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## Mathematical and Computer Modelling

journal homepage: [www.elsevier.com/locate/mcm](http://www.elsevier.com/locate/mcm)Complexity and mathematical tools toward the modelling of multicellular growing systems<sup>☆</sup>N. Bellomo<sup>a,\*</sup>, A. Bellouquid<sup>b</sup>, J. Nieto<sup>c</sup>, J. Soler<sup>c</sup><sup>a</sup> Department of Mathematics, Politecnico di Torino, Italy<sup>b</sup> Ecole Nationale des Sciences Appliquées, Safi, Maroc<sup>c</sup> University of Granada, Departamento de Matemática Aplicada, 18071 Granada, Spain

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## ABSTRACT

This paper deals with a multiscale modelling approach to complex biological systems constituted by several interacting entities. The methodology is based on mathematical kinetic theory for active particles and is focused on the modelling of complex multicellular systems under therapeutic actions at the cellular level and mutations with onset of new populations. Asymptotic hyperbolic methods are developed to derive models at the macroscopic scale of tissues from the underlying description at the level of cells for a open system with variable number of populations.

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## 1. Introduction

The aim of this paper is to deal with the development of mathematical tools for the modelling of complex biological systems constituted by diverse entities such as genes or cells, which have the ability of expressing heterogeneously different functions and that interact, *in vivo*, under external actions. The contents are focused on theoretical issues, pursuing the hints posed in [1,2]. In this framework it is relevant to consider that the different cells cohabit taking into account short and long range interactions between them. On the other hand, the influence on the different cell populations of some possible therapies as well as how these therapies modify the dynamical behavior and those of the immune system are one of the objectives of this paper. Regarding these effects, it is possible to consider the influence of different kind of therapies. Those more aggressive, as in tumor growth, could be the chemo- and radio-therapies, or others whose objective is to control the information between cells through the proteins pathways. The problem when such number of populations is considered (cells, therapies, biochemical interactions, gens, ...) is to manage with the resulting system of equations. The idea of this paper is to deduce a hydrodynamical limit of hyperbolic type (we try to skip diffusive phenomena) in order to propose new macroscopic models when studying these kind of problems.

The above objective is pursued by the mathematical methods of the kinetic theory for active particles [3] (KTAP), which has been applied to model various complex systems in life sciences, for instance social systems [4,5], behavioral economy [6] or epidemics with gene mutations [7]. This theory is here properly developed to describe, by mathematical equations,

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multicellular systems according to a multiscale approach where the dynamics of cells is determined by the dynamics at the molecular scale, while models at tissue level are derived from the underlying description at the cellular scale.

The main difficulty consists in taking into account the different complexity sources that characterize living systems. Specifically, their ability to organize the dynamics following specific strategies rather than rules of classical mechanics. These systems are *complex* considering that the dynamics of a few entities does not generate straightforwardly the dynamics of the whole system. Emerging collective behaviors do not appear to be related to the individual dynamics and not even to the dynamics of a few entities. The above mentioned strategy developed by the interacting individuals depends on their density and topological distribution.

The contents are focused on mathematical aspects with the aim of covering the whole path from the lower scale to the higher macroscopic of tissues. The final aim consists of contributing to a background for a mathematical theory of *complex biological system*. This challenging objective means that such a theory should be valid for a broader variety of systems rather than for specific systems only.

This paper is organized through three more sections that follow this introduction. Section 2 analyzes some common features of the class of biological systems under consideration viewed as a complex system. Several sources of complexity are considered: the ability to express a strategy which modifies laws of classical mechanics, the ability to adapt such a strategy to the presence and localization of other cells of different populations, Darwinian evolution due to adaptation to the mutating environmental conditions, competition for survival followed by proliferative and destructive actions, and so on. All these characteristics represent a target for the development of mathematical tools. In other words, the mathematical approach is required to possess the ability to describe all the above characteristics. Section 3 deals with the derivation of the mathematical tools first for closed systems in absence of external actions, and subsequently for open systems. The first step consists in the decomposition of the overall systems, to reduce its complexity, into functional subsystems by a suitable development of the theory of functional modules by Hartwell [8] revisited in [2]. The second step is the modelling of interactions at the individual level of active particles, where the output is determined by stochastic games. Subsequently, a mathematical framework is derived, using the modelling of microscopic interactions, by a suitable balance equation in the elementary space of microscopic states. The third step is modelling open systems. The final objective consists in the derivation of suitable frameworks which act as background paradigm for the derivation of specific models. Section 4 applies the mathematical frameworks offered by the preceding section to modelling some specific phenomena of interest in biological sciences. After a preliminary analysis on the modelling multicellular systems, onset of pathological states and competitions with the immune system under the specific action of external therapeutic actions, the contents are focused on the derivation of macroscopic models of biological growing and progressing tissues from the underlying description at the cellular scale.

## 2. Complexity analysis

This section provides a brief overview of various common features of large living systems constituted by several interacting entities, for instance genes or cells. These characteristics are viewed as sources of complexity to be taken into account in the derivation of the mathematical tools to be used towards modelling. The contents of this section do not claim to be exhaustive, but simply to identify an essential set of characteristics that cannot be neglected in the modelling approach.

- *Expression of strategic ability*: Living entities have the ability to express, at all scales, an individual strategy that depends also on the behavior of the surrounding entities and on environmental conditions. This strategy is the cause of their dynamics, which is not generally in agreement with the laws of classical mechanics. This strategy evolves in time due to Darwinian selection, and, in some cases, may even generate proliferative and/or destructive events.
- *Heterogeneity*: The ability to express a strategy is heterogeneously distributed over the interacting entities. Consequently, also the parameters of the dynamics are distributed. The heterogeneous distribution implies that the deterministic expression of a reductionistic approach should be replaced by a stochastic representation by means of random variables.
- *Interactions*: Interactions modify the state of the interacting entities according to the strategy they develop based on their space and state distribution. These play a game at each interaction, and the output is technically related to the ability they have to develop a certain strategy. Given a certain input, the output cannot, in general, be deterministically identified.
- *Distance and topology in interactions*: Interactions can occur not only by contacts, but can also be distributed in space considering that living systems have the ability to communicate even for long range distances. Interactions may not be homogeneous in space considering that interacting entities may, in some cases, choose different observation paths. Topological distribution plays a role when communication among entities selects specific paths and directions.
- *Mutations, learning, and evolution*: Characteristics of living systems, in some cases, evolve in time. This evolution can correspond with mutations to adaptation to mutating environmental conditions. Learning processes can generate an evolution of the ability to express specific strategies [9].
- *Multiscale aspects and interaction of several components*: Generally, complex systems are constituted by interacting components distributed in space, in some cases constrained along networks. Each component is constituted by several interacting entities, while the scale (microscopic or macroscopic) suitable to describe each component may not be the same for all of them, and while interactions between different scales characterizes each element.

