Qualitative Analysis of a Mean Field Model of Tumor-Immune System Competition

Elena De Angelis[(1)] and Pierre-Emmanuel Jabin[(2)]

[(1)]Dipartimento di Matematica, Politecnico di Torino
Corso Duca degli Abruzzi 24, 10129 Torino, Italy
email: deangeli@calvino.polito.it

[(2)]École Normale Supérieure
Département de Mathématiques et Applications, CNRS UMR 8553
45 rue d'Ulm, 75230 Paris Cedex 05, France
email: jabin@dma.ens.fr

Abstract

This paper deals with the qualitative analysis of a model related to the immune response to the evolution of the progression of endothelial cells which have lost their differentiation and start their evolution toward methastatic states. We prove the existence of solutions to the Cauchy problem related to the model. The asymptotic behavior in time of our solutions is also investigated.

Keywords: Vlasov kinetic theory, Cauchy problem, cell population, tumor-immune competition

1 Introduction

This paper deals with the qualitative analysis of the initial value problem for a mathematical model designed to describe the interaction and the competition between immune and cancer cells mediated by environmental cells which provide the feeding for the growth related to the mitosis process.
The mathematical model was proposed in [1] derived on the basis of mathematical methods typical for nonequilibrium statistical mechanics and generalized kinetic theory. The general idea, as documented in [2], consists in deriving an evolution equation for the first distribution function over the

variable describing the microscopic internal state of the individuals. Generally, this variable may include position and velocity, but it can also refer to some additional specific microscopic states. Interactions between pairs have to be modelled taking into account not only mechanical rules but also modifications of the non-mechanical physical (internal) state.
This model refers to the early stage of tumor development when tumor cells are not yet aggregated into a solid form. This situation also occur when cells are residually dispersed in the environment after removal of solid form. Developments of modeling methods for large dispersed systems by methods of the mathematical kinetic theory is documented in the collection of surveys edited in [3] and [4]. Specifically the mathematical model dealt with in this paper is based on a mean field description corresponding to the Vlasov equation. This generalization is applied to various fields of applied sciences, an example is the modeling of dispersed bubbles in a fluid, see [5] and [6].
Cellular phenomena, related to inner properties of the cell, play a relevant role in the evolution of the physical system we are dealing with, see e.g. Greller, Tobin and Poste [8]. The cellular scale refers to the main (interactive) activities of the cells: activation and proliferation of tumor cells and competition with immune cells. In particular, proliferation of tumor cells, which are often degenerated endothelial cells, happens when an environmental cell looses its death program and/or starts to undergoing mitosis without control. Moreover, competition with the immune system starts if tumor cells are recognized by immune cells. Activation and inhibition of the immune cells in their competition with tumor is regulated by cytokine signals. Tumor cells can be additionally activated towards proliferation due to nutrient supply from environmental cells.
Specifically the present paper aims to analyze the model proposed in [1] through a qualitative analysis whose main result refers to existence and uniqueness of the solution to the initial value problem under suitable assumptions on the initial data. An asymptotic analysis is also developed to better understand the relevance of some phenomena described by the model. Particular attention is given to the qualitative analysis of the asymptotic behavior of the solutions which may either show the blow up of tumor cells, or the progressive destruction of tumor cells due to the action of immune cells. Indeed, the qualitative analysis developed in this paper points out the above behavior with reference to the parameters which characterize the model. As it will be shown in what follows an interesting biological interpretation can be given with reference to the above asymptotic analysis.
The contents of this paper are proposed in five sections:

– This first section deals with this introduction concerning the aims and the organization of the paper;

– Section 2 deals with the presentation of the analytic results concerning the qualitative analysis of the solutions to the initial value problem;

– Section 3 deals with a concise review of the mathematical model proposed in [1] and of the role of the parameters characterizing the mathematical model;

– The interpretation of the mathematical results from a biological point of view is proposed in Section 4. This section also indicates some research perspectives;

– Technical aspects of the mathematical proofs are reported in Section 5.

2 Analytic Results

The model proposed in [1] considers three interacting cell ***populations***: cells of the aggressive host, immune cells, and environmental cells labeled, respectively, by the indexes $i = 1, 2$ and $i = 3$. Each cell is characterized by a certain ***state***, a real variable $u \in I = [0, +\infty)$ describing its main activity: ***progression*** for the host cells, ***activation*** for the immune cells, and ***feeding ability*** for the environmental cells. The state of each type of cells is described by its distribution function $f_i(t, u)$, for $i = 1, 2, 3$.
Interesting quantities to be computed are defined by the zeroth and first order moments of the distribution functions. Specifically

$$n_i(t) = \int_0^\infty f_i(t, u)\, du, \quad i = 1,\ 2,\ 3, \tag{2.1}$$

is the size of the populations, while

$$A_i(t) \equiv A[f_i](t) = \int_0^\infty u f_i(t, u)\, du, \quad i = 1,\ 2,\ 3. \tag{2.2}$$

is the activity of each cell population.

As already mentioned in the introduction this paper deals with the qualitative analysis for the following problem

$$\begin{cases} \partial_t f_1 + \partial_u\big(-\alpha_{12} u A[f_2] f_1 + \alpha_{13} u A[f_3] f_1\big) \\ \qquad = -\beta_{12} A[f_2] f_1 + \beta_{13} u A[f_3] f_1 \\ \\ \partial_t f_2 + \partial_u\big(-\alpha_{21} u A[f_1] f_2\big) = \beta_{21} u A[f_1] f_2 \\ \\ \partial_t f_3 + \partial_u\big(-\alpha_{31} u A[f_1] f_3\big) = -\beta_{31} A[f_1] f_3 \end{cases} \tag{2.3}$$

for all $t,\ u\ \in \mathbb{R}^+$, with initial conditions

$$f_1(t=0,u) = f_1^0(u), \quad f_2(t=0,u) = f_2^0(u), \quad f_3(t=0,u) = f_3^0(u). \tag{2.4}$$

An account of the biological justification of the above model and mathematical problem will be given in Sec. 3.
In equations (2.3), all constants α_{ij} and β_{ij} are assumed to be positive.
The system (2.3) is non linear, however the main difficulty comes from the unboundedness in the activity u (which is in all $\mathbb{R}^+$) combined with the creation terms of the form $uA[f_j]f_i$ in the equations for f_1 and f_2.
Notice that no boundary condition is needed on $u = 0$ because the transport fields all vanish at this point. We also point out that the equation on f_3 is not really necessary. Indeed the only interesting quantity is A_3 and by multiplying the equation for f_3 in (2.3) by u and integrating, we see that it satisfies

$$\frac{d}{dt} A_3 = -(\alpha_{31} + \beta_{31}) A_1\ A_3, \quad A_1(t=0) = A_1^0. \tag{2.5}$$

