Density-Profile Processes Describing Biological Signaling Networks: Almost Sure Convergence to Deterministic Trajectories

Roberto Fernández¹, Luiz Renato Fontes²†, E. Jordão Neves²‡

July, 2007

Abstract

We introduce jump processes in $\mathbb{R}^k$, called density-profile process, to model biological signaling networks. They describe the macroscopic evolution of finite-size spin-flip models with $k$ types of spins interacting through a non-reversible Glauber dynamics. We focus on the the $k$-dimensional empirical-magnetization vector in the thermodynamic limit, and prove that, within arbitrary finite time-intervals, its path converges almost surely to a deterministic trajectory determined by a first-order (non-linear) differential equation. As parameters of the spin-flip dynamics change, the associated dynamical system may go through bifurcations, associated to phase transitions in the statistical mechanical setting. We present a simple example of spin-flip stochastic model leading to a dynamical system with Hopf and pitchfork bifurcations; depending on the parameter values, the magnetization random path can either converge to a unique stable fixed point, converge to one of a pair of stable fixed points, or asymptotically evolve close to a deterministic orbit in $\mathbb{R}^k$.

1 Motivation and introduction

The models in this paper are motivated by the mathematical problem of modeling and analyzing biological signaling networks in cancer research. Understanding how cells manage to respond properly to noisy signals from its environment is an important research challenge in molecular cell biology, which requires a systems biology point of view, with emphasis on the analysis of global aspects of the system, like modularity, robustness and control mechanisms.

Extra-cellular information is often transmitted through cell-membrane receptors activated by ligands, such as hormones, neurotransmitters or growth

¹roberto.fernandez@univ-rouen.fr
²lrenato@ime.usp.br
³neves@ime.usp.br
factors, which may trigger complex time-dependent cascades of internal cellular biochemical transformations and lead to quite different cellular responses, like cell-cycle, cell arrest or cellular suicide (apoptosis) [2]. Signaling pathways had to survive strong selective pressures and therefore must contain sophisticated control mechanisms [3] in order to avoid inappropriate responses which are associated to several diseases, like cancer.

Several signaling pathways databases are available nowadays [4] which collect knowledge about components and their putative interactions. Information is usually presented as an oriented graph whose nodes are the pathway components or group of components and whose (oriented) edges indicate some sort of interaction like activation or a repression. There is usually no detailed information about the biochemical mechanisms associated to these interactions. In fact a single oriented edge may actually turn out to involve several different processes like regulations of gene transcription/translation, protein transformations (like phosphorylation) or active (non-diffusive) transport from one cellular compartment to another. The mathematical challenge is to propose useful models of this complex situation, which lend themselves to rigorous analysis but at the same time provide experimentally verifiable predictions.

Given the lack of precise information about the biochemical processes involved in most pathways, specially those of interest in cancer research, the usual modeling approach based in chemical kinetics [5] seems to be unrealistic. In particular, it involves too many assumptions whose validity can not be checked at present. We seek, therefore, an alternative approach to derive the differential equations that grasp the qualitative continuous-time behavior of those networks. In turn, these differential equations provide a general framework —based on dynamical systems ideas [10]— to analyze important cellular behaviors like cell-cycle restriction points [6] and pathway control mechanisms [7].

In this paper we present microscopic models of the following situation. Suppose \( k \) types of molecules interact in a cellular biochemical network and that each one may be in one of two states, say, active or inactive. Suppose further that there are a large number \( N \) of molecules of each type and that the collective state of the \( kN \) molecules evolve like a continuous-time Markov process. This process is not the usual finite-volume stochastic spin model [8] because, in view of our motivation, we must allow asymmetric interactions among different types of molecules. Indeed, it can happen that the activation of a molecule of type A is triggered by the enzymatic effect of an active B molecule, while the activation of a molecule of type B does not depend on those of type A. In view of our biochemical motivation it is also natural to assume that any molecule may interact which any other. These assumptions define spin models what we call \textit{type-dependent interaction models}, which are formally presented in Section 3.

The dynamics of the \( k \)-dimensional empirical density vector of these spin models are described by a the so-called density-profile process introduced below. These are random walk jump-processes in \( \mathbb{R}^k \) with jumps of size \( 1/N \), whose expected drift velocity \( V(x) \) does not depend on \( N \). The main result of this paper (Theorem 2.1) is the proof that the paths of such a process converge almost surely to the trajectories of the dynamical system having \( V \) as the velocity field. While similar models where considered in the literature [11], the issue of the almost sure convergence has not been addressed before. As we show in an example, the resulting dynamical systems can exhibit a very rich behavior,
including bifurcations.

The main mathematical steps in our convergence proof are the following:

(i) A graphical construction (Section 4.2) that allows a coupled simultaneous construction of density-profile processes for different $N$.

(ii) An auxiliary process $\{\hat{m}_t^{x,N}\}_{t \geq 0}$ (Section 4.1) defined through a simple spin-flip model (independent flips with time-dependent rates) which shadows the deterministic dynamical system (Lemma 4.1).

(iii) A coupling between the auxiliary and the density-profile processes that keep both processes as close to each other as possible (Section 4.4). Instants where they move further apart define a process of discrepancies. Bounds on the rate of these discrepancies yield our convergence theorem (Theorem 2.1).

2 Convergence of density profile process to dynamical systems

In this section we define our basic processes and present the main mathematical result of the paper. In next section we shall realize them through the macroscopic dynamics of stochastic Ising models.

2.1 Density-profile processes $\{m_t^{x0,N}\}_{t \geq 0}$

A density-profile process is a continuous time jump process in the hypercube $D_N = (-\frac{1}{N}, 1 + \frac{1}{N})^k$, for $k, N \geq 1$. At each jump, a point $x \in D_N$ changes one of its coordinates by $\pm \frac{1}{N}$, with rates that depend smoothly on $x$. These rates are defined in the following way. We start with two bounded Lipschitz functions $\lambda, \mu : \mathbb{R}^k \to \mathbb{R}^k$ which, in turn, define functions $f, g : \mathbb{R}^k \to \mathbb{R}^k$ through the relations:

$$f_i(x) = \begin{cases} (1 - x_i)\lambda_i(x) & \text{if } 0 \leq x_i \leq 1 \\ \lambda_i(0^+) & \text{if } x_i \\
0 & \text{if } x_i \geq 1 \end{cases}$$

and

$$g_i(x) = \begin{cases} x_i\mu_i(x) & \text{if } 0 \leq x_i \leq 1 \\ 0 & \text{if } x_i \\
\mu_i(1^-) & \text{if } x_i \geq 1 \end{cases}$$

for $i = 1, \ldots, k$.

