On the Stochastic Modelling of Interacting Populations. A Multiscale Approach Leading to Hybrid Models

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Summary. In this paper a review by the research work of the authors on the stochastic modelling of interacting individuals is presented. Both cases of direct and indirect interaction (via underlying fields) are considered. Due to the strong coupling among individuals, the evolution of each individual is governed by a stochastic equation whose parameters are themselves stochastic; as a consequence we are dealing with a doubly stochastic system, and this is a source of complexity which may tremendously increase as the number of individuals becomes extremely large. A possible way to reduce complexity is to apply suitable laws of large numbers, at a mesoscale, in order to obtain a mean field governed now by deterministic PDEs. In this way we may obtain an approximation of the driving fields which are deterministic at the macroscale, thus driving, at the microscale, a simply stochastic evolution for the individuals. Such models are called hybrid models.

Key words: Stochastic differential equations, measure-valued processes, empirical measures, law of large numbers, invariant measures, ant colonies, tumour-induced angiogenesis, hybrid models, multiscales

1 Introduction

In biology and medicine it is possible to observe a wide spectrum of formation of patterns and clustering, usually due to self-organization phenomena. This may happen at any scale; from the cellular scale of embryonic tissue formation, wound healing or tumor growth, and angiogenesis, the microscopic scale of life cycles of bacteria or social amoebae, to the larger scale of animal grouping. Patterns are usually explained in terms of forces, external and/or internal, acting upon individuals. In this way formation of aggregating networks are shown as a consequence of collective behavior. Evidence of stochasticity are often shown. A fruitful approach to the mathematical description of such phenomena, suggested since long by various authors [10, 14, 19, 23, 28, 29], is based on the so called *individual based models*, i.e. the "movement" of each

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individual embedded in the total population is described. This is known as *Lagrangian approach*, i.e. individuals are followed in their motion. Possible randomness may be included in the motion, so that the variation in time of the (random) location of the individuals in a group composed of $N(t)$ individuals at time $t \geq 0$, $X_N^k(t) \in \mathbb{R}^d$, $k = 1, \ldots, N(t)$, is described by a family of stochastic equations. On the other hand, particles are subject to specific forces of interaction which are responsible of the reaction term.

A classical widespread approach has been given in terms of PDEs [20, 24, 25]. This is due, above all, to the wider spread knowledge on nonlinear PDEs; so grouping behavior has been described by relevant quantities such as scalar or vector fields. Such kind of models are often called *Eulerian models*, since they describe the evolution of population densities; they are based on continuum equations, typically (deterministic) partial differential equations of the advection–reaction–diffusion type

$$\rho_t + \nabla \cdot (\mathbf{v}\rho) = \nabla \cdot (D\nabla\rho) + \nu(\rho), \tag{1}$$

where ρ is the population density and $\mathbf{v}$ is the velocity field, and $\nu(\rho)$ is a possible additive reaction term which may include birth and death processes. The advection term may describe the interaction mechanisms among individuals (via the velocity $\mathbf{v}$), while the non-convective (diffusive) flux takes into account the spatial spread of the population.

In conclusion, the two different approaches (Lagrangian and Eulerian) describe the system at different scales: the finer scale description is based on the (stochastic) behavior of individuals (microscale), and the larger scale description is based on the (continuum) behavior of population densities (macroscale). The central problem is to determine how information is transferred across scales; one of the aims of the modelling is to catch the main features of the interaction at the scale of single individuals that are responsible, at a larger scale, for a more complex behavior that leads to the formation of patterns [10]. Often a multiple scale approach is preferable: the global behavior of the population is described, at the macroscopic scale, by a continuum density whose evolution in terms of integro-differential equations is derived by a limiting process from the empirical distribution associated with a large number of particles. From the mathematical point of view this means to perform some kind of law of large numbers, in such a way that one may identify a possibly regular measure of the population distribution, having a density which satisfies a PDE similar to the equation (1).

This is a way to reduce the complexity of Lagrangian models. Indeed, the evolution equation of each individual is usually a stochastic equation whose parameters are themselves stochastic. This is a source of complexity which may tremendously increase as the number of individuals becomes extremely large, as it may happen in many cases of real interest. Applying suitable laws of large numbers at the mesoscale, we obtain an approximation of the driving

fields which are deterministic at the macroscale. They drive, at the microscale, a simply stochastic evolution for the individuals. Here we consider a review of the investigation programme on the subject, that the authors have been carrying out during the last decade [1, 2, 5, 6, 21–23].

In Section 2 we discuss the mathematical modelling of the stochastic interacting population when the number of individuals is finite, both in the cases of direct and indirect interaction. We consider both Lagrangian and Eulerian (discrete) descriptions. In Sections 3 and 4, we look at two specific cases: a model for stochastic aggregating–repelling individuals (direct interaction), and a model for a branching and growth of vessels in tumor induced angiogenesis, an example of stochastic fiber processes, coupled with the continuum underlying field of a chemoattractor released by the tumor (indirect interaction). In Section 5 we study the derivation of the corresponding hybrid models, for the two working examples. In the first one we recall the mathematically rigorous derivation of the limit model as the number of individuals increases to infinity, via a law of large numbers; in the second example, we handle a heuristic derivation of an hybrid model. Finally in Section 6, we address the problem of the long time behavior of a stochastic interacting particle model, as the number of particle N is still finite. In particular, we consider the case of example one, discussed previously.

2 Individuals, Interactions and Evolution

We consider a population composed, at time $t \geq 0$, by a (possibly random) number $N(t)$ of individuals. Let the random variable $X_N^k(t)$ represent the random state in $\mathbb{R}^d$, e.g., the spatial location, of the kth individual, for $k = 1, \ldots, N(t)$. From a Lagrangian point of view, the state of the system of $N(t)$ particles may be described as a family of $N(t)$ stochastic processes $\{X_N^k(t)\}_{t\in\mathbb{R}_+}$, $k = 1, \ldots, N(t)$, defined on a common probability space $(\Omega, \mathcal{F}, P)$ and valued in $(\mathbb{R}^d, \mathcal{B}_{\mathbb{R}^d})$, where $\mathcal{B}_{\mathbb{R}^d}$ is the usual Borel σ-algebra generated by intervals. A convenient description of the state of the kth individual may achieved via a random Dirac-measure $\varepsilon_{X_N^k(t)}$, defined as follows:

$$\varepsilon_{X_N^k(t)}(B) = \begin{cases} 1 & \text{if } X_N^k(t) \in B \\ 0 & \text{if } X_N^k(t) \notin B \end{cases} \quad \forall B \in \mathbb{R}^d. \tag{2}$$

It is a random element of $\mathcal{M}_P(\mathbb{R}^d)$, the space of probability measures on $\mathbb{R}^d$; for any sufficiently smooth function $f : \mathbb{R}^d \to \mathbb{R}$

$$\int_{\mathbb{R}^d} f(y)\varepsilon_{X_N^k(t)}(dy) = f\left(X_N^k(t)\right)$$

is a real valued random variable.

