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► **To cite this version:**

Joseba Dalmau. Convergence of a Moran model to Eigen's quasispecies model. *Journal of Theoretical Biology*, 2017, 420, pp.36-40. 10.1016/j.jtbi.2017.02.035 . hal-03852260

HAL Id: hal-03852260

<https://hal.science/hal-03852260v1>

Submitted on 14 Nov 2022

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Convergence of a Moran model to Eigen's quasispecies model

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January 13, 2017

Abstract

We prove that a Moran model converges in probability to Eigen's quasispecies model in the infinite population limit. We show further that the invariant probability measure of the Moran model converges to the unique stationary solution of Eigen's quasispecies model.

1 Introduction

The concept of quasispecies was proposed by Manfred Eigen in order to explain how a population of macromolecules behaves when subject to an evolutionary process with selection and mutation. In his celebrated paper [9], Eigen models the evolution of a population of macromolecules via a system of differential equations, which arises from the laws of chemical kinetics. Selection is performed according to a fitness landscape, and mutations occur in the course of reproductions, independently at each locus with rate q . On the sharp peak landscape—all but one sequence, the master sequence, have the same fitness and the master sequence has higher fitness than the rest—Eigen discovered that an error threshold phenomenon takes place: there exists a critical mutation rate q^* such that if $q > q^*$ then at equilibrium the population is totally random, while if $q < q^*$ then at equilibrium the population forms a quasispecies, i.e., it contains a positive fraction of the master sequence along with a cloud of mutants that closely resemble the master sequence. The concepts of error threshold and quasispecies might not only be relevant in molecular genetics, but also in several other areas of biology, namely population genetics or virology [8]. Nevertheless, in Eigen's model the dynamics of the concentrations of the different genotypes is driven by a system of differential equations, which is a major drawback for the viability of the model in settings more complex than the molecular level [22].

A stochastic version of Eigen’s quasispecies model, for a finite population, would be much more suitable to expand the quasispecies theory to other areas [10, 19, 22].

The issue of designing a finite population version of the quasispecies model has been tackled by several authors. Different approaches have been considered in the literature: Alves and Fontanari [1] propose a finite population model and they study the dependence of the error threshold on the population size, a similar approach is taken by McCaskill [14], Park, Muñoz and Deem [17], and Saakian, Deem and Hu [18], who all suggest different kinds of finite population models. Nowak and Schuster [16] derive the error threshold for finite populations using a birth and death chain. More recently, Cerf [3, 4], shows that the error threshold and quasispecies concepts arise for both the Moran model and the Wright–Fisher model in the appropriate asymptotic regimes. Some other authors propose stochastic models that converge to Eigen’s model in the infinite population limit, this is the approach taken by Demetrius, Schuster and Sigmund [6], who use branching processes, Dixit, Srivastava and Vishnoi [7] or Musso [15].

Showing convergence of a finite population model to Eigen’s model is in general a delicate matter; to our knowledge, all the works that have been done in this direction prove that some stochastic process converges to Eigen’s model in expectation. As pointed out in [6], convergence in expectation can be misleading sometimes, mainly due to the fact that variation might increase as expectation converges, leading to a poor understanding of the asymptotic behaviour of the stochastic process. In the current work we consider the Moran model studied by Cerf [3] driving the evolution of a finite population subject to selection and mutation effects. This Moran model is shown to converge to Eigen’s quasispecies model in the infinite population limit, independently of the fitness landscape: on any finite time interval, we prove convergence in probability for the supremum norm. The interest of our result not only lies on the type of convergence, but also on the choice of the model: the Moran model is possibly one of the simplest models for which such a result can be expected. The result is proven by means of a theorem due to Kurtz [13], which gives sufficient conditions for the convergence of a sequence of Markov processes to a deterministic trajectory, characterised by a system of differential equations. In Eigen’s system of differential equations, the error threshold and quasispecies phenomena arise by studying the equilibrium solutions. The Moran model being a Markov chain, in analogy with the equilibrium solutions of the differential system, we study its invariant probability measure. We show that, in the infinite population limit,

this measure concentrates around the unique stationary solution of Eigen's system of differential equations.

