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A STOCHASTIC ANALYSIS OF PARTICLE SYSTEMS WITH PAIRING

VINCENT FROMION, PHILIPPE ROBERT, AND JANA ZAHERDDINE

ABSTRACT. Motivated by a general principle governing numerous regulation mechanisms in biological cells, we investigate a general interaction scheme between different populations of particles and specific particles, referred to as agents. Assuming that each particle follows a random path in the medium, when a particle and an agent meet, they may bind and form a pair which has some specific functional properties. Such a pair is also subject to random events and it splits after some random amount of time. In a stochastic context, using a Markovian model for the vector of the number of paired particles, and by taking the total number of particles as a scaling parameter, we study the asymptotic behavior of the time evolution of the number of paired particles. Two scenarios are investigated: one with a large but fixed number of agents, and the other one, the dynamic case, when agents are created at a bounded rate and may die after some time when they are not paired. A first order limit theorem is established for the time evolution of the system in both cases. The proof of an averaging principle of the dynamic case is one of the main contributions of the paper. Limit theorems for fluctuations are obtained in the case of a fixed number agents. The impact of dynamical arrivals of agents on the level of pairing of the system is discussed.

CONTENTS

1. Introduction	1
2. Stochastic Model	5
3. Fixed Number of Agents	8
4. Dynamical Arrivals	16
References	27
Biological Background	28

1. INTRODUCTION

In this paper we investigate a general mechanism of interaction between different populations of particles and specific particles, agents, in some environment. Assuming that each of the particles follows a random path in the medium, when a particle and an agent meet, they may form a pair which has a specific functional property in the medium. Such a pair is also subject to random events, it splits after some random amount of time. The efficiency of the pairing mechanism is analyzed with the time evolution of the number of paired particles of each type.

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1.1. Motivation. The initial motivation comes from molecular biology where this is an almost ubiquitous phenomenon occurring in biological cells. It can be (roughly) described as follows: different types of macro-molecules (ribosomes, or polymerases for example), referred to as *particles*, are in charge of producing some of the functional components necessary to the development of the cell (mRNAs, proteins). Specific macro-molecules, referred to as *agents* in the paper, like small RNAs, have a regulation role in the cell. Agents can pair/bind with particles to block, or to speed-up, their activity. Due to thermal noise, a pair agent-particle splits after some time. The dynamic behavior of the systems investigated are described in terms of binding/unbinding operations of agents and particles. See Section A of the Appendix for a more detailed presentation of these aspects.

1.2. Literature. A typical representation of pairing mechanisms in the literature, written as a chemical reaction, is of the type,



where the chemical species are as follows: \mathcal{Z} is associated to what we call agents (enzymes, small RNAs, ...), \mathcal{F}_j is for particles of type $j \in \{1, \dots, J\}$ (RNAs, polymerases, ...). The species $\mathcal{Z}\mathcal{F}_j$ is for pairs of \mathcal{Z} and \mathcal{F}_j and \mathcal{G}_j is for a “product” of type j , it can be \mathcal{F}_j . In a deterministic setting the leads to a set of ODEs for a dynamical system $(X_A(t), A \in \mathcal{Z}, \mathcal{F}_j, \mathcal{Z}\mathcal{F}_j, \mathcal{G}_j)$, for example, for $(X_{\mathcal{Z}\mathcal{F}_j}(t))$ it gives

$$(2) \quad \frac{d}{dt} X_{\mathcal{Z}\mathcal{F}_j}(t) = \kappa_j^+ X_{\mathcal{Z}}(t) X_{\mathcal{F}_j}(t) - \kappa_j^- X_{\mathcal{Z}\mathcal{F}_j}(t)$$

for some constants $\kappa_j^\pm \geq 0$. Note the quadratic term on the right hand side. Investigations are generally on the stability of these dynamical systems. See Petrides and Vinnicombe [24], Del Giudice et al. [7] and Jayaprakash and Das [18]. See Section 2 for a brief presentation of this formalism.

In a stochastic context, this is represented as a Markov process whose state descriptor is the vector of the number of copies of the different chemical species. Simulations and numerical analysis of the associated Fokker-Planck equations have been used to study these phenomena, see Petrides and Vinnicombe [24].

The technical context is related to the celebrated Michaelis-Menten kinetics. These chemical reactions involve enzyme, substrate and product macro-molecules, whose associated chemical species are denoted respectively as \mathcal{E} , \mathcal{S} and \mathcal{P} . The chemical reaction



has been investigated for some time now. The basic assumption for these models is that there are few copies of chemical species \mathcal{E} but a large number of copies of substrate, so that the reaction rate is large (for the chemical reaction on the left). In a deterministic setting it leads to a system of non-polynomial ODEs. In a stochastic context, these ODEs can be obtained via the proof of an averaging principle. See Michaelis and Menten [21] and for a general overview Sanft et al. [28] and Cornish-Bowden [5].

Averaging principles also play an important role in our paper. For the mathematical point of view, agents may be seen as playing the role of enzymes in our model. Nevertheless our framework is not really that of Michaelis-Menten. Their number is nevertheless not fixed in our main model of Section 4. As we will see, the production of agents has a strong impact on the qualitative behavior of the system.

As it can be expected, the quadratic expressions due to pairing mechanisms, like in Relation (2), are at the origin of some technical difficulties in the proof of limit theorems.

1.3. Stochastic Model. There are J types of particles. For $1 \leq j \leq J$, N_j is the total number of particles of type j , this quantity is assumed to be fixed. The total number of particles is $N = N_1 + \dots + N_J$, it is our scaling parameter. A Markovian stochastic model is considered, each event occurs after an amount of time with an exponential distribution and the corresponding random variables are assumed to be independent.

There is only type of agent. An agent and a particle of type $j \in \{1, \dots, J\}$ bind/pair at rate λ_j , and, in a reverse operation, such a pair split into an agent and a particle of type j at rate η_j . An agent or a particle which is not paired is said to be *free*.

The variables of interest are

$$(F_N(t), Z_N(t)) \stackrel{\text{def.}}{=} ((F_{N,j}(t), j=1, \dots, J), Z_N(t))$$

where, for $1 \leq j \leq J$ and $t \geq 0$, $F_j(t)$ is the number of free particles of type j , i.e. not paired with an agent, and $(Z_N(t))$ is the process for the number of free agents. When the goal of pairing mechanism is of reducing the activity of the particles, this will be referred to as *sequestration* of particles, the objective is of minimizing

$$\left(\sum_{j=1}^J \frac{F_{N,j}(t)}{N} \right)$$

the process of the fraction of the number of free particles. We analyze the asymptotic behavior, when N goes to infinity, of the time evolution of the J -dimensional process $(F_{j,N}(t)/N)$ associated to the free particles. An appropriate timescale for a non-trivial asymptotic evolution when N goes to infinity has to be determined.

In Fromion et al. [14], a related model of sequestration has been analyzed, to study the regulation of transcription. It also includes additional variables which are not considered in this paper. A component of the stochastic model is a related Markov process but in dimension 1, i.e. for $J=1$. As it will be seen, compared to the case $J=1$, the multi-dimensional aspect of our model has a significant impact on the scaling properties of the associated stochastic processes.

Two types of models for agents are analyzed.

- (a) Agents are neither created nor removed: the number of agents is fixed, of the order of N .
- (b) An agent is created at rate β and, only when it is not paired with a particle, it dies at rate δ .

Case a) is used to investigate the case when the environment does not change significantly and when there is already a large number of agents to regulate the system. Two cases are considered. In Section 3.1 the total number of agents is of the order of rN with $r \in (0, 1)$, there are much more particles than agents. It is shown that the process $(F_{j,N}(t)/N)$ is converging in distribution to the solution of an ODE. The equilibrium point of this ODE is unique and its coordinates are positive. For this system the number of free particles of type $j \in \{1, \dots, J\}$ is, of course, of the order of N .

In Section 3.2 the total number of agents is N the same as the total number of particles. It is shown that with, appropriate initial conditions, the process $(F_{j,N}(t/\sqrt{N})/\sqrt{N})$ is converging in distribution to the solution of an ODE and a central limit theorem is proved, it shows that the fluctuations are of the order of $\sqrt[4]{N}$. In this case the impact of stochasticity on the pairing mechanism is minimal since there is a fraction of the order of $1/\sqrt{N}$ of free particles.

Case b) is investigated in Section 4 for the case when, initially, there few agents (free or paired) are in the system, the goal is of investigate the growth of the number of paired particles. The proof of an averaging principle in this context is challenging for several reasons.

Since a paired agent does not die (it is not degraded), one can expect an asymptotic situation as in Section 3.2 with a negligible fraction of free particles. We show that this is not the case, in fact, formally, the behavior is similar to that of Section 3.1, but on a faster time scale and with important qualitative and technical differences.

If the system starts with few agents, in this case most of N particles are initially “free”, all agents created will pair with a free particle right away and will keep doing that, via the successive steps of pairing/splitting, as long the number of free particles is “large” so that, with high probability, pairing occurs before degradation for agents. Given the rate of creation of agents, the natural timescale to study this problem is (Nt) .

It can be expected that the multi-dimensional process

$$\left(\frac{F_N(Nt)}{N} \right) = \left(\frac{F_{j,N}(Nt)}{N} \right)$$

converges in distribution to a continuous process reflecting the asymptotic degree of pairing of the system. Due to their large transition rates, the integer-valued processes $(Z_N(Nt))$ and $(F_N(Nt))$ are “fast” processes. Because of the space scaling, $(F_N(Nt)/N)$ is an a priori “slow” process. Following the classical approach in this domain, see Papanicolaou et al. [23] in a stochastic calculus context and Kurtz [20] for its formulation for jump process. For $T > 0$, one has to consider the occupation measure associated to $(Z_N(Nt))$, i.e. this is the functional on non-negative Borelian functions on $[0, T] \times \mathbb{N}$,

$$g \longrightarrow \int_0^T g(s, Z_N(Ns)) ds.$$

If this approach allows us to derive the results of Section 3.1 for case a), where an averaging principle is proved, it does not work for case b). The sequence of processes $(F_{j,N}(Nt)/N, j=1, \dots, J)$ does *not* converge in distribution in fact. It is not tight for the topology associated to uniform convergence if the initial state does not converge to some one-dimensional curve of $[0, 1]^J$. The main convergence result of this case is Theorem 13 of Section 4. It shows that the process associated to the total number of free particles,

$$\|F_N(Nt)\| \stackrel{\text{def.}}{=} \left(\sum_{j=1}^J \frac{F_{N,j}(Nt)}{N} \right),$$

converges in distribution to a continuous process. The sequence of $[0, 1]^J$ -valued processes $(F_{j,N}(Nt)/N, 1 \leq j \leq J)$ converges in distribution, but in a weak form, via

its associated occupation measure. It turns out that the process $(\|F_N(Nt)\|)$ determines, in some way, the behavior of the coordinates of $(F_N(Nt))$. For N large $(F_{N,j}(Nt))$ can in fact be represented as a curve of $[0, 1]^J$ determined by $\|F_N(Nt)\|$. In Fromion et al. [14], no such difficulty shows up since $J=1$.

Intuitively, it is shown that, in the limit, the number of free particles is of the order of N , as in case a) but for some specific $r < 1$. These results stress the impact of dynamical arrivals and departures of agents. In particular the fraction of paired particles is asymptotically strictly less than 1.

Technical difficulties are related to the lack of tightness properties of the process $(F_{j,N}(Nt)/N)$. For this reason the definition of the occupation measure is extended to include also “slow” processes and not only the fast processes as it is classical in the context of averaging principles. As a functional on Borelian functions on $[0, T] \times [0, 1]^J \times \mathbb{N}$, the occupation measure is expressed as

$$g \longrightarrow \int_0^T g \left(s, \frac{F_N(Ns)}{N}, Z_N(Ns) \right) ds.$$

The investigation of the limiting behavior of this sequence of occupation measures is the main topic of Section 4, including the identification of possible limiting points.