A density-profile process $\{m_t^{x0,N}\}_{t \geq 0}$ is a random-walk process in $D_N$ which starts at $x^0$ and evolves in continuous time through jumps of size $1/N$ along the coordinate directions. From each position $x$, the rates for jumps forward or backwards along the coordinate direction $i$ are, respectively, $Nf_i(x)$ and $Ng_i(x)$. That is, for $1 \leq i \leq k$ and $x \in D_N$,

$$Nf_i(x) = \frac{d}{dt} P\left(m_t^{x,N} = x + \frac{e_i}{N}\right)|_{t=0}$$

and

$$Ng_i(x) = \frac{d}{dt} P\left(m_t^{x,N} = x - \frac{e_i}{N}\right)|_{t=0},$$

(2.3)
where \( \mathbf{e}_i \) denotes the unit vector along direction \( i \).

In our applications, the variable \( x_1, \ldots, x_k \) represent the densities of \( k \) types of objects that can be present at \( N \) different sites. The function \( \lambda_i \) is the rate of creation or activation of an object of type \( i \) at a site where the object is absent or inhibited. The function \( \mu_i \) is the rate for the opposite move. Thus, \( N f_i \) (resp. \( g_i \)) is the total rate of creation (resp. destruction) of an object of type \( i \) throughout the entire collection of sites.

In the sequel we assume the choice of a common probability space where the density-profile processes (and other auxiliary processes defined below) are simultaneously realized for all \( N \) and \( x^0 \). The corresponding probability measure will be denoted \( P \). (The graphical constructions introduced in Section 4 offer, in fact, a concrete way of defining this common space.)

### 2.2 Convergence to a dynamical system \( \{x^{t^0}_t\}_{t \geq 0} \)

Let \( \{m^{t^0,N}_t\}_{t \geq 0} \) be the density-profile process in \( D_N \) defined as above for a given pair of appropriate functions \( (\lambda, \mu) \), and let \( V : \mathbb{R}^k \to \mathbb{R}^k_+ \) be its associated velocity field:

\[
V(x) = \lim_{t \to 0} \frac{E(m^{x^0,N}_t - x)}{t} = f(x) - g(x),
\]

that is,

\[
V_i(x) = \begin{cases} 
(1 - x_i)\lambda_i(x) - x_i\mu_i(x) & \text{if } 0 \leq x_i \leq 1 \\
\lambda_i(0^+) & \text{if } x_i \leq 0 \\
\mu_i(1^-) & \text{if } x_i \geq 1
\end{cases}
\]

Let \( \{x^{t^0}_t\}_{t \geq 0} \) be the solution of the dynamical system

\[
\dot{x}_t = V(x_t)
\]

starting at \( x^0 \in (0,1)^k \). The global trajectory exists by the smoothness of the field \( V \). Furthermore, the flow does not leave \( (0,1)^k \) because \( V_i(0^+) > 0 \) and \( V_i(1^-) < 0 \) for \( i = 1, \ldots, k \).

The main result of this paper is the convergence of the sequence of density profile processes \( (m^{t^0,N}_t)_N \) to the trajectory \( x^{t^0}_t \). For \( \epsilon > 0 \) let \( \tau^N_\epsilon \) be the stopping time

\[
\tau^N_\epsilon = \inf \left\{ t \geq 0 : |m^{t^0,N}_t - x^{t^0}_t| > \frac{1}{N^{\frac{1}{2}\epsilon}} \right\}
\]

and, for a given \( T, 0 \leq T < \infty \), write \( A^T_{N\epsilon} = \{\tau^N_\epsilon < T\} \). The following is our main result.

**Theorem 2.1** Let \( \lambda \) and \( \mu \) be bounded functions from \( \mathbb{R}^k \) to \( \mathbb{R}^k_+ \) satisfying the Lipschitz condition

\[
|\lambda(x) - \lambda(y)| \leq K|x - y| \quad ; \quad |\mu(x) - \mu(y)| \leq K|x - y|
\]

for some \( K > 0 \) and all \( x, y \in (0,1)^k \). Then, for any finite \( T \), initial position \( x^0 \) and \( \epsilon > 0 \),

\[
P\left(\lim_{N \to \infty} A^T_{N\epsilon}\right) = 0
\]
That is, for typical realizations there exists some $N_{\epsilon,T}$ such that for $N > N_{\epsilon,T}$ each process $\{m_t^{x_0^N}\}_{t \geq 0}$ stays within a distance $N^{-1/2+\epsilon}$ of the deterministic path $\{x_t^0\}_{t \geq 0}$ at least up to time $T$.

Dynamical systems of the form (2.7)/(2.6) can exhibit quite complex dynamics—even for simple choices of $\lambda$ and $\mu$—, including stable orbits and chaotic behavior. In Section 3.2 we present an example of a system leading to a Hopf bifurcation.

3 Associated stochastic spin models

We present here a family of stochastic spin models, motivated by biological cellular systems, whose empirical densities evolve as density-profile processes.

3.1 General definition

We consider a discrete set $\Lambda$ of sites and a finite set $T = \{1, \ldots, k\}$ of types. Each type $i \in T$ can be present at each site $\ell \in \Lambda$. Thus, we choose our configuration space as $\Sigma = \{-1, +1\}^{T \times \Lambda}$, where for each $\eta \in \Sigma$, the value $\eta(i, \ell) = +1$ ($\eta(i, \ell) = -1$) indicates the presence (absence) of a particle of type $i$ at site $\ell$.

We consider continuous-time processes in $\Sigma$ in which only single spin flips are allowed. For $\eta \in \Sigma$ and $(i, \ell) \in T \times \Lambda$, let $\eta^{(i,\ell)}$ denote the configuration which is equal to $\eta$ except at site $\ell$ where the spin of type $i$ is flipped.

$$\eta^{(i,\ell)}(j, n) = \begin{cases} 
\eta(j, n) & \text{if } (j, n) \neq (i, \ell) \\
-\eta(i, \ell) & \text{otherwise}
\end{cases} \tag{3.1}$$

We shall consider type-dependent interaction models, for which the flip rate for the spin-flip transition $\eta \rightarrow \eta^{(i,\ell)}$ is a monotone non-increasing function of

$$\Delta(i, \ell, \eta) = H_i(\eta^{(i,\ell)}) - H_i(\eta) \tag{3.2}$$

for a Hamiltonian vector $H(\eta) = (H_1(\eta), \ldots, H_k(\eta))$.

A simple choice is

$$c(i, \ell, \eta) = \exp[-\Delta(i, \ell, \eta)]. \tag{3.3}$$

We focus on the particular case

$$H_i(\eta) = -\frac{1}{2} \sum_{\ell \in \Lambda} \left( \sum_{(j, n) \in T \times \Lambda} \frac{\alpha_{ji}}{[\Lambda]} \eta(j, n) \eta(i, \ell) + a_i \eta(i, \ell) \right). \tag{3.4}$$

This corresponds to a mean-field interaction, where $\alpha_{ji}$ is the strength of the influence of spins of type $j$ on those of type $i$ and each $a_i$ acts as a type-dependent external field. The most interesting phenomena appear when $\alpha$ is not symmetric. The empirical density profile of a configuration $\eta$, is the $k$-uple $m(\eta) = (m_1(\eta), \ldots, m_k(\eta)) \in \mathbb{R}_+^k$, where

$$m_i(\eta) = \frac{|\{\ell \in \Lambda : \eta(i, \ell) = +1\}|}{|\Lambda|}. \tag{3.5}$$
for $1 \leq i \leq k$.

