t \in [t_0, T]} v_A(t) > \varepsilon^q \right) \leq P\left( w[\tau(t)] > \frac{\varepsilon^q}{\mathcal{V}(t_0)} \right)
$$

$$
\leq \int P\left( w[\tau(t)] > O\left( \exp \left[ -O\left( \frac{1}{\varepsilon^m} \right) \right] \right) \right) \leq O(\varepsilon^2).
$$

$$
(7.71)
$$

Finally assuming that $v(t_1) \neq 0$, we consider the dynamics of $v$ on $[t_1, T_{III}]$.
Lemma 7.5 Assume $v(t_1) = \eta v(t_0)$ for some $\eta > 0$. Then for $t \in [t_1, T_{II}]$ outside a set $\Omega$ with $P(\Omega) < \varepsilon^{q-2}$ we have,

$$|v^*(t) - f| \leq O \left( \varepsilon^{\frac{q+1}{2}} \right)$$  \hspace{1cm} (7.72)

$$p(T_{II}) = \bar{p}(\bar{T}_{II}) - \varepsilon \alpha \frac{\bar{p}^2(\bar{T}_{II})}{1 - f - \bar{p}(T_{II})} \log \eta + O(\varepsilon^2).$$ \hspace{1cm} (7.73)

Proof After time $t_1$ the system returns to deterministic behavior. By the same arguments used in Lemma 7.3 we have,

$$|v^*(t) - \bar{v}^*_1(t)| \leq \varepsilon^{\frac{q+1}{2}}$$  \hspace{1cm} (7.74)

$$|p(t) - \bar{p}_1(t)| \leq \varepsilon^{\frac{q+1}{2}}. $$  \hspace{1cm} (7.75)

In Lemma 7.3 we showed that in $[T_I, t_0]$, $v$ is well approximated by $\bar{v}$. The same holds in $[t_1, T_{II}]$, except that now we must restart the deterministic system so that $\bar{v}(t_1) = v(t_1)$. With this in mind we can apply the arguments of Lemma 7.3 to justify the following relation.

$$v(t) = \eta v(t_1) \exp \left[ \phi(t) - \phi(t_1) + O(\varepsilon^{\frac{q+1}{2}}) \right]$$ \hspace{1cm} (7.76)

Then if we use the arguments of Lemma 7.3 in which we prove $|v - \bar{v}| \leq \varepsilon \bar{v}$ we can argue as follows,

$$v(t) = \eta \bar{v}(t)(1 + O(\varepsilon)) \exp[-(\phi(t_1) - \phi(t_0))]
= \eta \bar{v}(t)(1 + O(\varepsilon)) \exp[-(\phi''(s_{II})(t_1 - s_{II})^2 - (s_{II} - t_0)^2)]
+ O(\bar{v}''(s_{II})(t_1 - t_0)^3]
= \eta \bar{v}(t)(1 + O(\varepsilon^{2-3m}))$$ \hspace{1cm} (7.77)

Now we consider $T_{II}$ in comparison to $\bar{T}_{II}$. Perturbing off of $\bar{T}_{II}$ gives,

$$v(\bar{T}_{II} + \Delta t)
= \eta \bar{v}(\bar{T}_{II})(1 + O(\varepsilon^{2-3m})) \exp \left[(1 - f)\Delta t - \frac{1}{\alpha \varepsilon} \log(1 + \alpha \varepsilon \bar{p}(\bar{T}_{II}))\Delta t \right]$$ \hspace{1cm} (7.78)

A Taylor expansion on $\Delta t$ leads to

$$v(\bar{T}_{II} + \Delta t) = \eta \bar{v}(\bar{T}_{II})(1 + O(\varepsilon^{2-3k})) \exp[(1 - f)\Delta t - \bar{p}(\bar{T}_{II})\Delta t + O(\Delta t^2)]$$ \hspace{1cm} (7.79)
We want to find \( \Delta t \) such that \( v(\overline{T}_{II} + \Delta t) = \varepsilon^q \) since then we will have \( T_{II} = \overline{T}_{II} + \Delta t \). Solving using (7.79) gives,

\[
\Delta t = \left( \frac{1}{\delta(T_{II})} \right) \log \eta + O(\varepsilon^2) \tag{7.80}
\]