This indicates that the equation on f_3 does not pose any real problem contrary to equations for f_1 and f_2. It is nevertheless possible to prove a global in time existence for the initial value problem (2.3)-(2.4) but by assuming exponential decay on f_1 and f_2 in u. More precisely we need that

$$\int_0^\infty e^{\lambda u} f_1^0(u) du < \infty, \quad \forall \lambda > 0. \tag{2.6}$$

For f_2, the assumption is less restrictive

$$\int_0^\infty e^{\beta_{21} u/\alpha_{21}} f_2^0(u) du < \infty. \tag{2.7}$$

As to f_3, it only has to be integrable with respect to $1 + u$

$$\int_0^\infty (1+u) f_3^0(u) du < \infty. \tag{2.8}$$

With these assumptions, existence is given by the following

Theorem 2.1 *Assume that f_1^0, f_2^0, and f_3^0 satisfy (2.6), (2.7) and (2.8). Then there exists solutions*

$$f_1, f_2, f_3 \in C([0,\ \infty), L^1((1+u)du))$$

to the initial value problem (2.3)-(2.4) (in the distributional sense) which satisfy

$$\begin{aligned}
&\int_0^\infty e^{\lambda u} f_1(t,u)du \ \in\ L^\infty([0,\ T]), \quad \forall\ \lambda,\ T>0,\\
&\int_0^\infty e^{\beta_{21}u/\alpha_{21}} f_2(t,u)du \le \int_0^\infty e^{\beta_{21}u/\alpha_{21}} f_2^0(u)du,\\
&\int_0^\infty (1+u) f_3(t,u)du \ \le\ \int_0^\infty (1+u) f_3^0(u)du.
\end{aligned} \tag{2.9}$$

Remarks.

1. In the case where $\alpha_{21} \le \alpha_{31} + \beta_{31}$ and A_2^0 is large enough with respect to A_3^0, it is possible to relax somehow the assumption on f_1^0 and ask only that f_1^0 be integrable against $exp((\beta_{13}+\alpha_{13})A_3^0/(\alpha_{12}A_2^0))$.

2. It is also possible to deduce from this theorem an existence result of classical solutions and the uniqueness provided the initial data are regular enough (typically $\partial_u f_i^0$ has a better than exponential decay). The techniques are exactly the same as the ones we use here.

A very natural question now is whether this assumption of exponential decay is really necessary or only technical. We can offer only a partial answer:

Theorem 2.2 *Suppose that*

$$\int_0^\infty e^{\lambda u} f_2^0(u)du = \infty, \quad \forall\ \lambda > 0.$$

Then no weak solutions f_1, f_2 and f_3 in $C([0,\ T],\ L^1((1+u)du))$ to the system of (2.3)-(2.4) exist whatever, and how small, the time T is, except the trivial one with $A_1(t) = 0$, $0 \le t \le T$.

Remarks.

1. The same theorem may be written for f_1^0 instead of f_2^0. The proof would be exactly the same with a bit more complicated computations due to the structure of the equations for f_1 which has more terms than the equation for f_2.

2. This theorem leaves open the question of whether a blow-up in finite time (but also the existence of solutions up to this finite time) is possible when the initial data f_2^0 has precisely exponential decay but do not satisfy (2.7).

Now we investigate the asymptotic behavior in time of our solutions. It turns out that only two cases are possible. Either the immune system wins and completely eliminate the tumor cells of the organism or the organism eventually dies. We need here an assumption a bit stronger than (2.7) to state a quite precised result, which is

$$\int_0^\infty u^\gamma e^{\beta_{21}u/\alpha_{21}} f_2^0(u)du < \infty, \quad \textit{for some } \gamma > 1. \tag{2.10}$$

We now have

Theorem 2.3 *Assume that f_1^0, f_2^0 and f_3^0 satisfy (2.6), (2.10) and (2.8) and consider a solution (f_1, f_2, f_3) given by Theorem 2.1. Then as $t \to \infty$, there are only the two possibilities*

(i)

$$n_1(t) \longrightarrow 0, \quad \int_0^\infty A_1(t)dt < \infty, \quad n_2(t) \longrightarrow n_2(\infty) < \int_0^\infty e^{\beta_{21}u/\alpha_{21}} f_2^0(u)du,$$

but n_3, A_3, n_2, A_2 are bounded from below.

(ii)

$$\int_0^\infty A_1(t)dt = \infty, \quad n_2(t) \longrightarrow \int e^{\beta_{21}u/\alpha_{21}} f_2^0(u)du, \quad A_2(t), n_3(t), A_3(t) \longrightarrow 0.$$

Remarks.
We are not able to indicate how the system chooses between the two behaviors. This certainly depends highly on the exact initial data and the value of the constants.

3 On the Derivation of the Model

The aim of this section is to provide a concise description of the model proposed in [1] where the framework proposed is the one of the mean field modelling, according to the fact that a ***test cell*** feels the presence and interacts with the surrounding ***field cells*** localized in a suitable volume.
The mathematical model consists in evolution equations for the distribution functions f_i corresponding to the above mentioned cell populations. Referring to Sections 5 and 7 of [1] a specific model is summarized in what follows. According to [1], consider a large system of cells homogeneously distributed in space. Microscopic cells interactions are also distributed in space and are capable both to modify the state of the cells (by interactions defined ***conservative*** in [1]), and the size (by interactions defined ***nonconservative***). The mathematical structure of the model proposed in Section 5 of [1] is as follows:

$$\begin{aligned}\partial_t f_i(t,u)+\partial_u\big[k_i(t,u)f_i(t,u)\big] + \partial_u[f_i(t,u)\sum_{j=1}^{3}\int_I \varphi_{ij}(u,w)f_j(t,w)\,dv] \\ =\sum_{k=1}^{3}\int_I\int_I \psi_{ik}(v,w;u)f_i(t,v)f_k(t,w)\,dv\,dw,\end{aligned} \tag{3.1}$$

where

$$\mathcal{I}_i[\mathbf{f}] = \partial_u\left[k_i(t,u)f_i(t,u)\right] \tag{3.2}$$

is the inner-outer dynamic evolution operator which takes into account the evolution of the distribution functions due to the dynamics of the variable u governed by an intrinsic evolution which may depend on u and to an external action.