Let $\{\sigma_i^0\}_{t \geq 0}$ be the spin-flip process starting at the configuration $\eta_0 \in \Sigma$ with rates defined by (3.4) and (3.3). Then, if $|\Lambda| = N$, the density-profile process $m(\sigma_i^0)$ approximates, in the sense of Theorem 2.1, the dynamical system (2.7)/(2.6), defined by

$$
\lambda_i(x) = \exp\left(\sum_{j \in T} \alpha_{ji}x_j + a_i\right) \quad (3.6)
$$

and

$$
\mu_i(x) = \exp\left(-\sum_{j \in T} \alpha_{ji}x_j - a_i\right). \quad (3.7)
$$

Given our biological motivation, models with mean-field interaction like (3.4) are natural. They are also the simplest models with type-dependent rates of the form (3.3). From the mathematical point of view, though, the analysis of models with local interaction [12], possibly with stirring [13] are much more interesting.

### 3.2 Example: Cyclic-interaction model

We exhibit now a model—called the cyclic-interaction model—defined through a simple choice of the interaction matrix $\alpha$ which nevertheless leads to interesting (deterministic) dynamical behavior. Think $\{1, \ldots, k\}$ as points on the circle and, for each $i \in T$ let $c(i)$ denote the nearest-neighbor of $i$ in the counter-clockwise direction. We assume that $\alpha_{ji} = 0$ unless $j = c(i)$ and that, furthermore, all non-zero terms in $\alpha$ have the same absolute value. That is,

$$
\alpha_{ji} = \begin{cases} 
s_i J & \text{if } j = c(i) \\
0 & \text{otherwise} \end{cases} \quad (3.8)
$$

where $s_i \in \{-1, +1\}$ representing the signals, and $J > 0$. We also set $a_i = -J/2$, for $1 \leq i \leq k$. In this way, once the signs $\{s_i\}_{i=1}^k$ are chosen, $J$ is the only free parameter of the model.

If $s_i = 1$, the rate with which spins of type $i$ flip from $-1$ to $+1$ [defined in (3.6)], is an increasing function of $x_{c(i)}$, the density of spins $+1$ of type $c(i)$. Borrowing statistical mechanical nomenclature, we say that the interaction of spins of type $c(i)$ with those of type $i$ is ferromagnetic [9]. In the biochemical context, where $x_i$ measures the density of some chemical component $i$, this means that the component $c(i)$ activates the production of component $i$. On the other hand, if $s_i = -1$ the rate for a spin of type $i$ to flip from $+1$ to $-1$ [defined in (3.7)], decreases as a function of $x_{c(i)}$, and the interaction of spins of type $c(i)$ with those of type $i$ is anti-ferromagnetic. In biochemical terms, the component $c(i)$ inhibits the production of component $i$.

The dynamical system (2.7) associated to the cyclic-interaction model (3.8) is:

$$
\dot{x}_i = e^{s_iJ(x_{c(i)} - \frac{1}{2})} - x_i \left( e^{s_iJ(x_{c(i)} - \frac{1}{2})} + e^{-s_iJ(x_{c(i)} - \frac{1}{2})} \right) \quad (3.9)
$$

for $1 \leq i \leq k$. If $J$ is small, this system has a single stable equilibrium point at $(1/2, \ldots, 1/2) \in \mathbb{R}^k$, whichever the choice of signs $s_i$. For larger $J$, the behavior of the dynamical system (3.9) crucially depends on whether the product of
signals is positive or negative. If $\Pi_{i=1}^k s_i = -1$ — a frustrated model in statistical mechanical terms — there is no (global) density-profile where all pairs of types of spins minimize their mutual interaction. This system exhibits a Hopf bifurcation as $J$ exceeds a critical value, which depends on $k$. In the non-frustrated case, the model behaves as the Curie-Weiss model. Formally:

**Theorem 3.1** Consider the dynamical system \((3.9)\) with \(k \geq 3\).

(a) If $\Pi_{i=1}^k s_i = 1$, there is a bifurcation at $J_c = 2$: the fixed point \((1/2, \ldots, 1/2)\) loses stability and two stable points appear for $J > J_c$.

(b) If $\Pi_{i=1}^k s_i = -1$, there is a Hopf bifurcation at $J_c = 2/\cos(\pi/k)$.

**Proof:** Write $s = \Pi_{i=1}^k s_i$. A simple computation shows that near \(1/2 = (1/2, \ldots, 1/2) \in \mathbb{R}^k\) the dynamical system \((3.9)\) is close to \(\dot{x} = A(x - 1/2)\), where $A$ is a $k \times k$ real matrix with eigenvalues $sJ e^{2\pi ik l/2}, l = 0, 1, \ldots, k - 1$. The fixed point is stable if the real parts of all eigenvalues are strictly negative, and stability is lost when one one of the real parts becomes positive. Thus, if $s = 1$ the fixed point \(1/2\) loses stability at $J_c = 2$ when the eigenvalue corresponding to $l = 0$ crosses the imaginary axis through the origin. On the other hand, if $s = -1$, the stability is lost when two eigenvalues, symmetric around the real axis, cross the imaginary axis. This occurs at $J_c = 2/\cos(\pi/k)$. \(\Box\)

**Remark 3.2** For instance, if $k = 3$ and all interactions are antiferromagnetic ($s_i = -1$ for $i = 1, 2, 3$), the dynamical system has stable orbits for $J > J_c = 4$. The convergence result, Theorem \((2.1)\) implies that, within any finite time interval, the density-profile process evolves as close to this orbit as wished, for $N$ sufficiently large.

### 4 Proof of the convergence theorem

#### 4.1 The auxiliary process \(\{\tilde{m}_{x^{0}}^N_t\}_{t \geq 0}\)

To prove Theorem \((2.1)\) we introduce an auxiliary stochastic spin model with independent spins flips but time-dependent rates.

Let $\Lambda = \{1, \ldots, N\}$ and let $\{\eta_t(i, n) : (i, n) \in T \times \Lambda\}_{t \geq 0}$, be $kN$ independent Markov chains with state space $\{-1, +1\}$. Thus, for each $t \geq 0$, $\eta_t \in \Sigma = \{-1, +1\}^{T \times \Lambda}$, with $T = \{1, \ldots, k\}$, as defined in the previous section. For each Markov chain $\{\eta_t(i, n)\}_{t \geq 0}$ the flips from $-1$ to $+1$ and from $+1$ to $-1$ have time-dependent rates given, respectively, by $\lambda_i(x_t^{0})$ and $\mu_i(x_t^{0})$, where $\{x_t^{0}\}_{t \geq 0}$ is the solution of the dynamical system \((2.4)\) from the initial position $x^0$. We initialize these chains with the uniform distribution on configurations $\eta_0$ with $m(\eta_0) = x^0$, where $m(\eta_t)$ is defined in \((4.5)\). The total number of spins of each type $i$ is, thus, fixed and equal to $x_i^0$, but he initial density components $m_1(\eta_0), \ldots, m_k(\eta_0)$ are independent. We denote $\{\tilde{m}_{x^{0}}^N_t\}_{t \geq 0}$ the corresponding density-profile process.

