

# MULLER'S RATCHET WITH COMPENSATORY MUTATIONS

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We consider an infinite dimensional system of stochastic differential equations which describes the evolution of type frequencies in a large population. Random reproduction is modeled by a Wright-Fisher noise whose inverse diffusion coefficient  $N$  corresponds to the total population size. The type of an individual is the number  $k$  of deleterious mutations it carries. We assume that fitness of individuals carrying  $k$  mutations is decreased by  $\alpha k$  for some  $\alpha > 0$ . Along the individual lines of descent, (new) mutations accumulate at rate  $\lambda$  per generation, and each of these mutations has a small probability  $\gamma$  per generation to disappear. While the case  $\gamma = 0$  is known as (the Fleming-Viot version of) *Muller's ratchet*, the case  $\gamma > 0$  is referred to as that of *compensatory mutations* in the biological literature. In the former case ( $\gamma = 0$ ), an ever increasing number of mutations is accumulated over time, while in the latter ( $\gamma > 0$ ) this is prevented by the compensatory mutations which in this sense *halt the ratchet*. We show that the system under consideration ( $\gamma \geq 0$ ) has a unique weak solution. For  $N = \infty$ , we obtain the solution in a closed form by analyzing a probabilistic particle system that represents this solution. In particular, we show that the unique equilibrium state in the case  $\gamma > 0$  and  $N = \infty$  is the Poisson distribution with parameter  $\lambda/(\gamma + \alpha)$ .

**1. Introduction and outline.** Our objective is the study of a system of a multitype Wright-Fisher SDE (or *Fleming-Viot process*) of the form

$$(*) \quad dX_k = \left( \alpha \left( \sum_{\ell=0}^{\infty} (\ell - k) X_{\ell} \right) X_k + \lambda (X_{k-1} - X_k) + \gamma ((k+1)X_{k+1} - kX_k) \right) dt + \sum_{\ell \neq k} \sqrt{\frac{1}{N} X_k X_{\ell}} dW_{k\ell},$$

for  $k = 0, 1, \dots$  with  $X_{-1} := 0$  and  $\sum_{k=0}^{\infty} X_k = 1$ . Here  $\alpha$ ,  $\lambda$  and  $\gamma$  are (small) non-negative constants,  $N$  is a (large) number (or equals infinity in which

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case the last term on the r.h.s of (\*) vanishes), and  $(W_{k\ell})_{k>\ell}$  is a family of independent Brownian motions with  $W_{k\ell} = -W_{\ell k}$ .

The interest in this system comes from population genetics (see Section 2 for some background). The equations (\*) provide a diffusion approximation of the evolution of the *type frequencies*  $X_k$ ,  $k \in \mathbb{N}_0$  in a population consisting of a large number  $N$  of individuals evolving in discrete time. The type  $k$  of an individual is given by the number of deleterious mutations it carries. Briefly, the *fitness* (which is proportional to the average number of offspring) of a type- $k$  individual is proportional to  $(1 - \alpha)^k$ , which is approximately  $1 - \alpha k$  for small  $\alpha > 0$ , termed the *selection coefficient*. The parameter  $\lambda$  is the expected number of additional mutations accumulating per individual and generation, and for each of the mutations present,  $\gamma$  is the probability that this mutation disappears in one generation.

In this work we will not be concerned with proving the convergence of the discrete-generation dynamics to the diffusion approximation. Still, in Section 3.3 we will use the discrete generation scheme as just described in order to present a few simulation results which illustrate how certain functionals of the solution of (\*) (in particular the mean and the variance of the probability vector  $(X_k)_{k=0,1,2,\dots}$ ) depend on the model parameters.

Theorem 1 in Section 3.1 states that (\*) has a unique weak solution. Note that (\*) is an infinite dimensional SDE with an *unbounded non-linear drift coefficient*. Related existence and uniqueness results were obtained by Ethier and Shiga (2000). However, these authors only cover the case of parent-independent mutation and not the situation of (\*).

Theorem 2 in Section 3.2 gives the explicit solution of (\*) in the (deterministic) case  $N = \infty$ . This extends results from Haigh (1978) and Etheridge et al. (2008) for the case  $\gamma = 0$ . In particular, we show that the Poisson weights with parameter  $\lambda/(\gamma + \alpha)$  constitute the only equilibrium state of (\*) for  $N = \infty$ . The proofs of Theorems 1 and 2 are given in Sections 4 and 5, respectively. An essential step in the proof of Theorem 2 is Proposition 5.2 which in the case  $N = \infty$  provides the solution of (\*) in terms of a probabilistic particle system.

**2. History and background of the model.** For  $\gamma = 0$ , the system (\*) is known as (the Fleming-Viot version of) Muller's ratchet, a population genetic model introduced by Hermann Muller (1964): A clonal population of fixed size reproduces randomly. Each individual carries a number of mutations, all of which are assumed to be deleterious. Fitness decreases linearly with the number of mutations. The offspring of an individual has a small chance to gain a new deleterious mutation. In particular, offspring of an

individual has at least as many mutations as the parent and mutation is an irreversible process. Hence, eventually the ratchet will *click* in the sense that the so far fittest type will irreversibly disappear from the population. In this way, the mutation process drives the population to a larger number of deleterious mutations while selection acts in the opposite direction, leading to a form of mutation-selection quasi-balance. Gabriel et al. (1993) consider a related model of a clonally reproducing population in which the evolution of the population size is coupled with the mean fitness of the population, eventually leading to extinction of the population. The prediction of this *mutational meltdown* requires information on the rate at which deleterious mutations accumulate in the population (Loewe, 2006), i.e. on the *rate of Muller's ratchet*.

Various quantitative treatments of Muller's ratchet have been given (Haigh, 1978; Stephan et al., 1993; Gessler, 1995; Higgs and Woodcock, 1995; Gordo and Charlesworth, 2000; Maia et al., 2003; Rouzine et al., 2003; Etheridge et al., 2008; Jain, 2008; Waxman and Loewe, 2010; Audiffren and Pardoux, 2011). The most interesting question concerns the rate of Muller's ratchet. This has so far only been studied by simulations, or approximations which seem ad hoc.

We study an extension of Muller's ratchet where deleterious mutations are allowed to be compensated by (back-)mutations. It is important to note that such *compensatory mutations* are different from *beneficial mutations*, although both increase the fitness of an individual. In our model, compensatory mutations can only remove the effects of previously gained deleterious mutations. In contrast to this, beneficial mutations are usually assumed to have an effect that does not depend on the genetic background.

The possibility of compensatory mutations was discussed already by Haigh (1978) (see also Maynard Smith, 1978). He argued that they rarely occur in realistic parameter ranges, because the deleterious mutation rate is proportional to the full length of the genome of a clonally reproducing individual, while the compensatory mutation rate scales with the length of a single base within the full genome. Therefore, he concluded that compensatory mutations are too rare to halt the accumulation of deleterious mutations in realistic parameter ranges. However, when several deleterious mutations are gained, the total rate of accumulation of deleterious mutations increases and may therefore halt the ratchet. An equilibrium is approached where a certain number of deleterious mutations is fixed. If this number is large enough, these may lead to extinction of the population. While Antezana and Hudson (1997) argue that the effects of compensatory mutations can be an important factor for small viruses, Loewe (2006) concludes that com-

pensatory mutations are still too rare to halt the mutational meltdown of human mitochondria.

Clearly, the relevance of compensatory mutations is greatest for species with a short genome and a high mutation rate. One of the most extreme groups in these respects are RNA viruses (for which the genome length is of the order of  $10^3$  to  $10^4$  bases and the per base mutation rate is around  $10^{-5}$  to  $10^{-4}$ ). As discussed in Chao (1990), back mutations can hardly stop Muller's ratchet even in this case. We will come back to this numerical example in Section 3.3 below.

The relevance of Muller's ratchet with compensatory mutations is supported by the fact that deleterious mutations might be compensated not only by back mutations at the same genomic position. As discussed by Wagner and Gabriel (1990), restoring the function of a gene which was subject to a mutation is as well possible by mutating a second site within the gene or at another gene. Maisnier-Patin and Andersson (2004) give the following generalizations of (single-base) compensatory mutations: (i) point mutations which restore the RNA secondary structure of a gene or the protein structure, (ii) an up-regulation of gene expression of the mutated gene, (iii) a mutation in another gene restoring the structure of a multi-unit protein complex and (iv) a bypass mechanism where the function of the mutated is taken over by another gene.

Various examples give clear evidence for the existence of compensatory mutations. It has been shown by Poon and Chao (2005) that a deleterious mutation in the DNA bacteriophage phiX174 can be compensated by about nine different intragenic compensatory mutations. This implies that the rate of compensatory mutations can be high enough to halt accumulation of deleterious mutations under realistic scenarios. In fact, compensatory mutations have been observed in various species. Howe and Denver (2008) showed that deletions in protein-coding regions of the mitochondrial genome in *Caenorhabditis briggsae* lead to heteroplasmy, a severe factor in mitochondrial diseases. They also found compensatory mutations leading to a decrease in heteroplasmy. Mutations for antibiotic resistance of bacteria are known to be deleterious in a wild-type population. Fitness can be increased by a compensatory mutation (see e.g. Handel et al., 2006). Plastid genomes of mosses are studied in Depperschmidt et al. (2011). Here, deleterious mutations are compensated by RNA editing, a mechanism by which the base *C* in DNA is transcribed to *U* on the level of RNA for specific bases in the genome.

All these examples indicate that the role of compensatory mutations should be taken into account. A relevant question to be addressed in fu-

ture research is which parameter constellations (of the selection coefficient, the mutation rate, the compensatory mutation rate and the population size) can halt the ratchet before the mutational meltdown leads to extinction of the population.