### 3. Mathematical tools of the kinetic theory for active particles

This section deals with the derivation of mathematical structures suitable to act as a background paradigm for the derivation of models of large systems of interacting entities, which are not subject to external actions. The type of entities is not yet specified, leaving this matter to the next sections.

The above objective is pursued in three steps. The first one is focused on the problem of reducing the complexity which is generated when the number of species is large. This is a relevant source of complexity. Indeed, living systems, differently from the greatest generality of systems of the inert matter, are characterized by the presence of a variety of components. In some cases, such a number can be so large that the complexity of analytic and computational methods developed towards modelling cannot be effectively dealt with. Therefore, it is useful reducing it by decomposing the system into suitable functional subsystems according to well defined rules. The second step consists in the development, in absence of external actions, of the kinetic theory for active particles, which provides a general mathematical structure that acts as a background paradigm for the derivation of specific models for closed systems. The third step generalizes the modelling approach to the case of open systems by taking into account the role of external actions.

#### 3.1. Decomposition into functional subsystems

As already mentioned, the overall system needs to be decomposed into subsystems, which, according to [2], are identified by the biological functions that are collectively expressed by a number of entities, which cooperate with the same strategy. The modular approach by Hartwell [8] already allows one to reduce complexity by decomposing biological systems into several interacting subsystems. Indeed, this approach can be possibly considered the first fundamental contribution to system biology [10]. Hartwell's theory has been revisited in [2] focusing on multicellular systems described by the kinetic theory for active particles [11–13]. For instance, in the case of multicellular systems, modules are identified by populations of cells which have the ability to express collectively a certain behavior, which is the same in each module and has to be identified by a scalar variable. Some technical definitions are useful to clarify these issues.

- A *functional subsystem* is a collection of active particles which have in common the same *functionality*, whose intensity or *activity* is regarded as a scalar variable. Then, the *activity* variable has a different meaning for each particular subsystem. The whole system is constituted by several interacting functional subsystems.
- The physical variable charged to describe the state of each active particle is called *microscopic state*, which is constituted by the *activity*, described before, the *geometrical microscopic state* and the *mechanical microscopic state*. When the active particles are points of the Euclidean space, their position  $\mathbf{x}$  is the geometrical microscopic state, while the mechanical microscopic state is their velocity  $\mathbf{v}$ . The space of the states of the active particles is called *microscopic state space*.

Let us now consider the mathematical representation of a large system constituted by active particles belonging to different functional subsystems. The physical microscopic state of the particles is identified by a variable suitable to describe their state, while the overall state of the whole system is described by a probability distribution over the microscopic state of the particles according to the following definition:

- The description of the overall state of the system is defined by the distribution function  $f_i$  over position and velocity, which identify the mechanical state of the active particles, and the activity variable, which identifies the biological function:

$$f_i = f_i(t, \mathbf{x}, \mathbf{v}, u) : [0, T] \times D_{\mathbf{x}} \times D_{\mathbf{v}} \times D_u \rightarrow \mathbb{R}_+,$$

where  $i = 1, \dots, n$  refers to the specific subsystem. The function  $f_i$  is called *generalized distribution function*, and is such that  $\int_{D_{\mathbf{x}} \times D_{\mathbf{v}} \times D_u} f_i(t, \mathbf{x}, \mathbf{v}, u) d\mathbf{x}d\mathbf{v}du$  denotes, for the  $i$ th subsystem, the number of active particles whose state, at time  $t$ , is in the elementary volume of the space of microscopic states. The whole domain of the microscopic states has been defined by  $D_{\mathbf{x}} \times D_{\mathbf{v}} \times D_u$ .

In particular, the *local density* of the  $i$ th functional subsystem is given by:

$$\rho[f_i](t, \mathbf{x}) = \int_{D_{\mathbf{v}} \times D_u} f_i(t, \mathbf{x}, \mathbf{v}, u) d\mathbf{v}du, \tag{3.1}$$

while, integration over the volume  $D_{\mathbf{x}}$  containing the particles gives the *total mass* of the  $i$ th subsystem:

$$N_i(t) = \int_{D_{\mathbf{x}}} \rho_i(t, \mathbf{x}) d\mathbf{x},$$

which depends on time due to the role of proliferative or destructive interactions, as well as to the flux of particles through the boundaries of the volume. The *total mass*  $N = N(t)$  of all subsystems is given by the sum of all  $N_i(t)$ .

First order moments provide either *linear mechanical macroscopic* quantities, or *linear activity macroscopic* quantities. For instance, the *local velocity* of particles, at time  $t$  in the position  $\mathbf{x}$ , is defined by

$$\mathbf{U}[f_i](t, \mathbf{x}) = \frac{1}{\rho[f_i](t, \mathbf{x})} \int_{D_{\mathbf{v}} \times D_u} \mathbf{v} f_i(t, \mathbf{x}, \mathbf{v}, u) d\mathbf{v}du, \tag{3.2}$$

while the *local activation density* is given by:

$$a[f_i](t, \mathbf{x}) = \frac{1}{\rho[f_i](t, \mathbf{x})} \int_{D_v \times D_u} u f_i(t, \mathbf{x}, \mathbf{v}, u) d\mathbf{v} du.$$

Additional moment calculations and their interpretation are delivered in [3].

### 3.2. Mathematical structures for closed systems

This subsection is focused on the derivation, in absence of external actions, of mathematical structures suitable to describe the evolution in time and space of the stochastic variables that model, according to the preceding subsection, the state of the system.

The strategy to derive these equations follows the guidelines of the classical kinetic theory – namely, by a balance equation for net flow of particles in the elementary volume of the microscopic state space by transport and interactions. In the interactions among active particles we will use the notation  $(\mathbf{x}, \mathbf{v}, u)$  for the microscopic state of *test* particles, i.e., the particles under study, and  $(\mathbf{x}_*, \mathbf{v}_*, u_*)$  for the *candidate* particles which can become a test particle after a potential interaction with a *field* particle, whose microscopic state will be denoted by  $(\mathbf{x}^*, \mathbf{v}^*, u^*)$ .

Following the scheme proposed in [13], see also [3], two different types of interactions are considered: *conservative interactions*, when particles modify only their microscopic state, and *non conservative interactions*, when interactions generate proliferation or destruction of particles in their microscopic state.

The mathematical framework refers to the evolution in time and space of the test particle. The derivation for  $f_i$  is based on the following balance equation in the elementary volume  $d\mathbf{x}d\mathbf{v}du$  of the phase space:

$$\frac{df_i}{dt} d\mathbf{x}d\mathbf{v}du = \left( G_i[\mathbf{f}] - L_i[\mathbf{f}] + S_i[\mathbf{f}] \right) d\mathbf{x}d\mathbf{v}du, \tag{3.3}$$

where interactions of candidate and test particles refer to the field particles and  $\mathbf{f} = \{f_i\}_{i=1}^n$ . Moreover, for the  $i$ th functional subsystem:

$G_i[\mathbf{f}]$  denotes the *gain* of candidate particles into the state  $(\mathbf{x}, \mathbf{v}, u)$  of the test particle;

$L_i[\mathbf{f}]$  models the *loss* of test particles with state  $(\mathbf{x}, \mathbf{v}, u)$ ;

$S_i[\mathbf{f}]$  models *proliferation/destruction* of test particles in their microscopic state.