We observe that the chain at each $(i, n) \in T \times \Lambda$ satisfies Kolmogorov’s equation. Hence, for $p_t(i, n) = P(\eta_t(i, n) = +1)$, we have

$$
\dot{p}_t(i, n) = [1 - p_t(i, n)] \lambda_i(x_t^{0}) - p_t(i, n) \mu_i(x_t^{0}).
$$

(4.1)
Therefore each function \( t \to p_t(i, n) \) is a solution of the differential equation (2.7) with \( V \) as in (2.9). Hence

\[
p_0(i, n) = (x^0)_i \quad \implies \quad p_t(i, n) = (x^0_t)_i \quad \forall t \geq 0 ,
\]

for all \( i \in \mathcal{T} \) and \( n \in \Lambda \) \([y]_i \) indicates the \( i \)-th component of vector \( y \in \mathbb{R}^k \). While (4.2) is true for the auxiliary process \( \{\hat{m}^0_t\} \), we are interested in following the actual empirical densities. Next lemma proves that also the path followed by these densities remain, at all times, close to the trajectories of the dynamical system.

**Lemma 4.1** For \( \delta > 0 \) there exists \( c > 0 \) such that

\[
P \left( |\hat{m}^0_t,N - x^0_t| > N^{\delta - 1/2} \right) < \exp(-cN^{\delta})
\]

for \( t \geq 0 \).

**Proof:** Let us introduce yet another auxiliary process, denoted \( \{\hat{m}^{b(x^0)}_t,N\} \) to zero, but with initial spins chosen independently with 

\[
P(\eta_0(i, n) = +1) = (x^0)_i . 
\]

Hence, the density components \( m_1(\eta), \ldots, m_k(\eta) \) are independent and each \( m_i(\eta) \) has a binomial distribution with parameters \( N \) and \( p_i = (x^0)_i, \, i = 1, \ldots, k \). (This means that, for large \( N \), \( \hat{m}^{b(x^0)}_0 \) starts at a random position in \( D \) close to \( x^0 \), while \( \hat{m}^{b(x^0)}_t \) starts precisely at \( x^0 \).)

This new auxiliary process also satisfies (4.2) but has the advantage that the spin chains remain independent at all times, and, by (4.2), the proportions of spins of each type coincide with the components of \( x^0_t \). Therefore \( N\hat{m}^{b(x^0)}_t,N \) is a vector of independent binomial random variables

\[
N \left( \hat{m}^{b(x^0)}_t,N \right)_i \sim \text{Bin}(N, (x^0_t)_i) \quad (4.4)
\]

for \( t \geq 0 \) and \( i \in \mathcal{T} \). In particular the the variances of the components of \( \hat{m}^{b(x^0)}_t,N \) are proportional to \( 1/N \). Thus, the large-deviation properties of binomial distributions [14] imply that for any \( \delta > 0 \) there exists a constant \( c \) such that

\[
P \left( |\hat{m}^{b(x^0)}_t,N - x^0_t| > \frac{1}{2} N^{\delta - 1/2} \right) < \exp(-cN^{\delta}) \quad (4.5)
\]

for any \( t \geq 0 \).

To conclude the proof of the lemma we must show that both auxiliary processes \( \hat{m}^{b(x^0)}_t,N \) and \( \hat{m}^{x^0}_t,N \) remain close to each other. This is more easily done through a coupling argument [15, 16]. We construct a coupled realization \( (\eta_t^{b(x^0)} , \eta_t^{x^0}) \) of the spin systems defining both processes as follows. Spins in both systems flip with the same time-dependent rates given in (11). At sites \( (i, n) \) with \( \eta_0^{b(x^0)}(i, n) = \eta_0^{x^0}(i, n) \), the spins evolve together. Otherwise, the spins for both processes evolve independently until one of them makes a transition, thereby bringing them to a common value. They evolve together ever after. As the distance between the corresponding coupled density profiles decreases with time,

\[
| m(\eta_t^{b(x^0)} , \eta_t^{x^0}) - m(\eta_t^{b(x^0)},N) | \leq | m(\eta_0^{b(x^0)} , \eta_0^{x^0}) - m(\eta_0^{b(x^0)},N) | \leq | m(\eta_0^{b(x^0)},N) - x^0 | \quad (4.6)
\]
and, therefore,
\[
P\left(\left|\tilde{m}_0^{x_0,N} - x_t^0\right| > N^{\delta - 1/2}\right) \leq
\]
\[
P\left(\left|\tilde{m}_0^{x_0,N} - \tilde{m}_0^{b(x_0),N}\right| > \frac{1}{2} N^{\delta - 1/2}\right) + P\left(\left|\tilde{m}_0^{b(x_0),N} - x_t^0\right| > \frac{1}{2} N^{\delta - 1/2}\right).
\]
(4.7)

To prove (4.5) we bound the right-hand side using (4.6) and (4.5) (for \(t = 0\)) for the first term and again (4.5) for the second one.

To prove Theorem 2.1 we will show that, for \(N\) large, \(\tilde{m}_0^{x_0,N}\) and \(m_0^{x_0,N}\) remain close within arbitrary finite time intervals. To achieve this we will couple both stochastic evolutions with the help of a graphical construction.

### 4.2 Graphical construction: The process \(\{g_{t}^{x_0,N}\}_{t\geq 0}\)

We resort to a graphical construction of density-profile processes with different \(N\) through time-rescaling of auxiliary processes \(\{g_{t}^{x_0,N}\}_{t\geq 0}\). The latter is defined through paths determined by Poissonian “marks”. This construction will be adapted in next section to couple the processes \(\tilde{m}_0^{x_0,N}\) and \(m_0^{x_0,N}\).

To each \(y\in D_N\) we associate 2\(k\) independent Poisson processes: \(N_{t}^{1+}(y)\), \(N_{t}^{1-}(y)\), \ldots, \(N_{t}^{k+}(y)\), \(N_{t}^{k-}(y)\), where each \(N_{t}^{i+}(y)\) has rate \(f_{i}(y)\) and each \(N_{t}^{i-}(y)\) rate \(g_{i}(y)\). We associate a particular type of mark for the events of each type of process and place these marks along the time axis of \(y\). A Poisson mark associated to the process \(N_{t}^{i+}(y)\) (\(N_{t}^{i-}(y)\)) carries the instruction to jump along the positive (negative) \(i\) coordinate direction.