$$\mathcal{F}_i[\mathbf{f}](t,u) = \partial_u[f_i(t,u)\sum_{j=1}^{3}\int_I \varphi_{ij}(u,w)f_j(t,w)\,dw] \tag{3.3}$$

corresponds to actions of the field cells in the state w of the j-th population which modify the state u of the test cells of the i-th population into a new one and are modelled by the ***conservative action function*** $\varphi_{ij} = \varphi_{ij}(u,w)$. Finally

$$\mathcal{S}_i(t,u) = \sum_{j=1}^{3}\int_I\int_I \psi_{ij}(v,w;u)f_i(t,v)f_j(t,w)\,dv\,dw \tag{3.4}$$

corresponds to proliferation and/or death phenomena. The ***nonconservative action function*** $\psi_{ij} = \psi_{ij}(v,w;u)$ models the generation or the

destruction of the cells of the i-th population in the state u as a consequence of the actions of the field cells in the state w of the j-th population over test cells of the i-th population in the state v.
We point out that this framework refers to the evolution in absence of source terms. This means that cells are contained in a vessel and the system is closed. Tumor cells can then replicate exploiting the existing environmental cells. This supply is, in some cases, sufficient to generate an uncontrolled growth of tumor cells.
This general framework can generate specific models after a detailed modelling of the cell interactions. Still referring to [1], Section 7, the specific model we are going to deal is given by (2.3) which corresponds to the following phenomenological assumptions on the terms modelling the cell interactions in (3.1) - (3.4):

- The intrinsic evolution of the cells is negligible and no external actions are taken into account, i.e. $k_i(t,u) = 0, \forall\ i = 1,2,3$.

- The progression of neoplastic cells is not modified by interactions with other cells of the same type: $\varphi_{11} = 0$. On the other hand, it is weakened by interaction with immune cells (linearly depending on their activation state) and it is increased by interactions with environmental cells (linearly depending on their feeding ability). The effect increases with increasing values of the progression: $\varphi_{12} = -\alpha_{12} w u, \quad \varphi_{13} = \alpha_{13} w u$.

- The defense ability of immune cells is not modified by interactions with other cells of the same type and with environmental cells: $\varphi_{22} = \varphi_{23} = 0$. On the other hand, it is weakened by interactions with tumor cells (linearly depending on their activation state) due to their ability to inhibit the immune system: $\varphi_{21} = -\alpha_{21} w u$.

- The feeding ability of environmental cells is not modified by interactions with other cells of the same type and with immune cells $\varphi_{32} = \varphi_{33} = 0$. On the other hand, it is weakened by interaction with tumor cells linearly depending on their activation state: $\varphi_{31} = -\alpha_{31} w u$.

- The nonconservative action function ψ_{ij} is assumed to be a delta function over the state v of the interacting test cell: $\psi_{ij}(v, w; u) = p_{ij}(v, w)\ \delta(u - v)$.

- No proliferation of neoplastic cells occurs due to interactions with other cells of the same type: $p_{11} = 0$. On the other hand, interactions

with immune cells generate a destruction linearly depending on their activation state and a proliferation by interactions with environmental cells depending on their feeding ability and the progression of tumor cells: $p_{12} = -\beta_{12} w\,, \quad p_{13} = \beta_{13} v w$.

- No proliferation of immune cells occurs due to interactions with other cells of the same type and with environmental cells: $p_{22} = p_{23} = 0$. On the other hand, interactions with tumor cells generate a proliferation linearly depending on their defense ability and on the activation state of tumor cells: $p_{21} = \beta_{21} v w$.

- No proliferation of environmental cells occurs due to interactions with other cells of the same type and with immune cells: $p_{32} = p_{33} = 0$. On the other hand, interactions with tumor cells generate a destruction linearly depending on the activation state of tumor cells: $p_{31} = -\beta_{31} w$.

The mathematical model described is characterized by various phenomenologic parameters which may be classified into two groups:

α-parameters which refer to conservative encounters and, specifically, to inhibition activity of tumor cells, to weakening ability of immune cells, and to modifications of the feeding ability of environmental cells. Interactions modify the state of the cells, but not their number.

β-parameters which refer to encounters that modify the number of cells due to proliferative or destructive actions.

All parameters α and β have to be regarded as positive, small with respect to one, constants, to be identified by suitable experiments.

4 Interpretation of the Analytic Results and Perspectives

The aim of this section is to analyze, from a biological point of view, the mathematical results given by Theorem 2.3. The Theorem indicates two different asymptotic behaviors of the competition: regression of progressed cells due to an effective action of the immune system, and the opposite one: with the blow up of progressed cells and progressive inhibition of the immune system.

This kind of analysis corresponds to a well defined medical motivation related to the action of cytokine signals [7]: one is interested in understanding whether a suitable action on the immune system may make it able to recognize and possibly destroy the tumor cells.

The model introduces the concept of progression for the host cells, identified by the variable u, with values on the whole positive real line, in such fashion that the higher is the progression value, the greater is the strength (degree of malignancy) of the tumor cells. The progression moves from small to large values due to inner degenerating dynamics. The dynamics is contrasted by the immune system which may be inhibited by tumor cells.
The results given by Theorem (2.3) refer to the time evolution of the distribution function as well as of the zero-th moments, Eq. (2.1), and first order moments, Eq. (2.2): the zero-th order moments refer to the number densities, and the first order moments refer to the activities. The activities are proportional to the mean progression speed, describing the velocity of evolution toward larger or lower values of the cells states. In detail, this means, for tumor system, evolution toward higher or lower degree of malignity, while for immune system toward higher or lower activation. When tumor cells are progressing, not only their number increases but also their progression values moves toward higher values. On the other side, immune cells may increase in time, but their effective action is significant only if their activation is not strongly weakened by the competition.
When the tumor cells blow up, they inhibit the immune system and the evolution has a trend to increase the number of progressed cells with increasing number and value of the progression. In this case, the immune system is not able to contrast the neoplastic growth; tumor cells are able to increase their progression and to inhibit immune cells. The distribution function of the tumor cells f_1 evolves toward larger values of the state u, while the distribution of the immune cells is shifting toward lower values of u.
In this case we observe that the immune system saturates, because n_2 reaches its maximal value whereas A_2 converges toward zero: the immune system has produced as many cells as it could but their activities have all vanished because of the effect of the tumor cells. One of the most interesting features is of course this notion of a maximal number of immune cells. And as it will appear in the a priori estimates, the closer the number n_2 is to this maximal number, the smaller the activity necessarily is. It is nevertheless possible that A_1 also vanishes. It would mean that the immune system manages to kill the invading cells but not fast enough to save the environment or itself, a sort of mutual destruction.
When the opposite behavior is observed, the immune system is able to control the growth of tumor cells. As a consequence of the activation of the immune system, the number of tumor cells will decrease and their progression will shift toward lower values. Competitions which end up with the destruction of the host are characterized by a modest inhibition ability of

