On the local kinetics component of biological systems in competition

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Abstract. In various previous papers, mathematical models describing the evolution of a tumor in presence of an immune system response are proposed by using the concept of cellular activity. The activities of the biological systems in competition are described by a functional operator which has been stationary. In this paper, within the kinetic cellular theory, the functional operator which characterizes the biological states of the cells is chosen to depend on the cellular densities and the time. Using this new model, three examples are discussed and the results are compared with other models proposed in literature.

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Key words: Nonlinear evolution equations; problem related to evolution.

1 Introduction

In these last years, various mathematical models have been proposed for the study of competition between tumor cells and immune systems, which generalize some dynamic systems typical of competition between populations. These models can be grouped into three classes:

I. A first class is based on a system of ordinary equations [27] with constant coefficients:

$$\dot{n}_1^T = b_1 \left(1 - b_2 n_1^T\right) n_1^T - p k_2 n_1^T n_2^A \tag{1.1}$$

$$\dot{n}_2^A = r + \left[\frac{f\, n_1^T}{g + n_1^T}\right] n_2^A - d n_2^A - (1-p)\, k_2 n_1^T n_2^A \tag{1.2}$$

- n_1^T: number of cancer cells present at time t,
- n_2^A: number of cytotoxic killer cells present at time t,
- r: base rate of arrival of killer cells at the tumor via the lymphatic system,

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- d: rate killer cells death,
- $\dfrac{f}{g+n_1^T}$: logistic growth rate,
- pk_2: kinetic constant rate of destruction of tumor cells,
- $(1-p)k_2$: rate of killer cell inactivity.

II. A second class has non-constant coefficients and with the addition of the therapeutic action [24, 25, 26, 17, 18, 19, 20, 9]:

$$\dot{\bar{n}}_1{}^T = \left[\delta g(\bar{n}_1^T) - \phi(\bar{n}_1^T)\bar{n}_2^A\right]\bar{n}_1^T, \tag{1.3}$$

$$\dot{\bar{n}}_2{}^A = -\Psi\left(\bar{n}_1^T\right)\bar{n}_2^A + \sigma q\left(\bar{n}_1^T\right) + \theta\left(t\right), \tag{1.4}$$

where:

- $\bar{n}_1^T$ and $\bar{n}_2^A$ are the non-dimensionalized numbers of, respectively, tumor cells and of effectors cells,
- δ and σ parameters constants,
- $\phi(\bar{n}_1^T)$ and $q(\bar{n}_1^T)$ functions over the $\bar{n}_1^T$,
- $g(\bar{n}_1^T)$ summarizes many widely used models of tumor growth rates,
- $\Psi\left(\bar{n}_1^T\right)$ ranking the tumors depending on their degree of aggressiveness against the immune system.
- $\theta(t)$ therapeutic action

III. A third class is based on integral-differential equations [4, 6, 22, 23] having the unknown distribution functions $f(t,u)$, which depend on time and on the biological activity u:

$$\partial_t f_i(t,u) + F_i(t)\partial_u f_i(t,u) = C_i[f](t,u) + D_i[f](t,u) + P_i[f](t,u), \tag{1.5}$$

where

- u: activity variable of cells,
- i: i-th population, with $i = 1, 2, \ldots, M$,
- $f_i(t,u)$: distribution functions over the microscopic state u at time t,
- $F_i(t)$: models the external action over the i-th population,
- $C_i[f](t,u)$: models the flow, at time t, into the elementary volume of the state space of the i-th population due to conservative interactions,
- $D_i[f](t,u)$: models the net flow, at time t, into the elementary volume of the state space of the i-th population due to proliferative and destructive interactions without transition of population,
- $P_i[f](t,u)$: models the flow, at time t, into the elementary volume of the state space of the i-th population due to proliferation.

Recently, a model Generalized Hybrid Kinetic (GHK) [10, 11, 21, 12, 13, 14, 15, 16] was proposed in which, by using the concept of cellular activity, a system of equations coupling ordinary differential equations to integral differential equations is determined. In this model the biological cell activity has always been considered stationary:

$$\frac{dn_i}{dt} = G_i\left(n_i; \check{\mu}[\mathbf{f}]\right)(t)) \tag{1.6}$$

$$\partial_t f_i\left(t,u\right) + \mathtt{K}(t,u)\partial_u\left[\mathbf{f}\left(t,u\right)\right] = A_i[f]\left(t,u\right), \tag{1.7}$$

where

- i: i-th population, with $i = 1, 2, \ldots, M$,
- $\check{\mu}[\mathbf{f}](t) = 1 - \frac{1}{2}\sum\limits_{i,j=1}^{M}\left\{\int\limits_{D_u}\left[f_i(t,u) - f_j(t,u)\right]^2 du\right\}$: functional operator on the vector $\mathbf{f}$ distributions,
- $G_i(n_i; \check{\mu}[\mathbf{f}](t))$: parametric i-th function in $\check{\mu}[\mathbf{f}](t)$,
- $f_i(t,u)$: distribution functions over the microscopic state u at time t,
- $A_i[f](t,u)$: biological interactions,
- $\mathtt{K}(t,u)$: is an analytic function of t and u.