The process \(\{g_{t}^{x_0,N}\}_{t\geq 0}\) is defined by _open paths_ in \(D_N \times \mathbb{R}_+\) determined by the marks. These are piecewise linear curves that move along the positive time axis until a Poisson mark is met. At these times the trajectory moves by \(\pm 1/N\) along a coordinate direction according to the type of mark. The process \(\{g_{t}^{x_0,N}\}_{t\geq 0}\) is at position \(x\) at time \(t\) if there exists an open path from \((x_0, 0)\) to \((x, t)\).

We see that the evolution of \(\{g_{t}^{x_0,N}\}\) differs from that of \(\{m_{t}^{x_0,N}\}\) only in that the rates of the latter \(\{\text{given by } (2.3)\text{ and } (2.4)\}\) are \(N\) times those of the former. Thus, one process can be constructed from the other by a simple change in the time scale:

\[
m_{t}^{x_0,N} = g_{Nt}^{x_0,N}.
\]
(4.8)

In words: a _density-profile time_ \(t\) corresponds to a _graphical-construction time_ \(Nt\).

### 4.3 Main coupling and discrepancy process

We now use the graphical-construction strategy to produce coupled realizations of the density-profile processes \(m_0^{x_0,N}\) and \(\tilde{m}_0^{x_0,N}\) with an appropriate control of their distance. Our coupling forces both processes to keep their relative distance as much as possible, evolving as a rigid system. Of course, since their rates are not equal, they will make occasional asynchronous moves that may take them increasingly apart with the passing of time. The coupling is designed so to minimize this asynchrony.
The coupling involves a number of Poissonian mark processes at different sites which are updated every time there is an asynchronous move. The successive times of these moves correspond to a sequence of stopping times \( \{\tau_n\}_{n \geq 1} \); the coupling is defined in a recursive fashion within successive time intervals \([\tau_{n-1}, \tau_n)\), \(n \geq 1\). The auxiliary processes, which arise directly from such graphical coupled construction will be denoted, respectively, by \(g_{t_0}^0\) and \(\widehat{g}_{t_0}^0\). They differ from the density profiles \(m_{t_0}^{x_0,N}\) and \(\widehat{m}_{t_0}^{x_0,N}\) only in the time scale, which in the graphical construction is slower by a factor \(N\).

**Initial stage of the coupling** Initially, \(g_{0}^0 = \widehat{g}_{0}^0 = x^0\) and up to the first stopping time \(\tau_1\) (to be defined) we couple them through what is known as basic coupling in particle systems. For each \(y \in D_N\) and coordinate direction \(i = 1, \ldots, k\) we define six Poissonian mark processes:

1. **Marks associated to jumps from \(y\) to \(y + \epsilon_i/N\):** They are defined by independent Poisson processes \(\hat{N}_{i,+}^{t_i}(y), \hat{E}_{i,+}^{t_i}m(y)\) and \(\hat{E}_{i,+}^{t_i}\wedge m(y)\) with respective rates
   \[
   \begin{align*}
   \hat{u}_{i,+}^{t_i}(y) &= \min\{1 - y_i \mu_i(y), (1 - y_i) \mu(x_{t_i/N}^0)\}, \\
   \hat{e}_{i,+}^{t_i}m(y) &= \left|1 - y_i \mu_i(y) - \hat{u}_{i,+}^{t_i}\right| + \\
   \hat{e}_{i,+}\wedge m(y) &= \left|1 - y_i \mu_i(x_{t_i/N}^0) - \hat{u}_{i,+}\right|.
   \end{align*}
   \]
   Note the rescaling in time for the deterministic path \(x_{t_i}^0\) needed to represent it on the graphical construction time scale.

2. **Marks associated to jumps from \(y\) to \(y - \epsilon_i/N\):** Defined by three independent Poissonian processes \(\hat{N}_{i,-}^{t_i}(y), \hat{E}_{i,-}^{t_i}m(y)\) and \(\hat{E}_{i,-}\wedge m(y)\) which are independent from the precedent ones and have respective rates
   \[
   \begin{align*}
   \hat{u}_{i,-}^{t_i}(y) &= \min\{y_i \mu_i(y), y_i \mu(x_{t_i/N}^0)\}, \\
   \hat{e}_{i,-}^{t_i}m(y) &= \left|y_i \mu_i(y) - \hat{u}_{i,-}^{t_i}\right| + \\
   \hat{e}_{i,-}\wedge m(y) &= \left|y_i \mu_i(x_{t_i/N}^0) - \hat{u}_{i,-}\right|.
   \end{align*}
   \]
   As before, we think that occurrence of each of these processes are associated to particular marks indicating where to jump. The jumps of the process \(\{\hat{g}_{t_i}^{x_0,N}\}\) occur at the marks of \(\{\hat{E}_{i,+}^{t_i}m(y)\}\) and \(\{\hat{E}_{i,-}^{t_i}m(y)\}\); while those of the process \(\{\hat{g}_{t_i}^{x_0,N}\}\) are at \(\{\hat{E}_{i,+}^{t_i}\wedge m(y)\}\) and \(\{\hat{E}_{i,-}\wedge m(y)\}\). The marks of the four processes \(\{\hat{E}_{i,+}^{t_i}m(y)\}, \{\hat{E}_{i,+}\wedge m(y)\}, \{\hat{E}_{i,-}^{t_i}m(y)\}\) and \(\{\hat{E}_{i,-}\wedge m(y)\}\) are thus seen by only one of \(\{\hat{g}_{t_i}^{x_0,N}\}\) or \(\{\hat{g}_{t_i}^{x_0,N}\}\) and will be called discrepancies. The basic Poisson processes \(\{\hat{N}_{i}^{t_i}(y)\}\), on the other hand, are introduced to ensure that \(\{\hat{g}_{t_i}^{x_0,N}\}\) and \(\{\hat{g}_{t_i}^{x_0,N}\}\) remain equal until they find the first discrepancy. This defines a stopping time \(\tau_1\) at which the processes get separated by a distance of \(1/N\). At this time we can not continue using the basic coupling.

Formally, we define a first-discrepancy process
   \[
   D_{t_1}^0 = \sum_{i=1}^{k} \left[\hat{E}_{i,+}^{t_i}m(y^0) + \hat{E}_{i,-}^{t_i}m(y^0) + \hat{E}_{i,+}\wedge m(y^0) + \hat{E}_{i,-}\wedge m(y^0)\right].
   \]
where \( y^0 \) is the density-profile path defined by the preceding (level-0) construction. The first discrepancy time \( \tau_1 \) is the time of the first event of this process. A new coupling definition must be introduced at this time, which will be applied until the second discrepancy time \( \tau_2 \). This iterative procedure continues up to the time \( T \) chosen in Theorem [2.1]. We now present the recursive step in the definition of such a coupling.

