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On the mean field approximation of a stochastic model of tumour-induced angiogenesis

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In the field of Life Sciences, it is very common to deal with extremely complex systems, from both analytical and computational points of view, due to the unavoidable coupling of different interacting structures. As an example, angiogenesis has revealed to be an highly complex, and extremely interesting biomedical problem, due to the strong coupling between the kinetic parameters of the relevant branching – growth – anastomosis stochastic processes of the capillary network, at the microscale, and the family of interacting underlying biochemical fields, at the macroscale. In this paper, an original revisited conceptual stochastic model of tumour-driven angiogenesis has been proposed, for which it has been shown that it is possible to reduce complexity by taking advantage of the intrinsic multiscale structure of the system; one may keep the stochasticity of the dynamics of the vessel tips at their natural microscale, whereas the dynamics of the underlying fields is given by a deterministic mean field approximation obtained by an averaging at a suitable mesoscale. While in previous papers, only an heuristic justification of this approach had been offered; in this paper, a rigorous proof is given of the so called 'propagation of chaos', which leads to a mean field approximation of the stochastic relevant measures associated with the vessel dynamics, and consequently of the underlying tumour angiogenic factor (TAF) field. As a side, though important result, the non-extinction of the random process of tips has been proven during any finite time interval.

Key words: Cell movement; Interacting particle systems; Convergence of probability measures; PDEs in connection with biology and other natural sciences; Stochastic analysis.

1 Introduction

In Life Sciences, we may observe a wide spectrum of self-organisation phenomena. In most of these phenomena, randomness plays a major role; see [7] for a general discussion. As a working example, in this paper, we refer to tumour-driven angiogenesis; in this case, cells organise themselves as a capillary network of vessels, the organisation being driven by a family of underlying fields, such as nutrients, growth factors, and alike [12,20,23]. Indeed, an angiogenic system is extremely complex due to its intrinsic multiscale structure. We need to consider the strong coupling between the kinetic parameters of the relevant stochastic processes describing branching, vessel extension, and anastomosis of the capillary network at the microscale, and the family of interacting underlying fields at the macroscale [1, 10, 17, 22, 25].

The kinetic parameters of the mentioned stochastic processes depend on the concentrations of certain chemical factors, which satisfy reaction-diffusion equations (RDEs) [1, 21, 35]. Viceversa, the RDEs for such underlying fields contain terms that depend on the spatial distribution of vascular cells. As a consequence, a full mathematical model of angiogenesis consists of the (stochastic) evolution of vessel cells, coupled with a system of RDEs containing terms that depend on the distribution of vessels. The latter is random and therefore the equations for the underlying fields are random RDEs; thus, inducing randomness in the kinetic parameters of the relevant stochastic geometric processes describing the evolution of the vessel network; we might say that the vessel dynamics is a 'doubly' stochastic process.

This strong coupling leads to an highly complex mathematical problem from both analytical and computational points of view. A possibility to reduce complexity is offered by the so called hybrid models, which exploit the natural multiscale nature of the system.

The idea consists of approximating the random RDEs by deterministic ones, in which the microscale (random) terms depending on cell distributions are replaced by their (deterministic) mesoscale averages. In this way, the mentioned kinetic parameters may be taken as depending on the mean field approximation of the underlying fields, thus, leading to a ' simple' stochasticity of the random processes of branching – vessel extension – anastomosis [5].

The way to obtain a deterministic mesoscale approximation of the stochastic process of the relevant empirical measures by means of laws of large numbers is known as 'mean field approximation'. Examples of rigorous derivations of mean field equations for stochastic individual-based models can be found, e.g., in [15, 28, 29], and references therein; other authors refer to this kind of approximation as propagation of chaos' (see, e.g., [14, 33], [2, p. 235], and references therein). However, to the best of the authors' knowledge, for the kind of models considered here, a rigorous proof of the required mean-field approximation has not yet been given, though heuristic derivations by the same authors are available (see [4], [5], and references therein). For a direct formulation of similar systems in hybrid form the reader may refer to [27].

Eventually, in this paper, the authors have been able to derive mean field equations with the required, non trivial, rigorous approach. As a side result to understand the impact of anastomosis, in the appendix, it has been proven that the random measure of tips never vanishes during any finite time interval (see Appendix A).

The proof that the number of new tips cannot grow without control, given in Section 5.3, is highly nontrivial. This is the first work that deals rigorously with this question, namely the size of growth when tips may emerge from created vessels and the length of the vessel is potentially unbounded, in finite time, due to the Gaussian fluctuations of the noise. The usual control from above by a Yule process does not work here and new tools have been used. At the technical level, let us also highlight the proof of uniqueness of measure-valued solutions, that seems to be original with respect to the related literature.

We wish to mention that here we are referring to the early stages of the process of tumour-driven angiogenesis, so that we may assume that the shape of the tumour mass does not change in time. This is the reason why in Section 2, the region Σ occupied by the tumour, and the related tumour angiogenic factor (TAF) production function g_Σ are both taken as time independent.

The paper is organised as follows. Section 2 introduces our stochastic model and all relevant random measures associated with. Section 3 is devoted to the evolution of the empirical measure and an heuristic derivation of the mean field equations for the deterministic measure of tips, and the associated TAF concentrations, based on a conjectured 'propagation of chaos'. Section 4 presents our main mathematical results. Section 5 contains a detailed proof of Theorem 4.1, as far as the tightness of the sequence of laws of $(Q_N, C_N)_{N\in\mathbb{N}}$ is concerned, and consequently, the existence of a weakly convergence subsequence; thus, anticipating the existence part claimed in Theorem 4.3. All required estimates are rigorously derived here. The proof of Theorem 4.3, concerning the claimed uniqueness is concerned, can be found in Appendix C.

2 A mathematical model for tumour induced angiogenesis

The main features of the process of formation of a tumour-driven vessel network are (see [5, 16, 22])

(i) vessel branching;

(ii) vessel extension;

(iii) chemotaxis in response to a generic TAF, released by tumour cells;

(iv) haptotactic migration in response to fibronectin gradient, emerging from the extracellular matrix and through degradation and production by endothelial cells themselves;

(v) anastomosis, the coalescence of a capillary tip with an existing vessel.

We will limit ourselves to describe the dynamics of tip cells at the front of growing vessels, as a consequence of chemotaxis in response to a generic tumour factor (TAF) released by tumour cells, in a space $\mathbb{R}^d$, of dimension $d \in \{2, 3\}$.

The number of tip cells changes in time, due to proliferation and death. For our convenience, we shall denote by N_t, the random number of tip cells however born up to time $t \in \mathbb{R}_+$. We shall refer to $N := N_0$ as the scale parameter of the system. The ith tip cell is characterised by the random variables $T^{i,N}$ and $\Theta^{i,N}$, representing the birth (branching) and death (anastomosis) times, respectively, and by its position and velocity $\left(\mathbf{X}^{i,N}(t), \mathbf{V}^{i,N}(t)\right) \in \mathbb{R}^{2d}$, $t \in [T^{i,N}, \Theta^{i,N})$. Its entire history is then given by the stochastic process

$$\left(\mathbf{X}^{i,N}(t), \mathbf{V}^{i,N}(t)\right)_{t\in[T^{i,N},\Theta^{i,N})}.$$

All random variables and processes are defined on a filtered probability space $(\Omega, \mathcal{F}, \mathcal{F}_t, \mathbb{P})$.

The growth factor is a random function $C_N : \Omega \times [0, \infty) \times \mathbb{R}^d \to \mathbb{R}$, that we write as $C_N(t, \mathbf{x})$.

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For the elongation of vessels, we assume a Langevin description, according to which tip cells and growth factor satisfy the stochastic system

$$d\mathbf{X}^{i,N}(t) = \mathbf{V}^{i,N}(t)\,dt, \tag{2.1}$$

$$d\mathbf{V}^{i,N}(t) = \left[-k_1\mathbf{V}^{i,N}(t) + f\left(C_N\left(t,\mathbf{X}^{i,N}(t)\right)\right)\nabla C_N\left(t,\mathbf{X}^{i,N}(t)\right)\right]dt + \sigma d\mathbf{W}^i(t), \tag{2.2}$$

$$\partial_t C_N(t,\mathbf{x}) = k_2 g_\Sigma(\mathbf{x}) + d_1 \Delta C_N(t,\mathbf{x}) - \eta\left(t,\mathbf{x},\{Q_N(s)\}_{s\in[0,t]}\right)C_N(t,\mathbf{x}), \tag{2.3}$$

where $k_1, k_2, \sigma, d_1 > 0$, are given; $\mathbf{W}^i(t)$, $i \in N$, are independent Brownian motions.

Let us denote by $\mathcal{B}_{\mathbb{R}^d}$ the Borel sigma-algebra on $\mathbb{R}^d$; by $\Sigma \in \mathcal{B}_{\mathbb{R}^d}$, we denote the tumoural region acting as a source of TAF; in the equation (2.3), we have taken $g_\Sigma \in UC_b^1\left(\mathbb{R}^d\right)$, with support Σ, to represent the spatial density of the tumour mass.

The initial condition $C_N(0,\mathbf{x})$ is also given, while the initial conditions on $X^{i,N}(t)$, and $V^{i,N}(t)$ depend upon the process at the time of birth $T^{i,N}$ of the ith tip; the term $\eta(t,\mathbf{x},\{Q_N(s)\}_{s\in[0,t]})$ will be described below.

As it will appear more explanatory in Section 2.1, the choice of the Langevin model leads to more regular trajectories of the tip cells, with respect to pure Brownian trajectories. Anyhow, it is well known that pure Brownian trajectories can be obtained from Langevin trajectories as an approximation in the case of large frictions (see, e.g., [8, p. 439]).

In the equation (2.2), besides the friction force, there is a chemotactic force due to the underlying TAF field $C_N(t,x)$; as in relevant literature (see, e.g., [1,31]), we assume that f decreases as a function of $C_N(t,x)$; but here we assume further that it also depends upon the absolute value of the gradient of the TAF field; with an abuse of notations, we will write

$$f(C_N(t,\mathbf{x})) := \frac{d_2}{(1+\gamma_1|\nabla C_N(t,\mathbf{x})| + \gamma_2 C_N(t,\mathbf{x}))^q}.$$

This choice, requested by mathematical issues, leads to upper bounds of the term

$$f\left(C_N\left(t,\mathbf{X}^{i,N}(t)\right)\right)\nabla C_N\left(t,\mathbf{X}^{i,N}(t)\right), \tag{2.4}$$

for large values of the gradient of the TAF field; indeed, this makes the model more realistic, since it bounds the effect of possible large values of this gradient. For $q = 1$, we would have a saturating limit value for the term in equation (2.4).

Let us describe the term $\eta\left(t,\mathbf{x},\{Q_N(s)\}_{s\in[0,t]}\right)$. For every $t \geqslant 0$, we introduce the scaled measure on $\mathcal{B}_{\mathbb{R}^{2d}}$

$$Q_N(t) := \frac{1}{N}\sum_{i=1}^{N_t} \mathbb{I}_{t\in[T^{i,N},\Theta^{i,N})}\epsilon_{(\mathbf{X}^{i,N}(t),\mathbf{V}^{i,N}(t))}, \tag{2.5}$$

where ϵ denotes the usual Dirac measure, having the Dirac delta δ as its generalised density with respect to the usual Lebesgue measure. With these notations, and denoting by $\mathcal{M}_+\left(\mathbb{R}^d\times\mathbb{R}^d\right)$, the set of all finite positive Borel measures on $\mathbb{R}^d\times\mathbb{R}^d$, we may assume that, for every $t \geqslant 0$, the function $\eta(t,\cdot,\cdot)$ maps $\mathbb{R}^d \times L^\infty\left(0,t;\mathcal{M}_+\left(\mathbb{R}^d\times\mathbb{R}^d\right)\right)$ into $\mathbb{R}$

$$\eta(t,\cdot,\cdot) : \mathbb{R}^d \times L^\infty\left(0,t;\mathcal{M}_+\left(\mathbb{R}^d\times\mathbb{R}^d\right)\right) \to \mathbb{R},$$

for which we will assume the following structure:

$$\eta\left(t,\mathbf{x},\{Q_N(s)\}_{s\in[0,t]}\right)=\int_0^t\left(\int_{\mathbb{R}^d\times\mathbb{R}^d}K_1\left(\mathbf{x}-\mathbf{x}'\right)|\mathbf{v}'|\,Q_N(s)\left(d\mathbf{x}',d\mathbf{v}'\right)\right)ds,$$

for a suitable smooth bounded kernel $K_1:\mathbb{R}^d\to\mathbb{R}$.

2.1 The capillary network

The capillary network of endothelial cells $\mathbf{X}^N(t)$ consists of the union of all random trajectories representing the extension of individual capillary tips from the (random) time of birth (branching) $T^{i,N}$, to the (random) time of death (anastomosis) $\Theta^{i,N}$

$$\mathbf{X}^N(t)=\bigcup_{i=1}^{N_t}\{\mathbf{X}^{i,N}(s)\,|\,T^{i,N}\leqslant s\leqslant\min\{t,\Theta^{i,N}\}\},\tag{2.6}$$

giving rise to a stochastic network. Thanks to the choice of a Langevin model for the vessels extension, we may assume that the trajectories are sufficiently regular and have an integer Hausdorff dimension 1.

Since $1<d$, the random measure

$$B\in\mathcal{B}_{\mathbb{R}^d}\mapsto\mathcal{H}^1(\mathbf{X}^N(t)\cap B)\in\mathbb{R}_+\tag{2.7}$$

is singular with respect to the usual Lebesgue measure on $\mathbb{R}^d$. Hence, [11] it admits a random generalised density $\delta_{\mathbf{X}^N(t)}(x)$ such that, for any $B\in\mathcal{B}_{\mathbb{R}^d}$,

$$\mathcal{H}^1(\mathbf{X}^N(t)\cap B)=\int_B\delta_{\mathbf{X}^N(t)}(\mathbf{x})d\mathbf{x}.\tag{2.8}$$

By Theorem 11 in [9], we may then state that

$$\mathcal{H}^1\left(\mathbf{X}^N(t)\cap B\right)=\int_0^t\sum_{i=1}^{N_s}\epsilon_{\mathbf{X}^{i,N}(s)}(B)\left|\frac{d}{ds}\mathbf{X}^{i,N}(s)\right|\mathbb{I}_{s\in[T^{i,N},\Theta^{i,N})}ds.\tag{2.9}$$

Hence,

$$\delta_{\mathbf{X}^N(t)}(\mathbf{x})=\int_0^t\sum_{i=1}^{N_s}\delta_{\mathbf{X}^{i,N}(s)}(\mathbf{x})\left|\frac{d}{ds}\mathbf{X}^{i,N}(s)\right|\mathbb{I}_{s\in[T^{i,N},\Theta^{i,N})}ds.\tag{2.10}$$

With this in mind, we may write

$$\begin{aligned}&\eta\left(t,\mathbf{x},\{Q_N(s)\}_{s\in[0,t]}\right)\\&=\frac{1}{N}\int_0^t ds\sum_{i=1}^{N_s}\mathbb{I}_{s\in[T^{i,N},\Theta^{i,N})}K_1(\mathbf{x}-\mathbf{X}^{i,N}(s))|\mathbf{V}^{i,N}(s)|\\&=\frac{1}{N}(K_1*\delta_{\mathbf{X}^N(t)})(\mathbf{x}).\end{aligned}\tag{2.11}$$

Remark 2.1 We wish to remark here that, while apparently the term $\eta\left(t, \mathbf{x}, \{Q_N(s)\}_{s\in[0,t]}\right)$ contains a memory of the whole history of the measure process Q_N up to time t, if we refer to joint process $\{(Q_N(t), \mathbf{X}^N(t)); t \geqslant 0\}$, this is not true any more. The same will apply in the process of branching and anastomosis, so that the Markov properties of the whole process still hold true.

2.1.1 *Branching*

Two kinds of branching have been identified, either from a tip or from a vessel. The birth process of new tips can be described in terms of a marked point process (see, e.g., [6]), by means of a random measure Φ on $\mathcal{B}_{\mathbb{R}^+\times\mathbb{R}^d\times\mathbb{R}^d}$ such that, for any $t \geqslant 0$ and any $B \in \mathcal{B}_{\mathbb{R}^d\times\mathbb{R}^d}$,

$$\Phi((0,t]\times B) := \int_0^t \int_B \Phi(ds \times d\mathbf{x} \times d\mathbf{v}), \tag{2.12}$$

where $\Phi(ds \times d\mathbf{x} \times d\mathbf{v})$ is the random variable that counts those tips born either from an existing tip, or from an existing vessel, during times in $(s, s+ds]$, with positions in $(\mathbf{x}, \mathbf{x}+d\mathbf{x}]$, and velocities in $(\mathbf{v}, \mathbf{v}+d\mathbf{v}]$. By our definition of N_t, as the number of tip cells, however, born up to time $t \geqslant 0$, we may state that

$$N_t = N_0 + \Phi((0,t]\times\mathbb{R}^d).$$

As an additional simplification, we will further assume that the initial value of the state of a new tip is $(\mathbf{X}^{N_t+1,N}_{T^{N_t+1,N}}, \mathbf{V}^{N_t+1,N}_{T^{N_t+1,N}})$, where $T^{N_t+1,N}$ is the random time of branching, $\mathbf{X}^{N_t+1,N}_{T^{N_t+1,N}}$ is the random point of branching, and $\mathbf{V}^{N_t+1,N}_{T^{N_t+1,N}}$ is a random velocity, selected out of a probability distribution $G_{\mathbf{v}_0}$ with mean $\mathbf{v}_0$.