Our main interest in determining \( T_{II} \) is our need to compute an expansion for \( p(T_{II}) \). We have,

\[
p(T_{II}) = \tilde{p}(\overline{T}_{II}) + \tilde{p}'(\overline{T}_{II}) \frac{\Delta t}{\varepsilon} + O(\varepsilon^2)
\]

\[
= \tilde{p}(\overline{T}_{II}) - \varepsilon \alpha \frac{p^2(\overline{T}_{II})}{\delta(\overline{T}_{II})} \log \eta + O(\varepsilon^2) \tag{7.81}
\]

\[\square\]

7.4 Stage IV

Stage IV is similar to stage II. As in stage II, using Lemmas 6.3 and 7.2 we have outside of a set of vanishing probability \(|v(T_{III}) - (1 - p(T_{III}))| = O(\varepsilon)\) and \(\delta(T_{III}) < 0\).

On \([T_{III}, T_{IV}]\), we have \(dv^*(t)/dt \approx v^*(f - (1 - p))\). We set \(\psi(t) = \int_{T_{III}}^{t} ds \tilde{p}(s) - (1 - f)\). Then \(\psi\) has a single critical point which we label \(s_{IV}^*\). In stage II we define \(t_0 = \frac{2\mu}{\varepsilon} - \frac{1}{\varepsilon^m}\) and \(t_1 = \frac{2\mu}{\varepsilon} + \frac{1}{\varepsilon^m}\). In this section, for stage IV we define \(t_0^* = \frac{2\mu}{\varepsilon} - \frac{1}{\varepsilon^m}\) and \(t_1^* = \frac{2\mu}{\varepsilon} + \frac{1}{\varepsilon^m}\).

The proofs of stage IV are almost identical to those of stage II. We simply state the analogues of the stage II lemmas since the proofs follow identical arguments. In Lemma 7.7 we only keep \(O(1)\) terms for the \(p(T_{IV})\) because we do not need \(O(\varepsilon)\) accuracy after the first cycle.

**Lemma 7.6** Outside of a set \(\Omega\) such that \(P(\Omega) \leq O(\varepsilon^2)\) we have for any \(t \in [T_{III}, t_0^*]\),

\[
|v(t) - \tilde{v}(t)| \leq \varepsilon^{\frac{q+1}{2}}. \tag{7.82}
\]

\[
|v^*(t) - \tilde{v}^*(t)| \leq \varepsilon v^*(t) \tag{7.83}
\]

\[
|p(t) - \tilde{p}(t)| \leq \varepsilon^{\frac{q+1}{2}}. \tag{7.84}
\]

**Lemma 7.7** Suppose \(v^*(t_0^*) = \eta v^*(t_0^*)\). Then for \(t \in [t_1, T_{IV}]\),

\[
|v(t) - (1 - p(t))| \leq O(\varepsilon) \tag{7.85}
\]

\[
p(T_{IV}) = \tilde{p}(\overline{T}_{IV}) + O(\varepsilon)
\]

Now we turn to the analogue of Lemma 7.4. The arguments are essentially the same, but we consider \(\psi\) instead of \(\phi\). We have,
\[ s_{IV} = \varepsilon T_{III} + \log \left[ \frac{(1 - f)(1 - (1 + \alpha)p(T_{III}))}{(f - \alpha(1 - f))p(T_{III})} \right], \]

\[ \psi \left( \frac{s_{IV}}{\varepsilon} \right) = \frac{1}{\varepsilon} \left[ \frac{1}{1 + \alpha} \log \left( \frac{1 - (1 + \alpha)p(T_{III})}{f - \alpha(1 - f)} \right) - (1 - f) \log \left( \frac{(1 - f)(1 - (1 + \alpha)p(T_{III}))}{(f - \alpha(1 - f))p(T_{III})} \right) \right], \]

(7.86)

\[ \psi'' \left( \frac{s_{IV}}{\varepsilon} \right) = \varepsilon(f - \alpha(1 - f)) + O(\varepsilon^2). \]

\[ \psi''' \left( \frac{s_{IV}}{\varepsilon} \right) = O(\varepsilon^2). \]

Then the analogue to Lemma 7.4 is the following result. We do not need the expression \( \int_{t_0}^{t_1} ds \frac{1}{\sqrt{v^*(s)}} \) because the lineages of the mutant type must coalesce to the original mutant cell by time zero.

