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A MATHEMATICAL MODEL FOR CLONAL EXPANSION OF ANTIGEN SPECIFIC T CELLS

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Abstract In this paper a macroscopic phenomenological model for the T cell mediated immune response due to a single type of antigen challenge is developed in the framework of the thermodynamic theory of fluid mixtures. Proliferation events accounting for the generation of T cell clones are considered, determining a non conservative balance for mass and momentum densities for the mixture as a whole in a way analogous to some cases in tumor modelling and growth of tissues.

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1. INTRODUCTION

In this paper, we elaborate a mathematical model on the *activation* and *clonal expansion* of T cells during the immune response to a single type of antigen challenge.

In constructing our model, we use an approach based on the phenomenology of the problem under consideration and we obtain the field equations governing the dynamics and the interactions of *Antigen Non Experienced T cells* (naive T cells) and *Antigen Experienced T cells* (T helper cells) in presence of *Antigen Presenting Cells* (dendritic cells), i.e. cells bearing the antigen [1]-[4], taking into account that the interactions among these three populations of cells are due to the presence of chemicals (cytokines in our case) which act as soluble *mediators*. At the same time the populations of cells secrete cytokines in a feedback effect [5]-[10]. The field equations are mathematically constructed in the framework of the thermodynamic of reacting fluid mixtures adapted to the case in which proliferative events (i.e. events which do not satisfy the law of conservation of mass for the mixture as a whole) occur ([11] for analogies in the case of growth of soft tissues).

We take into consideration two fundamental phases: the *activatio*n and the *clonal expansion*. Basing on biological considerations, we assume that the proliferation of T helper cells, generating clones, which happens during the clonal expansion phase is not a conservative event, i.e. it does not satisfy the mass density conservation of the mixture of biological fluids as a whole, at least during the acute phase of inflammation (about 24-48 hours after the encounter with the antigen).

Our model is based on the fundamental picture of sensing and response mechanism of the above introduced three populations of cells in the presence of a set of

cytokines which act as mediators via signaling inducing genetic pathways inside the cells and determining the genetic mutation of naive T cells into T helper cells. In fact the dynamics of the introduced populations of cells involve *genetic mutations* (naive T cells mutating into T helper cells) and *proliferation events* (see eq.(16)) due to the generation of clones of T helper cells, then it cannot be simply related to fundamental mechanistic properties of individual cell response (see [12] for analogies in the case of bacterial populations or [13] for analogies in the case of dynamics of leukocytes in tissue inflammatory response). The macroscopic dynamics is fundamentally related to the biological phenomena of *motility of cells* [13, 14] (which results in avoiding *overcrowding* [15]) and *chemotactic response* of the cells [16] together with the *diffusion* of the chemicals (cytokines in our case) [17]-[18].

The *motility of cells* is introduced via a flux in the balance equations of the three population of cells [13], the *diffusion* of the chemicals (cytokines) is of the Fick's type and the *chemotactic* effect is introduced via a force in the balance equations of momenta of the cell populations [16].

In particular, in section 2 we illustrate the modelled aspects of the dynamics of the *activation* of naive T cells and the *clonal expansion* of T helper cells during the immune response to a single type of antigen challenge by adopting a phenomenological point of view which uses observations at the meso- and microscopic level.

In section 3 we derive explicit expressions for the balance equations of mass density for all the constituents of the mixture, by phenomenologically specifying the fluxes and productions of mass densities.

In section 5 we derive explicit expressions for the balance equations of momentum densities for all the constituents of the mixture by phenomenologically specifying the production of momentum densities and by defining appropriate equations of state for the involved stresses.

In sections 4 and 6 we derive explicit expressions for the balance equations for mass and momentum densities for the mixture of biological fluids as a whole, by applying the thermodynamical theory of reacting mixtures of fluids, in the particular case in which proliferative events occur [11].

In section 7, a quasi-linear system of PDEs with terms of the second order is obtained governing the dynamics of *activation* of naive T cells and *clonal expansion* of T helper cells during the immune response to a single type of antigen challenge, by summarizing the balance equations for the mass and momentum densities obtained in the previous sections. A particular case in which the *motility of the cells* and the *diffusion* of the chemicals are not taken into account is considered, obtaining an associated quasi-linear system of PDEs of the first order . In a forthcoming paper, the hyperbolicity of this last system of equations is proved and the propagation of non linear waves in the general case is studied by using an asymptotic perturbative method.

2. PHENOMENOLOGY OF SOME ASPECTS OF THE DYNAMICS OF T CELL MEDIATED IMMUNE RESPONSE

In this section we present some phenomenological aspects regarding the *activation* and *clonal expansion* of T cells during the immune response to a single type of antigen challenge. The schematization which follows is the result of a deep analysis of a part of the huge biomedical and biomathematical literature on the topic of T cell mediated immune response[1]-[18].

The immune system is a complex system of cells and molecules distributed throughout living bodies and providing mainly a basic defense against bacteria, virus, fungi and other pathogenic agents (referred to as antigens). It offers also a defense against pathologically transformed cells. In the immune system response to antigens, an important involved population of cells is that of lymphocytes. Lymphocytes are divided into two groups: T cells and B cells. The mathematical modellization of this paper regards only some particular dynamics involving T cells. T cells are produced in the thymus and they are antigen specific (bearing specific antigen receptors) but they do not have specific functionalities; in this state they are called *naive* T cells. Due to the first encounter with the antigen, naive T cells take specific functionalities and are called in general Antigen Experienced (or Antigen activated) T cells. Antigen Experienced T cells divide mainly into three subgroups, depending on their different functionalities: the *T helper cells*, the *cytotoxic* T cells and the *suppressor* T cells. Our modellization regards a particular T helper cell dynamics which happens mainly in lymph nodes. In the *activation* and *clonal expansion* of T cells an important role is played by some soluble mediators (chemicals) which are collectively called cytokines and which induce signal transductions inside the nucleus of the cell, determining the genetic mutation of Antigen Not Experienced cells (naive T cells) into Antigen Experienced cells (T helper cells in our model); in modelling the dynamics of *activation* of naive T cells, we use a macroscopic approach considering only the macroscopic phenomenological effect (the changing of naive T cells into T helper cells in this case) of dynamics which happen at a meso- and microscopic level. For instance, the transduction signals induced by the cytokines happen at the mesoscopic level, but we consider only the macroscopic output, i.e. the production of T helper cells and their clones and the related decrement of naive T cells.

The most important difference of functionalities between Antigen Not Experienced T cells (naive T cells) and Antigen Experienced ones (T helper in our case), consists in the fact that the activated ones may divide mitotically (generating clones) due to a second encounter with the same type of antigen; this phenomenon is called *clonal expansion* [1]-[4]. We will consider this phenomenon in our model as a proliferative event [11].

