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APPROXIMATE SMOOTH SOLUTIONS OF A MATHEMATICAL MODEL FOR THE ACTIVATION AND CLONAL EXPANSION OF T CELLS

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Abstract. In a previous paper a mathematical model was developed for the dynamics of activation and clonal expansion of T cells during the immune response to a single type of antigen challenge, constructed phenomenologically in the macroscopic framework of a thermodynamic theory of continuum mechanics for reacting and proliferating fluid mixtures. The present contribution deals with approximate smooth solutions, called asymptotic waves, of the system of PDEs describing the introduced model, obtained using a suitable perturbative method. In particular, in the one-dimensional case, after deriving the expression of the velocity along the characteristic rays and the equation of the wave front, the transport equation for the first perturbation term of the asymptotic solution is obtained. Finally, it is shown that this transport equation can be reduced to an equation similar to Burgers equation.

1. **Introduction.** In a previous paper [1], a mathematical model was proposed regarding the dynamics of *activation* and *clonal expansion* of T cells during the immune response to a single type of antigen challenge. This model was constructed phenomenologically, deriving the balance equations for the densities and velocities of four populations of cells (naive T, Th_1, Th_2 and dendritic cells) and two populations of chemical mediators (two sets of cytokines); all the populations were modelled as a mixture of interacting fluids in which proliferative events occur. *Interactions* are characterized by the genetic mutations of naive T cells into Th_1 or Th_2 cells and the phenomenon of chemotaxis acting on Th_1 and Th_2 cells, while *proliferative events* (i.e. resulting in non conservative balance equations for the densities of two populations of Th_1 and Th_2 cells) characterize the clonal expansion of Th_1 and Th_2 cells.

The present paper deals with approximate smooth solutions, called asymptotic waves, of a system of PDEs describing the above introduced model of activation

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and clonal expansion of T cells. To obtain a class of approximate smooth solutions for the considered system of PDEs, we adopt a perturbative method derived by Boillat [2, 3] and generalized by Fusco in [4], following also [5]-[15]. Applications of the mathematical theory of asymptotic waves were carried out in the context of mechanical media (Maxwell, viscoelastic media with and without memory) by one of the authors (see for instance [16, 17, 18]). The applied method analyzes systems of PDEs including terms that contain second order derivatives multiplied by a very small parameter. These terms play a very important role because they usually have a balancing effect on the non-linear steepening of the waves (called dissipative waves because their amplitude attenuate with time). Following A. Jeffrey in [19], the solution of systems of PDEs are referred to as waves, because they may be interpreted as representing propagating wavefronts. The solution on the side of the wavefronts towards which propagation takes place may be regarded as being the *undisturbed solution* ahead of the wavefront, while the solution on the other side may be regarded as a propagating disturbance wave which is entering a region occupied by the undisturbed solution.

In Section 2, the phenomenology of the activation and clonal expansion of cells during the immunoresponse to an antigen challenge is briefly introduced; moreover the matrix form of the balance equations for the density and velocities of the constituents of the mixture of reacting-proliferating fluids modelling the introduced immunoresponse is given. In Section 3, an approximate smooth solution of the introduced system of balance equations is analyzed, in the one-dimensional case. In particular, after deriving the expressions of the velocities along the characteristic rays and the equation of the wave front, the transport equation for the first perturbation term of the asymptotic solution is obtained. Finally, it is shown that this transport equation, using a suitable Hopf's transformation, can be reduced to a Burgers equation [4].

2. **Mixture of reacting-proliferating T cells: Phenomenology and modelization.**

In this Section we briefly recall the mathematical model developed in [1] whose approximate solutions will be analyzed in the next sections by means of an asymptotic perturbative method.

We remark that in the modeling we consider only the macroscopic phenomenological outputs of phenomena which happen at the meso- and microscopic levels. Although the dynamics under observation happen mainly in lymph nodes, to reduce the complexity in this first effort of modeling, we consider an unbounded tissue medium.

In the immune system response to antigens an important involved population of cells is that of lymphocytes, which is divided into two main groups: T cells and B cells. The mathematical modeling of this paper regards some particular dynamics of the immune response involving T cells only. T cells are produced in the thymus and they are antigen specific, bearing specific antigen receptors, but in their first stage of maturation they do not have specific functionalities and they are called in general Antigen Not Experienced T cells (or naive T cells). Due to the first encounter with the specific antigen of which they bear the receptors (primary immune response), naive T cells undertake genetic mutations acquiring specific functionalities and at this first stage of maturation they are called in general Antigen Experienced T cells (this process regards the so called activation phase).

Antigen Experienced T cells are collected into three main groups, depending on their functionalities: T helper cells, cytotoxic T cells and suppressor T cells. T helper cells divide into two main groups: T helper 1 (Th_1) and T helper 2 (Th_2). The main characteristic of Antigen Experienced T cells is that due to a second encounter with the same type of antigen (secondary immune response), they can proliferate generating clones; (this process regards the so called clonal expansion phase). During the activation and clonal expansion phases of T cells a crucial role is played by some chemical soluble mediators 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 into Antigen Experienced cells.

T lymphocytes cannot recognize antigens directly, but recognize peptides derived from antigens which have been processed and appropriately presented. This function is performed mainly by two classes of so called accessory cells: macrophages and dendritic cells. The presence of accessory cells bearing the antigen is necessary for the induction of both cell activation and clonal expansion; in our model we have introduced the population of dendritic cells which play a major role in the case of naive T cell activation. Dendritic cells "capture" the antigen "presenting" very small parts of the antigen (peptides) on the surface and they are then driven to the lymph nodes by the chemoattraction induced by some specific cytokines. In our model we consider the population of dendritic cells as one of the constituents of the mixture of biological fluids modeling the activation and clonal expansion of T cells due to their basic role in presenting the antigen T helper cells.

The proposed mathematical model has been constructed in the macroscopic framework of a thermodynamic theory for reacting fluid mixtures [20, 21] of continuum mechanics, by using a phenomenological approach, adapting the balance equations to the case in which proliferative events occur, i.e. events which do not preserve the mass of the mixture as a whole, in the present case the clonal expansion of T cells. The introduced field equations describe some dynamics and interactions of Antigen Not Experienced T cells (*naive T cells*) and two types of Antigen Experienced T helper cells (Th_1 and Th_2 *cells*) in presence of Antigen Presenting Cells, i.e. cells bearing the antigen (*dendritic cells* in our case). The interactions (due to chemotaxis and genetic mutations) among these four populations of cells are induced by the presence of two sets of chemicals (*cytokines*) which act as chemical mediators among the involved cell populations during the immune response, inducing genetic mutations and clonal expansion by means of signaling pathways. Cytokines are produced by the dendritic cells bearing the antigen but the populations of Th_1 and Th_2 cells secrete the same cytokines determining a feedback effect.