**Lemma 7.8** If \( \frac{1}{2} < m < \frac{2}{3} \) then outside of a set \( \Omega \) with \( P(\Omega) \leq O(\varepsilon^2) \) we have,

\[
\sup_{t \in [t_0, t_1]} |p(t) - \bar{p}(t)| < O \left( \varepsilon^{\frac{q+1}{2}} \right) \tag{7.87}
\]

\[
\sup_{t \in [t_0, t_1]} |v^*(t) - \bar{v}^*(t)| > O \left( \varepsilon^{-\frac{q+1}{2}} \right)
\]

Set,

\[
\Xi_{IV} = \sqrt{\frac{1}{(f - \alpha(1 - f))} \left( \exp \left[ -\psi \left( \frac{s_{IV}}{\varepsilon} \right) \right] \right) \frac{\sqrt{\psi(T_{III})}}{\sqrt{\varepsilon}}} \tag{7.88}
\]

Then,

\[
\Upsilon_2 = \lim_{\mathcal{V} \to \infty} \Xi_{IV}
\]

\[
\begin{aligned}
&= \sqrt{\frac{1}{(f - \alpha(1 - f))} \exp \left[ \frac{(f - \alpha(1 - f))(J_I + J_{III}) + \alpha(1 - f)J_{III}H_{II}}{\alpha H_{II}} \right]}
\times \left( \frac{1 + \alpha(1 + H_{II})}{(1 + \alpha)\alpha(1 + H_{II})} \right)^{\frac{1}{\eta_{II}}} \left( \frac{1}{\kappa} \right) \tag{7.89}
\end{aligned}
\]

(recall the definition of \( \eta_{II} \) in (3.12) from Theorem 2),

\[
v^*(t_1) = w \left[ \sqrt{2\pi}(k^* + f) \Xi_{IV} \right] \bar{v}^*(t_0)(1 + O(\varepsilon^{2-3m})) \tag{7.90}
\]

The expression \( \eta_{II} \) in (7.89) requires explanation. If the wild type is not lost, then it experiences a stochastic perturbation in stage II. As Lemmas 7.4 and 7.5 show, this perturbation is \( O(1) \) and influences \( p(T_{II}) \) by \( O(\varepsilon) \). The \( O(\varepsilon) \) perturbation on \( p(T_{II}) \) is integrated over stage IV which is of duration \( O(\frac{1}{\varepsilon}) \) and so the perturbation has an
$O(1)$ effect on $v^*$ during stage IV. When we expand $\psi$ in Taylor series to obtain an expansion in terms of $\psi_{\text{lim}}$, the $O(\epsilon)$ term in (7.73) in Lemma 7.5 is responsible for $\eta_{III}$.

Acknowledgments
I thank two anonymous reviewers for numerous comments that greatly improved the quality of this work.

Appendix

Here, we explain the rescaling of Sect. 2 precisely. We introduce constants $V$, $P$, $T$ for the units of infected cells, CD8 cells, and time, respectively, and define the variables $\tilde{v}$, $v^*$, $\tilde{p}$ by setting

$$
\tilde{v}(\tilde{t}) = \frac{v(T\tilde{t})}{V}, \quad v^*(\tilde{t}) = \frac{v^*(T\tilde{t})}{V}, \quad \tilde{p}(\tilde{t}) = \frac{p(T\tilde{t})}{P}, \quad \tilde{t} = \frac{t}{T}.
$$

(A.1)

We can then approximate the birth–death process through the following SDE.

$$
d\tilde{v} = T\tilde{v}(\Delta k - cV(\tilde{v} + v^*) - aP\tilde{p})d\tilde{t} + \sqrt{\tilde{v}T(k + cV(\tilde{v} + v^*) + aP\tilde{p})}dB_1(\tilde{t}),
$$

(A.2)

$$
d\tilde{v}^* = T\tilde{v}^*(\Delta k^* - cV(\tilde{v} + v^*))d\tilde{t} + \sqrt{\tilde{v}^*T(k^* + cV(\tilde{v} + v^*))}dB_2(\tilde{t}),
$$

$$
d\tilde{p} = T\tilde{p}(bV\tilde{v} - dP\tilde{p})d\tilde{t} + \sqrt{\tilde{p}T(h + bV\tilde{v} + dP\tilde{p})}dB_3(\tilde{t}).
$$