In our initial efforts in the modellization of this complex dynamics we consider an *unbounded tissue medium*.

2.1. SOME CYTOKINES RELATED TO PARTICULAR FUNCTIONALITIES OF T CELLS

In this section, we illustrate some aspects of the important connection among a specified set of cytokines and some fundamental functionalities of naive T cells and T helper cells [20]-[25].

The functional *activation* of naive T cells into T helper cells follows the first encounter with the antigen. The presence of T helper cells is connected to the secretion of some specific cytokines. Some T helper cells are mainly connected to the secretion of the cytokines Il-2, IFN-γ and TNF-α while some others T helper cells are mainly connected to the secretion of cytokines IL-4, IL-5, IL-13 and IL-10 [4]. We kindly refer the reader to a forthcoming paper [26], where a specific differentiation of the T helper set into T helper cell of type 1 (Th_1) and T helper cells of type 2 (Th_2) is modelled. The presence of specific cytokines in the lymphatic micro-environment is also certainly connected to the functional *activation* of naive T cells into T helper cells. In particular we have chosen to collect seven types of cytokines (IL-2, INF-γ, INF-α, IL-4, IL-5, IL-13 and IL-10) under the name of *set of cytokines* due to the role played in the *activation* and *clonal expansion* of T cells. The effect of these cytokines is taken into account in our model by using phenomenologically derived explicit expressions for the production of mass densities in the balance equations of mass and momentum densities for the populations cells depending on the specified set of cytokines.

2.2. APOPTOSIS

Apoptosis (or cell death) is the fate of many of activated T lymphocytes. Activated lymphocytes die because of a monotonous, repeated stimulations due to the presence of antigens and/or concentrations of cytokines [4]. This phenomenon is called *activation induced cell death* and is taken into account in our model (see section 3.4). Antigen Not Experienced lymphocytes die by apoptosis unless they are rescued from it by their specific antigen. This phenomenon is called *programmed cell death*. We consider also this phenomenon in our model (see section 3.3).

2.3. CLONAL EXPANSION OF ACTIVATED T CELLS

Clonal expansion of T cells is a dynamics involved in the so called *secondary immune response*, which is the immune response due to a second encounter with a specific type of antigen. The activated T helper cells produced in the first encounter due to the *activation*, produce *clones* due to a second encounter with the specific type of antigen. The phase of proliferation of activated T cells as clones is also called *clonal expansion phase* [10].

2.4. CHEMOTAXIS

Here we introduce the biological phenomenon of *chemotaxis*, which is taken into account in our model via interactions forces acting on T helper and dendritic cells (see sections 5.3 and 5.4) and determined by the presence of the specific cytokines.

The response of a biological population to a stimulus of the environment is called *taxis* (from the Greek "to arrange"). There are lots of kind of "taxis"; the type of stimulus determines the prefix on the word taxis. For instance geotaxis is the response to the gravitational force and acts on flies and birds while in the aerotaxis the stimulus is determined by oxygen and acts on bacteria.

Specifically, a chemical directed movement is called *chemotaxis* and it describes the influence of chemical substances present in the environment on the movement of mobile species (such as bacteria or lymphocytes as in our case).

To make an example, when a bacterial infection invades the body it may be attacked by movement of cells towards the source as a result of chemotaxis [18]. In this case one speaks of positive chemotaxis and the chemical is called a *chemoattractant*. Regarding to the specific dynamics involved in the T cell mediated immune response, it is for instance experimentally proved that lymphocytes cells move toward a region of bacterial inflammation by moving up a chemical gradient [13].

Phisically, the *chemotactic interaction* can be introduced as a force that tends to aggregate the cells, driving them along the direction of the chemoattractor chemical gradient [16], i.e.

$$\mathbf{f}_c = \chi \nabla c, \tag{1}$$

where c is the concentration of the chemoattractant and χ is the *chemotactic sensitivity coefficient* [17, 18] which may, in general, depend on the concentrations of the mobile specie and of the chemoattractant; in this paper it is taken as constant to enlight the fundamental behaviors. The bulk force per unit mass $\mathbf{f}_c$ is then introduced in the balance equation for the momentum density of the cells and accounts for cell-cell interaction via the chemotactic signaling [16]. In our model we introduce the chemotactic interactions following [16], by introducing appropriate forces into the balance equations of momentum densities for the populations of activated T helper and dendritic cells (see section 5). In our case the role of chemoattractor is played by the specified cytokines.

3. BALANCE EQUATIONS OF MASS DENSITIES FOR THE CONSTITUENTS OF THE MIXTURE OF BIOLOGICAL FLUIDS

We model the populations of cells (naive T, T helper and dendritic cells) and the chemicals (the set of cytokines) as an homogeneous mixture of biological fluids. Following Muller [27], we suppose that each point is occupied by "particles of all constituents". The equations of balance of mass and momentum densities in regular

points of the mixture differ from the corresponding equations of balance in a single body fluid by a production term [27, 28]: in fact mass of a constituent may be produced by chemical reactions and momentum may be produced by interaction forces and by the production due to the chemical reactions. In our model, mass of a constituent may be produced by *genetic mutations* of naive T cells into T helper cells, in a sense analogous to chemical reactions among the constituents. Moreover, in the thermodynamic theory of mixtures of fluids, the production densities of mass of the constituents are constrained by the requirement that the sum of the productions densities of all the constituents is zero [27, 28], in order to achieve the conservation of mass density for the mixture as a whole. This requirement still applies in our model, except that for the *net generation of clones* of T helper cells which is the net number of clones produced during the clonal expansion phase; this *generation of clones* represents a *proliferative* event in which *the mass density of the mixture is not conserved* (see [11] for analogies in growth phenomena in soft tissues and [29] and [30] for analogies in tumor modeling).

By analyzing the biological phenomenon under consideration, one may deduce that this proliferative phenomenon regards only the *acute phase* of the immune response, while for large values of time the number of lymphocytes is kept constant [1, 4]. We take into consideration this particular dynamics into our model by introducing a *proliferation rate function* for the T helper cell clones with a special dependance on time in order to mimic the dependance on time of the immune response (see sections 3.4 and 4); in particular the proliferation rate function is assumed to be the solution of the logistic equation of Verhulst. As a result of this assumption, the mass density of the mixture as a whole is conserved for large values of time, although it is not conserved for the first phase of the immune response to the antigen challenge (the acute phase of the immunological response is of the order of 24-48 hours [4]).

In this section we present explicit expressions for the balance equations of mass densities for all the constituents of the mixture modeling some aspects of the dynamics of *activation* of naive T cells and subsequent *clonal expansion* of T helper cells.

