A Mathematical Model for Single Cell Cancer—Immune System Dynamics

M. KOLEV
Department of Mathematics and Information Technology
University of Warmia and Mazury
Zolnierska 14A, 10-561 Olsztyn, Poland
kolev@matman.uwm.edu.pl

E. KOZŁOWSKA
Department of Immunology, Faculty of Biology
Warsaw University, Miecznikowa 1, PL-02096 Warsaw
ekozlowska@biol.uw.edu.pl

M. LACHOWICZ
Institute of Applied Mathematics and Informatics
Faculty of Mathematics, Informatics and Mechanics
Warsaw University, Banacha 2, PL-02097 Warsaw
lachovic@mimuw.edu.pl

Abstract—In this paper, we propose and analyse the model of competition between a single cell cancer and the immune system. The model is a system of integro-differential bilinear equations and it describes both very early stage of a solid tumor and all stages of leukemias. © 2005 Elsevier Ltd. All rights reserved.

Keywords—Leukemia, Integro-differential equations, Nonlinear dynamics.

1. INTRODUCTION

Cancer has become the second-ranking cause of death in the Western world. There is a growing interest in cancer research. One of the main topics is the interaction between the immune system and cancer. The model which we propose describes the interactions between a single cell cancer and the immune system. Our model applies to a very early stage of a solid tumor and all stages of the leukemias [1,2].

In a multi-cellular organism each cell is under control so that, the number of any particular cell type remains constant. Occasionally, a cell becomes no longer responsive to growth-control mechanisms and gives a rise to cancer.

In each particular moment, the fate of cancer depends upon: the immune system responses, number and type of cancer cells and their localization in the body (environment).
Rising cancer cells could be recognized by the immune system and an immune response will develop. In general, the cell-mediated immune response appears to play a major role in the cancer cells elimination. There are three types of the immune cells able to destroy a cancer cell: natural killers (NK cells), macrophages and T cytotoxic lymphocytes (the notation Tc cells or CTL is often used). After recognition of a cancer cell all three types of the immune cells start to produce new proteins (like receptors and cytokines) which facilitate the process of killing. Tc cells are activated by interaction with altered self cells (e.g., tumor cells). This activation results in final differentiation to CTLs. CTLs interact with tumor cells and undergo conjugate formation. Immediately following the formation of the conjugate, the CTL is starting to secrete cytotoxins (perforins, granzymes) and cytokines (IFNγ, TGFβ). Secreted factors mediate target-cell (tumor cell) destruction.

NK cells are the first line of defense to virus infection and tumors. NK cells are a small but always present population of lymphocytes. Cytokines like IFNα, IFNβ and IL-12 increase the number of NK. The mechanism of killing tumor cells by NK is similar to that employed by CTLs. The NK cells secrete cytotoxins (granzymes, perforins) and TNFα thus starting the process of destruction.

Tumor cells coated by specific antibodies could be killed in the process of antibody-dependent cell-mediated cytotoxicity (ADCC). Macrophages and NK cells express membrane receptors for the antibody. When an antibody is specifically bound to the tumor cell, these receptor-bearing cells (NK or macrophage) can bind to the antibody and subsequently become more active. Activation is followed by the release of several lytic components (lytic enzymes, perforin, TNFα) at the site of antibody mediated contact and may cause lysis of the tumor cell. A model describing ADCC stated in terms of a system of integro-differential equations was recently proposed in [3].

The anti-cancer response also involves other elements of the immune system, e.g., cytokines secreted by variety of cells of the immune system. Cytokines generally function as intercellular messenger molecules that evoke particular biological activities after binding to a receptor on responsive target cell. Cytokines rarely act alone. Instead, target cell is exposed to a mixture of cytokines, whose combined effects can have very different consequences than separated cytokine.

There is a network of cytokines, the cytokine released from one activated cell may activate an entire network of interacting cells. Among the numerous physiologic responses that require cytokine involvement are development of cellular and humoral immune responses, induction of inflammatory response, regulation of hematopoiesis, control of cellular proliferation and differentiation and induction of anti-cancer responses. Some of cytokines like IL-10, TGFβ, IFNγ, TNFα, IL-2, IL-4, IL-12 are believed to be particularly involved in the tumor immunology [1,2,4-7].

Cancer cells are able to evade the immune response by becoming invisible to the immune system, suppressing activity of immune cells (by secreting cytokines, e.g., IL-10) or actively killing immune cells (by expression dead molecules, e.g., Fas ligand). Localization in the body could affect the growth of a tumor. Surrounding cells of healthy tissue may provide more or less favourable environment for a tumor. Similarly, depending upon the type of leukemia cells others immune cells may facilitate or limit growth of leukemia cells, e.g., by secreted cytokines [1,5-7].