The article is organised as follows: first we briefly introduce Eigen's quasispecies model and the Moran model. We state the main results in section 3. In section 4 we adapt Kurtz's theorem, which originally deals with continuous state space Markov chains, to the discrete state space setting. In section 5, we apply Kurtz's theorem in order to prove the convergence of the Moran model to Eigen's model. Finally, in section 6, we prove the convergence of the invariant probability measure of the Moran model to the unique stationary solution of Eigen's system of differential equations.

2 The Eigen and Moran models

We present here Eigen's quasispecies model and a discrete Moran model. Consider a set of N different genotypes, labelled from 1 to N . Both Eigen's model and the Moran model describe the evolution of a population of individuals having genotypes $1, \dots, N$. In both models the evolution of the population is driven by two main forces: selection and mutation. The selection and mutation mechanisms depend only on the genotypes, and are common to both models. Selection is performed with a fitness landscape $(f_i)_{1 \leq i \leq N}$, f_i being the reproduction rate of an individual having genotype i . The mutation scheme is encoded in a mutation matrix $(Q_{ij})_{1 \leq i, j \leq N}$, Q_{ij} being the probability that an individual having genotype i mutates into an individual having genotype j . The mutation matrix is assumed to be stochastic, i.e., its entries are non-negative and the rows add up to 1. Eigen's model is a system of differential equations, while the Moran model is a Markov chain. In order to ensure existence and uniqueness of the stationary solutions of Eigen's model, as well as of the invariant probability measure of the Moran model, we will further assume that the matrix $(W(i, j))_{1 \leq i, j \leq N}$ defined by $W(i, j) = f_i Q_{ij}$ is irreducible.

Eigen's model. Eigen originally formulated the quasispecies model to explain the evolution of a population of macromolecules. The evolution of the concentration of the different genotypes is driven by a system of differential equations, obtained from the theory of chemical kinetics. Let us denote by \mathcal{S}^N the unit simplex, i.e.,

$$\mathcal{S}^N = \{x \in \mathbb{R}^N : x_i \geq 0, 1 \leq i \leq N \text{ and } x_1 + \dots + x_N = 1\}.$$

An element $x \in \mathcal{S}^N$ represents a population in which the concentration of the individuals having the i -th genotype is x_i , for $1 \leq i \leq N$. Let us denote by $x(t)$ the population at time $t \geq 0$. Eigen's model describes the dynamics of $x(t)$ through the following system of differential equations:

$$(*) \quad x'_j(t) = \sum_{i=1}^N x_i(t) f_i Q_{ij} - x_j(t) \sum_{i=1}^N x_i(t) f_i, \quad 1 \leq j \leq N.$$

The first term in the differential equation accounts for the production of individuals having genotype j , while the second term accounts for the destruction of individuals having genotype j , and helps to keep the total concentration constant.

Theorem 2.1. *Under the hypothesis that the matrix W is irreducible, the system (*) has a unique stationary solution ρ^* . Moreover, for every $x^0 \in \mathcal{S}^N$, the solution $x(t)$ of (*) with initial condition $x(0) = x^0$ converges to ρ^* when t goes to infinity.*

The proof of this theorem can be found in several different articles [2, 11, 12, 21], it relies on the Perron–Frobenius theorem for positive irreducible matrices. In fact, the stationary solution ρ^* is nothing but the Perron–Frobenius eigenvector of the matrix W . The Perron–Frobenius eigenvalue ϕ of the matrix W corresponds to the mean fitness of the population at equilibrium:

$$\phi = \sum_{i=1}^N \rho_i^* f_i.$$

A recent review on Eigen's quasispecies model can be found in [20].