3.1. CONSTITUENTS OF THE MIXTURE OF BIOLOGICAL FLUIDS

The constituents of the mixture of biological fluids under consideration are:

1 *naive T cells* of mass density ρ_T and concentration c_T,

2 antigen activated *T helper cells* of mass density ρ_{T_h} and concentration c_{T_h},

3 *dendritic cells* of mass density ρ_d and concentration c_d,

4 *a* set of cytokines (IL-2, IFN-γ, INF-α, IL-4, IL-5, IL-13, IL-10) of mass density ρ_1 and concentration c_1.

The density of the mixture of fluids is given by [27, 28]

$$\rho = \rho_T + \rho_{T_h} + \rho_d + \rho_1 \tag{2}$$

where

$$c_T = \frac{\rho_T}{\rho},\ c_{T_h} = \frac{\rho_{T_h}}{\rho},\ c_d = \frac{\rho_d}{\rho},\ c_1 = \frac{\rho_1}{\rho},\ \text{ with } c_T + c_{T_h} + c_d + c_1 = 1. \tag{3}$$

3.2. LOCAL FORM OF THE GENERAL BALANCE EQUATION OF MASS DENSITY

The local form of the general balance equation for a generic biological specie of mass density ϱ is assumed analogous to the usual balance equation of mass density in the thermodynamics of continuum media [27] as

$$\frac{\partial \varrho}{\partial t} + \nabla \cdot (\varrho \mathbf{v}_\varrho + \mathbf{J}_\varrho) = \tau_\varrho + s \tag{4}$$

where $\mathbf{v}_\varrho$ is the velocity of the specie, $\mathbf{J}_\varrho$ is the local flux of the specie at any point in the tissue space, τ_ϱ is the local production of the specie (or local net generation rate [13]) and s is the supply from outside. Supply is different from production because it may be controlled from the exterior [27]. In eq.(4) the differential operator nabla is $\nabla = (\frac{\partial}{\partial x^k})$ where x^k, $(k = 1, 2, 3)$ represent the spatial coordinates (i.e. the components of the position vector $\mathbf{x}$ in Eulerian coordinates in a cartesian reference frame) and t is time. By using biological considerations [1, 4], we assume that no supply from outside is present in our case. In the following we continue to call the *local net generation rate* with the name *production of mass density* in analogy to the usual terminology of continuum mechanics.

In the next sections, we deduce phenomenologically explicit expressions characterizing the fluxes and productions of mass densities for the three populations of cells (T naive, T helper and dendritic cells) and the chemical *mediators* represented by the set of cytokines.

3.3. NAIVE T CELL BALANCE EQUATION OF MASS DENSITY

Regarding the naive T cells, we model the biological phenomenon of *random motility of cells* (which results in avoiding *overcrowding* [15]), with a diffusion-like flux [12, 13, 31, 14]

$$\mathbf{J}_T = -r \nabla \rho_T \tag{5}$$

where $\mathbf{J}_T$ have units of viable cell biomass/volume and r is the so called *random motility coefficient* (analogous to a molecular *diffusion coefficient*) (see [12] for the case of dynamics of bacterial populations and [13] for the dynamics of leukocyte

in tissue inflammatory response). Data fit with experimental results show that the *random motility coefficient* is of the order of $10^{-5} cm^2/s$ [12].

The production of mass density of naive T cells (τ_T) is due to the following four contributions

- *activation* of naive T cells mutating into T helper cells (see section 2),
- *generation* of newly borne naive T cells in the thymus (idem),
- *programmed cell death* of naive T cells (idem).

The first contribution is modeled as a negative term inducing a decrement in the number of naive T cells, linearly depending on the actual value of the density of naive T cells via a parameter depending on the concentration of cytokines (because of the fact that the cytokines belonging to the introduced set induce the activation of naive T cells into T helper cells); this term is given by $-h(c_1)\rho_T$ where $h(c_1)$ is the *activation rate factor* of naive T cells into T helper cells. Assuming a linear relation regarding the dependance of h on c_1, one finally writes the explicit phenomenological form of the first contribution as

$$-\tilde{h}c_1\rho_T \tag{6}$$

where $\tilde{h}$ is the constant *activation rate* of naive T cells into T helper cells. In the following we continue to call $\tilde{h}$ by the name h. More complicated choices are also possible however and do not affect the model qualitatively. The second contribution can be modelled via a first order term depending on the actual value of the mass density of naive T cells ρ_T as

$$k_0\rho_T \tag{7}$$

where k_0 is the constant *growth rate* of naive T cells produced by the thymus. The third contribution can be modeled as a negative first order term inducing a decrement in the number of naive T cells due to the *apoptosis*, depending on the actual value of the mass density of naive T cells

$$-k_{ap}\rho_T \tag{8}$$

where k_{ap} is the constant *apoptotic rate* of naive T cells. All these terms have units of viable cell biomass/volume·time [13].

By summing up the three contributions (6), (7) and (8), one obtains the production density of naive T cells as

$$\tau_T = (k_0 - k_{ap} - hc_1)\rho_T. \tag{9}$$

All the introduced constants are positive. (For some experimental data on coefficients see [32]). By plugging in the general form of the balance of mass density (4),

the phenomenologically assumed flux (5) and production of mass density (9), one obtains the balance equation of mass density for naive T cells as

$$\frac{\partial \rho_T}{\partial t} + \nabla \cdot (\rho_T \mathbf{v}_T) - r \triangle \rho_T = (k_0 - k_{ap} - hc_1)\rho_T \tag{10}$$

where $\mathbf{v}_T$ is the velocity of naive T cells and remembering that the *random motility coefficient* r is constant.

3.4. *TH* CELL BALANCE EQUATION OF MASS DENSITY

Regarding the T helper cells, we model again the phenomenon of *random motility of cells* (which results in avoiding *overcrowding* [15]) with a diffusion-like flux [12, 13, 31, 14]

$$\mathbf{J}_{T_h} = -r \nabla \rho_{T_h} \tag{11}$$

where, basing on biological considerations [17], the same random motility coefficient r has been assumed as for naive T cells. To phenomenologically determine the production of mass density in the case of T helper cells, one has to consider firstly the phase of *activation* (i.e. the phase of genetic mutation of naive T cells into T helper cells) and then the phase of *clonal expansion* (generation of clones of T helper cells) (see section 2).

The production of mass density of T helper cells (τ_{T_h}) is due to the following three contributions

- *genetic mutation* of naive T cells into T helper cells (see section 2),
- *activation induced cell death* of T helper cells (idem),
- *clonal expansion* of T helper cells produced during the activation phase (idem)

The first two contributions are determined during the *activation* phase. The first contribution is modelled as a term equal and opposite in sign to the term (6)

$$hc_1 \rho_T. \tag{12}$$

The second contribution is modeled as a term linearly depending on the actual value of density of T helper cells

$$-h_{ap}(c_1)\rho_{T_h}, \tag{13}$$

where the *induced cell death rate* k_{ap} depends on the concentration of the considered set of cytokines (see section 2 for the biological based motivation of this assumption).