Let us consider the interactions among candidate or test particles of the  $i$ th population and the field particles of the  $j$ th population. The derivation of the expression of the above quantities needs the following hypothesis:

**H.3.1.** The candidate and test particles in  $\mathbf{x}$ , with state  $\mathbf{v}_*, u_*$  and  $\mathbf{v}, u$ , respectively, interact with the field particles in  $\mathbf{x}^*$ , with state  $\mathbf{v}^*, u^*$  located in its interaction domain  $\mathbf{x}^* \in \Omega \subseteq D_{\mathbf{x}}$ .

**H.3.2.** Interactions are weighted by a suitable term  $\eta_{ij}[\rho_j](\mathbf{x}^*)$ , that can be interpreted as an *interaction rate*, which depends on the local density in the position of the field particles.

**H.3.3.** The distance and topological distribution of the intensity of the interactions is weighted by a function  $p_{ij}(\mathbf{x}, \mathbf{x}^*)$  such that:

$$\int_{\Omega} p_{ij}(\mathbf{x}, \mathbf{x}^*) d\mathbf{x}^* = 1.$$

**H.3.4.** The candidate particle modifies its state according to the probability density  $\mathcal{A}$  defined as follows:

$$\mathcal{A}_{ij}(\mathbf{v}_* \rightarrow \mathbf{v}, u_* \rightarrow u | \mathbf{v}_*, \mathbf{v}^*, u_*, u^*),$$

where  $\mathcal{A}$  denotes the probability density that a candidate particle with state  $\mathbf{v}_*, u_*$  reaches the state  $\mathbf{v}, u$  after an interaction with the field particles with state  $\mathbf{v}^*, u^*$ , while the test particle loses its state  $\mathbf{v}$  and  $u$  after interactions with field particles with velocity  $\mathbf{v}^*$  and activity  $u^*$ .

**H.3.5.** The test particle, in  $\mathbf{x}$ , can proliferate or disappear, due to encounters with field particles in  $\mathbf{x}^*$ , with rate  $\mu_{jk}^i(u_* \rightarrow u | u_*, u^*)$ , which denotes the proliferation/destruction rate into the functional subsystem  $i$  and state  $u$ , due to the encounter of particles belonging to the functional subsystems  $j$  and  $k$ . Destructive events can occur only within the same population with rate  $\mu_{ik}^i(u, u^*)$ , namely in the state of the test particle.

**Remark 3.1.** The following factorization, proposed in [3],

$$\mathcal{A}_{jk}(\mathbf{v}_* \rightarrow \mathbf{v}, u_* \rightarrow u | \mathbf{v}_*, \mathbf{v}^*, u_*, u^*) = \mathcal{B}_{jk}(u_* \rightarrow u, | u_*, u^*) \mathcal{C}_{jk}(\mathbf{v}_* \rightarrow \mathbf{v} | \mathbf{v}_*, \mathbf{v}^*, u_*, u^*)$$

can be used in a variety of applications including those dealt with in the second part of this paper. If these quantities are probability densities, then the following properties hold true:

$$\int_{D_u} \mathcal{B}_{jk}(u_* \rightarrow u, | u_*, u^*) du = 1, \quad \forall u_*, u^*,$$

and

$$\int_{D_v} C_{jk}(\mathbf{v}_* \rightarrow \mathbf{v} | \mathbf{v}_*, \mathbf{v}^*, u_*, u^*) d\mathbf{v} = 1, \quad \forall \mathbf{v}_*, \mathbf{v}^*, u_*, u^*,$$

and therefore that of  $\mathcal{A}_{jk}$ :

$$\int_{D_v \times D_u} \mathcal{A}_{jk}(\mathbf{v}_* \rightarrow \mathbf{v}, u_* \rightarrow u | \mathbf{v}_*, \mathbf{v}^*, u_*, u^*) d\mathbf{v} du = 1, \quad \forall \mathbf{v}_*, \mathbf{v}^*, u_*, u^*.$$

The derivation of the mathematical framework is obtained by replacing the expression of the gain and loss terms into (3.3), where the total derivative of the distribution function has to be written using the transport with velocity  $\mathbf{v}$ . The result derived by Assumptions H.3.1–3.5 is as follows:

$$(\partial_t + \mathbf{v} \cdot \nabla_{\mathbf{x}}) f_i(t, \mathbf{x}, \mathbf{v}, u) = J_i[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u), \tag{3.4}$$

where

$$J_i[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u) = \sum_{j=1}^n \left( G_{ij}[\mathbf{f}] - L_{ij}[\mathbf{f}] \right) (t, \mathbf{x}, \mathbf{v}, u) + \sum_{j=1}^n \sum_{k=1}^n S_{jk}^i[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u), \tag{3.5}$$

and more precisely

$$\begin{aligned} G_{ij}[\mathbf{f}] &= \int_{\Lambda} \eta_{ij}[\rho_j](t, \mathbf{x}^*) p_{ij}(\mathbf{x}, \mathbf{x}^*) \mathcal{B}_{ij}(u_* \rightarrow u | u_*, u^*) C_{ij}(\mathbf{v}_* \rightarrow \mathbf{v} | \mathbf{v}_*, \mathbf{v}^*, u_*, u^*) \\ &\quad \times f_i(t, \mathbf{x}, \mathbf{v}_*, u_*) f_j(t, \mathbf{x}^*, \mathbf{v}^*, u^*) du_* du^* d\mathbf{v}_* d\mathbf{v}^* d\mathbf{x}^*, \\ L_{ij}[\mathbf{f}] &= f_i(t, \mathbf{x}, \mathbf{v}, u) \int_{\Gamma} \eta_{ij}[\rho_j](t, \mathbf{x}^*) p_{ij}(\mathbf{x}, \mathbf{x}^*) f_j(t, \mathbf{x}^*, \mathbf{v}^*, u^*) du^* d\mathbf{v}^* d\mathbf{x}^* \end{aligned}$$

and

$$S_{jk}^i[\mathbf{f}] = \int_{\Gamma \times D_u} \eta_{jk}[\rho_k](t, \mathbf{x}^*) p_{jk}(\mathbf{x}, \mathbf{x}^*) \mu_{jk}^i(u_* \rightarrow u | u_*, u^*) f_j(t, \mathbf{x}, \mathbf{v}, u_*) f_k(t, \mathbf{x}^*, \mathbf{v}^*, u^*) du_* du^* d\mathbf{v}^* d\mathbf{x}^*,$$

with  $\Lambda = \Omega \times D_v^2 \times D_u^2$  and  $\Gamma = \Omega \times D_v \times D_u$ .