the host against the immune system. It follows that immune cells are always able to attack and destroy the host; the uncertain variable of the competition is the time needed to reach the above result. In fact, proliferation of the host occurs with the contribution of environmental cells, that may progressively weak the organism where the competition developed.
The result summarized here are certainly useful to research activity in immunology addressed to control, by cytokine signals, the activation of the immune system to prevent the inhibition action of the tumor cells. In particular, an iperactivation of the immune system does not seem useful if not accompanied by a control of the above mentioned inhibition activity.
As already mentioned the above qualitative analysis has been developed for a system of cells such that no inlet of environmental cells is allowed. This is a situation which is apparently favorable to control tumor growth.
On the other hand, as we have seen, if the number of environmental cells is sufficiently large at $t = 0$, then the blow up of tumor cells is possible.
Similarly, it may be possible analyzing a problem such that the inlet from outer environment maintains constant the quantity of environmental cells. The problem which is definitively interesting to analyze is the qualitative analysis of the solutions related to the above quantity of environmental cells. In principle the control of such a quantity may be related to the blow up or depletion of tumor cells according to the experiments on control of angiogenesis developed by Folkmann and coworkers [9]

5 Estimates and Proofs

We first prove some important a priori estimates and then we give the proofs of Theorems 2.1, 2.2 and 2.3.
Throughout this section we consider the equations in (2.3), namely

$$\begin{aligned} &\partial_t f_1 + \partial_u\big(-\alpha_{12} u A[f_2] f_1 + \alpha_{13} u A[f_3] f_1\big) \\ &\qquad = -\beta_{12} A[f_2] f_1 + \beta_{13} u A[f_3] f_1, \end{aligned} \tag{5.1}$$

$$\partial_t f_2 + \partial_u\big(-\alpha_{21} u A[f_1] f_2\big) = \beta_{21} u A[f_1] f_2, \tag{5.2}$$

$$\partial_t f_3 + \partial_u\big(-\alpha_{31} u A[f_1] f_3\big) = -\beta_{31} A[f_1] f_3, \tag{5.3}$$

for all $t,\ u\ \in R^+$, and we assume Hypotheses (2.6), (2.7) and (2.8). The main a priori estimates which we prove, are summarized in the following proposition

Proposition 5.1 *Any solutions f_1, f_2, and f_3 to (2.3)-(2.4), which are the weak limits of compactly supported solutions in $L^\infty_t L^1_u$, satisfy Estimates (2.9) in Theorem 2.1. Moreover Equation (2.5) holds in distributional sense and we have for f_3*

$$\begin{aligned} &\exists\ \phi_3(u)\ \textit{with}\ \frac{\phi_3(u)}{1+u} \longrightarrow \infty,\ \textit{as}\ u \to \infty, \\ &\int_0^\infty \Phi_3(u) f_3(u)\, du\ \in\ L^\infty([0,\ \infty[). \end{aligned} \tag{5.4}$$

Notice that Proposition 5.1 trivially implies

Corollary 5.1 *The macroscopic quantities n_i and A_i satisfy*

$$\begin{aligned} &(i)\ \forall\ T>0, \quad n_1,\ A_1\ \in\ L^\infty([0,\ T]), \\ &(ii)\ n_2(t) \le \int_0^\infty e^{\beta_{21}u/\alpha_{21}} f_2^0\, du, \quad A_2(t) \le \int_0^\infty \left(e^{\beta_{21}u/\alpha_{21}} - 1\right) f_2^0\, du, \\ &(iii)\ n_3(t) \le n_3^0, \quad A_3(t) \le A_3^0. \end{aligned}$$

We begin with estimates for f_3 because they are the easiest ones and then for f_2 and at last f_1. All computations are in fact formal but they may be made rigorous. Since the weak solutions we consider are limits of solutions with compact support, the question of integrability at infinity in u poses no problem. Then since the equations are linear in the f_i, we can regularize the solutions simply by convolution, work with regular and compactly supported functions and eventually pass to the limit.

5.1 Estimates for Equation (5.3)

The function f_3^0 is integrable with respect to $(1+u)du$ so it is in fact a little more than that. More precisely, there exists a positive and nondecreasing function $\phi_3 \in C^1(\mathbb{R}^+)$ with

$$\frac{\phi_3(u)}{1+u} \longrightarrow \infty, \quad \textit{as}\ u \to \infty, \tag{5.5}$$

and

$$\int_0^\infty \phi_3(u) f_3^0(u) du < \infty.$$

Multiply Equation (5.3) by $\phi_3(u)$ and integrate over $\mathbb{R}^+$, after integrating by part the transport term, we obtain

$$\frac{d}{dt}\int_0^\infty \phi_3(u) f_3(t,u)du = -A_1 \int_0^\infty (\alpha_{31} u\phi_3'(u) + \beta_{31}\phi_3(u))\ f_3(t,u)du \leq 0.$$

Consequently, we know that

$$\int_0^\infty \phi_3(u) f_3(t,u)du \ \in\ L^\infty([0,\ \ \infty\,[). \tag{5.6}$$

Let us prove now that Equation (2.5) holds true. The idea is of course to multiply Equation (5.3) by u and integrate by part. But contrary to the previous estimate, we want to obtain an equality and not only an inequality. Hence we need to control the queue in u.
Consider a non negative function $\phi_R \in C^\infty(\mathbb{R}_+)$ with value 1 in $[0,\ R]$, compactly supported in $[0,\ 2R]$ and such that ϕ_R' is less than $2/R$. Since f_3 is a solution to (5.3) in the distributional sense and since $u\phi_R \in C_c^\infty(\mathbb{R})$, multiplying (5.3) by $u\phi_R(u)$, we have for any $\alpha(t) \in C_c^\infty(\mathbb{R})$

$$\begin{aligned} &-\int_{t>0} \alpha'(t) \int_0^\infty u\phi_R(u) f_3(t,u)dudt - \int_0^\infty \alpha(0) u\phi_R(u) f_3^0(u)du \\ &= -\int_{t>0} \alpha(t) A_1(t) \int_0^\infty \big(u\phi_R(\alpha_{31}+\beta_{31}) + \alpha_{31}\phi_R'(u)u^2\big) f_3(t,u)\, dudt. \end{aligned} \tag{5.7}$$