Our model describes the interactions between single cell system of a tumor and the immune system. The model is a system of Boltzmann-type integro-differential bilinear equations. An integro-differential equation of the Boltzmann-type in the context of biological processes was first used by Jäger et al. [8] and related to a certain population or interacting insects. The Jäger and Segel model [8] was generalized or particularized by Arlotti et al. [9,10], Arlotti et al. [11], Lachowicz et al. [12] and Geigant et al. [13]. The general class of bilinear systems of Boltzmann-type integro-differential equations (General Kinetic Models) [11,12] can model the dynamics of individuals (of various populations) undergoing kinetic (stochastic) interactions.

Such a class of systems were used to model various important natural processes like the angular self-organization of the actin cytoskeleton as a process of changing of filament orientation in course
of specific actin-actin interaction—see [13]—and the interaction between tumor cells and immune system—see [14–18] as well as [19–27] for the complete bibliography.

In the paper [25] the relationships between the solutions to Boltzmann-type integro-differential equations and the corresponding macroscopic equations are discussed.

In the present paper, we modify the model of [17] in order to describe early stages of solid tumor or all stages of leukemias.

2. MATHEMATICAL MODEL

We consider a model with possibly small number of factors involved in dynamics

(B1) tumor (leukemia) cells,
(B2) macrophages,
(B3) NK-cells,
(B4) Tc-cells,
(B5) suppressors (all factors that can lower the activation of tumor cells), e.g., TGFβ, IL-10,
(B6) all other factors that are involved in the dynamics.

The populations B_i, i = 2, ..., 4, are well-known in the literature as “effector cells”. We associate to each cell of the populations B_i, i = 1, ..., 4, a “stage of activity” u ∈ [0, 1] related to the ability of protein production (cf. [2]).

The function f_i = f_i(t, u), f_i : [0, c_i] × [0, 1] → R_+ defines the density of B_i-cells with stage of activity u ∈ [0, 1] at time t ≥ 0. The number of B_i-cells per unit volume at time t is n_i(t) = \int_0^1 f_i(t, u) du.

For the remaining populations (B_5, B_6) we neglect the presence of “internal degrees of freedom” (stage of activity) and assume that only some fixed stage of activity (say u = 1/2) is possible.

The function f_5 = f_5(t), f_5 : [0, c_5] → R_+ defines the concentration of B_5-factors at time t ≥ 0. The distribution function f_6 of B_6-factors is assumed to be constant during the evolution.

We assume that the interactions between cells are homogeneous in space and instantaneous (without time delay). They may change the activity of cells as well as the population size by destroying or creating cells or factors.

The following processes are described by the model. The suppressors of cancer, which are produced by the populations of effector cells, can lower the activity of cancer cells. The effector cells, produced and activated by the immune system, which is a part of the population B_6, can destroy a fraction of cancer cells. After this process a part of the effector cells dies. Cancer cells, which can be produced and activated by some B_6-factors, are also able to destroy a fraction of suppressors and effector cells and eventually to lower the activity of effector cells. Possibility of death of a fraction of suppressors and effector cells due to some other factors is also described as well as the influx of suppressors and effector cells due to some source, for instance a medical therapy.

The equation for the B_1 population reads

\partial_t f_1 = A_{1,5}[f_1, f_5] + A_{1,6}f_1 - \sum_{i=2}^4 A_{1,i}[f_1, f_i]. \tag{2.1}

The term A_{1,5}[f_1, f_5] describes the inhibition of activity of tumor cells B_1 by suppressors B_5,

A_{1,5}[f_1, f_5] = \gamma_{1,5}f_5C_L f_1, \tag{2.2}

C_L f(u) = \int_0^1 A_L(u; v)a_L(v)f(v) dv - a_L(u)f(u), \quad u ∈ [0, 1], \tag{2.3}

\gamma_{1,5} \text{ is a nonnegative constant, the function } A_L = A_L(u; v), \quad A_L : [0, 1]^2 → R, \text{ describes the probability density that a } B_1\text{-cell with activity } v ∈ [0, 1] \text{ transits to the activity } u ∈ [0, 1] \text{ due to}
the interaction with a $B_5$-factor, $A_L$ is a measurable function such that

$$A_L \geq 0, \quad (2.4a)$$

$$\int_0^1 A_L(u; v) \, du = 1, \quad \text{for } v \in [0, 1], \quad (2.4b)$$

$$A_L(u; v) = 0, \quad \text{for } u > v, \quad (2.4c)$$

for all $v \in [0, 1] : \max_{u \in [0,1]} A_L(u; v) = A_L \left( \frac{v}{2}; v \right). \quad (2.4d)$$

