

## Research Article

# A Class of Solutions for the Hybrid Kinetic Model in the Tumor-Immune System Competition

Carlo Cattani<sup>1</sup> and Armando Ciancio<sup>2</sup>

<sup>1</sup>Department of Mathematics, University of Salerno, Via Ponte Don Melillo, 84084 Fisciano, Italy

<sup>2</sup>Department of Mathematics and Computer Science, University of Messina, Viale Ferdinando d'Alcontres 31, 98166 Messina, Italy

Correspondence should be addressed to Armando Ciancio; [aciancio@unime.it](mailto:aciancio@unime.it)

Received 6 March 2013; Accepted 7 April 2013

Academic Editor: Ezzat G. Bakhoun

Copyright © 2013 C. Cattani and A. Ciancio. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

In this paper, the hybrid kinetic models of tumor-immune system competition are studied under the assumption of pure competition. The solution of the coupled hybrid system depends on the symmetry of the state transition density which characterizes the probability of successful occurrences. Thus by defining a proper transition density function, the solutions of the hybrid system are explicitly computed and applied to a classical (realistic) model of competing populations.

## 1. Introduction

In this paper, the two-scale tumor immune-system competition hybrid model [1–6] is studied under the assumption that the transition density function is a symmetric and separable function. The competition between tumor and immune-system can be modeled at different scales. Cells of different populations are characterized by biological functions heterogeneously distributed, and they are represented by some probability distributions. The interacting system is characterized at a macroscopic scale by a density distribution function which describes the cells activity during the interaction proliferation. At this level, the distribution of cells fulfills some partial differential equations taken from the classical kinetic theory. In this case, the more general model consists in a nonlinear system of partial differential equations. From the solution of this system, one can define a parameter which defines the time evolving distance between the two distributions, and this parameter is the characterizing coefficient of the microscopic equations, typically an ordinary differential system for the competition of two populations.

This parameter has been considered [4, 5] as a random coefficient whose probability density distribution is modeled by the hiding-learning dynamics referred to biological events where tumor cells attempt to escape from immune cells which, conversely, attempt to learn about their presence.

Therefore, when the coupling parameter is obtained by solving the kinetic equations for the distribution functions, then it will be included in the classical Lotka-Volterra competition equations. We will analyze on a concrete example the influence of this stochastic parameter on the evolution. This method can be easily extended to more realistic competition models (see, e.g., [7–20]).

## 2. The Hybrid Model for the Tumor-Immune System Competition

Let us consider a physical system of two interacting populations, each one constituted by a large number of active particles with sizes:

$$n_i = n_i(t), \quad (n_i(t) : [0, T] \longrightarrow \mathbb{R}_+) \quad (1)$$

for  $i = 1, 2$  and  $\mathbb{R}_+ \stackrel{\text{def}}{=} [0, +\infty)$ .

Particles are homogeneously distributed in space, while each population is characterized by a microscopic state, called *activity*, denoted by the variable  $u$ . The physical meaning of the microscopic state may differ for each population. We assume that the competition model depends on the activity through a function of the overall distribution:

$$\mu = \mu[f_i(t, u)], \quad (\mu[f_i(t, u)] : \mathbb{R}_+ \longrightarrow \mathbb{R}_+). \quad (2)$$

The description of the overall distribution over the microscopic state within each population is given by the probability density function:

$$f_i = f_i(t, u), \quad (f_i(t, u) : [0, T] \times D_u \longrightarrow \mathbb{R}_+, D_u \subseteq \mathbb{R}) \quad (3)$$

for  $i = 1, 2$ , such that  $f_i(t, u)du$  denotes the probability that the activity  $u$  of particles of the  $i$ th population, at the time  $t$ , is in the interval  $[u, u + du]$ :

$$d\mu = f_i(t, u) du. \quad (4)$$

Moreover, it is

$$\forall i, \forall t \geq 0 : 0 \leq f_i(t, u) \leq 1, \quad \int_{D_u} f_i(t, u) du = 1. \quad (5)$$

We consider, in this section, the competition between two cell populations. The first one with uncontrolled proliferating ability and with hiding ability; the second one with higher destructive ability, but with the need of learning about the presence of the first population. The analysis developed in what follows refers to a specific case where the second population attempts to learn about the first population which escapes by modifying its appearance. The hybrid evolution equations specifically can be formally written as follows [4, 5]:

$$\begin{aligned} \frac{dn_i}{dt} &= G_i(n_1, n_2; \mu[f]), \\ \frac{\partial f_i}{\partial t} &= \mathcal{A}_i[f], \end{aligned} \quad (6)$$

where  $G_i$ , for  $i = 1, 2$ , is a function of  $n = \{n_1, n_2\}$  and  $\mu$  acts over  $f = \{f_1, f_2\}$ , while  $\mathcal{A}_i$ , for  $i = 1, 2$ , is a nonlinear operator acting on  $f$  and  $\mu[f]$  is a functional ( $0 \leq \mu \leq 1$ ) which describes the ability of the second population to identify the first one. Then, (6) denotes a hybrid system of a deterministic system coupled with a microscopic system statistically described by a kinetic theory approach. In the following the evolution of density distribution will be taken within the kinetic theory.

The derivation of (6)<sub>2</sub> can be obtained starting from a detailed analysis of microscopic interactions. Consider *binary interactions* specifically between a *test*, or *candidate*, particle with state  $u_*$  belonging to the  $i$ th population and *field particle* with state  $u^*$  belonging to the  $j$ th population. The modelling of microscopic interactions is supposed to lead to the following quantities.