After illustrating the concept of local kinetics components and of cellular activity (§2), in §3 we indicate the procedure which defines the GHK model with a new definition of the functional operator, the Ciancio-Flora model. This allows us to calculate the evolution of the competing system in case of unsteady deterministic type. In §4 there are given three examples of solutions of the kinetic integro-differential equations. In §5, this is compared to the Kuznetsov and Knott models with the GHK Ciancio-Flora model, with reference to the study of tumoral BCL1 cells injected in spleen of murine and chimeric mice.

2 Preliminaries

The solid tumor or neoplasm is produced by abnormal cells. This grows quickly in absence of immune system response. In presence of immune system response, the tumor growth is slow and, in some cases, regresses. Let's examine, as shown in Figure 1, the kinetic aspect. We consider at an initial instant t_0 two populations: T-tumor cells (BCL1, in red) in an small avascular tumour and A-immune cells (Cytotoxic T-lymphocytes, in green).

At time $t_0 + \Delta t$, we can observe possible formation of conjugate cells C (conjugate tumor-immune cells), as shown in Figure 2.

Subsequently, at time $t_0 + N\Delta t$ we observe, in Figure 3, two process and four possible events (two for every single process):

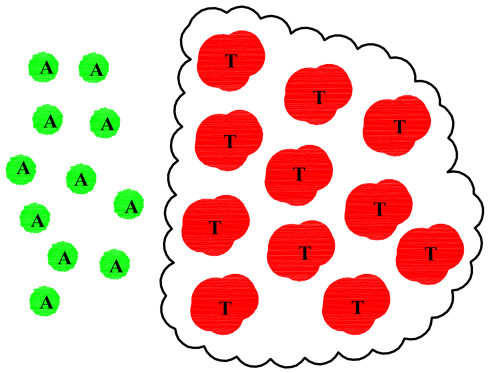

Figure 1: Possible scenario at $t = t_0$; T: Tumor cells; A: Active immune cells

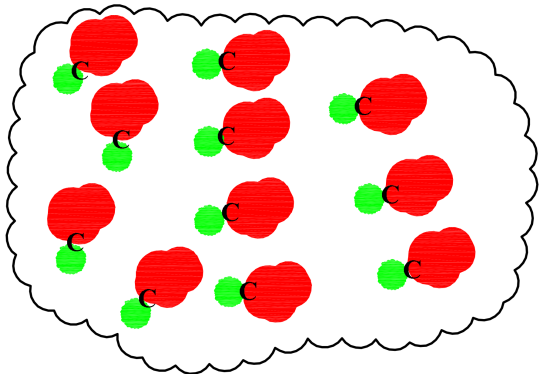

Figure 2: Possible scenario at $t = t_0 + \Delta t$; C: Conjugate tumor-immune cells

a) two reversible processes: formation or dissociation conjugate tumor-immune cells;

b) two irreversible processes: death tumor cells (in yellow) or immune cells become inactive (in light blue).

where p is the probability that some immune cells destroy tumoral cells; $(1-p)$ represents the probability that some immune cells have been inactivated; k_1 is the formation rate and k_{-1} is rate dissociation reversible process (without any damage of cells); k_2 is lysis rate of tumor cells or inactive immune-cells.

So we get the equations for the evolution of n_1^T , n_2^A and n^C:

$$\left(\dot{n}_1^T\right)^{Kinetic} = -k_1 n_1^T n_2^A + k_{-1} n^C + k_2 \left(1-p\right) n^C, \tag{2.1}$$

$$\left(\dot{n}_2^A\right)^{Kinetic} = -k_1 n_1^T n_2^A + k_{-1} n^C + k_2 p n^C, \tag{2.2}$$

$$\left(\dot{n}^C\right)^{Kinetic} = k_1 n_1^T n_2^A - \left(k_{-1} + k_2\right) n^C. \tag{2.3}$$

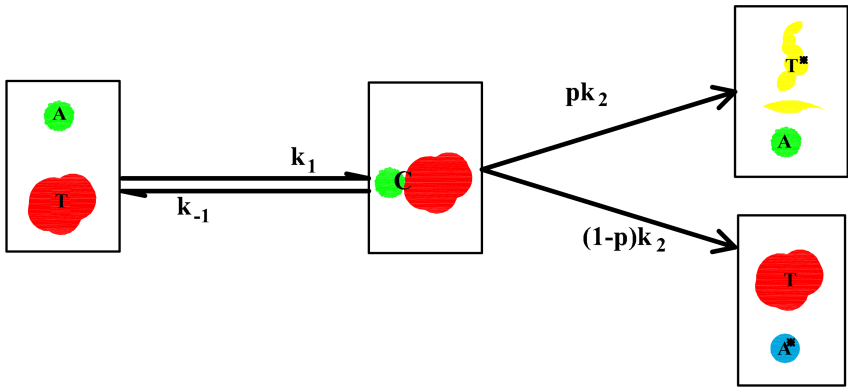

Figure 3: Possible scenario at $t = t_0 + N\Delta t$, where T^* is death tumor cells and A^* are inactive immune cells.