Because of Estimate (5.6) or Proposition 5.1, the last term vanish as R goes to infinity. Indeed

$$\begin{aligned} &\left| \int_{t>0} \alpha(t) A_1(t) \int_0^\infty \phi_R'(u) u^2 f_3\, dudt \right| \\ &\leq 2\int_{t>0} |\alpha(t)| A_1(t) \int_R^{2R} \frac{u^2}{R} f_3\, dudt \\ &\leq 4\int_{t>0} |\alpha(t)|\, A_1(t)dt \times \sup_t \int_{u>R} u f_3(t,u)\, du, \end{aligned}$$

and this last integral is converging to zero with R.
Now passing to the limit in R in (5.7), since for any bounded function $\alpha(t)$

$$\int_{t>0} \alpha(t) \int_0^\infty u\phi_R f_3(t,u)dudt \longrightarrow \int_{t>0} \alpha(t) A_3(t)dt,$$

we obtain

$$-\int_{t>0} \alpha'(t) A_3(t)\, dt - \alpha(0) A_3^0 = -(\alpha_{31}+\beta_{31}) \int_{t>0} \alpha(t) A_1(t) A_3(t) dt,$$

which is exactly Equation (2.5) written in a weak sense.

5.2 Estimates for Equation (5.2)

Multiplying Equation (5.2) by $exp(\beta_{21}u/\alpha_{21})$ and integrating in u, we formally find after one integration by part

$$\frac{d}{dt}\int_0^\infty e^{\beta_{21}u/\alpha_{21}} f_2(t,u)du = A_1 \int_0^\infty \left(\beta_{21} - \alpha_{21}\frac{\beta_{21}}{\alpha_{21}}\right) e^{\beta_{21}u/\alpha_{21}}\, f_2(t,u)du = 0.$$

As a consequence, we also obtain a priori for any solution f_2

$$\int_0^\infty e^{\beta_{21}u/\alpha_{21}} f_2(t,u)du \;\le\; \int_0^\infty e^{\beta_{21}u/\alpha_{21}} f_2^0(u)du. \tag{5.8}$$

With the same computation, we can show that

$$\int_0^\infty u^\gamma e^{\beta_{21}u/\alpha_{21}} f_2(t,u)du \;\le\; \int_0^\infty u^\gamma e^{\beta_{21}u/\alpha_{21}} f_2^0(u)du. \tag{5.9}$$

We now prove the following lemma

Lemma 5.2 *Given $A_1 \in C([0,\ \infty[)$, consider any weak solution*

$$f_2 \in C([0,\ \infty[\ ,\ L^1((1+u)du))$$

to (5.2) (solution in a distributional sense), satisfying (2.10), then

$$\int_0^\infty e^{\beta_{21}u/\alpha_{21}} f_2(t,u)du = \int_0^\infty e^{\beta_{21}u/\alpha_{21}} f_2^0(u)du.$$

Proof. As in the rigorous derivation of Equation (2.5), the control of the decay in u of f_2 is fundamental, hence the need of Estimate (5.9).
We consider a sequence of functions $\psi_R \in C_c^1([0,\ \infty[)$ satisfying the properties $\psi_R(u) \le exp(\beta_{21}u/\alpha_{21})$, equality on $[0,\ R]$ and $|\psi_R'| \le Cexp(\beta_{21}u/\alpha_{21})$. Now given any time T and any $\varepsilon > 0$, we choose R large enough such that

$$\frac{1}{R^{\gamma-1}} \int_0^T \int_0^\infty A_1(t) u^\gamma e^{\beta_{21}u/\alpha_{21}} f_2(t,u)\, dudt \;<\; \varepsilon,$$

and

$$\frac{1}{R^\gamma} \sup_{t\le T} \int_0^\infty u^\gamma e^{\beta_{21}u/\alpha_{21}} f_2(t,u)du < \varepsilon.$$

This has for immediate consequence that for any t

$$\int_R^\infty e^{\beta_{21}u/\alpha_{21}} f_2(t,u)dudt \le \int_R^\infty \frac{u^\gamma}{u^\gamma} e^{\beta_{21}u/\alpha_{21}} f_2(t,u)du < \varepsilon.$$

On the other hand since f_2 is a weak solution to (5.2),

$$\int \psi_R(u) f_2(T,u)du - \int \psi_R(u) f_2^0(u)du = \int_0^T \int A_1 u(\beta_{21}\psi_R - \alpha_{21}\psi_R')f_2 dtdu.$$

And as a consequence

$$\begin{aligned}
&\left| \int \psi_R(u) \left(f_2(T,u) - f_2^0(u)\right) du \right| \\
&\leq (1+C) \int_0^T \int_R^\infty A_1(t) u e^{\beta_{21}u/\alpha_{21}} f_2(t,u) dudt \\
&\leq \frac{(1+C)}{R^{\gamma-1}} \int_0^T \int_0^\infty A_1 u^\gamma e^{\beta_{21}u/\alpha_{21}} f_2 dudt < \varepsilon,
\end{aligned}$$

for R large enough. Finally for such R, we obtain that

$$\left| \int_0^\infty e^{\beta_{21}u/\alpha_{21}} (f_2(T,u) - f_2^0(u)) du \right| < 2\varepsilon,$$

which proves the lemma. □

5.3 Estimates for Equation (5.1)

Let us fix any time interval $[0,\ T]$. On this time interval, for any $\mu > 0$, if we multiply Equation (5.1) by $exp(uexp(\mu(T-t)))$ and integrate, we formally obtain

$$\begin{aligned}
&\frac{d}{dt} \int_0^\infty e^{u\, exp(\mu(T+1-t))} f_1(t,u) du \leq \int_0^\infty u e^{u\, exp(\mu(T+1-t))} \\
&\times \left(-\mu e^{\mu(T+1-t)} + \alpha_{13} e^{\mu(T+1-t)} A_3 + \beta_{13} A_3 \right) \times f_1(t,u) du \leq 0,
\end{aligned}$$

if $\mu \geq (\alpha_{13} + \beta_{13}) \sup_t A_3$. Now given any $\lambda > 0$, we consider a constant μ satisfying this last inequality and such that $\exp \mu$ is larger than λ, then for any $0 \leq t \leq T$,

$$\int_0^\infty e^{\lambda u} f_1(t,u) \leq \int_0^\infty e^{u\, exp(\mu(T+1-t))} f_1(t,u) du.$$