Given the history $\mathcal{F}_{t^-}$ of the whole process up to time t^-, we assume that the compensator (intensity measure) of the random measure $\Phi(ds \times d\mathbf{x} \times d\mathbf{v})$ is given by (see, e.g., [8], pp. 122, and 157)

$$\begin{aligned}
&\mathbb{E}\left[\Phi(ds \times d\mathbf{x} \times d\mathbf{v}) \mid \mathcal{F}_{s^-}\right] \\
&= \alpha(C_N(s,\mathbf{x}))G_{\mathbf{v}_0}(\mathbf{v}) \sum_{i=1}^{N_{s-}} \mathbb{I}_{s\in[T^{i,N},\Theta^{i,N})} \epsilon_{\mathbf{X}^{i,N}(s)}(d\mathbf{x})\, d\mathbf{v}ds \\
&\quad + \beta(C_N(s,\mathbf{x}))G_{\mathbf{v}_0}(\mathbf{v})\epsilon_{\mathbf{X}^N(s)}(d\mathbf{x})\, d\mathbf{v}ds,
\end{aligned}$$

where $\alpha(C), \beta(C)$ are non-negative smooth functions, bounded with bounded derivatives; for example, we may take

$$\alpha(C) = \alpha_1 \frac{C}{C_R + C},$$

where C_R is a reference density parameter [10]; and similarly for $\beta(C)$.

The term corresponding to tip branching

$$\alpha(C_N(s,\mathbf{x}))G_{\mathbf{v}_0}(\mathbf{v}) \sum_{i=1}^{N_{s-}} \mathbb{I}_{s\in[T^{i,N},\Theta^{i,N})} \epsilon_{\mathbf{X}^{i,N}(s)}(d\mathbf{x})\, d\mathbf{v}ds, \tag{2.13}$$

comes from the following argument: a new tip may arise only at positions $\mathbf{X}^{i,N}(s)$ with $s \in [T^{i,N}, \Theta^{i,N})$ (the positions of the tips existing at time s); the birth is modulated by $\alpha(C_N(s,x))$, since we want to take into account the density of the growth factor; and the velocity of the new tip is chosen at random with density $G_{\mathbf{v}_0}(\mathbf{v})$. It can be rewritten as

$$N\alpha(C_N(s,x))G_{\mathbf{v}_0}(\mathbf{v})d\mathbf{v} \int_{\mathbb{R}^d} Q_N(s)\,(d\mathbf{x}, d\mathbf{v})\; ds, \tag{2.14}$$

The term corresponding to vessel branching

$$\beta(C_N(s,\mathbf{x}))G_{\mathbf{v}_0}(\mathbf{v})\epsilon_{\mathbf{X}^N(s)}\,(d\mathbf{x})\; d\mathbf{v}ds, \tag{2.15}$$

tells us that a new tip may stem at time s from a point x belonging to the stochastic network $\mathbf{X}^N(s)$ already existing at time s, at a rate depending on the concentration of the TAF via $\beta(C_N(s,x))$, for the reasons described above. Again the velocity of the new tip is chosen at random with density $G_{\mathbf{v}_0}(\mathbf{v})$. Because of (2.9), it can be rewritten as

$$N\beta(C_N(s,\mathbf{x}))G_{\mathbf{v}_0}(\mathbf{v})d\mathbf{v} \int_0^s \int_{\mathbb{R}^d} |\mathbf{v}|\, Q_N\,(r)\,(d\mathbf{x}, d\mathbf{v})\, dr ds. \tag{2.16}$$

It may be useful to remind that, thanks to Doob–Meyer decomposition theorem, what is left of the measure process $\Phi(ds \times d\mathbf{x} \times d\mathbf{v})$ after subtracting its compensator, is a zero-mean martingale (see, e.g., [8, p. 122]).

2.1.2 *Anastomosis*

When a vessel tip meets an existing vessel, it joins it at that point and time and it stops moving. This process is called tip-vessel anastomosis.

As in the case of the branching process, we may model this process via a marked counting process; anastomosis is modelled as a 'death' process.

Let Ψ denote the random measure on $\mathcal{B}_{\mathbb{R}^+\times\mathbb{R}^d\times\mathbb{R}^d}$ such that, for any $t \geqslant 0$, and any $B \in \mathcal{B}_{\mathbb{R}^d\times\mathbb{R}^d}$

$$\Psi((0,t] \times B) := \int_0^t \int_B \Psi(ds \times d\mathbf{x} \times d\mathbf{v}), \tag{2.17}$$

where $\Psi(ds \times d\mathbf{x} \times d\mathbf{v})$ is the random variable counting those tips that are absorbed by the existing vessel network during time $(s, s + ds]$, with position in $(\mathbf{x}, \mathbf{x} + d\mathbf{x}]$, and velocity in $(\mathbf{v}, \mathbf{v} + d\mathbf{v}]$.

We assume that the compensator of the random measure $\Psi(ds \times d\mathbf{x} \times d\mathbf{v})$ is

$$\mathbb{E}\left[\Psi(ds \times d\mathbf{x} \times d\mathbf{v}) \mid \mathcal{F}_{s-}\right] \tag{2.18}$$

$$= \gamma \sum_{i=1}^{N_s} \mathbb{I}_{s\in[T^{i,N},\Theta^{i,N})} h\left(\frac{1}{N}\left(K_2 * \delta_{\mathbf{X}^N(s)}\right)(\mathbf{x})\right) \epsilon_{(\mathbf{X}^{i,N}(s),\mathbf{V}^{i,N}(s))}(d\mathbf{x} \times d\mathbf{v})\, ds$$

$$= \gamma N h\left(\frac{1}{N}\left(K_2 * \delta_{\mathbf{X}^N(s)}\right)(\mathbf{x})\right) Q_N(s)(d\mathbf{x}, d\mathbf{v})ds, \tag{2.19}$$

where γ is a suitable constant, and $K_2 : \mathbb{R}^d \to \mathbb{R}$ is a suitable mollifying kernel,

$h : \mathbb{R}_+ \to \mathbb{R}_+$ is a saturating function of the form $h(r) = \frac{r}{1+r}$. This compensator expresses the death rate of a tip located at $\left(\mathbf{X}^{i,N}(s), \mathbf{V}^{i,N}(s)\right)$ at time s; the death rate is modulated by γ and by a scaled thickened version of the capillary network existing at time s, given by (see equation (2.9))

$$\frac{1}{N}\left(K_2 * \delta_{\mathbf{X}^N(s)}\right)(\mathbf{x}) = \int_0^s \frac{1}{N}\sum_{i=1}^{N_r} K_2\left(\mathbf{x} - \mathbf{X}^{i,N}(r)\right)\left|\mathbf{V}^{i,N}(r)\right| \mathbb{I}_{r\in[T^{i,N},\Theta^{i,N})} dr$$
$$= \int_0^s \int_{\mathbb{R}^d\times\mathbb{R}^d} K_2\left(\mathbf{x} - \mathbf{x}'\right)|\mathbf{v}'|\, Q_N(r)\left(d\mathbf{x}', d\mathbf{v}'\right) dr.$$

Let us set

$$g(s, \mathbf{x}, \{Q_N(r)\}_{r\in[0,s]}) := h\left(\frac{1}{N}\left(K_2 * \delta_{\mathbf{X}^N(s)}\right)(\mathbf{x})\right).$$

Thanks to the above, the compensator (2.19) can be rewritten as

$$\gamma N g(s, \mathbf{x}, \{Q_N(r)\}_{r\in[0,s]}) Q_N(s)(d\mathbf{x}, d\mathbf{v})\, ds. \tag{2.20}$$

Here, we wish to stress a couple of technical issues, which have led to the substantial modification of the structure of the compensator with respect to previous models (see, e.g., [5]). The first one is mainly motivated by the case of dimension $d = 3$, but then for simplicity, we adopt it also in $d = 2$; since, for mathematical convenience, we have modelled a vessel as a 1-dimensional curve in $\mathbb{R}^d$, it is essentially impossible that anastomosis takes place, since the probability that two curves meet in $\mathbb{R}^3$ is negligible, even though they may get very close to each other: the mathematical abstraction 'vessel=curve' would have not been realistic here. In order to overcome this technical issue, we have introduced a thickness of the curve, described by a kernel K_2 (this is equivalent to keep vessels as curves and introduce a thickness of tips). With this technical modification, the model has become more realistic, since real vessels do not have dimension 1. Anyhow, this choice has implied a second issue. The thickening of vessels induce a mathematical modelling problem whenever the vessel network is highly dense in space; indeed, in such a situation at a same point $\mathbf{x}$ more than one vessel may contribute to the quantity

$$\frac{1}{N}\left(K_2 * \delta_{\mathbf{X}^N(s)}\right)(\mathbf{x}), \tag{2.21}$$

which is not realistic. In order to compete with this anomalous effect, we have introduced a saturation via the function h.

Thanks to the above considerations, on one hand, we have solved significant modelling biases, on the other hand, we have made the model more tractable from a mathematical point of view.

3 Evolution of the empirical measure

The evolution of the empirical measure $Q_N(t)$ is obtained by application of Itô formula to the expression

$$\frac{1}{N}\sum_{i=1}^{N_t} \mathbb{I}_{t\in[T^{i,N},\Theta^{i,N})}\phi\left(\mathbf{X}^{i,N}(t),\mathbf{V}^{i,N}(t)\right),$$

where ϕ is a C^2 test function.

From Itô–Levy formula and the expressions of the compensators of the branching and anastomosis processes, we obtain the identity

$$\begin{aligned}
&\int_{\mathbb{R}^d\times\mathbb{R}^d}\phi(\mathbf{x},\mathbf{v})\,Q_N(t)(d\mathbf{x},d\mathbf{v}) = \int_{\mathbb{R}^d\times\mathbb{R}^d}\phi(\mathbf{x},\mathbf{v})\,Q_N(0)(d\mathbf{x},d\mathbf{v})\\
&\quad+\int_0^t\int_{\mathbb{R}^d\times\mathbb{R}^d}\mathbf{v}\cdot\nabla_x\phi(\mathbf{x},\mathbf{v})\,Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds\\
&\quad+\int_0^t\int_{\mathbb{R}^d\times\mathbb{R}^d}\left[f(C_N(s,\mathbf{x}))\nabla C_N(s,\mathbf{x})-k_1\mathbf{v}\right]\cdot\nabla_v\phi(\mathbf{x},\mathbf{v})\,Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds\\
&\quad+\int_0^t\int_{\mathbb{R}^d\times\mathbb{R}^d}\frac{\sigma^2}{2}\Delta_v\phi(\mathbf{x},\mathbf{v})\,Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds\\
&\quad+\int_0^t\int_{\mathbb{R}^d\times\mathbb{R}^d}\phi_G(\mathbf{x})\,\alpha(C_N(s,\mathbf{x}))Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds\\
&\quad+\int_0^t\int_{\mathbb{R}^d\times\mathbb{R}^d}\phi_G(\mathbf{x})\,\beta(C_N(s,\mathbf{x}))\,|\mathbf{v}|\int_0^s Q_N(r)(d\mathbf{x},d\mathbf{v})\,dr\,ds\\
&\quad-\gamma\int_0^t\int_{\mathbb{R}^d\times\mathbb{R}^d}\phi(\mathbf{x},\mathbf{v})\,g\left(s,\mathbf{x},\{Q_N(r)\}_{r\in[0,s]}\right)Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds\\
&\quad+\widetilde{M}_N(t).
\end{aligned}\tag{3.1}$$

The martingale

$$\widetilde{M}_N(t)=\widetilde{M}_{1,N}(t)+\widetilde{M}_{2,N}(t)+\widetilde{M}_{3,N}(t)$$

is the sum of three zero-mean martingales, namely

$$\widetilde{M}_{1,N}(t)=\int_0^t\frac{1}{N}\sum_{i=1}^{N_s}\nabla_v\phi(X^{i,N}(s),V^{i,N}(s))I_{s\in[T^{i,N},\Theta^{i,N})}\cdot dW^i(s);\tag{3.2}$$

$$\begin{aligned}
\widetilde{M}_{2,N}(t)=\int_0^t\int_{\mathbb{R}^d\times\mathbb{R}^d}&\left[\phi(\mathbf{x},\mathbf{v})\Phi_N(ds\times d\mathbf{x}\times d\mathbf{v})\right.\\
&-\phi_G(\mathbf{x})\,\alpha(C_N(s,\mathbf{x}))Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds\\
&\left.-\phi_G(\mathbf{x})\,\beta(C_N(s,\mathbf{x}))\,|\mathbf{v}|\int_0^s Q_N(r)(d\mathbf{x},d\mathbf{v})\,dr\,ds\right];
\end{aligned}\tag{3.3}$$

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$$\widetilde{M}_{3,N}(t) = \int_0^t \int_{\mathbb{R}^d \times \mathbb{R}^d} \phi(\mathbf{x},\mathbf{v})[\Psi_N(ds \times d\mathbf{x} \times d\mathbf{v}) - \gamma g\left(s, \mathbf{x}, \{Q_N(r)\}_{r\in[0,s]}\right) Q_N(s)(d\mathbf{x}, d\mathbf{v})\, ds]. \tag{3.4}$$

In the above, we have denoted

$$\phi_G(\mathbf{x}) := \int_{\mathbb{R}^d} G_{v_0}(\mathbf{v})\phi(\mathbf{x},\mathbf{v})\, d\mathbf{v}. \tag{3.5}$$

3.1 Heuristic derivation of the limit PDE

It is now clear that the only source of stochasticity in the above system is in the martingale terms. Classical laws of large numbers for martingales, allow us to conjecture that the martingales are negligible. Consequently, if we assume we already know that the sequences $(Q_N)_{N\in\mathbb{N}}$ and $(C_N)_{N\in\mathbb{N}}$ converge, to a deterministic time-dependent measure $p_t(d\mathbf{x}, d\mathbf{v})$ and a deterministic function $C_t(\mathbf{x})$, respectively, the limit partial differential equation (PDE) for the measure p_t is conjectured to be

$$\begin{aligned}
\int_{\mathbb{R}^d \times \mathbb{R}^d} \phi(\mathbf{x},\mathbf{v})\, p_t(d\mathbf{x}, d\mathbf{v}) &= \int_{\mathbb{R}^d \times \mathbb{R}^d} \phi(\mathbf{x},\mathbf{v})\, p_0(d\mathbf{x}, d\mathbf{v}) \\
&+ \int_0^t \int_{\mathbb{R}^d \times \mathbb{R}^d} \mathbf{v}\cdot\nabla_x \phi(\mathbf{x},\mathbf{v})\, p_s(d\mathbf{x}, d\mathbf{v})\, ds \\
&+ \int_0^t \int_{\mathbb{R}^d \times \mathbb{R}^d} [f(C_N(s,\mathbf{x}))\nabla C_s(\mathbf{x}) - k_1\mathbf{v}]\cdot\nabla_v \phi(\mathbf{x},\mathbf{v})\, p_s(d\mathbf{x}, d\mathbf{v})\, ds \\
&+ \int_0^t \int_{\mathbb{R}^d \times \mathbb{R}^d} \frac{\sigma^2}{2} \Delta_v \phi(\mathbf{x},\mathbf{v})\, p_s(d\mathbf{x}, d\mathbf{v})\, ds \\
&+ \int_0^t \int_{\mathbb{R}^d \times \mathbb{R}^d} \phi_G(\mathbf{x})\, \alpha(C_s(\mathbf{x})) p_s(d\mathbf{x}, d\mathbf{v})\, ds \\
&+ \int_0^t \int_0^s \int_{\mathbb{R}^d \times \mathbb{R}^d} \phi_G(\mathbf{x})\, \beta(C_s(\mathbf{x}))\, |\mathbf{v}|\, p_r(d\mathbf{x}, d\mathbf{v})\, dr ds \\
&- \gamma \int_0^t \int_{\mathbb{R}^d \times \mathbb{R}^d} \phi(\mathbf{x},\mathbf{v})\, g\left(s, \mathbf{x}, \{p_r\}_{r\in[0,s]}\right) p_s(d\mathbf{x}, d\mathbf{v})\, ds,
\end{aligned} \tag{3.6}$$

with

$$\begin{aligned}
g\left(s, \mathbf{x}, \{p_r\}_{r\in[0,s]}\right) &= h\left(\int_0^s \int_{\mathbb{R}^d \times \mathbb{R}^d} K_2(\mathbf{x}-\mathbf{x}')\, |\mathbf{v}'|\, p_r(d\mathbf{x}', d\mathbf{v}')\, dr\right) \\
&= h\left(\int_0^s \int_{\mathbb{R}^d} K_2(\mathbf{x}-\mathbf{x}')\, \widetilde{p}_r(d\mathbf{x}')\, dr\right),
\end{aligned}$$

having set

$$\widetilde{p}_r(d\mathbf{x}) = \int_{\mathbb{R}^d} |\mathbf{v}|\, p_r(d\mathbf{x}, d\mathbf{v}).$$