We choose $T$, $V$, and $P$ so that $\Delta kT = 1$, $cVT = 1$, and $aPT = 1$. Plugging this into (A.2) gives

$$
d\tilde{v} = \tilde{v}(1 - (\tilde{v} + v^*) - \tilde{p})d\tilde{t} + \sqrt{\tilde{v}(\tilde{k} + (\tilde{v} + v^*) + \tilde{p})}dB_1(\tilde{t}),
$$

(A.3)

where,

$$
\tilde{k} = \frac{k}{\Delta k}, \quad \tilde{k}^* = \frac{k^*}{\Delta k}, \quad \epsilon = \frac{b}{c}, \quad \alpha = \frac{dc}{ab}.
$$

(A.4)

We assume that the coefficients in (A.3) are all $O(1)$. This will be true if $V$, $P$ are on the order of the infected cell and CTL population counts and the system is assumed
to vary on that scale. We now drop the tildes and, for simplicity, the variance terms in the \( \tilde{p} \) equation. This gives (2.1).

**References**

Althaus C, de Boer R (2008) Dynamics of immune escape during HIV/SIV infection. PLOS Comput Biol 4(7):1–10

Athreya K, Ney P (1972) Branching processes. Dover Publications, NY

Bhattacharya T et al (2007) Founder effects in the assessment of HIV polymorphisms and HLA allele associations. Science 315:1583–1586

Crandal K (1999) The evolution of HIV. Johns Hopkins Press, Baltimore

DeFranco A, Locksley R, Robertson M (2007) Immunity: the immune response in infectious and inflammatory disease. New Science Press, USA

Delport W et al (2008) Frequent toggling between alternative amino acids is driven by selection in hiv-1. PLOS Pathog 4(12):1–13

Durrett R (2002) Probability models for DNA sequence evolution. Springer, Berlin

Emimi E (2002) The human immunodeficiency virus: biology, immunology, and therapy. Princeton University Press, NJ

Frahm N et al (2006) Control of HIV replication by CTL targeting subdominant epitopes. Nat Immunol 7(2):173–178

Goulder P, Watkins D (2008) Impact of MHC class I diversity on immune control of HIV replication. Nat Rev 8:619–629

Hartl D, Clark A (1997) Principles of population genetics, 3rd edn. Sinauer Associates, Sunderland

Ho D et al (1995) Rapid turnover of plasma virions and CD4 lymphocytes in HIV-1 infection. Nature 373:123–126

Karatzas I, Shreve S (1991) Brownian motion and stochastic calculus. Springer, Berlin

Kouyos R et al (2006) Stochastic or deterministic: what is the effective population size of hiv-1. Trends Microbiol 14(12):507–511

Kurtz T (1981) Approximation of population processes. In: 36, CBMS-NSF regional conference series in applied mathematics

Leigh-Brown A (1997) Analysis of HIV-1 env gene sequences reveals evidence for a low effective number in the viral population. PNAS 94:1862–1865

Leslie A et al (2005) Transmission and accumulation of CTL escape variants drive negative association between HIV and HLA. J Exp Med 201(6):891–902

Ngumbela K et al (2008) Targeting of a CD8 T cell env epitope presented by HLA-B*5802 is associated with markers of HIV disease progression and lack of selection pressure. AIDS Res Hum Retrovir 24(1):72–82

Nowak M, May R (2000) Virus dynamics: mathematical principles of immunology and virology. Oxford University Press, Oxford

Perelson A (2002) Modeling viral and immune system dynamics. Nat Rev 2:28–36

Rousseau C et al (2008) Hla class I-driven evolution of HIV type I subtype c proteome: immune escape and viral load. J Virol 82(13):6434–6446

Rouzine I, Coffin J (1999) Linkage disequilibrium test implies a large effective population number for HIV in-vivo. PNAS 96:10758–10763

Tavare S (2001) Ancestral inference in population genetics. St Flour probability summer school lecture notes. Springer, Berlin

Wakeley J, Sargsyan O (2009) The conditional ancestral selection graph with strong balancing selection. Theor Popul Biol 75:355–364