The Moran model. Moran models aim at describing the evolution of a finite population. The dynamics of the population is stochastic, the evolution is described by a Markov chain. Loosely speaking, the Moran model evolves as follows: at each step of time, an individual is selected from the current population according to its fitness, this individual then produces an offspring, which is subject to mutations. Finally, an individual chosen uniformly at random from the population is replaced by the offspring. The state space of the Moran process will be the set \mathcal{P}_N^m of the ordered partitions of the integer m in at most N parts:

$$\mathcal{P}_N^m = \{ z \in \mathbb{N}^N : z_1 + \dots + z_N = m \}.$$

An element $z \in \mathcal{P}_N^m$ represents a population in which z_i individuals have the genotype i , for $1 \leq i \leq N$. The only allowed changes at each time step

consist in replacing an individual from the current population by a new one. If we denote by $(e_i)_{1 \leq i \leq N}$ the canonical basis of \mathbb{R}^N , the only allowed changes in a population are of the form

$$z \longrightarrow z - e_h + e_j \quad 1 \leq h, j \leq N.$$

Let λ be a constant such that $\lambda \geq \max\{f_i : 1 \leq i \leq N\}$. The Moran process is the Markov chain $(Z_n)_{n \geq 0}$ having state space \mathcal{P}_N^m and transition matrix p given by: for all $z \in \mathcal{P}_{\ell+1}^m$ and $h, j \in \{1, \dots, N\}$ such that $h \neq j$,

$$p(z, z - e_h + e_j) = \frac{z_h}{m} \times \frac{1}{\lambda m} \sum_{i=1}^N z_i f_i Q_{ij}.$$

The other non-diagonal coefficients of the transition matrix are null, the diagonal coefficients are arranged so that the matrix is stochastic, i.e., the entries are non-negative and the rows add up to 1. Under the hypothesis that the matrix W is irreducible, the Moran process is an ergodic Markov chain, and has a unique invariant probability measure μ .

3 Main results

Our aim is to show that Eigen's quasispecies model arises as the infinite population limit of the Moran model. More precisely, we will prove the following result:

Theorem 3.1. *Let $(Z_n)_{n \geq 0}$ be the Moran process described above. Suppose that we have the convergence of the initial conditions towards $x^0 \in \mathcal{S}^N$:*

$$\lim_{m \rightarrow \infty} \frac{1}{m} Z_0 = x^0.$$

Then, for every $\delta, T > 0$, we have

$$\lim_{m \rightarrow \infty} P \left(\sup_{0 \leq t \leq T} \left| \frac{1}{m} Z_{\lfloor \lambda m t \rfloor} - x(t) \right| > \delta \right) = 0,$$

where $(x(t))_{t \geq 0}$ is the solution of () with initial condition $x(0) = x^0$.*

This result is a consequence of theorem 4.7 in [13]. In order to prove the result, we proceed in two steps. In section 4, we state theorem 4.7 in [13],

and in section 5, we show that all the hypotheses needed to apply the theorem are fulfilled in our particular setting. We remark that a similar result has been proven in [5], for a continuous-time model where mutations are not coupled to the reproduction events.

We have denoted by μ the unique invariant probability measure of the Moran process. Consider the image ν of the measure μ by the map $z \in \mathcal{P}_N^m \mapsto z/m \in \mathcal{S}^N$. We will show that the probability measure ν converges to the Dirac mass at the unique stationary solution of Eigen's system, ρ^* .

Theorem 3.2. *When m goes to infinity, the measure ν converges weakly to the Dirac mass at ρ^* , i.e., for every continuous mapping $g : \mathcal{S}^N \rightarrow \mathbb{R}$,*

$$\lim_{m \rightarrow \infty} \int_{\mathcal{P}_N^m} g\left(\frac{z}{m}\right) \mu(dz) = \lim_{m \rightarrow \infty} \int_{\mathcal{S}^N} g(x) \nu(dx) = g(\rho^*).$$

This theorem will be proven in section 6. For $1 \leq i \leq N$, let us define the quantity ρ_i by:

$$\rho_i = \lim_{n \rightarrow \infty} E\left(\frac{Z_n(i)}{m}\right).$$

Since the Markov chain $(Z_n)_{n \geq 0}$ is ergodic, the limits are well defined. The following corollary is an immediate consequence of the previous theorem.