For any $t \geq 0$, given the particle locations $X_N^k(t)$, $k = 1, \ldots, N(t)$, an *Eulerian (discrete) description* of the system can be given in terms of the random probability measure on $\mathbb{R}^d$

$$X_N(t) = \frac{1}{N(t)} \sum_{k=1}^{N(t)} \varepsilon_{X_N^k(t)} \in \mathcal{M}_P(\mathbb{R}^d). \tag{3}$$

This measure may be regarded as the empirical distribution of the location of a single particle of the system in $\mathbb{R}^d$ at time $t \in \mathbb{R}_+$. Note that the number of particles may be either constant over time, say $N(t) = N$, for all $t \in \mathbb{R}_+$, or a dynamical variable itself, described, e.g., by a suitable birth and death process.

A key question concerns the modelling of the *interaction*; interaction among particles may be direct or indirect. In the first case individuals interact directly, i.e. the force exerted on each of them depends on the distribution of the individuals in the population. In the case of indirect interaction the force exerted on each particle depends on an underlying field whose evolution depends on the distribution of the entire population; as a consequence the dependence of the evolution of the spatial distribution of a single individual upon the spatial distribution of the whole population is mediated by the underlying field.

2.1 Direct Interaction and System Evolution

For sake of simplicity, let $N(t) = N$, independent of $t \in \mathbb{R}_+$. Generally speaking, in this first case we may describe the evolution of the system by a system of N random equations

$$dX_N^k(t) = h_N(X_N^1(t), \ldots, X_N^N(t), B_t, t)\, dt, \quad k = 1, 2, \ldots, N, \tag{4}$$

where $h_N : (\mathbb{R}^d)^n \times \mathbb{R}^d \times R_+ \to \mathbb{R}$ is a suitable function modelling the interaction. The random perturbing function B_t may model a random forcing factor.

If we consider pairwise interaction, the interaction between a couple of individuals is mathematically modelled by a reference potential K_1, depending on the distance between the two particles. In this way the range of the potential kernel represents the spatial region of influence of the interaction.

A good choice is $K_1 = W_1 * W_1$, a kernel given by the convolution of a sufficiently regular probability density W_1 with itself; we assume that the interaction of two particles, out of N, located in x and y, respectively, is modelled by

$$\frac{1}{N} K_N(x - y), \quad \text{where } K_N(z) = N^\beta K_1(N^{\beta/d} z), \tag{5}$$

which expresses the rescaling of K_1 with respect to the total member N of particles, in terms of a scaling coefficient $\beta \in [0, 1]$. Particles X_N^i and X_N^j

interact if the supports of the associated smoothed measures $W_N * \varepsilon_{X_N^l}$, $l = i, j$, overlap. As a consequence, if we denote by $W_N(z) = N^{\beta} W_1(N^{\beta/d} z)$, the interaction of the single k-particle, out of N, located at $X_N^k(t)$, with all the others in the population is given by

$$\begin{aligned} J\left(X_N^1(t), \ldots, X_N^N(t)\right)\left(X_N^k(t)\right) &= \frac{1}{N} \sum_j \int_{\mathbb{R}^d} W_N(X_N^k - y) W_N(y - X_N^j) dy \\ &= (W_N * W_N * X_N(t))(X_N^k(t)) \\ &= \sum_{i=1}^{N} \frac{1}{N} K_N\left(X_N^i(t) - X_N^k(t)\right) \\ &= (K_N * X_N(t))(X_N^k(t)) \\ &=: I\left[X_N(t)\right]\left(X_N^k(t)\right). \end{aligned} \tag{6}$$

In many cases a convenient way to model randomness is to consider an independent additive noise, acting on each particle; so that a possible model for (4) is

$$dX_N^k(t) = \left[f_N^k(t) + I\left[X_N(t)\right]\left(X_N^k(t)\right)\right] dt + \sigma dW^k(t), \quad k = 1, \ldots, N; \tag{7}$$

the term given in (6) describes any interaction of the kth particle with other particles in the system, the function $f_N^k : \mathbb{R}_+ \to \mathbb{R}$ describes the individual dynamics which may depend only on time or on the state of the particle itself, and, finally, $\{W^k\}$, $k = 1, \ldots N$ is a family of independent standard Wiener processes. In this review the diffusion coefficient σ is kept constant.

The system (7) offers a *Lagrangian description* of the stochastic model; from the fact that for any real function g on $\mathbb{R}^d \times \mathbb{R}_+$,

$$\int_{\mathbb{R}^d} g(x,t) X_N(t)(dx) = \frac{1}{N} \sum_{k=1}^{N} g(X_N^k(t), t).$$

Itô's formula leads to the *Eulerian (discrete) description* via an evolution equation for the empirical measure $X_N(t)$ [4, 6, 23]; indeed, for any $g \in C_b^{2,1}(\mathbb{R}^d \times \mathbb{R}_+)$,

$$\begin{aligned} \int_{\mathbb{R}^d} g(x,t) X_N(t)(dx) = \int_{\mathbb{R}^d} g(x,0) X_N(0)(dx) + \int_0^t Op_1\left(X_N(s), g(\cdot, s)\right) ds \\ + M_N\left[\underline{X}, \underline{W}\right](t), \end{aligned} \tag{8}$$

where

$$M_N\left[\underline{X}, \underline{W}\right](t) = \int_0^t \frac{\sigma}{2N} \sum_{k=1}^{N} \nabla g(X^k(s), s) dW^k(s) \tag{9}$$

is a zero mean martingale, so that, by the Doob inequality [4],

$$E\left[\sup_{t\le T}|M_N[\underline{X},\underline{W}](t)|\right]^2 \le E\left[\sup_{t\le T}|M_N[\underline{X},\underline{W}](t)|^2\right]$$
$$\le 4\frac{4\sigma^2}{N^2}\sum_{k=1}^{N} E\left[\int_0^T |\nabla g(X_N^k(s),s)|^2 ds\right]$$
$$\le \frac{4\sigma^2\|\nabla g\|_\infty^2 T}{N}. \tag{10}$$