The reason of this behavior is essentially due to the interaction of several fast time scales. At the normal time scale (t) , if the components of the vector $F_N(t)$ are already of the order of N , the pairing/splitting events occur at a rate proportional to N . Since the natural time scaling for case b) is sped-up as (Nt) , roughly speaking, the pairing/splitting events will be instantaneously at equilibrium, at the first order, at any “time” t for the current “mass” $\|F_N(Nt)\|$. In particular, if the initial point $\bar{F}_N(0)$ does not converge to the equilibrium associated to the mass $\|F_N(0)\|$, there cannot be a convergence in a neighborhood of $t=0$, this is the one-dimensional curve mentioned above.

Outline of the Paper. Section 2 introduces notations and the Markovian process used to investigate pairing mechanisms. Section 3 analyzes the static case when the number of agents is fixed and in Section 4 a stochastic averaging principle is proved when agents are created and degraded. To motivate the design of such stochastic models, Section A of the appendix presents several examples of regulation mechanisms in biological cells. Section B of the appendix is a quick reminder of classical limit results for $M/M/1$ and $M/M/\infty$ queues. These queues play an important role in the design of couplings used in the proofs of our limit theorems.

2. STOCHASTIC MODEL

Definitions and Notations. If H is a locally compact metric space, $\mathcal{C}_c(H)$ is the space of continuous functions with compact support endowed with the topology of uniform convergence. We denote by $\mathcal{M}^+(H)$ the set of non-negative Radon measures on H and $\mathcal{M}_1(H)$, the set of probability distributions on H , both spaces are endowed with the weak topology. See Rudin [27]. Throughout the paper convergence in distribution of a sequence of jump processes $(U_N(t))$ to a process $(U(t))$ is understood with respect to the topology of uniform convergence on compact sets for càdlàg functions. See Chapter 2 of Billingsley [4] for example.

For $J \in \mathbb{N}$, if $x = (x_i)$, $y = (y_i) \in \mathbb{R}^J$, define

$$(3) \quad \|x\| \stackrel{\text{def.}}{=} |x_1| + \cdots + |x_J|, \quad \langle x, y \rangle = x_1 y_1 + \cdots + x_J y_J,$$

and,

$$(4) \quad \bar{x} = \max(x_j, 1 \leq j \leq J) \text{ and } \underline{x} = \inf(x_j, 1 \leq j \leq J).$$

We now introduce the main definitions for our stochastic model. There are J different types of particles. The total number of particles of type $j \in \{1, \dots, J\}$ is $C_{j,N}$, and $N = C_{1,N} + \dots + C_{J,N}$, the total number of particles is a fixed number, it is also our scaling parameter. It is assumed that,

$$(5) \quad \lim_{N \rightarrow +\infty} \left(\frac{C_{j,N}}{N} \right) = c = (c_j)$$

holds, for some $c \in (0, 1)^J$ such that $c_1 + c_2 + \dots + c_J = 1$.

State Space. The state space is

$$\mathcal{S}_N = \{x = (f, z) = ((f_j), z) \in \mathbb{N}^{J+1} : f_j \leq C_{j,N}, \forall 1 \leq j \leq J\},$$

and, if $t \geq 0$,

- for $1 \leq j \leq J$, $F_{j,N}(t)$ denotes the number of free particles of type j at time t and $F_N(t) = (F_{j,N}(t), 1 \leq j \leq J)$;
- The number of free agents at time t is $Z_N(t)$;
- The state of the process at time t is $X_N(t) = (F_N(t), Z_N(t)) \in \mathcal{S}_N$.

The number of agents paired with a particle of type j at time t is therefore $S_{j,N}(t) = C_{j,N} - F_{j,N}(t)$. In state $(F_N(t), Z_N(t))$, the total number of free particles is $\|F_N(t)\|$.

Transitions. The dynamical behavior of $(X_N(t))$ is driven by several types of transitions.

- (a) A given particle of type j and a given agent are paired at rate λ_j ;
- (b) A pair (particle of type j , agent) is split at rate $\eta_j > 0$ to give a particle of type j and a free agent;
- (c) Agents are created at rate $\beta \geq 0$ and a *free* agent dies, is degraded, at rate $\delta > 0$. An agent paired to a particle cannot die.

The state process $(X_N(t)) = (F_N(t), Z_N(t))$ is almost surely a *càdlàg function*, i.e. a right-continuous function with left limits at any point of $(0, +\infty)$. It is described as an irreducible Markov process on \mathcal{S}_N whose Q -matrix Q_F is given by

$$(f, z) = ((f_j), z) \longrightarrow (f, z) + \begin{cases} (-e_j, -1) & \lambda_j f_j z, \\ (+e_j, +1) & \eta_j (C_{j,N} - f_j), \\ (0, +1) & \beta, \\ (0, -1) & \delta z, \end{cases}$$

where e_j is the j th unit vector of \mathbb{N}^J .

Note that the pairing mechanism induces quadratic transition rates in the Q -matrix.

Definition 1.

$$c = (c_j), \eta = (\eta_j), \lambda = (\lambda_j), \quad \rho_0 = \frac{\beta}{\delta} \text{ and } \rho_j = \frac{\eta_j}{\lambda_j}, j = 1, \dots, J.$$

For $y \in (0, 1)$, $\phi(y)$ is defined as the unique solution of the equation

$$(6) \quad \sum_{j=1}^J \frac{\rho_j}{\rho_j + \phi(y)} c_j = y.$$



FIGURE 1. Transitions of Pairing Mechanism, with $s = (s_j) \stackrel{\text{def.}}{=} (C_{j,N} - f_j)$.

Stochastic Differential Equations. The process $(X_N(t)) = (F_N(t), Z_N(t))$ is represented as the solution of a system of SDEs (Stochastic Differential Equations). On the probability space there are $2(J+1)$ independent Poisson processes on \mathbb{R}_+^2 with intensity measure $dx \otimes dt$, \mathcal{P}_z^+ , \mathcal{P}_z^- , \mathcal{P}_j^+ , \mathcal{P}_j^- , $j=1, \dots, J$. See Rogers and Williams [26] for example. The underlying filtration (\mathcal{F}_t) is defined by, for $t > 0$,

$$\mathcal{F}_t = \sigma \left\langle \mathcal{P}_{j/z}^\pm([a, b] \times [0, s], j=1, \dots, J), a \leq b, s \leq t \right\rangle.$$

In the following, measurability properties are assumed to be with respect to this filtration.

Let $(F_N(t), Z_N(t))$ be the solution of the SDE, for $j=1, \dots, J$,

$$(7) \quad dF_{j,N}(t) = \mathcal{P}_j^+((0, \eta_j(C_{j,N} - F_{j,N}(t-))), dt) - \mathcal{P}_j^-((0, \lambda_j F_{j,N}(t-) Z_N(t-)), dt),$$

$$(8) \quad dZ_N(t) = \mathcal{P}_z^+((0, \beta), dt) - \mathcal{P}_z^-((0, \delta Z_N(t-)), dt) + \sum_{j=1}^J dF_{j,N}(t),$$

where $U(t-)$ denotes the left-limit of the càdlàg process $(U(s))$ at $t > 0$ and with the usual notation, if $A \geq 0$ and \mathcal{P} is a Poisson point process on \mathbb{R}_+^2 ,

$$(9) \quad \mathcal{P}((0, A), dt) = \int \mathbb{1}_{\{x \leq A\}} \mathcal{P}(dx, dt).$$

By integrating these relations, we obtain, for $j=1, \dots, J$,

$$(10) \quad F_{j,N}(t) = F_{j,N}(0) + M_{j,N}(t) + \eta_j \int_0^t (C_{j,N} - F_{j,N}(s)) ds - \lambda_j \int_0^t F_{j,N}(s) Z_N(s) ds,$$

and

$$(11) \quad Z_N(t) = Z_N(0) + M_{z,N}(t) + \beta t - \delta \int_0^t Z_N(s) ds + \sum_{j=1}^J \eta_j \int_0^t (C_{j,N} - F_{j,N}(s)) ds - \lambda_j \int_0^t F_{j,N}(s) Z_N(s) ds,$$

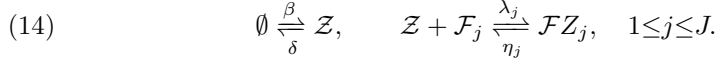
where $(M_{j,N}(t))$ and $(M_{z,N}(t))$ are square integrable martingales whose previsible increasing processes are given by

$$(12) \quad \langle M_{j,N} \rangle (t) = \left(\eta_j \int_0^t (C_{j,N} - F_{j,N}(s)) ds + \lambda_j \int_0^t F_{j,N}(s) Z_N(s) ds \right),$$

$$(13) \quad \langle M_{z,N} \rangle (t) = \left(\beta t + \delta \int_0^t Z_N(s) ds + \sum_{j=1}^J \langle M_{j,N} \rangle (t) \right).$$

Invariant Distribution. As explained in the introduction, our model can be expressed in the framework of chemical reaction networks (CRN). Since we are mainly interested in the transient behavior of our system, we just give a quick sketch. It is only mentioned as an interesting aspect of our system. See Feinberg [9] for a general introduction on CRNs.

The corresponding chemical reactions are represented as



The associated dynamical system $((f_j(t), g_j(t)), z(t))$ is defined by the ODEs

$$\begin{cases} \dot{f}_j(t) = \lambda_j f_j(t) z(t) - \eta_j g_j(t), & 1 \leq j \leq J, \\ \dot{f}_j(t) + \dot{g}_j(t) = 0, & 1 \leq j \leq J, \\ \dot{z}(t) = \beta - \delta z(t). \end{cases}$$

Its fixed point is given by $((u_j, v_j), w)$ with

$$(15) \quad w = \rho_0, \quad u_j = \frac{C_j^N}{1 + \rho_0 \rho_j} = C_j^N - v_j, \quad 1 \leq j \leq J,$$

with $\rho_0 = \beta/\delta$ and $\rho_j = \lambda_j/\eta_j$, for $1 \leq j \leq J$.

The characteristics of this CRN are:

- $m=2J+2$ chemical species: $\mathcal{Z}, \mathcal{F}_j, \mathcal{F}Z_j, j=1, \dots, J$;
- $\ell=J+1$ cycles, these are the *single linkage classes* of the CRN;
- The range, the dimension of the stoichiometric space, is $s=J+1$.

This is a CRN with deficiency $\delta=m-\ell-s=0$. A standard result, see Anderson et al. [1], gives an explicit expression of the invariant distribution π_N of $(X_N(t))$ on \mathcal{S}_N .

Proposition 2. *The invariant distribution of $(X_N(t))$ on \mathcal{S}_N is given by,*

$$\pi(f, s) = \frac{1}{Z_N} \frac{w^z}{z!} \prod_{j=1}^J \frac{u_j^{f_j}}{f_j!} \frac{v_j^{C_j^N - f_j}}{(C_j^N - f_j)!}, \quad (f, z) = ((f_j), z) \in \mathcal{S}_N,$$

where Z_N is the normalization constant and (u_j) and (v_j) are defined by Relation (15).

3. FIXED NUMBER OF AGENTS

Throughout this section the number of agents C_Z^N is fixed, of the order of rN , with $r < 1$ in Section 3.1, and is exactly N , the total number of particles, in Section 3.2. There are no creations or degradation of agents. Only pairing and splitting mechanisms operate in these cases. As explained in the introduction, the purpose

is of understanding the behavior of the system when the total number of agents does not change. Section 4 investigate a much more dynamic version of the system.