**3. Results.** We show that for finite  $N$  the system  $(*)$  has a unique weak solution (Theorem 1). For the system  $(*)$  without noise (i.e. the case  $N = \infty$ ) we provide in Theorem 2 the explicit form of the solution as well as the equilibrium state. For this we use a stochastic particle model (including accumulation and loss of mutations, as well as a state-dependent death rate of the particles) and show in Proposition 5.2 that a solution of  $(*)$  with  $N = \infty$  is given by the distribution of the particle model conditioned on non-extinction. After stating the theorems, we compare in Section 3.3 the cases of large  $N$  with the theoretical considerations for  $N = \infty$  using simulations.

**3.1. Existence and uniqueness.** The system  $(*)$  of Muller's ratchet with compensatory mutations takes values in the space of probability vectors indexed by  $\mathbb{N}_0$ , i.e. sequences whose entries are probability weights on  $\mathbb{N}_0$ . We restrict the state space to the subset of probability vectors with finite exponential moment of a certain order, and show uniqueness in this space. Throughout, we abbreviate  $\underline{x} := (x_0, x_1, \dots) \in \mathbb{R}_+^{\mathbb{N}_0}$ .

**DEFINITION 3.1 (Simplex).** *The infinite-dimensional simplex is given by*

$$(3.1) \quad \mathbb{S} := \left\{ \underline{x} \in \mathbb{R}_+^{\mathbb{N}_0} : \sum_{k=0}^{\infty} x_k = 1 \right\}.$$

Moreover, for  $\xi > 0$ , set

$$(3.2) \quad h_{\xi}(\underline{x}) := \sum_{k=0}^{\infty} x_k e^{\xi k}$$

and consider elements of  $\mathbb{S}$  with  $\xi$ th exponential moment, forming the space

$$(3.3) \quad \mathbb{S}_{\xi} := \{ \underline{x} \in \mathbb{S} : h_{\xi}(\underline{x}) < \infty \}.$$

**REMARK 3.2 (Topology on  $\mathbb{S}_{\xi}$ ).** We note that

$$(3.4) \quad r(\underline{x}, \underline{y}) := \sum_{k=0}^{\infty} e^{\xi k} |x_k - y_k|, \quad \underline{x}, \underline{y} \in \mathbb{S}_{\xi},$$

defines a complete and separable metric on  $\mathbb{S}_{\xi}$ .

**THEOREM 1** (Well-posedness of Fleming-Viot system). *Let  $\underline{x} \in \mathbb{S}_\xi$  for some  $\xi > 0$ . Then, for  $N \in (0, \infty)$ ,  $\alpha, \lambda, \gamma \in [0, \infty)$ , the system (\*) starting in  $\underline{X}(0) = \underline{x}$  has a unique  $\mathbb{S}$ -valued weak solution  $\mathcal{X} = (\underline{X}(t))_{t \geq 0}$ , taking values in the space  $\mathcal{C}_{\mathbb{S}_\xi}([0, \infty))$  of continuous functions on  $\mathbb{S}_\xi$ . The process  $\mathcal{X}$  is referred to as Muller's ratchet with compensatory mutations with selection coefficient  $\alpha$ , mutation rate  $\lambda$ , compensatory mutation rate  $\gamma$  and population size  $N$ .*

**REMARK 3.3** (Population size  $N$ ). Resampling models are usually studied either for a finite population of constant size  $N$  (e.g. using a Wright-Fisher model), or in the large population limit with a suitable rescaling of time, leading to Fleming-Viot processes. For a bounded fitness function and a compact type space, it is well known that a sequence of (discrete time) Wright-Fisher processes, indexed by  $N$ , converges weakly to a Fleming-Viot process (or Wright-Fisher diffusion) if the selection and mutation coefficients are scaled down by  $N$  and one unit of time is taken as  $N$  generations; see e.g. Ethier and Kurtz (1993). In our situation it may thus be expected (though we do not prove this claim here) that for large  $N$  and for  $\alpha N$ ,  $\lambda N$  and  $\gamma N$  of order one, the Wright-Fisher process described in Section 3.3, run with a time unit of  $N$  generations, is close to the solution of (\*), with 1 instead of  $\sqrt{1/N}$  as the coefficient of the noise, and  $\alpha N$ ,  $\lambda N$  and  $\gamma N$  in place of  $\alpha$ ,  $\lambda$  and  $\gamma$ . (Note that we do not prove this claim here.) However, this system is (\*) with time speeded up by a factor  $N$ . In other words, for large  $N$ , and  $\alpha N$ ,  $\lambda N$  and  $\gamma N$  of order one, the solution of (\*) should be close to the corresponding Wright-Fisher model as introduced in Section 3.3, with time unit being one generation. This is the reason why we refer to the model parameter  $N$  in (\*) as the population size. We use this terminology in interpreting the simulation results for the Wright-Fisher model in Section 3.3.

**REMARK 3.4** (Connection to previous work for  $\gamma = 0$ ). For the case  $\mu = 0$ , variants of Theorem 1 appear in Cuthbertson (2007) and in Audiffren and Pardoux (2011). The latter makes (in the terminology of our Theorem 1) the special choice  $\xi = \alpha N$  and refers to Audiffren (2011) for the proof. Cuthbertson (2007) treats also the case of  $\alpha < 0$ , assuming the existence of all exponential moments of the initial state.

**REMARK 3.5** (Strategy of the proof of Theorem 1). For  $\alpha = 0$ , it follows from classical theory (Dawson, 1993, Theorem 5.4.1) that (\*) has a unique weak solution. The same is true if the selection term  $\alpha(\sum_{\ell=0}^{\infty}(\ell - k)X_\ell)X_k$  is replaced by a bounded function of  $\underline{X}$ . This can be shown by a Girsanov change of measure from the case  $\alpha = 0$ , an idea going back to Dawson (1978)

in the measure-valued context. So, the main difficulty in the proof is to deal with the unbounded selection term. This is overcome by showing that the change of measure still works when using  $\mathbb{S}_\xi$  as the state space for  $\mathcal{X}$ .

**3.2. The case  $N = \infty$ .** This case (which is not included in Theorem 1) leads to a deterministic dynamics. For  $\gamma = 0$ , Haigh (1978) was the first to obtain results on the deterministic evolution of  $\mathcal{X}$  in a discrete time setting. These results were later refined by Maia et al. (2003). Here, we work with continuous time, and our next theorem generalizes Proposition 4.1 in Etheridge et al. (2008) to the case  $\gamma > 0$ . We are dealing with the system

$$(3.5) \quad \dot{x}_k = \alpha \left( \sum_{\ell=0}^{\infty} (\ell - k) x_\ell \right) x_k + \lambda (x_{k-1} - x_k) + \gamma ((k+1)x_{k+1} - kx_k)$$

for  $k = 0, 1, 2, \dots$  with  $x_{-1} := 0$  and  $\sum_{k=0}^{\infty} x_k = 1$ .

**THEOREM 2.** *Let  $\alpha, \lambda, \gamma \in [0, \infty)$  and  $\underline{x}(0) \in \mathbb{S}_\xi$  for some  $\xi > 0$ . Then, the system (3.5) has a unique  $\mathbb{S}$ -valued solution  $(\underline{x}(t))_{t \geq 0}$  which takes values in  $\mathbb{S}_\xi$ . It is given by*

$$(3.6) \quad x_k(t) = \frac{\sum_{i=0}^{\infty} x_i(0) \sum_{j=0}^{i \wedge k} \binom{i}{j} \left( \frac{\gamma(1-e^{-(\alpha+\gamma)t})}{\alpha+\gamma} \right)^{i-j} e^{-j(\alpha+\gamma)t} \frac{1}{(k-j)!} \left( \frac{\lambda(1-e^{-(\alpha+\gamma)t})}{\alpha+\gamma} \right)^{k-j}}{\sum_{i=0}^{\infty} x_i(0) \left( \frac{\gamma}{\alpha+\gamma} - \frac{\alpha}{\alpha+\gamma} e^{-(\alpha+\gamma)t} \right)^i \cdot \exp \left( \frac{\lambda}{\alpha+\gamma} (1 - e^{-(\alpha+\gamma)t}) \right)}.$$

In particular, if either  $\gamma > 0$  or  $x_0(0) > 0$ , then

$$(3.7) \quad x_k(t) \xrightarrow{t \rightarrow \infty} \frac{e^{-\lambda/(\alpha+\gamma)}}{k!} \cdot \left( \frac{\lambda}{\alpha+\gamma} \right)^k, \quad k = 0, 1, 2, \dots$$

i.e. the limiting state is the vector of Poisson weights with parameter  $\lambda/(\alpha+\gamma)$ .

**REMARK 3.6 (Equilibria).** In the case  $\gamma = 0$  it is known already from the work of Haigh (1978) that the vector of Poisson weights with parameter  $\lambda/\alpha$  is an equilibrium state. Moreover, Poisson states which are shifted by  $k = 1, 2, \dots$  are equilibria as well. This is in contrast to  $\gamma > 0$  where only a single equilibrium state exists. Moreover, this equilibrium state depends on the model parameters only through  $\lambda/(\alpha+\gamma)$ . This is surprising since the dynamics of the process is much different for different combinations of  $\lambda, \alpha$  and  $\gamma$  with the same value of  $\lambda/(\alpha+\gamma)$ . See Figure 3 for a simulation study of this feature for  $N < \infty$ .

REMARK 3.7 (Connection to the rate of adaptation). Although the strategy of our proof requires that  $\alpha \geq 0$  (i.e. the mutations are deleterious), it can be shown by taking the time-derivative of the right hand side of (3.6) that this equation is a solution for  $\alpha < 0$  as well. This model is frequently termed *rate of adaptation* and has gained some interest in the case  $\gamma = 0$  and  $N < \infty$  (Gerrish and Lenski, 1998; Desai and Fisher, 2007; Park and Krug, 2007; Yu et al., 2010).