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Notice that

$$\begin{aligned}
&\int_{\mathbb{R}^d\times\mathbb{R}^d} \phi_G(\mathbf{x})\,\alpha(C_s(\mathbf{x}))p_s(d\mathbf{x},d\mathbf{v})\\
&\quad= \int_{\mathbb{R}^d\times\mathbb{R}^d\times\mathbb{R}^d} G_{v_0}(\mathbf{v}')\phi\left(\mathbf{x},\mathbf{v}'\right)\alpha(C_s(\mathbf{x}))p_s(d\mathbf{x},d\mathbf{v})\,d\mathbf{v}'\\
&\quad= \int_{\mathbb{R}^d\times\mathbb{R}^d\times\mathbb{R}^d} G_{v_0}(\mathbf{v})\phi(\mathbf{x},\mathbf{v})\,\alpha(C_s(\mathbf{x}))p_s\left(d\mathbf{x},d\mathbf{v}'\right)d\mathbf{v}\\
&\quad= \int_{\mathbb{R}^d\times\mathbb{R}^d} G_{v_0}(\mathbf{v})\phi(\mathbf{x},\mathbf{v})\,\alpha(C_s(\mathbf{x}))\left(\int_{\mathbb{R}^d} p_s\left(d\mathbf{x},d\mathbf{v}'\right)\right)d\mathbf{v}\\
&\quad= \int_{\mathbb{R}^d\times\mathbb{R}^d} G_{v_0}(\mathbf{v})\phi(\mathbf{x},\mathbf{v})\,\alpha(C_s(\mathbf{x}))\,(\pi_1 p_s)(d\mathbf{x})\,d\mathbf{v},
\end{aligned}$$

where we set

$$(\pi_1 p_s)(d\mathbf{x}) = \int_{\mathbb{R}^d} p_s(d\mathbf{x},d\mathbf{v})$$

and similarly

$$\begin{aligned}
&\int_0^s\int_{\mathbb{R}^d\times\mathbb{R}^d} \phi_G(\mathbf{x})\,\beta(C_s(\mathbf{x}))\,|\mathbf{v}|\,p_r(d\mathbf{x},d\mathbf{v})\,dr\\
&\quad= \int_0^s\int_{\mathbb{R}^d\times\mathbb{R}^d\times\mathbb{R}^d} G_{v_0}(\mathbf{v}')\phi\left(\mathbf{x},\mathbf{v}'\right)\beta(C_s(\mathbf{x}))\,|\mathbf{v}|\,p_r(d\mathbf{x},d\mathbf{v})\,drd\mathbf{v}'\\
&\quad= \int_0^s\int_{\mathbb{R}^d\times\mathbb{R}^d\times\mathbb{R}^d} G_{v_0}(\mathbf{v})\phi(\mathbf{x},\mathbf{v})\,\beta(C_s(\mathbf{x}))\,|\mathbf{v}'|\,p_r\left(d\mathbf{x},d\mathbf{v}'\right)drd\mathbf{v}\\
&\quad= \int_{\mathbb{R}^d\times\mathbb{R}^d} G_{v_0}(\mathbf{v})\phi(\mathbf{x},\mathbf{v})\,\beta(C_s(\mathbf{x}))\int_0^s\int_{\mathbb{R}^d} |\mathbf{v}'|\,p_r\left(d\mathbf{x},d\mathbf{v}'\right)drd\mathbf{v}\\
&\quad= \int_{\mathbb{R}^d\times\mathbb{R}^d} G_{v_0}(\mathbf{v})\phi(\mathbf{x},\mathbf{v})\,\beta(C_s(\mathbf{x}))\int_0^s \widetilde{p}_r(d\mathbf{x})\,drd\mathbf{v}.
\end{aligned}$$

Consequently, the limit PDE for $C_t(\mathbf{x})$ is conjectured to be

$$\frac{\partial}{\partial t}C_t(\mathbf{x}) = k_2\delta_A(\mathbf{x}) + d_1\Delta C_t(\mathbf{x}) - \eta\left(t,\mathbf{x},\{p_s\}_{s\in[0,t]}\right)C_t(\mathbf{x}),$$

where

$$\eta\left(t,\mathbf{x},\{p_s\}_{s\in[0,t]}\right) = \int_0^t\left(\int_{\mathbb{R}^d\times\mathbb{R}^d} K_1\left(\mathbf{x}-\mathbf{x}'\right)|\mathbf{v}'|\,p_s\left(d\mathbf{x}',d\mathbf{v}'\right)\right)ds. \tag{3.7}$$

4 Main results

A rigorous proof of the above mentioned convergence of the evolution equations for the empirical measure $Q_N(t)$ to the evolution equation of the corresponding deterministic limit measure p_t requires various steps, including (i) tightness of the sequences of the laws of $(Q_N)_{N\in\mathbb{N}}$, and $(C_N)_{N\in\mathbb{N}}$; (ii) existence and uniqueness of the solution of the deterministic evolution equation of the limiting measure p_t (see, e.g., [8] and references therein).

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4.1 Assumptions and notations

Denote by $\mathcal{M}_+\left(\mathbb{R}^d\times\mathbb{R}^d\right)$, the space of positive Radon measures and by $\mathcal{M}_1\left(\mathbb{R}^d\times\mathbb{R}^d\right)$ the space of those $\rho\left(d\mathbf{x},d\mathbf{v}\right)$ such that

$$\int_{\mathbb{R}^{2d}}\left(1+|\mathbf{v}|\right)\rho\left(d\mathbf{x},d\mathbf{v}\right)<\infty.$$

Denote by $L^\infty\left(0,T;\mathcal{M}_1\left(\mathbb{R}^d\times\mathbb{R}^d\right)\right)$, the space of time-dependent Radon measures $p_t\left(d\mathbf{x},d\mathbf{v}\right)$ such that $t\mapsto\int_{\mathbb{R}^{2d}}\phi\left(\mathbf{x},\mathbf{v}\right)\left(1+|\mathbf{v}|\right)p_t\left(d\mathbf{x},d\mathbf{v}\right)$ is measurable for all $\phi\in C_c^\infty\left(\mathbb{R}^d\times\mathbb{R}^d\right)$ and

$$\sup_{t\in[0,T]}\int_{\mathbb{R}^{2d}}\left(1+|\mathbf{v}|\right)p_t\left(d\mathbf{x},d\mathbf{v}\right)<\infty.$$

Denote by $C\left([0,T];\mathcal{M}_+\left(\mathbb{R}^d\times\mathbb{R}^d\right)\right)$ the space of time-dependent measures that are continuous when $\mathcal{M}_+\left(\mathbb{R}^d\times\mathbb{R}^d\right)$ is endowed of a metric corresponding to weak convergence of measures.

Moreover, denote by $\mathbb{D}\left([0,T];\mathcal{M}_+\left(\mathbb{R}^d\times\mathbb{R}^d\right)\right)$, the Skorohod space of càdlàg functions with values in $\mathcal{M}_+\left(\mathbb{R}^d\times\mathbb{R}^d\right)$, as defined in [3]. We use the Skorohod space because birth and death of particles change discontinuously the empirical measure of the process. However, the limit (deterministic) process is continuous, it belongs to $C\left([0,T];\mathcal{M}_+\left(\mathbb{R}^d\times\mathbb{R}^d\right)\right)$ and therefore, even on $\mathbb{D}\left([0,T];\mathcal{M}_+\left(\mathbb{R}^d\times\mathbb{R}^d\right)\right)$, it is sufficient to use the uniform topology, also for tightness arguments, as explained in [3, p. 157].

For a positive integer k, we denote by $C_b^k\left(\mathbb{R}^d\right)$ the space of all functions on $\mathbb{R}^d$, which are differentiable k times with bounded derivatives up to order k. We denote by $UC_b^k\left(\mathbb{R}^d\right)$ the subspace of $C_b^k\left(\mathbb{R}^d\right)$ of functions, which are uniformly continuous, with their derivatives up to order k.

We assume that the initial conditions $\left(\mathbf{X}_0^N,\mathbf{V}_0^N\right)$ are independent and identically distributed (i.i.d.) random vectors, with a compact support law $p_0\in\mathcal{M}_1\left(\mathbb{R}^d\times\mathbb{R}^d\right)$. Recall the definition of the empirical measure $Q_N\left(t\right)$ given in (2.5). From the previous assumption on the initial conditions $\left(\mathbf{X}_0^N,\mathbf{V}_0^N\right)$, we deduce that $Q_N\left(0\right)$ converges to p_0 in the following sense:

$$\int_{\mathbb{R}^d\times\mathbb{R}^d}\phi\left(\mathbf{x},\mathbf{v}\right)\left(1+|\mathbf{v}|\right)Q_N\left(0\right)\left(d\mathbf{x},d\mathbf{v}\right)\to$$
$$\to\int_{\mathbb{R}^d\times\mathbb{R}^d}\phi\left(\mathbf{x},\mathbf{v}\right)\left(1+|\mathbf{v}|\right)p_0\left(d\mathbf{x},d\mathbf{v}\right),$$

for every $\phi\in C_b\left(\mathbb{R}^d\times\mathbb{R}^d\right)$, where the convergence is understood in probability.

The initial condition C_0 of the concentration is independent of N, just for simplicity. We assume it of class $UC_b^2\left(\mathbb{R}^d\right)$. Moreover, we assume

$$0\leqslant C_0\left(\mathbf{x}\right)\leqslant C_{\max},$$

for some constant $C_{\max}>0$. The convolution kernel K_1 appearing in the TAF absorption rate η and the convolution kernel K_2 of the anastomosis, are both assumed of class

$UC_b^1(\mathbb{R}^d)$ and nonnegative

$$K_1(\mathbf{x}) \geqslant 0, \qquad K_2(\mathbf{x}) \geqslant 0.$$

for all $x \in \mathbb{R}^d$. The function $G_{v_0}(\mathbf{v})$ appearing in the vessel branching rate is assumed of class $UC_b^1(\mathbb{R}^d)$, with compact support, non negative, and such that

$$\int_{\mathbb{R}^d} G_{v_0}(\mathbf{v})\left(1+|\mathbf{v}|\right) d\mathbf{v} < \infty.$$

Several constants appear in the model; we assume

$$k_1, k_2, d_1, d_2, \gamma_1, \alpha_1, C_R > 0.$$

4.2 Theorems of convergence and well posedness of the limit PDE system

Under these assumptions, we prove our main result.

Theorem 4.1 *As $N \to \infty$, $Q_N(t)$ converges in probability, in the space $\mathbb{D}([0,T];\mathcal{M}_+(\mathbb{R}^d \times \mathbb{R}^d))$ with the uniform topology, to a time-dependent deterministic Radon measure p_t on $\mathbb{R}^d \times \mathbb{R}^d$, also of class $L^\infty(0,T;\mathcal{M}_1(\mathbb{R}^d \times \mathbb{R}^d))$ and C_N converges in $C([0,T];C_b^1(\mathbb{R}^d))$ to a deterministic function C of this space. The measure p_t is a weak solution in the sense specified in Definition 4.2 (unique in $L^\infty(0,T;\mathcal{M}_1(\mathbb{R}^d \times \mathbb{R}^d))$ thanks to Theorem (4.3) below) of the equation*

$$\begin{aligned}\partial_t p_t + \mathbf{v}\cdot\nabla_{\mathbf{x}} p_t + \mathrm{div}_{\mathbf{v}}\left(\left[f(C_t)\nabla C_t - k_1\mathbf{v}\right] p_t\right) &= \frac{\sigma^2}{2}\Delta_{\mathbf{v}} p_t \\ &+ G_{\mathbf{v}_0}(\mathbf{v})\, d\mathbf{v}\left(\alpha(C_t)(\pi_1 p_t)(d\mathbf{x}) + \beta(C_t)\int_0^t \widetilde{p}_r(d\mathbf{x})\, dr\right) \\ &- \gamma p_t h\left(\int_0^t (K_2 * \widetilde{p}_r)(\mathbf{x})\, dr\right). \qquad (4.1)\end{aligned}$$

The function C_t is a mild solution (in the sense specified in Definition 4.2) of the equation

$$\partial_t C_t(\mathbf{x}) = k_2 g_\Sigma(\mathbf{x}) + d_1 \Delta C_t(\mathbf{x}) - \eta\left(t, \mathbf{x}, \{p_s\}_{s\in[0,t]}\right) C_t(\mathbf{x}), \qquad (4.2)$$

where η is given in equation (3.7).

Definition 4.2 We say that a measure-valued function p_t of class

$$C\left([0,T];\mathcal{M}_+\left(\mathbb{R}^d \times \mathbb{R}^d\right)\right) \cap L^\infty\left(0,T;\mathcal{M}_1\left(\mathbb{R}^d \times \mathbb{R}^d\right)\right)$$

is a weak solution of equation (4.1) if, for every compact support test function $\phi(\mathbf{x},\mathbf{v})$ of class C^2, identity (3.6) holds true.

Moreover, we say that a function C_t of class

$$C\left([0,T];UC_b^1\left(\mathbb{R}^d\right)\right)$$

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is a mild solution of equation (4.2) if, it satisfies the identity

$$C_t = e^{tA}C_0 + \int_0^t e^{(t-s)A}\left(k_2\delta_A - \eta\left(s,\cdot,\{p_r\}_{r\in[0,s]}\right)C_s\right)ds,$$

where e^{tA} is the heat semigroup in $UC_b\left(\mathbb{R}^d\right)$ generated by the operator $A = d_1\Delta$.

As anticipated above, the proof of Theorem 4.1 is based on several arguments including a uniqueness result for the system of PDEs (4.1)–(4.2), which we state separately because of its independent interest.

Theorem 4.3 *There exists a unique solution of System (4.1)–(4.2), with* $p \in L^\infty\left(0,T;\mathcal{M}_1\left(\mathbb{R}^d\times\mathbb{R}^d\right)\right)$ *and* $C \in C\left([0,T];C_b^1\left(\mathbb{R}^d\right)\right)$.

The proof of Theorem 4.1 is given in Section 5. The proof of Theorem 4.3 is given in Appendix C.

Remark 4.4 In the framework of this paper, the PDE for the measure p_t will be always interpreted as a PDE for measure-valued functions. However, under suitable assumptions, the relevant measure may admit a density $\rho_t(x,v)$, which is a classical function, so that the PDE can be interpreted in a more classical sense (we do not investigate rigorously this issue here, we only give the heuristic result). The formal expression for the evolution equation of the density $\rho_t(x,v)$ would then be

$$\begin{aligned}
&\partial_t\rho_t(\mathbf{x},\mathbf{v}) + \mathbf{v}\cdot\nabla_{\mathbf{x}}\rho_t(\mathbf{x},\mathbf{v}) + \mathrm{div}_{\mathbf{v}}\left([f(C_t(\mathbf{x}))\nabla C_t(\mathbf{x}) - k_1\mathbf{v}]\,\rho_t(\mathbf{x},\mathbf{v})\right)\\
&\quad= \frac{\sigma^2}{2}\Delta_{\mathbf{v}}\rho_t(\mathbf{x},\mathbf{v}) + G_{\mathbf{v}_0}(\mathbf{v})\left(\alpha(C_t(\mathbf{x}))(\pi_1\rho_t)(\mathbf{x}) + \beta(C_t(\mathbf{x}))\int_0^t \widetilde{\rho}_r(\mathbf{x})\,dr\right)\\
&\quad\quad- \gamma\rho_t h\left(\int_0^t (K_2 * \widetilde{\rho}_r)(\mathbf{x})\,dr\right).
\end{aligned} \tag{4.3}$$

Here, we have taken

$$(\pi_1\rho_t)(\mathbf{x}) = \int_{\mathbb{R}^d}\rho_t(\mathbf{x},\mathbf{v})\,d\mathbf{v},$$

and

$$\widetilde{\rho}_r(\mathbf{x}) = \int_{\mathbb{R}^d}|\mathbf{v}|\rho_r(\mathbf{x},\mathbf{v})\,d\mathbf{v}.$$

5 Proof of Theorem 4.1

Let us explain the steps of the proof. First, we prove bounds, uniform in N, on the particle system (2.1) and the PDE (2.3). This is the core of the method. From these bounds, we deduce tightness of the sequence of laws of $\{Q_N, N \in \mathbb{N}\}$ and $\{C_N, N \in \mathbb{N}\}$, and therefore the existence of a weakly convergent subsequence. Then, we show that the limit of this subsequence is concentrated on solutions of the limit system (4.1)–(4.2). This provides, in particular, the existence claim of Theorem 4.3. From the uniqueness claim of that theorem, proved in Appendix C, we deduce that the whole sequence $\{(Q_N, C_N), N \in \mathbb{N}\}$, converges weakly; and converges also in probability because the limit is deterministic (again due to uniqueness).