### 3.3. Mathematical structures for open systems

Modelling the structure in the case of open systems means taking into account, in (3.4), also the action of external agents added by therapies which may act, for each functional subsystem, either at the macroscopic scale on the variable  $u$ , or at the microscopic scale on the distribution function  $f_i$ .

The derivation of the mathematical structure proposed in this subsection does not consider actions on the mechanical variables, and is developed in view of the applications to modelling multicellular systems that is dealt with in the next section. A useful reference is offered by [14] and [15], where this topic is developed for a mathematical model where the kinetic theory is applied to describe the competition between cancer and immune cells under therapeutic actions, and by [16], where various models of space dynamics are compared within the framework of the kinetic theory for active particles.

Modelling macroscopic actions essentially means the identification of the term  $K_i = K_i(t, \mathbf{x}, u)$  supposed to be a known function of its arguments. The action  $K_i$  acts over the variable  $u$  for each functional subsystem. The resulting equation, for  $i = 1, \dots, n$ , is as follows:

$$(\partial_t + \mathbf{v} \cdot \nabla_{\mathbf{x}}) f_i(t, \mathbf{x}, \mathbf{v}, u) + \partial_u \left( K_i(t, \mathbf{x}, u) f_i(t, \mathbf{x}, \mathbf{v}, u) \right) = J_i[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u). \tag{3.6}$$

In the following, we are interested in external actions related to therapies, which act in a microscopic level. Then, we will not include these macroscopic actions in the next sections.

Modelling external actions at the microscopic scale means modelling of functional subsystems generated by the outer system. Their representation can be delivered by the distribution functions:

$$g_j(t, \mathbf{x}, w), \quad r = 1, \dots, m, \quad w \in D_w = D_u, \tag{3.7}$$

depending on time, space and on a variable  $w$  modelling the activity of the outer functional subsystem. We have assumed, for simplicity, that the domain of  $w$  coincides with that of  $u$ .

The action of the outer system generates a dynamics analogous to that of the inner system, namely the modification of the activity variable for each functional subsystem, transition from one subsystem to the other, and proliferative/destructive events. Therefore, by following the same reasoning of Section 3, the following mathematical structure is derived:

$$(\partial_t + \mathbf{v} \cdot \nabla_{\mathbf{x}}) f_i(t, \mathbf{x}, \mathbf{v}, u) = J_i[\mathbf{f}](t, \mathbf{x}, \mathbf{v}, u) + Q_i[\mathbf{f}, \mathbf{g}](t, \mathbf{x}, \mathbf{v}, u), \tag{3.8}$$

where the operators  $J_i[\mathbf{f}]$  are given by (3.5), while the operator  $Q_i[\mathbf{f}, \mathbf{g}]$  describes interactions with the outer system corresponding to the distribution functions  $\mathbf{g} = \{g_j\}_{j=1}^m$ . The detailed expression is as follows:

$$Q_i[\mathbf{f}, \mathbf{g}] = \sum_{j=1}^m \left( G_{ij}^e[\mathbf{f}, \mathbf{g}] - L_{ij}^e[\mathbf{f}, \mathbf{g}] + S_{ij}^e[\mathbf{f}, \mathbf{g}] \right) (t, \mathbf{x}, \mathbf{v}, u), \tag{3.9}$$

where

$$\begin{aligned} G_{ij}^e[\mathbf{f}, \mathbf{g}] &= \int_{\Lambda} \eta_{ij}^e[\rho_j](t, \mathbf{x}^*) p_{ij}^e(\mathbf{x}, \mathbf{x}^*) \mathcal{B}_{ij}^e(u_* \rightarrow u | u_*, u^*) \mathcal{C}_{ij}^e(\mathbf{v}_* \rightarrow \mathbf{v} | \mathbf{v}_*, \mathbf{v}^*, u_*, u^*) \\ &\quad \times f_i(t, \mathbf{x}, \mathbf{v}_*, u_*) g_j(t, \mathbf{x}^*, \mathbf{v}^*, w^*) du_* dw^* d\mathbf{v}_* d\mathbf{v}^* d\mathbf{x}^*, \\ L_{ij}^e[\mathbf{f}, \mathbf{g}] &= f_i(t, \mathbf{x}, \mathbf{v}, u) \int_{\Gamma} \eta_{ij}^e[\rho_j](t, \mathbf{x}^*) p_{ij}^e(\mathbf{x}, \mathbf{x}^*) g_j(t, \mathbf{x}^*, \mathbf{v}^*, w^*) dw^* d\mathbf{v}^* d\mathbf{x}^*. \end{aligned}$$

and

$$S_{ij}^e[\mathbf{f}, \mathbf{g}] = f_i \int_{\Gamma} \eta_{ij}^e[\rho_j](t, \mathbf{x}^*) p_{ij}^e(\mathbf{x}, \mathbf{x}^*) \mu_{ij}^e(t, u, w^*) g_j(t, \mathbf{x}^*, \mathbf{v}^*, w^*) dw^* d\mathbf{v}^* d\mathbf{x}^*.$$

Here,  $\eta_{ij}^e[\rho_j]$  models the encounter rates between the  $j$ th external action with state  $w^*$  and the  $i$ th candidate particle with state  $u_*$ , and depends on the local density  $\rho_j$  associated with the external action  $g_j$ .

$\mathcal{B}_{ij}^e(u_* \rightarrow u, v^*)$  denotes the probability density that the candidate particle of the  $i$ th subsystem with state  $u_*$  falls into the state  $u$  of the same subsystem due to interactions with the  $j$ th action with state  $w^*$ . The corresponding variation of velocity is denoted by  $\mathcal{C}_{ij}^e(\mathbf{v}_* \rightarrow \mathbf{v} | \mathbf{v}_*, \mathbf{v}^*, u_*, u^*)$ .

$\mu_{ij}^e(t, u, w^*)$  models the net proliferation/destruction into the  $i$ th population of the *test* particle with state  $u$ , due to interactions, which occur with rate  $\eta_{ij}^e$ , with the  $j$ th action with state  $w^*$ . We remark here the time dependence introduced, which will be explained in the next section.

**Remark 3.2.** The mathematical framework related to non conservative actions is slightly less general than that proposed for closed systems. In fact, it has been assumed that therapeutic actions do not have the ability to induce mutations. Possibly future therapeutic actions can induce this type of repair.

The above framework is very general, although some particular applications can be developed by taking advantage of some particularizations or developments of the above equations. The particular case, which is here considered, has been used to model the competition between cancer and immune cells and the derivation of macroscopic equations [13]. It can be rapidly shown how such a particularization can be obtained also in the case with a variable number of equations including the presence of therapeutic actions.

