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MULTICELLULAR BIOLOGICAL GROWING SYSTEMS: HYPERBOLIC LIMITS TOWARDS MACROSCOPIC DESCRIPTION

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This paper deals with the analysis of the asymptotic limit towards the derivation of hyperbolic macroscopic equations for a class of equations modeling complex multicellular systems. Cellular interactions generate both modification of biological functions and proliferating destructive events related to growth of tumor cells in competition with the immune system. The asymptotic analysis refers to the hyperbolic limit to show how the macroscopic tissue behavior can be described by linear and nonlinear hyperbolic systems which seem the most natural in this context.

Keywords: Living systems; kinetic theory; multicellular systems; asymptotic limits; hyperbolic limits; high-field limits.

1. Introduction

The aim of this paper is to deduce macroscopic models to describe the dynamics of complex multicellular systems starting from microscopic kinetic descriptions. To deal with this derivation we consider here hyperbolic limits of the multicellular microscopic system that connects the biological parameters involved in this level of description. In other words, we develop asymptotic methods which amount to

expand the distribution function in terms of a small dimensionless parameter related to the intermolecular distances (the space-scale dimensionless parameter) which is equivalent to the connections between the biological constants. The limit that we obtain is singular and the convergence properties can be proved under suitable technical assumptions.

Deriving macroscopic equations, in terms of the density, the current or other macroscopic quantities, from a large kinetic system of interacting particles is an interesting problem that on the one hand relates different levels of descriptions of the same problem and, on the other hand, allows the study of relevant mathematical tools necessary to apply these techniques. In fact, a classical problem of mathematical kinetic theory is the development of asymptotic methods to derive macroscopic equations from the underlying microscopic description providing the evolution of the first distribution function over the microscopic state of large systems of interacting particles. A classical model in mathematical kinetic theory is the Vlasov/Boltzmann equation, which deals with the evolution of a system of equal particles considered as point masses with a microscopic state simply identified by position and velocity (or linear momentum). In recent years, the analysis of the applicability of this procedure to different systems has reached an important development in the so-called parabolic and hyperbolic limits or equivalently low and high field limits. The parabolic (low field) limit of kinetic equations leads to a drift–diffusion type system (or reaction–diffusion system) in which the diffusion processes dominate the behavior of the solutions. The specialized literature offers a number of recent contributions concerning various limits for parabolic diffusive models of the mathematical kinetic theory.[31,21,35] On the other hand, in the hyperbolic (high field) limit the influence of the diffusion terms is of lower (or equal) order of magnitude in comparison with other convective or interaction terms and the aim is to derive hyperbolic macroscopic models.[28,12,20]

In principle, a similar procedure can be implemented to derive macroscopic equations for biological systems viewed as large systems of interacting cells. This approach may allow us to avoid purely phenomenological derivations, based on heuristic modeling of the material behavior of the system under consideration. However, several difficulties should be addressed in this case, which arise from the fact that particles are elements of inert matter, while cells are active particles, belonging to living matter. In particular:

(i) The microscopic state of an active particle is characterized not only by position and velocity, but also by an additional microscopic state (we may call it *activity*) which represents the biological functions at a cellular level.
(ii) Microscopic interactions not only modify the microscopic state, but may also generate proliferation and/or destruction phenomena.

Various models have been proposed to describe biological systems which are characterized by the behaviors we have just outlined above. Referring to tumor-immune cell competition, the existing literature in the relatively simpler case of

spatial homogeneity case is reported in Ref. 4. Mathematical frameworks for a large variety of biological systems can be found in Ref. 9, and in Ref. 10, where different types of microscopic interactions are analyzed and the corresponding evolution equations are derived and applied to the study of specific biological phenomena.

Some interesting results concerning the derivation of macroscopic equations by suitable asymptotic methods in some multicellular biological systems are already available from which we can cite among others.[27,8] Reference 29 is arguably the first one where this interesting topic was addressed. Subsequent relevant contributions in this area are due to various authors, among others.[23,34,30,15,18,26,16] In these works biological systems are considered for which interactions do not follow classical mechanical rules, and biological activity may play a relevant role in determining the dynamics. Specifically, the analysis developed in Ref. 5 for a system constituted by only one population, and in Ref. 6 for a system of two interacting populations (limited, however, to the case of mass conservative encounters), shows that interactions that change the biological functions of cells may substantially modify the structure of the macroscopic equations in the diffusion limit. In particular, the analysis proposed in Ref. 6 has shown the onset of linear and nonlinear diffusion terms departing from the simple mass conservation equation.

Although different limit models have been proved to be efficient in several problems related to cellular dynamics, the parabolic diffusive limit does not seem the more appropriate or natural for our interest because there are no collisions between cells, which is one of the reasons that can be argued to derive diffusive limits. On the contrary, we want to preserve encounters and interactions between biological particles and in this way hyperbolic limits could produce the suitable approach to derive macroscopic models. The diffusion processes in this limit could come only from the interaction between the cells with the surrounding biological fluid from which the cells also take their food and therefore there is a mass transfer.

The idea of this paper is not to analyze the interaction fluid–cell for which we refer to Ref. 24. There is another possible coupling with the kinetic and the fluid systems which seems necessary to complete the description of the cellular dynamics. In fact, at the sub-cellular level of description there is enormous activity that in particular implies the transmission of information (duplication, cell differentiation, tumor anomalies, etc.) between cells through proteins. Some models of reaction–diffusion type have been proposed to analyze this sub-cellular activity.