Taking  $\alpha < 0$  in our model, all mutations are beneficial and  $\gamma$  is the rate by which any beneficial mutation is compensated. Interestingly, only in the case  $|\alpha| < \gamma$  (i.e. selection is weaker than the compensatory mutation rate) an equilibrium state exists, and is still Poisson with parameter  $\lambda/(\gamma - |\alpha|)$ . In the case  $|\alpha| \geq \gamma$ , no equilibrium exists because new beneficial mutations spread through the population quicker than compensatory mutations can halt this process. It will be interesting to investigate the switch between these two scenarios in the case of finite  $N$ .

3.3. *Simulations.* We use simulations based on a discrete Wright-Fisher model to study the evolution of the mean fitness, and to investigate the dependence of the mean and the variance of the type frequency distribution on the model parameters. Fixing a population size  $N$ , this model is a discrete time Markov chain  $(\underline{Y}(t))_{t=0,1,2,\dots}$  taking values in  $\{\underline{y} \in \mathbb{S} : N\underline{y} \in \mathbb{N}_0^{\mathbb{N}_0}\}$  and such that

$$\mathbf{P}(\underline{Y}(t+1) = \underline{y} | \underline{Y}(t)) = \binom{N}{N_{y_0} N_{y_1} N_{y_2} \dots} \prod_{j=0}^{\infty} p_j^{N_{y_j}}$$

where

$$\begin{aligned} \text{(i)} \quad \tilde{p}_j &= \frac{(1-\alpha)^j Y_j(t)}{\sum_{k=0}^{\infty} (1-\alpha)^k Y_k(t)}, \\ \text{(ii)} \quad \hat{p}_j &= \sum_{m=j}^{\infty} \tilde{p}_m \binom{m}{j} \gamma^{m-j} (1-\gamma)^j, \\ \text{(iii)} \quad p_j &= \sum_{l=0}^j \hat{p}_l e^{-\lambda} \frac{\lambda^{j-l}}{(j-l)!} \end{aligned}$$

for *small* parameters  $\alpha, \lambda$  and  $\gamma$ . The sampling weights  $(p_j)_{j=0,1,\dots}$  describe selection, mutation and compensatory mutation. The idea in this scheme (which is standard in population genetics) is that (i) any individual produces a large number of gametes, but an individual with  $k$  deleterious mutations only contributes a number proportional to  $(1-\alpha)^k$  to the gamete pool, (ii)



every deleterious mutation has a small, independent chance  $\gamma$  to be removed while the gamete is built, and (iii) the number of new deleterious mutations is Poisson distributed with parameter  $\lambda$ . After building these gametes,  $N$  individuals are randomly chosen from the gamete pool to form the next generation. Since  $\alpha, \gamma$  and  $\lambda$  are assumed to be small, the order in which the three mechanisms (i), (ii), (iii) come into play is negligible. (E.g., if we would assume – in contrast to our simulation scheme above – that compensatory mutations arise before gametes are built proportional to the relative fitness of individuals. Then an individual with a high number of deleterious mutations would produce slightly more gametes than in our simulation scheme.) For our simulations, the working hypothesis is that  $(\underline{Y}(Nt))_{t \geq 0}$  behaves similar to  $\mathcal{X} = (\underline{X}(Nt))_{t \geq 0}$  where  $\mathcal{X}$  is the solution of (\*) with parameter  $N$ ; see Remark 3.3.

We simulated  $(\underline{Y}(Nt))_{t \geq 0}$  for various combinations of  $N, \alpha, \lambda$  and  $\gamma$ , starting with  $\underline{Y}(0) = \delta_0$ , i.e. no deleterious mutations are present at start. Since in reality compensatory mutations are less probable than mutations, we mostly simulate scenarios with  $\gamma \ll \lambda$ . (For the biological background of this assumption, see Section 2.) Hence, our simulations can be considered as a small perturbation of the case  $\gamma = 0$ , the case of Muller's ratchet (without compensatory mutations). We compare scenarios where Muller's ratchet clicks rarely with others in which it clicks more frequently. For example, in Figure 1(A) we use  $N = 10^3, \lambda = 0.1, \alpha = 0.03$  where the ratchet has about 5.7 clicks in  $N$  generations. In Figure 1(B) we use  $N = 10^4$  where the ratchet has only about 0.34 clicks in  $N$  generations. Both figures show the initial phase of the simulation for a small compensatory mutation rate of  $\gamma = 10^{-4}$ . Recall that Theorem 2 predicts an equilibrium number of  $\lambda/(\alpha + \gamma) \approx 3.3$  deleterious mutations in the case  $N = \infty$ . This value is reflected in our simulations only in Figure (B) where Muller's ratchet clicks rarely. In Figure (A), not only is the average number of deleterious mutations much larger than the prediction from Theorem 2, but also the fluctuations are much larger than in Figure (B). However, in both parameter constellations we see that the accumulation of deleterious mutations by Muller's ratchet is slowed down (and sooner or later halted) due to the compensatory mutations.

Figure 2 illustrates for a finite  $N$ , how far the mean and variance of the number of deleterious mutations deviate from those Poisson distribution, which appears in Theorem 2 for the case  $N = \infty$ . Again, we see that for fixed  $\alpha, \lambda$  and small compensatory mutation rate  $\gamma$ , the equilibrium for  $\kappa_1$  is close to  $\lambda/(\alpha + \gamma)$  only if the ratchet without compensatory mutations ( $\gamma = 0$ ) does not click too often. If  $N = 10^4$  in Figure 2(A), there are approximately 152 clicks in  $N$  generations in the absence of compensatory

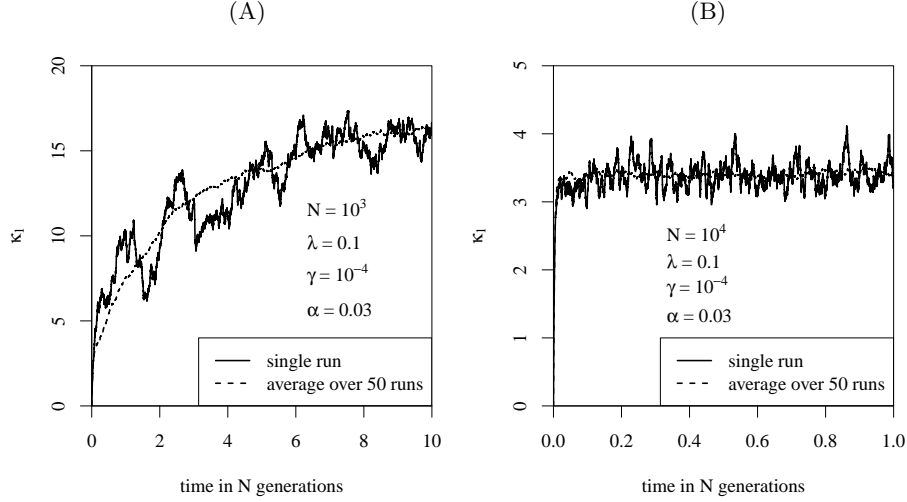


FIG 1. The evolution of the average number of deleterious mutations  $\kappa_1$  is plotted. In addition, the single path is compared to the average over 50 different simulations. (A) A parameter combination where Muller's ratchet without compensatory mutations (i.e.  $\gamma = 0$ ) clicks frequently, while it clicks much less frequent in (B).

mutations while in Figure 2(B) this rate is much lower, approximately 0.34 clicks per  $N$  generations (we use the same parameter values  $\alpha$ ,  $\lambda$  and  $\gamma$  as in Figure 1(B)). These examples show that compensatory mutations halt the ratchet quite efficiently. Note that the parameter values  $\lambda = 0.1$  and  $\gamma = 10^{-4}$  fit to the evolution of RNA viruses, e.g. for a genome of length  $10^3$  bases, if the per base mutation rate is  $10^{-4}$  and a population of size  $10^4$ . As our simulations show, the ratchet is halted provided the selection coefficient is large enough. This is in some contrast to Chao (1990) who argues that compensatory mutations are too rare in RNA viruses to halt the ratchet.

Another surprising fact in Figure 2(A) is that the empirical variance of the number of deleterious mutations in the population is always close to the prediction of  $\lambda/(\alpha + \gamma)$  from the Poisson state appearing in Theorem 2. This would be compatible with the hypothesis that the type frequencies for the Wright-Fisher model are (in equilibrium) close to a shifted Poisson distribution. The detailed study of the amount of this shift, in particular for a parameter constellation for which  $\gamma = 0$  leads to frequent clicks, is a delicate issue. Its answer certainly depends on the rate of clicking of Muller's ratchet without compensatory mutations, a problem which remains unsolved until now.

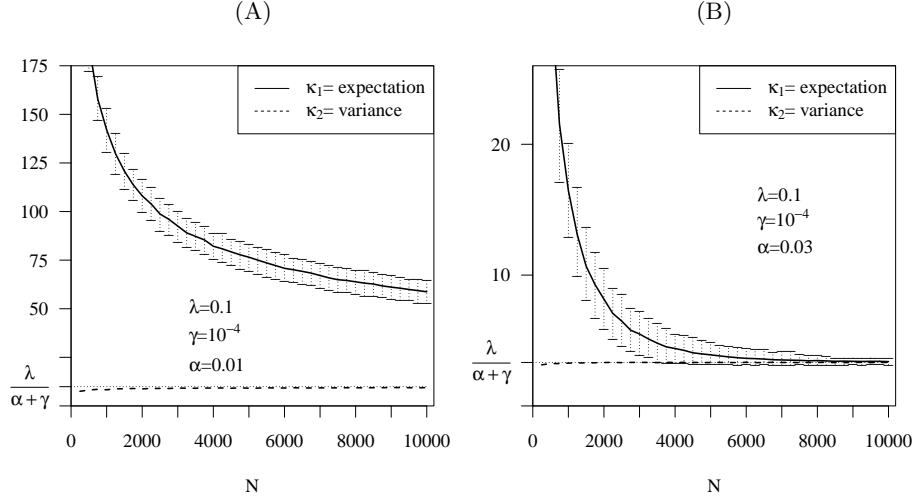


FIG 2. The empirical distribution of  $\kappa_1$  and  $\kappa_2$  are evaluated between generations  $5 \cdot 10^2 N$  and  $10^3 N$ . The plot for  $\kappa_1$  includes the resulting 10% and 90% quantiles. In absence of compensatory mutations and with  $N = 10^4$ , the same parameters lead to approximately 152 clicks per  $N$  time units for Figure (A), while 0.34 clicks per  $N$  time units are obtained for Figure (B).