If we consider also the aspects of population growth and external sources, there is the Lotka-Volterra model [28, 29]

$$\dot{n}_1^T = \overbrace{g_1(n_1^T)n_1^T}^{logistic\,growth} - \overbrace{k_1 n_1^T n_2^A + k_{-1} n^C + k_2\,(1-p)\,n^C}^{local\,kinetics}, \tag{2.4}$$

$$\dot{n}_2^A = -\overbrace{k_1 n_1^T n_2^A + k_{-1} n^C + k_2 p n^C}^{local\,kinetics} + \overbrace{g_3(n_1^T)n_2^A}^{proliferation} - \overbrace{g_4(n_2^A)}^{decay} + \overbrace{s}^{supply}, \tag{2.5}$$

$$\dot{n}^c = \overbrace{k_1 n_1^T n_2^A - (k_{-1} + k_2)\,n^C}^{local\,kinetics}. \tag{2.6}$$

If the concentration variation of C cells is proximal to zero $\dot{n}^C \approx 0$, we have only two equations in the variables n_1^T and n_2^A:

$$\dot{n}_1^T = \overbrace{g_1(n_1^T)n_1^T}^{logistic\,growth} - \overbrace{pkn_1^T n_2^A}^{local\,kinetics}, \tag{2.7}$$

$$\dot{n}_2^A = -\overbrace{(1-p)\,kn_1^T n_2^A}^{local\,kinetics} + \overbrace{g_3(n_1^T)n_2^A}^{proliferation} - \overbrace{g_4(n_2^A)}^{decay} + \overbrace{s}^{supply}, \tag{2.8}$$

with:

$$n^c = \frac{k}{k_2} n_1^T n_2^A,\ k = \frac{k_1 k_2}{k_{-1} + k_2}. \tag{2.9}$$

3 The GHK Ciancio-Flora model

The microscopic state or intensity of the biological activity $u(t)$, in general, is a stochastic process and the functions:

$$f_{1,2}(t,u) : D_t \times D_u \to \mathbb{R}^+$$

with $u \in D_u \subseteq \mathbb{R}$ and $t \in D_t = [0, T_{Oss}]$ are the density distribution, normalized with respect to the total number cells and for unit volume, such that $f_i(t,u)\,du$ denotes the probability that the biological activity, u, of particles of the i-th population, at time t, is in the interval $[u, u+du]$ and T_{Oss} is the observation time.

The balance equation for probability density functions can be written in vectorial form:

$$\mathbf{f}(t+dt, u+du) \,-\, \mathbf{f}(t,u) \,=\, \mathcal{A}[\mathbf{f}](t+dt, u+du)] \,-\, \mathcal{A}[\mathbf{f}](t,u)] \tag{3.1}$$

where $\mathcal{A}$ is the matrix of cellular interactions. Developing in Taylor's series, we infer:

$$\begin{gathered} \partial_t \left[\mathbf{f}\,(t,u)\right] dt + \nabla_u \left[\mathbf{f}\,(t,u)\right] du + \tfrac{1}{2}\nabla_u^2 \left[\mathbf{f}\,(t,u)\right] du^2 + \cdots = \\ \mathcal{A}^{(0)}\left[\mathbf{f}\right](t,u)\, dt + \mathcal{A}^{(1)}\left[\mathbf{f}\right](t,u)\, du + \tfrac{1}{2}\mathcal{A}^{(2)}\left[\mathbf{f}\right](t,u)\, du^2 + \ldots \ . \end{gathered} \tag{3.2}$$

The differential stochastic process du is by Ito's lemma, defined by means of two components, a deterministic one, and another stochastic:

$$du = \mathtt{K}(t,u)dt + \sigma(t,u)d\xi \tag{3.3}$$

where $d\xi^2 = dt$ is a Wiener stochastic process. $\mathtt{K}(t,u)$ is the drift and $\sigma(t,u)$ is diffusive component. Substituting the expression for du and neglecting the terms upper order to dt we have:

$$\begin{gathered} \left\{ \partial_t \left[\mathbf{f}\,(t,u)\right] + \mathtt{K}\,(t,u)\, \nabla_u \left[\mathbf{f}\,(t,u)\right] + \frac{1}{2}\sigma^2(t,u)\nabla_u^2 \left[\mathbf{f}\,(t,u)\right] \right\} dt + \\ +\sigma\,(t,u)\, \nabla_u \left[\mathbf{f}\,(t,u)\right] d\xi = \mathcal{A}\left[\mathbf{f}\right](t,u)\, dt + \sigma\,(t,u)\, \mathcal{A}^{(1)}\left[\mathbf{f}\right](t,u)\, d\xi \end{gathered} \tag{3.4}$$

with:

$$\mathcal{A}\left[\mathbf{f}\right](t,u) = \mathcal{A}^{(0)}\left[\mathbf{f}\right](t,u) + \mathtt{K}\,(t,u)\, \mathcal{A}^{(1)}\left[\mathbf{f}\right](t,u) + \frac{1}{2}\sigma^2(t,u)\mathcal{A}^{(2)}\left[\mathbf{f}\right](t,u)\,. \tag{3.5}$$