This paper analyzes a class of equations modeling complex multicellular systems where interactions generate both modification of biological functions and proliferating destructive events related to growth of tumor cells in competition with the immune system. The asymptotic analysis refers to the hyperbolic limit to show how the macroscopic tissue behavior can be described by linear and nonlinear hyperbolic systems.

We now briefly describe the contents of this paper. Section 2 deals with the description of the class of equations dealt with herein, which include, as particular cases, specific models such as those proposed in Ref. 4. As it will be shown here, the

model considered is a Boltzmann-type equation in which microscopic interactions include both mass conservative encounters, which modify the cellular biological functions, and proliferating or destructive events. Section 3 is concerned with the development of the asymptotic analysis needed to derive the corresponding macroscopic equations. Section 4 analyzes some specific applications related to the analysis of the preceding section. Finally, Sec. 5 outlines some research perspectives arising from conceivable applications of our approach to complex biological situations.

2. The Mathematical Model

Consider a physical system constituted by a large number of cells interacting in the environment of a vertebrate (or in an *in vitro* experiment). The physical variable used to describe the state of each cell, called *microscopic state*, is denoted by the variable $w = \{x\,, v\,, u\}$, where $\{x, v\} \in \Omega \times V \subset \mathbb{R}^n \times \mathbb{R}^n$ is the *mechanical microscopic state* and $u \in D_u \subseteq \mathbb{R}^m$ is the *biological microscopic state*. The statistical collective description of the system is encoded in the statistical distribution $f = f(t, x, v, u)$, which is called a *generalized distribution function*. Weighted moments provide, under suitable integrability properties, the calculation of macroscopic variables.[4]

As we mentioned in the Introduction of this paper, we do not consider the interaction of the particles with the surrounding biological fluid nor with the sub–cellular dynamics. We also assume that the transport in position is linear with respect to the velocity. It is not difficult to extend our approach to a nonlinear dependence of the velocity $k(v)$ which gives a change in the second term in Eq. (2.1) with $k(v)$ replacing v. Then, the evolution of f can be modeled as follows:

$$\left(\frac{\partial}{\partial t} + v \cdot \nabla_x\right) f(t, x, v, u) = L(f)(t, x, v, u) + \mathcal{G}(f, f)(t, x, v, u) + \mathcal{I}(f, f)(t, x, v, u), \tag{2.1}$$

where

• The linear transport term has been proposed by various authors, see Refs. 30, 15 and 5 to describe the dynamics of biological organisms modeled by a velocity-jump process,

$$L(f) = \nu \int_V \big[T(v, v^*) f(t, x, v^*, u) - T(v^*, v) f(t, x, v, u)\big] dv^*, \tag{2.2}$$

where ν is the turning rate or turning frequency and $T(v, v^*)$ is the probability kernel for the new velocity $v \in V$ assuming that the previous velocity was v^*.

• The operator $\mathcal{G}$ (for a one-dimensional biological state $D_u \subset \mathbb{R}$), defined as

$$\mathcal{G}(f, f) = \int_{D_u} \int_{D_u} \eta\, \varphi(u_*, u^*, u)\, f(t, x, v, u_*)\, f(t, x, v, u^*)\, du_* du^* - f(t, x, v, u) \int_{D_u} \eta\, f(t, x, v, u^*)\, du^*, \tag{2.3}$$

corresponds respectively to the gain and loss of cells in state u due to conservative encounters, namely those which modify the biological state without generating proliferation or destruction phenomena.

In particular, η denotes the biological interaction rate, which is here assumed (for simplicity) constant. The kernel φ models the transition probability density of the candidate cell with state u_* into the state u, of the test cell, after interaction with the field cell with state u^*. We recall that the kernel φ is a probability density not symmetrical with respect to u.

• Finally, the operator $\mathcal{I}$ is defined as follows:

$$\mathcal{I}(f,f) = f(t,x,v,u) \int_{D_u} \eta\, \mu\, f(t,x,v,u^*)\, du^* \tag{2.4}$$

and corresponds to proliferation and destruction of cells, where the terms μ correspond to the net proliferation/destruction rates.

The above set of equations describes the evolution in the space $x \in \mathbb{R}^n$ and in the biological state $u \in D_u \subseteq \mathbb{R}$ of a large system of interacting cells. Interactions occur within the action domain Ω of the test cell. Ω is assumed to be relatively small, so that only binary localized encounters are relevant. Of course, this assumption excludes the possibility of crowding and multiple interactions.

Diffusion may be seen as the limit of (2.1) as ε goes to zero after the scaling $t \longrightarrow \varepsilon^2 t$, $x \longrightarrow \varepsilon x$, and scaling of mechanical and biological parameters, which shows how various types of diffusion phenomena, linear and nonlinear, can be obtained in suitable asymptotic limits. A more recent tendency has been to use hyperbolic equations to describe intermediate regimes at the macroscopic level rather than parabolic equations, see Ref. 12 and 28. Our purpose is to indicate a number of ways to model this. In this paper, we will show that hyperbolic models may also be derived as a fluid limit of the transport Eq. (2.1), but with a different scaling, the hydrodynamic scaling $t \longrightarrow \varepsilon t$, $x \longrightarrow \varepsilon x$.

The next section is devoted to a general formal study of the hydrodynamical limit of (2.1) under three different regimes related with the nonlinear operators $\mathcal{G}(f,f)$ and $\mathcal{I}(f,f)$; we shall present the required hypothesis on the operator $L(f)$ to have an asymptotic behavior. In Sec. 4 we analyze these three regimes for the particular case of a relaxation model by describing more concretely the limiting equations. Finally, we analyze the rigorous passage to the limit.