Corollary 3.3. *For every $i \in \{1, \dots, N\}$, we have, $\lim_{m \rightarrow \infty} \rho_i = \rho_i^*$.*

4 Convergence of a family of Markov chains

Let $d \geq 1$ and let E be a subset of \mathbb{R}^d . Let $((X_n^m)_{n \geq 0}, m \geq 1)$ be a sequence of discrete time Markov chains with state spaces $E_m \subset E$ and transition matrices $(p^m(x, y))_{x, y \in E_m}$. Let $F : \mathbb{R}^d \rightarrow \mathbb{R}^d$ and consider the system of differential equations

$$x'_i(t) = F_i(x(t)), \quad 1 \leq i \leq N.$$

Theorem 4.7 in [13] gives a series of sufficient conditions under which the sequence of Markov chains $(X^m)_{m \geq 1}$ converges to a solution of the above system of differential equations. The original statement of theorem 4.7 in [13] is written for the more general setting of continuous state space Markov chains. We modify just the notation in [13] in order to state the result in a way which is more suited to our particular setting. Theorem 4.7 in [13] can be applied if the following set of conditions is satisfied. There exist sequences of positive numbers $(\alpha_m)_{m \geq 1}$ and $(\varepsilon_m)_{m \geq 1}$ such that

1. $\lim_{m \rightarrow \infty} \alpha_m = \infty$ and $\lim_{m \rightarrow \infty} \varepsilon_m = 0$.
2. $\sup_{m \geq 1} \sup_{x \in E_m} \alpha_m \sum_{y \in E_m} |y - x| p^m(x, y) < \infty$.
3. $\lim_{m \rightarrow \infty} \sup_{x \in E_m} \alpha_m \sum_{y \in E_m: |y-x| > \varepsilon_m} |y - x| p^m(x, y) = 0$.

Define, for $m \geq 1$, $F^m(x) = \alpha_m \sum_{y \in E_m} (y - x) p^m(x, y)$.

4. $\lim_{m \rightarrow \infty} \sup_{x \in E_m} |F^m(x) - F(x)| = 0$.
5. There exists a constant M such that

$$\forall x, y \in E, \quad |F(x) - F(y)| \leq M|x - y|.$$

Theorem 4.1 (Kurtz). *Suppose that conditions 1–5 are satisfied. Suppose further that we have the convergence of the initial conditions*

$$\lim_{m \rightarrow \infty} X_0^m = x^0.$$

Then, for every $\delta, T > 0$, we have

$$\lim_{m \rightarrow \infty} P\left(\sup_{0 \leq t \leq T} |X_{[\alpha_m t]}^m - x(t)| > \delta\right) = 0.$$

5 Proof of theorem 3.1

Let $(Z_n)_{n \geq 0}$ be the Moran process defined in section 2. Our aim is to apply theorem 4.1 to the sequence of Markov chains $((Z_n/m)_{n \geq 0}, m \geq 1)$. We only need to find the appropriate sequences $(\alpha_m)_{m \geq 1}$ and $(\varepsilon_m)_{m \geq 1}$ and verify that conditions 1–5 are satisfied in our setting. For $m \geq 1$, let $\alpha_m = \lambda m$ and $\varepsilon_m = 2/m$. The sequences $(\alpha_m)_{m \geq 1}$ and $(\varepsilon_m)_{m \geq 1}$ obviously verify condition 1. As for condition 2, we have, for $z \in \mathcal{P}_N^m$

$$\sum_{z' \in \mathcal{P}_N^m} \left| \frac{z}{m} - \frac{z'}{m} \right| p(z, z') = \sum_{i,j=1}^N \left| -\frac{e_i}{m} + \frac{e_j}{m} \right| p(z, z - e_i + e_j) \leq \frac{\sqrt{2}}{m}.$$

Thus,

$$\sup_{m \geq 1} \sup_{z \in \mathcal{P}_N^m} \alpha_m \sum_{z' \in \mathcal{P}_N^m} \left| \frac{z'}{m} - \frac{z}{m} \right| p(z, z') \leq \lambda \sqrt{2} < \infty,$$

as required for condition 2. Since $p(z, z') > 0$ if and only if $|z - z'| \leq \sqrt{2}$, for all $m \geq 1$ and $z \in \mathcal{P}_N^m$, we have

$$\sum_{z' \in \mathcal{P}_N^m: |z' - z| > m\epsilon_m} \left| \frac{z'}{m} - \frac{z}{m} \right| p(z, z') = 0,$$

and condition 3 is also satisfied. Let $F : \mathbb{R}^N \rightarrow \mathbb{R}^N$ be the function defined by

$$\forall i \in \{1, \dots, N\}, \quad \forall x \in \mathbb{R}^N, \quad F_i(x) = \sum_{j=1}^N f_j Q_{ji} x_j - x_i \sum_{j=1}^N f_j x_j.$$