The state space of the system is $\mathcal{S}_N \stackrel{\text{def.}}{=} \prod_{j=1}^J \{0, \dots, C_j^N\}$. For a state $x=(x_j) \in \mathcal{S}_N$, the total number of paired particles with an agent is $N-x_1-\dots-x_J$. The associated process in \mathcal{S}_N is denoted as $(F_N^r(t))$ has the Markov property, its Q -matrix is given by, for $x \in \mathcal{S}_N$,

$$x \rightarrow \begin{cases} x+e_j & \eta_j (C_j^N - x_j), \\ x-e_j & \lambda_j x_j (C_Z^N - (N-x_1-\dots-x_J)), \end{cases}$$

where e_j is the j th unit vector of \mathbb{N}^J .

3.1. Overloaded Case. In this section the total number of agents is of the order of rN , with $r < 1$,

$$(16) \quad \lim_{N \rightarrow +\infty} \frac{C_Z^N}{N} = r.$$

Since there are not enough agents to handle all particles, it is clear that the number of free particles of type j , $1 \leq j \leq J$, should be of the order of N . The SDE (10) for $(F_N^r(t))$ becomes, for $1 \leq j \leq J$,

$$(17) \quad dF_{N,j}^r(t) = \mathcal{P}_{S_j}((0, \eta_j(C_j^N - F_{N,j}^r(t-))), dt) \\ - \mathcal{P}_{F_j}((0, \lambda_j F_{N,j}^r(t-) Z_N^r(t-)), dt),$$

where $(Z_N^r(t))$ is the process of free agents,

$$(18) \quad (Z_N^r(t)) = \left(C_Z^N - \sum_{j=1}^J (C_j^N - F_{N,j}^r(t)) \right) = (C_Z^N + \|F_N^r(t)\| - N).$$

We assume that the initial conditions are such that $Z_N(0) = z_0$, for some fixed $z_0 \in \mathbb{N}$, and

$$(19) \quad \lim_{N \rightarrow +\infty} \frac{F_N^r(0)}{N} = \bar{f}_0 = (\bar{f}_{0,j}) \in [0, 1]^J,$$

such that

$$(20) \quad \sum_{j=1}^J \bar{f}_{0,j} = 1 - r.$$

The last condition expresses simply that most of the agents are initially paired with particles. We will see that the number of free agents remains a finite random variable.

Definition 3. For $N > 0$, the scaled process is defined as

$$(21) \quad (\bar{F}_N^r(t)) \stackrel{\text{def.}}{=} \left(\frac{F_{N,j}^r(t)}{N}, j=1, \dots, J \right).$$

If g is non-negative Borelian function on $\mathbb{R}_+ \times \mathbb{N}$, we define the occupation measure

$$(22) \quad \langle \Lambda_N^r, g \rangle \stackrel{\text{def.}}{=} \int_{\mathbb{R}_+} g(s, Z_N^r(s)) ds.$$

Since $F_{N,j}^r(t) \leq C_j^N \leq N$, $1 \leq j \leq J$, for $t \geq 0$, the state space of the process $(\bar{F}_N^r(t))$ is included in $[0, 1]^J$.

Lemma 4. *If N is sufficiently large, there exists a coupling of the process $(Z_N^r(t))$ with $(L(Nt))$, where $(L(t))$ is an $M/M/\infty$ queue with input rate $\bar{\eta}$ and service rate $\underline{\lambda}r/2$, with*

$$\bar{\eta} = \max_j \eta_j, \text{ and } \underline{\lambda} = \min_j \lambda_j,$$

such that $L(0)=z_0$ and $Z_N^r(t) \leq L(Nt)$ holds for all $t \geq 0$.

See Section B.2 of the appendix on the $M/M/\infty$ queue.

Proof. This is a simple consequence of the fact that if $Z_N^r(t)=z \in \mathbb{N}$, the rate at which there is a jump of size $+1$, resp. -1 , is

$$\sum_{j=1}^N \eta_j (C_j^N - F_{N,j}^r(t)) \leq \bar{\eta} \sum_{j=1}^N C_j^N = \bar{\eta}N,$$

resp.

$$\sum_{j=1}^N \lambda_j F_{N,j}^r(t) \geq \underline{\lambda}(N - C_Z^N) \geq \underline{\lambda}(1-\varepsilon)N,$$

for some $\varepsilon \in (0, 1)$ if N is large enough. It is then straightforward to construct the desired coupling. \square

The integration of the SDE (17) gives the relation

$$(23) \quad \bar{F}_{j,N}^r(t) = \bar{F}_{j,N}^r(0) + M_{j,N}^r(t) - \lambda_j \int_0^t \bar{F}_{N,j}^r(s) Z_N^r(s) ds + \eta_j \int_0^t \left(\frac{C_j^N}{N} - \bar{F}_{N,j}^r(s) \right) ds,$$

The process $(M_{j,N}^r(t))$ is a martingale whose previsible increasing process is

$$(24) \quad (\langle M_{j,N}^r \rangle (t)) = \left(\frac{\lambda_j}{N} \int_0^t \bar{F}_{j,N}^r(s) Z_N^r(s) ds + \frac{\eta_j}{N} \int_0^t \left(\frac{C_j^N}{N} - \bar{F}_{N,j}^r(s) \right) ds \right).$$

Proposition 5. *Under the assumptions (5), (19), and (20) for the initial state, then for the convergence in distribution the relation*

$$\lim_{N \rightarrow +\infty} \left(\frac{F_N^r(t)}{N} \right) = (f^r(t)) = (f_j^r(t)),$$

holds, where $(x(t))$ is the solution of the ODEs, for $1 \leq j \leq J$ and $t > 0$,

$$(25) \quad \frac{d}{dt} f_j^r(t) = \lambda_j f_j^r(t) \frac{\langle \eta, c - x(t) \rangle}{\langle \lambda, x(t) \rangle} - \eta_j (c_j - f_j^r(t)),$$

with Definition 1.

Proof. By using the notations of Lemma 4 and the ergodic theorem for positive recurrent Markov processes, it is not difficult to prove that the sequence of processes

$$\left(\int_0^t L(Ns) ds \right)$$

is tight with the criterion of the modulus of continuity, see Theorem 7.3 of Billingsley [4], and that its limiting point is necessary $(\bar{\eta}/\underline{\lambda} \cdot t)$.

Since $F_{N,j}^r(t) \leq C_j^N \leq N$, for $1 \leq j \leq J$ and $t \geq 0$, with Relation (24), we obtain therefore that the process $(\langle M_{j,N}^r \rangle (t))$ is converging in distribution to 0, Doobs' Inequality gives that the same result holds for the martingale $(M_{j,N}^r(t))$.

For $T > 0$, with Relation (23), the modulus of continuity of $(\overline{F}_{j,N}^r(t))$ on the time interval $[0, T]$ is

$$\begin{aligned} \omega_{F_N, T}(\delta) &\stackrel{\text{def.}}{=} \sup_{\substack{s, t \leq T \\ |s-t| \leq \delta}} \left| \overline{F}_{j,N}^r(t) - \overline{F}_{j,N}^r(s) \right| \\ &\leq \sup_{s \leq T} |M_{j,N}^r(s)| + \lambda_j \sup_{\substack{s \leq t \leq T \\ |s-t| \leq \delta}} \int_s^t L(Nu) \, du + \delta \eta_j \frac{C_j^N}{N}. \end{aligned}$$

Again with Theorem 7.3 of Billingsley [4], we deduce that the sequence of processes $(\overline{F}_{N,j}^r(t))$ is tight.

For $K > 0$,

$$\mathbb{E}(\Lambda_N^r([0, T] \times [K, +\infty))) \leq \int_0^T \mathbb{P}(L(Ns) \geq K) \, ds = \frac{1}{N} \int_0^{NT} \mathbb{P}(L(s) \geq K) \, ds,$$

since $(L(s))$ converges in distribution to a Poisson distribution, see Section B.2 of the appendix, the last term can be made arbitrarily small for K sufficiently large. Lemma 1.3 of Kurtz [20] gives the tightness of the sequence of random measures (Λ_N^r) and any of its limiting points Λ_∞^r can be represented as,

$$\langle \Lambda_\infty^r, f \rangle = \int_{\mathbb{R}_+ \times [0,1]^J \times \mathbb{N}} f(s, x) \mu_s(dx) \, ds,$$

if f is a non-negative Borelian function on $[0, T] \times \mathbb{N}$, where (μ_s) is an optional process on $\mathcal{M}_1(\mathbb{N})$.

Hence the sequence of random variables $((\overline{F}_N^r(t)), \Lambda_\infty^r)$ is tight, we denote by $((f^r(t)), \Lambda_\infty^r)$ one of its limiting points. Since Proposition 19 establishes a similar result, but in a more difficult technical framework. The analogue of the sequence of processes $(\overline{F}_N^r(t))$ is *not* tight in this case. For this reason, we skip the proof of the fact that, in the above representation of Λ_∞^r , μ_s can be expressed as a Poisson distribution with parameter

$$\frac{\langle \eta, c - f^r(s) \rangle}{\langle \lambda, f^r(s) \rangle},$$

and that $(f^r(t))$ satisfies the ODE (25). The proposition is proved. \square

Corollary 6. *With the notations of Proposition 5, the equilibrium point f_∞^r of $(f^r(t))$ is given by*

$$f_\infty^r = \left(\frac{\eta_j c_j}{\eta_j + \lambda_j h_\infty} \right),$$

where $h_\infty = \phi(1-r)$ and ϕ is defined by Relation (6).

3.2. Critical Case. The number of agents is exactly N , the total number of particles and there are still no creation or degradation of agents. We prove that the process of the number of free particles of type $j \in \{1, \dots\}$, $(F_{N,j}^1(t))$, is of the order of \sqrt{N} , with fluctuations of the order of $\sqrt[4]{N}$. See Theorems 9 and 10.

Note that, for $t \geq 0$, the total number of free agents at time t is

$$N - \sum_{j=1}^J (C_j^N - F_{N,j}^1(t)) = \sum_{j=1}^J F_{N,j}^1(t) = \|F_N^1(t)\|.$$

The Q -matrix Q_f of $(F_{N,j}^1(t))$ is thus given by, for $x \in \mathcal{S}_N$,

$$x \rightarrow \begin{cases} x+e_j & \eta_j (C_j^N - x_j), \\ x-e_j & \lambda_j x_j \|x\|. \end{cases}$$

Lemma 7. *If, for $\eta, \lambda > 0$ and $N \geq 1$, if $(X_N(t))$ is the solution of the SDE,*

$$dX_N(t) = \mathcal{P}_{S_1}((0, \eta N), dt) - \mathcal{P}_{F_1}((0, \lambda X_N(t-)^2), dt),$$

with $X(0)=0$, then for any $T \geq 0$, there exists $K_1 > 0$ such that,

$$\lim_{N \rightarrow +\infty} \mathbb{P} \left(\sup_{t \leq NT} \frac{X_N(t)}{\sqrt{N}} \geq K_1 \right) = 0,$$

and

$$\sup_{t \geq 0} \mathbb{E} (X_N(t)^2) < +\infty.$$

Proof. We fix K_0 such that $\lambda K_0^2 > \eta$. If we define the process $(Y(t))$ by the SDE

$$dY(t) = \mathcal{P}_{S_1}((0, \eta), dt) - \mathbb{1}_{\{Y(t-) > 0\}} \mathcal{P}_{F_1}((0, \lambda K_0^2), dt),$$

with $Y(0)=0$. As in the proof of Proposition 8, by induction on the successive jumps of $(X_N(t))$, it is easy to show that the relation

$$X_N(t) \leq K_0 \sqrt{N} + Y(Nt)$$

holds almost surely for all $t > 0$. The process $(Y(t))$ is a reflected random walk on \mathbb{N} , it is usually associated to the $M/M/1$ queue. See Chapter 5 of Robert [25]. Proposition 5.11 of this reference gives that if T_A is the hitting time of A by $(Y(t))$ then the random variable

$$\left(\frac{\eta}{\lambda K_0^2} \right)^A T_A$$

is converging in distribution to an exponential random variable when A goes to infinity. This shows in particular that (T_A/A^2) is converging in distribution to infinity, hence, for any $K > 0$,

$$\lim_{N \rightarrow +\infty} \mathbb{P} \left(\sup_{t \leq T} \frac{Y(tN)}{\sqrt{N}} \geq 1 \right) = \lim_{N \rightarrow +\infty} \mathbb{P} \left(T_{\lceil \sqrt{N} \rceil} \leq TN \right) = 0.$$

This gives the first part of the lemma. We conclude the proof by setting $K_1 = K_0 + 1$ and remarking that the invariant distribution of $(Y(t))$ is a geometric distribution with parameter $\eta/(\lambda K_0^2)$ and that, with a simple coupling argument, the mapping $t \rightarrow \mathbb{E}(Y(t)^2)$ is non-decreasing. \square

The next result shows that all coordinates of $(F_N^1(t))$ are at most of the order of \sqrt{N} very quickly independently of the initial point. Theorem 9 completes this result by showing that the order of magnitude of its coordinates is exactly \sqrt{N} .