The constituents of the mixture of reacting-proliferating biological fluids modeling activation and clonal expansion of T cells due to a single type of antigen challenge are characterized by the following quantities:

1. *naive T cells*: mass density ρ_T, concentration c_T and population velocity $\mathbf{v}_T$;
2. Th_1 *cells*: mass density ρ_{T_1}, concentration c_{T_1} and population velocity $\mathbf{v}_{T_1}$;
3. Th_2 *cells*: mass density ρ_{T_2}, concentration c_{T_2} and population velocity $\mathbf{v}_{T_2}$;
4. *dendritic cells*: mass density ρ_d, concentration c_d and population velocity $\mathbf{v}_d$;
5. 1^{th} *set of cytokines* (IFN-γ, IL-2): mass density ρ_1, concentration c_1 and population velocity $\mathbf{v}_1$;
6. 2^{th} *set of cytokines* (IL-10, IL-4, IL-5, IL-13): mass density ρ_2, concentration c_2 and population velocity $\mathbf{v}_2$.

The density ρ of the mixture of fluids is given by

$$\rho = \rho_T + \rho_{T_1} + \rho_{T_2} + \rho_d + \rho_1 + \rho_2. \tag{1}$$

The concentrations of the constituents are $c_T = \frac{\rho_T}{\rho}$, $c_{T_1} = \frac{\rho_{T_1}}{\rho}$, $c_{T_2} = \frac{\rho_{T_2}}{\rho}$, $c_d = \frac{\rho_d}{\rho}$, $c_1 = \frac{\rho_1}{\rho}$, $c_2 = \frac{\rho_2}{\rho}$, with $c_T + c_{T_1} + c_{T_2} + c_d + c_1 + c_2 = 1$, and the baricentral velocity $\mathbf{v}$ of the mixture has the form

$$\mathbf{v} = \frac{1}{\rho}\left(\rho_T \mathbf{v}_T + \rho_{T_1}\mathbf{v}_{T_1} + \rho_{T_2}\mathbf{v}_{T_2} + \rho_d \mathbf{v}_d + \rho_1 \mathbf{v}_1 + \rho_2 \mathbf{v}_2\right). \tag{2}$$

Regarding the constituents of the mixture, the following biological and physical phenomena are taken into account by the model:

- genetic mutations of naive T cells into Th_1 or Th_2 cells,
- chemotaxis induced by the cytokines on Th_1, Th_2 and dendritic cells,
- random motility of cells (describing diffusion-like phenomena),
- activation of naive T cells mutating into Th_1 or Th_2 cells,
- generation of newly borne naive T cells in the thymus,
- programmed cell death of naive T cells,
- activation induced cell death of Th_1 and Th_2 cells,
- production of cytokines by means of dendritic, Th_1 and Th_2 cells,
- consumption of the cytokines,
- diffusion of the cytokines.

The balance equation of mass density of naive T cells is

$$\frac{\partial \rho_T}{\partial t} + \nabla \cdot (\rho_T \mathbf{v}_T) + r\nabla \cdot \mathbf{J}_T = (k_0 - k_{ap})\rho_T - h_1 \rho_T c_1 - h_2 \rho_T c_2, \tag{3}$$

where r is the *random cell motility coefficient* and the contributions $-h_1\rho_T c_1$ and $-h_2\rho_T c_2$ describe the activation of naive T cells into Th_1 and Th_2 cells, respectively, due to the "interactions" with the two sets of cytokines. Taking into account the random motility of cells, generating a diffusion-like flux [22, 23]

$$\mathbf{J}_T = -r\nabla \rho_T, \tag{4}$$

eq.(3) reads

$$\frac{\partial \rho_T}{\partial t} + \nabla \cdot (\rho_T \mathbf{v}_T) - r \triangle \rho_T = (k_0 - k_{ap})\rho_T - h_1 \rho_T c_1 - h_2 \rho_T c_2, \tag{5}$$

where k_0 is the constant growth rate of naive T cells, k_{ap} is its constant apoptotic rate, h_1 and h_2 are the constant activation rate of naive T cells into Th_1 and Th_2 cells respectively and r is the random motility coefficient nof the cells. Furthermore, the local form of the balance equation of momentum density of naive T cells has the form

$$\frac{\partial \rho_T \mathbf{v}_T}{\partial t} + \nabla \cdot (\rho_T \mathbf{v}_T \otimes \mathbf{v}_T) = \mathbf{m}_T \tag{6}$$

with $\mathbf{m}_T = (k_0 - k_{ap} - h_1 c_1 - h_2 c_2)\rho_T \mathbf{v}_T$. $\mathbf{m}_T$ is the production of momentum density and it was obtained by multiplying the produced mass in the specific case by the related velocity $\mathbf{v}_T$.

Among the seven introduced mass densities $(\rho, \rho_T, \rho_{T_1}, \rho_{T_2}, \rho_d, \rho_1, \rho_2)$ only $7 - 1 = 6$ are independent (see eq. (1)). Then, we choose the following set $\mathbf{C}$ of independent unknown fields

$$\mathbf{C} = (\rho, \rho_{T_1}, \rho_{T_2}, \rho_d, \rho_1, \rho_2, \mathbf{v}, \mathbf{v}_{T_1}, \mathbf{v}_{T_2}, \mathbf{v}_d, \mathbf{v}_1, \mathbf{v}_2). \tag{7}$$

For the determination of these fields we need the appropriate number of field equations [21]. They are based on the balance equations of density of mass and momentum of the constituents; these equations have been deduced in [1] and are summarized in the following

$$\begin{cases}
\frac{\partial \rho}{\partial t} + \nabla \cdot (\rho \mathbf{v}) - r\triangle\rho + (r-D)\triangle(\rho_1+\rho_2) = [\alpha-1]\tilde{\rho}_{T_1} + [\beta-1]\tilde{\rho}_{T_2}, \\
\frac{\partial \rho_{T_1}}{\partial t} + \nabla \cdot (\rho_{T_1}\mathbf{v}_{T_1}) - r\triangle\rho_{T_1} = \alpha\tilde{\rho}_{T_1}, \\
\frac{\partial \rho_{T_2}}{\partial t} + \nabla \cdot (\rho_{T_2}\mathbf{v}_{T_2}) - r\triangle\rho_{T_2} = \beta\tilde{\rho}_{T_2}, \\
\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 = (\rho_1^{(int)} - \frac{1}{\gamma_1})\rho_1, \\
\frac{\partial \rho_2}{\partial t} + \nabla \cdot (\rho_2\mathbf{v}_2) - D\triangle\rho_2 = (\rho_2^{(int)} - \frac{1}{\gamma_2})\rho_2, \\
\frac{\partial (\rho\mathbf{v})}{\partial t} + \nabla \cdot [\rho\mathbf{v}\otimes\mathbf{v} - \mathbf{t}] = [\alpha-1]\tilde{\rho}_{T_1}\mathbf{v}_{T_1} + [\beta-1]\tilde{\rho}_{T_2}\mathbf{v}_{T_2}, \\
\frac{\partial (\rho_{T_1}\mathbf{v}_{T_1})}{\partial t} + \nabla \cdot [\rho_{T_1}\mathbf{v}_{T_1}\otimes\mathbf{v}_{T_1} - \mathbf{t}_{T_1}] = \alpha\tilde{\rho}_{T_1}\mathbf{v}_{T_1} + \chi_1\rho_{T_1}\nabla\frac{\rho_1}{\rho}, \\
\frac{\partial (\rho_{T_2}\mathbf{v}_{T_2})}{\partial t} + \nabla \cdot [\rho_{T_2}\mathbf{v}_{T_2}\otimes\mathbf{v}_{T_2} - \mathbf{t}_{T_2}] = \beta\tilde{\rho}_{T_2}\mathbf{v}_{T_2} + \chi_2\rho_{T_2}\nabla\frac{\rho_2}{\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} + \nabla\frac{\rho_2}{\rho}), \\
\frac{\partial \rho_1\mathbf{v}_1}{\partial t} + \nabla \cdot [\rho_1\mathbf{v}_1\otimes\mathbf{v}_1 - \mathbf{t}_1] = (\rho_1^{(int)} - \frac{1}{\gamma_1})\rho_1\mathbf{v}_1, \\
\frac{\partial \rho_2\mathbf{v}_2}{\partial t} + \nabla \cdot [\rho_2\mathbf{v}_2\otimes\mathbf{v}_2 - \mathbf{t}_2] = (\rho_2^{(int)} - \frac{1}{\gamma_2})\rho_2\mathbf{v}_2,
\end{cases} \tag{8}$$