2.2 Indirect Interaction and System Evolution

As said above, in the case of indirect interaction the force exerted on each particle depends on an external field. As an example of self-organization mediated by a system of underlying fields, we may consider a process of individual organization that occurs at a microscopic scale, while diffusion of an underlying field occurs at a macroscopic scale. The dynamics of the field depends on the individuals themselves (for example, a degradation phenomenon may be due to an interaction with individuals at relevant spatial locations). Let $Z_N^k(t)$ be the state of the kth individual out of $N(t)$, at time t. Again, note that $N(t)$ may be itself a stochastic process. A general model might appear of the following form: for any $t \ge 0$

$$dZ_N^k(t) = F[C(\cdot,t)](Z_N^k(t))dt + \sigma\, dW^k(t), \quad k = 1,\dots,N(t), \tag{11}$$
$$\frac{\partial}{\partial t}C(x,t) = Op_2(C(\cdot,t))(x) + \widetilde{I}[Z_N(t)](x), \qquad x \in \mathbb{R}^d. \tag{12}$$

In this case the evolution of an individual state $Z_N^k(t)$ is driven by an underlying field $C(x,t)$, via the operator $F[C(\cdot,t)]$ depending on the field and acting on each individual; on the other hand, the evolution equation of the field $C(x,t)$ depends itself upon the structure of the system of individuals by means of $\widetilde{I}[Z_N(t)](x)$, an operator which depends on the empirical measure

$$Z_N(t) = \frac{1}{N(t)}\sum_{k=1}^{N(t)} \varepsilon_{Z_N^k(t)}$$

of individuals, acting at a spatial location x. For simplicity, also here we consider a diffusion coefficient σ in the SDEs (11) constant in time and space. Note that also the evolution of the stochastic process $\{N(t)\}_{t\in\mathbb{R}_+}$ may depend upon the underlying field $C(t,x)$.

Again, Itô's formula may lead to an *Eulerian (discrete) description* of the spatial structure of the population $Z_N(t)$ coupled with the equation (12) for $C(x,t)$, i.e. for any $g \in C_b^{2,1}(\mathbb{R}^d \times \mathbb{R}_+)$,

$$\int_{\mathbb{R}^d} g(x,t)Z_N(t)(dx) = \int_{\mathbb{R}^d} g(x,0)Z_N(0)(dx) + \int_0^t Op_3\left(Z_N(s), C(x,t), g(\cdot,s)\right) ds + M_N\left[\underline{Z}, \underline{W}\right](t). \quad (13)$$

In the next two sections we provide two examples of self organization phenomena, in which the dynamics depends upon direct interaction among individuals, in the first case, and upon indirect interaction in the second case.

3 Direct Interaction: an Aggregation–Repulsion Model

As an example of direct interaction we consider a stochastic system of $N(t) \equiv N$ individuals, subject to an advection term and a stochastic individual component. Here we specify the advection components on the basis of possible assumptions inducing self-organization of biological populations. "Social" forces are responsible for interaction of each individual with other individuals in the population within suitable neighborhoods. We consider both aggregating and repelling forces, which compete, but act at different scales. They are modelled by two regular kernels $G, K_N : \mathbb{R}^d \to \mathbb{R}$, with $G, K_N \in C_b^2(\mathbb{R}^d, \mathbb{R}_+)$, as given by (6).

In the case of aggregation the parameter β in (6) is equal to zero, so that the aggregating force exerted on the kth individual is given by $(\nabla G * X_N(t))X_N^k(t)$ (McKean–Vlasov interaction); in the case of repulsion, the repelling force is given by $(\nabla K_N * X_N(t))X_N^k(t)$, with $\beta \in (0,1)$, where K_N and the empirical measure X_N are given by (5) and (3) (moderate interaction) [23, 26, 27]. It is clear how the choice of β may determine the range and the strength of the influence of neighboring particles; indeed, any particle interacts (repelling) with $O(N^{1-\beta})$ other particles in a volume of order $O(N^{-\beta})$.

Additionally, the movement of each individual particle might be driven by an external information coming from the environment, expressed via a suitable potential $U : \mathbb{R}^d \to \mathbb{R}$. The potential

$$U \in C_b^2(\mathbb{R}^d, \mathbb{R}_+) \quad (14)$$

is taken as a smooth non-negative even function; we assume that it satisfies the following condition [33–35]: there exist constants $M_0 \geq 0$ and $r > 0$ such that

$$\left(\nabla U(x), \frac{x}{|x|}\right) \leq -\frac{r}{|x|}, \quad |x| \geq M_0, \quad (15)$$

where $(\cdot,\cdot)$ denotes the usual scalar product in $\mathbb{R}^d$.

Again the stochastic component is modelled by a family of independent standard Wiener processes $\{W^k,\ k = 1, \ldots\}$. These systems have been already discussed by the authors in several papers [1, 2, 6, 21–23].

Based on these modelling assumptions, we consider the following system of SDEs:

$$dX_N^k(t) = \left[\gamma_1 \nabla U(X_N^k(t)) + \gamma_2 \left(\nabla \left(G - K_N\right) * X_N\right)\left(X_N^k(t)\right)\right] dt + \sigma dW^k(t), \quad k = 1, \ldots, N, \quad (16)$$

where $\gamma_1, \gamma_2, \sigma \in \mathbb{R}_+$. In the case $\gamma_1 = 0$, the system is a purely diffusive interacting particle system.

By standard arguments [4], we can prove that the system admits a unique solution $X(t) = (X_N^1(t), \cdots, X_N^N(t))$ for all $t \in [0, T]$, with almost surely continuous trajectories [6]. From the system (16), Itô's formula applied to a function $f \in C_b^{2,1}(\mathbb{R}^d \times \mathbb{R}_+)$ of $X_N^k(t)$, for any $k = 1, \ldots, N$, gives the evolution equation of the empirical measure (3) as follows:

$$\begin{aligned}\int_{\mathbb{R}^d} f(x,0) X_N(s)(dx) = &\int_{\mathbb{R}^d} f(x,0) X_N(0)(dx) \\ &\int_0^t \int_{\mathbb{R}^d} \left(\left[\gamma_1 \nabla U + \gamma_2 \left(\nabla \left(G - K_N\right) * X_N\right)\right](x)\right. \\ &\qquad \left. \nabla f(x,s)\right) X_N(s)(dx) ds \\ &+ \int_0^t \int_{\mathbb{R}^d} \left(\frac{\sigma^2}{2} \triangle f(x,s) + \frac{\partial}{\partial s} f(x,s)\right) X_N(s)(dx) ds \\ &+ \sigma \frac{1}{N} \int_0^t \sum_{k=1}^N \nabla f\left(X_N^k(s), s\right) dW^k(s), \end{aligned} \quad (17)$$

where again the last term in (17) is a zero mean martingale with respect to the natural filtration of the process $\{X_N(t),\ t \in \mathbb{R}_+\}$.