Since all the partial derivatives of F are bounded on the simplex \mathcal{S}_N , F is a Lipschitz function on \mathcal{S}_N , i.e., condition 5 holds. Finally, let us compute, for $m \geq 1$ and $x \in \mathcal{P}_N^m/m$, the value of $F^m(x)$. By definition,

$$F^m(x) = \lambda m \sum_{z \in \mathcal{P}_N^m} \left(\frac{z}{m} - x \right) p(mx, z) = \lambda \sum_{i,j=1}^N (-e_i + e_j) p(mx, mx - e_i + e_j).$$

Thus, for $i \in \{1, \dots, N\}$ we have

$$\begin{aligned} F_i^m(x) &= \lambda \sum_{k:k \neq i} p(mx, mx - e_k + e_i) - \lambda \sum_{k:k \neq i} p(mx, mx - e_i + e_k) \\ &= \sum_{k:k \neq i} x_k \sum_{j=1}^N f_j Q_{ji} x_j - \sum_{k:k \neq i} x_i \sum_{j=1}^N f_j Q_{jk} x_j. \end{aligned}$$

Since $x_1 + \dots + x_N = 1$ and for all $i \in \{1, \dots, N\}$, $Q_{i1} + \dots + Q_{iN} = 1$,

$$F_i^m(x) = (1 - x_i) \sum_{j=1}^N f_j Q_{ji} x_j - x_i \sum_{j=1}^N f_j (1 - Q_{ji}) x_j = \sum_{j=1}^N f_j Q_{ji} x_j - x_i \sum_{j=1}^N f_j x_j.$$

Thus, the function F^m coincides with the function F on the set \mathcal{P}_N^m/m , which readily implies condition 4. Since all five conditions are satisfied, we can apply theorem 4.1 to the sequence of Markov chains $((Z_n/m)_{n \geq 0}, m \geq 1)$ and we obtain the desired result.

6 Proof of theorem 3.2

We proceed now to the proof of theorem 3.2. Throughout this whole section, we work with the 1-norm on \mathbb{R}^N , which we denote by $|\cdot|_1$. An open ball of

radius r (with respect to the distance derived from the 1–norm) and center x will be represented by $B(x, r)$. The proof will rely on the theorem 3.1 as well as on the properties of the system of differential equations (*). Let us define the mapping $b : \mathcal{S}^N \rightarrow \mathcal{S}^N$ by

$$\forall x \in \mathcal{S}^N \quad \forall j \in \{1, \dots, N\} \quad b_j(x) = \sum_{i=1}^N x_i f_i Q_{ij} - x_j \sum_{i=1}^N x_i f_i.$$

Lemma 6.1. *The mapping $b : \mathcal{S}^N \rightarrow \mathcal{S}^N$ is a Lipschitz function with Lipschitz constant $L \leq 3\lambda N$, i.e.,*

$$\forall x, y \in \mathcal{S}^N \quad |b(x) - b(y)|_1 \leq 3\lambda N |x - y|_1.$$

Proof. Let $x, y \in \mathcal{S}^N$ and $j \in \{1, \dots, N\}$. We have,

$$\begin{aligned} |b_j(x) - b_j(y)| &\leq \sum_{i=1}^N |x_i - y_i| f_i Q_{ij} + \left| x_j \sum_{i=1}^N x_i f_i - y_j \sum_{i=1}^N y_i f_i \right| \\ &\leq \lambda \sum_{i=1}^N |x_i - y_i| + x_j \sum_{i=1}^N |x_i - y_i| f_i + |x_j - y_j| \sum_{i=1}^N y_i f_i \\ &\leq \lambda \sum_{i=1}^N |x_i - y_i| + \lambda \sum_{i=1}^N |x_i - y_i| + \lambda \sum_{i=1}^N |x_i - y_i| \leq 3\lambda |x - y|_1. \end{aligned}$$

We conclude that for all $x, y \in \mathcal{S}^N$,

$$|b(x) - b(y)|_1 = \sum_{j=1}^N |b_j(x) - b_j(y)| \leq 3\lambda N |x - y|_1,$$

as desired. □

The system of differential equations (*) can now be expressed by means of the map b as $x'(t) = b(x(t))$.