where we have made the positions

$$\tilde{\rho}_{T_1} = c_1(h_1\rho_T - h_{ap}\rho_{T_1}),\ \tilde{\rho}_{T_2} = c_2(h_2\rho_T - h_{ap}\rho_{T_2}), \tag{9}$$

and the above quantities come from the *activation phase* due to the interactions with the cytokines (for details about the phenomenology see [1]). Moreover, we have made the positions

$$\rho_1^{(int)} = \mu_1\frac{\rho_{T_1}}{\rho} + \nu_1\frac{\rho_d}{\rho},\ \rho_2^{(int)} = \mu_2\frac{\rho_{T_2}}{\rho} + \nu_2\frac{\rho_d}{\rho}. \tag{10}$$

Furthermore, α and β are the proliferation rate factors of Th_1 and Th_2 cells, respectively. The coefficients μ_1, ν_1 and μ_2, ν_2 describe the interactions of the first and second set of cytokines with the Th_1, Th_2 and dendritic cells. Also, in the right hand side of eq. $(8)_1$, the source term is due only to the interaction of the two components ρ_{T_1} and ρ_{T_2} with the two sets of cytokines. Consequentely, in eq. $(8)_7$, the contributes of the other components different from ρ_{T_1} and ρ_{T_2} are null. The last term on the right hand side of eq. $(8)_8$ (analogously for eq. $(8)_9$) is due

to the chemotaxis acting on the Th_1 cells due to the presence of the first set of cytokines (chemotactic force) and the source term of eq. $(8)_{10}$ is due to the chemotaxis exerted by both set of cytokines on dendritic cells. The effect of chemotaxis is introduced as a source term in the balance equations of momentum for the involved quantities [24, 25]. Regarding eq. $(8)_1$, it was obtained by summing the equation (5) and equations $(8)_2$, $(8)_3$, $(8)_4$, $(8)_5$ and $(8)_6$ and by considering a first phase of activation followed by a second phase of clonal expansion. During the first phase phenomena are conservative (the sum of the production terms is null)

$$(k_0-k_{ap})\rho_T-h_{ap}c_1\rho_T-h_{ap}c_2\rho_T+\left(\mu_1 c_{T_1}+\nu_1 c_d-\frac{1}{\gamma_1}\right)\rho_1+\left(\mu_2 c_{T_2}+\nu_2 c_d-\frac{1}{\gamma_2}\right)\rho_2=0. \tag{11}$$

In eq. $(8)_1$, the second and third terms on the left hand side account for the fact that the motility is due only to the Th_1, Th_2 and dendritic cells of densities ρ_{T_1}, ρ_{T_2} and ρ_d respectively (see eq. (1) and that only the two sets of cytokines, of densities ρ_1 and ρ_2, diffuse, where D is the diffusion coefficient characterizing the fluxes $\mathbf{J}_1$ and $\mathbf{J}_2$ of the two sets of cytokines ($\mathbf{J}_1=-D\nabla\rho_1$, $\mathbf{J}_1=-D\nabla\rho_1$). Regarding the momentum balance equations, the production of momentum density for each equation was obtained by multiplying the production of mass density of each quantity by the related velocity of the constituents of the mixture and by introducing for the Th_1 and Th_2 cells the interaction forces due to the chemotaxis induced by the two sets of cytokines ($\chi_1\rho_{T_1}\nabla\frac{\rho_1}{\rho}$ and $\chi_2\rho_{T_2}\nabla\frac{\rho_2}{\rho}$, respectively). Finally, the equation for the mixture momentum density was obtained by summing up eq. (6) and eq.s $(8)_7$, $(8)_8$, $(8)_9$, $(8)_{10}$, $(8)_{11}$ and $(8)_{12}$, and by taking into account the relation defining the density of the mixture (1) and that the mixture stress tensor $\mathbf{t}$ is defined as follows (see [20, 21])

$$\begin{aligned}\mathbf{t}=\mathbf{t}_T+\mathbf{t}_{T_1}+\mathbf{t}_{T_2}+\mathbf{t}_d+\mathbf{t}_1+\mathbf{t}_2-\rho_T\mathbf{u}_T\otimes\mathbf{u}_T-\rho_{T_1}\mathbf{u}_{T_1}\otimes\mathbf{u}_{T_1}-\rho_{T_2}\mathbf{u}_{T_2}\otimes\mathbf{u}_{T_2}+\\ -\rho_d\mathbf{u}_d\otimes\mathbf{u}_d-\rho_1\mathbf{u}_1\otimes\mathbf{u}_1-\rho_2\mathbf{u}_2\otimes\mathbf{u}_2,\end{aligned} \tag{12}$$

where the partial velocities (i. e. the velocity of the constituents with respect to the baricentral velocity $\mathbf{v}$) $\mathbf{u}_T=\mathbf{v}_T-\mathbf{v}$, $\mathbf{u}_{T_1}=\mathbf{v}_{T_1}-\mathbf{v}$, $\mathbf{u}_{T_2}=\mathbf{v}_{T_2}-\mathbf{v}$, $\mathbf{u}_d=\mathbf{v}_d-\mathbf{v}$, $\mathbf{u}_1=\mathbf{v}_1-\mathbf{v}$ and $\mathbf{u}_2=\mathbf{v}_2-\mathbf{v}$ have been introduced.

The balance equations of mixture mass and momentum densities are obtained by summing up all the balance equations of mass and momentum for the constituents of the mixture and by applying the requirements of conservation of mass and momentum densities regarding the conservative event of activation of T cells (for details about their derivation the reader is kindly suggested to see [1]).