The operators $\mathcal{A}^{(0)}[\mathbf{f}](t,u)$, $\mathcal{A}^{(1)}[\mathbf{f}](t,u)$ and $\mathcal{A}^{(2)}[\mathbf{f}](t,u)$ must be specified in relation to the biological interactions between the competing populations, i.e., stationary, drift and diffusive type respectively.

In case of the steady biological interaction, we have: $\mathtt{K} = 0$ and $\sigma = 0 \Rightarrow du = 0$,

$$\partial_t \left[\mathbf{f}\,(t,u)\right] = \mathcal{A}\left[\mathbf{f}\right](t,u)\,, \tag{3.6}$$

$$\mathcal{A}\left[\mathbf{f}\right](t,u) = \mathcal{A}^{(0)}\left[\mathbf{f}\right](t,u)\,. \tag{3.7}$$

By neglecting the only diffusive process, i.e., $\sigma\,(t,u) = 0$, we have the deterministic unsteady case

$$du = \mathtt{K}(t,u)dt, \tag{3.8}$$

$$\partial_t \left[\mathbf{f}\,(t,u)\right] + \dot{u}\nabla_u \left[\mathbf{f}\,(t,u)\right] = \mathcal{A}\left[\mathbf{f}\right](t,u), \tag{3.9}$$

where:

$$\dot{u} = \mathtt{K}(t,u) \tag{3.10}$$

and

$$\mathcal{A}\left[\mathbf{f}\right](t,u) \approx \mathcal{A}^{(0)}\left[\mathbf{f}\right](t,u), \tag{3.11}$$

with:

$$\mathcal{A}^{(1)}\left[\mathbf{f}\right](t,u) \approx 0. \tag{3.12}$$

Recalling the generalized Kuznetsov-Knott model given by (2.7) and (2.8), the GHK Ciancio-Flora model is obtained by making a correction of the local kinetics component given from (3.13) and (3.14), through the functional operator $\mu\left[\mathbf{f}\right](t)$ which is determinated by solving the IDEs system (3.15):

$$\dot{n}_1^T = \overbrace{g_1(n_1^T)n_1^T}^{logistic\,growth} - \overbrace{p\mu\left[\mathbf{f}\right](t)\, g_2\left(n_1^T\right) n_2^A}^{local\,kinetics}, \tag{3.13}$$

$$\dot{n}_2^A = -\overbrace{\left\{1-p\mu\left[\mathbf{f}\right](t)\right\} g_2\left(n_1^T\right) n_2^A}^{local\,kinetics} + \overbrace{g_3(n_1^T)n_2^A}^{proliferation} - \overbrace{g_4(n_2^A)}^{decay} + \overbrace{s}^{supply}, \tag{3.14}$$

$$\partial_t\left[\mathbf{f}\left(t,u\right)\right] + \dot{u}\nabla_u\left[\mathbf{f}\left(t,u\right)\right] = \mathcal{A}\left[\mathbf{f}\right](t,u), \tag{3.15}$$

with the boundary and initial conditions:

$$\mathbf{n}\left(0\right) = \mathbf{n}^0 = \left[n_1^T\left(0\right) n_2^A\left(0\right)\right]^T, \dot{\mathbf{n}}\left(0\right) = 0, \tag{3.16}$$

$$\mathbf{f}\left(0,u\right) = \mathbf{h}\left(u\right), \tag{3.17}$$

$$\lim_{u\to\pm\infty}\left[\mathbf{f}\left(t,u\right)\right] = 0, \forall t \in \mathbb{R}_0^+, \tag{3.18}$$

$$\mathbf{i}_{\perp\partial D_u}\cdot\nabla_u[f]|_{\partial D_u} = 0,\ \|\mathbf{i}_{\perp\partial D_u}\| = 1. \tag{3.19}$$

The probability that p depends on the distributions of biological states u of the cells through the functional operator $\mu[\mathbf{f}](t)$, is:

$$\mu[\mathbf{f}]\left(t\right) = 1 - \frac{\int_{D_u}\left[f_1\left(t,u\right) - f_2\left(t,u\right)\right]^2 du}{\sqrt{\int_{D_t\times D_u}\left[f_1^2\left(t,u\right) + f_2^2\left(t,u\right)\right] dudt}}. \tag{3.20}$$