Condition (2.4d) states that the most probable are changes $v \rightarrow u = v/2$ of the $B_1$-cell activity. In this paper in numerical calculations we assume

$$A_L(u; v) = \begin{cases} \frac{4u}{v^2}, & 0 \leq u \leq \frac{v}{2}, \\ \frac{4(v - u)}{v^2}, & \frac{v}{2} \leq u < v, \\ 0, & v \leq u. \end{cases} \quad (2.5)$$

It is easy to check that the function (2.5) satisfies the conditions (2.4). The function $a_L = a_L(u)$, $a_L : [0, 1] \rightarrow \mathbb{R}$, describes the rate of interaction between the $B_1$-cells with activity $u \in [0, 1]$ and the $B_5$-factors. It is a measurable function such that

$$0 < a_L(u) < a(L \circ) < C_\infty, \quad u \in [0, 1], \quad (2.6)$$

where $a_L^{(0)}$ is a constant. For simplicity in numerical calculations we assume

$$a_L(u) = u^2, \quad u \in [0, 1]. \quad (2.7)$$

The linear term

$$A_{1,6}(u) = \lambda_{1,6} uf(1) + \gamma_{1,6} C_R f(u), \quad (2.8)$$

describes the production of new tumor cells (the term $\lambda_{1,6} uf(1)$) and the progress of $B_1$-cells towards increasing their activity states (the term $\gamma_{1,6} C_R f(1)$), $\lambda_{1,6}$ and $\gamma_{1,6}$ are nonnegative constants.

$$C_R f(u) = \int_0^1 A_R(u; v)a_R(v)f(v) \, dv - a_R(u)f(u), \quad u \in [0, 1]. \quad (2.9)$$

The function $A_R = A_R(u; v)$, $A_R : [0, 1]^2 \rightarrow \mathbb{R}$, describes the probability density that a $B_6$-cell with the activity $v \in [0, 1]$ transits to the activity $u \in [0, 1]$ due to the interaction with $B_5$-factors, $A_R$ is a measurable function such that

$$A_R \geq 0, \quad (2.10a)$$

$$\int_0^1 A_R(u; v) \, du = 1, \quad \forall v \in [0, 1], \quad (2.10b)$$

$$A_R(u; v) = 0, \quad \text{for } u < v, \quad (2.10c)$$

for all $v \in [0, 1] : \max_{u \in [0,1]} A_R(u; v) = A_R \left( \frac{v + 1}{2}; v \right). \quad (2.10d)$$

Condition (2.10d) states that the most probable are changes $v \rightarrow u = (v + 1)/2$ of the $B_1$-cell activity. In numerical calculations we assume