### 3.4. Stochastically perturbed systems

Let us finally consider a stochastic perturbation in velocity of the whole system,

$$(\partial_t + \mathbf{v} \cdot \nabla_{\mathbf{x}}) f_i = \nu_i L_i[f_i] + J_i[\mathbf{f}] + Q_i[\mathbf{f}, \mathbf{g}], \tag{3.10}$$

where  $J_i[\mathbf{f}]$  and  $Q_i[\mathbf{f}, \mathbf{g}]$  are the inner and outer operators defined in (3.8). Here:

- $\nu_i$  is the turning rate or turning frequency, hence  $\tau_i = \frac{1}{\nu_i}$  is the mean run time.
- The linear transport term describes the dynamics of biological organisms modelled by a velocity-jump process,

$$L_i[f_i] = \int_{D_{\mathbf{v}}} \left( T_i(\mathbf{v}^* \rightarrow \mathbf{v}) f_i(t, \mathbf{x}, \mathbf{v}^*, u) - T_i(\mathbf{v} \rightarrow \mathbf{v}^*) f_i(t, \mathbf{x}, \mathbf{v}, u) \right) d\mathbf{v}^*, \tag{3.11}$$

where  $T_i(\mathbf{v}^* \rightarrow \mathbf{v})$  is, for the  $i$ th subsystem, the probability kernel for the new velocity  $\mathbf{v} \in D_{\mathbf{v}}$  assuming that the previous velocity was  $\mathbf{v}^*$ .

As usual, we mention here the hypotheses on the turning operators  $L_i$ :

**H.3.5.** Each turning operator  $L_i$  satisfies the following solvability conditions:

$$\int_{D_{\mathbf{v}}} L_i[f] d\mathbf{v} = \int_{D_{\mathbf{v}}} \mathbf{v} L_i[f] d\mathbf{v} = 0. \tag{3.12}$$

**H.3.6.** There exists a unique function  $M_{\rho, \mathbf{U}}^i \in L^1(D_{\mathbf{v}}, (1 + |\mathbf{v}|) d\mathbf{v})$ , for all  $\rho \geq 0$  and  $\mathbf{U} \in D_{\mathbf{v}}$ , verifying

$$L_i(M_{\rho, \mathbf{U}}^i) = 0, \quad \int_{D_{\mathbf{v}}} M_{\rho, \mathbf{U}}^i(\mathbf{v}) d\mathbf{v} = \rho, \quad \int_{D_{\mathbf{v}}} \mathbf{v} M_{\rho, \mathbf{U}}^i(\mathbf{v}) d\mathbf{v} = \rho \mathbf{U}. \tag{3.13}$$

Here, variables  $t, x$  and  $u$  act as parameters. These hypotheses allow to derive in the next section macroscopic scale hyperbolic systems.

#### 4. On the modelling of complex biological systems

This section aims at showing how the mathematical tools derived in the preceding sections can be applied both to the modelling of complex biological systems constituted by different cell populations, interacting in vivo, which are carrier of a pathological state and to derive macroscopic tissue level equations from the underlying description delivered by the kinetic theory for active particles. A well settled literature exists for both topics. Therefore, the content is focused on the technical developments introduced in this present paper.

##### 4.1. Modelling the competition between cancer and immune cell under therapeutic actions

Let us consider the modelling of the competition between cells that mutated towards highly progressing states and that are contrasted both by the immune system and suitable therapeutic actions. The literature on the application of the methods of the kinetic theory for active particles to modelling the above phenomena is documented in various papers as well as in the book [12] and in the review paper [17] and references therein.

This paper shows how the approach proposed in [12] can be generalized to deal with therapeutic actions. Here only a few guidelines are given to contribute to the conceptual background for the derivation of tissue level models that will be performed in the second part of this section.

In general, the modelling approach should take into account the following aspects:

- (i) Physical characteristics of the functional subsystems constituting the overall system including that of new born subsystems, and physical meaning of the activity variable corresponding to each functional subsystems;
- (ii) Conservative and proliferative/destructive interactions within closed systems;
- (iii) Specific role of therapeutic actions;

A few more details can be added, focused on a system of four populations such that only two functional subsystems exist at the initial time  $t = 0$ . Subsequently the dynamics of the interactions generate the onset of new subsystems. The generalization to a higher number of populations is immediate. In detail, the following guidelines can be applied toward modelling:

• *Functional subsystems and activity variables.* Let us consider the following functional subsystems:

$i = 1$ , immune cells whose activity variable is defined over the positive real line  $u \in \mathbb{R}_+$ , where increasing values of  $u$  correspond to increasing activation.

$i = 2$ , endothelial cells whose activity variable is defined over the positive real line  $u \in \mathbb{R}_+$ , where increasing values of  $u$  correspond to higher trend to mutations.

$i = 3, 4$ , mutated abnormal cells, or tumor cells, whose activity variable is defined over the positive real line  $u \in \mathbb{R}_+$ , where increasing  $i$  corresponds to cells with increasing progression and mutation ability.

• *Interactions within closed systems.* Modelling cell interactions is a crucial step in the derivation of specific models. In the interaction of the different subsystems with the neighborhood we have to consider two different actions. There is a short range interaction with the closer cells (independent of their character: tumor, endothelial cells, ...) which provides a term of interaction which is a function inversely proportional to the distance between cells. At the same time, there is another influence coming from the genetic scale which takes into account the transfer of information between cells that have a component of closeness but also the signals could produce a long range communication affecting cells to large distances while other closer to the signal source could not transduce this information and as a consequence do not activate some specific gene codes; see [18,19]. Then we consider that the topological distribution of the intensity of the interactions  $p_{ij}(\mathbf{x}, \mathbf{x}^*)$  is constituted by a short range and a long range part, i.e.,  $p_{ij}(\mathbf{x}, \mathbf{x}^*) = \beta_S + \beta_L$ , where  $\beta_S$  is some increasing function of the inverse of the distances between cells (i.e.  $\beta_S = \beta_S(|\mathbf{x} - \mathbf{x}^*|^{-1})$ ), being  $\mathbf{x}$  and  $\mathbf{x}^*$  the corresponding positions of the test and field cells, while  $\beta_L$  collects the different signals independently of the source origin (i.e.  $\beta_L = \beta_L(\mathbf{x}^*)$ ).

The other kernels involved in (3.10) should be specified in agreement with the molecular biology relationship between interacting entities. We only impose some integrability conditions in the next section.