Proposition 8 (Coupling). *For all $j \in \{1, \dots, J\}$,*

$$(26) \quad F_{N,j}^1(t) \leq F_{N,j}^1(0) + X_{N,j}(t), \quad t \geq 0,$$

where the $(X_{N,j}(t))$ are the solutions of the SDEs

$$(27) \quad dX_{N,j}(t) = \mathcal{P}_{S_j}((0, \bar{\eta}N), dt) - \mathcal{P}_{F_j}((0, \underline{\lambda}X_{N,j}(t-)^2), dt), \quad 1 \leq j \leq J,$$

with $(X_j(0))=0$ and $\bar{\eta}$ and $\underline{\lambda}$ are defined by Relation (4).

There exists $\ell_0 > 0$ such that if

$$\tau_N \stackrel{\text{def.}}{=} \inf \left\{ t > 0 : F_{N,j}^1(t) \leq \left\lceil \ell_0 \sqrt{N} \right\rceil, \forall j \in \{1, \dots, J\} \right\},$$

then

$$\sup_{N \geq 1} \sup_{x \in \mathcal{S}_N} \mathbb{E}_x(\tau_N) < +\infty.$$

Proof. The Q -matrix Q_X of the Markov process $(X_{N,j}(t))$ defined by the SDEs (27) is

$$x \rightarrow \begin{cases} x + e_j & \bar{\eta}N, \\ x - e_j & \underline{\lambda}x_j^2, \end{cases}$$

clearly $q_f(x, x + e_j) \leq q_X(x, x + e_j)$ and $q_f(x, x - e_j) \geq q_X(x, x - e_j)$.

A simple coupling, by induction on the successive jumps of $(F_{N,j}^1(t))$, gives that the relation

$$F_{N,j}^1(t) \leq F_{N,j}^1(0) + X_{N,j}(t)$$

holds for all $t \geq 0$.

To prove the last assertion, in view of Relation (26), it is enough to prove it for the “maximal” initial state, i.e. $(F_{N,j}^1(0)) = (C_j^N)$. If, for $A > 0$, $\|x\| > JA\sqrt{N}$, then, if $g(x) = \|x\|$, for $x \in \mathbb{N}^J$,

$$Q_f(g)(x) \leq J\bar{\eta}N - \underline{\lambda}J^2A^2N.$$

If we choose $\ell = JA$ such that $\gamma = \underline{\lambda}\ell^2 - J\bar{\eta} > 0$, by using Proposition 8.14 and Theorem 8.13 of Robert [25], we obtain

$$\mathbb{E}(\tau_N) \leq \frac{g(F_N^1(0))}{N\gamma} = \frac{1}{\gamma}.$$

The proposition is proved. \square

Theorem 9 (Law of Large Numbers). *If*

$$\lim_{N \rightarrow +\infty} \frac{F_N^1(0)}{\sqrt{N}} = \bar{f}_0^1 = (\bar{f}_{0,j}^1), \text{ and } (\bar{F}_N(t)) \stackrel{\text{def.}}{=} \left(\frac{F_{N,j}^1(t/\sqrt{N})}{\sqrt{N}} \right),$$

then the sequence of processes $(\bar{F}_N(t))$ is converging in distribution to the solution $(\bar{f}^1(t)) = (\bar{f}_j^1(t))$ of the ODE,

$$(28) \quad (\bar{f}_j^1)'(t) = c_j \eta_j - \lambda_j \bar{f}_j^1(t) \|\bar{f}^1(t)\|,$$

with $\bar{f}^1(0) = \bar{f}_0^1$.

The equilibrium point of the ODE (28) is given by

$$(29) \quad \bar{f}_{j,\infty}^1 = (c_j \rho_j / \sqrt{c_1 \rho_1 + \dots + c_J \rho_J}),$$

where (ρ_j) is given by Definition 1.

Proof. By integration of Relation (34), we obtain, for $t \geq 0$,

$$(30) \quad \bar{F}_{N,j}(t) = \bar{F}_{N,j}(0) + M_{N,j}^0(t) + \eta_j \int_0^t \left(\frac{C_j^N}{N} - \frac{\bar{F}_{N,j}(s)}{\sqrt{N}} \right) ds - \lambda_j \int_0^t \bar{F}_{N,j}(s) \sum_{k=1}^J \bar{F}_{N,k}(s) ds,$$

where $(M_N^0(t))=(M_{N,j}^0(t), 1 \leq j \leq J)$ is the martingale defined by, for $1 \leq j \leq J$,

$$(31) \quad M_{N,j}^0(t) \stackrel{\text{def.}}{=} \frac{1}{\sqrt{N}} \int_0^{t/\sqrt{N}} [\mathcal{P}_{S_j}((0, \eta_j(C_j^N - F_{N,j}^1(s-))), ds) - \eta_j(C_j^N - F_{N,j}^1(s)) ds] \\ - \frac{1}{\sqrt{N}} \int_0^{t/\sqrt{N}} \left[\mathcal{P}_{F_j} \left(\left(0, \lambda_j F_{N,j}^1(s-) \sum_{k=1}^J \bar{F}_{N,k}(s-) \right), ds \right) \right. \\ \left. - \lambda_j F_{N,j}^1(s) \sum_{k=1}^J \bar{F}_{N,k}(s) ds \right].$$

Its previsible increasing process is given by

$$(32) \quad (\langle M_{N,j}^0 \rangle (t)) = \left(\frac{\eta_j}{\sqrt{N}} \int_0^t \left(\frac{C_j^N}{N} - \frac{\bar{F}_{N,j}(s)}{\sqrt{N}} \right) ds \right. \\ \left. + \frac{\lambda_j}{\sqrt{N}} \int_0^t \bar{F}_{N,j}(s) \sum_{k=1}^J \bar{F}_{N,k}(s) ds \right),$$

and $\langle M_{N,j}^0, M_{N,k}^0 \rangle (t) = 0$, for $1 \leq j \neq k \leq J$. Lemma 7 shows the convergence

$$\lim_{N \rightarrow +\infty} (\mathbb{E} (\langle M_{N,j}^0(t), M_{N,k}^0 \rangle (t)), 1 \leq j, k \leq J) = 0,$$

and, with Doob's Inequality, the martingale $(M_N^0(t))$ converges to 0, and also that, for the convergence in distribution

$$\lim_{N \rightarrow +\infty} \left(\frac{\bar{F}_{N,j}(t)}{\sqrt{N}} \right) = 0.$$

Standard arguments, using the criterion of the modulus of continuity, see Theorem 7.3 Billingsley [4] for example, give that the sequence of processes $(\bar{F}_N(t))$ is tight and that any limiting point $(\bar{f}^1(t))=(\bar{f}_j^1(t))$ satisfies the identity

$$(33) \quad \bar{f}_j^1(t) = \bar{f}_j^1(0) + \eta_j c_j t - \lambda_j \int_0^t \bar{f}_j^1(s) \sum_{k=1}^J \bar{f}_k^1(s) ds.$$

The theorem is proved. \square

The fluctuations of $(F_N^1(t))$ on the timescale (t/\sqrt{N}) are now developed in the following theorem.

Theorem 10 (Central Limit Theorem). *Under the assumption on the initial state of Theorem 9, if*

$$\left(\widehat{F}_N^1(t) \right) = \left(\widehat{F}_{N,j}^1(t) \right) \stackrel{\text{def.}}{=} \left(\frac{F_{N,j}^1(t/\sqrt{N}) - \sqrt{N} \bar{f}_j^1(t)}{\sqrt{N}} \right),$$

where $(\bar{f}^1(t))$ is defined by Relation (28) and

$$\lim_{N \rightarrow +\infty} \widehat{F}_N^1(0) = \widehat{f}_0^1 \in \mathbb{R}^J,$$

then the sequence of processes $(\widehat{F}_N^1(t))$ is converging in distribution to $(\widehat{F}^1(t))$, the solution of the SDE

$$(34) \quad d\widehat{F}_j^1(t) = \sqrt{-\left(\overline{f}_j^1\right)'(t) + 2\eta_j c_j} dB_j(t) - \lambda_j \left(\widehat{F}_j^1(t) \left\| \overline{f}_j^1(t) \right\| + \overline{f}_j^1(t) \left\| \widehat{F}_j^1(t) \right\| \right) dt,$$

with $\widehat{F}^1(0) = \widehat{f}_0^1$, where $(B_j(t))$ is the standard Brownian motion in \mathbb{R}^J .

Proof. Relations (34) and (33) give the identity,

$$(35) \quad \begin{aligned} \widehat{F}_{N,j}^1(t) &= \sqrt[4]{N} \left(\overline{F}_{N,j}^1(t) - \overline{f}_j^1(t) \right) = \widehat{F}_{N,j}^1(0) + \sqrt[4]{N} M_{N,j}^0(t) \\ &\quad + \eta_j \frac{C_j^N - c_j N}{N^{3/4}} t - \eta_j \int_0^t \frac{\overline{F}_{N,j}^1(s)}{\sqrt[4]{N}} ds \\ &\quad - \lambda_j \int_0^t \widehat{F}_{N,j}^1(s) \sum_{k=1}^J \overline{F}_{N,k}^1(s) ds - \lambda_j \int_0^t \overline{F}_{N,j}^1(s) \sum_{k=1}^J \widehat{F}_{N,k}^1(s) ds, \end{aligned}$$

and, with Relation (32), for $1 \leq j \leq J$,

$$\begin{aligned} \left(\left\langle \sqrt[4]{N} M_{N,j}^0 \right\rangle (t) \right) &= \left(\eta_j \int_0^t \left(\frac{C_j^N}{N} - \frac{\overline{F}_{N,j}^1(s)}{\sqrt{N}} \right) ds \right. \\ &\quad \left. + \lambda_j \int_0^t \overline{F}_{N,j}^1(s) \sum_{k=1}^J \overline{F}_{N,k}^1(s) ds \right). \end{aligned}$$

From Lemma 7 and Theorem 9, we obtain that, for the convergence in distribution, the relation

$$\begin{aligned} \lim_{N \rightarrow +\infty} \left(\left\langle \sqrt[4]{N} M_{N,j}^0 \right\rangle (t) \right) &= \left(\eta_j c_j t + \lambda_j \int_0^t \overline{f}_j^1(s) \sum_{k=1}^J \overline{f}_k^1(s) ds \right) \\ &= \left(\overline{f}_j^1(0) - \overline{f}_j^1(t) + 2\eta_j c_j t \right), \end{aligned}$$

holds, by Relation (33). Recall that

$$\left(\left\langle \sqrt[4]{N} M_{N,j}^0, \sqrt[4]{N} M_{N,k}^0 \right\rangle (t) \right) = 0$$

holds for $1 \leq j \neq k \leq J$. Theorem 1.4 page 339 of Ethier and Kurtz [8] shows that the sequence of martingales $(\widehat{M}_N^0(t))$ converges in distribution to the distribution of the process

$$\left(\int_0^t \sqrt{-\left(\overline{f}_j^1\right)'(s) + 2\eta_j c_j} B_j(ds) \right),$$

where $(B_j(t))$ is a standard Brownian motion on \mathbb{R}^J . Using again Lemma (7), we have

$$\lim_{N \rightarrow +\infty} \left(\int_0^t \frac{\overline{F}_{N,j}^1(s)}{\sqrt[4]{N}} ds \right) = (0).$$

The rest of the proof is standard, first by showing the tightness of $(\widehat{F}_N^1(t))$ and secondly by identifying it as the solution of an SDE. See the proof of Theorem 6.14 of [25] for example. The theorem is proved. \square

The following proposition shows that the invariant distribution of the Markov process $(F_N^1(t))$ has in fact a simple expression. This is a consequence of Proposition 2, the reversibility property is in fact the additional (simple) result.