- (i) *The encounter rate*, which depends for each pair of interacting populations on a suitable average of the relative velocity  $\eta_{ij}$ , with  $i, j = 1, 2$ .
- (ii) *The transition density function*  $\varphi_{ij}(u_*, u^*, u)$ , which is such that  $\varphi_{ij}(\cdot; u)$  denotes the probability density that a candidate particle with activity  $u_*$  belonging to the  $i$ th population falls into the state  $u \in D_u$ , of the test particle, after an interaction with a field entity,

belonging to the  $j$ th population, with state  $u^*$ . The transition density  $\varphi_{ij}(u_*, u^*, u)$  fulfills the condition

$$\begin{aligned} \forall i, j, \forall u_*, u^* : \int_{D_u} \varphi_{ij}(u_*, u^*, u) du &= 1, \\ \varphi_{ij}(u_*, u^*, u) &> 0, \end{aligned} \quad (7)$$

when  $\varphi_{ij}(u_*, u^*, u) \neq 0$  and

$$\forall u_*, u^* : \int_{D_u} \varphi_{ij}(u_*, u^*, u) du = 0 \iff \varphi_{ij}(u_*, u^*, u) = 0. \quad (8)$$

The state transition

$$u_* \xrightarrow{u^*} u \quad (9)$$

follows from the mutual action of the field particle ( $F$ ) of the  $i$ th population on the test particle ( $T$ ) of the  $j$ th population and vice versa so that

$$u_*(F) \xrightarrow{u^*(T)} u \iff u^*(T) \xrightarrow{u_*(F)} u. \quad (10)$$

With respect to this mutual action, we can assume that this function depends on the biological model, as follows.

- (1) Competition within the first group and with others: particles of the  $i$ th population interact with any other particle both from its own  $i$ th population and from the  $j$ th population so that

$$\varphi_{ij}(u_*, u^*, u) \neq 0, \quad (i \text{ fixed}, \forall j). \quad (11)$$

In this case, each particle of the  $i$ th population can change its state not only due to the competition with the  $j$ th population but also by interacting with particles of its own population. Instead, the individuals of the  $j$ th population change their state only due to the interaction with the other  $i$ th populations. They do not interfere with each other within their  $i$ th group.

- (2) Competition within the second group and with others: particles of the  $j$ th population interact with any other particles both from its own  $j$ th population and from the  $i$ th population so that

$$\varphi_{ij}(u_*, u^*, u) \neq 0, \quad (j \text{ fixed}, \forall i). \quad (12)$$

- (3) Full competition within a group and with others: particles of each population interact with any other particles both from its own population and from the other population so that

$$\varphi_{ij}(u_*, u^*, u) \neq 0, \quad (\forall i, \forall j). \quad (13)$$

- (4) Competition of two groups: particles of each population interact only with particles from the other population so that

$$\varphi_{ij}(u_*, u^*, u) = 0, \quad (i = j). \quad (14)$$

We can assume that this kind of competition arises when the dynamics in each population are stable and each population behaves as a unique individual.

Then, by using the mathematical approach, developed in [1, 2], it yields the following class of evolution equations:

$$\begin{aligned} \frac{\partial f_i}{\partial t}(t, u) = & \sum_{j=1}^2 \int_{D_{u_*} \times D_u} \eta_{ij} \varphi_{ij}(u_*, u^*, u) f_i(t, u_*) \\ & \times f_j(t, u^*) du_* du^* \\ & - f_i(t, u) \sum_{j=1}^2 \int_{D_u} \eta_{ij} f_j(t, u^*) du^*, \end{aligned} \quad (15)$$

(i = 1, 2)

which can be formally written as (6)<sub>2</sub>.

### 3. Transition Density Function Based on Separable Functions

In this section, we give the solution of (15) under some simple assumptions on the form of the transition density (7).

*3.1. On the Symmetries of the State Transition Density.* We assume that the integrability condition on  $\varphi_{ij}$ ,

$$\frac{\partial^2}{\partial u_* \partial u^*} \varphi_{ij}(u^*, u_*, u) = 0, \quad (16)$$

holds true. As a consequence, if we write the transition density as a linear combination of separable functions, this definition implies some symmetries which will be useful for the following computations, in particular.

**Theorem 1.** *If one defines the transition density as*

$$\varphi_{ij}(u^*, u_*, u) \stackrel{\text{def}}{=} \frac{1}{2} [a_i \psi_j(u_*, u) + a_j \psi_i(u^*, u)], \quad (17)$$

(a<sub>i</sub>, a<sub>j</sub> ≥ 0; i, j = 1, 2)

with  $\psi_i(u^*, u), \psi_j(u_*, u) > 0$  (i, j = 1, 2), the following symmetry holds true:

$$\int_{D_u} \varphi_{ij}(u_*, u^*, u) du = \int_{D_u} \varphi_{ji}(u^*, u_*, u) du. \quad (18)$$

*Proof.* From (7), (17), we have

$$\int_{D_u} [a_i \psi_j(u_*, u) + a_j \psi_i(u^*, u)] du = 2. \quad (19)$$

There follows, with i = 1, j = 2 and i = 2, j = 1,

$$\begin{aligned} \int_{D_u} [a_1 \psi_2(u_*, u) + a_2 \psi_1(u^*, u)] du &= 2, \\ \int_{D_u} [a_2 \psi_1(u_*, u) + a_1 \psi_2(u^*, u)] du &= 2 \end{aligned} \quad (20)$$

so that by a comparison of

$$\begin{aligned} \int_{D_u} \{a_1 [\psi_2(u_*, u) - \psi_2(u^*, u)] \\ + a_2 [\psi_1(u^*, u) - \psi_1(u_*, u)]\} du &= 0 \end{aligned} \quad (21)$$

to be valid for all a<sub>1</sub>, a<sub>2</sub>, that is, as a consequence of the definition (17),

$$\begin{aligned} \int_{D_u} \psi_2(u_*, u) du &= \int_{D_u} \psi_2(u^*, u) du, \\ \int_{D_u} \psi_1(u^*, u) du &= \int_{D_u} \psi_1(u_*, u) du. \end{aligned} \quad (22)$$