5.1 Regularity of η and C_N

We interpret equation (2.3) for C_N in the mild semigroup form

$$C_N(t) = e^{tA}C_0 + \int_0^t e^{(t-s)A}\left(k_2 g_\Sigma - \eta\left(s, \cdot, \{Q_N(r)\}_{r\in[0,s]}\right) C_N(s)\right) ds.$$

Here, e^{tA} denotes the heat semigroup associated with the operator $A := d_1 \Delta$ on $\mathbb{R}^d$; $A : UC_b^2(\mathbb{R}^d) \subset UC_b^0(\mathbb{R}^d) \to UC_b^0(\mathbb{R}^d)$.

Lemma 1 *Given a measure $\mu \in L^\infty(0, T; \mathcal{M}_1(\mathbb{R}^d \times \mathbb{R}^d))$, the function*

$$\eta(t, \mathbf{x}) := \eta\left(t, \mathbf{x}, \{\mu_s\}_{s\in[0,t]}\right) = \int_0^t \left(\int_{\mathbb{R}^d\times\mathbb{R}^d} K_1(\mathbf{x} - \mathbf{x}') |\mathbf{v}'| \mu_s(d\mathbf{x}', d\mathbf{v}')\right) ds$$

is of class $C([0, T]; UC_b^1(\mathbb{R}^d))$.

Proof It follows from the assumption $K_1 \in C_b^1(\mathbb{R}^d)$ and repeated application of Lebesgue dominated convergence theorem and the definition of uniform continuity, applied first to check continuity, then differentiability, finally, uniform continuity of the derivatives. Boundedness of $\eta\left(t, \mathbf{x}, \{Q_N(s)\}_{s\in[0,t]}\right)$ and its derivatives comes from the boundedness of K_1 and its derivatives and from the bound fulfilled by elements of $L^\infty(0, T; \mathcal{M}_1(\mathbb{R}^d \times \mathbb{R}^d))$. □

The equation for C_N is not closed, since it depends on Q_N, which depends on C_N via (2.1). However, let us first understand the regularity of C_N when Q_N is given. So, in the next lemma, the tacit assumption is that Q_N is a well-defined adapted random element of $L^\infty(0, T; \mathcal{M}_1(\mathbb{R}^d \times \mathbb{R}^d))$.

Corollary 1 *C_N is an adapted process with paths of class $C([0, T]; UC_b^1(\mathbb{R}^d))$. Moreover,*

$$\begin{aligned}\|\partial_i C_N(t)\|_\infty &\leqslant c\|\partial_i C_0\|_\infty \\ &+ \int_0^t \frac{c}{\sqrt{t-s}}\left(\|k_2\delta_A\|_\infty + \left\|\eta\left(s, \cdot, \{Q_N(r)\}_{r\in[0,s]}\right)\right\|_\infty \|C_N(s)\|_\infty\right) ds\end{aligned}$$

for some constant $c > 0$.

Proof It is clear that the sum of the first two terms

$$w(t) := e^{tA}C_0 + \int_0^t e^{(t-s)A} k_2 g_\Sigma ds$$

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is an element of $C\left([0,T];UC_b^1\left(\mathbb{R}^d\right)\right)$, since derivatives commute with the heat semigroup and we use the assumption $C_0, g_\Sigma \in UC_b^1\left(\mathbb{R}^d\right)$. Then, taken a single realisation of $\eta\left(t,\mathbf{x},\{Q_N(s)\}_{s\in[0,t]}\right)$, thanks to the previous lemma, it is sufficient to apply the contraction principle to the map

$$C_N \mapsto \Lambda(C_N)(t) := w(t) - \int_0^t e^{(t-s)A}\eta\left(s,\cdot,\{Q_N(r)\}_{r\in[0,s]}\right)C_N(s)\,ds,$$

in the space $C\left([0,T];UC_b^1\left(\mathbb{R}^d\right)\right)$ (first locally in time, then on repeated intervals of equal length). A posteriori, the unique fixed point C_N depends measurably on the randomness, being the limit of iterates that are measurable by direct construction. To check that C_N is adapted, it is sufficient to apply the previous measurability argument to each interval $[0,t]$. Let us prove the inequality in the claim of the corollary. From the mild formulation of the PDE for C_N, we have

$$\partial_i C_N(t) = e^{tA}\partial_i C_0 + \int_0^t \partial_i e^{(t-s)A}\left(k_2 g_\Sigma - \eta\left(s,\cdot,\{Q_N(r)\}_{r\in[0,s]}\right)C_N(s)\right)ds, \tag{5.1}$$

where we have used the fact that $\partial_j e^{tA} f = e^{tA}\partial_j f$ for every $f \in UC_b^1\left(\mathbb{R}^d\right)$. It is well known that there exists a constant $C > 0$ such that

$$\left\|\partial_i e^{tA} f\right\|_\infty \leqslant \frac{C}{\sqrt{t}}\|f\|_\infty, \tag{5.2}$$

for all $t > 0$ and $f \in C_b^0\left(\mathbb{R}^d\right)$. The inequality of the corollary readily follows. □

In fact, due to the regularisation properties of the heat semigroup, the paths of C_N are more regular. We express here only one regularity property, not the maximal one.

Proposition 5.1 *C_N has a.e. path of class $C\left([0,T];UC_b^2\left(\mathbb{R}^d\right)\right)$, and*

$$\begin{aligned}\|\partial_i\partial_j C_N(t)\|_\infty \leqslant{}& c\|\partial_i\partial_j C_0\|_\infty + \int_0^t \frac{c}{\sqrt{t-s}} k_2 \|\partial_j g_\Sigma\|_\infty\,ds \\ &+ \int_0^t \frac{c}{\sqrt{t-s}}\left\|\partial_j\eta\left(s,\cdot,\{Q_N(r)\}_{r\in[0,s]}\right)\right\|_\infty \|C_N(s)\|_\infty\,ds \\ &+ \int_0^t \frac{c}{\sqrt{t-s}}\left\|\eta\left(s,\cdot,\{Q_N(r)\}_{r\in[0,s]}\right)\right\|_\infty \|\partial_j C_N(s)\|_\infty\,ds,\end{aligned}$$

for some constant $c > 0$.

Proof From the mild formulation of the PDE for C_N, as in the previous proof, we have

$$\begin{aligned}\partial_i\partial_j C_N(t) ={}& e^{tA}\partial_i\partial_j C_0 \\ &+ \int_0^t \partial_i e^{(t-s)A}\partial_j\left(k_2 g_\Sigma - \eta\left(s,\cdot,\{Q_N(r)\}_{r\in[0,s]}\right)C_N(s)\right)ds,\end{aligned} \tag{5.3}$$

where we have used the fact that $C_0 \in UC_b^2\left(\mathbb{R}^d\right)$ by assumption. We know from the assumption on g_Σ, from Lemma 1 and Corollary 1, that

$$\partial_j\left(k_2 g_\Sigma - \eta\left(s, \cdot, \{Q_N(r)\}_{r\in[0,s]}\right) C_N(s)\right)$$

has paths in $C\left([0,T]\,;UC_b^0\left(\mathbb{R}^d\right)\right)$. Hence,

$$\begin{aligned}&\left\|\partial_i e^{(t-s)A}\partial_j\left(k_2 g_\Sigma - \eta\left(s, \cdot, \{Q_N(r)\}_{r\in[0,s]}\right) C_N(s)\right)\right\|_\infty \\ &\quad \leqslant \frac{C}{\sqrt{t-s}}\left\|\partial_j\left(k_2 g_\Sigma - \eta\left(s, \cdot, \{Q_N(r)\}_{r\in[0,s]}\right) C_N(s)\right)\right\|_\infty \leqslant \frac{C'}{\sqrt{t-s}},\end{aligned}$$

for a suitable constant $C' > 0$. Since $\frac{1}{\sqrt{t-s}}$ is integrable on $[0, t]$, it follows that

$$\int_0^t \partial_i e^{(t-s)A}\partial_j\left(k_2 g_\Sigma - \eta\left(s, \cdot, \{Q_N(r)\}_{r\in[0,s]}\right) C_N(s)\right) ds$$

is an element of $C\left([0,T]\,;UC_b^0\left(\mathbb{R}^d\right)\right)$. The same holds for $e^{tA}\partial_i\partial_j C_0$ since $C_0 \in UC_b^2\left(\mathbb{R}^d\right)$. Therefore, $\partial_i\partial_j C_N$ is in $C\left([0,T]\,;UC_b^0\left(\mathbb{R}^d\right)\right)$. This proves the regularity claim. The inequality is obtained by the estimates explained during the proof. □

Finally, from the property $0 \leqslant C_0(x) \leqslant C_{\max}$, by classical maximum principle estimates, we deduce:

Lemma 2

$$0 \leqslant C_N(t, \mathbf{x}) \leqslant C_{\max},$$

for all $t \geqslant 0$ *and* $x \in \mathbb{R}^d$.

We have used also the fact that $\eta\left(t, \mathbf{x}, \{Q_N(s)\}_{s\in[0,t]}\right) \geqslant 0$.

5.2 Preliminary estimates on C_N based on $\left|\mathbf{V}^{i,N}\right|$

We summarise the result of the previous section in the following lemma.

Lemma 3 *There exist constants* $a_0, a_1, a_2, a_3, a_4 > 0$ *such that, for* $i, j = 1, ..., d$,

$$\|\partial_i C_N(t)\|_\infty \leqslant a_0 + \int_0^t \frac{a_1}{\sqrt{t-s}}\int_0^s \frac{1}{N}\sum_{i=1}^{N_r} \mathbb{I}_{r\in[T^{i,N},\Theta^{i,N})}\left|\mathbf{V}^{i,N}(r)\right| dr ds, \tag{5.4}$$

$$\begin{aligned}\|\partial_i\partial_j C_N(t)\|_\infty &\leqslant a_2 + \int_0^t \frac{a_3}{\sqrt{t-s}}\int_0^s \frac{1}{N}\sum_{i=1}^{N_r} \mathbb{I}_{r\in[T^{i,N},\Theta^{i,N})}\left|\mathbf{V}^{i,N}(r)\right| dr ds \\ &+ \int_0^t \frac{a_4}{\sqrt{t-s}}\left(\int_0^s \frac{1}{N}\sum_{i=1}^{N_r} \mathbb{I}_{r\in[T^{i,N},\Theta^{i,N})}\left|\mathbf{V}^{i,N}(r)\right| dr\right)\|\partial_j C_N(s)\|_\infty ds.\end{aligned} \tag{5.5}$$

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Proof Recall that

$$\eta\left(s,\mathbf{x},\{Q_N(r)\}_{r\in[0,s]}\right)=\int_0^s\frac{1}{N}\sum_{i=1}^{N_r}\mathbb{I}_{r\in[T^{i,N},\Theta^{i,N})}K_1\left(\mathbf{x}-\mathbf{X}^{i,N}(r)\right)\left|\mathbf{V}^{i,N}(r)\right|dr. \tag{5.6}$$

Hence,

$$\left\|\eta\left(s,\mathbf{x},\{Q_N(r)\}_{r\in[0,s]}\right)\right\|_\infty\leqslant\|K_1\|_\infty\int_0^s\frac{1}{N}\sum_{i=1}^{N_r}\mathbb{I}_{r\in[T^{i,N},\Theta^{i,N})}\left|\mathbf{V}^{i,N}(r)\right|dr, \tag{5.7}$$

$$\left\|\partial_j\eta\left(s,\mathbf{x},\{Q_N(r)\}_{r\in[0,s]}\right)\right\|_\infty\leqslant\|\partial_jK_1\|_\infty\int_0^s\frac{1}{N}\sum_{i=1}^{N_r}\mathbb{I}_{r\in[T^{i,N},\Theta^{i,N})}\left|\mathbf{V}^{i,N}(r)\right|dr. \tag{5.8}$$

From Lemma 2, we have

$$\|C_N\|_\infty\leqslant C_{\max}.$$

Then, from the inequality of Corollary 1, we have

$$\begin{aligned}\|\partial_iC_N(t)\|_\infty&\leqslant c\,\|\partial_iC_0\|_\infty+\int_0^t\frac{c}{\sqrt{t-s}}\|k_2g_\Sigma\|_\infty ds\\&+\int_0^t\frac{cC_{\max}\|K_1\|_\infty}{\sqrt{t-s}}\int_0^s\frac{1}{N}\sum_{i=1}^{N_r}\mathbb{I}_{r\in[T^{i,N},\Theta^{i,N})}\left|\mathbf{V}^{i,N}(r)\right|drds,\end{aligned}$$

hence, we have the first inequality of the lemma, taking

$$a_0=c\,\|\nabla C_0\|_\infty+2ck_2\|g_\Sigma\|_\infty T^{1/2},\quad\text{and}\quad a_1=c\,C_{\max}\|K_1\|_\infty.$$

Now, from the inequality of Proposition 5.1, we have

$$\begin{aligned}\|\partial_i\partial_jC_N(t)\|_\infty&\leqslant c\,\|\partial_i\partial_jC_0\|_\infty+\int_0^t\frac{c}{\sqrt{t-s}}k_2\|\partial_j\delta_A\|_\infty ds\\&+\int_0^t\frac{cC_{\max}\|\partial_jK_1\|_\infty}{\sqrt{t-s}}\int_0^s\frac{1}{N}\sum_{i=1}^{N_r}\mathbb{I}_{r\in[T^{i,N},\Theta^{i,N})}\left|\mathbf{V}^{i,N}(r)\right|drds\\&+\int_0^t\frac{c}{\sqrt{t-s}}\|K_1\|_\infty\int_0^s\frac{1}{N}\sum_{i=1}^{N_r}\mathbb{I}_{r\in[T^{i,N},\Theta^{i,N})}\left|\mathbf{V}^{i,N}(r)\right|dr\,\|\partial_jC_N(s)\|_\infty ds.\end{aligned}$$

Hence, we have the second inequality of the lemma, taking

$$a_2=c\left\|D^2C_0\right\|_\infty+2ck_2\|\nabla g_\Sigma\|_\infty T^{1/2},a_3=c\,C_{\max}\|\nabla K_1\|_\infty\quad\text{and}\quad a_4=c\,\|K_1\|_\infty.$$

□

5.3 Upper bound on the number of particles

Let us recall that N_t denotes the number of tip cells however born up to time $t\geqslant 0$. Clearly, this number depends on the initial number N of tips; we might have written N_t^N to emphasise this dependence, but we have preferred to keep the simpler notation N_t. In

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this section, we establish bounds on N_t; actually, we mean bounds on the ratio

$$\frac{N_t}{N}$$

since this is the only quantity that may have bounds (on the average) independent of N.

Theorem 5.2 *There exists a $\lambda > 0$ such that*

$$\mathbb{E}\left[\sup_{t\in[0,T]} \frac{N_t}{N}\right] \leqslant e^{\lambda T},$$

for all $N \in \mathbb{N}$ and $T \geqslant 0$.

Remark 5.3 The rest of this section is devoted to the proof of this result. In the classical case, when branching of particles occurs only at the particle position, it is usual to introduce a Yule process that dominates the branching process under study: one has to take, as parameter of the Yule process, any number that bounds from above the variable rates of branching of the particles, see for instance [21]. In the case of the system studied here, we are faced with two difficulties. The first one is that branching occurs also along the vessels; there is now a spatial density rate and it is less easy to relate this variable density rate with a constant upper bound of Yule type. This is made even more difficult by the presence of the factor $|v|$ in the branching rates, a factor that is a priori unbounded (see (2.15), and (2.16)). We thus have to work much more than in the classical case.

5.3.1 *Proof of Theorem 5.2*

In order to obtain a preliminary domination from above of the counting process $\{N_t, t \geqslant 0\}$, it is sufficient to obtain a bound for the ratio $\frac{N_t}{N}$ for the case $\gamma = 0$, $\Theta^{i,N} = +\infty$, $i = 1, \ldots, N_t$.

With reference to this modified process, denote by

$$\left(\mathbf{X}^{i,N}(t), \mathbf{V}^{i,N}(t)\right)_{t\geqslant T^{i,N}}, \; i = 1, \ldots, N_t,$$

the active tips of this system. Each i-tip, for $i = 1, \ldots, N_t$, is able to create new tips either by branching at the tip itself, at position $\mathbf{X}^{i,N}(t)$, or by branching along the vessel $\left(\mathbf{X}^{i,N}(s)\right)_{s\in[T^{i,N},t]}$ that it has generated up to time $t \geqslant T^{i,N}$. The time-rate of creation of new particles, either by $\mathbf{X}^{i,N}(t)$ or by its vessel is obtained by the integral on space of the relevant space-time rates (2.13), or (2.15), respectively, and it tells us the rate of creations in time, independently of the position where creation occurs. The time-rate of creation at the tip position is then given by

$$\lambda^{i,1}(t) := \mathbb{I}_{t\geqslant T^{i,N}} \alpha(C_N(t, \mathbf{X}^{i,N}(t)))g_0,$$

where $g_0 = \int_{\mathbb{R}^d} G_{\mathbf{v}_0}(v)dv$; and the time-rate of creation along the vessel $\left(\mathbf{X}^{i,N}(s)\right)_{s\in[T^{i,N},t]}$

is given by

$$\lambda^{i,2}(t) := \mathbb{I}_{t\geqslant T^{i,N}}\beta(C_N(t,\mathbf{X}^{i,N}(t)))g_0\int_0^t \left|\mathbf{V}^{i,N}(s)\right| \mathbb{I}_{s\geqslant T^{i,N}}ds.$$

The two branching processes introduced above can be represented as two inhomogeneous Poisson processes with random rates, $N^{i,1}\left(\int_0^t \lambda^{i,1}(s)\,ds\right)$, and $N^{i,2}\left(\int_0^t \lambda^{i,2}(s)\,ds\right)$, for each particle $i = 1,\ldots,N_t$; here, $N^{i,1}(t)$, $N^{i,2}(t)$, are standard Poisson processes of rate 1. Notice that all processes in the family $\left\{N^{i,1}, N^{i,2}, \mathbf{W}^i; i = 1,\ldots,N_t\right\}$ are independent.