And therefore for any λ and any $T > 0$,

$$\int_0^\infty e^{\lambda u} f_1(t,u) \ \in \ L^\infty([0,\ T]). \tag{5.10}$$

Let us indicate now why if $\alpha_{21} \leq \alpha_{31} + \beta_{31}$ and A_2^0/A_3^0 is large enough, it is possible to precise Assumption 2.6. We notice that because of (2.5)

$$A_3(t) \leq A_3^0 e^{-(\alpha_{31}+\beta_{31})\int_0^t A_1(s)ds}.$$

On the other hand, multiplying (5.2) by u and integrating we find

$$\frac{dA_2}{dt} \geq -\alpha_{21} A_2 A_1,$$

and thus

$$A_2(t) \geq A_2^0 e^{-\alpha_{21}\int_0^t A_1(s)ds}.$$

Consequently, if $\alpha_{21} \leq \alpha_{31} + \beta_{31}$,

$$\frac{A_2(t)}{A_3(t)} \geq \frac{A_2^0}{A_3^0}.$$

Assuming that $\alpha_{12}A_2^0 \geq \alpha_{13}A_3^0$, we also have for $\lambda > \beta_{13}A_3^0/\alpha_{12}A_2^0$

$$\frac{d}{dt}\int_0^\infty e^{\lambda u} f_1(t,u)du \leq \int_0^\infty u e^{\lambda u}\left(-\alpha_{12}\lambda A_2 + \alpha_{13}\lambda A_3 + \beta_{13}A_3\right)\ f_1(t,u) \leq 0,$$

which implies that the integral of f_1 against $exp(\lambda u)$ remains bounded. This is an interesting example because it shows all the importance which the exact value of the constants and the initial data have when we work with only exponential decay for f_1.

5.4 Continuity in time

The a priori estimates (2.9) proved in Proposition 5.1 imply that f_3, f_2 and f_3 belong to $L^\infty([0,\ T],\ L^1((1+u)du))$ for any $T > 0$. To conclude this section, we explain how we can obtain continuity in time.

Lemma 5.3 *Given $A_i \in L^\infty([0,\ T])$, $\forall i$, weak solutions f_1, f_2, f_3 to (2.3)-(2.4), satisfying (2.9) and (5.4), also belongs to $C([0,\ T],\ L^1((1+u)du))$.*

Proof. We do the proof for f_3 but it would be exactly the same for f_2 or f_1.
We can solve explicitly Equation (5.3) in terms of $a_1(t) = \int_0^t A_1(s)ds$ and we obtain

$$f_3(t,u) = e^{(\alpha_{31}-\beta_{31})a_1(t)} f_3^0\left(u e^{\alpha_{31}a_1(t)}\right). \tag{5.11}$$

Since a_1 belongs to $W^{1,\infty}([0,\ T])$ for any T (thanks to point (i) in Corollary 5.1), it is obvious that f_3 belongs to $C([0,\ T], L^1_{loc}(\mathbb{R}_+))$ (continuity locally in u).
To conclude, it only remains to prove that we control the integral of f against $1+u$, uniformly in time, outside any bounded domain in u.
For $R>0$, we consider a sequence of function $\phi_R^n \in C_c^1(\mathbb{R}_+)$ with $\mathrm{supp}\phi_R^n \subset [R/2,\ 2n]$, $\phi_R^n = 1$ on $[R,\ n]$ and $|\phi_R^{n\prime}(u)| \leq 10/(1+u)$. Since f_3 satisfies (5.3) in distributional sense, we have

$$\begin{aligned}
&\frac{d}{dt}\int_0^\infty \phi_R^n(u)(1+u)f_3(t,u)\,du \\
&= A_1(t)\int_0^\infty \big(\alpha_{31}(u+u^2)\phi_R^{n\prime}(u) + \alpha_{31}u\phi_R^n(u) \\
&- \beta_{31}(1+u)\phi_R^n(u)\big)f_3(t,u)\,du.
\end{aligned}$$

Therefore, we obtain thanks to the choice of ϕ_R^n

$$\begin{aligned}
&\int_0^\infty \phi_R^n(u)(1+u)f_3(t,u)\,du \leq \int_0^\infty \phi_R^n(u)(1+u)f_3^0(u)\,du \\
&+ \int_0^t A_1(s)(\alpha_{31}+\beta_{31})\int_{R/2}^{2n}(1+u)f_3(s,u)\,duds.
\end{aligned}$$

Letting n converge toward infinity, we obtain

$$\begin{aligned}
&\int_R^\infty (1+u)f_3(t,u)\,du \leq \int_{R/2}^\infty (1+u)f_3^0(u)\,du \\
&+ \int_0^t A_1(s)(\alpha_{31}+\beta_{31})\int_{R/2}^\infty (1+u)f_3(s,u)\,duds.
\end{aligned}$$

Now thanks to Estimate (5.4) in Proposition 5.1, the last integral converges toward zero with R uniformly in t. The same is true for the first integral in the right hand side and hence so does the integral in the left hand side. □

5.5 Proof of Theorem 2.1

The existence result is an almost direct consequence of the following stability result

Lemma 5.4 *(Stability) Let*

$$f_1^n, f_2^n, f_3^n \in C([0,\ \infty),\ L^1((1+u)du))$$

be sequences of solutions in the distributional sense to (2.3)-(2.4). Assume that they satisfy Estimates (2.9), (5.4) in Proposition 5.1 uniformly in n. Then any weak limits f_1, f_2 and f_3 of converging subsequences also belong to $C([0,\ \infty),\ L^1((1+u)du))$ and are solutions to (2.3)-(2.4) in distributional sense with as initial data the weak limits of the initial data.

Proof. Because of Estimates (2.9) and (5.4), we may indeed extract converging subsequences in $L^\infty([0,\ T],\ L^1((1+u)du)$ toward f_1, f_2 and f_3. Because of (2.6), (2.7) and (2.8) we may do the same for the initial data, obtaining f_1^0, f_2^0 and f_3^0.
Now notice that for any $T>0$

$$A_1^n \in W^{1,\infty}([0,\ T]). \tag{5.12}$$

Indeed consider a sequence of test functions $\psi_R \in C_c^1(\mathbb{R})$ with $\psi_R(u) \le u$ in $\mathbb{R}_+$, equality on $[0,\ R]$ and $\psi_R' \le 1+u$, then thanks to Equation (5.1)

$$\left|\frac{d}{dt}\int_0^\infty \psi_R f_1^n(t,u)\right| \le (A_2+A_3)\,(\alpha_{12}+\alpha_{13}+\beta_{12}+\beta_{13})\int_0^\infty (1+u^2) f_1^n(t,u)du.$$