2.1. **Physical assumptions.** Constitutive equations for the stress tensor of each constituent of the mixture are needed in order to close the system of equations (8). In our model, we assume that the fluids modelling the populations of cells and the chemicals are *non-viscous and simple* [20, 21], i. e. the following relations hold

$$\mathbf{t}_T=-p_T(\rho_T,T)\mathbf{I},\ \mathbf{t}_{T_1}=-p_{T_1}(\rho_{T_1},T)\mathbf{I},\ \mathbf{t}_{T_2}=-p_{T_2}(\rho_{T_2},T)\mathbf{I}$$
$$\mathbf{t}_d=-p_d(\rho_d,T)\mathbf{I},\ \mathbf{t}_1=-p_1(\rho_1,T)\mathbf{I},\ \mathbf{t}_2=-p_2(\rho_2,T)\mathbf{I}$$

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 [21]. In our model the process is *isothermal*.

By substituting the constitutive equations (13) into the expression for the stress tensor of the mixture (12), the following equation is obtained

$$\begin{aligned}\mathbf{t} = -p\mathbf{I} - (&\rho_T \mathbf{u}_T \otimes \mathbf{u}_T + \rho_{T_1}\mathbf{u}_{T_1} \otimes \mathbf{u}_{T_1} + \rho_{T_2}\mathbf{u}_{T_2} \otimes \mathbf{u}_{T_2} + \\ &\rho_d \mathbf{u}_d \otimes \mathbf{u}_d + \rho_1 \mathbf{u}_1 \otimes \mathbf{u}_1 + \rho_2 \mathbf{u}_2 \otimes \mathbf{u}_2)\end{aligned} \tag{13}$$

where $p = p_T + p_{T_1} + p_{T_2} + p_d + p_1 + p_2$ is the scalar pressure of the mixture. In the case of *isothermal processes in non-viscous fluids*, the following *equation of state* holds [26] $p = \frac{\partial F}{\partial \rho}\rho^2$ where F is the free energy and T the absolute temperature. By assuming a linear relation regarding the dependance of the free energy on the density, we obtain the following *equations of state* for the partial pressures

$$p_T = \hat{p}_T \rho_T^2,\ p_{T_1} = \hat{p}_{T_1}\rho_{T_1}^2,\ p_{T_2} = \hat{p}_{T_2}\rho_{T_2}^2,\ p_d = \hat{p}_d\rho_d^2,\ p_1 = \hat{p}_1\rho_1^2,\ p_2 = \hat{p}_2\rho_2^2, \tag{14}$$

where the quantities $\hat{p}_T, \tilde{p}_{T_1}, \hat{p}_{T_2}, \hat{p}_d, \hat{p}_1, \hat{p}_2$ are positive constants [27, 28]. Because of the low involved velocities of the cells and the chemicals [27, 28], we disregard all the inertial terms in the balance equations of momentum densities; from a modelization 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*. The system (8), together with (13) and (14) (and neglecting the effect of persistence in cell motion), takes the form

$$\begin{aligned}
\frac{\partial \rho}{\partial t} + \nabla\cdot(\rho\mathbf{v}) - r\triangle\rho + (r-D)\triangle(\rho_1+\rho_2) &= [\alpha(t)-1]\tilde{\rho}_{T_1} + [\beta(t)-1]\tilde{\rho}_{T_2},\\
\frac{\partial \rho_{T_1}}{\partial t} + \nabla\cdot(\rho_{T_1}\mathbf{v}_{T_1}) - r\triangle\rho_{T_1} &= \alpha(t)\tilde{\rho}_{T_1},\\
\frac{\partial \rho_{T_2}}{\partial t} + \nabla\cdot(\rho_{T_2}\mathbf{v}_{T_2}) - r\triangle\rho_{T_2} &= \beta(t)\tilde{\rho}_{T_2},\\
\frac{\partial \rho_d}{\partial t} + \nabla\cdot(\rho_d\mathbf{v}_d) - r\triangle\rho_d &= 0,\\
\frac{\partial \rho_1}{\partial t} + \nabla\cdot(\rho_1\mathbf{v}_1) - D\triangle\rho_1 &= (\rho_1^{(int)}\rho_1 - \frac{1}{\gamma_1}),\\
\frac{\partial \rho_2}{\partial t} + \nabla\cdot(\rho_2\mathbf{v}_2) - D\triangle\rho_2 &= (\rho_2^{(int)}\rho_2 - \frac{1}{\gamma_2}),\\
\frac{\partial(\rho\mathbf{v})}{\partial t} + 2\hat{p}\rho\nabla\rho &= [\alpha(t)-1]\tilde{\rho}_{T_1}\mathbf{v}_{T_1} + [\beta(t)-1]\tilde{\rho}_{T_2}\mathbf{v}_{T_2},\\
\frac{\partial \rho_{T_1}\mathbf{v}_{T_1}}{\partial t} + 2\hat{p}_{T_1}\rho_{T_1}\nabla\rho_{T_1} - \chi_1\rho_{T_1}\nabla\frac{\rho_1}{\rho} &= \alpha(t)\frac{\rho_1}{\rho}\tilde{\rho}_{T_1}\mathbf{v}_{T_1} + \chi_1\rho_{T_1}\nabla\frac{\rho_1}{\rho},\\
\frac{\partial \rho_{T_2}\mathbf{v}_{T_2}}{\partial t} + 2\hat{p}_{T_2}\rho_{T_2}\nabla\rho_{T_2} - \chi_2\rho_{T_2}\nabla\frac{\rho_2}{\rho} &= \beta(t)\frac{\rho_2}{\rho}\tilde{\rho}_{T_2}\mathbf{v}_{T_2} + \chi_2\rho_{T_2}\nabla\frac{\rho_2}{\rho},\\
\frac{\partial \rho_d\mathbf{v}_d}{\partial t} + 2\hat{p}_d\rho_d\nabla\rho_d - \rho_d\chi_d(\nabla\frac{\rho_1}{\rho} + \nabla\frac{\rho_2}{\rho}) &= \mathbf{0},
\end{aligned} \tag{15}$$

$$\begin{aligned}
\frac{\partial \rho_1\mathbf{v}_1}{\partial t} + 2\hat{p}_1\rho_1\nabla\rho_1 &= (\rho_1^{(int)} - \frac{1}{\gamma_1})\rho_1\mathbf{v}_1,\\
\frac{\partial \rho_2\mathbf{v}_2}{\partial t} + 2\hat{p}_2\rho_2\nabla\rho_2 &= (\rho_2^{(int)} - \frac{1}{\gamma_2})\rho_2\mathbf{v}_2.
\end{aligned} \tag{16}$$

Eqs. (15) form a system of 24 quasi-linear second order PDEs for mass density of the mixture, Th_1, Th_2, dendritic cells and the 1^{th} and 2^{th} sets of cytokines together

with the related velocities. Let

$$\mathbf{U} = (\rho, \rho_{T_1}, \rho_{T_2}, \rho_d, \rho_1, \rho_2, \mathbf{v}, \mathbf{v}_{T_1}, \mathbf{v}_{T_2}, \mathbf{v}_d, \mathbf{v}_1, \mathbf{v}_2)^T. \tag{17}$$

Then the system of equations (15) can be written in the following matrix form

$$\mathbf{A}^\alpha(\mathbf{U})\frac{\partial \mathbf{U}}{\partial x^\alpha} + \epsilon \mathbf{H}^k(\mathbf{U})\frac{\partial^2 \mathbf{U}}{\partial (x^k)^2} + \mathbf{B}(\mathbf{U}, x^0) = \mathbf{0}, \tag{18}$$

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 $\alpha = 0, 1, 2, 3$) and $\mathbf{H}^k(\mathbf{U})$(with $k = 1, 2, 3$) are appropriate 24×24 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 a very small parameter $\epsilon \ll 1$. Throughout this paper the dummy index convention is understood.