In particular, to fulfill (20), we can assume

$$\begin{aligned} \int_{D_u} a_1 \psi_2(u_*, u) du = 1, \quad \int_{D_u} a_2 \psi_1(u^*, u) du &= 1, \\ \int_{D_u} a_2 \psi_1(u_*, u) du = 1, \quad \int_{D_u} a_1 \psi_2(u^*, u) du &= 1, \end{aligned} \quad (23)$$

from which, by taking into account (22), we get

$$\begin{aligned} \int_{D_u} a_2 \psi_1(u_*, u) du &= \int_{D_u} a_2 \psi_1(u^*, u) du \\ &= 1 \implies \int_{D_u} \psi_1(w, u) du = \frac{1}{a_2}, \\ \int_{D_u} a_1 \psi_2(u_*, u) du &= \int_{D_u} a_1 \psi_2(u^*, u) du \\ &= 1 \implies \int_{D_u} \psi_2(w, u) du = \frac{1}{a_1} \end{aligned} \quad (24)$$

so that, by a difference,

$$\begin{aligned} \int_{D_u} [a_i \psi_j(v, u) - a_j \psi_i(w, u)] du &= 0, \\ (v, w = u_*, u^*; i, j = 1, 2). \end{aligned} \quad (25)$$

Thus, according to (25), the mutual action of the state transition given by the definition (7) can be summarized by (18).  $\square$

Equations (17), (18) imply that the functions  $\psi_i$  have to be carefully chosen so that (22), (24), and (18) are fulfilled.

In the following, we will consider a special choice for the transition density (17) as

$$\begin{aligned} \varphi_{ij}(u^*, u_*, u) \stackrel{\text{def}}{=} \frac{1}{2} a_{ij} [\psi(u_*, u) + \psi(u^*, u)], \\ (a_{ij} \geq 0; i, j = 1, 2) \end{aligned} \quad (26)$$

so that (18) is fulfilled.

*3.2. Preliminary Theorems.* The special choice of  $\varphi_{ij}(u_*, u^*, u)$ , as defined in (26), enables us to explicitly solve (15); however, prior to computing the analytical solutions of (15), we need to show these preliminary theorems.

**Theorem 2.** *Let X(t, u) be a function satisfying*

$$\int_{D_u} X(t, u) du = K \quad (|f(t, u)| < M < \infty; K \geq 0) \quad (27)$$

and  $\psi(w, u)$  a given function for which

$$\int_{D_u} \psi(w, u) dw = \frac{b}{a} \quad (0 \leq \psi(w, u) \leq 1; a \neq 0) \quad (28)$$

holds, then the equation

$$\frac{\partial X}{\partial t}(t, u) = a \int_{D_u} \psi(w, u) X(t, w) dw - bf(t, u) \quad (29)$$

$$(a \geq 0, b \geq 0)$$

is solved by

$$X(t, u) = F(u) e^{-(b-a/\lambda)t} + KG(u) \quad (K \geq 0), \quad (30)$$

where  $F(u)$  is the solution of the second kind homogeneous Fredholm integral equation

$$F(u) = \lambda \int_{D_u} \psi(w, u) F(w) dw, \quad \int_{D_u} F(u) du = 0, \quad (31)$$

with  $\lambda$  being the eigenvalue of the integral equation, and

$$G(u) = \frac{a}{b} \int_{D_u} \psi(w, u) G(w) dw, \quad (32)$$

$$\int_{D_u} G(u) du = 1 \quad (b \neq 0),$$

when  $b = 0$ ,  $G(u)$  is any arbitrary function fulfilling (32)<sub>2</sub>.

*Proof.* Let us first notice that in the trivial case of  $a = 0$ , there is no dependence on the function  $\psi$

$$\frac{\partial X}{\partial t}(t, u) = -bX(t, u) \quad (b \geq 0), \quad (33)$$

but this equation is also solved by (30) being

$$X(t, u) = F(u) e^{-bt} + KG(u). \quad (34)$$

In the more general case, (31)<sub>2</sub>, (32)<sub>2</sub> are direct consequence of the condition (5).

By a simple computation, (29) can be transformed into the Fredholm integral equations (31), (32).

In fact, by deriving (30), we have

$$\frac{\partial X}{\partial t} \stackrel{(30)}{=} -\left(b - \frac{a}{\lambda}\right) F(u) e^{-(b-a/\lambda)t} \quad (35)$$

so that (29), taking into account (30), becomes

$$-\left(b - \frac{a}{\lambda}\right) F(u) e^{-(b-a/\lambda)t}$$

$$= a \int_{D_u} \psi(w, u) \left[ F(w) e^{-(b-a/\lambda)t} + KG(w) \right] dw \quad (36)$$

$$- b \left[ F(u) e^{-(b-a/\lambda)t} + KG(u) \right],$$

that is,

$$\left[ \left(\frac{a}{\lambda}\right) F(u) - a \int_{D_u} \psi(w, u) F(w) dw \right] e^{-(b-a/\lambda)t}$$

$$= K \left[ a \int_{D_u} \psi(w, u) G(w) dw - bG(u) \right], \quad (37)$$

from which (31), (32) and (30) hold true.

When  $b = 0$ , from the r.h.s, we have

$$\int_{D_u} \psi(w, u) dw = 0, \quad \int_{D_u} G(w) dw = 1 \quad (38)$$

so that  $G(u)$  cannot be univocally determined.  $\square$

When the initial conditions are given, we have the following corollary.

**Corollary 3.** Let  $X(t, u)$  be a function satisfying (27) that is

$$\int_{D_u} X(t, u) du = K, \quad (|f(t, u)| < M < \infty; K \geq 0) \quad (39)$$

and  $\psi(w, u)$  a given function for which

$$\int_{D_u} \psi(w, u) du = \frac{b}{a} \quad (0 \leq \psi(w, u); a > 0, b \geq 0) \quad (40)$$

holds, then the solution of the initial value problem

$$\frac{\partial X}{\partial t}(t, u) = a \int_{D_u} \psi(w, u) X(t, w) dw - bf(t, u),$$

$$X(t, u)|_{t=0} = X(0, u) \quad (41)$$

$$(a \geq 0, b \geq 0)$$

is as follows:

(1)  $a > 0, b > 0, K > 0$

$X(t, u)$

$$= \frac{\lambda b/a}{\lambda b/a - 1} \left[ X(0, u) \right.$$

$$\left. - \frac{a}{b} \int_{D_u} \psi(w, u) f(0, w) dw \right] e^{-(b-a/\lambda)t}$$

$$+ \frac{1}{1 - \lambda b/a} \left[ X(0, u) - \lambda \int_{D_u} \psi(w, u) X(0, w) dw \right],$$

$$\lambda \neq 1, \quad (42)$$

$$X(t, u) = 0, \quad \lambda = 1, \quad (43)$$

(2)  $a > 0, b > 0, K = 0$ .