In other words, p depends on the error square with respect to u states's variable:

$$\int_{D_u}[f_1(t,u) - f_2(t,u)]^2 du,$$

normalized with respect to distance:

$$\sqrt{\int_{D_t\times D_u}[f_1^2(t,u) + f_2^2(t,u)]dudt}$$

between the two density distributions. In Figure 4 it is shown the trend of $\mu[\mathbf{f}]\left(t\right)$ when $\dot{u} = \mathtt{K}\left(t,u\right) = -u$, with $0 \leq \mu[\mathbf{f}](t) \leq 1$ and such that:

- $\mu\left[\mathbf{f}\right](t) = 0 \Longrightarrow \dot{n}_1^T = g_1\left(n_1^T\right) n_1^T$, i.e., in absence of immune response;
- $\mu\left[\mathbf{f}\right](t) = 1 \Longrightarrow \dot{n}_1^T = g_1\left(n_1^T\right) n_1^T - pg_2\left(n_1^T\right) n_2^A$, i.e., when the two populations have the same density, $f_1(t,u) = f_2(t,u)$; we obtain the classical macroscopic model type Lotka-Volterra.

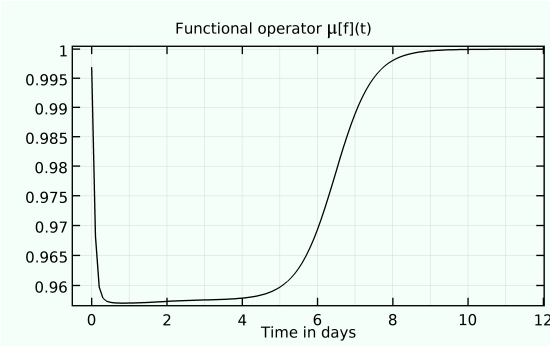

Figure 4: $\mu[\mathbf{f}](t)$

Here $\mu[f](t)$ is an adimensional functional operator that includes the biological interaction at microscopic level and characterizes the unsteady kinetic behavior, in particular, in the early instants in which competing cells interact with each other.
For $\sigma(t,u) = 0$ and $\mathcal{A}^{(1)}\left[\mathbf{f}\right](t,u) \approx 0$, the operator diagonal matrix $\mathcal{A}\left[\mathbf{f}\right](t,u)$ from (3.5) becomes:

$$\mathcal{A}\left[\mathbf{f}\right](t,u) \approx \mathcal{A}^{(0)}\left[\mathbf{f}\right](t,u), \tag{3.21}$$

where $\mathcal{A}^{(0)}\left[\mathbf{f}\right](t,u)$, based on the theory in [7, 2, 3, 8, 5], is expressed by its components $\mathcal{A}_{11}^{(0)}[\mathbf{f}](t,u)$ and $\mathcal{A}_{22}^{(0)}[\mathbf{f}](t,u)$:

$$\begin{aligned}\mathcal{A}_{11}^{(0)}[\mathbf{f}](t,u) &= \eta_{11}\left[f_1\left(t,u-\alpha_{11}\right) - f_1\left(t,u\right)\right] \int_{-\infty}^{+\infty} f_1\left(t,u\right) du \\ &+\eta_{12} f_1\left(t,u+\alpha_{12}\right) H\left(u+\alpha_{12}\right) \int_{0}^{+\infty} f_2\left(t,u\right) du \\ &+\left[\eta_{11}\beta_{11} \int_{-\infty}^{0} f_1\left(t,u\right)\, du - \eta_{12}\left(\beta_{12}+1\right) \int_{0}^{+\infty} f_2\left(t,u\right) du\right] H\left(u\right) f_1\left(t,u\right),\end{aligned} \tag{3.22}$$

where:

- α_{11} is the tendency of the environmental cells to degenerate,
- α_{12} is the ability of the active immune cells to reduce the state of abnormal cells,
- β_{11} is the growth-rate of cancerous cells,

- β_{12} is the capacity of kill-cells to destroy the cancerous cells,

$$\mathcal{A}_{22}^{(0)}[\mathbf{f}](t,u) = \eta_{21} H\left(u+\alpha_{21}\right) f_2\left(t,u+\alpha_{21}\right) \int_0^{+\infty} f_1\left(t,u\right) du$$
$$+\eta_{21}\left(\beta_{21}-1\right) f_2\left(t,u\right) H\left(u\right) \int_0^{+\infty} f_1\left(t,u\right) du, \tag{3.23}$$

- α_{21} is the ability of abnormal cells to inhibit the active immune cells,
- β_{21} is the reproductive rate of immune-cells,
- η_{ij} is the encounter rate of cells assuming they are constant and $H(u)$ is the Heaviside function. These kinetic parameters can be estimated using the method illustrated in [1].