Assuming a linear relation regarding the dependance of h_{ap} on c_1, this last term takes the form

$$\tilde{h}_{ap} c_1 \rho_{T_1}, \tag{14}$$

where $\tilde{h}_{ap}$ is the constant *induced cell death coefficient* characterizing the apoptosis of T helper cells. More complicated choices are also possible however and do not affect the model qualitatively. In the following we will continue to call $\tilde{h}_{ap}$ by the name h_{ap}.

By summing up the two terms (12) and (14), one obtains the production of mass density of T helper cells during the *activation phase*

$$(\tau_{T_h})_{activ.} = \underbrace{h c_1 \rho_T}_{genetic\ mutation} - \underbrace{h_{ap} c_1 \rho_{T_h}}_{cell\ death}. \tag{15}$$

During the subsequent phase of proliferation called *clonal expansion phase*, the T helper cells (produced during the *activation phase*) proliferate by *generation of clones* so that the total production of mass of T helper cells is given by

$$\tau_{T_h} = \overbrace{\alpha(t)(\tau_{T_h})_{activ.}}^{activ.\ and\ prolif.}, \tag{16}$$

where α is the *proliferation rate factor* of T helper cells characterizing the clonal expansion phase. By biological considerations, we assume that the *proliferation rate factor* is function of time.

Remark 3.1. *The function of time representing the proliferation rate factor may be characterized by the property that* $\alpha(t) \to 1$ *when* $t \to \infty$ *in order to mimic the fact that the peak of the T cells differentiation happens within 24-48 hours after the antigen intrusion and then decreases disappearing within 5-10 days [1, 4]. To mimic this observed phenomenon, one may choose the function* $\alpha(t)$ *to be the analytical solution of the logistic equation of Verhulst* $\frac{d\alpha}{dt} = r(1 - \frac{\alpha}{k})\alpha$, *i.e.* $\alpha(t) = \frac{\alpha_0 k}{\alpha_0 + (k - \alpha_0)e^{-rt}}$ *where* r *is the intrinsic growth rate factor and* k *is the saturation level. One may assumes the saturation level* $k = 1$ *in order to mimic the fact that the total number of lymphocytes in the organism is kept constant for large values of time with respect to the time interval of the acute phase of the immune response.*

Then we define the *net generation of clones* of T helper cells as the difference between the total number of T helper cell clones which results from the activation and clonal expansion phases and the initial set of the same cells, i.e. the T helper cells produced during the activation phase

$$(\tau_{T_h})_{prolif.} = \alpha(t)(\tau_{T_h})_{activ.} - (\tau_{T_h})_{activ.} = [\alpha(t) - 1](h c_1 \rho_T - h_{ap} c_1 \rho_{T_h}) \tag{17}$$

and we classify it as a *proliferation event*. Eq.(17) will be used in the following.

By plugging in the general form of the balance equation of mass density (4) the phenomenologically derived flux (11) and production of mass density (16), one obtains the balance equation of mass density for T helper cells as

$$\frac{\partial \rho_{T_h}}{\partial t} + \nabla \cdot (\rho_{T_h} \mathbf{v}_{T_h}) - r \triangle \rho_{T_h} = \alpha(t)(hc_1 \rho_T - h_{ap} c_1 \rho_{T_h}) \tag{18}$$

where $\mathbf{v}_{T_h}$ is the velocity of the T helper cells and remembering that the *random motility coefficient* r is kept constant.

3.5. DENDRITIC CELL BALANCE EQUATION OF MASS DENSITY

Regarding the dendritic cells, we model again the *random motility of cells* (which results in avoiding overcrowding [15]) with a diffusion-like flux [12, 13, 31, 14]

$$\mathbf{J}_d = -r \nabla \rho_d \tag{19}$$

where for simplicity and not affecting the model qualitatively, the same random motility coefficient r has been assumed as for naive T cells and T helper cells.

By analyzing the phenomenology of the dynamics of *activation* and *clonal expansion* of T cells with a special regard to the Antigen Presenting Cells (dendritic cells in this case) [1, 4] one may deduce that the production of mass density of dendritic cells is zero

$$\tau_d = 0. \tag{20}$$

By plugging into the general form of the balance of mass density (4) the phenomenologically derived flux (19) and production of mass density (20), one obtains the balance of mass density for dendritic cells as

$$\frac{\partial \rho_d}{\partial t} + \nabla \cdot (\rho_d \mathbf{v}_d) - r \triangle \rho_d = 0 \tag{21}$$

where $\mathbf{v}_d$ is the velocity of dendritic cells and remembering again that the *random motility coefficient* r is kept constant.

3.6. SET OF CYTOKINES BALANCE EQUATION OF MASS DENSITY

Chemoattractant (cytokines in this case) diffusion is assumed to follow Fick's law, with *diffusion coefficient* D [13],

$$\mathbf{J}_1 = -D \nabla \rho_1. \tag{22}$$

In general D could be function of the concentration of the attractant [21, 22], however we will assume it constant in order to elucidate the most fundamental behavior. The diffusion coefficient has unit of area/time. In [12] one can find interesting observations about the effect of the diffusion coefficient with respect to the chemotactic response; in fact the larger the diffusion coefficient, the faster the gradient of the attractant will decay and the smaller the chemotactic response.

The production of mass density of the set of cytokines (τ_1) is due to the following three contributions

- *secretion* of cytokines of the considered set by the T helper cells (see section 2),
- *secretion* of cytokines of the considered set by the dendritic cells (idem),
- *consuption* of cytokines of the considered set due to degradation processes.

The first two contributions to the production of mass density of the set of cytokines can be modeled as the sum of two terms both depending on the actual value of the mass density of the set of cytokines via two functions of the concentration of T helper and dendritic cells respectively

$$\mu(c_{T_h})\rho_1 + \nu(c_d)\rho_1, \tag{23}$$

where $\mu(c_{T_h})$ is the production rate of the set of cytokines due to the production by the T helper cells and $\nu(c_d)$ is the production rate of the set of cytokines due to the production by the dendritic cells. Assuming a linear relation regarding the dependance of $\mu(c_{T_h})$ on c_{T_h} and the dependance of $\nu(c_d)$ on c_d, the term (23) takes the form

$$(\tilde{\mu}c_{T_h} + \tilde{\nu}c_d)\rho_1, \tag{24}$$

where $\tilde{\mu}$ is the constant *production rate* of the set of cytokines by the T helper cells and $\tilde{\nu}$ is the constant *production rate* of the set of cytokines by the dendritic cells. More complicated choices are also possible however and do not affect the model qualitatively. In the following we continue to call the quantities $\tilde{\mu}$ and $\tilde{\nu}$ with the name μ and the name ν respectively. The third contribution to the production of the considered set of cytokines, i.e. the *consumption* due to degradation processes, can be modelled via the following first order term [16]