3. Hydrodynamical Limit

In order to justify rigorously the hyperbolic scaling we introduce some typical constants of the system which allow us to write it in nondimensional form. We first consider the macroscopic mean velocity of the (initial) distribution

$$v_0 := \frac{1}{M} \int_\Omega \int_{D_u} \int_V v\, f(0,x,v,u)\, dv\, du\, dx,$$

where $M = \int_\Omega \int_{D_u} \int_V f(0,x,v,u)\,dv\,du\,dx$, stands for the total (initial) mass of the system. We also introduce a typical time τ and a typical length R of the system verifying the relation $\tau\, v_0 = R$ so that τ and R are the mechanical variables of the system. On the other hand, for the biological microscopic state we introduce a typical value denoted by U. Then, we rescale the system by using the following nondimensional variables (denoted by $\hat{}$):

$$t := \tau\,\hat{t}, \quad x := R\,\hat{x}, \quad v := v_0\,\hat{v} \quad \text{and} \quad u := U\,\hat{u}.$$

Thus, we rewrite the distribution function in a nondimensional form:

$$\hat{f}(\hat{t},\hat{x},\hat{v},\hat{u}) := \frac{R^n v_0^n U}{M}\, f(t,x,v,u).$$

For the operators $\mathcal{L}$, $\mathcal{I}$ and $\mathcal{G}$ we define T_0 and φ_0 such that

$$T(v,v^*) = T_0\,\hat{T}(\hat{v},\hat{v}^*), \quad \varphi(u_*,u^*,u) = \varphi_0\,\hat{\varphi}(\hat{u}_*,\hat{u}^*,\hat{u}),$$

$\hat{T}$ and $\hat{\varphi}$ being nondimensional versions of these kernels. With the aim of having the same dimensional order in the two terms involved in (2.3), we can assume $\varphi_0\, U = 1$. Also, to normalize the velocity-jump kernel we can assume $T\, v_0^n = 1$. Then, Eqs. (2.1)–(2.4) can be rewritten as:

$$\left(\frac{\partial}{\partial \hat{t}} + \hat{v}\cdot\nabla_{\hat{x}}\right)\hat{f}(\hat{t},\hat{x},\hat{v},\hat{u}) = \tau\,\nu\,L(\hat{f}) + \frac{\tau\,\eta\,M}{R^n v_0^n}\big(G(\hat{f},\hat{f}) + \mu\, I(\hat{f},\hat{f})\big), \tag{3.1}$$

where the nondimensional operators are defined by

$$L(\hat{f}) = \int_{\hat{V}} \big[\hat{T}(\hat{v},\hat{v}^*)\hat{f}(\hat{t},\hat{x},\hat{v}^*,\hat{u}) - \hat{T}(\hat{v}^*,\hat{v})\hat{f}(\hat{t},\hat{x},\hat{v},\hat{u})\big]d\hat{v}^*, \tag{3.2}$$

$$G(\hat{f},\hat{f}) = \int_{D_{\hat{u}}}\int_{D_{\hat{u}}} \hat{\varphi}(\hat{u}_*,\hat{u}^*,\hat{u})\,\hat{f}(\hat{t},\hat{x},\hat{v},\hat{u}_*)\,\hat{f}(\hat{t},\hat{x},\hat{v},\hat{u}^*)\,d\hat{u}_* d\hat{u}^*$$

$$-\hat{f}(\hat{t},\hat{x},\hat{v},\hat{u})\int_{D_{\hat{u}}} \hat{f}(\hat{t},\hat{x},\hat{v},\hat{u}^*)\,d\hat{u}^*, \tag{3.3}$$

$$I(\hat{f},\hat{f}) = \hat{f}(\hat{t},\hat{x},\hat{v},\hat{u})\int_{D_{\hat{u}}} \hat{f}(\hat{t},\hat{x},\hat{v},\hat{u}^*)\,d\hat{u}^*, \tag{3.4}$$

with integrals defined over the nondimensional sets: $\hat{V} = V/v_0$ and $U_{\hat{u}} = U_u/U$. In the rest of the paper the notation can be simplified by skipping the "hat" for the nondimensional variables. Then, the hyperbolic scaling: $t \to \varepsilon t$ and $x \to \varepsilon x$, is equivalent to the choice

$$\tau\,\nu = \frac{1}{\varepsilon}, \tag{3.5}$$

i.e. the turning time (the inverse of the turning frequency $1/\nu$) is small compared with the typical mechanical time of the system τ. For the other two biological rates involving this system (conservative interactions which modify the biological state-related to G- and proliferating/destructive encounters-related to I), we assume

that the scaled biological interaction frequency (actually $\eta\, M/(R^n\, v_0^n)$) is small compared with the turning frequency and that the (nondimensional) proliferation destruction rate μ is itself small. More precisely, we will deal with the following relations between mechanical and biological constants

$$\eta\,\frac{M}{R^n\, v_0^n} = \varepsilon^q \nu = \varepsilon^{q-1}\frac{1}{\tau}, \quad \mu = \varepsilon^\delta, \quad q \geq 1,\ \delta \geq 0.$$