4 Critical density immune-system

We further consider:

- the density of environmental cells u-state: $\Upsilon^E(t) = \int_{-\infty}^0 f_1(t,u)\,du$,
- the density of tumoral cells u-state: $\Upsilon^T(t) = \int_0^{\infty} f_1(t,u)\,du$,
- the density of inactive immune cells u-state: $\Upsilon^I(t) = \int_0^{\infty} f_2(t,u)\,du$,
- the density of active immune cells u-state: $\Upsilon^A(t) = \int_0^{\infty} f_2(t,u)\,du$,

with $\dot{u}=0$. The kinetic IDEs is:

$$\partial_t\left[f_1\left(t,u\right)\right] = \zeta\left(t\right) f_1\left(t,u\right) H\left(u\right), \tag{4.1}$$

$$\partial_t\left[f_2\left(t,u\right)\right] = \beta_{21}\Upsilon^T\left(t\right) f_2\left(t,u\right) H\left(u\right), \tag{4.2}$$

where

$$\zeta(t) = \beta_{11}\Upsilon^E\left(t\right) - \beta_{12}\Upsilon^A\left(t\right)$$

Let the initial conditions density u-states be:

$$\Upsilon_0^E = \Upsilon^E(0)$$

and

$$\Upsilon_0^A = \Upsilon^A(0);$$

then the parameter

$$\zeta_0 = \zeta\left(0\right) = \beta_{11}\Upsilon_0^E - \beta_{12}\Upsilon_0^A \tag{4.3}$$

is called *critical density immune-system*. We consider below three examples.

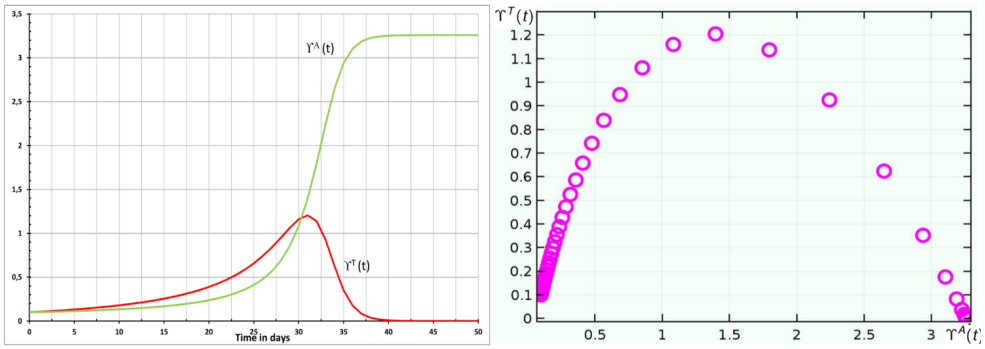

Figure 5: $\zeta_0 > 0$

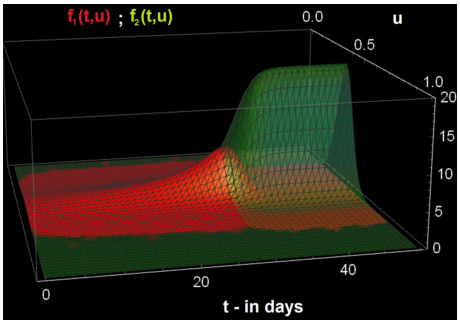

Figure 6: $f_1(t,u)$ and $f_2(t,u)$ solutions of IDEs for $u > 0$

Example 1: Consider $\zeta_0 = 0.1(\beta_{11} - \beta_{12}) > 0$ and the initial conditions:
(4.4)

$$f_1(0,u) = f_2(0,u) = 0.1\sqrt{\frac{100}{\pi}}e^{-100(u+0.4)^2}H(-u) + 0.1\sqrt{\frac{100}{\pi}}e^{-100(u-0.4)^2}H(u)$$

with the kinetic parameter: $\beta_{11} = 0.53$; $\beta_{12} = 0.267$; $\beta_{21} = 0.214$.

In the left side of Figure 5, the density of the u-state tumoral cells has been indicated with red line and with green line that of immune-cells. We observe an outbreak at around 30-th day. In the right side of Figure 5 it shows the phase space of density u-state. Figure 6 shows the trends of the IDEs solutions for $\zeta_0 > 0$.

Example 2: Consider $\zeta_0 = 0.1(\beta_{11} - \beta_{12}) < 0$ and the initial conditions:
(4.5)

$$f_1(0,u) = f_2(0,u) = 0.1\sqrt{\frac{100}{\pi}}e^{-100(u+0.4)^2}H(-u) + 0.1\sqrt{\frac{100}{\pi}}e^{-100(u-0.4)^2}H(u)$$

with kinetic parameter: $\beta_{11} = 0.2$; $\beta_{12} = 0.7$; $\beta_{21} = 0.6$.