Yet another interesting feature seen in Theorem 2 is the symmetric dependence on  $\alpha$  and  $\gamma$  of the equilibrium state. We checked in which direction this symmetry is violated for finite  $N$ . As seen from Figure 3, compensatory mutations can halt the ratchet more efficiently than selection. The reason is that compensatory mutations reduce the number of mutations no matter how many mutations are fixed in the population, whereas the number of fixed mutations cannot decrease due to selection.

**4. Proof of Theorem 1.** Our approach is inspired by Ethier and Shiga (2000), who deal with the case of unbounded selection if mutation is parent-independent. In order to prove that (\*) has a unique weak solution, we use the equivalent formulation by a martingale problem and show its well-posedness (see Proposition 4.4). We provide bounds on exponential moments for any solution of the martingale problem associated with the generator of (\*) in Lemma 4.5. The central step is Proposition 4.8 which provides a Girsanov change of measure by which solutions of the martingale problem for  $\alpha = 0$  are transformed to solutions for any  $\alpha > 0$ . Proposition 4.4 and Theorem 1 then follow because the martingale problem for  $\alpha = 0$  is well-posed, and can be transformed to a solution for the martingale problem for

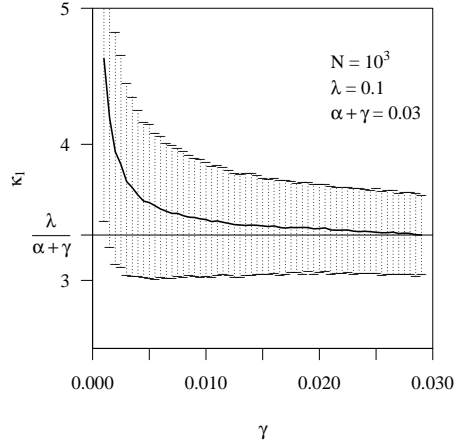


FIG 3. The parameter  $\lambda/(\alpha + \gamma)$  of the Poisson equilibrium state in the case  $N = \infty$  is symmetric in  $\alpha$  and  $\gamma$  (see Theorem 2). We fix  $\alpha + \gamma$  and see that the average number of deleterious mutations is higher for low values of  $\gamma$ . Again, the 10% and 90% quantiles are given.

$\alpha > 0$  which also solves (\*). This shows existence. Uniqueness again follows by using a Girsanov transform.

4.1. *Martingale problem.* We start by defining the generator for the Fleming-Viot system of Muller's ratchet with compensatory mutations. The unboundedness in the selection term of this generator requires particular care in the analysis of the corresponding martingale problem. First we give some notation.

REMARK 4.1 (Notation). For a complete and separable metric space  $(\mathbb{E}, r)$ , we denote by  $\mathcal{P}(\mathbb{E})$  the space of probability measures on (the Borel sets of)  $\mathbb{E}$ , and by  $\mathcal{M}(\mathbb{E})$  (resp.  $\mathcal{B}(\mathbb{E})$ ) the space of real-valued, measurable (and bounded) functions. If  $\mathbb{E} \subseteq \mathbb{R}^{N_0}$ , we let  $\mathcal{C}^k(\mathbb{E})$  ( $\mathcal{C}_b^k(\mathbb{E})$ ) be the (bounded),  $k$  times partially continuously differentiable functions (with bounded derivatives). Partial derivatives of  $f \in \mathcal{C}^2(\mathbb{E})$ ,  $\mathbb{E} \subseteq \mathbb{R}^{N_0}$  will be denoted by

$$(4.1) \quad f_k := \frac{\partial f}{\partial x_k}, \quad f_{k\ell} := \frac{\partial^2 f}{\partial x_k \partial x_\ell}, \quad k, \ell = 0, 1, 2, \dots$$

DEFINITION 4.2 (Martingale problem). Let  $(\mathbb{E}, r)$  be a complete and separable metric space,  $x \in \mathbb{E}$ ,  $\mathcal{F} \subseteq \mathcal{M}(\mathbb{E})$  and  $G$  a linear operator on  $\mathcal{M}(\mathbb{E})$  with domain  $\mathcal{F}$ . A (distribution  $\mathbf{P}$  of an)  $\mathbb{E}$ -valued stochastic process

$\mathcal{X} = (X_t)_{t \geq 0}$  is called a solution of the  $(\mathbb{E}, x, G, \mathcal{F})$ -martingale problem if  $X_0 = x$  and  $\mathcal{X}$  has paths in the space  $\mathcal{D}_{\mathbb{E}}([0, \infty))$ , almost surely, and for all  $f \in \mathcal{F}$ ,

$$(4.2) \quad \left( f(X_t) - f(X_0) - \int_0^t Gf(X_s) ds \right)_{t \geq 0}$$

is a  $\mathbf{P}$ -martingale with respect to the canonical filtration. Moreover, the  $(\mathbb{E}, x, G, \mathcal{F})$ -martingale problem is said to be well-posed if there is a unique solution  $\mathbf{P}$ .

For a fixed  $\xi > 0$ , our state space will be  $(\mathbb{S}_\xi, r)$ , cf. Definition 3.1 and Remark 3.2. We now specify the generator and its domain.

DEFINITION 4.3 (Generator for Fleming-Viot system).

1. On  $\mathbb{S}$ , consider functions of the form

$$(4.3) \quad \begin{aligned} f(\underline{x}) &:= f_{\varphi_1, \dots, \varphi_n}(\underline{x}) := \langle \underline{x}, \varphi_1 \rangle \cdots \langle \underline{x}, \varphi_n \rangle, \\ \langle \underline{x}, \varphi \rangle &:= \sum_{k=0}^{\infty} x_k \varphi(k) \end{aligned}$$

for  $n = 1, 2, \dots$  and  $\varphi, \varphi_1, \dots, \varphi_n \in \mathcal{M}(\mathbb{N}_0)$ . Let

$$(4.4) \quad \begin{aligned} \mathcal{F} &:= \text{the algebra generated by} \\ &\{f_{\varphi_1, \dots, \varphi_n} : \varphi_i \in \mathcal{M}(\mathbb{N}_0) \text{ with bounded support,} \\ &\quad i = 1, \dots, n, \ n \in \mathbb{N}\}. \end{aligned}$$

2. We define the operator  $G_{\mathcal{X}}^\alpha$  as the linear extension of

$$(4.5) \quad \begin{aligned} G_{\mathcal{X}}^\alpha f(\underline{x}) &= G_{sel}^\alpha f(\underline{x}) + G_{mut} f(\underline{x}) + G_{cmut} f(\underline{x}) + G_{res}^N f(\underline{x}), \\ G_{sel}^\alpha f(\underline{x}) &= \alpha \sum_{k=0}^{\infty} \sum_{\ell=0}^{\infty} (\ell - k) x_\ell x_k f_k(\underline{x}), \\ G_{mut} f(\underline{x}) &= \lambda \sum_{k=0}^{\infty} (x_{k-1} - x_k) f_k(\underline{x}), \\ G_{cmut} f(\underline{x}) &= \gamma \sum_{k=0}^{\infty} ((k+1)x_{k+1} - kx_k) f_k(\underline{x}), \\ G_{res}^N f(\underline{x}) &= \frac{1}{2N} \sum_{k, \ell=0}^{\infty} x_k (\delta_{k\ell} - x_\ell) f_{k\ell}(\underline{x}) \end{aligned}$$

with  $\alpha, \lambda, \gamma \in [0, \infty)$ ,  $N \in (0, \infty)$ , for  $f$  of the form (4.3) whenever the right hand sides of (4.5) exist (which is certainly the case if  $\underline{x}$  has a first moment and the  $\varphi_1, \dots, \varphi_n$  have bounded support). In particular, for all  $f \in \mathcal{F}$  and  $\xi > 0$ , the function  $G_{\mathcal{X}}^{\alpha} f$  is defined on  $\mathbb{S}_{\xi}$ .

3. For  $f = f_{\varphi_1, \dots, \varphi_n}$ , we define  $\mathcal{N}_f = (N_f(t))_{t \geq 0}$  by

$$(4.6) \quad N_f(t) := f(\underline{X}(t)) - \int_0^t G_{\mathcal{X}}^{\alpha} f(\underline{X}(s)) ds$$

whenever  $G_{\mathcal{X}}^{\alpha} f(\underline{X}(t))$  exists for all  $t \geq 0$ .

PROPOSITION 4.4 (Martingale problem is well-posed in  $\mathbb{S}_{\xi}$ ). *Let  $\underline{x} \in \mathbb{S}_{\xi}$  for some  $\xi > 0$ ,  $G_{\mathcal{X}}^{\alpha}$  as in (4.5) and  $\alpha, \lambda, \gamma \in [0, \infty)$ ,  $N \in (0, \infty)$  and  $\mathcal{F}$  be as in (4.4). Then, the  $(\mathbb{S}, \underline{x}, G_{\mathcal{X}}^{\alpha}, \mathcal{F})$ -martingale problem is well-posed and is a process with paths in  $\mathcal{C}_{\mathbb{S}_{\xi}}([0, \infty))$ .*

Proposition 4.4 is a crucial step in the proof of Theorem 1. Both proofs are carried out in Section 4.3. Now we start with bounds on exponential moments, which will be crucial in further proofs.