The solution

$$X(t, u) = X(0, u) e^{-(b-a/\lambda)t} \quad (44)$$

exists only for  $X(0, u) = \lambda \int_{D_u} \psi(w, u) X(0, w) dw$ ,

(3)  $a > 0, b \geq 0$ . The solution

$$X(t, u) = X(0, u) e^{a/\lambda t} \quad (45)$$

exists only for  $X(0, u) = \lambda \int_{D_u} \psi(w, u) X(0, w) dw$ ,

(4)  $a = 0, b \geq 0$ . For  $K > 0$ , the solution of (41) does not exist. When  $K = 0$ , the solution is

$$X(t, u) = X(0, u) e^{-bt}. \quad (46)$$

*Proof.* According to Theorem 2, the solution of (41)<sub>1</sub> is (30) with derivative (35). In the more general case, these two equations, at the initial time, give

$$X(0, u) = F(u) + KG(u),$$

$$-\left(b - \frac{a}{\lambda}\right) F(u) = a \int_{D_u} \psi(w, u) X(0, w) dw - bX(0, u) \quad (47)$$

having taken into account (41)<sub>1</sub>.

The proof of all cases above is followed by solving these two equations in  $F(u), G(u)$  with respect to the initial condition  $X(0, u)$ .

For instance, for the first case (1), there follows

$$\begin{aligned} KG(u) &= X(0, u) - F(u), \\ F(u) &= -\frac{1}{b/a - 1/\lambda} \int_{D_u} \psi(w, u) X(0, w) dw \\ &\quad + \frac{b/a}{b/a - 1/\lambda} X(0, u), \end{aligned} \quad (48)$$

that is

$$\begin{aligned} KG(u) &= \frac{1}{1 - \lambda b/a} \left[ X(0, u) - \lambda \int_{D_u} \psi(w, u) X(0, w) dw \right], \\ F(u) &= \frac{\lambda b/a}{\lambda b/a - 1} \left[ X(0, u) - \frac{a}{b} \int_{D_u} \psi(w, u) X(0, w) dw \right] \end{aligned} \quad (49)$$

so that (42) holds true.

When

$$X(0, u) = \frac{a}{b} \int_{D_u} \psi(w, u) X(0, w) dw \quad (50)$$

which implies  $\lambda = 1$ , from (49), we get a trivial solution of (29), (31), (32) and (47); that is,

$$F(u) = 0, \quad G(u) = 0. \quad (51)$$

Analogously, for the case (2) system (47) becomes

$$\begin{aligned} X(0, u) &= F(u) + KG(u), \\ -F(u) &= \lambda \int_{D_u} \psi(w, u) X(0, w) dw. \end{aligned} \quad (52)$$

However, if  $K \neq 0$ , the integral of the right side of the second equation is  $K$ , while the integral of the first side must be zero.

With similar reasonings, we get the proof of the remaining cases.  $\square$

#### 4. Solution of the System (15)

In this section, we will give the explicit solution of the system (15) under some suitable hypotheses on both the encounter rate  $\eta_{ij}$  and the transition density  $\varphi_{ij}(u_*, u^*, u)$ . Let us assume the symmetry of  $\eta_{ij}$  so that

$$\eta_{11} \stackrel{\text{def}}{=} \eta_{11}, \quad \eta_{22} \stackrel{\text{def}}{=} \eta_{22}, \quad \eta_{10} \stackrel{\text{def}}{=} \eta_{12} = \eta_{21}. \quad (53)$$

Thanks to the previous theorems, and the symmetry of  $\varphi_{ij}(u_*, u^*, u)$  as given by (18), system (15) simplifies, the following.

**Theorem 4.** Let the transition density  $\varphi_{ij}(u_*, u^*, u)$  be defined as

$$\begin{aligned} \varphi_{ij}(u_*, u^*, u) &= \frac{1}{2} a_{ij} [\psi(u_*, u) + \psi(u^*, u)], \quad (i, j = 1, 2) \\ a_{11} &\stackrel{\text{def}}{=} a_{11}, \quad a_{22} \stackrel{\text{def}}{=} a_{22}, \quad a_{10} \stackrel{\text{def}}{=} a_{12} = a_{21}, \end{aligned} \quad (54)$$

which fulfills (7) and the symmetries conditions (18), and the density function  $\psi(w, u)$  such that

$$\frac{1}{2} a_{ij} \int_{D_u} [\psi(u_*, u) + \psi(u^*, u)] du \stackrel{(7)}{=} 1 \quad (55)$$

holds. Equation (15) can be simplified into

$$\begin{aligned} \frac{\partial f_1}{\partial t}(t, u) &= \eta_{11} a_{11} \int_{D_u} \psi(w, u) f_1(t, w) dw \\ &\quad + \frac{1}{2} \eta_{10} a_{10} \int_{D_u} \psi(w, u) [f_1(t, w) + f_2(t, w)] dw \\ &\quad - f_1(t, u) [\eta_{11} + \eta_{10}], \\ \frac{\partial f_2}{\partial t}(t, u) &= \frac{1}{2} \eta_{20} a_{20} \int_{D_u} \psi(w, u) [f_2(t, w) + f_1(t, w)] dw \\ &\quad + \eta_{22} a_{22} \int_{D_u} \psi(w, u) f_2(t, w) dw \\ &\quad - f_2(t, u) [\eta_{20} + \eta_{22}]. \end{aligned} \quad (56)$$