3. **Approximate asymptotic smooth solutions in the activation and clonal expansion of T cells.** In this Section we deal with approximate smooth solutions, called *asymptotic waves* of the system of PDEs characterizing the activation and clonal expansion of T cells during the immunoreaction, in the case of one space dimension for the sake of simplicity. In one space dimension the quasi linear system of PDEs (15) reads

$$\begin{aligned}
\frac{\partial \rho}{\partial t} + \frac{\partial \rho v}{\partial x} - r\frac{\partial^2 \rho}{\partial x^2} + (r - D)\frac{\partial^2 (\rho_1 + \rho_2)}{\partial x^2} &= [\alpha - 1]\tilde{\rho}_{T_1} + [\beta - 1]\tilde{\rho}_{T_2},\\
\frac{\partial \rho_{T_1}}{\partial t} + \frac{\partial (\rho_{T_1} v_{T_1})}{\partial x} - r\frac{\partial^2 \rho_{T_1}}{\partial x^2} &= \alpha \tilde{\rho}_{T_1},\\
\frac{\partial \rho_{T_2}}{\partial t} + \frac{\partial (\rho_{T_2} v_{T_2})}{\partial x} - r\frac{\partial^2 \rho_{T_2}}{\partial x^2} &= \beta \tilde{\rho}_{T_2},\\
\frac{\partial \rho_d}{\partial t} + \frac{\partial (\rho_d v_d)}{\partial x} - r\frac{\partial^2 \rho_d}{\partial x^2} &= 0,\\
\frac{\partial \rho_1}{\partial t} + \frac{\partial (\rho_1 v_1)}{\partial x} - D\frac{\partial^2 \rho_1}{\partial x^2} &= (\rho_1^{(int)}\rho_1 - \frac{1}{\gamma_1}),\\
\frac{\partial \rho_2}{\partial t} + \frac{\partial (\rho_2 v_2)}{\partial x} - D\frac{\partial^2 \rho_2}{\partial x^2} &= (\rho_2^{(int)}\rho_2 - \frac{1}{\gamma_2}),\\
\frac{\partial (\rho v)}{\partial t} + 2\hat{p}\rho\frac{\partial \rho}{\partial x} &= [\alpha - 1]\tilde{\rho}_{T_1} v_{T_1} + [\beta - 1]\tilde{\rho}_{T_2} v_{T_2},\\
\frac{\partial \rho_{T_1} v_{T_1}}{\partial t} + 2\hat{p}_{T_1}\rho_{T_1}\frac{\partial \rho_{T_1}}{\partial x} - \chi_1 \rho_{T_1}\frac{\partial (\frac{\rho_1}{\rho})}{\partial x} &= \alpha(t)\frac{\rho_1}{\rho}\tilde{\rho}_{T_1} v_{T_1} + \chi_1 \rho_{T_1}\frac{\partial (\frac{\rho_1}{\rho})}{\partial x},\\
\frac{\partial \rho_{T_2} v_{T_2}}{\partial t} + 2\hat{p}_{T_2}\rho_{T_2}\frac{\partial \rho_{T_2}}{\partial x} - \chi_2 \rho_{T_2}\frac{\partial (\frac{\rho_2}{\rho})}{\partial x} &= \beta(t)\frac{\rho_2}{\rho}\tilde{\rho}_{T_2} v_{T_2} + \chi_2 \rho_{T_2}\frac{\partial (\frac{\rho_2}{\rho})}{\partial x},\\
\frac{\partial \rho_d v_d}{\partial t} + 2\hat{p}_d\rho_d\frac{\partial \rho_d}{\partial x} - \rho_d\chi_d\left(\frac{\partial (\frac{\rho_1}{\rho})}{\partial x} + \frac{\partial (\frac{\rho_2}{\rho})}{\partial x}\right) &= 0,\\
\frac{\partial \rho_1 v_1}{\partial t} + 2\hat{p}_1\rho_1\frac{\partial \rho_1}{\partial x} &= \left(\rho_1^{(int)} - \frac{1}{\gamma_1}\right)\rho_1 v_1,\\
\frac{\partial \rho_2 v_2}{\partial t} + 2\hat{p}_2\rho_2\frac{\partial \rho_2}{\partial x} &= \left(\rho_2^{(int)} - \frac{1}{\gamma_2}\right)\rho_2 v_2.
\end{aligned} \tag{19}$$

Eqs. (19) form a system of 12 quasi-linear second order PDEs for mass density of the mixture, Th_1, Th_2, dendritic cells and the 1^{th} and 2^{th} sets of cytokines together with the related velocities. In matrix form and in one space dimension the quasi linear system of PDEs (19) reads

$$\mathbf{A}^{\alpha}(\mathbf{U})\frac{\partial \mathbf{U}}{\partial x^{\alpha}} + \epsilon \mathbf{H}(\mathbf{U})\frac{\partial^2 \mathbf{U}}{\partial x^2} + \mathbf{B}(\mathbf{U}, x^0) = \mathbf{0} \tag{20}$$

with $\alpha = 0, 1$, $x^0 = t$ and $x^1 = x$. The matrices of the coefficients can be written as the following block matrices

$$\mathbf{A}^0 = \left(\begin{array}{c|cc|c} & \mathbf{A}^0_{11} & & \mathbf{A}^0_{12} \\ - & - & - & - \\ & \mathbf{A}^0_{21} & & \mathbf{A}^0_{22} \end{array}\right), \tag{21}$$

$$\mathbf{A}^1 = \left(\begin{array}{c|cc|c} & \mathbf{A}^1_{11} & & \mathbf{A}^1_{12} \\ - & - & - & - \\ & \mathbf{A}^1_{21} & & \mathbf{A}^1_{22} \end{array}\right), \tag{22}$$

$$\mathbf{H}^1 = \left(\begin{array}{c|cc|c} & \mathbf{H}^1_{11} & & \mathbf{H}^1_{12} \\ - & - & - & - \\ & \mathbf{H}^1_{21} & & \mathbf{H}^1_{22} \end{array}\right), \tag{23}$$

where $\mathbf{A}^0_{11} = \mathbf{I}$ (identity matrix), $\mathbf{A}^0_{21} = \mathbf{A}^1_{11}$ are diagonal matrices having the velocities of the mixture constituents along the principal diagonal, $\mathbf{A}^0_{22} = \mathbf{A}^1_{12}$ are diagonal matrices having the densities of the mixture constituents along the principal diagonal, $\mathbf{A}^0_{12} = \mathbf{A}^1_{22} = \mathbf{H}_{12} = \mathbf{H}_{21} = \mathbf{H}_{22} = \mathbf{0}$ (null matrix) and