Then, Eq. (3.1) becomes

$$\left(\frac{\partial}{\partial t} + v\cdot\nabla_x\right) f_\varepsilon = \frac{1}{\varepsilon}\big(L(f_\varepsilon) + \varepsilon^q G(f_\varepsilon, f_\varepsilon) + \varepsilon^{q+\delta} I(f_\varepsilon, f_\varepsilon)\big), \tag{3.6}$$

where the scaled operators L, G and I are defined in (3.2)–(3.4). The purpose of this paper is to understand the asymptotic limit of (3.6) as ε goes to zero. We first mention some assumptions on the turning operator L:

Assumption 3.1. (Solvability conditions) The turning operator L satisfies the following solvability conditions:

$$\int_V L(f)\, dv = \int_V v L(f)\, dv = 0. \tag{3.7}$$

Assumption 3.2. (Kernel of L) There exists a unique function $M_{\rho,U} \in L^1(V, (1+|v|)\, dv)$, for all $\rho \in [0, +\infty)$ and $U \in \mathbb{R}^n$, such that

$$L(M_{\rho,U}) = 0, \quad \int_V M_{\rho,U}(v)\, dv = \rho, \quad \int_V v\, M_{\rho,U}(v)\, dv = \rho\, U. \tag{3.8}$$

Let us note that the variables t, x and u act as parameters in (3.8).

The above assumptions allow to derive, by a suitable asymptotic limit, macroscopic scale hyperbolic systems.

Multiplying (3.6) by ε and taking $\varepsilon = 0$ we formally obtain $L(f_0) = 0$, so f_0 verifies the conditions of Assumption 3.2. Then, by considering the following moments of f_ε

$$\rho_\varepsilon(t,x,u) = \int_V f_\varepsilon(t,x,v,u)\, dv, \quad \rho_\varepsilon(t,x,u)\, U_\varepsilon(t,x,u) = \int_V v\, f_\varepsilon(t,x,v,u)\, dv, \tag{3.9}$$

we have an equilibrium distribution of the form $f_0 = M_{\rho_0,U_0}$ given by (3.8) and we can see the solution f_ε as a perturbation of this equilibrium in the following way:

$$f_\varepsilon(t,x,v,u) = M_{\rho_0,U_0} + \varepsilon\, g(t,x,v,u). \tag{3.10}$$

In order to study the equations verified by the equilibrium variables ρ_0 and U_0, we integrate (3.6) over v, using (3.7) and (3.9), which yields

$$\frac{\partial \rho_\varepsilon}{\partial t} + \operatorname{div}(\rho_\varepsilon U_\varepsilon) = \varepsilon^{q-1}\int_V G(f_\varepsilon, f_\varepsilon)\, dv + \varepsilon^{q+\delta-1}\int_V I(f_\varepsilon, f_\varepsilon)\, dv. \tag{3.11}$$

Analogously, multiplying (3.6) by v and integrating with respect to v, and using (3.7) we obtain

$$\frac{\partial(\rho_\varepsilon U_\varepsilon)}{\partial t} + \mathrm{Div}\left(\int_V v \otimes v\, f_\varepsilon\, dv\right) = \varepsilon^{q-1}\int_V v\, G(f_\varepsilon, f_\varepsilon)\, dv + \varepsilon^{q+\delta-1}\int_V v\, I(f_\varepsilon, f_\varepsilon)\, dv, \tag{3.12}$$

where the operator Div acting on a matrix tensor denotes the classical divergence taken on the rows of the matrix. Inserting the expansion (3.10) of f_ε into (3.11) and (3.12) yields

$$\frac{\partial \rho_0}{\partial t} + \mathrm{div}(\rho_0 U_0) = \varepsilon^{q-1}\int_V G(M_{\rho_0,U_0}, M_{\rho_0,U_0})\, dv + \varepsilon^{q+\delta-1}\int_V I(M_{\rho_0,U_0}, M_{\rho_0,U_0})\, dv + \mathcal{O}(\varepsilon^q)$$

and

$$\frac{\partial(\rho_0 U_0)}{\partial t} + \mathrm{Div}\left(\int_V v \otimes v M_{\rho_0,U_0}\, dv\right) = \varepsilon^{q-1}\int_V v\, G(M_{\rho_0,U_0}, M_{\rho_0,U_0})\, dv + \varepsilon^{q+\delta-1}\int_V v\, I(M_{\rho_0,U_0}, M_{\rho_0,U_0})\, dv + \mathcal{O}(\varepsilon^q). \tag{3.13}$$

As the field U_0 denotes the expected mean velocity of the particles, we can measure the statistical variation in velocity by means of a pressure tensor given by

$$P_0(t,x,u) = \int_V (v - U_0) \otimes (v - U_0)\, M_{\rho_0,U_0}\, dv, \tag{3.14}$$

which is easily related to the second order moment involved in (3.13). In fact, one has

$$\int_V v \otimes v\, M_{\rho_0,U_0}\, dv = P_0 + \rho_0\, U_0 \otimes U_0. \tag{3.15}$$

Therefore (3.13) can be rewritten in the following form

$$\frac{\partial(\rho_0 U_0)}{\partial t} + \mathrm{Div}(\rho_0 U_0 \otimes U_0 + P_0) = \varepsilon^{q-1}\int_V v\, G(M_{\rho_0,U_0}, M_{\rho_0,U_0})\, dv + \varepsilon^{q+\delta-1}\int_V v\, I(M_{\rho_0,U_0}, M_{\rho_0,U_0})(v)\, dv + \mathcal{O}(\varepsilon^q).$$

Considering now the following specific cases which measure the relation between the mechanical variables and the biological rates, we can generate different

hyperbolic systems:

Case 1. $\delta \geq 0$, and $q > 1$: First-order moments with respect to ε give the hyperbolic system without source term:

$$\begin{cases} \dfrac{\partial \rho_0}{\partial t} + \operatorname{div}(\rho_0 U_0) = 0, \\ \dfrac{\partial (\rho_0 U_0)}{\partial t} + \operatorname{Div}(\rho_0\, U_0 \otimes U_0 + P_0) = 0. \end{cases} \tag{3.16}$$

Case 2. $\delta > 0$, and $q = 1$: In this case, in the first order with respect to ε, the following hyperbolic system source term related to conservative interactions is obtained:

$$\begin{cases} \dfrac{\partial \rho_0}{\partial t} + \operatorname{div}(\rho_0 U_0) = \displaystyle\int_V G(M_{\rho_0,U_0}, M_{\rho_0,U_0})\, dv, \\ \dfrac{\partial (\rho_0 U_0)}{\partial t} + \operatorname{Div}(\rho_0 U_0 \otimes U_0 + P_0) = \displaystyle\int_V v\, G(M_{\rho_0,U_0}, M_{\rho_0,U_0})\, dv. \end{cases} \tag{3.17}$$

Case 3. $\delta = 0$, and $q = 1$. In this case, in first order with respect to ε, the following hyperbolic system source term related to both conservative and proliferating interactions is obtained:

$$\begin{cases} \dfrac{\partial \rho_0}{\partial t} + \operatorname{div}(\rho_0 U_0) = \displaystyle\int_V G(M_{\rho_0,U_0}, M_{\rho_0,U_0})\, dv + \int_V I(M_{\rho_0,U_0}, M_{\rho_0,U_0})\, dv, \\ \dfrac{\partial (\rho_0 U_0)}{\partial t} + \operatorname{Div}(\rho_0\, U_0 \otimes U_0 + P_0) \\ \qquad = \displaystyle\int_V vG(M_{\rho_0,U_0}, M_{\rho_0,U_0})\, dv + \int_V vI(M_{\rho_0,U_0}, M_{\rho_0,U_0})\, dv. \end{cases} \tag{3.18}$$

We observe that the influence of the turning operator L on the macroscopic Eqs. (3.16)–(3.18) comes into play through the equilibrium state M_{ρ_0,U_0} in the computation of the right-hand side of (3.16)–(3.18) and the pressure tensor P_0.

The approach we developed in this section is quite general, while some simple examples are described in Sec. 4. Further generalizations will be discussed in the last section referring to cancer modeling.

4. Relaxation Models

Consider the case where the set for velocity is the sphere of radius $r > 0$, $V = r\mathbb{S}^{n-1}$. Let us take a kernel $T(v, v^*)$ in (2.2) in the form $T(v, v^*) = \lambda + \beta\, v \cdot v^*$, so that the operator $L(f)$ can be computed as follows:

$$\begin{aligned} L(f) &= \int_V \big((\lambda + \beta v \cdot v^*) f(v^*) - (\lambda + \beta v \cdot v^*) f(v)\big)\, dv^* \\ &= \lambda\rho + \beta\rho v \cdot U - \lambda |V| f(v) = \lambda |V| \left[\frac{\rho}{|V|} (1 + \frac{\beta}{\lambda}\, v \cdot U) - f(v) \right]. \end{aligned} \tag{4.1}$$

Then we have the following lemma.

Lemma 4.1. *Let $L(f)$ be given by* (4.1) *for $v \in V = r\mathbb{S}^{n-1}$ with the relation $\beta\, r^2 = \lambda\, n$. Then $L(f)$ verifies Assumptions* 3.1, 3.2 *for a function $M_{\rho,U}(v)$ given by*

$$M_{\rho,U}(v) = \frac{\rho}{|V|}\left(1 + \frac{\beta}{\lambda} v \cdot U\right) = \frac{\rho}{|V|}\left(1 + \frac{n}{r^2}\, v \cdot U\right), \tag{4.2}$$

and $L(f)$ is the relaxation operator

$$L(f) = \lambda |V| \big(M_{\rho,U}(v) - f(v)\big). \tag{4.3}$$

Moreover, the pressure tensor P_0 defined by (3.14) *associated with $M_{\rho,U}(v)$ is given by*:

$$P_0 = \frac{r^2}{n}\, \rho\, \mathbb{I} - \rho\, U \otimes U.$$

Proof. The solvability conditions (3.7) can be easily deduced from (4.1) by taking integrals and using

$$|V| = r^{n-1}|\mathbb{S}^{n-1}|, \quad \int_V v\, dv = 0, \quad \int_V v_i v_k\, dv = \frac{r^{n+1}}{n}|\mathbb{S}^{n-1}|\delta_{ik}. \tag{4.4}$$

On the other hand, (4.3), is just (4.1) by using the definition of $M_{\rho,U}$; then, $L(M_{\rho,U}) = 0$. The other two conditions in (3.8) are easily obtained after integration in (4.3). Actually, by using (4.4) we deduce

$$\int_V M_{\rho,U}(v)\, dv = \rho, \quad \int_V v M_{\rho,U}(v)\, dv = \frac{\beta\, r^2}{\lambda\, n}\rho U$$

and we conclude by using the condition $\beta\, r^2 = \lambda\, n$.

To calculate the pressure tensor we use (3.15) and (4.4) to compute

$$P_0 = \int_V v \otimes v\, M_{\rho,U}\, dv - \rho\, U \otimes U = \frac{r^2}{n}\, \rho\, \mathbb{I} - \rho\, U \otimes U,$$

which concludes the proof. □

Now, in order to compute the right-hand side terms of (3.17) and (3.18) we give some technical results.