$$-\frac{1}{\gamma}\rho_1, \tag{25}$$

where γ is the *half-life rate* of the set of cytokines. By summing up the contributions (24) and (25), one obtains the production density of the set of cytokines as

$$\tau_1 = (\mu c_{T_h} + \nu_1 c_d - \frac{1}{\gamma})\rho_1. \tag{26}$$

By plugging into the general form of the balance of mass density (4), the phenomenologically derived flux (22) and production of mass density (26), one obtains the balance of mass density for the set of cytokines as

$$\frac{\partial \rho_1}{\partial t} + \nabla \cdot (\rho_1 \mathbf{v}_1) - D\triangle\rho_1 = (\mu c_{T_h} + \nu c_d - \frac{1}{\gamma})\rho_1, \tag{27}$$

where $\mathbf{v}_1$ is the velocity of the set of cytokine and remembering that the *diffusion coefficient* D is kept constant in this case.

4. FLUID MIXTURE BALANCE EQUATION OF MASS DENSITY

We define the *baricentral velocity* of the mixture [27, 28] as

$$\mathbf{v} = \frac{1}{\rho}(\rho_T \mathbf{v}_T + \rho_{T_h}\mathbf{v}_{T_h} + \rho_d \mathbf{v}_d + \mathbf{v}_1). \tag{28}$$

The sum of all the productions of mass density of the constituents given by eqs. (9), (16), (20) and (26) is

$$(k_0 - k_{ap} - hc_1)\rho_T + (\mu c_{T_h} + \nu c_d - \frac{1}{\gamma})\rho_1 + \alpha(t)(hc_1\rho_T - h_{ap}c_1\rho_{T_h}) \tag{29}$$

which, by simple algebraic calculations, can be rewritten as

$$(k_0 - k_{ap} - h_{ap}c_1)\rho_T + (\mu c_{T_h} + \nu c_d - \frac{1}{\gamma})\rho_1 + [\alpha(t) - 1](hc_1\rho_T - h_{ap}c_1\rho_{T_h}). \tag{30}$$

As already said, the net generation of clones of T helper cells (17) represents a proliferative event (i.e. not conservative of the mass density, at least regarding to the acute phase of the immune response), so that by substracting the quantity (17) from eq. (30), one obtains the sum of productions of mass densities of the components of the fluid mixture subjected to the requirement to be zero because of the conservation of mass density of the mixture as a whole

$$(k_0 - k_{ap} - h_{ap}c_1)\rho_T + (\mu c_{T_h} + \nu c_d - \frac{1}{\gamma})\rho_1 = 0. \tag{31}$$

By summing up the balances of mass for all the constituents (10), (18), (21) and (27) and by taking into account the requirement (31), one obtains the balance equation of mass density for the mixture as

$$\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{v}) - r\triangle\rho + (r - D)\triangle\rho_1 = [\alpha(t) - 1](hc_1\rho_T - h_{ap}c_1\rho_{T_h}), \tag{32}$$

where relation (2) for the density of the mixture has been used.

The mass density of the mixture as a whole is not conserved in this case (see [11] for analogies in growth of soft tissues and [29] and [30] for analogies in tumor modeling). Remembering the observations made in Remark 3.1, one notices that due to the property of the function $\alpha(t)$ (in particular that for $t \to \infty$ it is $\alpha = 1$), for large values of t the production of mass density of the mixture as a whole tends to zero and

the conservation of mass is achieved. This fact mimics well the phenomenology of the T cell mediated immune response (see section 2).

5. BALANCE EQUATIONS OF MOMENTUM DENSITIES FOR THE CONSTITUENTS OF THE MIXTURE OF BIOLOGICAL FLUIDS

In this section we present explicit expressions for the balance equations of momentum densities for all the constituents of the mixture modeling some aspects of the dynamics of *activation* of naive T cells and *clonal expansion* of T helper cells.

In the thermodynamic theory of mixtures of fluids, the productions of momentum densities of mass of all the constituents are constrained by the requirement that the sum of the productions of momentum densities of all constituents is zero in order to a achieve the conservation of momentum density for the mixture as a whole [27, 28]. This requirement still applies in our model, except that for the production of momentum due to the *net generation of clones* of T helper cells. This generation of clones represents a *proliferative* event which determines that *the momentum density of the mixture as a whole is not conserved*, although only regarding the acute phase of the immune response to the antigen challenge.

5.1. LOCAL FORM OF THE GENERAL BALANCE EQUATION OF MOMENTUM DENSITY

Following [16], we assume the general form of the balance equation of momentum for the generic biological fluid of density ϱ, in a way analogous to the balance equation of momentum density for a constituent of a reacting mixture of fluids [27, 28]

$$\frac{\partial \varrho \mathbf{v}_\varrho}{\partial t} + \nabla \cdot [\varrho \mathbf{v}_\varrho \otimes \mathbf{v}_\varrho - \mathbf{t}_\varrho] = \mathbf{m} + \rho \mathbf{f}, \tag{33}$$

where $\mathbf{v}_\varrho$ is the velocity of the constituent, $\mathbf{f}$ is the external force per unit mass, $\mathbf{t}_\varrho$ is the stress tensor related to the considered constituent and $\mathbf{m}$ is the production of momentum density which is given by the sum of two terms

$$\mathbf{m} = \mathfrak{J} + \tau_\varrho \mathbf{U}. \tag{34}$$

In eq.(34), $\mathfrak{J}$ is the interaction force exerted on the constituent by the other constituents (chemotactic force in our model), $\mathbf{U}$ is the velocity of the produced mass density and $\tau_\varrho \mathbf{U}$ is the production of momentum density that accompanies the production of mass τ_ϱ.

In the case of the constituents of the mixture modeling the dynamics of *activation* and *clonal expansion* of T cells mediated immune response, from biological considerations, one can assume that no external forces are present [17], i.e. the force $\mathbf{f} = \mathbf{0}$ in eq.(33) is zero for all the constituents.

The production of momentum density of the mixture as a whole is constrained by the requirement that the sum of the productions of momentum density of all the constituents is zero [27]; it expresses the conservation of momentum of the mixture as a whole. This requirement still applies to the case of our model, with the exception of the production of momentum density due to the *net generation of clones* of T helper cells due to the *clonal expansion phase* (see the introduction to section 2). We remark here, following [16], that the first and second terms on the left hand side of eq.(33), are only formally identical to the usual material acceleration of a continuum but this does not mean that cells behave like particles, the Galilean inertia being negligible in this context. In particular the non linear term on the left hand side of eq.(33) accounts for *persistence in cell motion*, i.e. for the cells "inertia" in changing their direction [33].