$$A_R(u; v) = \begin{cases} \frac{4(u - v)}{(1 - v)^2}, & v < u < \frac{1 + v}{2}, \\ \frac{4(1 - u)}{(1 - v)^2}, & \frac{1 + v}{2} \leq u < 1, \\ 0, & u \leq v. \end{cases} \quad (2.11)$$
It is easy to check that the function \((2.11)\) satisfies the conditions \((2.10)\). The function \(a_R = a_R(u)\), \(a_R : [0,1] \rightarrow \mathbb{R}\), describes the rate of change for the \(B_1\)-cell with activity \(u \in [0,1]\). It is a measurable function such that
\[
0 \leq a_R(u) \leq a_R^{(0)} < \infty, \quad u \in [0,1],
\]
where \(a_R^{(0)}\) is a constant. For simplicity in numerical calculations we assume
\[
a_R(u) = (1 - u)^2, \quad u \in [0,1].
\]
The term \(A_{1,i}[f_1,f_i]\), describes the destroying of a \(B_1\)-cells fraction by \(B_i\)-cells, for \(i = 2, 3, 4\), respectively, we assume that
\[
A_{1,i}[f_1,f_i] = \lambda_{1,i}D[f_1,f_i], \quad i = 2, 3, 4,
\]
\(\lambda_{1,i}\) are given nonnegative constants,
\[
D[f_1,f_i](u) = (1 - u)f_i(u)f_i, \quad u \in [0,1],
\]
and
\[
f = \int_0^1 vf(v) \, dv.
\]
The equation for the population \(B_i, i = 2, 3, 4\), reads
\[
\frac{\partial_t f_i}{\partial t} = A_{1,i}f_1 + A_{i,i}[f_1,f_i] + A_{i,6}f_i + S_i, \quad i = 2, 3, 4.
\]
The terms \(A_{i,1}f_1\) describe the stimulation of immune response (production of \(B_i\)-cells),
\[
A_{i,1}f(u) = \lambda_{i,1}f, \quad \text{for } u \in [0,1],
\]
\[
f = \int_0^1 f(v) \, dv.
\]
\(\lambda_{i,1}\) is a nonnegative constant. The term \(A_{i,1}[f_1,f_i]\) describes the change of activity of \(B_i\)-cells by the \(B_1\)-cells (the term \(\gamma_{i,1}C[f_i,f_1]\)), the destroying of a \(B_i\)-cells fraction by the \(B_1\)-cells (the term \(\mu_{i,1}D[f_i,f_1]\)), and the lowering of \(B_i\)-cells number after destroying the tumor cells (the term \(\mu_{i,1}D[f_i,f_1]\)),
\[
A_{i,1}[f_1,f_i] = \gamma_{i,1}C[f_i,f_1] - \mu_{i,1}D[f_i,f_1] - \mu_{i,1}D[f_i,f_1],
\]
\(\gamma_{i,1}, \mu_{i,1}, \mu_{i,1}\) are nonnegative constants,
\[
C[f_i,f_1](u) = \int_0^1 \int_0^1 B(u;v,w)b(v,w)f_i(v)f_1(w) \, dv \, dw
\]
\[
- f_i(u) \int_0^1 b(u,v)f_1(v) \, dv, \quad u \in [0,1].
\]
The function \(B = B(u;v,w), B : [0,1]^3 \rightarrow \mathbb{R}\), describes the probability density that a \(B_i\)-cell with activity \(v \in [0,1]\) transits to the activity \(u \in [0,1]\) due to the interaction with a \(B_1\)-cell with the state \(w \in [0,1]\). The function \(B\) is a measurable function such that
\[
B \geq 0,
\]
\[
\int_0^1 B(u;v,w) \, du = 1, \quad \text{for } u, w \in [0,1],
\]
\[
\text{for } 0 \leq w < \frac{1}{2}, \text{ and } v \leq u \leq v^* : B(u;v,w) = \max_{u \in [0,1]} B(\tilde{u};v,w),
\]
\[
\text{where } v^* = v + (1 - v) \left( \frac{1}{2} - w \right),
\]
\[
\text{for } \frac{1}{2} \leq w \leq 1, \text{ and } v_\ast \leq u \leq v : B(u;v,w) = \max_{u \in [0,1]} B(\tilde{u};v,w),
\]
\[
\text{where } v_\ast = v - v \left( w - \frac{1}{2} \right).
\]
Conditions (2.22c,d) express the requirement that for a high (low) activity $u$ of $\text{Bl}$-cells the most probable are lowering (raising) the $\text{B}_1$-cell activity state (from $v$ to $u$). In numerical calculations we assume:

$$B(u; v, w) = \begin{cases} 
\gamma^* u, & 0 \leq u < v, \quad 0 < v \leq 1, \quad 0 \leq w < \frac{1}{2}, \\
\gamma^*, & v \leq u < v^*, \quad 0 \leq v \leq 1, \quad 0 \leq w < \frac{1}{2}, \\
\gamma^*(1 - u), & v^* \leq u \leq 1, \quad 0 \leq v \leq 1, \quad 0 \leq w < \frac{1}{2}, \\
\frac{\gamma u}{v^*}, & 0 \leq u \leq v^*, \quad 0 \leq v \leq 1, \quad \frac{1}{2} \leq w \leq 1, \\
\gamma^*, & v^* \leq u < v, \quad 0 \leq v \leq 1, \quad \frac{1}{2} \leq w \leq 1, \\
\frac{\gamma(1 - u)}{1 - v}, & v \leq u \leq 1, \quad 0 \leq v \leq 1, \quad \frac{1}{2} \leq w \leq 1,
\end{cases}$$

(2.23)

where $\gamma^* = 2/(1 + v^* - v)$ and $\gamma^* = 2/(1 + v - v_*)$. The function $b = b(u, v)$, $b : [0, 1]^2 \to \mathbb{R}$, describes the rate of interaction between the $\text{Bl}$-cells with activity $u \in [0, 1]$ and the $\text{B}_1$-cells with activity $v \in [0, 1]$. It is a measurable function such that

$$0 \leq b(u, v) \leq b(0) < \infty, \quad u \in [0, 1],$$

(2.24)

where $b(0)$ is a constant. In numerical calculations we assume

$$b(u, v) = u(1 - u), \quad (u, v) \in [0, 1]^2.$$

(2.25)