When the process $N^{i,1}\left(\int_0^t \lambda^{i,1}(s)\,ds\right)$ jumps from 0 to 1 a new particle is created at $X^{i,N}(t)$; when the process $N^{i,2}\left(\int_0^t \lambda^{i,2}(s)\,ds\right)$ jumps from 0 to 1 a new particle is created along the vessel $\left(\mathbf{X}^{i,N}(s)\right)_{s\in\left[T^{i,N},t\right]}$ (the position where it is created is assumed to be uniformly distributed along the vessel, with respect to the relevant Hausdorff measure). After each new creation, there is a new tip with a new index, and its own dynamics.

At the analytical level, we have the inequalities

$$\lambda^{i,1}(t) \leqslant \mathbb{I}_{t\geqslant T^{i,N}}\left\|\alpha\right\|_\infty g_0;$$
$$\lambda^{i,2}(t) \leqslant \mathbb{I}_{t\geqslant T^{i,N}}\left\|\beta\right\|_\infty g_0 T\left(C + CT + \sigma\sup_{s\in[0,T]}\left|\int_0^s e^{k_1 r}d\mathbf{W}^i(r)\right|\right),$$

the second one due to the following lemma, used also below in other sections. In the stochastic equation for $\mathbf{V}^{i,N}(t)$, it is not restrictive to assume that the Brownian motion $\mathbf{W}^i(t)$ are defined for all $t\geqslant 0$, not only for $t\geqslant T^{i,N}$.

Lemma 4 *There exists a constant $C > 0$ such that*

$$\left|\mathbf{V}^{i,N}(t)\right| \leqslant e^{-k_1\left(t-T^i\right)}\left|\mathbf{V}_0^{i,N}\right| + \int_{T^i}^t C\,ds + \sigma\int_0^t e^{k_1 s}d\mathbf{W}^i(s)$$

and also

$$\left|\mathbf{V}^{i,N}(t)\right| \leqslant C(1+T) + \sigma\int_0^t e^{k_1 s}d\mathbf{W}^i(s).$$

Proof From the variation of constant formula, we have

$$\begin{aligned}\left|\mathbf{V}^{i,N}(t)\right| \leqslant{}& e^{-k_1\left(t-T^i\right)}\left|\mathbf{V}_0^{i,N}\right| \\ &+ \int_{T^i}^t e^{-k_1(t-s)}f\left(C_N\left(s,\mathbf{X}^{i,N}(s)\right)\right)\left|\nabla C_N\left(s,\mathbf{X}^{i,N}(s)\right)\right|ds \\ &+ \sigma\int_{T^i}^t e^{-k_1(t-s)}d\mathbf{W}^i(s).\end{aligned}$$

Then, we use the bound from above for $f(r)\,r$ by a constant, see (2.4), and the boundedness of $\mathbf{V}_0^{i,N}$ (recall we have assumed that their laws are compact support). □

We now introduce a new dominating process, without space structure, where the times of birth of new particles are denoted by $\widetilde{T}^{i,N}$, for $i = 1, \ldots, \widetilde{N}_t$, having denoted by $\widetilde{N}_t$, the total number of particles at time t in this dominating process.

Given the same standard processes $N^{i,1}, N^{i,2}, W^i$ of the previous process, take now as time-rates of branching

$$\widetilde{\lambda}^{i,1}(t) = \mathbb{I}_{t \geqslant \widetilde{T}^{i,N}} \|\alpha\|_\infty g_0$$
$$\widetilde{\lambda}^{i,2}(t) = \mathbb{I}_{t \geqslant \widetilde{T}^{i,N}} \|\beta\|_\infty g_0 T \left(C + CT + \sigma \sup_{s \in [0,T]} \left| \int_0^s e^{k_1 r} d\mathbf{W}^i(r) \right| \right).$$

We then consider the inhomogeneous Poisson processes

$$N^{i,j}\left(\int_0^t \widetilde{\lambda}^{i,j}(s)\, ds \right), \; i = 1, \ldots, \widetilde{N}_t, \; j = 1, 2;$$

when they jump from 0 to 1, a new particle is created and the system with the two new particles restart with the same rules.

Due to the path by path inequalities $\lambda^{i,j}(t) \leqslant \widetilde{\lambda}^{i,j}(t)$ and the fact that $N^{i,1}(t)$, $N^{i,2}(t)$ are the same, the times when the processes $N^{i,j}(\int_0^t \lambda^{i,j}(s)ds)$ jump from 0 to 1 are posterior to the times when the processes $N^{i,j}(\int_0^t \widetilde{\lambda}^{i,j}(s)ds)$ jump from 0 to 1; precisely, this fact is established in iterative manner, first on the particles that have $T^{i,N} = \widetilde{T}^{i,N} = 0$ (for which the inequalities $\lambda^{i,j}(t) \leqslant \widetilde{\lambda}^{i,j}(t)$ are directly true), then for the newborn particles, where $T^{i,N} \geqslant \widetilde{T}^{i,N}$, hence, $\mathbb{I}_{t \geqslant T^{i,N}} \leqslant \mathbb{I}_{t \geqslant \widetilde{T}^{i,N}}$ and thus again $\lambda^{i,j}(t) \leqslant \widetilde{\lambda}^{i,j}(t)$.

The fact that the dominating process has the times of branching before the original process implies that the total number of particles in the dominating process is larger than in the original process, namely

$$N_t \leqslant \widetilde{N}_t.$$

This is the result we wanted to obtain. Therefore, in order to have bounds from above for N_t, it is sufficient to have them for $\widetilde{N}_t$. Until now, however, we have solved only one of the difficulties posed by branching along paths: we have dominated the space-dependent original process by a much simpler one, without space structure. However, the dominating process is not Yule, because the rate $\widetilde{\lambda}^{i,2}(t)$ is random, it depends on W^i. This dominating process, without spatial structure, is of Cox-type, being made of inhomogeneous Poisson processes with random rates of jump, but independent of the process itself. Hence, we are now faced with the second difficulty, namely estimating the number of particles in this new process.

When we deal with the dominating process itself, without exploiting the stochastic coupling with the original one, we may formalise it by saying that we have random variables Z^i distributed as

$$Z^i \overset{Law}{\sim} \|\alpha\|_\infty g_0 + C \|\beta\|_\infty g_0 T (T+1) + \|\beta\|_\infty g_0 T \sigma \sup_{s \in [0,T]} \left| \int_0^s e^{k_1 r} d\mathbf{W}^i(r) \right|,$$

that are independent and equally distributed. Particle i has a rate of branching given by

$$\widetilde{\lambda}^i(t) = \mathbb{I}_{t \geqslant \widetilde{T}^{i,N}} Z^i.$$

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We perform now a further reduction. The process we are considering starts with N particles. But due to its nature, completely non interacting, it is the same as N independent copies of the same process starting from one particle. Thus,

$$\widetilde{N}_t = \sum_{k=1}^{N} \widetilde{N}_t^{(k)},$$

where for each k, $\widetilde{N}_t^{(k)}$ is a process like the dominating one, but with only one particle at the beginning; and the processes with cardinality $\widetilde{N}_t^{(k)}$ are independent and equally distributed. We have

$$\mathbb{E}\left[\left(\frac{\widetilde{N}_t}{N}\right)^p\right] = \mathbb{E}\left[\left(\frac{1}{N}\sum_{k=1}^{N}\widetilde{N}_t^{(k)}\right)^p\right] \leqslant \mathbb{E}\left[\frac{1}{N}\sum_{k=1}^{N}\left(\widetilde{N}_t^{(k)}\right)^p\right]$$
$$= \frac{1}{N}\sum_{k=1}^{N}\mathbb{E}\left[\left(\widetilde{N}_t^{(k)}\right)^p\right] = \mathbb{E}\left[\left(\widetilde{N}_t^{(1)}\right)^p\right].$$

Hence, for the sake of p-moments of $\frac{\widetilde{N}_t}{N}$ (and a fortiori $\frac{N_t}{N}$), it is sufficient to bound the p-moments of $\widetilde{N}_t^{(1)}$. A similar fact holds for exponential moments, with a little more work. In the sequel, we shall denote $\widetilde{N}_t^{(1)}$ by $\overline{N}_t$.

Let us analyse the dominating process $\overline{N}_t$ with analogous formalism as the original space-dependent process; we do not need however to index by N all quantities, since this process starts with one particle only. Let us denote by $\overline{T}^i$ the birth time of particle i, by $\overline{Z}^i$ independent and identically distributed (i.i.d.) random variables as those above, and prescribe that the first particle has index $i = 1$, the second particle (the first newborn) has index $i = 2$, the third one $i = 3$, and so on. Then, branching is described by a random measure $\overline{\Phi}$ on $\mathcal{B}_{\mathbb{R}^+}$ with compensator given by

$$\sum_{i=1}^{\overline{N}_s} \mathbb{I}_{s \geqslant \overline{T}^i} \overline{Z}^i ds.$$

Moreover, the random measure $\overline{\Phi}$ is given by $\overline{\Phi}(ds) = \sum_{i=1}^{\overline{N}_s} \delta_{\overline{T}^i}(ds)$. Therefore, $\overline{N}_t$ satisfies

$$\overline{N}_t = 1 + \int_0^t \sum_{i=1}^{\overline{N}_s} \mathbb{I}_{s \geqslant \overline{T}^i} \overline{Z}^i ds + \overline{M}_t,$$

where $\overline{M}_t$ is the martingale

$$\overline{M}_t = \int_0^t \overline{\Phi}(ds) - \int_0^t \sum_{i=1}^{\overline{N}_s} \mathbb{I}_{s \geqslant \overline{T}^i} \overline{Z}^i ds.$$

We thus have

$$\mathbb{E}\left[\overline{N}_t\right] = 1 + \int_0^t \mathbb{E}\left[\sum_{i=1}^{\overline{N}_s} \mathbb{I}_{s \geqslant \overline{T}^i} \overline{Z}^i\right] ds$$
$$\leqslant 1 + \int_0^t \mathbb{E}\left[\sum_{i=1}^{\overline{N}_s} \overline{Z}^i\right] ds.$$

Wald's identity (proved below) tells us that $\mathbb{E}\left[\sum_{i=1}^{\overline{N}_s} \overline{Z}^i\right] = \mathbb{E}\left[\overline{Z}^1\right] \mathbb{E}\left[\overline{N}_s\right]$; hence,

$$\mathbb{E}\left[\overline{N}_t\right] \leqslant 1 + \int_0^t \mathbb{E}\left[\overline{Z}^1\right] \mathbb{E}\left[\overline{N}_s\right] ds,$$

which implies

$$\mathbb{E}\left[\overline{N}_t\right] \leqslant e^{\mathbb{E}\left[\overline{Z}^1\right] t}.$$

Since $\mathbb{E}\left[\sup_{s\in[0,T]} \left|\int_0^s e^{k_1 r} d\mathbf{W}^1(r)\right|\right] < \infty$, we have completed the proof of the theorem, with $\lambda = E\left[\overline{Z}^1\right]$.

Let us explain the validity of Wald's identity. Notice that $\overline{N}_t$ increases from value n to $n+1$ at time $\overline{T}_{n+1}$; this time depends only on the first n particles; hence, on the r.v.'s $Z^1, ..., Z^n$. Hence, $\overline{T}_{n+1}$ and Z^{n+1} are independent. Therefore,

$$\mathbb{E}\left[\sum_{n=1}^{\overline{N}_t} \overline{Z}^n\right] = \sum_{k=1}^{\infty} \sum_{n=1}^{k} \mathbb{E}\left[\overline{Z}^n 1_{\overline{N}_t = k}\right] = \sum_{n=1}^{\infty} \sum_{k=n}^{\infty} \mathbb{E}\left[\overline{Z}^n 1_{\overline{N}_t = k}\right]$$
$$= \sum_{n=1}^{\infty} \mathbb{E}\left[\overline{Z}^n 1_{\overline{N}_t \geqslant n}\right] = \sum_{n=1}^{\infty} \mathbb{E}\left[\overline{Z}^n 1_{T_n \leqslant t}\right] = \sum_{n=1}^{\infty} \mathbb{E}\left[\overline{Z}^n\right] P\left(T_n \leqslant t\right)$$
$$= \mathbb{E}\left[\overline{Z}\right] \sum_{n=1}^{\infty} P\left(\overline{N}_t \geqslant n\right) = \mathbb{E}\left[\overline{Z}\right] \mathbb{E}\left[\overline{N}_t\right].$$

5.4 Final bounds on C_N

Proposition 5.4 *For every $\epsilon > 0$, there is $R > 0$ such that*

$$\mathbb{P}\left(\sup_{t\in[0,T]} \left\|\nabla C_N(t)\right\|_E > R\right) \leqslant \epsilon, \tag{5.9}$$

$$\mathbb{P}\left(\sup_{t\in[0,T]} \left\|D^2 C_N(t)\right\|_E > R\right) \leqslant \epsilon, \tag{5.10}$$

for all $N \in \mathbb{N}$.

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Proof Using Lemma 4 in (5.4), we get

$$\begin{aligned}\|\partial_i C_N(t)\|_\infty &\leqslant a_0 + \int_0^t \frac{a_1}{\sqrt{t-s}} \int_0^s \frac{1}{N}\sum_{i=1}^{N_r} \mathbb{I}_{r\in[T^{i,N},\Theta^{i,N})} \left|\mathbf{V}^{i,N}(r)\right| drds \\ &\leqslant a_0 + \int_0^t \frac{a_1}{\sqrt{t-s}} \int_0^s \frac{N_r}{N} C(1+T)\, drds \\ &\quad + \int_0^t \frac{a_1}{\sqrt{t-s}} \int_0^s \frac{1}{N}\sum_{i=1}^{N_r} \left(\sigma \int_0^r e^{k_1 u} d\mathbf{W}^i(u)\right) drds \\ &\leqslant C + C \sup_{r\in[0,T]} \frac{N_r}{N} + C\frac{1}{N} \sum_{i=1}^{\sup_{r\in[0,T]} N_r} \sup_{r\in[0,T]} \left|\int_0^r e^{k_1 u} d\mathbf{W}^i(u)\right| ds,\end{aligned}$$

for some constant $C > 0$. We apply the estimates and arguments of the previous section (dominating $\sup_{r\in[0,T]} N_r$ from above as in that section), including Wald's identity for the second term, to get

$$\mathbb{E}\left[\sup_{t\in[0,T]} \|\nabla C_N(t)\|_E\right] \leqslant C$$

and thus (5.9). Using this bound and the same arguments, one gets (5.10) (here a bound in expected value is not known). □

5.5 End of the proof

Denote by $\mathcal{M}_+\left(\mathbb{R}^d \times \mathbb{R}^d\right)$, the space of finite positive Borel measures on $\mathbb{R}^d \times \mathbb{R}^d$. Following [32], Chapter 1, (see [24], Chapter 4), weak convergence of measures in $\mathcal{M}\left(\mathbb{R}^d \times \mathbb{R}^d\right)$ is metrisable and a metric is given by

$$\delta(\mu_1, \mu_2) = \sum_{k=1}^{\infty} 2^{-k} \left(|\mu_1(\phi_k) - \mu_2(\phi_k)| \wedge 1\right),$$

where $\{\phi_k\}$ is a suitable dense countable set in $C_b\left(\mathbb{R}^d \times \mathbb{R}^d\right)$, and one can take ϕ_k of class $UC_b^1\left(\mathbb{R}^d \times \mathbb{R}^d\right)$, the space of bounded uniformly continuous functions on $\mathbb{R}^d \times \mathbb{R}^d$, with their first derivatives. Consider the space $\mathcal{Y} := \mathbb{D}\left([0,T]; \mathcal{M}_+\left(\mathbb{R}^d \times \mathbb{R}^d\right)\right)$ endowed with the uniform topology. Our first aim in this section is to prove that the family of laws of Q_N, $N \in \mathbb{N}$, is tight on $\mathcal{Y}$, namely for every $\epsilon > 0$ there is a compact set $K_\epsilon \subset \mathcal{Y}$ such that $P(Q_N \in \mathcal{K}_\epsilon) > 1 - \epsilon$. From Proposition 1.7 of [24], if we show that for every $k \in \mathbb{N}$ the family of laws on $\mathbb{D}([0,T])$ (with the uniform topology) of the real-valued stochastic processes $\langle Q_N(t), \phi_k\rangle$, $N \in \mathbb{N}$, is tight, then the family of laws of Q_N, $N \in \mathbb{N}$, is tight on $\mathcal{Y}$. For every $k \in \mathbb{N}$, thanks to Aldous criterion (see [24], Chapter 4), it is sufficient to prove two conditions: for every $\epsilon > 0$ there is $R > 0$ such that

$$\mathbb{P}\left(|\langle Q_N(t), \phi_k\rangle| > R\right) \leqslant \epsilon, \tag{5.11}$$

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for all $t \in [0,T]$ and $N \in \mathbb{N}$; and that for every $\epsilon > 0$

$$\lim_{\eta\to 0}\limsup_{N\to\infty}\sup_{\substack{\tau\in\Upsilon_T\\ \theta\in[0,\eta]}} \mathbb{P}\left(\left|\langle Q_N(\tau+\theta),\phi_k\rangle - \langle Q_N(\tau),\phi_k\rangle\right| > \epsilon\right) = 0, \tag{5.12}$$

where Υ_T is the family of stopping times bounded by T.