• *Role of therapeutic actions*

The research on therapies against cancer is a hot topic with different points of view and approaches that range from the chemotherapy and radiotherapy to other less aggressive ones such as the control of the cellular information or micro-processing to restoring DNA, which could constitute the future for this area. The therapeutic actions exert specific reactions in the different cell populations as well as in the immune system. For instance, in the last few years the precision in the location and dosing of radio and chemotherapies has been improved considerably but in spite of this progress the application of these therapies affect not only the tumor cells but also, in a crucial way, the immune system, weakening it, and to normal cells. Concerning this point let us briefly comment that the optimization of the therapy protocols, and in particular for radio and chemotherapies, is an important problem that could produce immediate benefits because there are no reasons to support a protocol where the dose and the timing is equidistributed in order to optimize the reduction of the tumor size.

The function evolving in the therapy process modulates the activation variable. Then, in the case of applying such type of therapies the system must include the protocol timing affecting the different cells populations at punctual times  $t_1 < t_2 < \dots < t_{k_j}$  corresponding to the time of administration of the chemo or radio dose. But in addition the cells are affected during some typical action time  $\tau$  by their capacity of proliferation/destruction due, among other reasons, to the

presence of chemical substances and the acidity of the media after these aggressive therapies. Therefore, we have to include also the positive input to trigger and improve immune response to cancer incorporating new clinical trials that use a patient's own cells to destroy tumors. Then, the net proliferation/destruction coefficient  $\mu_{i,j}^e$  associated to the population  $i$  and the therapy  $j$ , can be decomposed in the form

$$\mu_{i,j}^e(t, u, w^*) = \sum_{k=1}^{t_{k_j}} (1 - \mu_{i,j}^1(u, w^*)) \delta_{t=t_k} + \mu_{i,j}^2(u, w^*) \chi_{[t_k, t_k+\tau]} \tag{4.1}$$

in such a way that  $t_k$  are the times in which the dose is applied,  $\delta_{t=t_k}$  and  $\chi_{[t_k, t_k+\tau]}$  stand for the Delta function at point  $t_k$  and the characteristic function of the time interval  $[t_k, t_k + \tau]$  respectively,  $\mu_{i,j}^1(u, w^*)$  is the (positive) rate of *immediate destruction*, and  $\mu_{i,j}^2(u, w^*)$  is the rate (with sign) of proliferation/destruction due to the therapy which acts during a given *action time*  $\tau$  after each treatment.

With regard to the non-aggressive therapies, the influence in the diverse populations under consideration is different to that in the previous cases because is based both on the protection and reinforcement of the immunologic system as well as in stopping or drastically diminishing the capacity of proliferation of tumor cell which allows the immune system to work in eliminating or reducing the invasive tumor cells. This way of action implies the aim of controlling the transport of cellular information (through morphogens) in order to avoid the activations of some genetic codes. In this spirit, let us mention the interesting work of A. Ruiz I Altaba and coworkers [20] about the direct relation between the concentration of Sonic Hedgehog (*Shh*) and the production of nuclear  $GLI_A$  in contrast with the evolution of tumor growth. In the same line, in [21] it is shown how the treatment reduces the transport of *Shh*, then inhibits the concentration of  $GLI_A$  and as a consequence the tumor disappears at least in experiments with rats. Modeling the transport of morphogens and the activation of genetic codes is an interesting subject that has been studied from the pioneering work of Turing [22] and that recently has been improved by different authors, see [23–26]. Coupling the system proposed in this work with the models for the transport of morphogens will provide an interesting micro and macro scale interaction. At this point it is also interesting to refer to the recent progress in modelling the influence of the activation and concentration of *P53* morphogen; see [27]. Therefore, these non-aggressive therapies are represented by positive coefficients  $\mu_{1,j}^2(u, w^*)$  which represent the reinforcement of the immunologic system and negative destruction rates  $\mu_{3,j}^2(u, w^*)$  and  $\mu_{4,j}^2(u, w^*)$  corresponding to a reduction of the possibility of duplication of tumor invasive cells. The rest of the work must be done by the immune response of the patient.

With respect to the distance of interactions between cells and external substances due to therapies, we can take into account the same considerations as those for closed systems and decompose the external topological distribution of the intensity of the interactions as follows:  $p_{ij}^e(\mathbf{x}, \mathbf{x}^*) = \beta_S^e(|\mathbf{x} - \mathbf{x}^*|^{-1}) + \beta_L^e(\mathbf{x}^*)$ , in short and long range parts.

#### 4.2. Derivation of macroscopic tissue models

After having shown how the mathematical frameworks proposed in the preceding sections can be used to model complex biological systems together with the action of therapeutic treatment, let us consider the derivation of macroscopic tissue equations from the underlying description offered by the kinetic theory.

This topic has been dealt with by various authors for less general models using both the diffusion (parabolic) or high-field (hyperbolic) scaling – see among others [28–38]. This literature refers to models with a fixed number of equations – specifically one component or binary mixtures. Some papers [28–30] also consider the modification of biological state and proliferative destructive events. This amounts to deriving macroscopic equations with source terms.

The essential novelty of this paper consists in dealing with a larger number of equations taking into account the role of external actions. Technically, asymptotic methods amount to expanding the distribution function in terms of a small dimensionless parameter related to the intermolecular distances (the space-scale dimensionless parameter) that is equivalent to the connections between the biological constants. The obtained limit is singular and the convergence properties can be proved under suitable technical assumptions. In this work biological interactions do not follow classical mechanical rules, and biological activity may play a relevant role in determining the dynamics and modifying the classical mechanics.

The derivation of macroscopic equations needs an assessment of a suitable scaling and asymptotic expansion. Bearing this in mind, let us consider a *hyperbolic scaling* formally corresponding to the following choice of scale:

$$t \rightarrow \varepsilon t, \quad x \rightarrow \varepsilon x \Rightarrow tv = \frac{1}{\varepsilon},$$

which, after a rigorous scaling of the system analogous to that given in [31,32], produces the following non-dimensional model:

$$\varepsilon (\partial_t + \mathbf{v} \cdot \nabla_{\mathbf{x}}) f_i^\varepsilon = L_i[f_i^\varepsilon] + \varepsilon^{q_i} J_i^\varepsilon[\mathbf{f}^\varepsilon] + \varepsilon Q_i^\varepsilon[\mathbf{f}^\varepsilon, \mathbf{g}], \quad i = 1, 2, 3, 4. \tag{4.2}$$

Here, the scaled turning operator  $L_i[f_i]$  is considered to have the same expression (3.11), but with non-dimensional constants. The closed system interaction operator is scaled as follows

$$J_i^\varepsilon[\mathbf{f}^\varepsilon] = \sum_{j=1}^4 (G_{ij}[\mathbf{f}^\varepsilon] - L_{ij}[f_i^\varepsilon])(t, \mathbf{x}, \mathbf{v}, u) + \varepsilon^{\delta_i} \sum_{j=1}^4 \sum_{k=1}^4 S_{jk}^i[\mathbf{f}^\varepsilon],$$

where we have retained the same notation for the non-dimensional gain  $G_{ij}$ , lost  $L_{ij}$  and proliferative/destructive  $S_{jk}^i$  term. Finally, the external therapeutic action preserves its own form (3.9) although it is multiplied by  $\varepsilon$  in (4.2). We do not introduce different scales for the external actions because we want to model the actions of therapies at a macroscopic level, and then we want to preserve these terms after the passage to the limit.