Proposition 11 (Invariant Distribution). *The Markov process $(F_N^1(t))$ is reversible, and its invariant distribution π_N*

$$(36) \quad \pi_N(x) = \frac{1}{Z_N} \frac{1}{\|x\|!} \prod_{j=1}^J \rho_j^{x_j} \frac{C_j^N!}{(C_j^N - x_j)! x_j!}, \quad x \in \mathcal{S}_N,$$

where Z_N is a normalizing constant.

A version of Theorems (9) and (10) could probably be considered via a saddle-point analysis of the constant Z_N . This is not done in this paper.

4. DYNAMICAL ARRIVALS

If the systems starts with few agents so that most of N particles are “free”, when an agent created, it is paired with a free particle right away, at a rate proportional to N . This will happen repeatedly, via the successive steps of sequestration/de-sequestration, as long the number of free particles is sufficiently “large” so that sequestration occurs always before the degradation/death of an agent. The precise result is in fact a little more subtle than that. We show that, in the limit, on the timescale $t \rightarrow Nt$, there remains a positive fraction of free particles of the order of N .

The state descriptor of the pairing process is in this case

$$(X_N(t)) = (F_N(t), Z_N(t)) = ((F_{j,N}(t), j=1, \dots, J), Z_N(t)).$$

It can be expressed as the solution of the SDEs (7) and (8), the initial conditions are assumed to satisfy the following scaling relations

$$(37) \quad \lim_{N \rightarrow +\infty} \frac{F_N(0)}{N} = \bar{f}_0 \neq 0, \bar{f}_0 = (\bar{f}_{0,j}) \in \prod_{j=1}^J [0, c_j]^J, \text{ and } Z_N(0) = z_0 \in \mathbb{N},$$

where $c = (c_j)$ is defined by Relation (5).

Initially, a fraction $\bar{f}_{0,j}$ of particles of type $j \in \{1, \dots, J\}$ are free and there are z_0 free agents. Since the external input rate of agents is constant and equal to β , in order to have a positive fraction in N of particles paired with an agent, the natural time scale to consider is, at least, $t \rightarrow Nt$.

The setting of the analysis will be that of averaging principles as presented in Kurtz [20]. As it will be seen there are specific technical difficulties related to the scaling framework which we introduce now.

Definition 12 (Scaled Processes). *For $N > 0$, $(\bar{X}_N(t)) \stackrel{\text{def.}}{=} (\bar{F}_N(t), Z_N(Nt))$, with*

$$(38) \quad (\bar{F}_N(t)) \stackrel{\text{def.}}{=} \left(\frac{F_N(Nt)}{N} \right) = \left(\frac{F_{j,N}(Nt)}{N}, j=1, \dots, J \right) \in \prod_{j=1}^J \left[0, \frac{C_{j,N}}{N} \right].$$

For $t \geq 0$, we have $\|F_N(t)\| \leq 1$ since $F_{j,N}(t) \leq C_j^N$, for all $1 \leq j \leq J$.

The occupation measure is the random measure on $H \stackrel{\text{def.}}{=} \mathbb{R}_+ \times [0, 1]^J \times \mathbb{N}$ defined by

$$(39) \quad \langle \Lambda_N, g \rangle \stackrel{\text{def.}}{=} \int_0^{+\infty} g \left(s, \left(\frac{F_{j,N}(Ns)}{N} \right), Z_N(Ns) \right) ds,$$

for a continuous function g with compact support on H ,

Note that the “slow” process $(\overline{F}_N(t))$ is included in the definition of the occupation measure Λ_N . The reason is that the timescale is too fast, of the order of N^2 in fact, to get directly convenient tightness properties for the sequence of processes $(\overline{F}_{j,N}(t))$.

We can have a glimpse of this problem as follows. If $(\overline{M}_{j,N}(t))$ is the martingale of Relation (10), it does not clearly converges in distribution to 0 as N gets large as it could be expected if a “standard” averaging principle were true. Indeed Relation (12) gives, for $1 \leq j \leq J$,

$$\langle \overline{M}_{j,N} \rangle (t) = \left(\eta_j \int_0^t \left(\frac{C_{j,N}}{N} - \overline{F}_{j,N}(s) \right) ds + \lambda_j \int_0^t \overline{F}_{j,N}(s) Z_N(Ns) ds \right),$$

which does not seem to vanish.

We state the main result of this paper.

Theorem 13 (Averaging Principle). *Under the scaling assumption (5) and if $(F_N(0)/N)$ converges to $\overline{f}_0 \neq 0$, then the sequence of processes $(\|F_N(Nt)\|/N)$ converges in distribution to $(H(t))$, defined by, for $t \geq 0$, $H(t) \in (0, 1)$ is the unique solution of the relation*

$$(40) \quad \int_{\|\overline{f}_0\|}^{H(t)} \frac{1}{\delta\phi(u) - \beta} du = t,$$

where ϕ is defined by Relation (6).

Furthermore the sequence (Λ_N) is converging in distribution to the measure Λ_∞ on $H = \mathbb{R}_+ \times [0, 1]^J \times \mathbb{N}$, such that

$$(41) \quad \langle \Lambda_\infty, g \rangle \stackrel{\text{def.}}{=} \int_{\mathbb{R}_+ \times \mathbb{N}} g(s, (f_j(s)), x) P_{\phi(H(s))}(dx) ds,$$

for a non-negative Borelian function g on H , where, for $1 \leq j \leq J$,

$$(42) \quad f_j(t) = \frac{\rho_j}{\rho_j + \phi(H(t))} c_j,$$

and, for $y > 0$, P_y is a Poisson distribution with parameter y .

Note that we have a convergence in distribution $(\|F_N(Nt)\|/N)$, but not of the processes $(F_{j,N}(Nt)/N)$, $j=1, \dots, J$. The convergence in distribution for this J -dimensional process is weaker, it is expressed through the sequence of occupation measures (Λ_N) . See Dawson [6] for general definitions and results for the convergence in distribution of random measures.

It is not difficult to see that, under Condition (37) for the initial conditions, one cannot have a convergence in distribution of $(F_{j,N}(Nt)/N)$. Otherwise, its limit would be $(f_j(t))$, but this would imply that the asymptotic initial point $(\overline{f}_{0,j})$ would satisfy the relation

$$\overline{f}_{0,j} = \frac{\rho_j}{\rho_j + \phi(\overline{f}_0)} c_j,$$

which is not the case a priori. Asymptotically the vector $(F_{j,N}(Nt)/N)$ lives in a one dimensional curve of the state space, this is due to the fast processes which lead to a kind of state space collapse. See Propositions 22 and 23.

Corollary 14 (Equilibrium). *Under the assumptions, and with the notations of, Theorem (13), for $1 \leq j \leq J$,*

$$\lim_{t \rightarrow +\infty} H(t) = H_\infty = \sum_{j=1}^J \frac{\rho_j}{\rho_j + \beta/\delta} c_j,$$

The quantity H_∞ is the asymptotic fraction of free particles. The proof of this theorem is achieved in several steps. The general picture is that nevertheless a kind of averaging principle holds, the slow process being $(\bar{F}_N(t))$ and the “fast” process is $(Z_N(Nt))$. The general method in this domain is described in Kurtz [20], see also Papanicolaou et al. [23] and Freidlin and Wentzell [13]. It turns out that, due to the very fast timescale mentioned above, the slow process has to be included in the definition of the occupation measure, see Definition 12. This situation leads to technical difficulties, to identify the invariant measures of fast processes in particular.

Definition 15. *For $a > 0$, the stopping time $\tau_N(a)$ is defined by*

$$(43) \quad \tau_N(a) \stackrel{\text{def.}}{=} \inf \left\{ t > 0 : \|F_N(Nt)\| = \sum_{j=1}^J F_{j,N}(Nt) \leq aN \right\}.$$

To prove convenient tightness properties of a scaled version of $(X_N(t))$, we first derive some technical results. In a first step, we fix some $a_0 \in (0, \|\bar{f}_0\|)$ and we will work with a “stopped” *occupation measure*, it is the random measure on H defined by

$$(44) \quad \langle \Lambda_N^0, g \rangle \stackrel{\text{def.}}{=} \int_0^{\tau_N(a_0)} g \left(s, \left(\frac{F_{j,N}(Ns)}{N} \right), Z_N(Ns) \right) ds,$$

for a continuous function g with compact support on H . The motivation of the stopped occupation is due to a technical argument used for the identification of the invariant distributions of fast processes. See Proposition 23.

Lemma 16. *If $\|\bar{f}_0\| > 0$, for $a \in (0, \|\bar{f}_0\|)$, we have*

$$\lim_{N \rightarrow +\infty} \mathbb{P}(\tau_N(a) < \ell(a)) = 0,$$

with $\ell(a) \stackrel{\text{def.}}{=} \|\bar{f}_0\| - a/(2\beta)$, and the relation

$$\lim_{N \rightarrow +\infty} \left(\frac{Z_N(Nt)}{\sqrt{N}} \right) = (0)$$

holds for the convergence in distribution.

Proof. For $t > 0$ and N sufficiently large, on the event $\{\|F_N(t)\| < aN\}$ there are at least $(\|F_N(0)\| - \lceil aN \rceil - z_0)$ new agents created up to time Nt . Consequently for $y > 0$,

$$\{\tau_N(a) \leq y\} \subset \{\mathcal{P}_z^+((0, \beta) \times (0, yN)) \geq \|F_N(0)\| - \lceil aN \rceil - z_0\},$$

by Relation (8). The first assertion follows from the law of large numbers for Poisson processes.

We now show that there exists a coupling of $(Z_N(t))$ with $(L_0(t))$, the state process of an $M/M/\infty$ queue such that the relation $Z_N(t) \leq (L_0(N^2t))$ holds for all $t < \tau_N(a)$. See Section B.2 of the appendix on the $M/M/\infty$ queue.