$$\mathbf{A}^1_{21} = \begin{pmatrix} 2\hat{p}\rho & 0 & 0 & 0 & 0 & 0 \\ \frac{\chi_1 \rho_{T_1} \rho_1}{\rho^2} & 2\hat{p}_{T_1}\rho_{T_1} & 0 & 0 & \frac{-\chi_1 \rho_{T_1}}{\rho} & 0 \\ \frac{\chi_2 \rho_{T_2} \rho_2}{\rho^2} & 0 & 2\hat{p}_{T_2}\rho_{T_2} & 0 & 0 & \frac{-\chi_2 \rho_{T_2}}{\rho} \\ \frac{\chi_d \rho_d (\rho_1 + \rho_2)}{\rho^2} & 0 & 0 & 2\hat{p}_d \rho_d & \frac{-\chi_d \rho_d}{\rho} & \frac{-\chi_d \rho_d}{\rho} \\ 0 & 0 & 0 & 0 & 2\hat{p}_1 \rho_1 & 0 \\ 0 & 0 & 0 & 0 & 0 & 2\hat{p}_2 \rho_2 \end{pmatrix}, \tag{24}$$

$$\mathbf{H}_{11} = \begin{pmatrix} -s & 0 & 0 & 0 & \frac{s(r-D)}{r} & \frac{s(r-D)}{r} \\ 0 & -s & 0 & 0 & 0 & 0 \\ 0 & 0 & -s & 0 & 0 & 0 \\ 0 & 0 & 0 & -s & 0 & 0 \\ 0 & 0 & 0 & 0 & -\frac{sD}{r} & 0 \\ 0 & 0 & 0 & 0 & 0 & -\frac{sD}{r} \end{pmatrix}, \tag{25}$$

where $s = r/\epsilon$. Finally, it is

$$\mathbf{B} = \begin{pmatrix} -[\alpha-1]\tilde{\rho}_{T_1} - [\beta-1]\tilde{\rho}_{T_2} \\ -\alpha\tilde{\rho}_{T_1} \\ -\beta\tilde{\rho}_{T_2} \\ 0 \\ -(\rho_1^{(int)} + \frac{1}{\gamma_1})\rho_1 \\ -(\rho_2^{(int)} + \frac{1}{\gamma_2})\rho_2 \\ -[\alpha-1]\tilde{\rho}_{T_1}v_{T_1} - [\beta-1]\tilde{\rho}_{T_2}v_{T_2} \\ -\alpha\tilde{\rho}_{T_1}\rho v_{T_1} \\ -\beta\tilde{\rho}_{T_1}\rho v_{T_2} \\ 0 \\ -(\rho_1^{(int)}\rho_1 + \frac{1}{\gamma_1})v_1 \\ -(\rho_2^{(int)} + \frac{1}{\gamma_2})\rho_2 v_2 \end{pmatrix}. \tag{26}$$

We consider a known uniform unperturbed state characterized by the following constant solution of the system (20)

$$\mathbf{U}^0 = (\rho^0, \rho^0_{T_1}, \rho^0_{T_2}, \rho^0_d, \rho^0_1, \rho^0_2, 0, 0, 0, 0, 0, 0). \tag{27}$$

We look for the solution of the equations as an asymptotic series of powers of the small parameter, say ϵ , namely with respect to the asymptotic sequence $\{1, \epsilon^{a+1}, \epsilon^{a+2}, ..., \}$ or $\{1, \epsilon^{\frac{1}{p}}, \epsilon^{\frac{2}{p}}, ..., \}$ as $\epsilon \to 0$. Following [3] in our case we consider $p = 1$, such that $\mathbf{U}$ is written as an asymptotic power series of ϵ, i.e. with respect to the asymptotic sequence $1, \epsilon, \epsilon^2, ...,$ as $\epsilon \to 0$, the $U^i (i = 1, 2, ...,)$ being functions of $x^\alpha (\alpha = 0, 1)$ and a new variable ξ. It is supposed [3, 4] that the vector $\mathbf{U}$ can be developed in the following asymptotic form around $\mathbf{U}^0$

$$\mathbf{U}(x^\alpha, \xi) = \mathbf{U}^0(x^\alpha, \xi) + \epsilon\mathbf{U}^1(x^\alpha, \xi) + \epsilon^2\mathbf{U}^2(x^\alpha, \xi) + ... \ (\alpha = 0, 1). \tag{28}$$

where $\xi = \epsilon^{-1}\varphi(x^\alpha)$ is asymptotically fixed, i.e. $\xi = Ord(1)$ as $\epsilon \to 0$, $\epsilon^{-1} >> 1$ is a large parameter and $\varphi(x^\alpha) = 0$ is the unknown so called *wave front* [5, 10] which is to be determined. In [3, 4] and [16, 17, 18]

ϵ is supposed a very small parameter and the equations of the system describing the proposed mathematical model are written in dimensional form. In our case ϵ is given by $\epsilon = r/s$ (see [3, 4] and [16, 18] for the definition of ϵ in other dimensional PDEs describing real physical problems). The variable ξ is a fast variable that characterizes the so-called interior-layers, across which the solution $\mathbf{U}(x^\alpha)$ or/and its derivatives undergo steep variations, situated in the neighbourhood of a family of moving surfaces $S(t)$ in E^3 (parametrized by the time t) of equation $\varphi(x^\alpha) = \bar{\xi}$, with $\bar{\xi} = const$, related to the wavefront $\varphi(x^\alpha) = 0$. On the contrary, along the surfaces $S(t)$ the variation of $\mathbf{U}$ is slow. In this case it is said that $\mathbf{U}$, starting from $\mathbf{U}_0$, evolves in progressives waves and the surfaces S(t) are the wave surfaces or, simply, waves. Then, we assume that the solution depends on the old variable x^α as well on the new variable ξ. From (28) we see that the following relations are valid

$$\mathbf{A}^\alpha(\mathbf{U}) = \mathbf{A}^\alpha(\mathbf{U}^0) + \epsilon\nabla\mathbf{A}^\alpha(\mathbf{U}^0)\mathbf{U}^1 + \mathcal{O}\left(\epsilon^2\right) \ (\alpha = 0, 1), \tag{29}$$

$$\mathbf{H}(\mathbf{U}) = \mathbf{H}(\mathbf{U}^0) + \epsilon\nabla\mathbf{H}(\mathbf{U}^0)U^1 + \mathcal{O}\left(\epsilon^2\right), \tag{30}$$

$$\mathbf{B}(\mathbf{U}) = \mathbf{B}(\mathbf{U}^0) + \epsilon\nabla\mathbf{B}(\mathbf{U}^0)\mathbf{U}^1 + \mathcal{O}(\epsilon^2) \tag{31}$$

where $\nabla = \frac{\partial}{\partial \mathbf{U}}$. Inserting the asymptotic expansion (28)-(31) into the system of PDEs (20) and matching the obtained series, one has the following results

$$(\mathbf{A}^{\alpha})_0 \Phi_{\alpha} \frac{\partial \mathbf{U}^1}{\partial \xi} = \mathbf{0} \quad (\alpha = 0, 1), \tag{32}$$