LEMMA 4.5 (Bounds on exponential moments). *Let  $\underline{x} \in \mathbb{S}_{\xi}$  for some  $\xi > 0$  and  $\mathcal{X} = (X(t))_{t \geq 0}$  be a solution of the  $(\mathbb{S}, \underline{x}, G_{\mathcal{X}}^{\alpha}, \mathcal{F})$ -martingale problem. Then,*

$$(4.7) \quad \mathbf{E}[h_{\xi}(\underline{X}(t))] \leq h_{\xi}(\underline{x}) \cdot \exp(\lambda t(e^{\xi} - 1))$$

and for all  $T > 0$  and  $\varepsilon > 0$ , there is  $C > 0$ , depending on  $T, \varepsilon, \xi$  and  $\lambda$  (but not on  $\alpha, \gamma, N$ ) with

$$(4.8) \quad \mathbf{P}\left[\sup_{0 \leq t \leq T} h_{\xi}(\underline{X}(t)) > C\right] \leq \varepsilon \cdot h_{\xi}(\underline{x}).$$

PROOF. Define for  $m = 0, 1, 2, \dots$  the function  $h_{\xi, m} \in \mathcal{F}$  by

$$h_{\xi, m}(\underline{x}) := \sum_{k=0}^m x_k e^{\xi k} + e^{\xi m} \left(1 - \sum_{k=0}^m x_k\right) = e^{\xi m} + \sum_{k=0}^m x_k (e^{\xi k} - e^{\xi m})$$

and note that

$$h_{\xi, m}(\underline{x}) = \sum_{k=0}^{\infty} x_k e^{\xi(k \wedge m)} \quad \text{for } \underline{x} \in \mathbb{S}.$$

First, we compute

(4.9)

$$\begin{aligned}
G_{\text{mut}}h_{\xi,m}(\underline{x}) &= \lambda \sum_{k=0}^m (x_{k-1} - x_k)(e^{\xi k} - e^{\xi m}) = \lambda \sum_{k=0}^{m-1} x_k (e^{\xi(k+1)} - e^{\xi k}) \\
&= \lambda(e^{\xi} - 1) \sum_{k=0}^{m-1} x_k e^{\xi k} \geq 0, \\
G_{\text{cmut}}h_{\xi,m}(\underline{x}) &= \gamma \sum_{k=0}^m ((k+1)x_{k+1} - kx_k)(e^{\xi k} - e^{\xi m}) \\
&= \gamma \sum_{k=1}^m kx_k (e^{\xi(k-1)} - e^{\xi k}) \leq 0. \\
G_{\text{sel}}^{\alpha}h_{\xi,m}(\underline{x}) &= \alpha \sum_{k=0}^m \sum_{\ell=0}^{\infty} (\ell - k)x_{\ell}x_k (e^{\xi k} - e^{\xi m}) \\
&= \alpha \sum_{k=0}^{\infty} \sum_{\ell=0}^{\infty} (\ell - k)x_{\ell}x_k (e^{\xi(k \wedge m)} - e^{\xi m}) \\
&= \alpha \sum_{k=0}^{\infty} \sum_{\ell=0}^{\infty} (\ell - k)x_{\ell}x_k e^{\xi(k \wedge m)} \leq 0,
\end{aligned}$$

where the calculation for the term  $G_{\text{sel}}^{\alpha}$  holds for  $\underline{x} \in \mathbb{S}$ . (For the last inequality, assume that  $Z$  is an  $\mathbb{N}_0$ -valued random variable with distribution  $\underline{x}$ . Then,  $G_{\text{sel}}h_{\xi,m}(\underline{x}) = -\alpha \mathbf{Cov}[Z, e^{\xi(Z \wedge m)}] \leq 0$ , since two increasing transformations of a random variable  $Z$  have a nonnegative correlation, or in other words, the singleton family  $\{Z\}$  is associated.)

In the next step we prove (4.7). We write

$$\begin{aligned}
(4.10) \quad \frac{d}{dt} \mathbf{E}[h_{\xi,m}(\underline{X}(t))] &= \mathbf{E}[G_{\mathcal{X}}^{\alpha}h_{\xi,m}(\underline{X}(t))] \leq \mathbf{E}[G_{\text{mut}}h_{\xi,m}(\underline{X}(t))] \\
&= \lambda(e^{\xi} - 1) \cdot \mathbf{E}\left[\sum_{k=0}^{m-1} X_k(t)e^{\xi k}\right] \\
&\leq \lambda(e^{\xi} - 1) \mathbf{E}[h_{\xi,m}(\underline{X}(t))].
\end{aligned}$$

So, by Gronwall's inequality,

$$\mathbf{E}[h_{\xi,m}(\underline{X}(t))] \leq h_{\xi,m}(\underline{x}) \cdot \exp(\lambda t(e^{\xi} - 1))$$

which gives (4.7) by monotone convergence.

Finally, by Doob's submartingale inequality and monotone convergence, using (4.10),

$$\begin{aligned}
\mathbf{P}\left[\sup_{0 \leq t \leq T} h_\xi(\underline{X}(t)) > C\right] &= \lim_{m \rightarrow \infty} \mathbf{P}\left[\sup_{0 \leq t \leq T} h_{\xi,m}(\underline{X}(t)) > C\right] \\
&\leq \lim_{m \rightarrow \infty} \mathbf{P}\left[\sup_{0 \leq t \leq T} \left(h_{\xi,m}(\underline{X}(t)) - \int_0^t G_{\text{cmut}} h_{\xi,m}(\underline{X}(s)) \right. \right. \\
&\quad \left. \left. + G_{\text{sel}} h_{\xi,m}(\underline{X}(s)) ds\right) > C\right] \\
&\leq \frac{1}{C} \lim_{m \rightarrow \infty} \mathbf{E}\left[h_{\xi,m}(\underline{X}(T)) - \int_0^T G_{\text{cmut}} h_{\xi,m}(\underline{X}(s)) + G_{\text{sel}} h_{\xi,m}(\underline{X}(s)) ds\right] \\
&\leq \frac{1}{C} \lim_{m \rightarrow \infty} \left(h_{\xi,m}(\underline{x}) + \int_0^T \mathbf{E}[G_{\text{mut}} h_{\xi,m}(\underline{X}(s))] ds\right) \\
&\leq \frac{1}{C} \left(h_\xi(\underline{x}) + \lambda(e^\xi - 1) h_\xi(\underline{x}) \int_0^T \exp(\lambda s(e^\xi - 1)) ds\right)
\end{aligned}$$

and the result follows.  $\square$

For the change of measure applied in the next subsection, we will need that the martingale property of  $N_f$  extends from  $\mathcal{F}$  to a wider class of functions.

LEMMA 4.6. *Let  $\underline{x} \in \mathbb{S}_\xi$  for some  $\xi > 0$  and  $\mathcal{X} = (\underline{X}_t)_{t \geq 0}$  be a solution of the  $(\mathbb{S}, \underline{x}, G_{\mathcal{X}}^\alpha, \mathcal{F})$ -martingale problem and*

$$\begin{aligned}
(4.11) \quad f = f_{\varphi_1, \dots, \varphi_n} \text{ be of the form (4.3) with } |\varphi_i(\cdot)| &\leq C e^\zeta. \\
&\text{for some } C > 0 \text{ and } \zeta < \xi, i = 1, \dots, n.
\end{aligned}$$

Then,  $(N_f(t))_{t \geq 0}$  given by (4.6) is a martingale.

PROOF. We first observe that  $G_{\mathcal{X}}^\alpha f(\underline{X}(t))$  exists for all  $t \geq 0$ , hence  $N_f$  is well-defined. For  $\varphi \in \mathcal{M}(\mathbb{N}_+)$ , let  $\varphi^m(k) := \varphi(k \wedge m)$ . We note that  $\sum_{k=0}^\infty x_k \varphi^m(k) = \varphi(m) + \sum_{k=0}^m x_k (\varphi(k) - \varphi(m))$  for  $\underline{x} \in \mathbb{S}$ . Hence, for  $f_{\varphi_1, \dots, \varphi_n}$  as given in the lemma, the function  $f_{\varphi_1^m, \dots, \varphi_n^m}$  coincides on  $\mathbb{S}$  with a function in  $\mathcal{F}$ . Clearly,  $(N_{f_{\varphi_1^m, \dots, \varphi_n^m}}(t))_{t \geq 0}$  is a martingale by assumption for all  $m = 0, 1, 2, \dots$ . Using (4.7) and dominated convergence

$$\begin{aligned}
\mathbf{E}[N_{f_{\varphi_1, \dots, \varphi_n}}(t) | (\underline{X}(r))_{r \leq s}] &= \lim_{m \rightarrow \infty} \mathbf{E}[N_{f_{\varphi_1^m, \dots, \varphi_n^m}}(t) | (\underline{X}(r))_{r \leq s}] \\
&= \lim_{m \rightarrow \infty} N_{f_{\varphi_1^m, \dots, \varphi_n^m}}(s) = N_{f_{\varphi_1, \dots, \varphi_n}}(s).
\end{aligned}$$

In other words,  $(N_f(t))_{t \geq 0}$  is a martingale.  $\square$



4.2. *Girsanov change of measure.* In Proposition 4.8 we establish a change of measure which shifts the selection coefficient  $\alpha$  of Muller's ratchet with compensatory mutations. Two assertions from semimartingale theory which will be required in the proof are recalled in the next remark..