In the left Figure 7, one observes the absence of outbreak and the density of u-state tumoral cells goes to zero as like as an negative exponential function. In the right

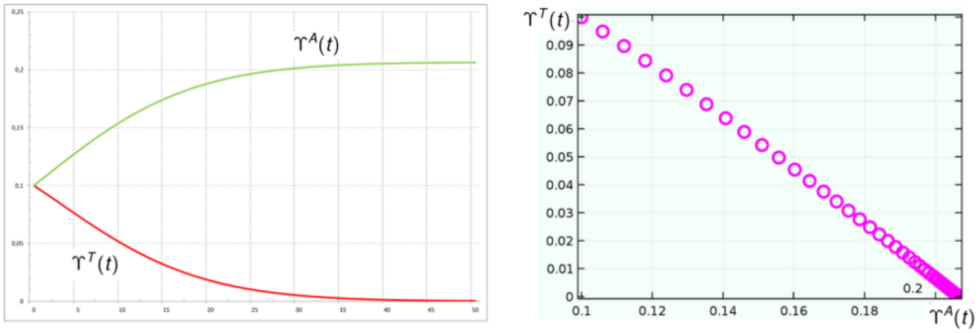

Figure 7: $\zeta_0 < 0$

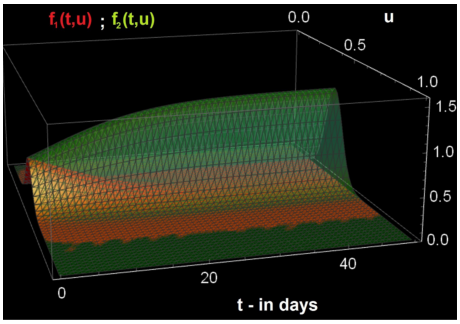

Figure 8: $f_1(t,u)$ and $f_2(t,u)$ solutions of IDEs for $u > 0$

Figure 7 it shows the phase space. The Figure 8 shows the trends of the IDEs solutions for $\zeta_0 < 0$.

Example 3: We consider the application model Ciancio-Flora - unsteady case: $\dot{u} = -u$. To satisfy the Dirichlet condition, $\forall t \in \mathbb{R}_0^+$, it is assumed that the density, $f_i(t,u)$, has the following expressions:

$$f_i(t,u) = \omega_i(t) e^{-\lambda_i u^2}, \tag{4.6}$$

where $\omega_i(t)$ and λ_i are the components to be determined by transforming the IDEs:

$$\partial_t \left[\mathbf{f}\left(t,u\right)\right] + \dot{u}\nabla_u \left[\mathbf{f}\left(t,u\right)\right] = \mathcal{A}\left[\mathbf{f}\right](t,u) \tag{4.7}$$

in an ODE system in the ω-functions.

5 Application unsteady case to the tumoral BCL1 cells in spleen of murine and chimeric mice

Some experimental data are analyzed in Figure 9 in which it is shows the development of BCL1 (lymphoma) cells after their inoculation in spleen of chimeric mice [30]. The different markers indicate different initial concentration of tumoral cells.

◯ : five-hundred-tausend cells per unit of volume,

□ : five millions cells per unit of volume,

△ : fifty millions cells per unit of volume.

In particular, it is noted that by inoculating the same amount of BCL1 tumor cells to normal mice (murine) and chimeric mice, normal ones exhibit metastasis after about 90 days while the latter tend to balance values after 110 days. We observe that we haven't any information about immune system in which it is shows the development of BCL1 (lymphoma) cells after their inoculation in chimeric mice.

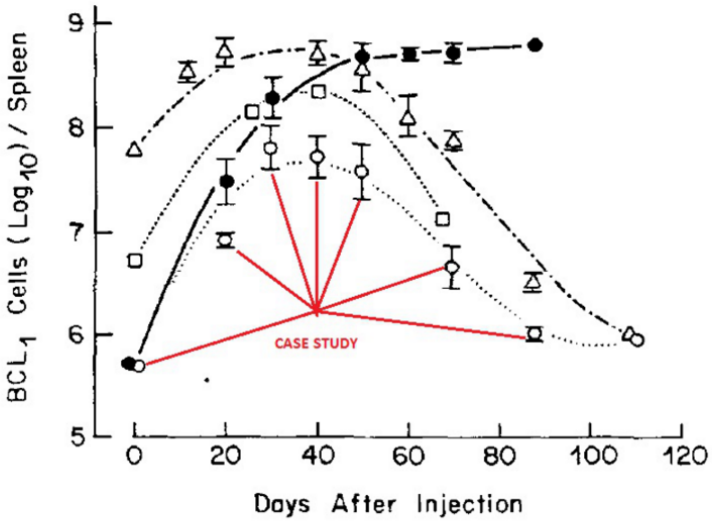

Figure 1. Growth of BCL_1 tumor in spleens of chimeric recipients. Viable BCL_1 cells—5×10^5 (○•••○), 5×10^6 (□---□), or 5×10^7 (△–•–•–△)—were injected i.v. into established chimeric recipients. Controls (●—●) were injected with 5×10^5 viable BCL_1 cells. Assays were performed by anti-Id staining and FACS analysis. Each point represents the average of values obtained from two experiments in which one spleen was assayed for each time point in each experiment; the 5×10^6 dose was only employed in one experiment. Computer generated lines were obtained by least squares fitting through experimental data points.