Proposition 5.5 *Conditions (5.11) and (5.12) hold true.*

Proof See Appendix B. □

We have proved that the family of laws of $\{Q_N, N \in \mathbb{N}\}$, is tight on $\mathcal{Y}$. The tightness of the sequence of laws of $\{C_N, N \in \mathbb{N}\}$, on $C\left([0,T]; C^1_{loc}\left(\mathbb{R}^d\right)\right)$ can be proved using (5.9)–(5.10) and a few classical additional PDE arguments for the compactness in time. A posteriori, using the mild formulations of the equations for C_N and C and the uniform convergence of $\eta(t,\mathbf{x},\{Q_N(s)\}_{s\in[0,t]})$ to $\eta(t,\mathbf{x},\{p_s\}_{s\in[0,t]})$, we deduce convergence of C_N to C in $C\left([0,T]; UC^1_b\left(\mathbb{R}^d\right)\right)$. We omit the details.

Therefore, the family of laws of the pair $\{(Q_N, C_N), N \in \mathbb{N}\}$, is tight on $\mathcal{Y} \times C\left([0,T]; UC^1_b\left(\mathbb{R}^d\right)\right)$. By Prohorov theorem, there exist weakly convergent subsequences. A uniform in N bound in expectation on Q_N in $L^\infty\left(0,T;\mathcal{M}_1\left(\mathbb{R}^d \times \mathbb{R}^d\right)\right)$ implies that that the same bound holds for any limit point of (Q_N, C_N).

The proof that the limit is supported on solutions of the limit system is again classical (see, e.g., [24], Chapter 4). The conclusion of the proof of Theorem 4.1 has been outlined at the beginning of the section.

6 Concluding remarks

As we have mentioned in Section 1, a large literature has been devoted to the mathematical modelling of angiogenesis, including tumour-driven angiogenesis, and retinal vasculogenesis. The existing literature offers a variety of interesting results based on hybrid models, consisting of discrete and stochastic models at the scale of cells, coupled with continuous models for the underlying fields that drive the dynamics of the cells. Interesting numerical simulations have been carried out, which exhibit realistic behaviours.

Actually, to the knowledge of the authors, for the kind of models considered here, a rigorous proof of the widely accepted mean-field approximation of the RDEs governing the underlying fields had not yet been given, though heuristic derivations are available for various models.

Eventually, in this paper, the authors have been able to derive mean field equations with the required, non trivial, rigorous approach. The reader may notice that throughout the proofs, peculiar mathematical structures have been adopted for functional responses; it is important to remark that these modifications, though required as sufficient conditions for the rigorous mathematical treatment, may inspire a more realistic structure of the proposed model.

An interesting fall out of the convergence results is the identification of a limit mean field equation for the relevant spatial measure of active tips. This equation, different from existing ones, presents a very peculiar structure, corrected with respect to the one anticipated in [4, 5] via heuristic derivations, thanks to a more rigorous treatment. It has been left to additional investigation a proper proof of the existence of a density for this measure, as mentioned in Remark 4.4.

The proofs presented here are based on several methodologies. The estimates on the TAF field are based on methods of semigroup theory, see for instance [30]. The estimates on tip cells contain a very difficult technical question, the control of the average number of cells, completely new with respect to classical Yule processes because of the generation along the paths; this is handled in Section 5.3 using a coupling argument with a Cox-type process and employing Wald's identity. Tightness and convergence argument are classical, see [24], [28]. The proof of uniqueness of measure-valued solutions is based on a strategy, which has been used sometimes in the literature [28], but estimates are more demanding than in classical cases and include specialised results like Lemma 5, see for instance [18] for related techinques. The proof of strict positivity of solutions is based on ideas from the theory of inverse uniqueness, see for instance [34].

Future investigations may concern the qualitative behaviour of the limiting equations, including regularity issues like the one mentioned in Remark 4.4, a rigorous justification of the statistical many replicas approach (see [5]) in contrast to the mean field approach presented here, and the numerical simulation of the system.

A more ambitious project would be to extend the modelling to the later evolution of the system, by including blood flow in the vessel network. Some attempts along this direction can be found in [26].

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Appendix A Strict positivity of the solution of the mean field PDE system

Let (p, C) be the solution on $[0, T]$ of the PDE system, with p_0 a non-negative measure. For every $t \in [0, T]$, p_t is also a non-negative measure. Let us denote by

$$M_t := \int_{\mathbb{R}^d \times \mathbb{R}^d} p_t (d\mathbf{x}, d\mathbf{v}),$$

its total mass. Moreover, let us denote by

$$M_t^N := \int_{\mathbb{R}^d \times \mathbb{R}^d} Q_N (t) (d\mathbf{x}, d\mathbf{v}),$$

the total empirical mass.

The following theorem excludes extinction of the tip cells, in the PDE limit, during any finite time interval $[0, T]$; as a consequence, for large N, the same holds for the random empirical measure of tips.

Theorem A.1 *If $M_0 > 0$ then, for any choice of $T > 0$,*

$$M_t > 0 \text{ for every } t \in [0, T].$$

More precisely, there is a constant $C_{p_0,T} > 0$, depending on p_0 and T such that $M_t \geqslant C_{p_0,T}$ for all $t \in [0, T]$. Due to the weak convergence result for the empirical measures, we also have

$$\lim_{N\to\infty} \mathbb{P}\left(M_t^N \geqslant C_{p_0,T}/2 \text{ for all } t \in [0, T]\right) = 1.$$

Proof In the weak formulation (21) of the equation for p_t, let us take the test function $\phi(\mathbf{x}, \mathbf{v})$ identically equal to 1 (more precisely, one has to take the limit of test functions converging to 1; we omit the details). We get, with $g_0 := \int_{\mathbb{R}^d} G_{v_0}(\mathbf{v})\, d\mathbf{v}$,

$$\begin{aligned} M_t = M_0 &+ g_0 \int_0^t \int_{\mathbb{R}^d} \alpha (C_s (\mathbf{x})) (\pi_1 p_s) (d\mathbf{x})\, ds \\ &+ g_0 \int_0^t \int_{\mathbb{R}^d} \beta (C_s (\mathbf{x})) \int_0^s \widetilde{p}_r (d\mathbf{x})\, dr ds \\ &- \gamma \int_0^t \int_{\mathbb{R}^d \times \mathbb{R}^d} h\left(\int_0^s (K_2 * \widetilde{p}_r)(\mathbf{x})\, dr\right) p_s (d\mathbf{x}, d\mathbf{v})\, ds. \end{aligned}$$

Since $M_0 > 0$ and the function M_t is continuous (p_t is weakly continuous), there is an open interval $(0, \tau)$, where $M_t > 0$, such that either $\tau = +\infty$, or $\tau < \infty$ and $M_\tau = 0$. We have to exclude the second case. For $t \in (0,\tau)$, we have

$$-\log M_t = -\log M_0 - \int_0^t \frac{1}{M_s}\frac{d}{ds}M_s ds,$$

hence, from the previous identity

$$\begin{aligned}-\log M_t = &-\log M_0 - \int_0^t \frac{1}{M_s} g_0 \int_{\mathbb{R}^d} \alpha\left(C_s(\mathbf{x})\right)(\pi_1 p_s)(d\mathbf{x})\, ds \\ &- \int_0^t \frac{1}{M_s} g_0 \int_{\mathbb{R}^d} \beta\left(C_s(\mathbf{x})\right) \int_0^s \widetilde{p}_r(d\mathbf{x})\, dr ds \\ &+ \int_0^t \frac{1}{M_s}\gamma \int_{\mathbb{R}^d\times\mathbb{R}^d} h\left(\int_0^s (K_2 * \widetilde{p}_r)(\mathbf{x})\, dr\right) p_s(d\mathbf{x}, d\mathbf{v})\, ds.\end{aligned}$$

Since $g_0 \geqslant 0$, $\alpha(\cdot) \geqslant 0$, $\beta(\cdot) \geqslant 0$, $\pi_1 p_s$ and $\widetilde{p}_r$ are non-negative measures, the first two integral terms are positive; hence, we have

$$-\log M_t \leqslant -\log M_0 + \int_0^t \frac{1}{M_s}\gamma \int_{\mathbb{R}^d\times\mathbb{R}^d} h\left(\int_0^s (K_2 * \widetilde{p}_r)(\mathbf{x})\, dr\right) p_s(d\mathbf{x}, d\mathbf{v})\, ds.$$

Since h is bounded, we have

$$\begin{aligned}-\log M_t &\leqslant -\log M_0 + \gamma \int_0^t \frac{1}{M_s} \int_{\mathbb{R}^d\times\mathbb{R}^d} p_s(d\mathbf{x}, d\mathbf{v})\, ds \\ &= -\log M_0 + \gamma \int_0^t 1 ds \leqslant -\log M_0 + \gamma T.\end{aligned}$$

It follows that

$$M_t \geqslant C_{p_0,T} := \exp\left(\log M_0 - \gamma T\right) > 0.$$

The last claim of the theorem, on M_t^N, is direct consequence of the convergence in probability of $Q_N(t)$ to p_t, in $L^\infty\left(0,T;\mathcal{M}_1\left(\mathbb{R}^d\times\mathbb{R}^d\right)\right)$. □

Appendix B Proof of Proposition 5.5

Step 1. To prove the first condition, notice that

$$\langle Q_N(t), \phi_k\rangle = \int_{\mathbb{R}^d\times\mathbb{R}^d} \phi_k(\mathbf{x},\mathbf{v})\, Q_N(t)(d\mathbf{x}, d\mathbf{v}) \leqslant \|\phi_k\|_\infty \frac{N_t}{N}$$

Hence, we deduce (5.11) from Chebyshev inequality and Theorem 5.2.

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Step 2. To prove the second condition, notice that, from the identity satisfied by Q_N,

$$\begin{aligned}
&\langle Q_N(\tau+\theta), \phi_k\rangle - \langle Q_N(\tau), \phi_k\rangle = \\
&= \int_\tau^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d} \mathbf{v}\cdot\nabla_x\phi_k(\mathbf{x},\mathbf{v})\, Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds \\
&\quad + \int_\tau^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d} \left[f(C_N(s,\mathbf{x}))\nabla C_N(s,\mathbf{x}) - k_1\mathbf{v}\right] \\
&\quad \times \nabla_v\phi_k(\mathbf{x},\mathbf{v})\, Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds \\
&\quad + \int_\tau^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d} \frac{\sigma^2}{2}\Delta_v\phi_k(\mathbf{x},\mathbf{v})\, Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds \\
&\quad + \int_\tau^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d} \phi_G^k(\mathbf{x})\,\alpha(C_N(s,\mathbf{x}))Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds \\
&\quad + \int_\tau^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d} \phi_G^k(\mathbf{x})\,\beta(C_N(s,\mathbf{x}))\,|\mathbf{v}|\int_0^s Q_N(r)(d\mathbf{x},d\mathbf{v})\,drds \\
&\quad - \gamma\int_\tau^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d} \phi_k(\mathbf{x},\mathbf{v})\, g\left(s,\mathbf{x},\{Q_N(r)\}_{r\in[0,s]}\right) Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds \\
&\quad + \widetilde{M}_N^k(\tau+\theta) - \widetilde{M}_N^k(\tau),
\end{aligned}$$

where $\phi_G^k(\mathbf{x}) := \int_{\mathbb{R}^d} G_{v_0}(\mathbf{v})\phi_k(\mathbf{x},\mathbf{v})\,d\mathbf{v}$ and $\widetilde{M}_N^k(t)$ is the martingale corresponding to the test function ϕ_k. Then,

$$\begin{aligned}
&|\langle Q_N(\tau+\theta), \phi_k\rangle - \langle Q_N(\tau), \phi_k\rangle| \\
&\leqslant \|\nabla_x\phi_k\|_\infty \int_\tau^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d} |\mathbf{v}|\, Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds \\
&\quad + \|\nabla_v\phi_k\|_\infty \int_\tau^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d} \left[C_f + k_1|\mathbf{v}|\right] Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds \\
&\quad + \frac{\sigma^2}{2}\|\Delta_v\phi_k\|_\infty \int_\tau^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d} Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds \\
&\quad + \|G_{v_0}\|_1\|\phi_k\|_\infty\|\alpha\|_\infty \int_\tau^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d} Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds \\
&\quad + \|G_{v_0}\|_1\|\phi_k\|_\infty\|\beta\|_\infty \int_\tau^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d} |\mathbf{v}|\int_0^s Q_N(r)(d\mathbf{x},d\mathbf{v})\,drds \\
&\quad + \gamma\|\phi_k\|_\infty\|g\|_\infty \int_\tau^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d} Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds \\
&\quad + \left|\widetilde{M}_N^k(\tau+\theta) - \widetilde{M}_N^k(\tau)\right|.
\end{aligned}$$

Using this inequality, if we prove the validity of the limit (5.12) for each term of this sum, then we have proved (5.12). In the next steps, we shall analyse the various terms.

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Step 3. Some of the terms above have the form ($C>0$ is a constant)

$$C\int_{\tau}^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d}Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds=C\int_{\tau}^{\tau+\theta}\frac{N_s}{N}ds\leqslant C\theta\sup_{s\in[0,T]}\frac{N_s}{N}$$

and therefore, for such terms,

$$\begin{aligned}&\lim_{\varsigma\to0}\limsup_{N\to\infty}\sup_{\substack{\tau\in\Upsilon_T\\ \theta\in[0,\varsigma]}}\mathbb{E}\left[C\int_{\tau}^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d}Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds\right]\\&\leqslant C\lim_{\varsigma\to0}\limsup_{N\to\infty}\varsigma\,\mathbb{E}\left[\sup_{s\in[0,T]}\frac{N_s}{N}\right]=0,\end{aligned}$$

because $\limsup_{N\to\infty}\mathbb{E}\left[\sup_{s\in[0,T]}\frac{N_s}{N}\right]$ is finite by Theorem 5.2. Therefore, for such terms, we have (5.12) by Chebishev inequality.

Step 4. Other terms above have the form

$$C\int_{\tau}^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d}|\mathbf{v}|\,Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds=C\int_{\tau}^{\tau+\theta}\frac{1}{N}\sum_{i=1}^{N_s}\mathbb{I}_{s\in[T^{i,N},\Theta^{i,N})}\left|\mathbf{V}^{i,N}(t)\right|ds. \tag{B 1}$$

From Lemma 4, we have

$$\begin{aligned}&\leqslant C'\int_{\tau}^{\tau+\theta}\left(\frac{N_s}{N}+\frac{1}{N}\sum_{i=1}^{N_s}\sup_{r\in[0,T]}\left|\int_0^r e^{k_1u}d\mathbf{W}^i(u)\right|\right)ds\\&=C'\theta\sup_{s\in[0,T]}\left(\frac{N_s}{N}+\frac{1}{N}\sum_{i=1}^{N_s}\sup_{r\in[0,T]}\left|\int_0^r e^{k_1u}d\mathbf{W}^i(u)\right|\right),\end{aligned}$$

for a new constant $C'>0$. We thus have

$$\begin{aligned}&\lim_{\varsigma\to0}\limsup_{N\to\infty}\sup_{\substack{\tau\in\Upsilon_T\\ \theta\in[0,\varsigma]}}\mathbb{E}\left[C\int_{\tau}^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d}|\mathbf{v}|\,Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds\right]\\&\leqslant C'\lim_{\varsigma\to0}\limsup_{N\to\infty}\varsigma\,\mathbb{E}\left[\sup_{s\in[0,T]}\left(\frac{N_s}{N}+\frac{1}{N}\sum_{i=1}^{N_s}\sup_{r\in[0,T]}\left|\int_0^r e^{k_1u}d\mathbf{W}^i(u)\right|\right)\right].\end{aligned}$$

The limit is zero concerning the first term, the one with $\frac{N_s}{N}$. Let us discuss the second term. We have

$$\sup_{s\in[0,T]}\frac{1}{N}\sum_{i=1}^{N_s}\sup_{r\in[0,T]}\left|\int_0^r e^{k_1u}d\mathbf{W}^i(u)\right|=\frac{1}{N}\sum_{i=1}^{N_T^*}\sup_{r\in[0,T]}\left|\int_0^r e^{k_1u}d\mathbf{W}^i(u),\right|$$

where $N_T^*=\sup_{s\in[0,T]}N_s$. Then, we apply the domination argument of Section 5.3 and Wald's identity, to deduce

$$\mathbb{E}\left[\frac{1}{N}\sum_{i=1}^{N_T^*}\sup_{r\in[0,T]}\left|\int_0^r e^{k_1u}d\mathbf{W}^i(u)\right|\right]\leqslant\mathbb{E}\left[\overline{N}_T\right]\mathbb{E}\left[\sup_{r\in[0,T]}\left|\int_0^r e^{k_1u}d\mathbf{W}^i(u)\right|\right]\leqslant C'', \tag{B 2}$$

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for a constant $C'' > 0$, for every N. We thus deduce

$$\lim_{\varsigma\to 0}\limsup_{N\to\infty}\sup_{\substack{\tau\in\Upsilon_T\\ \theta\in[0,\varsigma]}}\mathbb{E}\left[C\int_\tau^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d}|\mathbf{v}|\,Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds\right]=0$$

and, therefore, we have (5.12) by Chebishev inequality, for the terms just discussed. The proof for the term

$$\int_\tau^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d}|\mathbf{v}|\int_0^s Q_N(r)(d\mathbf{x},d\mathbf{v})\,drds$$

is similar.