*Proof.* By a substitution of (54) into (15), we get

$$\begin{aligned} \frac{\partial f_1}{\partial t}(t, u) &= \sum_{j=1}^2 \int_{D_u \times D_u} \eta_{1j} a_{1j} [\psi(u_*, u) + \psi(u^*, u)] \\ &\quad \times f_1(t, u_*) f_j(t, u^*) du_* du^* \\ &\quad - f_1(t, u) \sum_{j=1}^2 \int_{D_u} \eta_{1j} f_j(t, u^*) du^*, \end{aligned} \quad (57)$$

$$\begin{aligned} \frac{\partial f_2}{\partial t}(t, u) &= \sum_{j=1}^2 \int_{D_u \times D_u} \eta_{2j} a_{2j} [\psi(u_*, u) + \psi(u^*, u)] \\ &\quad \times f_2(t, u_*) f_j(t, u^*) du_* du^* \\ &\quad - f_2(t, u) \sum_{j=1}^2 \int_{D_u} \eta_{2j} f_j(t, u^*) du^*, \end{aligned}$$

that is,

$$\begin{aligned} \frac{\partial f_1}{\partial t}(t, u) &= \frac{1}{2} \left[ \int_{D_u \times D_u} \eta_{11} a_{11} [\psi(u_*, u) + \psi(u^*, u)] \right. \\ &\quad \times f_1(t, u_*) f_1(t, u^*) du_* du^* \\ &\quad + \int_{D_u \times D_u} \eta_{12} a_{12} [\psi(u_*, u) + \psi(u^*, u)] \\ &\quad \times f_1(t, u_*) f_2(t, u^*) du_* du^* \left. \right] \\ &\quad - f_1(t, u) \left[ \int_{D_u} \eta_{11} f_1(t, u^*) du^* \right. \\ &\quad \left. + \int_{D_u} \eta_{12} f_2(t, u^*) du^* \right], \end{aligned} \quad (58)$$

$$\begin{aligned} \frac{\partial f_2}{\partial t}(t, u) &= \frac{1}{2} \left[ \int_{D_u \times D_u} \eta_{21} a_{21} [\psi(u_*, u) + \psi(u^*, u)] \right. \\ &\quad \times f_2(t, u_*) f_1(t, u^*) du_* du^* \\ &\quad + \int_{D_u \times D_u} \eta_{22} a_{22} [\psi(u_*, u) + \psi(u^*, u)] \\ &\quad \times f_2(t, u_*) f_2(t, u^*) du_* du^* \left. \right] \\ &\quad - f_2(t, u) \left[ \int_{D_u} \eta_{21} f_1(t, u^*) du^* \right. \\ &\quad \left. + \int_{D_u} \eta_{22} f_2(t, u^*) du^* \right], \end{aligned}$$

from which,

$$\begin{aligned} \frac{\partial f_1}{\partial t}(t, u) &= \frac{1}{2} \eta_{11} a_{11} \left[ \int_{D_u \times D_u} \psi(u_*, u) f_1(t, u_*) \right. \\ &\quad \times f_1(t, u^*) du_* du^* \\ &\quad + \int_{D_u \times D_u} \psi(u^*, u) f_1(t, u_*) \\ &\quad \times f_1(t, u^*) du_* du^* \left. \right] \\ &\quad + \frac{1}{2} \eta_{12} a_{12} \left[ \int_{D_u \times D_u} \psi(u_*, u) f_1(t, u_*) \right. \\ &\quad \times f_2(t, u^*) du_* du^* \\ &\quad + \int_{D_u \times D_u} \psi(u^*, u) f_1(t, u_*) \\ &\quad \times f_2(t, u^*) du_* du^* \left. \right] \end{aligned}$$

$$\begin{aligned} &\quad - f_1(t, u) \left[ \eta_{11} \int_{D_u} f_1(t, u^*) du^* \right. \\ &\quad \left. + \eta_{12} \int_{D_u} f_2(t, u^*) du^* \right], \end{aligned}$$

$$\begin{aligned} \frac{\partial f_2}{\partial t}(t, u) &= \frac{1}{2} \eta_{21} a_{21} \left[ \int_{D_u \times D_u} \psi(u_*, u) f_2(t, u_*) \right. \\ &\quad \times f_1(t, u^*) du_* du^* \\ &\quad + \int_{D_u \times D_u} \psi(u^*, u) f_2(t, u_*) \\ &\quad \times f_1(t, u^*) du_* du^* \left. \right] \end{aligned}$$

$$\begin{aligned} &\quad + \frac{1}{2} \eta_{22} a_{22} \left[ \int_{D_u \times D_u} \psi(u_*, u) f_2(t, u_*) \right. \\ &\quad \times f_2(t, u^*) du_* du^* \\ &\quad + \int_{D_u \times D_u} \psi(u^*, u) f_2(t, u_*) \\ &\quad \times f_2(t, u^*) du_* du^* \left. \right] \end{aligned}$$

$$\begin{aligned} &\quad - f_2(t, u) \left[ \int_{D_u} \eta_{21} f_1(t, u^*) du^* \right. \\ &\quad \left. + \int_{D_u} \eta_{22} f_2(t, u^*) du^* \right]. \end{aligned} \quad (59)$$