Because of (2.9), for any $T>0$ we have uniformly in R and n

$$\int_0^\infty \psi_R f_1^n(t,u)du \ \in\ W^{1,\infty}([0,\ T]).$$

Letting R converge toward ∞ proves (5.12). This means that after a extraction, A_1^n converges strongly in $C([0,\ T])$ for any $T>0$.
We could of course do the same for A_2^n and A_3^n which are also compact. We may thus pass to the limit in Equations (5.1), (5.2) and (5.3) and we deduce that f_1, f_2 and f_3 are also solutions of these equations.
But we also know that f_1^n, f_2^n and f_3^n belong to $W^{1,\infty}([0,\ T], W^{-1,1}(\mathbb{R}_+))$ uniformly in n for any given $T>0$. Hence f_1, f_2 and f_3 are equal to f_1^0, f_2^0 and f_3^0 at $t=0$ at least in a weak sense.
To conclude, it is enough to apply Lemma 5.3 and its equivalents for f_1 and f_2. □

We now briefly indicate one possibility of proving Theorem 2.1 thanks to Lemma 5.4. We consider sequences f_i^N of the form

$$\begin{aligned} f_i^N(t,u) &= \frac{1}{N}\sum_{n=1}^N \mu_i^n(t)\delta(u-u_i^n(t)),\\ A_i^N(t) &= \frac{1}{N}\sum_{n=1}^N \mu_i^n(t)u_i^n(t). \end{aligned} \tag{5.13}$$

We take $\mu_i^n(0)$ and $u_i^n(0)$ such that (2.6), (2.7) and (2.8) are satisfied. We take for μ_i^n and u_i^n the solutions of the following differential system

$$\begin{aligned} \dot{\mu}_1^n(t) &= -\beta_{12} A_2^N \mu_1^n(t) + A_3^N \beta_{13} u_1^n(t) \mu_1^n(t), \\ \dot{u}_1^n(t) &= -\alpha_{12} A_2^N u_1^n + \alpha_{13} A_3^N u_1^n. \end{aligned} \tag{5.14}$$

As for $i = 2$

$$\begin{aligned} \dot{\mu}_2^n(t) &= \beta_{21} u_2^n(t) A_1^N \mu_2^n(t), \\ \dot{u}_2^n(t) &= -\alpha_{21} A_1^N u_2^n. \end{aligned} \tag{5.15}$$

And finally for $i = 3$,

$$\begin{aligned} \dot{\mu}_3^n(t) &= -\beta_{31} A_1^N \mu_3^n(t), \\ \dot{u}_3^n(t) &= -\alpha_{31} A_1^N u_3^n. \end{aligned} \tag{5.16}$$

The differential system composed of (5.14), (5.15) and (5.16) has solutions at least for a short time interval $[0,\ T]$. It is quite easy to check than f_1^N, f_2^N and f_3^N are then solutions to (5.1), (5.2) and (5.3). These sequences satisfy every a priori estimates listed in section 2 and applying a slighty modified version of Lemma 5.4 we would be able to take weak limits, obtaining solutions for any initial data satisfying (2.6), (2.7) and (2.8) on the time interval $[0,\ T]$. Since $f_1(t,.)$, $f_2(t,.)$ and $f_3(t,.)$ satisfy (2.6), (2.7) and (2.8) uniformly in t, we may extend indefinitely the time of existence.
Notice that of course other techniques could be applied (like a fixed point result for instance).

5.6 Proof of Theorem 2.2

Now the function f_2^0 is not integrable against any exponential. Suppose that there exist $A_1(t) \in C([0,\ T])$ and f_2 in $C([0,\ T],\ L^1((1+u)du))$ solution to (5.2) in a distributional sense and with $f_2(t=0) = f_2^0$.
Since $A_1 u$ belongs to $C([0,\ T],\ W^{1,\infty}([0,\ R]))$ for any $R > 0$, there is only one solution to (5.2) with f_2^0 as initial data. Define $U(t,u)$ the solution of

$$\partial_t U(t,u) = -\alpha_{21} A_1(t) U(t,u), \quad U(0,u) = 0,$$

or by a direct computation

$$U(t,u) = u e^{-\alpha_{21} \int_0^t A_1(s) ds}.$$

Then the solution f_2 is given by

$$\partial_t f_2(t, U(t,u)) = \beta_{21} A_1 U(t,u) f_2(t,U),$$

which means that

$$f_2(t,U) = f_2^0(t,u)e^{\beta_{21}\alpha_{21}^{-1}\,u\,\left(1-exp(-\alpha_{21}\int_0^t A_1(s)ds)\right)}. \tag{5.17}$$

Notice that the function f_2 given by (5.17) is perfectly well defined if $A_1 \in C([0,\ T])$. However given the assumption on f_2^0 it is impossible that this function be integrable against $1+u$ if A_1 is not always zero. Indeed suppose that at time t

$$\alpha_{21}\int_0^t A_1(s)ds \geq -\ln\varepsilon, \quad with\ 0<\varepsilon<1.$$

If f_2 were integrable, we would have

$$\int_0^\infty f_2(t,u)du = e^{\alpha_{21}\int_0^t A_1(s)ds}\int_0^\infty u f_2(t,U(t,u))du,$$

and

$$\int_0^\infty u f_2(t,U)du \geq \int_0^\infty u f_2^0 e^{\beta_{21}u(1-\varepsilon)/\alpha_{21}},$$

and this last quantity is equal to ∞ because of the hypothesis on f_2. Thus Theorem 2.2 is proved.

5.7 Proof of Theorem 2.3

Since A_3 is nonincreasing there are clearly only the two possibilities that A_3 converges toward zero or that A_3 is bounded from below.
Throughout all this subsection, we will use the following lemma

Lemma 5.5 *We have for the solutions given by Theorem 2.1*

$$\begin{aligned}
&\frac{d}{dt}A_3 = -(\alpha_{31}+\beta_{31})A_1\,A_3,\\
&\frac{d}{dt}n_3 = -(\alpha_{31}+\beta_{31})A_1\,n_3,\\
&\frac{d}{dt}A_2 \geq -\alpha_{21}A_1\,A_2,\\
&\frac{d}{dt}n_2 = \beta_{21}A_1\,A_2,\\
&\frac{d}{dt}n_1 = -\beta_{12}A_2\,n_1 + \beta_{13}A_3\,A_1.
\end{aligned}$$

Proof. It is easy to see that all estimates given in Lemma 5.5 are formally true. To prove them rigorously, we apply the same method which we used in Lemma 5.2: We take sequences ψ_R equal to 1 or u on $[0,\ R]$ and we let R converge to infinity. We do not repeat here the details of the proofs which are exactly the same. □