Lemma 4.2. *Let u^* and u_* be two microscopic states in D_u and let ρ^*, U^* and ρ_*, U_* be evaluations of functions $\rho(t,x,u)$, $U(t,u)$ in u^* and u_*, respectively. Then, the following equalities*:

$$\int_V M_{\rho^*,U^*} M_{\rho_*,U_*}\, dv = \frac{\rho^*\rho_*}{|V|}\left(1 + \frac{n}{r^2} U^* \cdot U_*\right),$$

$$\int_V v M_{\rho^*,U^*} M_{\rho_*,U_*}\, dv = \frac{\rho^*\rho_*}{|V|}(U^* + U_*),$$

hold true.

Proof. We first consider

$$M_{\rho^*,U^*}(v)M_{\rho_*,U_*}(v) = \frac{\rho^*\rho_*}{|V|^2}\left(1 + \frac{n}{r^2}v\cdot(U^*+U_*) + \frac{n^2}{r^4}(v\cdot U^*)(v\cdot U_*)\right).$$

Integrating over v and using (4.4) yields:

$$\int_V M_{\rho^*,U^*}(v)M_{\rho_*,U_*}(v) = \frac{\rho^*\rho_*}{|V|}\left(1 + \frac{n}{r^2}U^*\cdot U_*\right).$$

On the other hand, by noting that $\int_V v_i v_j v_l\, dv = 0$, for any $i,j,l = 1,\ldots,n$, we can compute

$$\int_V v\, M_{\rho^*,U^*}(v)M_{\rho_*,U_*}(v) = \frac{\rho^*\rho_*}{|V|}(U^*+U_*).$$

Now the proof is complete. □

Let us now define, for any vectorial function F defined in D_u, the following scalar quantities:

$$I(F,F) = F(u)\cdot\int_{D_u} F(u^*)\,du^*,$$

$$G(F,F) = \int_{D_u}\int_{D_u}\varphi(u_*,u^*,u)F(u^*)\cdot F(u_*)\,du_*du^* + F(u)\cdot\int_{D_u}F(u^*)\,du^*,$$

and for any scalar function f and any vectorial function F both defined in D_u, the following vectorial quantities:

$$I(f,F) = -\frac{1}{2}\left(f(u)\int_{D_u}F(u^*)\,du^* + F(u)\int_{D_u}f(u^*)\,du^*\right),$$

$$G(f,F) = \frac{1}{2}\int_{D_u}\int_{D_u}\varphi(u_*,u^*,u)\Big(f(u^*)F(u_*) + f(u_*)F(u^*)\Big)\,du_*du^* + I(f,F),$$

which generalize in a natural way the definition of operators G and I, so that we preserve the same name for these operators. Then we have the following:

Lemma 4.3. *If $M_{\rho,U}$ is that given in* (4.2)*, then the following equalities*:

(i) $\displaystyle\int_V G(M_{\rho,U}(v),M_{\rho,U}(v))dv = \frac{1}{|V|}\left(G(\rho,\rho) + \frac{n}{r^2}G(\rho U,\rho U)\right),$

(ii) $\displaystyle\int_V v\,G(M_{\rho,U}(v),M_{\rho,U}(v))dv = \frac{2}{|V|}\,G(\rho,\rho U),$

(iii) $\displaystyle\int_V I(M_{\rho,U}(v),M_{\rho,U}(v))dv = \frac{1}{|V|}\left(I(\rho,\rho) + \frac{n}{r^2}I(\rho U,\rho U)\right),$

(iv) $\displaystyle\int_V v\,I(M_{\rho,U}(v),M_{\rho,U}(v))dv = \frac{2}{|V|}\,I(\rho,\rho U),$

hold true.

Proof. Using Lemma 4.2 and Fubini's theorem, yields

$$\begin{aligned}\int_V G(M_{\rho,U}(v), M_{\rho,U}(v))dv &= \int_{D_u}\int_{D_u} \varphi(u_*, u^*, u)\frac{\rho^*\rho_*}{|V|}\Big(1 + \frac{n}{r^2}U^* \cdot U_*\Big)du_*du^* \\ &\quad - \int_{D_u} \frac{\rho(u)\rho^*}{|V|}\Big(1 + \frac{n}{r^2}U(u) \cdot U^*\Big)du^* \\ &= \frac{1}{|V|}\int_{D_u}\int_{D_u} \varphi(u_*, u^*, u)\rho^*\rho_*\, du_*du^* \\ &\quad + \frac{n}{r^2|V|}\int_{D_u}\int_{D_u} \varphi(u_*, u^*, u)(\rho^*U^*) \cdot (\rho_*U_*)du_*du^* \\ &\quad - \frac{1}{|V|}\rho(u)\int_{D_u}\rho^*du^* - \frac{n}{r^2|V|}(\rho U)(u) \cdot \int_{D_u}(\rho U)^*du^*,\end{aligned}$$

so that (i) is proved. In the same way we can compute the first-order moment:

$$\begin{aligned}\int_V v\, G(M_{\rho,U}(v), M_{\rho,U}(v))dv &= \int_V\int_{D_u}\int_{D_u} \varphi(u_*, u^*, u)vM_{\rho^*,U^*}\, M_{\rho_*,U_*}\, dvdu_*du^* \\ &\quad - \int_V\int_{D_u} vM_{\rho(u),U(u)}M_{\rho^*,U^*}\, dv\, du^* \\ &= \frac{1}{|V|}\int_{D_u}\int_{D_u} \varphi(u_*, u^*, u)(\rho_*(\rho^*U^*) + \rho^*(\rho_*U_*))du_*du^* \\ &\quad - \frac{1}{|V|}\Big((\rho U)(u)\int_{D_u}\rho^*du^* + \rho(u)\int_{D_u}(\rho^*U^*)du^*\Big),\end{aligned}$$

so that (ii) is also proved. Analogously we can derive (iii) and (iv) by integrating the operator I. Now we are done with the proof. □