**l-th stage of the coupling** Suppose that the graphical construction has been defined up to time \( \tau_l \), \( l \geq 1 \), determining \( x^l, \Delta^l \in \mathbb{D}_N \) such that

\[
g^{x^0,N}_{\tau_l} = x^l, \quad \tilde{g}^{x^0,N}_{\tau_l} = x^l + \Delta^l. \tag{4.12}
\]

[Thus, \( m_{\tau_l/N} = x^l \) and \( \tilde{m}_{\tau_l/N} = x^l + \Delta^l \).] From time \( \tau_l \) we start a new graphical construction, which defines the evolution of both processes until the next discrepancy appears at time \( \tau_{l+1} \). We define the following Poisson mark processes for each \( y \in \mathbb{D}_N \) and coordinate direction \( i = 1, \ldots, k \):

\[(i)\text{ Marks associated to jumps from } y \text{ to } y + e_i/N:\text{ Let } \hat{N}^{i,+}_{t,N}(y), \hat{N}^{i,+}_{t,N}(y), \tilde{E}^{i,+}_{t,y}(y) \text{ and } \tilde{E}^{i,+}_{t,y}(y) \text{ be Poisson processes with respective rates}
\]

\[
\hat{u}^{i,+}_{t,y}(y, \Delta^l) = \min \{ (1 - y_i) \lambda_i(y), (1 - y_i - \Delta^l_i) \lambda(x^0_{t_i/N}) \},
\]

\[
\hat{u}^{i,+}_{t,y}(y, \Delta^l) = \min \{ (1 - y_i) \lambda_i(x^0_{t_i/N}), (1 - y_i + \Delta^l_i) \lambda_i(y - \Delta^l) \},
\]

\[
c^{i,+}_{t,y}(y, \Delta^l) = |(1 - y_i) \lambda_i(y) - \hat{u}^{i,+}_{t,y}(y, \Delta^l)|_+ \quad \text{and}
\]

\[
\hat{e}^{i,+}_{t,y}(y, \Delta^l) = |(1 - y_i) \lambda_i(x^0_{t_i/N}) - \hat{u}^{i,+}_{t,y}(y, \Delta^l)|_+ .
\]

\[
\hat{N}^{i,+}_{t,N}(y) = \hat{N}^{i,+}_{t,y}(y + \Delta^l) \tag{4.13}
\]

We observe that \( \hat{u}^{i,+}_{t,y}(y, \Delta^l) = \hat{u}^{i,+}_{t,y}(y + \Delta^l, \Delta^l) \) for any \( y \in \mathbb{D} \), so we identify

\[
\hat{N}^{i,+}_{t,N}(y) = \hat{N}^{i,+}_{t,y}(y + \Delta^l). \tag{4.14}
\]

Except for this identification, the different processes are mutually independent and independent of all previous Poisson mark processes.

\[(ii)\text{ Marks associated to jumps from } y \text{ to } y - e_i/N:\text{ They are determined by}
\]

Poisson processes \( \hat{N}^{i,-}_{t,N}(y), \hat{N}^{i,-}_{t,N}(y), \hat{E}^{i,-}_{t,y}(y) \) and \( \hat{E}^{i,-}_{t,y}(y) \), respectively with rates

\[
\hat{u}^{i,-}_{t,y}(y, \Delta^l) = \min \{ y_i \mu_i(y), (y_i + \Delta^l_i) \mu(x^0_{t_i/N}) \},
\]

\[
\hat{u}^{i,-}_{t,y}(y, \Delta^l) = \min \{ y_i \mu_i(x^0_{t_i/N}), (y_i - \Delta^l_i) \mu(y - \Delta^l) \},
\]

\[
c^{i,-}_{t,y}(y, \Delta^l) = |y_i \mu_i(y) - \hat{u}^{i,-}_{t,y}(y, \Delta^l)|_+ \quad \text{and}
\]

\[
\hat{e}^{i,-}_{t,y}(y, \Delta^l) = |y_i \mu_i(x^0_{t_i/N}) - \hat{u}^{i,-}_{t,y}(y, \Delta^l)|_+ ;
\]

with the identification

\[
\hat{N}^{i,-}_{t,N}(y) = \hat{N}^{i,-}_{t,y}(y + \Delta^l) . \tag{4.15}
\]

All these processes are independent among themselves, except for the preceding identification, and independent of other mark processes.
The process \( \{\tilde{g}^{\xi,N}\} \) jumps only at the marks placed by the processes \( \{\tilde{E}^{i,\pm,m}(y)\} \), while process \( \{\tilde{g}^{\xi,N}\} \) does so at the marks of \( \{\tilde{E}^{i,\pm,\tilde{m}}(y)\} \). Due to identifications (4.13)/(4.10), the basic Poisson marks \( \{\tilde{N}^{i,\pm,m}(y)\} \) seen by \( \{\tilde{g}^{\xi,N}\} \) at a given position \( y \) coincide with the basic marks seen by \( \{\tilde{g}^{\xi,N}\} \) at its corresponding position \( y + \Delta^l \). Hence, the two graphic processes evolve rigidly, keeping a separation \( \Delta_i^l \), until a discrepancy is met, that is, until one of the processes responds to a Poisson mark that the other ignores. This happens either because \( \{\tilde{g}^{\xi,N}\} \) at a certain position \( y \) meets a mark of \( \{\tilde{E}^{i,\pm,m}(y) + \tilde{E}^{i,\pm,\tilde{m}}(y)\} \) or because \( \{\tilde{g}^{\xi,N}\} \), at the corresponding position \( y + \Delta^l \), meets a mark of \( \{E^{i,\pm,\tilde{m}}(y + \Delta^l) + E^{i,\pm,m}(y + \Delta^l)\} \). Therefore, this discrepancy, corresponding to the stopping time \( \tau_{l+1} \), is the first event of the \( l \)-th-discrepancy process \( \{D^l_t\}_{t \in [\tau_l, \tau_{l+1}]} \), given by

\[
D^l_t = \sum_{i=1}^k \left[ \tilde{E}^{i,\pm,m}(y^l_i) + \tilde{E}^{i,\pm,\tilde{m}}(y^l_i) 
+ \tilde{E}^{i,\pm,\tilde{m}}(y^l_i + \Delta^l) + \tilde{E}^{i,\pm,m}(y^l_i + \Delta^l) \right]
\]

(4.17)

where \( y^l_i \) is the density profile path defined by a realization of the \( (l \)-th) construction done at this stage.

The construction done at the \( l \)-th stage makes sense, and has the correct rates, for \( t \geq \tau_l \). Thus, together with the assumed graphical construction for \( t \in [0, \tau_l) \), it yields a well defined coupling for \( \tilde{g}^{\xi,N} \) and \( \tilde{g}^{\xi,N} \) at all times. Such a (level-\( l \)) coupling, however, loses precision after the next discrepancy is encountered. To improve it, we ignore it for \( t \geq \tau_{l+1} \) and replace it by the level-(\( l+1 \)) construction corresponding to the \( l+1 \)-th stage. This stage begins with \( \tilde{g}^{\xi,N} - \tilde{g}^{\xi,N}_{l+1} = \Delta_{l+1} \) with \( |\Delta_{l+1} - \Delta^l| = 1/N \).