To construct our model, in the following sections we write explicit phenomenological expressions for the quantity $\mathbf{m}$ for each constituent of the mixture of fluids and we assume specific constitutive relations for the stress tensor of each constituent of the mixture of biological fluids introduced in section 3.1.

5.2. NAIVE T CELL BALANCE EQUATION OF MOMENTUM DENSITY

Basing on biological considerations [17], we may neglect the chemotactic attraction on naive T cells due to the presence of the chemoattractors (cytokines) (in literature naive T cells are also called "*resting*" T cells [1, 4]). No other interaction forces, except the chemotactic one are taken into account in our model, so in the case of naive T cells the interaction force due to the other constituents is assumed to be zero

$$\mathfrak{I}_T = \mathbf{0}. \tag{35}$$

The production of momentum density for naive T cells due to the production of mass density τ_T (see eq.(9)) is given by

$$\mathbf{m}_T = \tau_T \mathbf{v}_T = (k_0 - k_{ap} - hc_1)\rho_T \mathbf{v}_T, \tag{36}$$

where $\mathbf{v}_T$ is the velocity of the produced mass in this case.

By using eqs.(35) and (36), the general form of the balance equation of momentum density (33) in the case of naive T cells takes the form

$$\frac{\partial(\rho_T \mathbf{v}_T)}{\partial t} + \nabla \cdot [\rho_T \mathbf{v}_T \otimes \mathbf{v}_T - \mathbf{t}_T] = (k_0 - k_{ap} - hc_1)\rho_T \mathbf{v}_T, \tag{37}$$

where $\mathbf{t}_T$ is the stress related to naive T cells.

5.3. T HELPER CELL BALANCE EQUATION OF MOMENTUM DENSITY

The chemotactic attraction acting on the T helper cells is introduced as a force that tends to aggregate the cells, driving them along the direction of the chemical gradient [16], which is set of cytokines (see section 2) in this case

$$\mathfrak{I}_{T_h} = \chi_h \rho_{T_h} \nabla c_1, \tag{38}$$

where χ_h is the *chemotactic sensitivity coefficient* measuring the strength of T helper cell response to chemotactic signaling [16].

The production density of mass τ_{T_h} given by eq.(16) determines a production of momentum density for the T helper cells given by

$$\mathbf{m}_{T_h} = \tau_{T_h} \mathbf{v}_{T_h} = \alpha(t)(h\rho_T - h_{ap}\rho_{T_h}) c_1 \mathbf{v}_{T_h}, \tag{39}$$

where $\mathbf{v}_{T_h}$ is the velocity of the produced mass (see eq.(34)) in this case. The production of momentum density for the T helper cells is given by the sum of eqs. (38) and (39)

$$\alpha(t)(h\rho_T - h_{ap}\rho_{T_h}) c_1 \mathbf{v}_{T_h} + \chi_h \rho_{T_h} \nabla c_1. \tag{40}$$

By using eq.(40), the general form of the balance of momentum density (33) in the case of T helper cells takes the form:

$$\frac{\partial(\rho_{T_h} \mathbf{v}_{T_h})}{\partial t} + \nabla \cdot [\rho_{T_h} \mathbf{v}_{T_h} \otimes \mathbf{v}_{T_h} - \mathbf{t}_{T_h}] = \alpha(t)(h\rho_T - h_{ap}\rho_{T_h}) c_1 \mathbf{v}_{T_h} + \chi_h \rho_{T_h} \nabla c_1 \tag{41}$$

where $\mathbf{t}_{T_h}$ is the stress tensor related to the T helper cells.

5.4. DENDRITIC CELL BALANCE EQUATION OF MOMENTUM DENSITY

The set of cytokines acts as chemoattractor on the dendritic cells [1, 4]; the chemotactic interaction is introduced also for the dendritic cells as a force that tends to aggregate the cells, driving them along the direction of the chemical gradient [16] of the chemoattractor (cytokines)

$$\mathfrak{I}_d = \chi_d \rho_d \nabla c_1. \tag{42}$$

The production of momentum density for dendritic cells due to the production of density of mass τ_d (see eq.(20)) is zero

$$\mathbf{m}_d = \tau_d \mathbf{v}_d = \mathbf{0}. \tag{43}$$

By using eqs.(42) and (43), the general form of the balance equation (33) in the case of the dendritic cells takes the form

$$\frac{\partial(\rho_d \mathbf{v}_d)}{\partial t} + \nabla \cdot [\rho_d \mathbf{v}_d \otimes \mathbf{v}_d - \mathbf{t}_d] = \chi_d \rho_d \nabla c_1. \tag{44}$$

5.5. SET OF CYTOKINES BALANCE EQUATION OF MOMENTUM DENSITY

We may assume that no interactions force are exerted on the set of cytokines, so that

$$\mathfrak{I}_{c_1} = \mathbf{0}. \tag{45}$$

The production of density of momentum for the set of cytokines is due to the production density of mass balance τ_1 (see eq.(26)) and is given by

$$\mathbf{m}_1 = \tau_1 \mathbf{v}_1 = (\mu_1 c_{T_h} + \nu_1 c_d - \frac{1}{\gamma_1})\rho_1 \mathbf{v}_1, \tag{46}$$

where $\mathbf{v}_1$ is the velocity of the produced mass in this case. By using eqs.(45) and (46), the general form of balance of density of momentum (33) in the case of the set of cytokines takes the form

$$\frac{\partial(\rho_1 \mathbf{v}_1)}{\partial t} + \nabla \cdot [\rho_1 \mathbf{v}_1 \otimes \mathbf{v}_1 - \mathbf{t}_1] = (\mu_1 c_{T_h} + \nu_1 c_d - \frac{1}{\gamma_1})\rho_1 \mathbf{v}_1. \tag{47}$$

6. BALANCE EQUATION OF MOMENTUM DENSITY OF THE MIXTURE

The *total net generation of clones* of T helper cells (17), determines a contribution to the production of momentum density of the mixture given by

$$\tau_\rho \mathbf{v}_{T_h} = [\alpha(t) - 1](h\rho_T - h_{ap}\rho_{T_h})c_1 \mathbf{v}_{T_h}. \tag{48}$$