Then, our main result can be summarized in the following theorem:

Theorem 4.1. *Let f_ε be a solution of* (3.6)*, with L that of the relaxation model given by* (4.1)*, verifying*

$$\sup_{t\geq 0}\int_\Omega\int_V\int_{D_u}(f_\varepsilon(t, x, v, u))^p\, du\, dv\, dx \leq C < \infty \tag{4.5}$$

for some $p > 2$, and such that f_ε converges a.e. in $[0, T] \times \Omega \times D_u \times r\mathbb{S}^{n-1}$ for some $T > 0$. We also assume that the kernel $\varphi(u_*, u^*, u)$ of the operator G is in $L^2((D_u)^3)$. Then, the pointwise limit of f_ε is the function $M_{\rho,U}$ given by (4.2)*, where*

$$\rho \equiv \rho_0 = \lim_{\varepsilon\to 0}\rho_\varepsilon, \quad U \equiv U_0 = \lim_{\varepsilon\to 0}U_\varepsilon,$$

i.e. *the weak and pointwise limit of the moments* (3.9) *of* f_ε. *Moreover, in the three presented regimes, the limiting density* ρ *and velocity* U *satisfy, respectively*:

(1) *If* $\delta \geq 0$ *and* $q > 1$, (ρ, U) *satisfies the following hyperbolic system without source term*:

$$\begin{cases} \dfrac{\partial \rho}{\partial t} + \operatorname{div}(\rho U) = 0, \\ \dfrac{\partial (\rho U)}{\partial t} + \dfrac{r^2}{n} \nabla_x \rho = 0. \end{cases}$$

(2) *If* $\delta > 0$ *and* $q = 1$, (ρ, U) *satisfies the following hyperbolic system with source term related to conservative interactions*:

$$\begin{cases} \dfrac{\partial \rho}{\partial t} + \operatorname{div}(\rho U) = \dfrac{1}{|V|} \left(G(\rho, \rho) + \dfrac{n}{r^2} G(\rho U, \rho U) \right), \\ \dfrac{\partial (\rho U)}{\partial t} + \dfrac{r^2}{n} \nabla_x \rho = \dfrac{2}{|V|} G(\rho, \rho U). \end{cases}$$

(3) *If* $\delta = 0$ *and* $q = 1$, (ρ, U) *verifies the following hyperbolic system whose source term preserves both conservative and proliferating interactions*:

$$\begin{cases} \dfrac{\partial \rho}{\partial t} + \operatorname{div}(\rho U) = \dfrac{1}{|V|} \left(H(\rho, \rho) + \dfrac{n}{r^2} H(\rho U, \rho U) \right), \\ \dfrac{\partial (\rho U)}{\partial t} + \dfrac{r^2}{n} \nabla_x \rho = \dfrac{2}{|V|} H(\rho, \rho U), \end{cases}$$

where the operator H *is given by* $H := G + I$.

Proof. We first observe that the hypothesis (4.5) on f_ε implies that f_ε converges weakly in $L^p([0,T] \times \Omega \times D_u \times r\mathbb{S}^{n-1})$ to its pointwise limit and, via the Dunford–Pettis Theorem, weakly in $L^1([0,T] \times \Omega \times D_u \times r\mathbb{S}^{n-1})$ locally, so then strongly in $L^1_{\mathrm{loc}}([0,T] \times \Omega \times D_u \times r\mathbb{S}^{n-1})$. Then, there exists a function $f_0(t,x,v,u)$ such that, when $\varepsilon \to 0$,

$$f_\varepsilon \to f_0 \quad \text{and} \quad L(f_\varepsilon) \to L(f_0).$$

On the other hand, from the definition of G and the hypotheses under f_ε and φ, we can also estimate $G(f_\varepsilon, f_\varepsilon)$ and $I(f_\varepsilon, f_\varepsilon)$ in L^{p-2} and conclude analogously that

$$G(f_\varepsilon, f_\varepsilon) \to G(f_0, f_0) \quad \text{and} \quad I(f_\varepsilon, f_\varepsilon) \to I(f_0, f_0)$$

strongly in $L^1_{\mathrm{loc}}([0,T] \times \Omega \times D_u \times r\mathbb{S}^{n-1})$. We first identify the limit f_0 by taking the limit in (3.8), in a distributional sense for example, to deduce that $L(f_0) = 0$ and then Lemma 4.1 ensures that $f_0 = M_{\rho_0, U_0} = M_{\rho, U}$.