$\mathcal{D}$ are given by (2.15) and

$$\mathcal{D}[f_1, f_1](u) = u f_1(u) \int_0^1 (1 - v) f_1(v) \, dv, \quad \forall u \in [0, 1].$$

(2.26)

The term $A_{i,6} f_i$ describes the production of $\text{B}_i$-cells (the term $\lambda_{i,6} \hat{f}_i$) and the natural death process (the term $\mu_{i,6} f_i)$,

$$A_{i,6} f = \lambda_{i,6} \hat{f} - \mu_{i,6} f,$$

(2.27)

$\lambda_{i,6}$ and $\mu_{i,6}$ are nonnegative constants. The term $S_i = S_i(t, u)$, $i = 2, 3, 4$, describes the source of $\text{B}_i$-cells with activity $u \in [0, 1]$ at time $t \geq 0$. It is such that

$$S_i \in C^0([0, \infty); L_1(0, 1)), \quad S_i \geq 0,$$

(2.28)

where $L_1(0, 1)$ is the Lebesgue space of measurable, real-valued functions which are integrable on $[0, 1]$. In numerical calculations we assume

$$\text{for each } i = 2, 3, 4, \quad S_i = \text{const}.$$

(2.29)

The equation for the population $\text{B}_5$ reads

$$\partial_t f_5 = \sum_{i=2}^4 A_{5,i} f_i - A_{5,1} f_5 f_1 - A_{5,6} f_5 + S_5.$$

(2.30)

The terms $A_{5,i} f_i$ describe the production of $\text{B}_5$-factors by the $\text{B}_i$-cells, $i = 2, 3, 4$,

$$A_{5,i} f(u) = \lambda_{5,i} \hat{f}, \quad i = 2, 3, 4, \quad \forall u \in [0, 1],$$

(2.31)

$\lambda_{5,i}$ are nonnegative constants. The term $A_{5,1} f_5 f_1$ describes the destroying of $\text{B}_5$-factors by the $\text{B}_1$-cells

$$A_{5,1} f_5 f_1 = \mu_{5,1} f_5 \hat{f}_1,$$

(2.32)
\( \mu_{5,1} \) is a nonnegative constant. The term \(-A_{5,6}f_2\) describes the natural death process,
\[
A_{5,6}f(u) = \mu_{5,6}f(u),
\]
(2.33)

\( \mu_{5,6} \) is a nonnegative constant. \( S_5 = S_5(t) \) is the source term describing a medical therapy. It is such that
\[
S_5 \in C^0([0, \infty[; \mathbb{R}_+^n). \tag{2.34}
\]
In numerical calculations we assume that
\[
S_5 = \text{const.} \tag{2.35}
\]

3. MATHEMATICAL ANALYSIS

The model introduced in the previous section reads
\[
\begin{align*}
\partial_t f_1(t, u) &= \gamma_{1,5} f_5(t) \left( \int_0^1 A_L(u; v) a_L(v) f_1(t, v) \, dv - a_L(u) f_1(t, u) \right) \\
&\quad + \lambda_{1,6} u f_1(t, u) + \gamma_{1,0} \left( \int_0^1 A_R(u; v) a_R(v) f_1(t, v) \, dv - a_R(u) f_1(t, u) \right) \\
&\quad - \left(1 - u\right) f_1(t, u) \sum_{i=2}^4 \lambda_{1,i} \int_0^1 v f_i(t, v) \, dv, \\
\partial_t f_i(t, u) &= \lambda_{i,1} \int_0^1 f_1(t, v) \, dv + \lambda_{i,6} \int_0^1 v f_i(t, v) \, dv \\
&\quad + \gamma_{i,1} \left( \int_0^1 \int_0^1 B(u; v, w) b(v, w) f_i(t, v) f_1(t, w) \, dv \, dw \\
&\quad - f_i(t, u) \int_0^1 b(u, v) f_1(t, v) \, dv \right) \\
&\quad - \left(1 - u\right) \mu_{i,1} f_i(t, u) \int_0^1 v f_1(t, v) \, dv \\\n&\quad - u \tilde{\mu}_{i,1} f_i(t, u) \left(1 - v\right) f_1(t, v) \, dv \\
&\quad - \mu_{i,6} f_i(t, u) + S_i(t, u), \quad i = 2, 3, 4, \\
\partial_t f_5(t) &= \sum_{i=2}^4 \lambda_{5,i} \int_0^1 v f_i(t, v) \, dv \\
&\quad - \mu_{5,1} f_5(t) \int_0^1 v f_1(t, v) \, dv - \mu_{5,6} f_5(t) + S_5(t),
\end{align*}
\]
(3.1a-3.1c)

where all coefficients denoted by \(\lambda_{i,j}, \gamma_{i,j}, \mu_{i,j}\), for \(i, j = 1, \ldots, 6\), are nonnegative.