In conclusion in the example presented here, the Lagrangian description of the system (7), discussed in the previous section, has the form of the system (16), while its Eulerian (discrete) description is given by the system (17). In Figure 1 simulation results for the same initial condition, and for different drifts, are shown. For more simulation results and comparison with experimental data, the interested reader may refer to [1, 22, 23].

4 Interaction via Underlying Fields: A Birth and Growth Model

An interesting example of formation of patterns may be found in the process of tumor growth and in particular in angiogenesis. Tumor-induced angiogenesis is believed to occur when normal tissue vasculature is no longer able to support growth of an avascular tumor. At this stage the tumor cells, lacking nutrients and oxygen, become hypoxic. This is assumed to trigger cellular release of

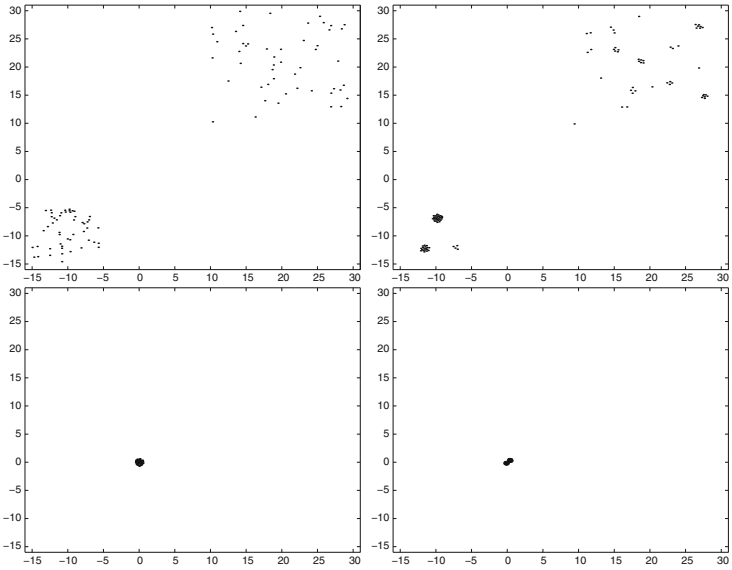

Fig. 1. Configuration of 100 particles for parameters values $\sigma = 0.02$, $\beta = 0.5$: (up left) $T = 0$, (up right) $T = 500$, $\gamma_1 = 0$, $\gamma_2 = 1$, (down left) $T = 1000$, $\gamma_1 = \gamma_2 = 1$, $\nabla U(x) = x/(1 + |x|)$, (down right) $T = 100$, $\gamma_1 = \gamma_2 = 1$, $\nabla U(x) = |x|^2$.

tumor angiogenic factors, TAF, which start to diffuse into the surrounding tissue and approach endothelial cells (ECs) of nearby blood vessels [13]. ECs subsequently respond to the TAF concentration gradients by forming sprouts, dividing and migrating towards the tumor. So, at an individual level, cells interact and perform a branching process coupled with elongation, under the stimulus of a chemical field produced by a tumor. In this way formation of aggregating networks (vessels) are shown as a consequence of collective behavior.

The initiation of sprouting from preexisting parental vessels is not considered here; in order to avoid further mathematical technicalities, we assume a given number N_0 of initial capillary sprouts; we refer to literature [16] for details on this topic. Let $N(t)$ be the number of tips at time t, and $X^i(t) \in \mathbb{R}^d$ the location of the tip of the ith vessel at time t. Furthermore, let us denote by T_i the branching time of the ith tip, i.e. the random time when the ith tip branches from an existing vessel. We model sprout extension by tracking the trajectory of individual capillary tips. The movement (extension) of the tips follows a Langevin model; at any $t > T^i$ and for any $k \in \{1, \ldots, N(t)\}$ we have

$$\begin{aligned} dX^i(t) &= v^i(t)(1 - \gamma \mathbb{I}_{X(t)}(X^i(t))dt, \\ dv^i(t) &= \left(-kv^i(t) + F\left(C(t, X^i(t))\right)\right) dt + \sigma dW^i(t), \end{aligned} \tag{18}$$

where $v^i(t)$ is the velocity of the ith tip at time t. According to a typical chemotaxis, velocity $v^i(t)$ is driven by a function F of the underlying field C. An example is $F(C(t, X^i(t))) = \nabla C(t, X^i(t)$, so that vessels follow the increasing density of the chemoattractor; the advection term includes the typical inertial component $-kv^i(t)$. A family of independent Wiener processes $W^i(t)$ model stochasticity. Finally, the network of endothelial cells is described by

$$X(t) = \bigcup_{i=1}^{N(t)} \{X^i(s), T_i \leq s \leq t\},$$

the union of the trajectories of the tips. In the equation (18) the parameter γ may assume only the 0 and 1 values; $\gamma = 0$ means that no impingement is considered; otherwise, for $\gamma = 1$ the phenomenon of anastomosis is taken into account (see [7] and references therein, for further information).

The branching process $\Phi_N(ds, dx)$ is modelled as a marked counting process with stochastic intensity

$$\alpha(t, x) = \alpha h(C(t, x)) \sum_{i=1}^{N(t^-)} \delta_{X^i(t)}(x), \tag{19}$$

where $h \in C_b(\mathbb{R}^d)$ is a non negative function. The equation (19) means that the probability that branching occurs exactly at the kth tip is given by

$$\text{prob}\left(\Phi(]t, t + dt] \times X^k(t)) \mid \mathcal{F}_{t^-}\right) = \frac{\alpha(t, X^k(t))}{\int_{\mathbb{R}^d} \alpha(t, x)dx}\, dt.$$

The counting process $N(t)$ is given by $N(t) = \Phi_N(]-\infty, t], \mathbb{R}^d)$, so that the probability of having a new tip during the time interval $]t, t + dt]$ is

$$\text{prob}\left(N(t + dt) - N(t) = 1 \mid \mathcal{F}_{t^-}\right) = \sum_{i=1}^{N(t^-)} \alpha(t, X^i(t))dt;$$

when a tip located in x branches, the initial value of the state of the new tip is taken as $(X^{N(t)+1}, v^{N(t)+1}) = (x, v_0)$, where v_0 is a non random velocity.