The hyperbolic macroscopic behavior is deduced from the limit  $\varepsilon \rightarrow 0$ . First, taking  $\varepsilon = 0$  in (4.2), we formally obtain  $L_i[f_i^0] = 0$ , so each  $f_i^0$  verifies the conditions of hypothesis H.3.6. Then, we have four limiting distributions of the form  $f_i^0 = M_{\rho_i^0, \mathbf{U}_i^0}$  corresponding to our four subsystems, and we have to study the equations satisfied by the equilibrium variables  $\rho_i^0$  and  $\mathbf{U}_i^0$ . To do that, integration over  $\mathbf{v}$  in (4.2) yields

$$\begin{aligned} \partial_t \rho_i^\varepsilon + \operatorname{div}(\rho_i^\varepsilon \mathbf{U}_i^\varepsilon) &= \varepsilon^{q_i-1} \sum_{j=1}^4 \int_{D_{\mathbf{v}}} (G_{ij}[\mathbf{f}^\varepsilon] - L_{ij}[\mathbf{f}^\varepsilon]) d\mathbf{v} + \varepsilon^{q_i+\delta_i-1} \sum_{j=1}^4 \sum_{k=1}^4 \int_{D_{\mathbf{v}}} S_{jk}^i[\mathbf{f}^\varepsilon] d\mathbf{v} \\ &+ \varepsilon^{q_i-1} \sum_{j=1}^m \int_{D_{\mathbf{v}}} (G_{ij}^e[\mathbf{f}^\varepsilon] - L_{ij}^e[\mathbf{f}^\varepsilon]) d\mathbf{v} + \varepsilon^{q_i+\delta_i-1} \sum_{j=1}^m \int_{D_{\mathbf{v}}} S_{ij}^e[\mathbf{f}^\varepsilon, \mathbf{g}] d\mathbf{v}. \end{aligned}$$

Analogously, multiplying (4.2) by  $\mathbf{v}$  and integrating leads to

$$\begin{aligned} \partial_t(\rho_i^\varepsilon \mathbf{U}_i^\varepsilon) + \operatorname{Div}\left(\int_{D_{\mathbf{v}}} \mathbf{v} \otimes \mathbf{v} f_i^\varepsilon d\mathbf{v}\right) &= \varepsilon^{q_i-1} \sum_{j=1}^4 \int_{D_{\mathbf{v}}} \mathbf{v} (G_{ij}[\mathbf{f}^\varepsilon] - L_{ij}[\mathbf{f}^\varepsilon]) d\mathbf{v} + \varepsilon^{q_i+\delta_i-1} \sum_{h=1}^4 \sum_{k=1}^4 \int_{D_{\mathbf{v}}} \mathbf{v} S_{hk}^i[\mathbf{f}^\varepsilon] d\mathbf{v} \\ &+ \varepsilon^{q_i-1} \sum_{j=1}^m \int_{D_{\mathbf{v}}} \mathbf{v} (G_{ij}^e[\mathbf{f}^\varepsilon] - L_{ij}^e[\mathbf{f}^\varepsilon]) d\mathbf{v} + \varepsilon^{q_i+\delta_i-1} \sum_{j=1}^m \int_{D_{\mathbf{v}}} \mathbf{v} S_{ij}^e[\mathbf{f}^\varepsilon, \mathbf{g}] d\mathbf{v}. \end{aligned}$$

Let us now consider a solution as a perturbation of the equilibrium  $f_i = M_{\rho_i^0, \mathbf{U}_i^0}^i + \varepsilon h_i$ , denoting  $\mathbf{M} = \{M_{\rho_i^0, \mathbf{U}_i^0}^i\}_{i=1}^4$  yields

$$\begin{aligned} \partial_t \rho_i^0 + \operatorname{div}(\rho_i^0 \mathbf{U}_i^0) &= O(\varepsilon^{q_i}) + \varepsilon^{q_i-1} \sum_{j=1}^4 \int_{D_{\mathbf{v}}} (G_{ij}[\mathbf{M}] - L_{ij}[\mathbf{M}]) d\mathbf{v} + \varepsilon^{q_i+\delta_i-1} \sum_{j=1}^4 \sum_{k=1}^4 \int_{D_{\mathbf{v}}} S_{jk}^i[\mathbf{M}] d\mathbf{v} \\ &+ \varepsilon^{q_i-1} \sum_{j=1}^m \int_{D_{\mathbf{v}}} (G_{ij}^e[\mathbf{M}, \mathbf{g}] - L_{ij}^e[\mathbf{M}, \mathbf{g}]) d\mathbf{v} + \varepsilon^{q_i+\delta_i-1} \sum_{j=1}^m \int_{D_{\mathbf{v}}} S_{ij}^e[\mathbf{M}, \mathbf{g}] d\mathbf{v}, \end{aligned}$$

and

$$\begin{aligned} \partial_t(\rho_i^0 \mathbf{U}_i^0) + \operatorname{Div}\left(\int_{D_{\mathbf{v}}} \mathbf{v} \otimes \mathbf{v} M_{\rho_i^0, \mathbf{U}_i^0}^i d\mathbf{v}\right) &= O(\varepsilon^{q_i}) + \varepsilon^{q_i-1} \sum_{j=1}^4 \int_{D_{\mathbf{v}}} \mathbf{v} (G_{ij}[\mathbf{M}] - L_{ij}[\mathbf{M}]) d\mathbf{v} \\ &+ \varepsilon^{q_i+\delta_i-1} \sum_{h=1}^4 \sum_{k=1}^4 \int_{D_{\mathbf{v}}} \mathbf{v} S_{hk}^i[\mathbf{M}] d\mathbf{v} + \varepsilon^{q_i-1} \sum_{j=1}^m \int_{D_{\mathbf{v}}} \mathbf{v} (G_{ij}^e[\mathbf{M}, \mathbf{g}] - L_{ij}^e[\mathbf{M}, \mathbf{g}]) d\mathbf{v} + \varepsilon^{q_i+\delta_i-1} \sum_{j=1}^m \int_{D_{\mathbf{v}}} \mathbf{v} S_{ij}^e[\mathbf{M}, \mathbf{g}] d\mathbf{v}. \end{aligned}$$

Let us define, as usual, the pressure tensor  $P_i^0$  as a measure of the statistical variation in velocity around the expected mean velocity  $\mathbf{U}_i^0$ ,

$$P_i^0(t, x, u) = \int_{D_{\mathbf{v}}} (\mathbf{v} - \mathbf{U}_i^0) \otimes (\mathbf{v} - \mathbf{U}_i^0) f_i^0 d\mathbf{v}. \tag{4.3}$$

Rewriting (4.3) as follows

$$\int_{D_{\mathbf{v}}} \mathbf{v} \otimes \mathbf{v} M_{\rho_i^0, \mathbf{U}_i^0}^i d\mathbf{v} = P_i^0 + \rho_i^0 (\mathbf{U}_i^0 \otimes \mathbf{U}_i^0), \tag{4.4}$$

is useful to eliminate  $\mathbf{v}$  in the second equation.