The present section provides a detailed exposition of qualitative behaviour of the solution of the initial value problem for the system (3.1).

In the Lebesgue space \(L_1(0, 1)\) of measurable, real-valued functions which are integrable on \([0, 1]\) the norm is denoted by \(\| \cdot \|\). Let
\[
X = \{ f = (f_1, \ldots, f_5) : f_i \in L_1(0, 1), \text{ for } i = 1, 2, 3, 4, \text{ and } |f_5| < \infty \},
\]
be the Banach space equipped with the norm \(\|f\| = \sum_{i=1}^4 \|f_i\| + |f_5|\). Let
\[
X^+ = \{ f = (f_1, \ldots, f_5) \in X : f_i \geq 0, \text{ a.e., and } f_5 \geq 0 \}.
\]
Throughout this section, we assume that the conditions stated in Section 2 (i.e., (2.4), (2.6), (2.10), (2.13), (2.22), (2.24), (2.25), (2.28), (2.33)) are satisfied. We have the following preliminary theorem.
THEOREM 3.1. For every $T > 0$ there exists a unique solution

$$f \in C^0([0, T]; X) \cap C^1([0, T]; X),$$

(3.2)

of the system (3.1) with the initial datum $f_0 \in X^+$. The solution satisfies

$$f(t) \in X^+, \quad \forall t \in [0, T],$$

(3.3)

and

$$\sup_{[0,T]} |||f||| \leq c_T \left( |||f_0||| + 4 \sup_{i=2}^{4} \| S_i \| + \sup_{[0,T]} S_5 \right),$$

(3.4)

for some constant $c_T$ (depending on $T$).

PROOF. Under the assumption of Section 2, we see that the operators defined by the right-hand side of equations (3.1) are Lipschitz-continuous in $X$. Therefore, local existence (and uniqueness) follows. On the other hand it is easy to see that the solution is a priori nonnegative. It remains to find a priori estimates for the solution.

Using the notations from Section 2, we have

$$\partial_t \bar{f}_1 = \lambda_{1,6} \bar{f}_1 - \left( \bar{f}_1 - \tilde{f}_1 \right) \sum_{i=2}^{4} \lambda_{i,1} \bar{f}_i,$$

(3.5a)

$$\partial_t \bar{f}_i = \lambda_{i,1} \bar{f}_1 + \lambda_{i,6} \tilde{f}_1 - \mu_{i,1} \left( \tilde{f}_1 - \bar{f}_1 \right) \bar{f}_1 - \tilde{\mu}_{i,1} \bar{f}_i \left( \tilde{f}_1 - \bar{f}_1 \right) - \mu_{i,6} \bar{f}_i + S_i, \quad i = 2, 3, 4,$$

(3.5b)

$$\partial_t \bar{f}_5 = \sum_{i=2}^{4} \lambda_{5,i} \bar{f}_i - \mu_{5,1} \bar{f}_5 \bar{f}_1 - \mu_{5,6} \bar{f}_5 + S_5.$$

(3.5c)

Given any $f \in L_1(0, 1)$ such that $f \geq 0$, a.e., in $[0, 1]$ we have

$$\bar{f} \geq \tilde{f}.$$  

(3.6)

Therefore, by (3.5) we see that, the nonlinear system (3.1) "behaves not worse" than a linear system. This finishes the proof.

4. NUMERICAL SIMULATIONS

Quantitative results have been obtained by classical discretization schemes, see, e.g., [24, 28]. The variable $u$ was discretized over a suitable set of 11 values. The densities were interpolated using the Lagrange-type interpolation, see [28]. The integrals were performed using the Simpson formula.

As a result, we transformed the system (3.1) of integro-differential equations into a suitable system of ordinary differential equations. The respective Cauchy problem was simulated by the use of Runge-Kutta and Adams methods for prognosis and correction of the results on each step of integration. In order to obtain the values of the solution with three decimal digits correct, it was sufficient to take the step of integration $h = 0.5$ (in some cases $h = 0.1$) conventional time units. (The time scale in all of the presented plots is conventional, cf. [17].)