Now, we recall that the velocity space $r\mathbb{S}^{n-1}$ has finite measure, so that the hypothesis (4.5) holds for the v-moments of f_ε, and then their convergence

$$\rho_\varepsilon \to \rho, \quad \int_V v\, f_\varepsilon \, dv \to \int_V v\, f_0 \, dv = \rho U$$

and

$$\int_V v \otimes v \, f_\varepsilon \, dv \to \int_V v \otimes v \, f_0 \, dv = \frac{r^2}{n} \rho \mathbb{I} \, ,$$

also follows the three regimes are straightforwardly obtained by taking the limit in Eqs. (3.11) and (3.12) and using Lemmas 4.1 and 4.3 to rewrite the limiting terms. □

Remark 4.1. The hypothesis $\beta \, r^2 = \lambda \, n$ for the turning (relaxation) operator (4.1) implies essentially the solvability condition

$$\int_V v \, L(f) \, dv = 0.$$

If it is not assumed, the stated regimes (up to some constants) are preserved, but with the addition of a damping term of the form

$$\left(\frac{\beta r^{n+1}}{n} - \lambda r^{n-1} \right) |\mathbb{S}^{n-1}| \, \rho U$$

on the right-hand side of the second equation for the evolution of ρU.

Remark 4.2. We can also identify the limit of the pressure tensor (or the second order moment in velocity) directly from the equation. More concretely, if we multiply (3.6) by $v \otimes v$ and integrate with respect to v we obtain

$$\varepsilon \left(\frac{\partial}{\partial t} \left(\int_V v \otimes v \, f_\varepsilon \, dv \right) + \sum_{i=1}^{3} \frac{\partial}{\partial x_i} \left(\int_V v_i \, v \otimes v \, f_\varepsilon \, dv \right) \right)$$

$$= \int_V v \otimes v \, L(f_\varepsilon, f_\varepsilon) \, dv + \varepsilon^q \left(\int_V v \otimes v \, G(f_\varepsilon, f_\varepsilon) \, dv + \varepsilon^\delta \int_V v \otimes v \, I(f_\varepsilon, f_\varepsilon) \, dv \right),$$

so that the convergence implies that

$$\int_V v \otimes v \, L(f_\varepsilon, f_\varepsilon) \, dv = \mathcal{O}(\varepsilon) + \mathcal{O}(\varepsilon^q) + \mathcal{O}(\varepsilon^{q+\delta}) \to 0.$$

For the relaxation model given by (4.1), we can compute the left-hand side term by using (4.4) as follows:

$$\int_V v \otimes v \, L(f_\varepsilon, f_\varepsilon) \, dv = \lambda |V| \left[\frac{r^2}{n} \rho_\varepsilon \, \mathbb{I} - \left(\int_V v \otimes v \, f_\varepsilon \, dv \right) \right].$$

Then, in the three studied regimes, we can identify the limit of the second-order moment of f_ε directly from this expression:

$$\left(\int_V v \otimes v \, f_\varepsilon \, dv \right) \; \to \; \frac{r^2}{n} \rho \, \mathbb{I} \Rightarrow \mathrm{Div} \left(\int_V v \otimes v \, f_\varepsilon \, dv \right) \; \to \; \frac{r^2}{n} \nabla \rho.$$

5. Perspectives

Modeling macroscopic phenomena in biological tissues by methods of continuum mechanics classically means deriving suitable evolution equations for the macroscopic variables which have to describe, in the model, the physical state of the system. The phenomenological derivation follows guiding lines which are typical of continuum mechanics: conservation of mass, momentum, and energy equations can be written and closure may be achieved by phenomenological models describing the material behavior of the system. A fundamental problem, often unsolved, is that these models are usually derived in equilibrium conditions, while the evolution equations should operate far from equilibrium. A variety of models in continuum mechanics are well known in the literature, among others.[11,17,19,25] See also the collection of surveys.[32]

The case of biological tissues is particularly difficult to deal with. Indeed, the material behavior of the system may be hardly constrained into simple mathematical relations, while equilibrium conditions may not even be identified. In some cases, the system steadily departs from equilibrium instead of approaching it.

This fact is stressed and subject to critical analysis in various biological articles,[22] satisfies as well as being emphasized by mathematicians.[33] Specifically, in biology, each of the components of a system is usually a microscopic device in itself, and is able to transduce energy and work far from equilibrium. This means that looking for an equilibrium configuration is not only a difficult task, while one may find non-equilibrium configurations where a classical system stays in equilibrium. Furthermore, what really distinguishes biology from physics are survival and reproduction, and the concomitant notion of function. One has therefore to deal with systems in which the microscopic entities are characterized by biological functions that may be modified by interactions with other entities, while proliferation or destruction phenomena may be generated.

The mathematical method proposed in this paper has been developed to derive macroscopic equations for biological tissues and for biological systems viewed as large systems of interacting cells.

As we have seen, the model is developed within the framework of the kinetic theory for active particles which are characterized not only by position and velocity, but also by an additional microscopic state called activity, which represents the biological functions at a cellular level. Then, microscopic interactions not only modify the microscopic state, but may also generate proliferation and/or destruction events.

The approach avoids purely phenomenological derivations, based on heuristic modeling of the material behavior of the system under consideration. The hyperbolic scaling has been properly chosen consistently with the phenomenological behavior which requires models with finite speed of propagation.

Hopefully, the method can be properly developed for mixtures of cell populations, which is particularly important for multiscale methods often related to

complex cancer systems constituted by networks of several nested subsystems.[1–3] In some cases the subsystems are developed at different scales, e.g. Refs. 13, 14 and 25. Moreover, macroscopic equations for biological tissues, as remarked in Ref. 7, may change type. Modifications of the structure of the model are induced by the biological evolution of some events, technically related to the parameters of the scaling, which become predominant with respect to others.

Indeed, the proposed class of models and the mathematical approach effectively take into account all the above issues. Therefore, we trust that future research developments may refer to the contents of this paper.

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