In state $z \in \mathbb{N}$, the jump rates of the process $(Z_N(t))$ in state $((f_j), z)$ at time t are given by

$$\begin{cases} +1, & \beta + \sum_{j=1}^J \eta_j (C_j^N - f_j), \\ -1, & \delta z + \sum_{j=1}^J \lambda_j f_j z. \end{cases}$$

Let $(L_0(t))$ the process of the $M/M/\infty$ queue with input rate $2\bar{\eta}$ and service rate $\delta + a\lambda$, with Definition (4), with $L_0(0) = Z_N(0) = z_0$. We take N sufficiently large so that $\beta \leq \bar{\eta}N$. By comparing the jump rates, one can construct a version of $(Z_N(t), L_0(t))$ such that the relation

$$(45) \quad Z_N(Nt) \leq L_0(N^2t)$$

holds for all $t < \tau_N(a)$. For $\varepsilon > 0$, let $T_N(\varepsilon) = \inf \{t : L_0(t) \geq \varepsilon \sqrt{N}\}$. Proposition 25 of the appendix shows that the sequence of random variables

$$\left(\left(\frac{2\bar{\eta}}{a\lambda} \right)^{\lceil \varepsilon \sqrt{N} \rceil} \frac{T_N(\varepsilon)}{(\lceil \varepsilon \sqrt{N} \rceil - 1)!} \right)$$

converges in distribution to an exponential random variable. In particular, for any $t > 0$,

$$\lim_{N \rightarrow +\infty} \mathbb{P}(T_N(\varepsilon) \leq N^2t) = 0.$$

The proof of the lemma follows from the relation

$$\mathbb{P} \left(\sup_{s \leq t} \frac{Z_N(N(s \wedge \tau_N(a_0)))}{\sqrt{N}} > \varepsilon \right) \leq \mathbb{P} \left(\sup_{s \leq t} \frac{L_0(N^2s)}{\sqrt{N}} > \varepsilon \right) = \mathbb{P}(T_N \leq N^2t).$$

□

Proposition 17. *The sequence of random measures (Λ_N^0) defined by Relation (44) is tight and any limiting point Λ_∞^0 can be expressed as*

$$(46) \quad \langle \Lambda_\infty^0, f \rangle = \int_{\mathbb{R}_+ \times [0,1]^J \times \mathbb{N}} f(s, x, p) \pi_s(dx, dp) ds,$$

for any function $f \in \mathcal{C}_c(\mathbb{R}_+ \times [0,1]^J \times \mathbb{N})$, where (π_s) is an optional process with values in the space of probability distributions on $[0,1]^J \times \mathbb{N}$.

If $(\Lambda_{N_k}^0)$ is a sub-sequence of (Λ_N^0) converging to Λ_∞^0 , then with the convention of Relation (9), for the convergence in distribution of processes,

$$(47) \quad \lim_{k \rightarrow +\infty} \left(\int g(x, z) z \Lambda_{N_k}^0([0, t], dx, dz) \right) = \left(\int g(x, z) z \Lambda_\infty^0([0, t], dx, dz) \right),$$

for any bounded continuous function g on $[0,1]^J \times \mathbb{N}$ and the limit is integrable for all $t \geq 0$.

Proof. For $K > 0$, with Relation (45) in the proof of Lemma 16, and with the same notations, the relation

$$\int_0^t \mathbb{1}_{\{Z_N(Ns) \geq K\}} \, ds \leq \int_0^t \mathbb{P}(L_0(N^2s) \geq K) \, ds$$

holds on the event $\{\tau_N(a_0) \geq t\}$. Consequently, for $t < \ell(a_0)$,

$$\begin{aligned} \mathbb{E}(\Lambda_N^0([0, t] \times [0, 1]^J \times [K, +\infty))) &= \mathbb{E}\left(\int_0^{t \wedge \tau_N(a_0)} \mathbb{1}_{\{Z_N(Ns) \geq K\}} \, ds\right) \\ &\leq \mathbb{E}\left(\mathbb{1}_{\{\tau_N(a_0) > t\}} \int_0^t \mathbb{1}_{\{L_0(N^2s) \geq K\}} \, ds\right) \leq \frac{1}{N^2} \int_0^{N^2t} \mathbb{P}(L_0(s) \geq K) \, ds. \end{aligned}$$

Since the Markov process $(L_0(t))$ converges in distribution to a Poisson distribution with parameter $2\bar{\eta}/(\underline{\Delta}a_0)$, see Section B.2 of the appendix. With Lemma 16, we obtain the relation

$$\limsup_{N \rightarrow +\infty} \mathbb{E}(\Lambda_N^0([0, t] \times [0, 1]^J \times [K, +\infty))) \leq \mathbb{P}(\mathcal{N}_1(0, 2\bar{\eta}/(\underline{\Delta}a_0)) \geq K) t,$$

where \mathcal{N}_1 is a Poisson process on \mathbb{R}_+ with rate 1. In particular, one can choose K sufficiently large such that

$$\sup_N \mathbb{E}(\Lambda_N^0([0, t] \times [0, 1]^J \times [K, +\infty)))$$

is arbitrarily small. Lemma 1.3 of Kurtz [20] shows that the sequence (Λ_N^0) is tight, and Lemma 1.4 of the same reference gives the representation (46).

For the second part of the proposition, Relation (45) in the proof of Lemma 16 and the Cauchy-Schwartz' Inequality give, for $s \leq t$,

$$\begin{aligned} \mathbb{E}\left(\left(\int g(x, z) z \Lambda_N^0([s, t], dx, dz)\right)^2\right) &= \mathbb{E}\left(\left(\int_{s \wedge \tau_N(a_0)}^{t \wedge \tau_N(a_0)} g(\bar{X}_N(s)) Z_N(Ns) \, ds\right)^2\right) \\ &\leq \|g\|_\infty \mathbb{E}\left(\left(\int_{s \wedge \tau_N(a_0)}^{t \wedge \tau_N(a_0)} L_0(N^2s) \, ds\right)^2\right) \leq \|g\|_\infty \mathbb{E}\left(\left(\int_s^t L_0(N^2s) \, ds\right)^2\right) \\ &\leq (t-s) \|g\|_\infty \int_s^t \mathbb{E}(L_0(N^2s)^2) \, ds \leq (t-s)^2 \|g\|_\infty \sup_{u \geq 0} \mathbb{E}(L_0(u)^2). \end{aligned}$$

Kolmogorov-Čentsov's criterion, implies that the sequence of processes

$$\left(\int g(x, z) z \Lambda_N^0([0, t], dx, dz)\right)$$

is tight for the convergence in distribution and any of its limiting points is a continuous process. See Theorem 2.8 and Problem 4.11, page 64 of Karatzas and Shreve [19] for example.

For $t > 0$ and $C > 0$, for the convergence in distribution we have

$$\lim_{k \rightarrow +\infty} \int g(x, z) (z \wedge C) \Lambda_{N_k}^0([0, t], dx, dz) = \int g(x, z) (z \wedge C) \Lambda_\infty^0([0, t], dx, dz).$$

Using again Relation (45), with the same argument as before,

$$\begin{aligned} & \mathbb{E} \left(\int g(x, z) (z \wedge C) \Lambda_{N_k}^0([0, t], dx, dz) \right) \\ & \leq \|g\|_\infty \int_0^t \mathbb{E} (L_0(N^2 u) \wedge C) du \leq t \|g\|_\infty \sup_{u \geq 0} \mathbb{E} (L_0(u)^2) < +\infty, \end{aligned}$$

by letting first k and then C go to infinity, we obtain the relation

$$\mathbb{E} \left(\int g(x, z) z \Lambda_\infty^0([0, t], dx, dz) \right) < +\infty,$$

for all $t \geq 0$. Similarly, we have

$$\begin{aligned} & \mathbb{E} \left(\int g(x, z) z \mathbb{1}_{\{z \geq C\}} \Lambda_{N_k}^0([0, t], dx, dz) \right) \\ & \leq \|g\|_\infty \int_0^t \mathbb{E} \left(L_0(N_k^2 u) \mathbb{1}_{\{L_0(N_k^2 u) \geq C\}} \right) du \leq \frac{t}{C} \|g\|_\infty \sup_{u \geq 0} \mathbb{E} (L_0(u)^2), \end{aligned}$$

and therefore the convergence in distribution

$$\lim_{k \rightarrow +\infty} \int g(x, z) z \Lambda_{N_k}^0([0, t], dx, dz) = \int g(x, z) z \Lambda_\infty^0([0, t], dx, dz),$$

for $t > 0$. For $p \geq 1$ and $0 \leq t_1 \leq \dots \leq t_p$, this convergence also clearly holds for finite marginals at (t_i) . The proposition is proved. \square

If f is a non-negative Borelian function on $\mathbb{R}_+^J \times \mathbb{N}$, the SDEs (7) and (8) give directly the relations

$$\begin{aligned} (48) \quad & f(\bar{F}_N(t), Z_N(Nt)) = f(\bar{F}_N(0), Z_N(0)) + M_{f,N}(t) \\ & + \sum_{j=1}^J \lambda_j \int_0^t N \Delta_{-e_j/N, -1}(f)(\bar{F}_N(s), Z_N(Ns)) F_{j,N}(Ns) Z_N(Ns) ds \\ & + \sum_{j=1}^J \eta_j \int_0^t N \Delta_{e_j/N, 1}(f)(\bar{F}_N(s), Z_N(Ns)) (C_j^N - F_{j,N}(Ns)) ds \\ & + \beta N \int_0^t \Delta_{0,1}(f)(\bar{F}_N(s), Z_N(Ns)) ds \\ & + \delta N \int_0^t \Delta_{0,-1}(f)(\bar{F}_N(s), Z_N(Ns)) Z_N(Ns) ds, \end{aligned}$$

with the notation, for $x, u \in \mathbb{R}_+^J$ and $y, b \in \mathbb{N}$,

$$\Delta_{u,v}(f)(x, y) \stackrel{\text{def.}}{=} f(x+u, y+v) - f(x, y),$$

and, for $1 \leq j \leq J$, e_j is the j th unit vector of \mathbb{R}^J .

The process $(M_{f,N}(t))$ is a square integrable martingale whose previsible increasing process is given by

$$\begin{aligned}
(49) \quad \langle M_{f,N} \rangle (t) &= \beta N \int_0^t \Delta_{0,1}(f) (\overline{F}_N(s), Z_N(Ns))^2 ds \\
&+ \delta N \int_0^t \Delta_{0,-1}(f) (\overline{F}_N(s), Z_N(Ns))^2 Z_N(Ns) ds \\
&+ \sum_{j=1}^J \lambda_j \int_0^t N \Delta_{-e_j/N,-1}(f) (\overline{F}_N(s), Z_N(Ns))^2 F_{j,N}(Ns) Z_N(Ns) ds \\
&+ \sum_{j=1}^J \eta_j \int_0^t N \Delta_{e_j/N,1}(f) (\overline{F}_N(s), Z_N(Ns))^2 (C_j^N - F_{j,N}(Ns)) ds.
\end{aligned}$$

If we divide by N Relation (48) taken at Nt , we get

$$\begin{aligned}
(50) \quad \frac{1}{N} \left(f(\overline{F}_N(t), Z_N(Nt)) - f(\overline{F}_N(0), Z_N(0)) \right) &= \frac{1}{N} M_{f,N}(t) \\
&+ \sum_{j=1}^J \lambda_j \int_0^t N \Delta_{-e_j/N,-1}(f) (\overline{F}_N(s), Z_N(Ns)) \overline{F}_{j,N}(s) Z_N(Ns) ds \\
&+ \sum_{j=1}^J \eta_j \int_0^t N \Delta_{e_j/N,1}(f) (\overline{F}_N(s), Z_N(Ns)) \left(\frac{C_j^N}{N} - \overline{F}_{j,N}(s) \right) ds \\
&+ \beta \int_0^t \Delta_{0,1}(f) (\overline{F}_N(s), Z_N(Ns)) ds \\
&+ \delta \int_0^t \Delta_{0,-1}(f) (\overline{F}_N(s), Z_N(s)) Z_N(Ns) ds.
\end{aligned}$$