Proposition 6.2. *For every $\delta > 0$, there exists $T(\delta) > 0$ such that for every $x^0 \in \mathcal{S}^N$*

$$\forall t \geq T(\delta) \quad |x(t) - \rho^*|_1 < \delta.$$

Where ρ^ is the unique stationary solution of (*), as given by theorem 2.1, and $(x(t))_{t \geq 0}$ is the solution of (*) with initial condition $x(0) = x^0$.*

Proof. Let $\delta > 0$. By theorem 2.1, there exists $0 < \delta' < \delta$ such that for every initial condition $x^0 \in B(\rho^*, \delta')$, the solution $(x(t))_{t \geq 0}$ of (*) satisfies

$$\forall t \geq 0 \quad |x(t) - \rho^*|_1 < \delta.$$

Define, for $x^0 \in \mathcal{S}^N$, the time $T(x^0)$ by:

$$T(x^0) = \inf \{ t \geq 0 : x(t) \in B(\rho^*, \delta'), x(0) = x^0 \}.$$

Note that in view of theorem 2.1, $T(x^0) < +\infty$ for every $x^0 \in \mathcal{S}^N$. For $x^0, y^0 \in \mathcal{S}^N$, let $(x(t))_{t \geq 0}$ and $(y(t))_{t \geq 0}$ be the solutions of (*) with initial conditions $x(0) = x^0$ and $y(0) = y^0$. Since $b : \mathcal{S}^N \rightarrow \mathcal{S}^N$ is a Lipschitz function with Lipschitz constant smaller than $3\lambda N$, we have, for every $t \geq 0$,

$$\begin{aligned} |x(t) - y(t)|_1 &\leq |x^0 - y^0|_1 + \int_0^t |b(x(s)) - b(y(s))|_1 ds \\ &\leq |x^0 - y^0|_1 + 3\lambda N \int_0^t |x(s) - y(s)|_1 ds. \end{aligned}$$

Thus, by Gronwall's lemma,

$$|x(t) - y(t)|_1 \leq |x^0 - y^0|_1 e^{3\lambda N t}.$$

We conclude from this inequality that $T(x^0)$ is an upper semi-continuous function of $x^0 \in \mathcal{S}^N$. Since \mathcal{S}^N is compact, $T(x^0)$ attains its maximum $T < +\infty$ on \mathcal{S}^N , from where the statement of the corollary follows. \square

We proceed now to the proof of theorem 3.2. Consider a continuous mapping $g : \mathcal{S}^N \rightarrow \mathbb{R}$, and let us show that

$$\lim_{m \rightarrow \infty} \int_{\mathcal{P}_{\ell+1}^m} g\left(\frac{z}{m}\right) \mu(dz) = g(\rho^*).$$

By the ergodic theorem for Markov chains, the first integral can be expressed as

$$\int_{\mathcal{P}_{\ell+1}^m} g\left(\frac{z}{m}\right) \mu(dz) = \lim_{T \rightarrow \infty} E\left(\frac{1}{T} \int_0^T g\left(\frac{Z_{\lfloor \lambda m t \rfloor}}{m}\right) dt\right).$$

Let $\varepsilon > 0$ and choose $\delta > 0$ such that

$$|x - \rho^*|_1 < \delta \implies |g(x) - g(\rho^*)|_1 < \varepsilon.$$

As we have shown in the previous proposition, there exists $T(\delta/3) > 0$ such that for every $x^0 \in \mathcal{S}^N$, the solution $(x(t))_{t \geq 0}$ of (*) with initial condition $x(0) = x^0$ satisfies

$$\forall t \geq T(\delta/3) \quad |x(t) - \rho^*|_1 < \delta/3.$$

Let $T_1 > T(\delta/3)$. By applying the Markov property on the times $T_1, 2T_1, \dots$, we get, for all $T > 0$,