- REMARK 4.7. 1. *A condition for a local martingale to be a martingale:* Let  $\mathcal{N} = (N_t)_{t \geq 0}$  be a local martingale. If  $\mathbf{E}[\sup_{0 \leq t \leq T} |N_t|] < \infty$  for all  $T > 0$ , then  $\mathcal{N}$  is a martingale (see e.g. Protter, 2004, Theorem I.51).
2. *Girsanov Theorem for continuous semimartingales:* If  $\mathcal{L} = (L_t)_{t \geq 0}$  is a continuous  $\mathbf{P}$ -martingale for some probability measure  $\mathbf{P}$  and assume that  $\mathcal{Z} = (Z_t)_{t \geq 0}$ , given by  $Z_t = e^{L_t - \frac{1}{2}\langle \mathcal{L} \rangle_t}$ , is a martingale (where  $\langle \mathcal{L} \rangle$  is the predictable quadratic variation of  $\mathcal{L}$ ). If  $\mathcal{N} = (N_t)_{t \geq 0}$  is a  $\mathbf{P}$ -local martingale, and  $\mathbf{Q}$  is defined via

$$\left. \frac{d\mathbf{Q}}{d\mathbf{P}} \right|_{\mathcal{F}_t} = Z_t,$$

then  $\mathcal{N} - \langle \mathcal{L}, \mathcal{N} \rangle$  is a  $\mathbf{Q}$ -local martingale. Here,  $\langle \mathcal{L}, \mathcal{N} \rangle$  is the (predictable) covariation process between  $\mathcal{L}$  and  $\mathcal{N}$ . (See e.g. Kallenberg, 2002, 18.19, 18.21.)

PROPOSITION 4.8 (Change of measure). For  $\underline{y} \in \mathbb{S}$ , let

$$(4.12) \quad \kappa_1(\underline{y}) := \sum_{k=0}^{\infty} k y_k, \quad \kappa_2(\underline{y}) := \sum_{k=0}^{\infty} (k - \kappa_1(\underline{y}))^2 y_k$$

be the expectation and variance of  $\underline{y}$ , provided they exist. Let  $\underline{x} \in \mathbb{S}_\xi$  for some  $\xi > 0$  and  $\mathcal{X} = (X(t))_{t \geq 0}$  be a solution of the  $(\mathbb{S}, \underline{x}, G_{\mathcal{X}}^\alpha, \mathcal{F})$ -martingale problem and denote its distribution by  $\mathbf{P}^\alpha$ . Then, the process  $\mathcal{Z}^{\alpha, \alpha'} = (Z_t^{\alpha, \alpha'})_{t \geq 0}$ , given by

$$(4.13) \quad Z_t^{\alpha, \alpha'} = \exp \left( N(\alpha - \alpha') \left( \kappa_1(\underline{X}(t)) - \kappa_1(\underline{x}) - \int_0^t \lambda - \gamma \kappa_1(\underline{X}(s)) - \frac{\alpha + \alpha'}{2} \kappa_2(\underline{X}(s)) ds \right) \right)$$

is a  $\mathbf{P}^\alpha$ -local martingale. If  $\alpha' > \alpha$  it is even a  $\mathbf{P}^\alpha$ -martingale and the probability measure  $\mathbf{P}^{\alpha'}$ , defined by

$$\left. \frac{d\mathbf{P}^{\alpha'}}{d\mathbf{P}^\alpha} \right|_{\mathcal{F}_t} = Z_t^{\alpha, \alpha'}$$

solves the  $(\mathbb{S}, \underline{x}, G_{\mathcal{X}}^{\alpha'}, \mathcal{F})$ -martingale problem.

PROOF. The proof is an application of the Girsanov transform for continuous semimartingales; see Remark 4.7.2. By assumption, the process  $\mathcal{X}$  is continuous, and so is the processes  $(f(\underline{X}(t)))_{t \geq 0}$  for  $f$  as in (4.11). Set

$$g(\underline{x}) := N(\alpha - \alpha')\kappa_1(\underline{x})$$

and define  $\mathcal{L} = (L_t)_{t \geq 0}$  by

$$\begin{aligned} L_t &= N(\alpha - \alpha') \left( \kappa_1(\underline{X}(t)) - \kappa_1(\underline{X}(0)) - \int_0^t G_{\mathcal{X}}^\alpha \kappa_1(\underline{X}(s)) ds \right) \\ &= N(\alpha - \alpha') \left( \kappa_1(\underline{X}(t)) - \kappa_1(\underline{X}(0)) - \int_0^t \lambda - \gamma \kappa_1(\underline{X}(s)) - \alpha \kappa_2(\underline{X}(s)) ds \right). \end{aligned}$$

Then,  $\mathcal{L}$  is a  $\mathbf{P}^\alpha$ -martingale by Lemma 4.6 with quadratic variation

$$\begin{aligned} \langle \mathcal{L} \rangle_t &= N^2(\alpha - \alpha')^2 \int_0^t G_{\text{res}}^N(\kappa_1(\underline{X}(s)))^2 ds \\ &= N(\alpha - \alpha')^2 \int_0^t \kappa_2(\underline{X}(s)) ds. \end{aligned}$$

For  $f \in \mathcal{F}$ , let  $\mathcal{N}_f = (N_f(t))_{t \geq 0}$  be as in (4.6). Then, for  $f = f_\varphi \in \mathcal{F}$ ,

$$\begin{aligned} \langle \mathcal{L}, \mathcal{N}^f \rangle_t &= \int_0^t G_{\text{res}}^N(g(\underline{X}(s))f(\underline{X}(s))) - g(\underline{X}(s))G_{\text{res}}^N f(\underline{X}(s)) ds \\ &= \frac{\alpha - \alpha'}{2} \int_0^t \sum_{k, \ell=0}^\infty X_k(s)(\delta_{k\ell} - X_\ell(s))(\varphi(k)\ell + k\varphi(\ell)) ds \\ &= \int_0^t G_{\text{sel}}^{\alpha'} f(\underline{X}(s)) - G_{\text{sel}}^\alpha f(\underline{X}(s)) ds. \end{aligned}$$

By an analogous calculation, one checks that the same identity is valid for all  $f \in \mathcal{F}$ . Since  $\mathcal{L}$  is a  $\mathbf{P}^\alpha$ (-local) martingale, the process  $\mathcal{Z}^{\alpha, \alpha'}$  as well is a  $\mathbf{P}^\alpha$ -local martingale (see Kallenberg, 2002, Lemma 18.21).

If  $\alpha < \alpha'$  and  $\underline{x} \in \mathbb{S}_\xi$  (and since  $e^{\xi \kappa_1(\underline{x})} \leq h_\xi(\underline{x})$  by Jensen's inequality), we have that  $\mathbf{E}[\sup_{0 \leq t \leq T} \mathcal{Z}_t^{\alpha, \alpha'}] < \infty$ . Hence, using Remark 4.7.1, we see that  $\mathcal{Z}^{\alpha, \alpha'}$  is a  $\mathbf{P}^\alpha$ -martingale. The above calculations and the Girsanov theorem for continuous semimartingales (recalled in Remark 4.7.2) then show that

$$N_f(t) - \langle \mathcal{L}, \mathcal{N}_f \rangle_t = f(\underline{X}(t)) - \int_0^t G_{\mathcal{X}}^{\alpha'} f(\underline{X}(s)) ds$$

is a  $\mathbf{P}^{\alpha'}$ -martingale. Since  $f \in \mathcal{F}$  was arbitrary,  $\mathbf{P}^{\alpha'}$  solves the  $(\mathbb{S}, \underline{x}, G_{\mathcal{X}}^{\alpha'}, \mathcal{F})$ -martingale problem.  $\square$

4.3. *Proof of Theorem 1.* First we will prove Proposition 4.4 on the well-posedness of the martingale problem for  $G_{\mathcal{X}}^{\alpha}$ . The proof of Theorem 1 will then be completed by observing that a process solves the system of SDEs (\*) iff it solves the martingale problem for  $G_{\mathcal{X}}^{\alpha}$  (Lemma 4.9).

PROOF OF PROPOSITION 4.4.

*Step 1: Existence of a solution of the martingale problem:*

For  $\alpha = 0$ , it follows from classical theory (e.g. Dawson, 1993, Theorem 5.4.1) that the  $(\mathbb{S}, \underline{x}, G_{\mathcal{X}}^0, \mathcal{F})$ -martingale problem has a unique solution  $\mathbf{P}^0$ . By Proposition 4.8, the change of measure using the martingale  $Z^{0,\alpha}$  leads to a distribution  $\mathbf{P}^{\alpha}$  that solves the  $(\mathbb{S}, \underline{x}, G_{\mathcal{X}}^{\alpha}, \mathcal{F})$ -martingale problem. This establishes existence.

*Step 2: Uniqueness of solutions of the martingale problem:*

As in Step 1, let  $\mathbf{P}^0$  be the unique solution of the  $(\mathbb{S}, \underline{x}, G_{\mathcal{X}}^0, \mathcal{F})$ -martingale problem. Assume  $\mathbf{P}_1^{\alpha}$  and  $\mathbf{P}_2^{\alpha}$  are two different solutions of the  $(\mathbb{S}, \underline{x}, G_{\mathcal{X}}^{\alpha}, \mathcal{F})$ -martingale problem. Let  $\tau_1, \tau_2, \dots$  be stopping times with  $\tau_n \rightarrow \infty$  as  $n \rightarrow \infty$  such that  $(Z_{t \wedge \tau_n}^{\alpha,0})_{t \geq 0}$ , given by (4.13), is both a  $\mathbf{P}_1^{\alpha}$ -martingale and a  $\mathbf{P}_2^{\alpha}$ -martingale. Since  $\mathbf{P}_1^{\alpha} \neq \mathbf{P}_2^{\alpha}$ , there must be  $t \geq 0$  such that the distributions of  $\underline{X}(t)$  under  $\mathbf{P}_1^{\alpha}$  and  $\mathbf{P}_2^{\alpha}$  are different (see Theorem 4.4.2 in Ethier and Kurtz, 1986). Hence, there is an  $n \in \mathbb{N}$  such that the distributions of  $\underline{X}(t \wedge \tau_n)$  under  $\mathbf{P}_1^{\alpha}$  and  $\mathbf{P}_2^{\alpha}$  are different. Since  $Z_{t \wedge \tau_n}^{\alpha,0}$  is positive  $\mathbf{P}_1^{\alpha}$ -a.s. and  $\mathbf{P}_2^{\alpha}$ -a.s., then also the distributions of  $\underline{X}(t \wedge \tau_n)$  under  $Z_{t \wedge \tau_n}^{\alpha,0} \cdot \mathbf{P}_1^{\alpha}$  and  $Z_{t \wedge \tau_n}^{\alpha,0} \cdot \mathbf{P}_2^{\alpha}$  are different. However, by the same arguments as in the proof of Proposition 4.8,  $Z_{t \wedge \tau_n}^{\alpha,0} \cdot \mathbf{P}_1^{\alpha}$  as well as  $Z_{t \wedge \tau_n}^{\alpha,0} \cdot \mathbf{P}_2^{\alpha}$  equal  $\mathbf{P}^0$  on the  $\sigma$ -algebra  $\sigma((\underline{X}(s))_{0 \leq s \leq t \wedge \tau_n})$ , which contradicts the assumed inequality of  $\mathbf{P}_1^{\alpha}$  and  $\mathbf{P}_2^{\alpha}$ . Thus, uniqueness of the  $(\mathbb{S}, \underline{x}, G_{\mathcal{X}}^{\alpha}, \mathcal{F})$ -martingale problem follows.  $\square$