$$(\mathbf{A}^{\alpha})_0 (\frac{\partial \mathbf{U}^1}{\partial x_{\alpha}} + \Phi_{\alpha} \frac{\partial \mathbf{U}^2}{\partial \xi}) + (\nabla \mathbf{A}^{\alpha})_0 \mathbf{U}^1 \big(\Phi \frac{\partial \mathbf{U}^1}{\partial \xi}\big) + (\mathbf{H}^k)_0 (\Phi_k)^2 \frac{\partial^2 \mathbf{U}^1}{\partial \xi^2} = (\nabla \mathbf{B})_0 \mathbf{U}^1 \tag{33}$$

where $\Phi_{\alpha} = \frac{\partial \varphi}{\partial x^{\alpha}}$ $(\alpha = 0, 1)$ and the symbol "$_0$" indicates that the quantities are calculated in $\mathbf{U}^0$. We introduce the notation

$$\lambda = -\frac{\partial \varphi / \partial t}{|grad \varphi|}, \tag{34}$$

being λ the velocity normal to the progressive waves. The unit vector normal to the wave front $\mathbf{n}$ is defined by

$$\mathbf{n} = \frac{grad \varphi}{|grad \varphi|}. \tag{35}$$

With these notations, eq. (32) takes the form

$$((\mathbf{A}_n)_0 - \lambda \mathbf{I}) \frac{\partial \mathbf{U}^1}{\partial \xi} = 0, \tag{36}$$

with $\mathbf{A}_n(\mathbf{U}) = \mathbf{A}\mathbf{n}$.

By integrating eq. (36), one obtains

$$\mathbf{U}^1(x^{\alpha}, \xi) = u(x^{\alpha}, \xi) \mathbf{r}(\mathbf{U}^0, \mathbf{n}) + \boldsymbol{\nu}^1(x^{\alpha}) \quad (\alpha = 0, 1), \tag{37}$$

where u is a scalar function to be determined and $\boldsymbol{\nu}^1$ is an arbitrary vector of integration which can be taken as zero, without loss of generality [2, 3].

We show now how the wave front φ can be determined. Eqs. (28)-(37) are also valid in three dimensional case (3D) when $\alpha = 0, 1, 2, 3$. In the general 3D theory [2, 3], by introducing the quantity

$$\Psi(\mathbf{U}, \Phi_{\alpha}) = \varphi_t + |grad \varphi| \lambda(\mathbf{U}, \mathbf{n}) \quad (\alpha = 0, 1, 2, 3), \tag{38}$$

the radial velocity $\boldsymbol{\Lambda}$ is defined by

$$\Lambda_i(\mathbf{U}, \mathbf{n}) = \frac{\partial \Psi}{\partial \Phi} = \lambda n_i + \frac{\partial \lambda}{\partial n_i} - \big(\mathbf{n} \cdot \frac{\partial \lambda}{\partial \mathbf{n}}\big) n_i \quad (i = 1, 2, 3). \tag{39}$$

Since we are considering the propagation into an uniform unperturbed state, it is known that the wave front φ, propagating with velocity λ, satisfy the partial differential equation

$$\Psi(\mathbf{U}^0, \Phi_{\alpha}) = \varphi_t + |grad \varphi| \lambda(\mathbf{U}^0, \mathbf{n}^0) = 0 \quad (\alpha = 0, 1, 2, 3). \tag{40}$$

The characteristic equations for (40) are

$$\frac{dx_{\alpha}}{d\sigma} = \frac{\partial \Psi^0}{\partial \Phi_{\alpha}} \quad (\alpha = 0, 1, 2, 3), \tag{41}$$

$$\frac{d\Phi_{\alpha}}{d\sigma} = -\frac{\partial \Psi^0}{\partial x_{\alpha}} \quad (\alpha = 0, 1, 2, 3), \tag{42}$$

where σ is the time along the rays. From (40) it is seen that Ψ^0 depends only on Φ_{α} $(\alpha = 0, 1, 2, 3)$ and eq. (42) gives that Φ_{α} are constants along the *characteristic*

rays. By virtue of (36), this property is also possessed by $\mathbf{n}$. By integration of (41) one has

$$x^0 = t = \sigma, \tag{43}$$

$$x_i = (x)_i^0 - \Lambda_i^0(\mathbf{U}^0, \mathbf{n}^0)t, \tag{44}$$

where

$$(x)_i^0 = (x_i)_{t=0} \tag{45}$$

and $\mathbf{n}^0$ indicates the constant value of $\mathbf{n}$ along the rays. If we denote by ϕ^0 the given initial surface, we have $(\phi)_{t=0} = \phi^0[(x^i)^0]$ and $\mathbf{n}^0$ represents the normal vector at the point $(x^i)^0$ defined by $\mathbf{n}^0 = \left(\frac{grad\phi}{|grad\phi|}\right)_{t=0} = \frac{grad^0\phi^0}{|grad^0\phi^0|}$, where $grad^0 \equiv \frac{\partial}{\partial(x)^0}$. Then $\mathbf{x} = \mathbf{x}|_{t=0} + \boldsymbol{\lambda}^0 t$ and, since the Jacobian of the transformation is not vanishing, $(x)_i^0$ can be deduced from equations (44) and ϕ in the first approximation takes the following form

$$\varphi(t, x^i) = \varphi^0(x^i - \Lambda_i^0 t). \tag{46}$$

In the one-dimensional case, when we have $\alpha = 0, 1$, eq. (39) gives the following result for the *radial velocity* calculated in $\mathbf{U}^0$

$$\Lambda^0 = \Lambda^0(\mathbf{U}^0, n^0) = \frac{\partial \Psi^0}{\partial \Phi} = \lambda n + \frac{\partial \lambda}{\partial n} - \left(n \frac{\partial \lambda}{\partial n}\right) n = n\sqrt{\frac{\partial p_1}{\partial \rho_1}}, \tag{47}$$

having chosen $\mathbf{n} = (n, 0, 0)$, and eq. (46) gives

$$\varphi(t, x) = \varphi^0\left(x - n\sqrt{\frac{\partial p_1}{\partial \rho_1}}\ t\right). \tag{48}$$

The method to obtain the approximate smooth solutions is valid only for waves propagating with a velocity λ such that $\nabla\lambda \cdot \mathbf{r} \neq 0$ (with $\mathbf{r}$ the right eigenvector of $\mathbf{A}_n)_0$ corresponding to the eigenvalue λ), i.e. with a velocity that does not satisfy the Lax-Boillat exceptionality condition [9]. We calculate the eigenvalues in the case of our system of PDEs (19), obtaining

$$\begin{aligned} &\lambda_1^{(\pm)} = \pm n\sqrt{\tfrac{\partial p}{\partial \rho}}, \qquad \lambda_2^{(\pm)} = \pm n\sqrt{\tfrac{\partial p_1}{\partial \rho_1}}, \qquad \lambda_3^{(\pm)} = \pm\sqrt{\tfrac{\partial p_2}{\partial \rho_2}}, \\ &\lambda_4^{(\pm)} = \pm n\sqrt{\tfrac{\partial p_d}{\partial \rho_d}}, \qquad \lambda_5^{(\pm)} = \pm n\sqrt{\tfrac{\partial p_{T_1}}{\partial \rho_{T_1}}}, \qquad \lambda_6^{(\pm)} = \pm n\sqrt{\tfrac{\partial p_{T_2}}{\partial \rho_{T_2}}}, \end{aligned} \tag{49}$$

where

$$\frac{\partial p}{\partial \rho}, \frac{\partial p_1}{\partial \rho_1}, \frac{\partial p_2}{\partial \rho_2}, \frac{\partial p_d}{\partial \rho_d}, \frac{\partial p_{T_1}}{\partial \rho_{T_1}}, \frac{\partial p_{T_2}}{\partial \rho_{T_2}}$$

are the velocities of the related *acoustic waves* of each constituent [20]. All the eigenvalues do not satisfy the Lax-Boillat exceptionality condition, so that the system of PDEs is genuinely non linear. In the following we fix our attention on the eigenvalue $\lambda_2^{(+)}$ (that is related to the first component of the mixture) which corresponds to a progressive longitudinal wave travelling to the right. Analogous results can be obtained for the other eigenvalues.