$$\begin{aligned} E \left(\left| \int_0^T g \left(\frac{Z_{\lfloor \lambda m t \rfloor}}{m} \right) dt - T g(\rho^*) \right| \right) &\leq \sum_{k=0}^{\lfloor T/T_1 \rfloor} \int_{kT_1}^{(k+1)T_1} \left| g \left(\frac{Z_{\lfloor \lambda m t \rfloor}}{m} \right) - g(\rho^*) \right|_1 dt \\ &\leq (\lfloor T/T_1 \rfloor + 1) \sup_{z \in \mathcal{P}_{\ell+1}^m} E \left(\int_0^{T_1} \left| g \left(\frac{Z_{\lfloor \lambda m t \rfloor}}{m} \right) - g(\rho^*) \right|_1 dt \mid Z_0 = z \right). \end{aligned}$$

Let $z \in \mathcal{P}_N^m$ and let us denote by P_z, E_z the probability and the expectation for the process $(Z_n)_{n \geq 0}$ with initial point z . Let $z \in \mathcal{P}_N^m$, and let $(x(t))_{t \geq 0}$ be the solution of (*) with initial condition $x(0) = z/m$. We have,

$$\begin{aligned} E_z \left(\int_0^{T_1} \left| g \left(\frac{Z_{\lfloor \lambda m t \rfloor}}{m} \right) - g(\rho^*) \right|_1 dt \right) &= E_z \left(\int_0^{T_1} \left| g \left(\frac{Z_{\lfloor \lambda m t \rfloor}}{m} \right) - g(\rho^*) \right|_1 dt \mathbf{1}_{\sup_{0 \leq t \leq T_1} \left| \frac{Z_{\lfloor \lambda m t \rfloor}}{m} - x(t) \right|_1 > \delta/3} \right) \\ &\quad + E_z \left(\int_0^{T_1} \left| g \left(\frac{Z_{\lfloor \lambda m t \rfloor}}{m} \right) - g(\rho^*) \right|_1 dt \mathbf{1}_{\sup_{0 \leq t \leq T_1} \left| \frac{Z_{\lfloor \lambda m t \rfloor}}{m} - x(t) \right|_1 \leq \delta/3} \right) \\ &\leq 2T_1 \sup_{x \in \mathcal{S}^N} |g(x)| P_z \left(\sup_{0 \leq t \leq T_1} \left| \frac{Z_{\lfloor \lambda m t \rfloor}}{m} - x(t) \right|_1 > \delta/3 \right) \\ &\quad + 2T(\delta/3) \sup_{x \in \mathcal{S}^N} |g(x)| + (T_1 - T(\delta/3))\varepsilon. \end{aligned}$$

Take T_1 large enough so that $2T(\delta/3) \sup_{x \in \mathcal{S}^N} |g(x)|/T_1 < \varepsilon$. If the probability in the above sum converges to zero when m goes to infinity, uniformly on $z \in \mathcal{P}_N^m$, we conclude that, for m large enough

$$E_z \left(\frac{1}{T_1} \int_0^{T_1} \left| g \left(\frac{Z_{\lfloor \lambda m t \rfloor}}{m} \right) - g(\rho^*) \right|_1 dt \right) \leq 3\varepsilon.$$

Thus, it remains to prove the uniformity of the limit. According to theorem 3.1, for every $\varepsilon, \delta, T > 0$ and $x^0 \in \mathcal{S}^N$, there exist $m(x^0) \in \mathbb{N}$ and $\delta'(x^0) > 0$ such that for all $m \geq m(x^0)$ and $z \in \mathcal{P}_N^m$ satisfying $z/m \in B(x^0, \delta'(x^0))$,

$$P_z \left(\sup_{0 \leq t \leq T} \left| \frac{Z_{\lfloor \lambda m t \rfloor}}{m} - x(t) \right|_1 > \delta \right) < \varepsilon,$$

where $(x(t))_{t \geq 0}$ is the solution of $(*)$ with initial condition $x(0) = x^0$. The collections of balls $\{B(x^0, \delta'(x^0)), x^0 \in \mathcal{S}^N\}$ being an open cover of the compact set \mathcal{S}^N , we can extract a finite subcover, and take the maximum of the $m(x^0)$ on this subcover, which proves the desired uniformity result.

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