Lemma 18. *If f is a bounded \mathcal{C}_1 function with compact support on $\mathbb{R}_+^J \times \mathbb{N}$, then the sequence of martingales $(M_{f,N}(t)/N, t < \ell(a_0))$ of Relation (50) converges in distribution to 0.*

Proof. We take care of the third term $(A_N(t))$ of $(\langle M_{f,N}/N \rangle (Nt))$ in Relation (49), the arguments are similar for the others, even easier. For $1 \leq j \leq J$, denote by $(A_{j,N}(t))$ the j th term of $(A_N(t))$, then

$$A_{j,N}(t) \stackrel{\text{def.}}{=} \frac{\lambda_j}{N} \int_0^t N \Delta_{-e_j/N,-1}(f) (\overline{F}_N(s), Z_N(Ns))^2 \overline{F}_{j,N}(s) Z_N(Ns) ds,$$

then, again with Relation (45) of the proof of Lemma 16, since $(\overline{F}_{j,N}(t))$ is bounded by 1,

$$\mathbb{E}(A_{j,N}(t)) \leq \frac{\lambda_j}{N} \left\| \frac{\partial f}{\partial x_j} \right\|_{\infty}^2 \left(\mathbb{E} \left(\int_0^t L_0(N^2 s) ds \right) + t \mathbb{P}(\tau_N(a_0) \leq \ell(a_0)) \right),$$

since $(\mathbb{E}(L_0(t)))$ is converging as t goes to infinity, we have

$$\lim_{N \rightarrow +\infty} \mathbb{E}(A_{j,N}(t)) = 0.$$

Doob's Inequality shows the convergence of $(M_{f,N}(t))/N, t < \ell(a_0)$ to 0. \square

Proposition 19. *If Λ_∞^0 is a limiting point of (Λ_N^0) with the representation (46) of Proposition 17 then, for any continuous function g on $\mathbb{R}_+^J \times \mathbb{N}$, the relation*

$$(51) \quad \left(\int_0^t \int_{[0,1]^J \times \mathbb{N}} g(x, p) \pi_s(dx, dp) ds, t < \ell(a_0) \right) \\ = \left(\int_0^t \int_{[0,1]^J} \mathbb{E} \left(g \left(x, \mathcal{N}_1 \left(\left[0, \frac{\langle \eta, c-x \rangle}{\langle \lambda, x \rangle} \right] \right) \right) \right) \pi_s^1(dx) ds, t < \ell(a_0) \right),$$

holds almost surely, where π_t^1 is the marginal of π_t on \mathbb{R}_+^J , λ , η and $c \in \mathbb{R}_+^J$ are given by Definition 1 and $\ell(a_0)$ in Lemma 16, and \mathcal{N}_1 is a Poisson process on \mathbb{R}_+ with rate 1.

Furthermore, almost surely,

$$(52) \quad \int_0^{\ell(a_0)} \pi_s^1 \left(x \in [0, 1]^J : \sum_{j=1}^J x_j < a_0 \right) ds = 0.$$

Relation (51) states that, for almost all $t < \ell(a_0)$, π_t conditioned on the first coordinate x is a Poisson distribution with parameter $\langle \eta, c-x \rangle / \langle \lambda, x \rangle$. Note that Relation (52) shows that the denominator $\langle \lambda, x \rangle$ is lower bounded by $\underline{\lambda} a_0$ almost surely for π_t , for $t < \ell(a_0)$.

Proof. Let $(\Lambda_{N_k}^0)$ be a subsequence of (Λ_N^0) converging to some Λ_∞^0 of the form (46). By letting k go to infinity in Relation (50), with Lemma 16, Relation (47) of Proposition 17, and Lemma 18, for any continuous function g with compact support on $[0, 1]^J \times \mathbb{N}$,

$$\int_0^t \int_{[0,1]^J \times \mathbb{N}} (g(x, p-1) - g(x, p)) \left(\sum_{j=1}^J \lambda_j x_j \right) p \pi_s(dx, dp) ds \\ + \int_0^t \int_{[0,1]^J \times \mathbb{N}} (g(x, p+1) - f(x, p)) \left(\sum_{j=1}^J \eta_j (c_j - x_j) \right) \pi_s(dx, dp) ds = 0,$$

holds almost surely for all $t < \ell(a_0)$. Hence we have

$$\int_{[0,1]^J \times \mathbb{N}} \lambda (g(x, p-1) - g(x, p)) \langle \lambda, x \rangle p \pi_t(dx, dp) \\ + \int_{[0,1]^J \times \mathbb{N}} \eta (g(x, p+1) - f(x, p)) \langle \eta, c-x \rangle \pi_t(dx, dp) = 0,$$

almost everywhere on $t \in \mathbb{R}_+$, or if $g(x, p) = g_1(x)g_2(p)$,

$$\int_{\mathbb{R}_+ \times \mathbb{N}} g_1(x) \Omega[x](g_2)(p) \pi_t(dx, dp) = 0,$$

where, for $h : \mathbb{N} \rightarrow \mathbb{R}_+$,

$$\Omega[x](h)(p) \stackrel{\text{def.}}{=} \langle \eta, c-x \rangle (h(p+1) - h(p)) + \langle \lambda, x \rangle p (h(p-1) - h(p)).$$

Let $\pi_t(\cdot | x)$ be the conditional probability measure $\pi_t(dx, dp)$ given $x \in \mathbb{R}_+$, then we have, $\pi_t(dx, \mathbb{N})$ almost everywhere

$$\int \Omega[x](g_2)(p) \pi_t(dp | x) = 0,$$

for all functions g_2 with finite support. Since, for $x > 0$, $\Omega[x]$ is the Q -matrix of an $M/M/\infty$ queue, the last relation gives that $\pi_t(dp|x)$ is its invariant distribution, i.e. it is a Poisson distribution with parameter $\langle \eta, c-x \rangle / \langle \lambda, x \rangle$.

Relation (52) is simple a consequence of Lemma 16.

The proposition is proved. \square

From now on, we fix (N_k) an increasing sequence such the sequence $(\Lambda_{N_k}^0)$ is converging to Λ_∞^0 with a representation given by Relations (46) and (51). The following corollary is a direct consequence of Propositions 17 and 19.

Corollary 20. *If g is a continuous bounded function on $[0, 1]^J$, then, for the convergence in distribution,*

$$(53) \quad \lim_{k \rightarrow +\infty} \left(\int_0^t g(\bar{F}_{N_k}(s)) Z_{N_k}(N_k s) ds, t < \ell(a_0) \right) \\ = \left(\int_0^t \int_{[0,1]^J} g(x) \frac{\langle \eta, c-x \rangle}{\langle \lambda, x \rangle} \pi_s^1(dx) ds, t < \ell(a_0) \right).$$

The following proposition is a convergence result for the scaled process $(\bar{F}_N(t))$. It is weaker than the convergence stated in Theorem 13 clearly, but this is a crucial ingredient to establish the theorem in fact.

Proposition 21. *The sequence of processes $(\|\bar{F}_{N_k}(t)\|, t < \ell(a_0))$ is converging in distribution to*

$$(H(t), t < \ell(a_0)) \stackrel{\text{def.}}{=} \left(\|\bar{F}_0\| + \int_0^t \int_{[0,1]^J} \left(\delta \frac{\langle \eta, c-x \rangle}{\langle \lambda, x \rangle} - \beta \right) \pi_s^1(dx) ds, t < \ell(a_0) \right).$$

Proof. We define, for $t \geq 0$,

$$(54) \quad \tilde{Z}_N(t) = Z_N(t) + \sum_{j=1}^J (N_j - F_{j,N}(t)) = N - \|F_N(t)\| + Z_N(t),$$

$\tilde{Z}_N(t)$ is the total number of agents (free or paired) of the system at time t . Using the SDEs (10) and (11), we have

$$(55) \quad \frac{\tilde{Z}_N(Nt)}{N} = M_{Z,N}(t) + \frac{\tilde{Z}_N(0)}{N} + \beta t - \delta \int_0^t Z_N(Ns) ds,$$

where $(M_{Z,N}(t))$ is a local martingale whose previsible increasing process is given by

$$(56) \quad (\langle M_{Z,N} \rangle(t)) = \left(\frac{1}{N} \left(\beta t + \delta \int_0^t Z_N(Ns) ds \right) \right).$$

Using again Doob's Inequality, Lemma 16 and Relation (54), the proposition is proved. \square

The next proposition gives a characterization of the process (π_s^1) which will be elucidated in Proposition 23.

Proposition 22. *If g is a \mathcal{C}_1 -function on $[0, 1]^J$, then, almost surely,*

$$(57) \quad \left(\int_0^t \int_{[0,1]^J} \sum_{j=1}^J \frac{\partial g}{\partial x_j}(x) \left(\lambda_j x_j \frac{\langle \eta, c-x \rangle}{\langle \lambda, x \rangle} - \eta_j (c_j - x_j) \right) \pi_s^1(dx) ds, t < \ell(a_0) \right) = (0).$$

Proof. For $t > 0$, let g be a \mathcal{C}_2 -function on $[0, 1]^J$, Relation (50) gives,

$$(58) \quad \begin{aligned} \frac{1}{N} g(\bar{F}_N(t)) &= \frac{1}{N} g(\bar{F}_N(0)) + M_{g,N}(t) \\ &+ \sum_{j=1}^J \lambda_j \int_0^t N \nabla_{-e_j/N}(g)(\bar{F}_N(s)) \bar{F}_{j,N}(s) Z_N(Ns) ds \\ &+ \sum_{j=1}^J \eta_j \int_0^t N \nabla_{e_j/N}(g)(\bar{F}_N(s)) \left(\frac{C_j^N}{N} - \bar{F}_{j,N}(s) \right) ds, \end{aligned}$$

and, since

$$\begin{aligned} (\langle M_{g,N} \rangle(t)) &= \left(\frac{1}{N^2} \sum_{j=1}^J \lambda_j \int_0^t \left(N \nabla_{-e_j/N}(g)(\bar{F}_N(s)) \right)^2 \bar{F}_{j,N}(s) Z_N(Ns) ds \right. \\ &\quad \left. + \frac{1}{N^2} \sum_{j=1}^J \eta_j \int_0^t \left(N \nabla_{e_j/N}(g)(\bar{F}_N(s)) \right)^2 \left(\frac{C_j^N}{N} - \bar{F}_{j,N}(s) \right) ds \right), \end{aligned}$$

Relation (47) shows that, for $t < \ell(a_0)$, $\mathbb{E}(\langle M_{g,N_k} \rangle(t))$ is converging to 0, the martingale $(M_{g,N_k}(t))$ converges therefore in distribution to 0 as k gets large. By using again Relation 47 and the differentiability properties of g , it is easy to conclude the proof of the proposition. \square

For $1 \leq j \leq J$, by taking a function $g(x) = h(x_j)$, $x = (x_i) \in [0, 1]^J$, where h is \mathcal{C}_2 , we obtain, that the relation

$$\left(\int_0^t \int_{[0,1]^J} h'(x_j) \left(\lambda_j x_j \frac{\langle \eta, c-x \rangle}{\langle \lambda, x \rangle} - \eta_j (c_j - x_j) \right) \pi_s^1(dx) ds, t < \ell(a_0) \right) = (0)$$

holds almost surely. Hence, almost surely, for any f in a dense subset of Borelian functions on $[0, 1]$, the identity

$$\int_{[0,1]^J} f(x_j) \left(\lambda_j x_j \frac{\langle \eta, c-x \rangle}{\langle \lambda, x \rangle} - \eta_j (c_j - x_j) \right) \pi_t^1(dx)$$

holds almost everywhere for $t \in \mathbb{R}_+$, with respect to Lebesgue's measure.