The chemotactic field $C(t, x)$ diffuses and degradates; the consumption is proportional to the extension velocities v^i, $i = 1, \ldots, N(t)$. So, for any $(t, x) \in \mathbb{R}_+ \times \mathbb{R}^d$,

$$\frac{\partial}{\partial t} C(t, x) = c_1 \delta_A(x) + d_1 \triangle C(t, x) - \eta C(t, x) \frac{1}{N} \sum_{i=1}^{N(t)} (v^i(t) \delta_{X^i(t)} * V_\varepsilon)(x). \tag{20}$$

We have considered a mollified version of the relevant random distributions, by means of a convolution with the kernel $V_\varepsilon(x)$, a smooth function with compact support of order ε. From a mathematical point of view, the use

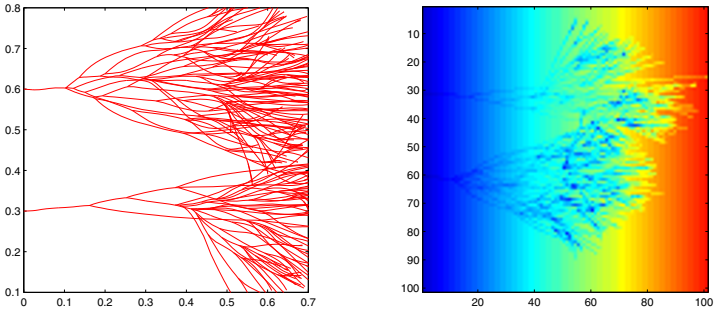

Fig. 2. A vessel network (on the left) interacting with a degrading TAF field (on the right) ($d_1 = 0, \gamma = 0$).

of mollifiers reduces analytical complexity; from a modelling point of view this might correspond to a nonlocal reaction with the relevant underlying fields. Parameters $c_1, d_1, \eta \in \mathbb{R}^+$ in the equation (20) represent the rate of production of a source located in a region $A \subset \mathbb{R}^d$, modelling, e.g., a tumor mass, the diffusivity and the rate of consumption, respectively. We have denoted by $\delta_{X^i(t)}(x)$ the random distribution (Dirac density) localized at the tip $X^i(t)$, for $i = 1, \ldots, N(t)$. Note that the equation (20) is a random partial differential equations, since the degradation term depends on the stochastic processes $\{(X^i(t), v^i(t))\}_t$, for any $i = 1, \ldots, N(t)$. The stochasticity of the underlying field leads to the stochasticity of the kinetic parameters of birth and growth of vessels. Figure 2 shows a simulation of the network coupled with a degradating field (for technical simplicity we have taken $d_1 = 0$, $\gamma = 0$).

To this process we may associate two fundamental random spatial measures, describing the network at time t; given a suitable scale parameter N, Q_N, the empirical measure associated with the processes $(X^k(t), v^k(t))$, $k = 1, \ldots, N(t)$, is given by

$$Q_N(t) = \frac{1}{N} \sum_{i=1}^{N(t)} \varepsilon_{(X^k(t), v^k(t))}, \tag{21}$$

while, $V_N(t)$, the empirical spatial distribution of velocities, is given by

$$V_N(t) = \frac{1}{N} \sum_{i=1}^{N(t)} v_k(t) \varepsilon_{X^k(t)} = \int_{\cdot \times \mathbb{R}^d} v \, Q_N(t)(d(x, v)).$$

We may write the equation (20) in the following form:

$$\frac{\partial}{\partial t} C(t, x) = c_1 \delta_A(x) + d_1 \triangle C(t, x) - \eta C(t, x)(V_N(t) * V_\varepsilon)(x). \tag{22}$$

Given a smooth function $g \in C_b(\mathbb{R}^d \times \mathbb{R}^d)$, by Itô's formula we obtain an evolution equation for the random measure Q_N [7]

$$\int_B g(x,v)Q_N(t)d(x,v) = \int_B g(x,v)Q_N(0)d(x,v) + \int_0^t \int_B \Big[\nabla_x g(x,v)v + g(x,v)\alpha_1(s,x)\delta_{v_0}(v) - \nabla_v g(x,v)\left[kv - F(C(t,x))\right] + \frac{\sigma^2}{2}\Delta_v g(x,v)\Big] Q_N(t)(d(x,v))ds + \tilde{M}_N(t), \quad (23)$$

where the last term

$$\tilde{M}_N(t) = \int_0^t \int_{\mathbb{R}^n} \left[\Phi_N(ds,dx) - N\alpha(s,x)Q_N(t)(dx \times \mathbb{R}^d)\, ds\right] + \int_0^t \frac{\sigma}{2N} \sum_{k=1}^{N(t)} \nabla_v g((X^k(t), v^k(t)))dW^k(t)$$

is a zero mean martingale, such that again by the Doob inequality, for N sufficiently large

$$E\left[\sup_{t\le T} |\tilde{M}_N(t)|\right]^2 \le C\frac{TN(t)}{N^2}(\|g\|_2^2 + \|\nabla g\|_2^2) < C\frac{T}{N}. \quad (24)$$

In conclusion in the example presented here, the Lagrangian description of the system (11)–(12), discussed in the previous section, has the form of the system (18), (19) and (20), while the Eulerian discrete description (12)–(13) is given by the system (22)–(23).

5 Hybrid Models: Large Population Behavior

Let us place our attention on the following facts. In the detailed models, in both examples, the evolution equation of each individual (either an individual in a population, or a tip in a vessel network) is a stochastic equation whose parameters are themselves stochastic; as a consequence we are dealing with a doubly stochastic system. A major difficulty, both analytical and computational, derives from the fact that, indeed, the parameters are $\{\mathcal{F}_{t^-}\}$-stochastic, i.e. their value at time $t > 0$ depends upon the actual *history* $\mathcal{F}_t$ of the whole system up to time t^-.

Let us remind the main features of the discrete systems, as already discussed in Section 2.

Direct Interaction

In this case each individual k, out of N, satisfies a system of SDEs of the form

$$dX_N^k(t) = Op\left[X_N(t)\right]\left(X_N^k(t)\right)dt + \sigma dW^k(t), \quad k = 1, \ldots, N, \tag{25}$$

where

$$X_N(t) = \frac{1}{N}\sum_{j=1}^{N} \varepsilon_{X_N^j(t)}$$

is the empirical measure at time t, and Op is a suitable operator which expresses the specific model of interaction.

Hence the analysis and the computation of the above system requires the knowledge of the evolution of all individuals up to time t; clearly $X_N(t)$ is an $\{\mathcal{F}_t\}$-stochastic quantity.

Indirect Interaction

In this case the individual dynamics is described by a system of the form

$$dZ_N^k(t) = Op\left[C(\cdot, t)\right]\left(Z_N^k(t)\right)dt + \sigma\, dW^k(t), \quad k = 1, \ldots, N(t), \tag{26}$$

whose kinetic parameters depend upon a biochemical underlying field $C(x, t)$ which obeys to a random evolution equation of the form

$$\frac{\partial}{\partial t}C(x,t) = Op_1[C(\cdot,t)](x) + Op_2\left[Z_N(t), C(\cdot,t)\right](x), \tag{27}$$

where $Z_N(t)$ is the empirical measure of the states $Z_N^k(t)$, and Op_1 and Op_2 are suitable operators which express the specific model of spatial spread and the interaction with the field produced by the whole system of individuals, respectively.