Figure 9: Experimental data

In Figure 10 we shows some results of Kuznetsov and Knott and it shows that the tumor cell trend is very close to the experimental data. Specifically, for the tumor in question, a range of 28 days was estimated from the inoculation of the immune system of the chimeric mouse to increase the concentration of killer cells.

In Figure 11 the evolution obtained highlights how the GHK Ciancio-Flora model allows for a better approximation of the experimental data than the Kuznetsov-Knott

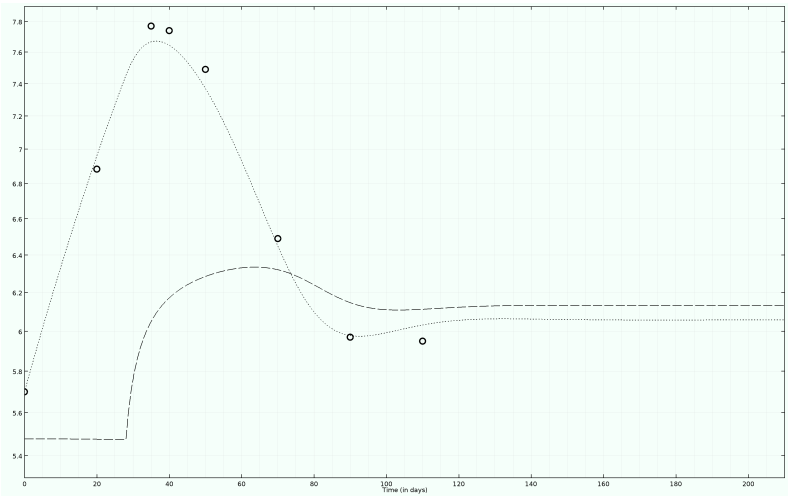

Figure 10: $Log_{10}(n_1^T)$: Dotted line; $Log_{10}(n_2^A)$: Dashed line

model. In addition, the non-stationarity of biological interaction, taken in the Ciancio-Flora model, allows for an initial and temporary decrease of killer cells.

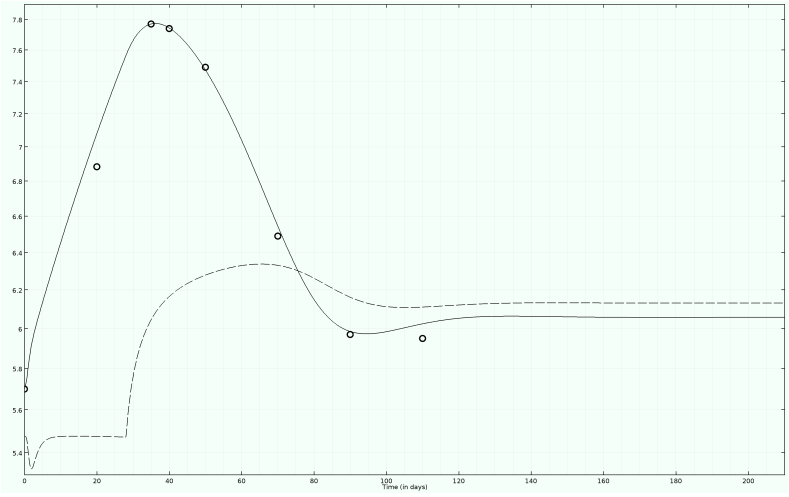

Figure 11: $Log_{10}(n_1^T)$: Dotted line; $Log_{10}(n_2^A)$: Dashed line

In Figure 12, using GHKM, shows an initial decrease in killer cells followed by their growth over tumor cells. As the observation time increases, the GHK and Kuznetsov models converge identically.

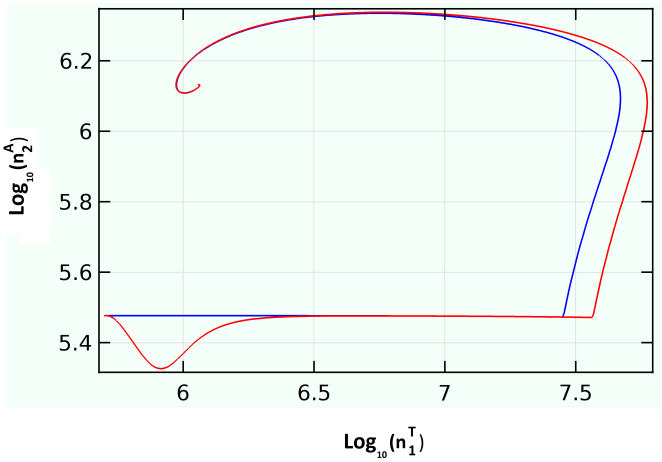

Figure 12: Model compared - GHK model in red line profile. Kuznetsov-Knot model in blu line profile

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