There follows

$$\begin{aligned} \frac{\partial f_1}{\partial t}(t, u) &= \frac{1}{2} \eta_{11} a_{11} \left[ \int_{D_u} \psi(u_*, u) f_1(t, u_*) du_* \right. \\ &\quad \times \int_{D_u} f_1(t, u^*) du^* \\ &\quad + \int_{D_u} \psi(u^*, u) f_1(t, u^*) du^* \\ &\quad \times \left. \int_{D_u} f_1(t, u_*) du_* \right] \\ &+ \frac{1}{2} \eta_{12} a_{12} \left[ \int_{D_u} \psi(u_*, u) f_1(t, u_*) du_* \right. \\ &\quad \times \int_{D_u} f_2(t, u^*) du^* \\ &\quad + \int_{D_u} \psi(u^*, u) f_2(t, u^*) du^* \\ &\quad \times \left. \int_{D_u} f_1(t, u_*) du_* \right] \\ &- f_1(t, u) \left[ \eta_{11} \int_{D_u} f_1(t, u^*) du^* \right. \\ &\quad \left. + \eta_{12} \int_{D_u} f_2(t, u^*) du^* \right], \end{aligned}$$

$$\begin{aligned} \frac{\partial f_2}{\partial t}(t, u) &= \frac{1}{2} \eta_{21} a_{21} \left[ \int_{D_u} \psi(u_*, u) f_2(t, u_*) du_* \right. \\ &\quad \times \int_{D_u} f_1(t, u^*) du^* \\ &\quad + \int_{D_u} \psi(u^*, u) f_1(t, u^*) du^* \\ &\quad \times \left. \int_{D_u} f_2(t, u_*) du_* \right] \\ &+ \frac{1}{2} \eta_{22} a_{22} \left[ \int_{D_u} \psi(u_*, u) f_2(t, u_*) du_* \right. \\ &\quad \times \int_{D_u} f_2(t, u^*) du^* \\ &\quad + \int_{D_u} \psi(u^*, u) f_2(t, u^*) du^* \\ &\quad \times \left. \int_{D_u} f_2(t, u_*) du_* \right] \end{aligned}$$

$$\begin{aligned} &- f_2(t, u) \left[ \eta_{21} \int_{D_u} f_1(t, u^*) du^* \right. \\ &\quad \left. + \eta_{22} \int_{D_u} f_2(t, u^*) du^* \right]. \end{aligned} \tag{60}$$

According to (5), we get

$$\begin{aligned} \frac{\partial f_1}{\partial t}(t, u) &= \frac{1}{2} \eta_{11} a_{11} \left[ \int_{D_u} \psi(u_*, u) f_1(t, u_*) du_* \right. \\ &\quad \left. + \int_{D_u} \psi(u^*, u) f_1(t, u^*) du^* \right] \\ &+ \frac{1}{2} \eta_{12} a_{12} \left[ \int_{D_u} \psi(u_*, u) f_1(t, u_*) du_* \right. \\ &\quad \left. + \int_{D_u} \psi(u^*, u) f_2(t, u^*) du^* \right] \\ &- f_1(t, u) [\eta_{11} + \eta_{12}], \end{aligned} \tag{61}$$

$$\begin{aligned} \frac{\partial f_2}{\partial t}(t, u) &= \frac{1}{2} \eta_{21} a_{21} \left[ \int_{D_u} \psi(u_*, u) f_2(t, u_*) du_* \right. \\ &\quad \left. + \int_{D_u} \psi(u^*, u) f_1(t, u^*) du^* \right] \\ &+ \frac{1}{2} \eta_{22} a_{22} \left[ \int_{D_u} \psi(u_*, u) f_2(t, u_*) du_* \right. \\ &\quad \left. + \int_{D_u} \psi(u^*, u) f_2(t, u^*) du^* \right] \\ &- f_2(t, u) [\eta_{21} + \eta_{22}]. \end{aligned}$$

Thus, we obtain, by a variable change,

$$\begin{aligned} \frac{\partial f_1}{\partial t}(t, u) &= \eta_{11} a_{11} \int_{D_u} \psi(w, u) f_1(t, w) dw \\ &\quad + \frac{1}{2} \eta_{12} a_{12} \int_{D_u} \psi(w, u) [f_1(t, w) + f_2(t, w)] dw \\ &\quad - f_1(t, u) [\eta_{11} + \eta_{12}], \\ \frac{\partial f_2}{\partial t}(t, u) &= \frac{1}{2} \eta_{21} a_{21} \left[ \int_{D_u} \psi(w, u) [f_2(t, w) + f_1(t, w)] dw \right] \\ &\quad + \eta_{22} a_{22} \int_{D_u} \psi(w, u) f_2(t, w) dw \\ &\quad - f_2(t, u) [\eta_{21} + \eta_{22}] \end{aligned} \tag{62}$$

so that (56) follows.  $\square$



4.1. *Pure Competition Model.* We will consider the solution of (56) when, together with the hypotheses (53), (54)<sub>2</sub>, some more conditions are given on the parameters.

According to (26), let us assume

$$\varphi_{ij}(u^*, u_*, u) \stackrel{\text{def}}{=} \frac{1}{2} a_{ij} [\psi(u_*, u) + \psi(u^*, u)], \quad (63)$$

$$(a_{ij} \geq 0; i, j = 1, 2)$$

together with the symmetries conditions (18).

If we define

$$\eta_1 \stackrel{\text{def}}{=} \eta_{11}, \quad \eta_2 \stackrel{\text{def}}{=} \eta_{22}, \quad \eta_0 \stackrel{\text{def}}{=} \eta_{12} = \eta_{21}, \quad (64)$$

$$a_1 \stackrel{\text{def}}{=} a_{11}, \quad a_2 \stackrel{\text{def}}{=} a_{22}, \quad a_0 \stackrel{\text{def}}{=} a_{12} = a_{21},$$

we will discuss only the following hypotheses:

$$a \stackrel{\text{def}}{=} a_1 = a_2 = 0, \quad (65)$$

$$\eta_1 = \eta_2 = \eta \neq 0, \quad \eta_0 a_0 \neq 0, \quad (66)$$

which seem to have some biological interpretations, being the pure encounter-competition model. This happens when the transition of state arises only when particles of one population interact only with an individual of the other population. In this case, individuals of one population do not interact with individuals of the same population.