Once again, the analysis and the computation of the above system requires the knowledge of the evolution of all individuals up to time t; clearly $Z_N(t)$ is an $\{\mathcal{F}_{t^-}\}$-stochastic quantity (in this case also the evolution of $N(t)$ is involved).

The strong coupling with the field (produced by the individuals themselves, in the first case, and external, in the second case) is a source of complexity which may tremendously increase as the number of individuals becomes extremely large, as it may happen in many cases of real interest. Under these circumstances, a possible way to reduce complexity, which has been suggested by the authors and by a large literature, is to apply suitable laws of large numbers at the mesoscale, i.e. in a suitable neighborhood of any relevant point $x \in \mathbb{R}^d$, such that, at that scale we may approximate, in the first case, $X_N(t)$ by a deterministic measure $X(t)$, possibly having a density $\rho(x, t)$ with respect

to the usual Lebesgue measure; in the second case we may approximate $Z_N(t)$ by a deterministic measure, possibly having a density $w(x,t)$ with respect to the usual Lebesgue measure. The relevant densities $\rho(x,t)$, and $w(x,t)$ will satisfy suitable deterministic evolution equations. In this way we obtain an approximation of the driving fields which are deterministic at the macroscale, which now drive, at the microscale, a simply stochastic evolution for the individuals. More specifically, a typical individual k in the first model (25) will satisfy the following SDE:

$$dY^k(t) = Op\left[\rho(\cdot,t)\right](Y^k(t))dt + \sigma dW^k(t), \quad k = 1, \ldots, N, \tag{28}$$

coupled with a deterministic equation for $\rho(x,t)$. For the second model (26)–(27), a typical individual k will satisfy the following SDE:

$$dY^k(t) = Op\left[\widetilde{C}(\cdot,t)\right](Y^k(t))dt + \sigma\, dW^k(t), \quad k = 1, \ldots, N(t), \tag{29}$$

where the evolution equation for the underlying field has become

$$\frac{\partial}{\partial t}\widetilde{C}(x,t) = Op_1[\widetilde{C}(\cdot,t)](x) + Op_2\left[w(\cdot,t), \widetilde{C}(\cdot,t)\right](x), \tag{30}$$

coupled with a deterministic equation for $w(x,t)$.

A more detailed analysis follows for the two models described in Sections 3 and 4. Though, for the aggregation–repulsion model we have been able to carry out a detailed rigorous analysis, while for tumor-driven angiogenesis only an heuristic derivation has been obtained, which leads to a system of evolution equations which is compatible with existing deterministic models already available in literature [30–32].

We wish to stress that anyhow substituting mean densities of individuals in the first model, or mean densities of tips in the second model, to the corresponding stochastic quantities, leads to an acceptable coefficient of variation (percentage error) only when a law of large numbers can be applied, i.e. whenever the relevant numbers per unit volume are sufficiently large; otherwise stochasticity cannot be avoided, and, in addition, to mean values, the mathematical analysis and/or simulations should provide confidence bands for all quantities of interest. Indeed, numerical simulations carried out for the fully stochastic model show that local coefficients of variation are, indeed, much smaller in regions of largely crowded populations (either individuals or vessels) [3].

5.1 The Aggregation–Repulsion Model

Following [6], we show how to derive rigorously an hybrid model, as described at the beginning of this section in the case of the aggregation–repulsion model

described in Section 3. For details the interested reader may refer to [6]. First note that from (17) we get an averaged equation

$$E\left[\langle X_N(t), f(\cdot,t)\rangle\right] = E\left[\langle X_N(0), f(\cdot,0)\rangle\right] + E\left[\int_0^t \langle X_N(s), \left[\gamma_1 \nabla U + \gamma_2 \left(\nabla \left(G - K_N\right) * X_N\right)\right](\cdot) \nabla f(\cdot,s)\rangle \, ds + \int_0^t \left\langle X_N(s), \frac{\sigma^2}{2} \triangle f(\cdot,s) + \frac{\partial}{\partial s} f(\cdot,s) \right\rangle ds\right]. \quad (31)$$

Furthermore, thanks to the inequality (10), the quadratic variation of the martingale term vanishes, in a finite time interval $[0,T]$. So we might expect a deterministic behavior of the system in the limit.

Let us sketch the mathematically rigorous proof of this behavior in the case of large populations.

A Relative Compactness Result

We assume some regularity conditions for the initial empirical measure $X_N(0)$,

$$\sup_{N\in\mathbb{N}} E\left[\int_{\mathbb{R}^d} |x| X_N(0)(dx)\right] < \infty, \quad (32)$$

$$\sup_{N\in\mathbb{N}} E\left[\int_{\mathbb{R}^d} |h_N(x,0)|^2 dx\right] = \sup_{N\in\mathbb{N}} E\left[||h_N(\cdot,0)||_2^2\right] < \infty, \quad (33)$$

where

$$h_N(x,t) = (W_N * X_N(t))(x), \quad (34)$$

is a mollified measure.

Furthermore, let us impose the following restriction on β in the definition of the scaled kernel (5), $\beta \in (0, d/(d+2))$.

We have proven [6] the tightness and then the boundedness of small variations of the process X_N, in the bounded Lipschitz metric [6]. This leads, by means of the characterization of relative compactness by Ethier and Kurtz [11], to the following result on the sequence of laws $\mathcal{L}(X_N)$ of $X_N = \{X_N(t),\ t \in \mathbb{R}_+,\ N \in \mathbb{N}\}$:

Theorem 1 ([6]). *Under the hypotheses listed above and in Section 3, the sequence* $\{\mathcal{L}(X_N)\}_{N\in\mathbb{N}}$ *is relatively compact in the space* $\mathcal{M}_{\mathcal{P}}(C([0,T], \mathcal{M}_{\mathcal{P}}(\mathbb{R}^d)))$.