LEMMA 4.9 (Equivalence of SDEs and martingale problem). *For  $\underline{x} \in \mathbb{S}_{\xi}$ , a process  $\mathcal{X} = (\underline{X}(t))_{t \geq 0}$  is a weak solution of the system of SDEs (\*) starting in  $\underline{x}$  iff the distribution of  $\mathcal{X}$  is a solution to the  $(\mathbb{S}, \underline{x}, G_{\mathcal{X}}^{\alpha}, \mathcal{F})$ -martingale problem.*

PROOF. 1. Assume that  $\mathcal{X} = (\underline{X}(t))_{t \geq 0}$  solves the system of SDEs (\*). Then, as a direct consequence of Itô's lemma, the distribution of  $\mathcal{X}$  is a solution to the  $(\mathbb{S}, \underline{x}, G_{\mathcal{X}}^{\alpha}, \mathcal{F})$ -martingale problem.

2. Conversely, let  $\mathcal{X} = (\underline{X}(t))_{t \geq 0}$  solve the  $(\mathbb{S}, \underline{x}, G_{\mathcal{X}}^{\alpha}, \mathcal{F})$ -martingale problem. To see that  $\mathcal{X}$  is a weak solution of (\*), we may appeal to Da Prato and Zabczyk, 1992, Theorem 8.2. Specifically, in their notation, choose  $H$  as the Hilbert-space of square-summable elements of  $\mathbb{R}^{\mathbb{N}_0}$ ,  $M = (\mathcal{N}_{fk})_{k=0,1,2,\dots}$

with  $f^k(\underline{x}) := x_k$ , let  $Q$  be the identity on  $\mathbb{R}^{\binom{N_0}{2}} = \{(w_{k\ell})_{k < \ell} : w_{k\ell} \in \mathbb{R}\}$ , and let  $\Phi(s) : \mathbb{R}^{\binom{N_0}{2}} \rightarrow \mathbb{R}^{N_0}$  be given through the matrix  $\Phi(s)_{i,k\ell} := (\delta_{ik} - \delta_{i\ell})\sqrt{X_k(s)X_\ell(s)}$ .  $\square$

**5. Proof of Theorem 2.** The key element in the proof of Theorem 2 is Proposition 5.2 which represents a solution of (3.5) through a Markov jump process. For uniqueness of the solution we rely on a duality derived in Section 5.2. The proof of Theorem 2 is given in Section 5.3.

**5.1. A particle system.** As a preparation to the proof of Theorem 2, we represent the system of ordinary differential equations by a jump process  $(K_t)_{t \geq 0}$ . Almost surely, the process will be killed (i.e. hit a cemetery state) in finite time. We show in Proposition 5.2 that a solution of (3.5) is given by the distribution of  $K_t$  conditioned on not being killed by time  $t$ ,  $t \geq 0$ .

**DEFINITION 5.1 (Jump process).** *Let  $(K_t)_{t \geq 0}$  be a pure Markov jump process which takes values in  $\{\dagger, 0, 1, 2, \dots\}$  and jumps from  $k$  to  $k+1$  at rate  $\lambda$ , from  $k$  to  $k-1$  at rate  $k\gamma$ , and from  $k$  to the cemetery state  $\dagger$  with rate  $\alpha k$ .*

**PROPOSITION 5.2 (Particle representation).** *Let  $\underline{x}(0) \in \mathbb{S}_\xi$  for some  $\xi > 0$  and  $(K_t)_{t \geq 0}$  be as in Definition 5.1 with initial distribution given by  $\mathbf{P}[K_0 = k] = x_k(0)$ . Then,*

$$(5.1) \quad x_k(t) := \mathbf{P}[K_t = k | K_t \neq \dagger].$$

*solves the system (3.5).*

**PROOF.** From the definition of  $(K_t)_{t \geq 0}$ , it is clear that for small  $\varepsilon > 0$ ,

$$\begin{aligned} x_k(t + \varepsilon) &= \frac{x_k(t)(1 - \alpha k\varepsilon) + \lambda(x_{k-1}(t) - x_k(t))\varepsilon + \gamma((k+1)x_{k+1}(t) - kx_k(t))\varepsilon}{1 - \alpha \sum_{\ell=0}^{\infty} \ell x_\ell(t)\varepsilon} \\ &\quad + \mathcal{O}(\varepsilon^2) \\ &= x_k(t) + \left( -\alpha \left( k - \sum_{\ell=0}^{\infty} \ell x_\ell(t) \right) x_k(t) + \lambda(x_{k-1}(t) - x_k(t)) \right. \\ &\quad \left. + \gamma((k+1)x_{k+1}(t) - kx_k(t)) \right) \varepsilon + \mathcal{O}(\varepsilon^2), \end{aligned}$$

which implies the result as  $\varepsilon \rightarrow 0$ .  $\square$

5.2. *Dynamics of the cumulant generating function.* The proof of uniqueness of (3.5) requires some preliminary computations which we carry out next. Recall the function  $h_\xi$  from (3.2). Note the function  $\zeta \mapsto \log h_\zeta(\underline{x})$  is the cumulant generating function of  $\underline{x} \in \mathbb{S}$ . Cumulants have already been proven to be useful in the study of Muller's ratchet; see Etheridge et al. (2008). Here, we compute the dynamics of the cumulant generating function.

PROPOSITION 5.3 (Dynamics of cumulant generating function). *For any solution  $t \mapsto \underline{x}(t)$  of (3.5) taking values in  $\mathbb{S}_\xi$  for  $\xi > 0$  and  $0 < \zeta < \xi$ ,*

$$\frac{d}{dt} \log h_\zeta(\underline{x}(t)) = \alpha \sum_{\ell=0}^{\infty} \ell x_\ell(t) + \lambda(e^\zeta - 1) - (\alpha + \gamma(1 - e^{-\zeta})) \frac{d}{d\zeta} \log h_\zeta(\underline{x}(t)).$$

PROOF. Abbreviating  $\underline{x} := \underline{x}(t)$ , we compute

$$\begin{aligned} h_\zeta(\underline{x}) \frac{d}{dt} \log h_\zeta(\underline{x}) &= \alpha \sum_{\ell=0}^{\infty} \sum_{k=0}^{\infty} (\ell - k) x_\ell x_k e^{\zeta k} + \lambda \sum_{k=0}^{\infty} (x_{k-1} - x_k) e^{\zeta k} \\ &\quad + \gamma \sum_{k=0}^{\infty} ((k+1)x_{k+1} - kx_k) e^{\zeta k} \\ &= \alpha \left( \left( \sum_{\ell=0}^{\infty} \ell x_\ell \right) h_\zeta(\underline{x}) - \frac{d}{d\zeta} h_\zeta(\underline{x}) \right) + \lambda(e^\zeta - 1) h_\zeta(\underline{x}) \\ &\quad - \gamma(1 - e^{-\zeta}) \frac{d}{d\zeta} h_\zeta(\underline{x}) \end{aligned}$$

and so

$$\frac{d}{dt} \log h_\zeta(\underline{x}) = \alpha \sum_{\ell=0}^{\infty} \ell x_\ell + \lambda(e^\zeta - 1) - (\alpha + \gamma(1 - e^{-\zeta})) \frac{d}{d\zeta} \log h_\zeta(\underline{x}).$$

□

The equation in Proposition 5.3 relates the time-derivative of  $\log h_\zeta(\underline{x}(t))$  with the  $\zeta$ -derivative of the same function and leads to a *duality relation* formulated in Corollary 5.4. In Markov process theory, dualities are particularly useful to obtain uniqueness results; cf. Ethier and Kurtz (1986), p. 188ff. Our application in Subsection 5.3 will be in this spirit.

COROLLARY 5.4 (Duality). *Let  $t \mapsto \underline{x}(t)$  be a solution of (3.5) taking values in  $\mathbb{S}_\xi$  for  $\xi > 0$ . Moreover let  $\zeta : t \mapsto \zeta(t)$  be the solution of  $\zeta' = -(\alpha + \gamma(1 - e^{-\zeta}))$ , starting in some  $\zeta(0) < \xi$ . Then,*

$$\log h_{\zeta(0)}(\underline{x}(t)) = \log h_{\zeta(t)}(\underline{x}(0)) + \int_0^t \left( \lambda(e^{\zeta(t-s)} - 1) + \sum_{\ell=0}^{\infty} \ell x_\ell(s) \right) ds.$$

PROOF. Using Proposition 5.3 and noting, for any differentiable  $g : \zeta \mapsto g(\zeta)$ , the equality

$$\frac{d}{ds} g(\zeta(t-s)) = (\alpha + \gamma(1 - e^{-\zeta(t-s)})) \frac{d}{d\zeta} g(\zeta(t-s)),$$

we obtain

$$\frac{d}{ds} \log h_{\zeta(t-s)}(\underline{x}(s)) = \lambda(e^{\zeta(t-s)} - 1) + \alpha \sum_{\ell=0}^{\infty} \ell x_\ell(s).$$

Now the assertion follows by integrating.  $\square$

5.3. *Proof of Theorem 2.* We proceed in two steps. First, we derive an explicit solution of (3.5) by using Proposition 5.2, i.e. by computing the distribution of the jump process  $(K_t)_{t \geq 0}$  conditioned on not being killed by time  $t$ . This will result in the right hand side of (3.6). In a second step, we show uniqueness of solutions of (3.5) in  $\mathbb{S}_\xi$ .