The sum of all the productions of momentum densities of the constituents given by eqs. (36, (40), (43) and (46) is

$$\begin{aligned}(k_0 - k_{ap} - hc_1)\rho_T \mathbf{v}_T + \alpha(t)(h\rho_T - h_{ap}\rho_{T_h})c_1 \mathbf{v}_{T_h} + \chi_h \rho_{T_h} \nabla c_1 + \\ + \chi_d \rho_d \nabla c_1 + (\mu c_{T_h} + \nu c_d - \frac{1}{\gamma})\rho_1 \mathbf{v}_1,\end{aligned} \tag{49}$$

which, by simple algebraic calculations, can be rewritten as

$$(k_0 - k_{ap} - hc_1)\rho_T \mathbf{v}_T + \chi_h \rho_{T_h} \nabla c_1 + \chi_d \rho_d \nabla c_1 + (\mu c_{T_1} + \nu c_d - \frac{1}{\gamma})\rho_1 \mathbf{v}_1 +$$

$$+[\alpha(t)-1](h\rho_T - h_{ap}\rho_{T_h})c_1\mathbf{v}_{T_h}. \tag{50}$$

As already said, the net generation of clones of T helper cells (17) represents a proliferative event (i.e. not conservative also of the momentum density, at least regarding to the acute phase of the immune response), so that by substracting the quantity (48) from eq. (50), one obtains the sum of productions of momentum densities of the components of the fluid mixture subjected to the requirement to be zero because of the conservation of momentum density of the mixture as a whole [27, 28]

$$(k_0 - k_{ap} - hc_1)\rho_T\mathbf{v}_T + \chi_h\rho_{T_h}\nabla c_1 + \chi_d\rho_d\nabla c_1 + (\mu c_{T_1} + \nu c_d - \frac{1}{\gamma})\rho_1\mathbf{v}_1 = \mathbf{0}. \tag{51}$$

By summing up equations (37), (41), (44) and (47), and by taking into account the requirement (51), one obtains the balance equation for the momentum density of the mixture of biological fluids as

$$\frac{\partial(\rho\mathbf{v})}{\partial t} + \nabla\cdot[\rho\mathbf{v}\otimes\mathbf{v} - \mathbf{t}] = [\alpha(t)-1](h\rho_T - h_{ap}\rho_{T_h})c_1\mathbf{v}_{T_h}. \tag{52}$$

To derive eq. (52), the following definition for the mixture stress $\mathbf{t}$ has been used [27, 28]

$$\mathbf{t} = \mathbf{t}_T + \mathbf{t}_{T_h} + \mathbf{t}_d + \mathbf{t}_h - \rho_T\mathbf{u}_T\otimes\mathbf{u}_T - \rho_{T_h}\mathbf{u}_{T_h}\otimes\mathbf{u}_{T_h} - \rho_d\mathbf{u}_d\otimes\mathbf{u}_d - \rho_1\mathbf{u}_1\otimes\mathbf{u}_1, \tag{53}$$

where

$$\mathbf{u}_T = \mathbf{v}_T - \mathbf{v}\ ,\mathbf{u}_{T_h} = \mathbf{v}_{T_h} - \mathbf{v}\ ,\mathbf{u}_d = \mathbf{v}_d - \mathbf{v}\ ,\mathbf{u}_1 = \mathbf{v}_1 - \mathbf{v} \tag{54}$$

are the partial velocities.

7. MATRIX FORM OF THE BALANCE EQUATIONS

Among the five introduced mass densities $(\rho,\rho_T,\rho_{T_h},\rho_d,\rho_1)$ only $5-1=4$ are independent. Then, we choose the following state space $\mathbf{C}$ of independent fields

$$\mathbf{C} = (\rho,\rho_{T_h},\rho_d,\rho_1,\mathbf{v},\mathbf{v}_{T_h},\mathbf{v}_d,\mathbf{v}_1). \tag{55}$$

To determine of these fields we need the appropriate number of field equations [28]. They are based on the balance equations of mass densities and momentum densities of the constituents; these equations have been deduced in section 3 and they form the

following system

$$\begin{cases} \frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{v}) - r\triangle\rho + (r-D)\triangle\rho_1 = [\alpha(t)-1](h\frac{\rho_1}{\rho}\rho_T - h_{ap}c_1\rho_{T_1}) \ , \\ \frac{\partial \rho_{T_h}}{\partial t} + \nabla \cdot (\rho_{T_h}\mathbf{v}_{T_h}) - r\triangle\rho_{T_h} = \alpha(t)(h\rho_T - h_{ap}\rho_{T_h})\frac{\rho_1}{\rho}, \\ \frac{\partial \rho_d}{\partial t} + \nabla \cdot (\rho_d \mathbf{v}_d) - r\triangle\rho_d = 0, \\ \frac{\partial \rho_1}{\partial t} + \nabla \cdot (\rho_1 \mathbf{v}_1) - D\triangle\rho_1 = (\mu\frac{\rho_{T_h}}{\rho} + \nu\frac{\rho_d}{\rho} - \frac{1}{\gamma})\rho_1, \\ \frac{\partial(\rho \mathbf{v})}{\partial t} + \nabla \cdot [\rho \mathbf{v} \otimes \mathbf{v} - \mathbf{t}] = [\alpha(t)-1](h\rho_T - h_{ap}\rho_{T_h})\frac{\rho_1}{\rho}\mathbf{v}_{T_h}, \\ \frac{\partial(\rho_{T_h}\mathbf{v}_{T_h})}{\partial t} + \nabla \cdot [\rho_{T_h}\mathbf{v}_{T_h} \otimes \mathbf{v}_{T_h} - \mathbf{t}_{T_h}] = \alpha(t)(h\rho_T - h_{ap}\rho_{T_h})\frac{\rho_1}{\rho}\mathbf{v}_{T_h} + \chi_h\rho_{T_h}\nabla\frac{\rho_1}{\rho}, \\ \frac{\partial(\rho_d \mathbf{v}_d)}{\partial t} + \nabla \cdot [\rho_d \mathbf{v}_d \otimes \mathbf{v}_d - \mathbf{t}_d] = \chi_d\rho_d\nabla\frac{\rho_1}{\rho}, \\ \frac{\partial \rho_1 \mathbf{v}_1}{\partial t} + \nabla \cdot [\rho_1 \mathbf{v}_1 \otimes \mathbf{v}_1 - \mathbf{t}_1] = (\mu\frac{\rho_{T_h}}{\rho} + \nu\frac{\rho_d}{\rho} - \frac{1}{\gamma})\rho_1\mathbf{v}_1, \end{cases} \tag{56}$$

where the relation defining the density of the mixture (2) and the definitions (53) and (54) have been considered.

7.1. CONSTITUTIVE ASSUMPTIONS

Constitutive equations for the stress tensor of each constituent of the mixture are needed in order to close the system of equations (56). In our model, we assume that the fluids modeling the populations of cells and the chemicals are *non-viscous and simple* [27, 28]; i.e. the following relations hold

$$\mathbf{t}_T = -p_T(\rho_T, T)\mathbf{I}, \ \mathbf{t}_{T_h} = -p_{T_h}(\rho_{T_h}, T)\mathbf{I}, \ \mathbf{t}_d = -p_d(\rho_d, T)\mathbf{I}, \ \mathbf{t}_1 = -p_1(\rho_1, T)\mathbf{I}, \tag{57}$$

where $\mathbf{I}$ is the identity matrix and T is the absolute temperature. Each fluid constituent of the mixture is *simple* in the sense that the *partial pressure* of each constituent depends only on its own density, and on T [28]. Regarding to our model the phenomenon under consideration is assumed *isothermal* so the dependance on T is not considered.