For simplicity, we consider the particular case when only one of the populations $B_i$, $i = 2, \ldots, 4$ of effector cells (say $B_2$) together with the suppressors of cancer take part in the immune response. (This particularization can be considered also as possible assuming that the action of the immune system can be summarized in a single population of effector cells and the population of suppressors of the cancer.)

Being aware that the determination of the values of the parameters of the system deserves a further experimental study, we consider here the following setting.

(4.1) As initial condition we assume the presence of a small amount of low-activity cancer cells and the absence of effector cells and suppressors.
(4.2) Referring to equations (3.1) we set the following values of parameters

\[\begin{align*}
\gamma_{1,5} &= 0.01, & \gamma_{1,6} &= 0.1, & \lambda_{1,2} &= 30, & \lambda_{1,6} &= 0.1, & \gamma_{2,1} &= 0.1, \\
\lambda_{2,1} &= 0.1, & \lambda_{2,6} &= 0.002, & \bar{\mu}_{2,1} &= 10, & \lambda_{5,2} &= 1, & \mu_{5,1} &= 0.01.
\end{align*}\]

All the other parameters except for these described in Cases 1, 2, and 3 below are equated to 0.

(4.3) We do not consider (in the first sequence of simulations) a continuous inlet of effector cells and suppressors, thus choosing \(S_2(t, u) = 0, S_5(t) = 0\).

We will then focus on the action of the following quantities: the ability \(\mu_{2,1}\) of the cancer cells to destroy the effector and the coefficients of the natural death process of the effector cells and of the suppressors \(\mu_{2,6}\) and \(\mu_{5,6}\), respectively.

The behaviour observed for a large variety of fixed values of the above mentioned parameters of the discretized system allows to conclude that \(\mu_{2,1}\) behaves as a bifurcation parameter: there exists a critical value \(\mu_c\) of \(\mu_{2,1}\) such that if \(\mu_{2,1} < \mu_c\) then the response of the immune system is able to control the growth of cancer cells, while if \(\mu_{2,1} > \mu_c\) then the cancer cells succeed inhibiting immune cells and grow without opposition. This conclusion shows the importance of the destructive ability of the cancer cells. It can be illustrated by the following examples. (Let us note that for the values of parameters given in (4.2) the critical value \(\mu_c \in [2, 3]\), see Cases 1 and 2.) We present the results of the cases

CASE 1. \(\mu_{2,1} = 3, \mu_{2,6} = \mu_{5,6} = 0\),
CASE 2. \(\mu_{2,1} = 2, \mu_{2,6} = \mu_{5,6} = 0\),
CASE 3. \(\mu_{2,1} = 0.01, \mu_{2,6} = \mu_{5,6} = 0.1\).

(a). Evolution of cancer cells densities in Case 1 (un-controllable growth).

(b). Evolution of the effector cells densities in Case 1 (insufficient reaction).

(c). Evolution of the suppressors in Case 1 (insufficient reaction).

Figure 1.
The simulation referred as Case 1 is shown in Figures 1a–1c. In this case, the cancer is able to neutralize the destruction capability of the immune system as well as its suppressing capability. The reaction of the immune system is unable to essentially stop the evolution of the cancer. The result of the interaction is unlimited growth of the number of cancer cells (Figure 1a).

An interesting observation was done analysing the temporal evolution of the population of the cancer. We mention the tendency of the activity of the cancer cells to accumulate near the highest value \( u = 1 \). This means that the immune system is able to destroy the cancer cells with low activity and the only cells of cancer which are able to survive in the competition with the immune system are those with very high activity (Figure 1a). This tendency to accumulation near \( u = 1 \) is very well observed also in the cases when the response of the immune system is prompt and sufficient to destroy the population of the cancer, like in Case 2. The temporal evolution of the activity of the cancer cells is presented in Figure 2a.

![Figure 1](image1.png)

(a). Case 2. Distribution, versus \( u \), of the activation state of cancer cells \( f_1 \) at \( t = 0, 30, 70 \).

![Figure 2](image2.png)

(b). Evolution of the number of the cancer cells in Case 2.

![Figure 2](image3.png)

(c). Evolution of the numbers of the effector cells and of the suppressors in Case 2.

Figure 2.

The dynamics of the distribution of the effector cells in some cases is similar to this of the cancer cells (see Figure 1b) but in some cases only slight shift towards high or low values of \( u \) was observed.

In Case 2, the number of the cancer cells initially grows, which causes an increase in the number of the immune system cells. This results in the eventual destruction of the population of the cancer. The dynamics of the whole numbers of the interacting populations is shown in Figures 2b and 2c.