*Step 1: Computation of the right hand side of (5.1):*

In order to derive an explicit formula for the probability specified in (5.1), we note that the process  $(K_t)_{t \geq 0}$  can be realized as the following mutation-couting process:

- Start with  $K_0$  mutations, with the random number  $K_0$  distributed according to  $(x_k(0))_{k=0,1,2,\dots}$ .
- New mutations arise at rate  $\lambda$ .
- Every mutation (present from the start or newly arisen) starts an exponential waiting time with parameter  $\alpha + \gamma$ . If this waiting time expires, then with probability  $\frac{\alpha}{\alpha + \gamma}$  the process jumps to  $\dagger$ , and with the complementary probability  $\frac{\gamma}{\alpha + \gamma}$  the mutation disappears.

With  $x_k(t)$  defined by (5.1), we decompose the probability of the event  $\{K_t = k\}$  with respect to the number of mutations present at time 0. If  $K_0 = i$ , a number  $j \leq i \wedge k$  of these initial mutations are not compensated by time  $t$  and the remaining  $i - j$  are compensated. In addition, a number

$l \geq k - j$  mutations arise at times  $0 \leq t_1 \leq \dots \leq t_l \leq t$ . From these,  $l - k + j$  are compensated and the remaining  $k - j$  are not compensated. These arguments lead to the following calculation, where we write  $\sim$  for equality up to factors not depending on  $k$ . The first  $\sim$  comes from the fact that the right hand side is the unconditional probability  $\mathbf{P}[K_t = k]$ ,

$$\begin{aligned}
x_k(t) &\sim \sum_{i=0}^{\infty} x_i(0) \sum_{j=0}^{i \wedge k} \binom{i}{j} \left( \frac{\gamma}{\alpha + \gamma} (1 - e^{-(\alpha + \gamma)t}) \right)^{i-j} \cdot e^{-j(\alpha + \gamma)t} \\
&\quad \sum_{l=k-j}^{\infty} \int_{\substack{\mathcal{T}=(t_1, \dots, t_l): \\ 0 \leq t_1 \leq \dots \leq t_l}} d(t_1, \dots, t_l) \lambda^l e^{-\lambda t_1} e^{-\lambda(t_2 - t_1)} \dots e^{-\lambda(t_l - t_{l-1})} e^{-\lambda(t - t_l)} \\
&\quad \sum_{\substack{\mathcal{S} \subseteq \mathcal{T} \\ |\mathcal{S}| = l - k + j}} \prod_{r \in \mathcal{S}} \frac{\gamma}{\alpha + \gamma} (1 - e^{-(\alpha + \gamma)(t-r)}) \cdot \prod_{s \in \mathcal{T} \setminus \mathcal{S}} e^{-(\alpha + \gamma)(t-s)} \\
&= \sum_{i=0}^{\infty} x_i(0) \sum_{j=0}^{i \wedge k} \binom{i}{j} \left( \frac{\gamma}{\alpha + \gamma} (1 - e^{-(\alpha + \gamma)t}) \right)^{i-j} \cdot e^{-j(\alpha + \gamma)t} \\
&\quad \sum_{l=k-j}^{\infty} \frac{\lambda^l}{l!} e^{-\lambda t} \int_{\substack{\mathcal{T}=(t_1, \dots, t_l): \\ 0 \leq t_1, \dots, t_l}} d(t_1, \dots, t_l) \sum_{\substack{\mathcal{S} \subseteq \mathcal{T} \\ |\mathcal{S}| = l - k + j}} \\
&\quad \prod_{r \in \mathcal{S}} \frac{\gamma}{\alpha + \gamma} (1 - e^{-(\alpha + \gamma)(t-r)}) \prod_{s \in \mathcal{T} \setminus \mathcal{S}} e^{-(\alpha + \gamma)(t-s)} \\
&\sim \sum_{i=0}^{\infty} x_i(0) \sum_{j=0}^{i \wedge k} \binom{i}{j} \left( \frac{\gamma}{\alpha + \gamma} (1 - e^{-(\alpha + \gamma)t}) \right)^{i-j} e^{-j(\alpha + \gamma)t} \\
&\quad \cdot \frac{\lambda^{k-j}}{(k-j)!} \left( \int_0^t e^{-(\alpha + \gamma)(t-s)} ds \right)^{k-j} \\
&\quad \cdot \sum_{l=0}^{\infty} \frac{\lambda^l}{l!} \left( \frac{\gamma}{\alpha + \gamma} \int_0^t 1 - e^{-(\alpha + \gamma)(t-r)} dr \right)^l \\
&\sim \sum_{i=0}^{\infty} x_i(0) \sum_{j=0}^{i \wedge k} \binom{i}{j} \left( \frac{\gamma}{\alpha + \gamma} (1 - e^{-(\alpha + \gamma)t}) \right)^{i-j} e^{-j(\alpha + \gamma)t} \\
&\quad \cdot \frac{\lambda^{k-j}}{(k-j)!} \left( \frac{1}{\alpha + \gamma} (1 - e^{-(\alpha + \gamma)t}) \right)^{k-j},
\end{aligned}$$

where the first '=' comes from the symmetry of the integrand. Summing the

right hand side gives

$$\begin{aligned}
& \sum_{i=0}^{\infty} x_i(0) \sum_{j=0}^i \binom{i}{j} \left( \frac{\gamma}{\alpha + \gamma} (1 - e^{-(\alpha+\gamma)t}) \right)^{i-j} e^{-j(\alpha+\gamma)t} \\
& \quad \cdot \sum_{k=j}^{\infty} \frac{\lambda^{k-j}}{(k-j)!} \left( \frac{1}{\alpha + \gamma} (1 - e^{-(\alpha+\gamma)t}) \right)^{k-j} \\
& = \sum_{i=0}^{\infty} x_i(0) \left( \frac{\gamma}{\alpha + \gamma} - \frac{\alpha}{\alpha + \gamma} e^{-(\alpha+\gamma)t} \right)^i \cdot \exp \left( \frac{\lambda}{\alpha + \gamma} (1 - e^{-(\alpha+\gamma)t}) \right).
\end{aligned}$$

Hence,

$$x_k(t) = \frac{\sum_{i=0}^{\infty} x_i(0) \sum_{j=0}^{i \wedge k} \binom{i}{j} \left( \frac{\gamma(1-e^{-(\alpha+\gamma)t})}{\alpha+\gamma} \right)^{i-j} e^{-j(\alpha+\gamma)t} \frac{1}{(k-j)!} \left( \frac{\lambda(1-e^{-(\alpha+\gamma)t})}{\alpha+\gamma} \right)^{k-j}}{\sum_{i=0}^{\infty} x_i(0) \left( \frac{\gamma}{\alpha+\gamma} - \frac{\alpha}{\alpha+\gamma} e^{-(\alpha+\gamma)t} \right)^i \cdot \exp \left( \frac{\lambda}{\alpha+\gamma} (1 - e^{-(\alpha+\gamma)t}) \right)}$$

which shows (3.6). To see (3.7), it suffices to note that all terms in the numerator except that for  $j = 0$  converge to 0 as  $t \rightarrow \infty$ . Hence the result is proved.

*Step 2: Uniqueness in  $\mathbb{S}_{\xi}$ :*

Let  $(\underline{y}(t))_{t \geq 0}$  be a solution of (3.5) starting in  $\underline{y}(0) \in \mathbb{S}_{\xi}$ . From the analogue of Lemma 4.5 in the case  $N = \infty$  we have  $h_{\xi}(\underline{y}(t)) \leq h_{\xi}(\underline{y}(0)) \exp(\lambda t(e^{\xi} - 1)) < \infty$ , i.e.  $\underline{y}(t) \in \mathbb{S}_{\xi}$  for all  $t \geq 0$ .

If  $(\underline{x}(t))_{t \geq 0}$  and  $(\underline{y}(t))_{t \geq 0}$  are solutions of (3.5) with  $\underline{x}(0) = \underline{y}(0) \in \mathbb{S}_{\xi}$ , then we obtain from Corollary 5.4 that for all  $0 < \zeta < \xi$  and any  $t \geq 0$

$$(5.2) \quad \log h_{\zeta}(\underline{x}(t)) - \log h_{\zeta}(\underline{y}(t)) = \int_0^t \sum_{\ell=0}^{\infty} \ell(x_{\ell}(s) - y_{\ell}(s)) ds.$$

Since only the left-hand side depends on  $\zeta$ , this enforces that both sides vanish. Indeed, taking derivatives with respect to  $\zeta$  at  $\zeta = 0$  the previous equality gives

$$\sum_{\ell=0}^{\infty} \ell(x_{\ell}(t) - y_{\ell}(t)) = 0, \quad t \geq 0.$$

Plugging this back into (5.2) gives

$$(5.3) \quad \log h_{\zeta}(\underline{x}(t)) = \log h_{\zeta}(\underline{y}(t)), \quad t \geq 0.$$

Since the function  $\zeta \mapsto \log h_{\zeta}(\underline{x})$  (for  $0 < \zeta < \xi$ ) characterizes  $\underline{x} \in \mathbb{S}_{\xi}$ , we obtain that  $\underline{x}(t) = \underline{y}(t)$ .



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