If $U(t) = (U_j(t))$ is a random variable with distribution π_t^1 , the last relation can be translated in terms of conditional expectation, almost surely

$$\lambda_j U_j(t) \mathbb{E} \left(\frac{\langle \eta, c - U(t) \rangle}{\langle \lambda, U(t) \rangle} \middle| U_j(t) \right) = \eta_j (c_j - U_j(t)),$$

almost everywhere for $t \geq 0$. The following proposition is the key step to identify completely the limit points of $(\|\bar{F}_N(t)\|, \Lambda_N^0)$.

Proposition 23. *Let $U=(U_j)$ be a random variable on $\prod_1^J [0, c_j]$, such that , almost surely, $\|U\|\geq\eta$, for some $\eta>0$, and, for $1\leq j\leq J$,*

$$(59) \quad \lambda_j U_j \mathbb{E} \left(\frac{\langle \eta, c-U \rangle}{\langle \lambda, U \rangle} \middle| U_j \right) = \eta_j (c_j - U_j),$$

then, almost surely,

$$U_j = \frac{\rho_j c_j}{\phi(\|U\|) + \rho_j},$$

where for $y\in(0, 1)$, $\phi(y)$ is the unique solution of the equation

$$\sum_{j=1}^J \frac{\rho_j}{\rho_j + \phi(y)} c_j = y,$$

and (ρ_j) is given by Definition 1 and ϕ in Theorem 13.

Proof. Define, for $1\leq j\leq J$,

$$A_j \stackrel{\text{def.}}{=} \frac{\eta_j (c_j - U_j)}{\lambda_j U_j}, \quad B_j \stackrel{\text{def.}}{=} \lambda_j U_j,$$

and \mathcal{F}_j is the σ -field associated to U_j . Note that, because of the assumptions the variables A_j and B_j are bounded by Relation (59), this identity can be re-written as

$$\mathbb{E} \left(\frac{\sum_k A_k B_k}{\sum_k B_k} \middle| \mathcal{F}_j \right) = A_j,$$

or, since A_j and B_j are \mathcal{F}_j -measurable

$$\mathbb{E} \left(\frac{\sum_k (A_k - A_j) A_j B_j B_k}{\sum_k B_k} \middle| \mathcal{F}_j \right) = 0,$$

this identity gives therefore the relation

$$\mathbb{E} \left(\frac{\sum_{j,k} (A_j - A_k)^2 B_j B_k}{\sum_k B_k} \right) = 2 \sum_{j=1}^J \mathbb{E} \left(\frac{\sum_k (A_j - A_k) A_j B_j B_k}{\sum_k B_k} \right) = 0,$$

since the variables $B_j, j=1, \dots, J$ are almost surely positive, this implies that, almost surely, $A_j=A_1$ for $j=1, \dots, J$, and therefore

$$U_j = \frac{\rho_j c_j}{A_1 + \rho_j},$$

the proposition is proved. \square

Proof of Theorem 12. We have only to gather all the results obtained up to now. Proposition 21 shows that, on the time interval $[0, \ell(a_0))$, the sequence of processes $(\|F_{N_k}(t)\|)$ converges in distribution to $(H(t))$ given by

$$(60) \quad (H(t)) = \left(\|\bar{\mathcal{F}}_0\| + \int_0^t \int_{[0,1]^J} \left(\delta \frac{\langle \eta, c-x \rangle}{\langle \lambda, x \rangle} - \beta \right) \pi_s^1(dx) ds \right) \\ = \left(\|\bar{\mathcal{F}}_0\| + \int_0^t (\delta \phi(H(s)) - \beta) ds \right),$$

by Proposition 23. This determines completely $(H(t))$ as the solution of Relation (40), and therefore the convergence of the sequence $(\|F_N(t)\|)$. Relation (57) of Proposition 22 and Proposition 23 gives the desired expression. Relation (41) for the limit of the sequence (Λ_N^0) of occupation measures.

It is easily seen that the solution of Relation (40) satisfies Corollary 14, in particular, if $H(0) > 0$, there exists $w > 0$ such that $H(t) \geq w$ for all $t \geq 0$. The convergence in distribution obtained can be therefore extended to any finite interval of \mathbb{R}_+ . The theorem is proved. \square

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APPENDIX A. BIOLOGICAL BACKGROUND

In bacterial cells, protein production uses an important number of cell resources: macro-molecules such as *polymerases* and *ribosomes*, biological bricks of proteins, i.e., amino acids, and the energy necessary to build proteins, such as GTP. The two main steps associated with protein and RNA production are

- *Transcription.* When an RNA polymerase is bound to an active gene, it starts to make a copy of this gene. The product which is a sequence of nucleotides is an *RNA*. If the gene is associated to a protein, it is a *messenger RNA*, an *mRNA*. When the full sequence of nucleotides of the RNA has been successively assembled, the RNA is released in the cytoplasm.
- *Translation.* The step is achieved through another large macro-molecule: a *ribosome*. When a ribosome is bound to an mRNA, it builds a chain of amino-acids using the mRNA as a template to produce a linked chain of amino-acids, a *protein*.

There are several types of RNAs, outside mRNAs, tRNAs to carry amino-acids for the translation phase, rRNAs which are (large) building blocks of ribosomes. The average size of an mRNA is of the order of 300 nucleotids (nt), the size of an rRNA is of the order of 5000nt. Another class of RNAs, the small RNAs, or sRNAs, has been discovered in the 1970's, the 6S sRNAs in particular. The size of a sRNA is of the order of 50-100nt and their functional role of regulation has been identified around 2000, quite recently in fact. See Hindley [16] and Beisel and Storz [3].

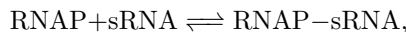
In a biological context, the internal dynamics of cells can be, essentially, expressed in terms of pairing mechanisms of various couples of macro-molecules. The quite recent discovery of the existence of small RNAs and of their functional role in the regulation of the protein production has shed a new light on pairing mechanisms as a general tool to control gene expression. Pairing mechanisms are to regulate the growth of cells in order to adapt to a varying environment. Depending on external conditions, it may be desirable to reduce or speed-up the growth of the cell, and so the use of these macro-molecules. A specific regulation mechanism relies on a type of macro-molecules, sRNAs, small RNAs, which we will refer to as *agents* in the following. Their functional role has been discovered only recently in fact, at the end of the 20th century. They may bind/pair with one of these macro-molecules and the pairing may have several effect, depending on the type of sRNA: it can sequester a macro-molecule/particle and, therefore, reduce significantly its interactions with other components of the cell. Or it may speed-up the activity of the macro-molecule by increasing its interaction rate (affinity) with other components of the cell.

Due to thermal noise inside the cell, a particle/agent pair will split after a certain time. These separation mechanisms are as important as binding events are. The quantity of agents presents within the cell is also highly variable, and their quantity is actively regulated by the cell through a variety of regulatory mechanisms. In most prokaryotes, when a cell grows, its size increases. Without any action, the concentrations of agents/particles inside the cell begin to decrease by dilution. In the case of a limited number of agents, the cell has specific means of degrading agents to rapidly reduce their quantity if dilution is not enough. When the cell environment changes, the number of active agents may have to increase to adapt. It can be done by either generating new agents and particles or, more rapidly, by altering the quantity of active agents, i.e., agents bound to particles, by enhancing couplings. The duration of these transitions is an important characteristic of the control mechanism under consideration. In general it has two terms. The first term is linked to the production of new agents (and is therefore rather slow), while the second term is linked to a (quick) change in the number of active

machines via bindings of agents with particles. The rate of adaptation depends on the combination of these two mechanisms, and is therefore a crucial issue in the case of cells. Assuming that the environment is such that regulation is necessary, the fraction of particles that are bound to an agent is a measure of the efficiency of these mechanisms. We refer to Section A of the appendix for references and further details on the biological context.

We describe several examples of regulation via pairing mechanisms. For the sake of simplicity, we give a rough description, not all macro-molecules, mechanisms involved are not mentioned. The main goal is of showing that pairing mechanisms play a major role concerning the regulation of the cell. References with much more details are mentioned.

Regulation of Transcription. The 6S sRNA is in charge of regulating the transcription phase, via a pairing with a σ -factor, a macromolecule necessary to the initiation of transcription. See Fromion et al. [14] for more details. With a slight abuse, by ignoring the σ -factor, the mechanism can be represented as a chemical reaction with three chemical species particles,



where RNAP stands for RNA polymerase. In such a context the pairing of RNAP and sRNA is seen as a sequestration of polymerases. See Waters and Storz [30], Wassarman and Storz [29] and Felden and Augagneur [10]. See Nitzan et al. [22].

Regulation of Translation. There is a similar regulation mechanism for ribosomes. The pairing of a macromolecule denoted as (p)ppGpp with the ribosome has the main effect of interfering with the initiation phase of translation and leading to abort the operation. See Yang et al. [31], Fer et al. [11] and Hauryliuk et al. [15] for more details.

Regulation of mRNAs by sRNAs. The translation can be also controlled via the mRNAs in the following way. The pairing of an sRNA and an mRNA modifies the translation efficiency of the mRNA. It can repress or enhance its activity. The pairing of an sRNA and mRNA. See Waters and Storz [30], Jagodnik et al. [17] and Beisel and Storz [3] for prokaryotic cells, and Flynt and Lai [12] for eukaryotic cells, with micro RNAs, miRNAs, acting on mRNAs. The references Jayaprakash and Das [18], Baker et al. [2] and Del Giudice et al. [7] study the Fokker-Planck equations for Markovian models of this mechanism.

APPENDIX B. TECHNICAL RESULTS

B.1. The $M/M/1$ queue. We introduce a birth and death process on \mathbb{N} which is in fact a reflected random walk on \mathbb{N} . An $M/M/1$ queue with input rate γ and service rate μ on \mathbb{N} is a Markov process $(L_1(t))$ with Q -matrix matrix given by

$$z \mapsto \begin{cases} z+1, & \gamma, \\ z-1, & \mu \mathbb{1}_{\{z \geq 1\}}. \end{cases}$$

If $\gamma < \mu$, its invariant distribution is a geometric distribution with parameter γ/μ . Define

$$T_K = \inf \{t : L_\infty(t) \geq K\},$$

Proposition 5.11 of Chapter 5 of Robert [25] gives the asymptotic behavior of T_K when K is large.

Proposition 24. *If $\gamma < \mu$ and $L(0) = z_0$, then, as K goes to infinity, the random variable*

$$\left(\frac{\gamma}{\mu}\right)^K T_K$$

converges in distribution to an exponential random variable.

B.2. The $M/M/\infty$ queue. This is another classical birth and death process on \mathbb{N} . An $M/M/\infty$ queue with input rate γ and service rate μ on \mathbb{N} is a Markov process with Q -matrix given by

$$z \mapsto \begin{cases} z+1, & \gamma, \\ z-1, & \mu z. \end{cases}$$

Its invariant distribution is a Poisson distribution with parameter γ/μ .

It can be seen in fact as a discrete Ornstein-Uhlenbeck process. See Chapter 6 of Robert [25] for example. For $K \in \mathbb{N}$, the hitting time of level K by the process $(L(t))$ of an $M/M/\infty$ input rate γ and service rate μ is defined by

$$T_K = \inf \{t : L_\infty(t) \geq K\}.$$

The following result, see Proposition 6.10 of [25] for example, is used to establish several tightness results.

Proposition 25. *If $L(0) = z_0$, as K goes to infinity, the random variable*

$$\left(\frac{\gamma}{\mu}\right)^K \frac{T_K}{(K-1)!}$$

converges in distribution to an exponential random variable.

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