**Theorem 5.** *Let the transition density  $\varphi_{ij}(u_*, u^*, u)$  be defined as*

$$\varphi_{ij}(u_*, u^*, u) = \frac{1}{2} a_{ij} [\psi(u_*, u) + \psi(u^*, u)], \quad (i, j = 1, 2) \quad (67)$$

with  $a_{ij}$  as given by (64), (65). This definition of the transition density fulfills (7) and the symmetries conditions (18). The density function  $\psi(w, u)$  is such that

$$\int_{D_u} \psi(w, u) du = \frac{1}{a}. \quad (68)$$

By assuming

$$a_1 = a_2 = 0, \quad \eta_1 = \eta_2 = \eta \neq 0 \quad (69)$$

and for  $a_0, \eta_0$ , the condition

$$\eta_0 a_0 \neq 0 \quad (70)$$

system (56) becomes

$$\frac{\partial f_1}{\partial t}(t, u) = \frac{1}{2} \eta_0 a_0 \int_{D_u} \psi(w, u) [f_1(t, w) + f_2(t, w)] dw$$

$$- f_1(t, u) [\eta + \eta_0],$$

$$\frac{\partial f_2}{\partial t}(t, u) = \frac{1}{2} \eta_0 a_0 \int_{D_u} \psi(w, u) [f_2(t, w) + f_1(t, w)] dw$$

$$- f_2(t, u) [\eta + \eta_0], \quad (71)$$

and its solution is given by

$$f_1(t, u) = e^{-[\eta + \eta_0]t} [F(u) e^{[\eta_0 a_0 / \lambda]t} + H(u)] + G(u),$$

$$f_2(t, u) = e^{-[\eta + \eta_0]t} [F(u) e^{[\eta_0 a_0 / \lambda]t} - H(u)] + G(u),$$

$$F(u) = \lambda \frac{\eta + \eta_0}{\eta_0 a_0} \int_{D_u} \psi(w, u) F(w) dw, \quad \int_{D_u} F(u) du = 0,$$

$$G(u) = \frac{\eta_0}{\eta + \eta_0} a_0 \int_{D_u} \psi(w, u) G(w) dw, \quad \int_{D_u} G(u) du = 1,$$

$$\int_{D_u} \psi(w, u) dw = \frac{\eta + \eta_0}{\eta_0 a_0},$$

$$\int_{D_u} H(w) dw = 0. \quad (72)$$

*Proof.* From (56), we have

$$\frac{\partial f_1}{\partial t}(t, u) = \frac{1}{2} \eta_0 a_0 \int_{D_u} \psi(w, u) [f_1(t, w) + f_2(t, w)] dw$$

$$- f_1(t, u) [\eta + \eta_0],$$

$$\frac{\partial f_2}{\partial t}(t, u) = \frac{1}{2} \eta_0 a_0 \int_{D_u} \psi(w, u) [f_2(t, w) + f_1(t, w)] dw$$

$$- f_2(t, u) [\eta + \eta_0], \quad (73)$$

from which by linear combination, we get

$$\frac{\partial}{\partial t} [f_1(t, u) + f_2(t, u)]$$

$$= \eta_0 a_0 \int_{D_u} \psi(w, u) [f_1(t, w) + f_2(t, w)] dw$$

$$- [f_1(t, u) + f_2(t, u)] [\eta + \eta_0],$$

$$\frac{\partial}{\partial t} [f_1(t, u) - f_2(t, u)] = - [f_1(t, u) - f_2(t, u)] [\eta + \eta_0]. \quad (74)$$

With the above positions, we have

$$\frac{\partial}{\partial t} X(t, u) = \eta_0 a_0 \int_{D_u} \psi(w, u) X(t, w) dw - X(t, u) [\eta + \eta_0],$$

$$\frac{\partial}{\partial t} Y(t, u) = -Y(t, u) [\eta + \eta_0] \quad (75)$$



so that, by taking into account Theorem 2, it is

$$\begin{aligned}
 X(t, u) &= F(u) e^{-[\eta+\eta_0-\eta_0 a_0/\lambda]t} + G(u), \\
 F(u) &= \lambda \frac{\eta + \eta_0}{\eta_0 a_0} \int_{D_u} \psi(w, u) F(w) dw, \\
 \int_{D_u} F(u) du &= 0, \\
 G(u) &= \frac{\eta_0}{\eta + \eta_0} a_0 \int_{D_u} \psi(w, u) G(w) dw, \\
 \int_{D_u} G(u) du &= 1, \\
 \int_{D_u} \psi(w, u) dw &= \frac{\eta + \eta_0}{\eta_0 a_0}, \\
 Y(t, u) &= H(u) e^{-[\eta+\eta_0]t}, \\
 \int_{D_u} H(w) dw &= 0
 \end{aligned} \tag{76}$$

from which (72) follows. □

*Example 6.* A transition density, which is compatible with this case, is the following:

$$\begin{aligned}
 \varphi_{ij}(u_*, u^*, u) &= \frac{a_0}{2} (1 - \delta_{ij}) [\psi(u_*, u) + \psi(u^*, u)], \\
 &\quad (i, j = 1, 2)
 \end{aligned} \tag{77}$$

with  $\delta_{ij}$ , Kronecker symbol.

### 5. Application to Lotka-Volterra Model

In this section, we will study a coupled system (6) where the macroscopic equations are the Lotka-Volterra equations (6)<sub>1</sub>. Concerning the coupling stochastic parameter  $\mu[f]$ , we have to define the functional  $\mu$  in (2), (6) depending on the “distance” between distributions; that is,

$$\mu[f_i, f_j](t) = \mu(|f_i - f_j|)(t) \tag{78}$$

with

$$\begin{aligned}
 0 \leq \mu[f_i, f_j](t) &\leq 1, \quad \forall u \in D_u \wedge t \in T, \\
 \mu[f_i, f_j](t) = 1 &\iff f_i = f_j, \\
 \mu[f_i, f_j](t) = 0 &\iff f_i = 0 \vee f_j = 0,
 \end{aligned} \tag{79}$$

where the maximum learning result is obtained when the second population is able to reproduce the distribution of the first one:  $f_1 = f_2$ , while the minimum learning is achieved when one distribution is vanishing.