This is the main result needed for the asymptotics of the evolution equation of the measure-valued process $\{X_N(t), t \in \mathbb{R}_+\}$. Indeed, Theorem 1 implies the existence of a subsequence $N_k \subset \mathbb{N}$, $N_1 < N_2 < \ldots$, such that the sequence $\{\mathcal{L}(X_{N_k})\}_{k\in\mathbb{N}}$ converges in $\mathcal{M}_{\mathcal{P}}(C([0,T], \mathcal{M}_{\mathcal{P}}(\mathbb{R}^d)))$ to some limit $\mathcal{L}(X)$, which is the distribution of some process $X = \{X(t),\ t \in [0,T]\}$, with trajectories in $C([0,T], \mathcal{M}_{\mathcal{P}}(\mathbb{R}^d))$. We discuss the uniqueness of the limit later on. By now we assume uniqueness, so that we may take $\{N_k\} = \mathbb{N}$;

by Skorokhod theorem [4] we may assert that, corresponding to the possible unique limit law, we can also have an almost sure convergence, i.e.

$$\lim_{N\to\infty} \sup_{t\le T} d_{BL}(X_N(t), X(t)) = 0 \quad \mathbb{P}-a.s. \tag{35}$$

Regularity Properties of the Limit Measure

It is possible to show that there exists a positive (random) function h defined on $[0,T]\times\mathbb{R}^d$ such that

$$\lim_{N\to\infty} \mathbb{E}\left[\int_0^T \int_{\mathbb{R}^d} |h_N(x,t) - h(x,t)|^2 dxdt\right] = 0. \tag{36}$$

The equation (36) shows that the limit measure $X \in \mathcal{M}_P([0,T]\times\mathbb{R}^d)$ has P-a.s. a density

$$h \in L^2\left([0,T]\times\mathbb{R}^d\right) \tag{37}$$

with respect to the Lebesgue measure on $[0,T]\times\mathbb{R}^d$, i.e. for any $f \in C_b([0,T]\times\mathbb{R}^d)$

$$\int_0^T \int_{\mathbb{R}^d} f(t,x)X(dx,dt) = \int_0^T \int_{\mathbb{R}^d} f(t,x)\, h(t,x)(dx,dt). \tag{38}$$

By now, we do not know neither whether the measure $X(t)$ has a density for any fixed $t\in[0,T]$ nor that the density is deterministic. The next step is the identification of the limit by acquiring information on the *limit dynamics*. We have proven the following:

Proposition 1. *Let us suppose that a law of large numbers holds at initial time*

$$\lim_{N\to\infty} \mathcal{L}(X_N(0)) = \delta_{\mu_0} \quad \textit{in } \mathcal{M}_{\mathcal{P}}(\mathcal{M}_{\mathcal{P}}(\mathbb{R}^d)), \tag{39}$$

where μ_0 has a density p_0 in $L^2(\mathbb{R}^d)$. Then, almost surely, for any $f \in C_b^{2,1}(\mathbb{R}^d,\mathbb{R}_+)$, $0\le t\le T$,

$$\begin{aligned}\langle X(t), f(\cdot,t)\rangle = \langle \mu_0, f(\cdot,0)\rangle + \int_0^t \langle\, h(\cdot,s), \frac{1}{2}\sigma^2\Delta f(\cdot,s) + \frac{\partial}{\partial s} f(\cdot,s)\\ + [(\nabla G_a * h(\cdot,s))(\cdot) + \nabla U(\cdot) - \nabla h(\cdot,s)]\cdot\nabla f(\cdot,s)\rangle ds.\end{aligned} \tag{40}$$

This means that any limit measure $X\in\mathcal{C}([0,T],\mathcal{M}_P(\mathbb{R}^d))$ is a solution of the equation (40), with $h\in L^2\left([0,T]\times\mathbb{R}^d\right)$, satisfying the relation (38).

So we have proven that for any $t\in[0,T]$, the measure $X(t)$ is absolutely continuous with respect to the Lebesgue measure, so that it admits a density for each t. We prove it by showing that the Fourier transform of the measure $X(t)$ is in L^2 for any $t\in[0,T]$, so that a density exists and the latter is also in $L^2(\mathbb{R}^d)$ and we prove that it is also L^2 uniformly bounded. So we have shown the following result:

Theorem 2. *Under the hypotheses of Theorem 1, let us suppose that a law of large numbers applies at initial time*

$$\lim_{N\to\infty} \mathcal{L}(X_N(0)) = \delta_{\mu_0} \quad \text{in } \mathcal{M}_{\mathcal{P}}(\mathcal{M}_{\mathcal{P}}(\mathbb{R}^d)), \tag{41}$$

where μ_0 has a density p_0 in $L^2(\mathbb{R}^d) \cap C_b^2(\mathbb{R}^d)$. Then, almost surely, the sequence X converges in law to a deterministic measure X. For any $t \in [0,T]$ the measure $X_N(t)$ has a density $h(\cdot,t)$ such that, for any $f \in C_b^{2,1}(\mathbb{R}^d, \mathbb{R}_+)$, $0 \le t \le T$,

$$\begin{aligned}\langle h(\cdot,t), f(\cdot,t)\rangle = \langle \mu_0, f(\cdot,0)\rangle + \int_0^t \langle h(\cdot,s), \frac{1}{2}\sigma^2 \Delta f(\cdot,s) + \frac{\partial}{\partial s} f(\cdot,s) \\ + [(\nabla G_a * h(\cdot,s))(\cdot) + \nabla U(\cdot) - \nabla h(\cdot,s)] \cdot \nabla f(\cdot,s)\rangle ds.\end{aligned} \tag{42}$$

One can easily see that the equation (42) is the weak form of the following partial differential equation:

$$\begin{aligned}\frac{\partial}{\partial t}\rho(x,t) = \frac{\sigma^2}{2}\triangle\rho(x,t) + \nabla\cdot(\rho(x,t)\nabla U(x)) \\ + \nabla\cdot[\rho(x,t)\nabla(\rho(x,t) - G * \rho(\cdot,t))(x)], \quad x \in \mathbb{R}^d, t \ge 0, \\ \rho(x,0) = p_0(x), \quad x \in \mathbb{R}^d.\end{aligned} \tag{43}$$

Regularity Properties of the Limit Measure

The uniqueness of the limit h derives from the uniqueness of the weak solution of the viscous equation (43), which can be achieved by classical arguments [12].

Hybrid Model

The equation (43) describes a mean field due to the large number of individuals. As far as the individual dynamics is concerned, for any k, we have that the typical particle $X^k(t) \sim Y^k(t)$, follows the SDE:

$$\begin{aligned}dY^k(t) = -\big[\nabla U(Y^k(t)) + \nabla G_a * \rho(\cdot,t)(Y^k(t)) - \nabla\rho(Y^k(t)) \\ -\nabla U(Y^k(t))\big]\, dt + \sigma dW^k(t),\end{aligned}$$

subject to the initial condition $Y^k(0) = X^k(0)$. While the Brownian stochasticity of the movement of each particle is preserved, the drift is now the same for each particle and depends on the mean field ρ in the equation (43).