Step 5. Finally, we have to prove

$$\lim_{\varsigma\to 0}\limsup_{N\to\infty}\sup_{\substack{\tau\in\Upsilon_T\\ \theta\in[0,\varsigma]}}\mathbb{P}\left(\left|\widetilde{M}_N^k(\tau+\theta)-\widetilde{M}_N^k(\tau)\right|>\epsilon\right)=0. \tag{B 3}$$

We prove this separately for each one of the three martingales which compose $\widetilde{M}_N^k$, that we call $\widetilde{M}_{i,N}^k$, $i=1,2,3$. We follow a standard approach (see, for instance, [24]). We use the fact that

$$\left(\widetilde{M}_{1,N}^k(t)\right)^2-\int_0^t\frac{1}{N^2}\sum_{i=1}^{N_s}\left|\nabla_v\phi_k(X^{i,N}(s),V^{i,N}(s))\right|^2\mathbb{I}_{s\in[T^{i,N},\Theta^{i,N})}ds$$

$$\begin{aligned}&\left(\widetilde{M}_{2,N}^k(t)\right)^2\\ &-\int_0^t\int_{\mathbb{R}^d\times\mathbb{R}^d}\int_{\mathbb{R}^d}G_{v_0}(\mathbf{v})\phi_k^2\left(\mathbf{x},\mathbf{v}'\right)d\mathbf{v}'\alpha(C_N(s,\mathbf{x}))Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds\\ &-\int_0^t\int_{\mathbb{R}^d\times\mathbb{R}^d}\int_{\mathbb{R}^d}G_{v_0}(\mathbf{v})\phi_k^2\left(\mathbf{x},\mathbf{v}'\right)d\mathbf{v}'\beta(C_N(s,\mathbf{x}))\,|\mathbf{v}|\int_0^s Q_N(r)(d\mathbf{x},d\mathbf{v})\,drds\end{aligned}$$

$$\left(\widetilde{M}_{3,N}^k(t)\right)^2-\int_0^t\int_{\mathbb{R}^d\times\mathbb{R}^d}\int_{\mathbb{R}^d}\phi_k^2(\mathbf{x},\mathbf{v})\,\gamma g\left(s,\mathbf{x},\{Q_N(r)\}_{r\in[0,s]}\right)Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds$$

are martingales. One has

$$\begin{aligned}\mathbb{E}\left[\left|\widetilde{M}_{1,N}^k(\tau+\theta)-\widetilde{M}_{1,N}^k(\tau)\right|^2\right]&=\mathbb{E}\left[\left|\widetilde{M}_{1,N}^k(\tau+\theta)\right|^2\right]-E\left[\left|\widetilde{M}_{1,N}^k(\tau)\right|^2\right]\\ &=\mathbb{E}\left[\int_\tau^{\tau+\theta}\frac{1}{N^2}\sum_{i=1}^{N_s}\left|\nabla_v\phi_k(X^{i,N}(s),V^{i,N}(s))\right|^2\mathbb{I}_{s\in[T^{i,N},\Theta^{i,N})}ds\right]\\ &\leqslant\theta\,\|\nabla_v\phi_k\|_\infty^2\,\mathbb{E}\left[\sup_{s\in[0,T]}\frac{N_s}{N^2}\right]\end{aligned}$$

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and this implies (B 3) for $\widetilde{M}^k_{1,N}$. Similarly,

$$\mathbb{E}\left[\left|\widetilde{M}^k_{2,N}(\tau+\theta)-\widetilde{M}^k_{2,N}(\tau)\right|^2\right]$$
$$=\mathbb{E}\left[\int_\tau^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d}\int_{\mathbb{R}^d}G_{\mathbf{v}_0}(\mathbf{v})\phi_k^2\left(\mathbf{x},\mathbf{v}'\right)d\mathbf{v}'\alpha(C_N(s,\mathbf{x}))Q_N(s)(d\mathbf{x},d\mathbf{v})\,ds\right]$$
$$+\mathbb{E}\left[\int_\tau^{\tau+\theta}\int_{\mathbb{R}^d\times\mathbb{R}^d}\int_{\mathbb{R}^d}G_{\mathbf{v}_0}(\mathbf{v})\phi_k^2\left(\mathbf{x},\mathbf{v}'\right)d\mathbf{v}'\beta(C_N(s,\mathbf{x}))\,|\mathbf{v}|\int_0^s Q_N(r)(d\mathbf{x},d\mathbf{v})\,drds\right].$$

We bound these terms as above by $C\theta$; we do not repeat the computations. Using the fact that g is bounded, the proof for $\widetilde{M}^k_{3,N}$ is similar. The proof of the proposition is complete.

Appendix C Proof of Theorem 4.3

The existence claim of Theorem 4.3 follows from the tightness and passage to the limit result proved above, with the limit taken along any converging subsequence. Here, we prove uniqueness; it provides the convergence of the full sequence above.

We will denote by $\Lambda_t\left(C_t,p_t,\{\widetilde{p}_r\}_{r\in[0,t]}\right)(d\mathbf{x},d\mathbf{v})$ the measure defined on test functions $\psi\in C_c^\infty\left(\mathbb{R}^d\times\mathbb{R}^d\right)$ as

$$\int_{\mathbb{R}^d\times\mathbb{R}^d}\psi(\mathbf{x},\mathbf{v})\,\Lambda_t\left(C_t,p_t,\{\widetilde{p}_r\}_{r\in[0,t]}\right)(d\mathbf{x},d\mathbf{v})$$
$$=\int_{\mathbb{R}^d\times\mathbb{R}^d}\psi(\mathbf{x},\mathbf{v})\,G_{v_0}(\mathbf{v})\left(\alpha(C_t(\mathbf{x}))(\pi_1p_t)(d\mathbf{x})+\beta(C_t(\mathbf{x}))\int_0^t\widetilde{p}_r(d\mathbf{x})\,dr\right)d\mathbf{v}$$
$$-\gamma\int_{\mathbb{R}^d\times\mathbb{R}^d}\psi(\mathbf{x},\mathbf{v})\,h\left(\int_0^t(K_2*\widetilde{p}_r)(\mathbf{x})\,dr\right)p_t(d\mathbf{x},d\mathbf{v}),\tag{C 1}$$

where $(K_2*\widetilde{p}_r)(\mathbf{x})$ is the function defined as

$$(K_2*\widetilde{p}_r)(\mathbf{x})=\int_{\mathbb{R}^d}K_2\left(\mathbf{x}-\mathbf{x}'\right)\widetilde{p}_r(d\mathbf{x}').$$

We may shorten the notations and set

$$\Lambda_t(C_t,p_t,\widetilde{p}_\cdot):=\Lambda_t\left(C_t,p_t,\{\widetilde{p}_r\}_{r\in[0,t]}\right)(d\mathbf{x},d\mathbf{v});$$

$$\eta_t(p_\cdot):=\eta\left(t,\mathbf{x},\{p_r\}_{r\in[0,t]}\right):=\int_0^t\left(\int_{\mathbb{R}^d\times\mathbb{R}^d}K_1\left(\mathbf{x}-\mathbf{x}'\right)\left|\mathbf{v}'\right|p_r\left(d\mathbf{x}',d\mathbf{v}'\right)\right)dr.$$

Further, we shall denote by

$$F(C_t):=f(C_t)\nabla C_t.$$

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With these notations in mind the PDE system (4.1)–(4.2) can be rewritten as follows:

$$\partial_t p_t + \mathbf{v}\cdot\nabla_x p_t + \mathrm{div}_v\left(\left[F\left(C_t\right)-k_1\mathbf{v}\right]p_t\right) = \frac{\sigma^2}{2}\Delta_v p_t + \Lambda_t\left(C_t, p_t, \{\widetilde{p}_r\}_{r\in[0,t]}\right)(d\mathbf{x}, d\mathbf{v}), \tag{C 2}$$

$$\partial_t C_t = k_2 g_\Sigma + d_1\Delta C_t - \eta\left(t, \mathbf{x}, \{p_r\}_{r\in[0,t]}\right)C_t \tag{C 3}$$

subject to initial conditions $p_0 \in \mathcal{M}_1\left(\mathbb{R}^d\times\mathbb{R}^d\right)$ and $C_0 \in C_b^1\left(\mathbb{R}^d\right)$. We study this system in the case when $C_t = C(t,\mathbf{x})$ is a regular function, of class $C\left([0,T];C_b^1\left(\mathbb{R}^d\right)\right)$ but $p_t = p_t(d\mathbf{x}, d\mathbf{v})$ is only a time-dependent finite measure. As anticipated in Definition 4.2, the solution of equation (C 2) has to be understood in the weak sense, while the solution of equation (C 3) has to be understood in the mild sense.

Let us recall or explain several notations. Given a measure $p_t(d\mathbf{x}, d\mathbf{v})$ in $L^\infty\left(0,T;\mathcal{M}_1\left(\mathbb{R}^d\times\mathbb{R}^d\right)\right)$, as above we denote by $\tilde{p}_t = \tilde{p}_t(dx)$ and $\pi_1 p_t = (\pi_1 p_t)(d\mathbf{x})$ the measures defined as

$$\tilde{p}_t(d\mathbf{x}) := \int_{\mathbb{R}^d} |\mathbf{v}|\, p_t(d\mathbf{x}, d\mathbf{v}),$$
$$(\pi_1 p_t)(d\mathbf{x}) := \int_{\mathbb{R}^d} p_t(d\mathbf{x}, d\mathbf{v}).$$

More formally, on test functions $\phi \in C_c^\infty\left(\mathbb{R}^d\right)$,

$$\int_{\mathbb{R}^d}\phi(\mathbf{x})\,\tilde{p}_t(d\mathbf{x}) := \int_{\mathbb{R}^d\times\mathbb{R}^d}\phi(\mathbf{x})\,|\mathbf{v}|\,p_t(d\mathbf{x}, d\mathbf{v}),$$

$$\int_{\mathbb{R}^d}\phi(\mathbf{x})\,(\pi_1 p_t)(d\mathbf{x}) := \int_{\mathbb{R}^d\times\mathbb{R}^d}\phi(\mathbf{x})\,p_t(d\mathbf{x}, d\mathbf{v}).$$

In the sequel, we denote by $\langle\mu,\phi\rangle$ the integral

$$\langle\mu,\phi\rangle = \int_{\mathbb{R}^{2d}}\phi(\mathbf{x},\mathbf{v})\,\mu(d\mathbf{x}, d\mathbf{v}),$$

when $\mu \in \mathcal{M}_1\left(\mathbb{R}^d\times\mathbb{R}^d\right)$ and ϕ is such that this integral is well defined.

Let $\left(p', C'\right)$ and $\left(p'', C''\right)$ be two solutions with the regularity required in the statement of the theorem. We use the distance

$$d\left(\mu', \mu''\right) := \sup_{\|\phi\|_\infty\leqslant 1}\left|\left\langle\mu_t^1 - \mu_t^2, \left(1+|\mathbf{v}|\right)\phi\right\rangle\right|,$$

on $\mathcal{M}_1\left(\mathbb{R}^d\times\mathbb{R}^d\right)$, where the supremum is taken over all measurable bounded functions

$\phi : \mathbb{R}^d \times \mathbb{R}^d \to \mathbb{R}$ with $\|\phi\|_\infty \leqslant 1$. Below, we repeatedly use the inequality

$$\left|\left\langle \mu_t^1 - \mu_t^2, (1+|\mathbf{v}|)\,\phi \right\rangle\right| \leqslant d\left(\mu', \mu''\right) \|\phi\|_\infty ,$$

which holds true for all bounded measurable functions ϕ; and therefore

$$\left|\left\langle \mu_t^1 - \mu_t^2, \varphi\psi \right\rangle\right| \leqslant d\left(\mu', \mu''\right) \|\varphi\|_\infty \left\| \frac{1}{1+|\mathbf{v}|}\psi \right\|_\infty ,$$

for all bounded measurable functions φ and all measurable functions ψ such that $\frac{1}{1+|\mathbf{v}|}\psi$ is bounded.

Let us introduce the operator $Lf = \frac{\sigma^2}{2}\Delta_{\mathbf{v}} f - \mathbf{v}\cdot\nabla_{\mathbf{x}} f - k_1\, \mathrm{div}_{\mathbf{v}}(\mathbf{v}f)$ over all smooth functions $f : \mathbb{R}^d \times \mathbb{R}^d \to \mathbb{R}$. We denote by L^* its dual operator

$$L^*\phi = \frac{\sigma^2}{2}\Delta_{\mathbf{v}}\phi + \mathbf{v}\cdot\nabla_{\mathbf{x}}\phi + k_1\mathbf{v}\cdot\nabla_{\mathbf{v}}\phi,$$

and by e^{tL^*} its associated semigroup. Formally, if p_t is a solution of the equation above, then we have (e^{tL} denotes the semigroup associated with L)

$$p_t = e^{tL}p_0 + \int_0^t e^{(t-s)L}\left(\Lambda_s\left(C_s, p_s, \tilde{p}_\cdot\right) - \mathrm{div}_{\mathbf{v}}\left(F\left(C_s\right)p_s\right)\right) ds$$

$$\langle p_t, \phi\rangle = \left\langle p_0, e^{tL^*}\phi\right\rangle + \int_0^t \left\langle \Lambda_s\left(C_s, p_s, \tilde{p}_\cdot\right) - \mathrm{div}_{\mathbf{v}}\left(F\left(C_s\right)p_s\right), e^{(t-s)L^*}\phi\right\rangle ds$$

and therefore

$$\begin{aligned}\langle p_t, \phi\rangle = \left\langle p_0, e^{tL^*}\phi\right\rangle &+ \int_0^t \left\langle \Lambda_s\left(C_s, p_s, \tilde{p}_\cdot\right), e^{(t-s)L^*}\phi\right\rangle ds \\ &+ \int_0^t \left\langle p_s, F\left(C_s\right)\cdot\nabla_v e^{(t-s)L^*}\phi\right\rangle ds. \end{aligned} \tag{C 4}$$

This identity can be rigorously proved from the weak formulation of the equation for p, first extending it to time-dependent test functions and then by taking the test function $e^{tL^*}\phi$; we omit the lengthy but not difficult computations.