This recursive construction is continued, for each trajectory, until the time \( t = NT \) is achieved. The procedure involves, almost surely, a finite number of stages. The process

\[
\mathcal{T}_l = D^l_t \quad \text{if } t \in (\tau_l, \tau_{l+1}]
\]

(4.18)

\( l = 0, 1, \ldots (\tau_0 = 0) \), counts the number of discrepancies. It satisfies the relation \( \{\mathcal{T}_l \geq 1\} = \{\tau_l \leq t\} \).

### 4.4 Discrepancy rates

The proof of Theorem 2.1 requires the control of the distance between \( m^{\xi,N}_t \) and \( \tilde{m}^{\xi,N}_t \). As each discrepancy brings an additional separation of \( 1/N \),

\[
|m^{\xi,N}_t - \tilde{m}^{\xi,N}_t| \leq \frac{\mathcal{T}_{Nt}}{N}
\]

(4.19)

To estimate the right-hand side we first determine upper bounds on the time-dependent rate of the process \( \{\mathcal{T}_l\} \).

**Lemma 4.2** Consider \( N \in \mathbb{N} \), \( T \geq 0 \) and \( \delta > 0 \). For each \( l \in \mathbb{N} \), let \( R^l_t \) be the instantaneous rate of the level-\( l \) discrepancy process \( D^l_t \), \( t \in [\tau_l, \tau_{l+1}] \) defined
above and let $R^l = \sup\{ R^l_t : t \in [\tau_l, \tau_{l+1}] \cap [0, NT] \}$. Then there exists a constant $A > 0$ such that the events
\[ R^N = \left\{ R_l \leq N^{\delta-1/2} + \frac{A l}{N} \quad \forall l \text{ s.t. } \tau_l \leq NT \right\} \] (4.20)
satisfy
\[ P\left( \lim_N R^N \right) = 1. \] (4.21)

Proof: Let $\Delta_t$ be the distance between the coupled geometrical realizations $g^{x^0, N}$ and $\hat{g}^{x^0, N}$:
\[ \Delta_t = \sum_{l \geq 0} \Delta^l 1_{t \in [\tau_l, \tau_{l+1})}. \] (4.22)

The discrepancy process can be written as
\[ D_t = -\sum_{i=1}^k \left[ \hat{E}_t^{i^+, b_m} (g_t^{x^0, N}) + \hat{E}_t^{i^-, b_m} (\hat{g}_t^{x^0, N}) \right. \]
\[ \left. + \hat{E}_t^{i^+, b_m} (\hat{g}_t^{x^0, N} + \Delta_t) + \hat{E}_t^{i^-, b_m} (g_t^{x^0, N} + \Delta_t) \right]. \] (4.23)

The rate of this process is zero at $t = 0$, but it increases as the processes $\{g^{x^0, N}\}$, $\{\hat{g}^{x^0, N}\}$ and $\{x^0_t\}$ move away from each other during the stochastic evolution.

We see from (4.13) and (4.15) that to bound this rate we must compare values of $x^0(x)$ and $x^0(y)$ for different densities $x$ and $y$. Due to the Lipschitz hypothesis (2.9), these difference increase at most linearly, and there exists a constant $A$ such that the rate of $D_t$ is bounded above by
\[ A \left| \hat{g}^{x^0, N} - x^0_t \right| + A \left| g_t^{x^0, N} - \hat{g}_t^{x^0, N} \right|. \] (4.24)

For a given realization of the graphical construction, the second term in (4.24) is bounded above by $\frac{\Delta^l}{N}$, as remarked in (4.19). Therefore
\[ \left| g_t^{x^0, N} - \hat{g}_t^{x^0, N} \right| \leq \frac{l}{N} \quad \text{if } t \in [\tau_l, \tau_{l+1}) \]. (4.25)

For the first term in (4.24) we apply first the probabilistic bound
\[ P\left( \left| \hat{g}^{x^0, N} - x^0_t \right| > \frac{1}{2A} N^{\delta-1/2} \right) \]
\[ = P\left( \left| \hat{g}^{x^0, N} - x^0_t \right| > \frac{1}{2A} N^{\delta-1/2} \right) \] (4.26)
\[ < \exp(-cN^\delta). \]
valid for each $t > 0$. The last inequality follows from (4.3). We need, however, a bound valid for all $t \in [0, NT]$. To this end, we apply (4.20) to a sufficiently thick collection of times. We pick a positive real $\gamma$ (soon to be chosen larger than 3) and denote $M$ the integer part of $N^\gamma$. For each $0 \leq j \leq M$ let
\[ C^j = \left\{ \left| \hat{g}_j^{x^0, N} - x^0_t \right| \leq N^{\delta-1/2} \right\} \] (4.27)
and

\[ \Theta = \inf \left\{ t : \left| \hat{g}_t^{b(x^0)} - x_{t/N}^{x^0} \right| > N^{\delta - 1/2} \right\}. \tag{4.28} \]

Then,

\[
P(\Theta \leq NT) \leq P(\Theta \leq NT, \cap_{t=0}^{M} C_t) + \sum_{l=0}^{M} (1 - P(C_l)) \leq M \left[ 1 - \left( 1 - \frac{dNT}{M} \right) \exp(-dNT/M) \right] + M \exp(-cN^\delta) \leq c N^{2-\gamma} \tag{4.29} \]

where \(d\) and \(c\) are positive constants. In the second line we used (4.26) to bound the last term. For the other term, we just observed that the conditions \(\Theta \leq NT\) and \(\cap_{t=0}^{M} C_t\) together imply that the process must have at least two transitions during the time interval of length \(NT/M\) containing \(\Theta\). The constant \(d\) bounds the rate of flips of the process \(\{\hat{g}_t^{b(x^0)}\}_{t \geq 0}\) (we can take \(d = \sum_{i=1}^{k} \|\lambda_i\|_{\infty} + \sum_{i=1}^{k} \|\mu_i\|_{\infty}\)). The choice \(\gamma > 3\) yields a summable bound in (4.29), which implies

\[
P\left(\lim_{N} \{\Theta \leq NT\} \right) = 0 \tag{4.30} \]

This result together with the bound (4.25) proves (4.21). \(\square\)

### 4.5 Conclusion of the proof

Due to Lemma 4.1 and relation (4.19), the following lemma concludes the proof of Theorem 2.1.

**Lemma 4.3** For any \(\varepsilon > 0\) and \(0 \leq t \leq T\),

\[
P\left( \lim_{N} \{ \overline{D}_{NT} \geq N^{\varepsilon + 1/2} \} \right) = 0. \tag{4.31} \]

**Proof:** Let us denote \(\tilde{N}_t = \overline{D}_{NT}\). This process—which has rates \(N\) times higher than those of \(\{\overline{D}_t\}_{t \geq 0}\)—counts discrepancies in the time scale of \(\{m_t^{x^0}\}_{t \geq 0}\). Let \(T_N\) be the time needed for the latter to collect \(N^{\varepsilon + 1/2}\) discrepancies:

\[
T_N = \min \{ t : \tilde{N}_t \geq N^{\varepsilon + 1/2} \}. \tag{4.32} \]

It can be written in the form

\[
T_N = \sum_{i=1}^{N^{\varepsilon + 1/2}} T_i \tag{4.33} \]

where \(T_1, T_2, \ldots\) are the independent successive times spent in between jumps and \(N^{\varepsilon + 1/2}\) is the smallest integer following \(N^{\varepsilon + 1/2}\).