By substituting the constitutive equations (57) into the expression for the stress tensor of the mixture (53), the following equation is obtained

$$\mathbf{t} = -p\mathbf{I} - (\rho_T \mathbf{u}_T \otimes \mathbf{u}_T + \rho_{T_h}\mathbf{u}_{T_h} \otimes \mathbf{u}_{T_h} + \rho_d \mathbf{u}_d \otimes \mathbf{u}_d + \rho_1 \mathbf{u}_1 \otimes \mathbf{u}_1), \tag{58}$$

where $p = p_T + p_{T_h} + p_d + p_1$ is the scalar pressure of the mixture. In the case of *isothermal processes in non-viscous fluids*, the following *equation of state* may be

assumed [34]

$$p = \frac{\partial F}{\partial \rho}\rho^2 \tag{59}$$

where F is the free energy and T the absolute temperature ([34]). By assuming a linear dependance of the free energy on the mass density for each constituent of the fluid mixture, we obtain the following *equations of state* for the partial pressures

$$p_T = \hat{p}_T \rho_T^2,\ p_{T_h} = \hat{p}_{T_h}\rho_{T_h}^2,\ p_d = \hat{p}_d\rho_d^2,\ p_1 = \hat{p}_1\rho_1^2, \tag{60}$$

where the quantities $\hat{p}_T = \frac{\partial F}{\partial \rho_T}, \hat{p}_{T_h} = \frac{\partial F}{\partial \rho_{T_h}}, \hat{p}_d = \frac{\partial F}{\partial \rho_d}, \hat{p}_1 = \frac{\partial F}{\partial \rho_1}$, are positive constants [17, 18]. Because of the low involved velocities of the cells and the chemicals [17, 18], we disregard all the quadratic terms in the velocities in the balance equations of momentum densities; from a modellization point of view this means that we do not take into account from now on in our model the effect of *persistence in cell motion* [35] (see section 5). The system (56), together with (57) and (60) (and neglecting the inertial terms), takes the form

$$\begin{cases} \frac{\partial \rho}{\partial t} + \nabla\cdot(\rho\mathbf{v}) - r\triangle\rho + (r-D)\triangle\rho_1 = [\alpha(t)-1](h\rho_T - h_{ap}\rho_{T_h})\frac{\rho_1}{\rho}, \\ \frac{\partial \rho_{T_h}}{\partial t} + \nabla\cdot(\rho_{T_h}\mathbf{v}_{T_h}) - r\triangle\rho_{T_h} = \alpha(t)(h\rho_T - h_{ap}\rho_{T_h})\frac{\rho_1}{\rho}, \\ \frac{\partial \rho_d}{\partial t} + \nabla\cdot(\rho_d\mathbf{v}_d) - r\triangle\rho_d = 0, \\ \frac{\partial \rho_1}{\partial t} + \nabla\cdot(\rho_1\mathbf{v}_1) - D\triangle\rho_1 = (\mu_1\frac{\rho_{T_h}}{\rho} + \nu_1\frac{\rho_d}{\rho} - \frac{1}{\gamma})\rho_1, \\ \frac{\partial(\rho\mathbf{v})}{\partial t} + 2\hat{p}\rho\nabla\rho = [\alpha(t)-1](h\rho_T - h_{ap}\rho_{T_h})\frac{\rho_1}{\rho}\mathbf{v}_{T_h}, \\ \frac{\partial \rho_{T_h}\mathbf{v}_{T_h}}{\partial t} + 2\hat{p}_{T_h}\rho_{T_h}\nabla\rho_{T_h} - \chi_h\rho_{T_h}\nabla\frac{\rho_1}{\rho} = \alpha(t)(h\rho_T - h_{ap}\rho_{T_h})\frac{\rho_1}{\rho}\mathbf{v}_{T_h}, \\ \frac{\partial \rho_d\mathbf{v}_d}{\partial t} + 2\hat{p}_d\rho_d\nabla\rho_d - \rho_d\chi_d\nabla\frac{\rho_1}{\rho} = \mathbf{0}, \\ \frac{\partial \rho_1\mathbf{v}_1}{\partial t} + 2\hat{p}_1\rho_1\nabla\rho_1 = (\mu\frac{\rho_{T_1}}{\rho} + \nu\frac{\rho_d}{\rho} - \frac{1}{\gamma})\rho_1\mathbf{v}_1, \end{cases} \tag{61}$$

Eqs.(61) give a system of 16 quasi-linear second order PDEs for the mass densities of the mixture of biological fluids considered, the T helper cells, the dendritic cells and the set of cytokines, together with the related velocities. We introduce

$$\mathbf{U} = (\rho, \rho_{T_h}, \rho_d, \rho_1, \mathbf{v}, \mathbf{v}_{T_h}, \mathbf{v}_d, \mathbf{v}_1)^T, \tag{62}$$

where again the relation defining the density of the mixture (2) has to be considered. Then, the system of equations (61) can be written in the following matrix form

$$\mathbf{A}^{\alpha}(\mathbf{U})\frac{\partial \mathbf{U}}{\partial x^{\alpha}} + r\mathbf{H}^{k}(\mathbf{U})\frac{\partial^{2}\mathbf{U}}{\partial (x^{k})^{2}} + \mathbf{B}(\mathbf{U}, x^{0}) = \mathbf{0}, \tag{63}$$

where $\alpha = 0, 1, 2, 3$ and the $x^k (k = 1, 2, 3)$, $x^0 = t$ represent, respectively, the spatial coordinates (i.e. the components of the position vector $\mathbf{x}$ in Eulerian coordinates in a cartesian reference frame) and time, $\mathbf{A}^{\alpha}(\mathbf{U})$ (with $\alpha = 0, 1, 2, 3$), $\mathbf{H}^{k}(\mathbf{U})$(with $k = 1, 2, 3$) are appropriate 16×16 square matrices and $\mathbf{B}(\mathbf{U}, x^0)$ is the appropriate column vector. The terms containing derivatives of the second order is multiplied by the *random motility coefficient* r which is a very little ($r \ll 1$) parameter (see section 3.3) and the Einstein summation convention over repeated indices is understood.

If one does not consider the terms of the second order into the system of PDEs (63) (corresponding in disregarding the effects of random motility of cells and diffusion of the cytokines), a quasi-linear system of equations of the first order is obtained; in a forthcoming paper [19] the hyperbolicity in time direction for this particular case is proved and the propagation of non linear waves in the general case represented by the system PDEs (63) is studied by using a perturbative method.

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