5.7.1 Case A_3 bounded from below

Because of Lemma 5.5,

$$A_3(t) \leq A_3^0 e^{-(\alpha_{31}+\beta_{31})\int_0^t A_1(s)ds},$$

we know that here

$$\int_0^\infty A_1(t)dt < \infty. \tag{5.18}$$

Lemma 5.5 immediately implies that n_3, A_2 and n_2 are also bounded from below.
Because of (2.10), we may apply Lemma 5.2 and thus

$$\frac{\beta_{21}}{\alpha_{21}} A_2(t) \leq \int_0^\infty \left(e^{\beta_{21}u/\alpha_{21}} - 1\right) f_2(t,u)du \leq \int_0^\infty e^{\beta_{21}u/\alpha_{21}} f_2^0 du - n_2(t).$$

Therefore

$$n_2(t) \longrightarrow n_2(\infty) < \int_0^\infty e^{\beta_{21}u/\alpha_{21}} f_2^0 du - n_2(t).$$

We also have

$$n_1(t) = e^{-\beta_{12}\int_0^t A_2(s)ds} \int \left(n_1^0 + \beta_{13}\int_0^t A_3(s)A_1(s)e^{\beta_{12}\int_0^s A_2(r)dr}ds\right).$$

Since $\beta_{12}A_2 \geq c > 0$ and A_3 is decreasing, we deduce that

$$\begin{aligned} n_1(t) &\leq C\left(e^{-ct} + \int_0^t A_1(s)e^{c(s-t)}ds\right) \\ &\leq C\left(e^{-ct} + e^{-ct/2}\int_0^\infty A_1(s)ds + \int_{t/2}^t A_1(s)ds\right), \end{aligned}$$

which is converging toward zero because of (5.18). We have proved all properties listed in point (i) of Theorem 2.3. We nevertheless point out that if for some $T > 0$

$$\alpha_{12}A_2(t) > \alpha_{13}A_3(t), \quad \forall\ t \geq T, \tag{5.19}$$

it is also possible to show that $A_1 \to 0$ (whereas for the moment A_1 could still exhibit some oscillations).
Indeed if (5.19) is true, take $\lambda > 0$ with

$$\lambda \ > \ \sup_{t \geq T} \frac{\alpha_{12} A_2(t) - \alpha_{13} A_3}{\beta_{13} A_3(t)}.$$

The constant λ is well defined because A_3 is bounded from below. We then have that, just as in the a priori estimates for f_1

$$\int_0^\infty e^{\lambda u} f_1(t,u) du \leq \int_0^\infty e^{\lambda u} f_1(T,u) du < \infty, \quad \forall \ t \geq T,$$

thanks also to (2.9). With this last inequality it is possible to show that

$$A_1 \ \in \ W^{1,\infty}([T, \ \infty[),$$

by the same method which is detailed in Lemma 5.4. However this bound combined with (5.18) directly implies that A_1 converges toward 0 as t goes to infinity.

5.7.2 Case $A_3 \to 0$

Here again because of Lemma 5.5, we know that

$$\int_0^\infty A_1(t) dt = \infty. \tag{5.20}$$

Lemma 5.5 then has for consequence that $n_3(t)$ converges toward zero as $t \to \infty$.
Since n_2 is bounded as given by Corollary 5.1, we nevertheless have that

$$\int_0^\infty A_1(t) \, A_2(t) dt < \infty.$$

Consequently, there necessarily exists a sequence of times $t_n \to \infty$ such that $A_2(t_n)$ converges toward zero. Now

$$\int_0^\infty \left(e^{\beta_{21} u/\alpha_{21}} - 1 \right) f_2(t,u) du \leq C e^{\beta_{21} R/\alpha_{21}} \int_0^R u f_2(t,u) du$$
$$+ \frac{C}{R} \int_R^\infty u \left(e^{\beta_{21} u/\alpha_{21}} - 1 \right) f_2(t,u) du \leq C A_2(t) e^{\beta_{21} R/\alpha_{21}} + \frac{C}{R},$$

because of (5.9). Let us denote g the function such that for any $x > 0$ $g(x)\, exp(\beta_{21} g(x)/\alpha_{21}) = 1/x$. Of course $g(x)$ converges toward infinity as $x \to 0$ and by taking in the last inequality $R = g(A_2)$

$$\int_0^\infty e^{\beta_{21} u/\alpha_{21}} f_2^0(u)du - n_2(t) = \int_0^\infty \left(e^{\beta_{21} u/\alpha_{21}} - 1\right) f_2(t,u)du \leq \frac{C}{g(A_2(t))}.$$

Therefore $n_2(t_n)$ converges toward $\int exp(\beta_{21} u/\alpha_{21}) f_2^0$. Since $n_2(t)$ is non-decreasing, $n_2(t)$ converges also toward the same quantity as $t \to \infty$. But finally

$$A_2(t) \leq \int_0^\infty e^{\beta_{21} u/\alpha_{21}} f_2^0(u)du - n_2(t) \longrightarrow 0,$$

and the proof of point (ii) is complete.

References

[1] De Angelis E. and Mesin L., On the kinetic (cellular) theory. Conceptual frameworks on modelling the immune response. *Math. Models Meth. Appl. Sci.*, 11, 1609-1630, (2001).

[2] Arlotti L., Bellomo N., De Angelis E., Generalized kinetic (Boltzmann) models: mathematical structures and applications, *Math. Models Meth. Appl. Sci.*, 12, 567–592, (2002).

[3] N. Bellomo and M. Pulvirenti, Eds., **Modeling in Applied Sciences: A Kinetic Theory Approach**, (Birkhäuser, Boston, 2000).

[4] N. Bellomo and M. Pulvirenti, Eds., Special Issue on the modeling in applied sciences by methods of transport and kinetic theory, *Math. Models Meth. Appl. Sci.*, 12, 909-990, (2002).

[5] Jabin P.E. and Perthame B., Notes on mathematical problems on the dynamics of dispersed particles interacting through a fluid, in **Modeling in Applied Sciences: A Kinetic Theory Approach**, N. Bellomo and M. Pulvirenti, Eds., Birkhäuser, Boston, 111–148, (2000).

[6] Jabin P.E., Various level of models for aereosol, *Math. Models Meth. Appl. Sci.*, 12, 813–830, (2002).

[7] Forni G., Foa R., Santoni A., and Frati L. eds., **Cytokine induced tumor immunogeneticity**, Academic Press, New York, (1994).

[8] Greller L., Tobin F., and Poste G., Tumor hetereogenity and progression: conceptual foundation for modeling, *Invasion and Metastasis*, 16, 177–208, (1996).

[9] P. Hahnfeldt, D. Panigrahy, J. Folkman, and L. Hlatky, Tumor development under angiogenic signaling, *Cancer Res.*, 59, 4770–4775, (1999).