We now choose some \(\delta\) with \(0 < \delta < \varepsilon\). By Lemma 1.2 the events

\[ D_r = \{ \text{condition (4.20) is valid for } N \geq r \} \tag{4.34} \]

satisfy

\[
P\left( \bigcup_{r \in \mathbb{N}} D_r \right) = 1. \tag{4.35} \]
In the sequel we shall show that
\[
\sum_N P(T_N < T; D_r) < \infty \tag{4.36}
\]
for each natural number \(r\). This concludes the proof because it implies that
\[
P\left(\lim_N \{T_N < T\}\right) \leq \sum_r P\left(\lim_N \{T_N < T\}; D_r\right) = 0. \tag{4.37}
\]

To prove (4.36) we partially resum the decomposition (4.33) in blocks of size
\[
Q = \frac{N^{\delta+1/2}}{N_+^{\delta+1/2}} \sim \frac{N^{\delta-\delta}}{N \to \infty} \to \infty \tag{4.38}
\]
We consider intervals \(I_l = [(l+1)N_+^{\delta+1/2} + 1, lN_+^{\delta+1/2}]\) and write
\[
T = \sum_{l=1}^Q G_l, \quad G_l = \sum_{j \in I_l} T_j. \tag{4.39}
\]
Within \(D_r\) the process \(\{\tilde{N}_t\}_{t \geq 0}\) jumps from \(i\) to \(i+1\) with rates bounded above by \(N_+^{\delta+1/2} + A l\), which is smaller than \((l+1)N_+^{\delta+1/2}\) if \(N\) is large enough. This shows that, for such \(N\)’s, the output of each variable \(G_l\) is no smaller than that of a sum of \(N_+^{\delta+1/2}\) i.i.d. exponential random variables with rate \((l+1)N_+^{\delta+1/2}\). Hence,
\[
P(T < T; D_r) \leq P\left(\sum_{l=1}^Q \frac{G_l(N_+^{\delta+1/2})}{(l+1)N_+^{\delta+1/2}} < T\right) \tag{4.40}
\]
where \(\{G(N_+^{\delta+1/2})\}_{l \geq 1}\) denotes an i.i.d. sequence of Gamma random variables with with parameters \(n = N_+^{\delta+1/2}\) and \(\lambda = 1\). The large-deviation properties of these distributions imply that each variable \(G_{l,N} = G_l(N_+^{\delta+1/2})/N_+^{\delta+1/2}\) satisfies
\[
P(G_{l,N} < 1/2) \leq \exp(-cN_+^{\delta+1/2}) \tag{4.41}
\]
for some positive constant \(c\) and all \(1 \leq l \leq Q\) and \(N\) large enough.

Denoting \(A_{l,N} = \{G_{l,N} \geq 1/2\}\) and \(B_{Q,N} = \cap_{l=1}^Q A_{l,N} \cap D_r\) we have
\[
P(T_N < T; D_r) \leq (1 - P(B_{Q,N})) + P(T_N < T, B_{Q,N}) \tag{4.42}
\]
On the event \(B_{Q,N}, T\) is bounded below by
\[
\frac{1}{2} \sum_{l=1}^Q \frac{1}{l+1} \sim \log Q \to \infty. \tag{4.43}
\]
Therefore the second term in the right-hand side of (4.42) is zero for \(N\) large enough. Bounding the first term by the large-deviation estimate (4.41) we conclude that
\[
P(T_N < T; D_r) \leq Q \exp(-cN_+^{\delta+1/2}) \tag{4.44}
\]
for \(N\) large enough. This proves (4.36). \(\square\)
Acknowledgments

The authors wish to thank the NUMEC and the University of São Paulo (R.F.) and the University of Rouen (E.J.N.) for hospitality during the completion of this work and to the USP-COFECUB agreement. E.J.N. also thanks Antonio Prudente Cancer Research (FAPESP-CEPID). L.R.F. is partially supported by the CNPq grant 307978/2004-4. E.J.N. and L.R.F. are partially supported by the by FAPESP grant 2004/07276-2. All three authors are partially supported by CNPq grant 484351/2006-0. R.F. benefited from the CNRS-FAPESP agreement.

References

[1] H. Kitano, Systems Biology: a brief overview, Science, 295:1662-1664, 2002.

[2] Molecular biology of the cell; Bruce Alberts, et al. 4th ed. ISBN 0-8153-3218-1, Published by Garland Science.

[3] J. J Tyson, K. C Chen and B. Novak; Sniffers, buzzers, toggles and blinkers: dynamics of regulatory and signaling pathways in the cell; Current Opinion in Cell Biology, Volume 15, Issue 2, April 2003, Pages 221-231;

Wolf D.M.; Arkin A.P.; Motifs, modules and games in bacteria: Current Opinion in Microbiology, April 2003, vol. 6, no. 2, pp. 125-134(10).

[4] http://stke.sciencemag.org/cm/ http://cgap.nci.nih.gov/Pathways

[5] Mathematical Biology I; J.D. Murray, Publisher: Springer;2005.

[6] Tyson JJ, Csikasz-Nagy A, Novak B.; The dynamics of cell cycle regulation. Bioessays. 2002 Dec;24(12):1095-109.

[7] Lauffenburger DA.; Cell signaling pathways as control modules: complexity for simplicity?; Proc. Natl. Acad. Sci. ; 2000;97(10):5031-3.

[8] T. M. Liggett (1985): Interacting particle systems. Springer-Verlag.

[9] Colin J. Thompson, Classical Equilibrium Statistical Mechanics (Clarendon Press, 1988).

[10] J. Guckenheimer and P. Holmes. Nonlinear Oscillations, Dynamical Systems, and Bifurcations of Vector Fields. Springer-Verlag, 1990.

[11] R. Durrett; Stochastic Spacial Models; SIAM review; Vol. 41; No. 4; pp. 677-718, 1999.

[12] D. Ruelle; Statistical Mechanics; W. A. Benjamin, Reading, MA.

[13] A. De Masi, P.A. Ferrari, J.L. Lebowitz Reaction-diffusion equations for interacting particle systems J. Stat. Phys. 44, 3/4:589-644 (1986).

[14] Richard S. Ellis; Entropy, Large Deviations, and Statistical Mechanics; Publisher: Springer; (2005); ISBN-10: 3540290591.
[15] Hermann Thorisson; Coupling, Stationarity, and Regeneration (Probability and its Applications); Hardcover: 536 pages; Publisher: Springer; 1 edition (2001).