The right and left eigenvectors corresponding to $\lambda_2^{(+)}$ are

$$\mathbf{r}_2^{(+)} = \frac{1}{2\rho(v_1-\sqrt{2\hat{p}_1\rho_1})}[0, \frac{\chi_1\rho_1\rho_{T_1}}{\hat{p}_1\rho_1-\hat{p}_{T_1}\rho_{T_1}}, 0, \frac{\chi_d\rho_1\rho_d}{\hat{p}_1\rho_1-\hat{p}_d\rho_d}, -2\rho\rho_1, 0, 0, \frac{\chi_1(-v_{T_1}+\sqrt{2\hat{p}_1\rho_1})\rho_1}{\hat{p}_1\rho_1-\hat{p}_{T_1}\rho_{T_1}}, 0, \frac{\chi_d(-v_d+\sqrt{2\hat{p}_1\rho_1})\rho_1}{\hat{p}_1\rho_1-\hat{p}_d\rho_d}, 2\rho(v_1-\sqrt{2\hat{p}_1\rho_1}), 0] \tag{50}$$

$$l_2^{(+)} = [0,0,0,0,\frac{v_1+\sqrt{2\hat{p}_1\rho_1}}{\rho_1},0,0,0,0,0,1,0]. \tag{51}$$

4. **First approximation of wavefront and of U.** In [4] it is shown that, by using (33) and (37) , the following equation for $u(x^\alpha,\xi)$ can be obtained:

$$\frac{\partial u}{\partial\sigma} + (\nabla\Psi\cdot\mathbf{r})_0 u\frac{\partial u}{\partial\xi} + \frac{1}{\vartheta}\frac{\partial\vartheta}{\partial\sigma}u + \mu_0\frac{\partial^2 u}{\partial\xi^2} = \nu_0 u, \tag{52}$$

where

$$\vartheta = \sqrt{J}, \tag{53}$$

$$(\nabla\psi\cdot\mathbf{r})_0 = (|grad\varphi|\{\nabla\lambda\cdot\mathbf{r}\})_0, \tag{54}$$

$$\mu_0 = \frac{(\mathbf{l})_0\cdot\{(\mathbf{H})_0\Phi^2\}(\mathbf{r})_0}{(\mathbf{l}\cdot\mathbf{r})_0}, \tag{55}$$

$$\nu_0 = \frac{(\mathbf{l}\cdot\nabla\mathbf{B}\mathbf{r})_0}{(\mathbf{l}\cdot\mathbf{r})_0}. \tag{56}$$

Straightforward calculations give in the case of $\lambda_2^{(+)}$, with $r_2^{(+)}$ and $l_2^{(+)}$ the corresponding right and left eigenvectors, the following results

$$\mu_0 = -\frac{1}{2}\frac{D}{r}\Phi_0^2, \tag{57}$$

$$\nu_0 = \frac{\chi_d\nu_1\rho_1^0\rho_d^0}{4(\rho^0)^2(\hat{p}_1\rho_1^0-\hat{p}_d\rho_d^0)} + \frac{\chi_1\mu_1\rho_1^0\rho_{T_1}^0}{4(\rho^0)^2(\hat{p}_1\rho_1^0-\hat{p}_{T_1}\rho_{T_1}^0)} + \frac{1}{2}(\frac{1}{\gamma_1} - \frac{\nu_1\rho_d^0}{\rho^0} - \frac{\mu_1\rho_{T_1}^0}{\rho^0}), \tag{58}$$

where it is supposed the conditions $\hat{p}_1\rho_1^0 \neq \hat{p}_d\rho_d^0$ and $\hat{p}_1\rho_1^0 \neq \hat{p}_{T_1}\rho_{T_1}^0$ are satisfied to provide the coefficient ν_0 (see eq. (56)) is limited in (52). By using the transformation of variables (see [4])

$$u = \frac{v}{\vartheta}e^w, \qquad \kappa = \int_0^\sigma \frac{1}{2}|grad\varphi|^0\frac{e^w}{\vartheta}d\sigma, \tag{59}$$

where

$$w = \nu^0\sigma, \tag{60}$$

eq. (52) can be reduced to an equation of the type

$$\frac{\partial v}{\partial\kappa} + v\frac{\partial v}{\partial\xi} + \hat{\mu}_0\frac{\partial^2 v}{\partial\xi^2} = 0, \quad \text{with} \quad \hat{\mu}_0 = \frac{2\mu_0\vartheta e^{-w}}{(|grad\varphi|)^0}. \tag{61}$$

Eq. (61) is valid along each characteristic ray and it is the generalized Burgers equation which has been extensively studied by many authors (see for instance [29]), the solution of which is known and asintotically stable for very large time.

5. **Appendix.** In this Appendix we present a table illustrating the involved parameters together with the involved biological phenomena.

Parameter	*Name*	*Biological phenomenon*
$\alpha(t)$	Proliferation rate of Th_1	clonal expansion of Th_1
$\beta(t)$	Proliferation rate of Th_2	clonal expansion of Th_2
h_1	Growth rate factor of Th_1	Genetic mutation into Th_1
h_2	Growth rate factor of Th_2	Genetic mutation into Th_2
k_0	Generation factor	Generation of T naive
k_{ap}	Death factor of Th_1 and Th_2	Programmed cell death of Th_1 and Th_2
r cells	Random cell motility	Motility of all cells
h_{ap}	Activation induced death factor	Activation induced cell death
χ_1	1^0 Chemotactic constant	chemotaxis of Th_1
χ_2	2^0 Chemotactic constant	chemotaxis of Th_2
χ_d	3^0 Chemotactic constant	chemotaxis of dendritic cells
D	Diffusivity constant	Diffusion of cytokines
μ_1	growth rate factor of 1^0 set cytokines	Production by the Th_1
ν_1	growth rate factor of 1^0 set cytokines	Production by the dendritic
γ_1	Consumption factor 1^0 set	Consumption of the 1^0 set
μ_2	growth rate factor of 2^0 set cytokines	Production of 2^0 set by the Th_2
ν_2	growth rate factor of 2^0 set cytokines	Production of 2^0 set by the dendritic
γ_2	Consumption factor 2^0 set	Consumption of the 2^0 set

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