5.2 The Branching and Growth Process

As discussed in [7], in the case of the branching and growth process described in Section 4, we may only give an heuristic convergence result. Starting from

the system (23), if, formally, we take $Q_N(t)(d(x,v)) \to Q_\infty(t)(d(x,v)) = p(t,x,v)dxdv$, then

$$\int_B g(x,v)p(t,x,v)dxdv = \int_0^t \int_B p(s,x,v)ds\,dxdv \left[\frac{\sigma^2}{2}\Delta_v g(x,v) + \nabla_x g(x,v)v + g(x,v)\alpha_1(s,x)\delta_{\{v_0\}}(v) - \nabla_v g(x,v)\left[kv - F\left(\widetilde{C}(t,x)\right)\right]\right] \tag{44}$$

$$\frac{\partial}{\partial t}\widetilde{C}(t,x) = c_1\delta_A(x) + d_1\triangle\widetilde{C}(t,x) - \eta\widetilde{C}(t,x)\int_{\mathbb{R}^d} p(t,x,v)dv. \tag{45}$$

The equation (44) may be seen as the weak form of the following partial differential equation for the density $p(t,x,v)$:

$$\frac{\partial}{\partial t}p(t,x,v) = -v\cdot\nabla_x p(t,x,v) + k\nabla_v\cdot(vp(t,x,v)) + \alpha_1(t,x)p(t,x,v_0) - \nabla_v\cdot\left[F\left(\widetilde{C}(t,x)\right)p(t,x,v)\right] + \frac{\sigma^2}{2}\Delta_v p(t,x,v). \tag{46}$$

The individual processes $(Y^i(t), v^i(t))_t$ obey to the following stochastic system:

$$\begin{aligned} dY^i(t) &= v^i(t)dt, \\ dv^i(t) &= \left(-kv^i(t) + F(\widetilde{C}(t,Y^i(t)))\right)dt + \sigma dW^i(t), \end{aligned} \tag{47}$$

coupled with a branching process with intensity

$$\alpha(t,x) = \alpha\, h(\widetilde{C}(t,x))\sum_{i=1}^{N(t^-)}\delta_{Y^i(t)}(x). \tag{48}$$

Note that both (47) and (48) depend on the mean field $\widetilde{C}(t,x)$ in the equation (45).

6 Long Time Behavior

In this section we investigate the long time behavior of the particle system described in Section 3, for a fixed number N of particles.

6.1 Interacting–Diffusing Particles

First of all, let us consider the system (16) with $\gamma_1 = 0$, i.e. the case in which the advection is due only to interactions among particles. Following [17], from (16) it follows that the location of the center of mass $\bar{X}_N$ of the N particles,

$$\bar{X}_N(t) = \frac{1}{N}\sum_{k=1}^{N} X_N^k(t),$$

evolves according the following equation:

$$d\bar{X}_N(t) = -\frac{1}{N^2}\sum_{k,j=1}^{N} \nabla(K_N - G)(X_N^k(t) - X_N^j(t))dt + \sigma d\bar{W}(t), \tag{49}$$

where $\bar{W}(t) = \frac{1}{N}\sum_{k=1}^{N} W^k(t)$ is still a Brownian motion; by the symmetry of the kernels K_1 and G, the first term on the right-hand side vanishes and we get

$$d\bar{X}_N(t) = \sigma d\bar{W}(t), \tag{50}$$

i.e. the stochastic process $\bar{X}_N$ is a Wiener process. Hence, its law, conditional upon the initial state, is

$$\mathcal{L}\left(\bar{X}_N(t)|\bar{X}_N(0)\right) = \mathcal{L}\left(\bar{X}_N(0), \sigma^2\bar{W}(t)\right) = \mathcal{N}\left(\bar{X}_N(0), \frac{\sigma^2}{N}t\right);$$

with variance $\frac{\sigma^2}{N}t$, which, for any fixed N, increases as t tends to infinity. Consequently, we may claim that the probability law of the system does not converge to any non trivial probability law, since otherwise the same would happen for the law of the center of mass.

6.2 Complete System

Let us now consider the complete system of SDEs (16) with $\gamma_1 > 0$. This means that particles are also subject to a confining potential U. Equations of the type

$$dX_t = -\nabla P(X_t) + \sigma dW_t \tag{51}$$

have been thoroughly analyzed in literature; under the sufficient condition of strict convexity of the symmetric potential U [8, 9, 17, 18], it has been shown that (51) does admit a nontrivial invariant distribution. From a biological point of view a strictly convex confining potential is difficult to explain; it would mean an infinite range of attraction of the force which becomes infinitely strong at infinity, with an at least constant drift even far from origin.

A weaker sufficient condition for the existence of a unique invariant measure has been more recently suggested by Veretennikov [34, 35], following Has'minski [15]. This condition states that there exist constants $M_0 \geq 0$ and $r > 0$ such that for $|x| \geq M_0$

$$\left(-\nabla P(\mu)(x), \frac{x}{|x|}\right) \leq -\frac{r}{|x|}. \tag{52}$$

It is ease to prove that without any further condition on the interaction kernels K_N and G, by considering the condition (15) on U, we may apply the

results by Veretennikov and prove the existence of an invariant measure for the joint law of the particles locations. The condition (15) means that ∇U may decay to zero as $|x|$ tends to infinity, provided that its tails are sufficiently "fat".

Proposition 2. *Under the hypotheses for the existence and uniqueness (hypotheses stated in Section 3) and the condition* (15)*, the system* (16) *admits a unique invariant measure.*

Let now $P_N^{x_0}(t)$ denote the joint distribution of the N particles at time t, conditional upon a non random initial condition x_0, and let P_S denote the invariant distribution. As far as the convergence of $P_N^{x_0}(t)$ is concerned, for t tending to infinity, as in [34], one can prove the following result.

Proposition 3. *Under the same assumptions of Proposition 2, for any* k, $0 < k < \tilde{r} - \frac{Nd}{2} - 1$ *with* $m \in (2k+2, 2\tilde{r} - Nd)$ *and* $\tilde{r} = \gamma_1 N r$*, there exists a positive constant* c *such that*

$$\left|P_N^{x_0}(t) - P_N^S\right| \leq c(1 + |x_0|^m)(1+t)^{-(k+1)},$$

where $\left|P_N^{x_0}(t) - P_N^S\right|$ *denotes the total variation distance of the two measures, i.e.*

$$\left|P_N^{x_0}(t) - P_N^S\right| = \sup_{A \in \mathcal{B}_{\mathbb{R}^d}} \left[P_N^{x_0}(t)(A) - P_N^S(A)\right],$$

and x_0 *the initial data.*

So Proposition 2 states a polynomial convergence rate to invariant measure. To improve the rate of convergence, one has to consider more restricted assumptions on U [35].

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