Let us now deal with the following specific cases which measure the relation between the mechanical variables, the biological rates and the therapies. Depending on the scales of the biological functions we can generate different hyperbolic systems, but we preserve, in the three cases, a source term modelling the proliferative/destructive action of the therapies.

Case 1.  $\delta_i \geq 0$  and  $q_i > 1$ : This is the simple conservative hyperbolic system:

$$\begin{cases} \partial_t \rho_i^0 + \operatorname{div}(\rho_i^0 \mathbf{U}_i^0) = 0, \\ \partial_t(\rho_i^0 \mathbf{U}_i^0) + \operatorname{Div}(\rho_i^0 (\mathbf{U}_i^0 \otimes \mathbf{U}_i^0) + P_i^0) = 0. \end{cases} \tag{4.5}$$

Case 2.  $\delta_i > 0$  and  $q_i = 1$ : In this case we preserve a source term related to conservative actions, and therapy actions into the closed system:

$$\begin{cases} \partial_t \rho_i^0 + \operatorname{div}(\rho_i^0 \mathbf{U}_i^0) = \sum_{j=1}^4 \int_{D_v} (G_{ij}[\mathbf{M}] - L_{ij}[\mathbf{M}]) \, dv + \sum_{j=1}^m \int_{D_v} (G_{ij}^e[\mathbf{M}, \mathbf{g}] - L_{ij}^e[\mathbf{M}, \mathbf{g}]) \, dv, \\ \partial_t (\rho_i^0 \mathbf{U}_i^0) + \operatorname{Div}(\rho_i^0 (\mathbf{U}_i^0 \otimes \mathbf{U}_i^0) + P^0) = \sum_{j=1}^4 \int_{D_v} \mathbf{v} (G_{ij}[\mathbf{M}] - L_{ij}[\mathbf{M}]) \, dv + \sum_{j=1}^m \int_{D_v} \mathbf{v} (G_{ij}^e[\mathbf{M}, \mathbf{g}] - L_{ij}^e[\mathbf{M}, \mathbf{g}]) \, dv. \end{cases} \quad (4.6)$$

Case 3.  $\delta_i = 0$  and  $q_i = 1$ : In this last case we preserve all the macroscopic information about the closed system, including proliferative, destructive interactions, and therapy actions:

$$\begin{cases} \partial_t \rho_i^0 + \operatorname{div}(\rho_i^0 \mathbf{U}_i^0) = \sum_{j=1}^4 \int_{D_v} (G_{ij}[\mathbf{M}] - L_{ij}[\mathbf{M}] + \sum_{k=1}^4 S_{jk}^i[\mathbf{M}]) \, dv + \sum_{j=1}^m \int_{D_v} (G_{ij}^e[\mathbf{M}, \mathbf{g}] - L_{ij}^e[\mathbf{M}, \mathbf{g}] + S_{ij}^e[\mathbf{M}, \mathbf{g}]) \, dv, \\ \partial_t (\rho_i^0 \mathbf{U}_i^0) + \operatorname{Div}(\rho_i^0 (\mathbf{U}_i^0 \otimes \mathbf{U}_i^0) + P^0) = \sum_{j=1}^4 \int_{D_v} \mathbf{v} (G_{ij}[\mathbf{M}, \mathbf{g}] - L_{ij}[\mathbf{M}, \mathbf{g}] + \sum_{k=1}^4 S_{jk}^i[\mathbf{M}]) \, dv \\ + \sum_{j=1}^m \int_{D_v} \mathbf{v} (G_{ij}^e[\mathbf{M}, \mathbf{g}] - L_{ij}^e[\mathbf{M}, \mathbf{g}] + S_{ij}^e[\mathbf{M}, \mathbf{g}]) \, dv. \end{cases} \quad (4.7)$$

The approach we have presented here is quite general. It is easy to describe some simple examples by choosing a concrete turning operator for which  $\mathbf{M}$  has an explicit form (see [31] for a relaxation model on a sphere). The general result presented here can be stated in the following theorem

**Theorem.** Let  $\mathbf{f}^\varepsilon$  be a solution of (4.2) verifying

$$\|\mathbf{f}^\varepsilon\|_{C(0, \infty; L^p(D_x \times D_v \times D_u))} \leq C < \infty \quad (4.8)$$

for some  $p > 2$ , and such that each  $f_i^\varepsilon$  converges pointwise. We also assume that the microscopic state space has finite measure and that the probability densities  $\mathcal{B}_{jk}$ ,  $\mathcal{C}_{jk}$ ,  $\mathcal{B}_{jk}^e$  and  $\mathcal{B}_{jk}^e$  are bounded functions while the interactions rates  $\eta_{ij}$  and  $\eta_{ij}^e$ , intensity rates  $p_{ij}$  and  $p_{ij}^e$  and proliferation/destruction rates  $\mu_{ij}^1$  are all square integrable with respect to their variables. Finally, we assume that  $\mu_{i,j}^1$  and  $\mu_{i,j}^2$  are continuous.

Then, the pointwise limit of  $\mathbf{f}^\varepsilon$  is the vector valued function  $\mathbf{M} = \{M_{\rho_i^0, \mathbf{U}_i^0}^i\}_{i=1}^4$  given by hypothesis H.3.6. with

$$\rho_i^0 = \lim_{\varepsilon \rightarrow 0} \rho[f_i^\varepsilon], \quad \mathbf{U}[f_i^0] = \lim_{\varepsilon \rightarrow 0} \mathbf{U}_i^\varepsilon,$$

i.e., the weak and pointwise limits of the local density (3.1) and the local velocity (3.2) of  $f_\varepsilon$ . Moreover, in the three regimes introduced above, the limiting densities  $\rho_i^0$  and velocities  $\mathbf{U}_i^0$  verify (4.5), (4.6) and (4.7), respectively.

**Proof.** We first note that (4.8) together with the hypothesis concerning the probability densities and the rates, allow us to rigorously understand all the involved terms in (4.2) from a mathematical point of view. On the other hand, combining (4.8) and the pointwise convergence, we can conclude (see [31]) the strong convergence of  $\mathbf{f}$  and of its local density and velocity as stated in the theorem. The convergence of all the gain, loss and proliferative/destructive terms is also straightforward from these hypotheses, by also noticing the weak-star convergence in the space  $C(0, \infty; L^p(D_x \times D_v \times D_u))$  to pass to the limit in the  $S_{ij}^e$  terms.  $\square$

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