From the previous identity, we estimate

$$\begin{aligned}&\left|\left\langle p_t' - p_t'', (1+|\mathbf{v}|)\,\phi\right\rangle\right| \\ &\leqslant \int_0^t \left\langle \Lambda_s\left(C_s', p_s', \tilde{p}_\cdot'\right) - \Lambda_s\left(C_s'', p_s'', \tilde{p}_\cdot''\right), e^{(t-s)L^*}\left(1+|\mathbf{v}|\right)\phi\right\rangle ds \\ &\quad + \int_0^t \left|\left\langle p_s', F\left(C_s'\right)\cdot\nabla_{\mathbf{v}} e^{(t-s)L^*}\left(1+|\mathbf{v}|\right)\phi\right\rangle\right. \\ &\quad - \left.\left\langle p_s'', F\left(C_s''\right)\cdot\nabla_{\mathbf{v}} e^{(t-s)L^*}\left(1+|\mathbf{v}|\right)\phi\right\rangle\right| ds. \end{aligned} \tag{C 5}$$

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Hence, with the notation $\widetilde{\phi} = \left(1 + |\mathbf{v}|\right)\phi$,

$$|\langle p_t' - p_t'', \phi \rangle| \leqslant \int_0^t \left(I_{s,t}^1 + I_{s,t}^2 + I_{s,t}^3\right) ds$$

$$\begin{aligned}
I_{s,t}^1 &= \left| \left\langle \Lambda_s\left(C_s', p_s', \tilde{p}_\cdot'\right) - \Lambda_s\left(C_s'', p_s'', \tilde{p}_\cdot''\right), e^{(t-s)L^*}\widetilde{\phi} \right\rangle \right| \\
I_{s,t}^2 &= \left| \left\langle p_s' - p_s'', F\left(C_s'\right) \cdot \nabla_{\mathbf{v}} e^{(t-s)L^*}\widetilde{\phi} \right\rangle \right| \\
I_{s,t}^3 &= \left| \left\langle p_s'', \left(F\left(C_s'\right) - F\left(C_s''\right)\right) \cdot \nabla_{\mathbf{v}} e^{(t-s)L^*}\widetilde{\phi} \right\rangle \right|.
\end{aligned}$$

Now, we estimate

$$I_{s,t}^1 \leqslant I_{s,t}^{1,1} + I_{s,t}^{1,2} + I_{s,t}^{1,3}$$

$$\begin{aligned}
I_{s,t}^{1,1} &= \left| \left\langle \pi_1 p_s' \otimes d\mathcal{L}_{\mathbf{v}}, G_{\mathbf{v}_0}\alpha(C_s')e^{(t-s)L^*}\widetilde{\phi} \right\rangle \right. \\
&\quad \left. - \left\langle \pi_1 p_s'' \otimes d\mathcal{L}_{\mathbf{v}}, G_{\mathbf{v}_0}\alpha(C_s'')e^{(t-s)L^*}\widetilde{\phi} \right\rangle \right| \\
&\leqslant \left| \left\langle \left(\pi_1 p_s' - \pi_1 p_s''\right) \otimes d\mathcal{L}_{\mathbf{v}}, G_{\mathbf{v}_0}\alpha(C_s')e^{(t-s)L^*}\widetilde{\phi} \right\rangle \right| \\
&\quad + \left| \left\langle \pi_1 p_s'' \otimes d\mathcal{L}_{\mathbf{v}}, G_{\mathbf{v}_0}\left(\alpha(C_s') - \alpha(C_s'')\right) e^{(t-s)L^*}\widetilde{\phi} \right\rangle \right| \\
&\leqslant \left\| G_{\mathbf{v}_0}\left(1 + |\mathbf{v}|\right) \right\|_{L^1} \|\alpha\|_\infty \left\| \frac{1}{1+|\mathbf{v}|} e^{(t-s)L^*}\widetilde{\phi} \right\|_\infty d\left(p_s', p_s''\right) \\
&\quad + \langle \pi_1 p_s'', 1 \rangle \left\| G_{\mathbf{v}_0}\left(1 + |\mathbf{v}|\right) \right\|_{L^1} \|\alpha'\|_\infty \left\| \frac{1}{1+|\mathbf{v}|} e^{(t-s)L^*}\widetilde{\phi} \right\|_\infty \|C_s' - C_s''\|_\infty ;
\end{aligned}$$

$$\begin{aligned}
I_{s,t}^{1,2} &= \int_0^s \left| \left\langle \tilde{p}_r' \otimes d\mathcal{L}_{\mathbf{v}}, G_{\mathbf{v}_0}\beta(C_s')e^{(t-s)L^*}\widetilde{\phi} \right\rangle \right. \\
&\quad \left. - \left\langle \tilde{p}_r'' \otimes d\mathcal{L}_{\mathbf{v}}, G_{\mathbf{v}_0}\beta(C_s'')e^{(t-s)L^*}\widetilde{\phi} \right\rangle \right| dr \\
&\leqslant \int_0^s \left| \left\langle \left(\tilde{p}_r' - \tilde{p}_r''\right) \otimes d\mathcal{L}_{\mathbf{v}}, G_{\mathbf{v}_0}\beta(C_s')e^{(t-s)L^*}\widetilde{\phi} \right\rangle \right| dr \\
&\quad + \int_0^s \left| \left\langle \tilde{p}_r'' \otimes d\mathcal{L}_{\mathbf{v}}, G_{\mathbf{v}_0}\left(\beta(C_s') - \beta(C_s'')\right) e^{(t-s)L^*}\widetilde{\phi} \right\rangle \right| dr \\
&\leqslant \left\| G_{\mathbf{v}_0}\left(1 + |\mathbf{v}|\right) \right\|_{L^1} \|\beta\|_\infty \left\| \frac{1}{1+|\mathbf{v}|} e^{(t-s)L^*}\widetilde{\phi} \right\|_\infty \int_0^s d\left(p_r', p_r''\right) dr \\
&\quad + \left\| G_{\mathbf{v}_0}\left(1 + |\mathbf{v}|\right) \right\|_{L^1} \|\beta'\|_\infty \left\| \frac{1}{1+|\mathbf{v}|} e^{(t-s)L^*}\widetilde{\phi} \right\|_\infty \left(\int_0^s \langle \tilde{p}_r'', 1 \rangle \, dr \right) \|C_s' - C_s''\|_\infty ;
\end{aligned}$$

$$
\begin{aligned}
I^{1,3}_{s,t} &= \gamma \left| \left\langle p'_s, h\left(\int_0^s \left(K_2 * \widetilde{p}'_r\right) dr\right) e^{(t-s)L^*}\widetilde{\phi} \right\rangle \right. \\
&\quad \left. - \left\langle p''_s, h\left(\int_0^s \left(K_2 * \widetilde{p}''_r\right) dr\right) e^{(t-s)L^*}\widetilde{\phi} \right\rangle \right| \\
&\leqslant \gamma \left| \left\langle p'_s - p''_s, h\left(\int_0^s \left(K_2 * \widetilde{p}'_r\right) dr\right) e^{(t-s)L^*}\widetilde{\phi} \right\rangle \right| \\
&\quad + \gamma \left\| h' \right\|_\infty \left| \left\langle p''_s, \int_0^s K_2 * \left(\widetilde{p}'_r - \widetilde{p}''_r\right) dr e^{(t-s)L^*}\widetilde{\phi} \right\rangle \right| \\
&\leqslant \gamma \left\| \frac{1}{1+|\mathbf{v}|} e^{(t-s)L^*}\widetilde{\phi} \right\|_\infty h\left(\int_0^s \left\| K_2 * \widetilde{p}'_r \right\|_\infty dr\right) d\left(p'_s, p''_s\right) \\
&\quad + \gamma \left\| h' \right\|_\infty \left\langle p''_s, 1+|\mathbf{v}| \right\rangle \left\| \frac{1}{1+|\mathbf{v}|} e^{(t-s)L^*}\widetilde{\phi} \right\|_\infty \int_0^s \left\| K_2 * \left(\widetilde{p}'_r - \widetilde{p}''_r\right) \right\|_\infty dr.
\end{aligned}
$$

Moreover, we estimate

$$
I^2_{s,t} \leqslant \|F\|_\infty \left\| \frac{1}{1+|\mathbf{v}|} \nabla_{\mathbf{v}} e^{(t-s)L^*}\widetilde{\phi} \right\|_\infty d\left(p'_s, p''_s\right);
$$

$$
I^3_{s,t} \leqslant \left\langle p''_s, 1+|\mathbf{v}| \right\rangle \left\| \frac{1}{1+|\mathbf{v}|} \nabla_{\mathbf{v}} e^{(t-s)L^*}\widetilde{\phi} \right\|_\infty \|\nabla F\|_\infty \left\| \nabla C'_s - \nabla C''_s \right\|_\infty .
$$

Now, we use Lemma 5 below, the finiteness of $\left\| G_{\mathbf{v}_0}\left(1+|\mathbf{v}|\right) \right\|_{L^1}, \|\alpha\|_\infty, \|\alpha'\|_\infty,$ $\|\beta\|_\infty, \|\beta'\|_\infty, \|K_2\|_\infty, \|f\|_\infty, \|f'\|_\infty$, the assumption $\|\phi\|_\infty \leqslant 1$ and the properties $p', p'' \in C\left([0,T]; \mathcal{M}_1\left(\mathbb{R}^{2d}\right)\right)$
(which implies $\pi_1 p', \pi_1 p'' \in C\left([0,T]; \mathcal{M}_1\left(\mathbb{R}^{d}\right)\right)$) and $\|\nabla C'\|_\infty < \infty$, to get

$$
I^{1,1}_{s,t} \leqslant c_1 d\left(p'_s, p''_s\right) + c_2 \left\| C'_s - C''_s \right\|_\infty
$$

$$
I^{1,2}_{s,t} \leqslant c_3 \int_0^s d\left(p'_r, p''_r\right) dr + c_4 \left\| C'_s - C''_s \right\|_\infty
$$

$$
I^{1,3}_{s,t} \leqslant c_5 d\left(p'_s, p''_s\right) + c_6 \int_0^s d\left(p'_r, p''_r\right) dr
$$

(we have used the fact that $\left|\left(K_2 * \left(\widetilde{p}'_r - \widetilde{p}''_r\right)\right)(\mathbf{x})\right|$ is bounded above by $\|K_2\|_\infty d\left(p'_r, p''_r\right)$ thanks to the presence of the factor $\left(1+|\mathbf{v}|\right)$ in the definition of the distance)

$$
I^2_{s,t} \leqslant \frac{c_7}{|t-s|^{1/2}} d\left(p'_s, p''_s\right)
$$

$$
I^3_{s,t} \leqslant \frac{c_8}{|t-s|^{1/2}} \left\| \nabla C'_s - \nabla C''_s \right\|_\infty .
$$

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It follows:

$$|\langle p_t' - p_t'', \phi\rangle| \leqslant \int_0^t \left(c_1 + c_5 + \frac{c_7}{|t-s|^{1/2}} \right) d\left(p_s', p_s''\right) ds$$
$$+ \int_0^t \left((c_2 + c_4) \|C_s' - C_s''\|_\infty + \frac{c_8}{|t-s|^{1/2}} \|\nabla C_s' - \nabla C_s''\|_\infty \right) ds$$
$$+ \int_0^t \left((c_3 + c_6) \int_0^s d\left(p_r', p_r''\right) dr \right) ds.$$

At the same time, from equation (C 3), we deduce

$$\partial_t \left(C_t' - C_t''\right) = d_1 \Delta \left(C_t' - C_t''\right) - \left(\eta_t\left(p_\cdot'\right) - \eta_t\left(p_\cdot''\right)\right) C_t' - \eta_t\left(p_\cdot''\right)\left(C_t' - C_t''\right).$$

Hence, by reminding that $A = d_1 \Delta$ is the linear unbounded operator in $UC_b\left(\mathbb{R}^d\right)$ introduced in Section 5.1 (the initial conditions being the same),

$$(1-A)^{1/2}\left(C_t' - C_t''\right) = -\int_0^t (1-A)^{1/2} e^{(t-s)A} \left(\eta_s\left(p_\cdot'\right) - \eta_s\left(p_\cdot''\right)\right) C_s' ds$$
$$- \int_0^t (1-A)^{1/2} e^{(t-s)A} \eta_s\left(p_\cdot''\right)\left(C_s' - C_s''\right) ds,$$

which gives us

$$\|\nabla C_t' - \nabla C_t''\|_\infty \leqslant \int_0^t \frac{c_{10}}{|t-s|^{1/2}} \left\|\eta_s\left(p_\cdot'\right) - \eta_s\left(p_\cdot''\right)\right\|_\infty ds$$
$$+ \int_0^t \frac{c_{10}}{|t-s|^{1/2}} \left\|\eta_s\left(p_\cdot''\right)\right\|_\infty \|C_s' - C_s''\|_\infty ds$$

and a similar easier estimate for $\|C_t' - C_t''\|_\infty$. Since $\|K_1\|_\infty < \infty$, we have $\left\|\eta_\cdot\left(p_\cdot''\right)\right\|_\infty < \infty$ and

$$\left\|\eta_s\left(p_\cdot'\right) - \eta_s\left(p_\cdot''\right)\right\|_\infty \leqslant \|K_1\|_\infty \int_0^s d\left(p_r', p_r''\right) dr.$$

Putting all together, we find an integral inequality for the quantity

$$\sup_{r\in[0,t]} d\left(p_r', p_r''\right) + \|C_t' - C_t''\|_\infty + \|\nabla C_t' - \nabla C_t''\|_\infty,$$

to which a generalised form of Gronwall inequality can be applied. It implies $d\left(p_t', p_t''\right) + \|C_t' - C_t''\|_\infty = 0$, namely uniqueness.

Lemma 5 *On a finite interval* $[0, T]$*, there is a constant* $C > 0$ *such that*

$$\left|\left(e^{tL^*}\left(1 + |\mathbf{v}|\right)\phi\right)(\mathbf{x}, \mathbf{v})\right| \leqslant C\|\phi\|_\infty \left(1 + |\mathbf{v}|\right)$$
$$\left|\nabla_{\mathbf{v}}\left(e^{tL^*}\left(1 + |\mathbf{v}|\right)\phi\right)(\mathbf{x}, \mathbf{v})\right| \leqslant \frac{C}{\sqrt{t}}\|\phi\|_\infty \left(1 + |\mathbf{v}|\right) + C\|\phi\|_\infty.$$

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Proof. Step 1. The generator $L^* = \frac{\sigma^2}{2}\Delta_{\mathbf{v}}\phi + \mathbf{v}\cdot\nabla_{\mathbf{x}}\phi + k_1\mathbf{v}\cdot\nabla_{\mathbf{v}}\phi$ is associated with the system

$$\begin{aligned} d\mathbf{x}_t &= \mathbf{v}_t dt \\ d\mathbf{v}_t &= k_1\mathbf{v}_t dt + \sigma d\mathbf{B}_t, \end{aligned}$$

where $\mathbf{B}_t$ is an auxiliary standard Brownian motion on $\mathbb{R}^d$. Set $\mathbf{z}_t = e^{-k_1 t}\mathbf{v}_t$; we have

$$d\mathbf{z}_t = e^{-k_1 t}\sigma d\mathbf{B}_t.$$

Using this trick, the computations in the case $k_1 \neq 0$ are very similar to those of the case $k_1 = 0$, just more cumbersome. We thus set $k_1 = 0$ for simplicity of notations; and we take $\sigma = 1$ for the same reason. In this case the solution of the system, called $(\mathbf{x}, \mathbf{v})$ the initial condition

$$\begin{aligned} \mathbf{v}_t &= \mathbf{v} + \mathbf{B}_t \\ \mathbf{x}_t &= \mathbf{x} + \mathbf{v}t + \int_0^t \mathbf{B}_s ds. \end{aligned}$$

We use the probabilistic formula

$$\left(e^{tL^*}\phi\right)(\mathbf{x},\mathbf{v}) = \mathbb{E}\left[\phi\left(\mathbf{x} + \mathbf{v}t + \int_0^t \mathbf{B}_s ds, \mathbf{v} + \mathbf{B}_t\right)\right].$$

One can prove

$$\left(\nabla_{\mathbf{v}} e^{tL^*}\phi\right)(\mathbf{x},\mathbf{v}) = \frac{6}{t}\mathbb{E}\left[\left(\frac{1}{t}\int_0^t \mathbf{B}_s ds - \frac{1}{3}\mathbf{v}_t\right)\phi\left(\mathbf{x} + \mathbf{v}t + \int_0^t \mathbf{B}_s ds, \mathbf{v} + \mathbf{B}_t\right)\right].$$

Step 2. We thus have

$$\left(e^{tL^*}\left(1 + |\mathbf{v}|\right)\phi\right)(\mathbf{x},\mathbf{v}) = \mathbb{E}\left[\left(1 + |\mathbf{v} + \mathbf{B}_t|\right)\phi\left(\mathbf{x} + \mathbf{v}t + \int_0^t \mathbf{B}_s ds, \mathbf{v} + \mathbf{B}_t\right)\right]$$

$$\begin{aligned} \left(\nabla_{\mathbf{v}} e^{tL^*}\left(1 + |\mathbf{v}|\right)\phi\right)(\mathbf{x},\mathbf{v}) = \frac{6}{t}\mathbb{E}\Bigg[\left(\frac{1}{t}\int_0^t \mathbf{B}_s ds - \frac{1}{3}\mathbf{B}_t\right)\left(1 + |\mathbf{v} + \mathbf{B}_t|\right) \times \\ \times\ \phi\left(\mathbf{x} + \mathbf{v}t + \int_0^t \mathbf{B}_s ds, \mathbf{v} + \mathbf{B}_t\right)\Bigg]. \end{aligned}$$

Hence,

$$\left|\left(e^{tL^*}\left(1 + |\mathbf{v}|\right)\phi\right)(\mathbf{x},\mathbf{v})\right| \leqslant \|\phi\|_\infty\left(1 + \sqrt{t} + |\mathbf{v}|\right),$$

which gives us the first bound; and

$$\left|\left(\nabla_{\mathbf{v}} e^{tL^*}\left(1+|\mathbf{v}|\right)\phi\right)(\mathbf{x},\mathbf{v})\right| \leqslant \|\phi\|_\infty \frac{6}{t}\mathbb{E}\left[\frac{1}{t}\left(\int_0^t |\mathbf{B}_s|\,ds\right)\left(1+|\mathbf{v}|+|\mathbf{B}_t|\right)\right] + \|\phi\|_\infty \frac{2}{t}E\left[|\mathbf{B}_t|\left(1+|\mathbf{v}|+|\mathbf{B}_t|\right)\right] \leqslant \frac{C}{\sqrt{t}}\|\phi\|_\infty\left(1+|\mathbf{v}|\right)+C\|\phi\|_\infty,$$

which gives the second bound.

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