In Case 3, when the natural death process of the cells of the immune system is present, a cyclic behaviour of the cancer—immune competition is clearly noticeable (with an accumulation of the cancer cells near \( u = 1 \) and a slight shift of the distribution of the effector cells towards low values.
of $u$). The growth of the number of the cancer cells induces a reaction of the immune system which depletes almost all cancer cells. Only a very small part of cancer cells survives. After that, the number of the effector cells and of the suppressors decreases and after some time this allows the cancer to exhibit. The increase of the number of the cancer cells induces after some period a new reaction of the immune system which leads to a cyclic behaviour. The peaks of the number of cancer cells can be almost the same or to decrease or increase for different values of parameters. The evolution of the competition in Case 3 is presented in Figures 3a and 3b.

Analysing the dynamics of the process in Case 3, one can see that the number of suppressors reaches the maximum values in instances of time when the number of cancer cells decreases close to its minimum value. After that, the number of suppressors begins to decrease. This observation suggested us to simulate a possible influx of suppressors in periods when the number of cancer cells is small. The values of the parameters in this Case 4 are the same as in Case 3 with the only difference that $S_0(t) = 0.1$ for $t \in [0, 7]$ and $t \in [240, 760]$, The result of such a simulation is presented in Figures 4a and 4b.

The simulation shows that, the external source of suppressors allows to keep their number large enough to inhibit the cancer cells after their first maximum and to brook no re-exhibition of the cancer. We can draw a conclusion that, if such an influx of suppressors is possible, it can play very important role in the medical therapy.
5. CONCLUSIONS

The aim of the present model is to try to improve the understanding of the interactions between
the immune system and the leukemia cells as well as another types of cancer during their early
stages. The obtained qualitative results can be observed in the immunological practice (see, for
example [1,29]).

The idea to use artificial external source of suppressors is one of the perspective for a successful
therapy. The vaccination with dendritic cells, which could be considered as kind of suppressors,
is developed very quickly lately. Thus, it could be useful to try to determine the values of
the parameters of the model and to compare the results with clinical data which could be an
interesting direction for future investigations. An important problem can be the determination
of the optimal regime of injection of suppressors. This might help to reduce the amount of
experiments which are necessary for therapy developments.

REFERENCES

1. P.M. Lydyard, A. Whelan and M.W. Fanger, Instant Notes in Immunology, BIOS Scientific Publishers Ltd.,
(2000).
3. M. Kolev, Mathematical modelling of the competition between tumors and immune system considering the
4. G.C. Blobe, W.P. Schemann and H.F. Lodish, Role of transforming growth factor beta in human disease,
5. S. Moeellin, E. Wang and F.M. Marincola, Cytokines and immune response in the tumor microenvironment,
6. M.J. Soloski, Recognition of tumor cells by the innate immune system, Current Opinion in Immunology 13,
8. E. Jäger and L. Segel, On the distribution of dominance in a population of interacting anonymous organisms,
10. L. Arlotti and N. Bellomo, Solution of a new class of nonlinear kinetic models of population dynamics, Appl.
11. L. Arlotti, N. Bellomo and M. Lachowicz, Kinetic equations modelling population dynamics, Transport Theory
13. E. Geigant, K. Ladiziansky and A. Mogilner, An integrodifferential model for orientational distribution of
14. N. Bellomo, L. Preziosi and G. Forni, On a kinetic (cellular) theory of the competition between tumors and
15. N. Bellomo and G. Forni, Dynamics of tumor interaction with the host immune system, Mathl. Comput.
16. L. Arlotti and M. Lachowicz, Qualitative analysis of a nonlinear integro-differential equation modelling tumour-host
17. L. Arlotti, A. Gamba and M. Lachowicz, A kinetic model of tumour/immune system cellular interactions, J.
18. M. Lachowicz, Competition tumor-immune system, Proceedings of the Sixth National Conference on Appli-
19. J.A. Adam and N. Bellomo, Editors, A Survey of Models for Tumor-Immune System Dynamics, Birkhäuser,
20. N. Bellomo and E. de Angelis, Strategies of applied mathematics towards an immuno mathematical theory
21. B. Firmani, L. Guerri and L. Preziosi, Tumor/immune system competition with medically induced activation/
23. B. Bellomo and M. Pulvirenti, Editors, Modelling in Applied Sciences, A Kinetic Theory Approach, Birk-
24. N. Bellomo and L. Preziosi, Modelling and mathematical problems related to tumor evolution and its inte-