In some recent papers; it has been assumed [4, 5] that

$$\begin{aligned}
 \mu[f_i, f_j](t) &= \mu(|f_i - f_j|)(t) \\
 &= 1 - \int_{D_u} |f_1(t, u) - f_2(t, u)| du.
 \end{aligned} \tag{80}$$

In this case, it is  $\mu = 1$ , when  $f_1 = f_2$ ; otherwise  $\mu \neq 1$  with  $\mu \downarrow 0$ , depending on the time evolution of the distance between  $f_1$  and  $f_2$ .

Let us notice that  $\mu$  is the coupling term which links the macroscopic model (6)<sub>1</sub> to the microscopic model (6)<sub>2</sub>. There follows that the solution of the hybrid system (6) depends on the coupling parameter  $\mu$  (80) which follows from the solution of (15). System (15) is a system of two nonlinear integrodifferential equations constrained by the conditions (7), (5). Moreover, its solution depends also the constant encounter rate  $\eta_{ij}$ , on the transition density function  $\varphi_{ij}$ , and the initial conditions  $f_i(0, u)$ . In the following section, we will study the solution of (6), under some suitable, but not restrictive, hypotheses on  $\varphi_{ij}$ .

Under the hypotheses of Theorem 5 and the solution (72), we have

$$f_1(t, u) - f_2(t, u) = \begin{cases} 2e^{-(\eta+\eta_0)t} H(u), & H(u) \neq 0, \\ 0, & H(u) = 0. \end{cases} \tag{81}$$

Let us take

$$D_u = [0, 1], \quad \eta + \eta_0 = p > 0, \quad H(u) = \sin 2\pi u \tag{82}$$

so that (72) are fulfilled. We have

$$\mu[f](t) = 1 - 2e^{-pt} \left[ \int_0^{1/2} \sin 2\pi u du - \int_{1/2}^1 \sin 2\pi u du \right], \tag{83}$$

that is

$$\mu[f](t) = \begin{cases} 1 - \frac{1}{\pi} e^{-pt}, & \sin 2\pi u \neq 0, \quad u \in [0, 1], \\ 1, & u \in \left\{0, \frac{1}{2}, 1\right\}. \end{cases} \tag{84}$$

In the last case we have the usual Lotka-Volterra system, therefore, we will investigate the first case. Thus, according to (6), we have the system

$$\begin{aligned}
 \frac{dn_1}{dt} &= \alpha n_1 - \left(1 - \frac{1}{\pi} e^{-pt}\right) n_1 n_2, \\
 \frac{dn_2}{dt} &= -\beta n_2 + \gamma n_1 n_2
 \end{aligned} \tag{85}$$

with

$$\alpha \geq 0, \quad \beta \geq 0, \quad \gamma \geq 0. \tag{86}$$

The numerical solution of this system depends on both the parameters  $\alpha, \beta, \gamma, p$  and on the initial conditions  $n_1(0), n_2(0)$ . We can see from Figures 1 and 2 that albeit the initial aggressive population  $n_2$  is greater than  $n_1$ , the first population can increase and keep nearly always over  $n_2$  in the quasilinear case in Figure 1(a) or always under  $n_2$  in presence of a strong nonlinearity in Figure 1(b).

If we invert the initial conditions so that the initial population of  $n_1$  is greater than  $n_2$ , we can see that in case of quasilinear conditions (see Figure 2(a)) the population  $n_1$  after some short time becomes lower than  $n_2$ . For a strong nonlinearity, instead after an initial growth  $n_1$ , it

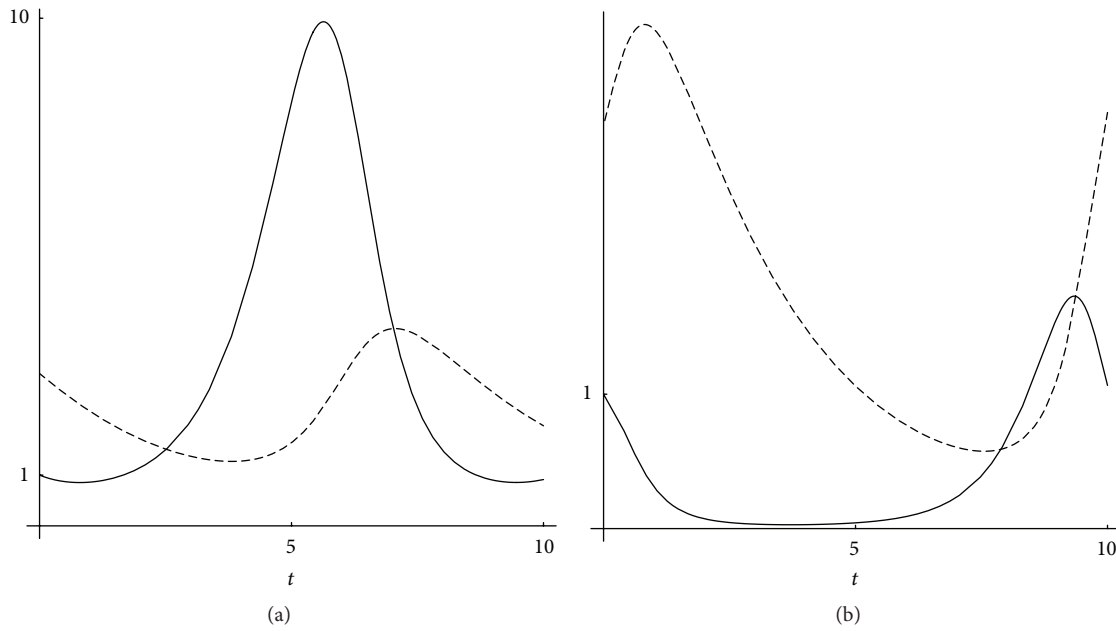


FIGURE 1: Numerical solution of  $n_1(t)$  (plain) and  $n_2(t)$  (dashed) of the system (85) with initial conditions  $n_1(0) = 1, n_2(0) = 3$ , for  $t \leq 10$ , and parameters  $\alpha = 1.636, \beta = 0.3743$  ((a) with parameters  $\gamma = 0.1, p = 0.01$ ) and ((b) with parameters  $\gamma = 0.9, p = 0.9$ ).

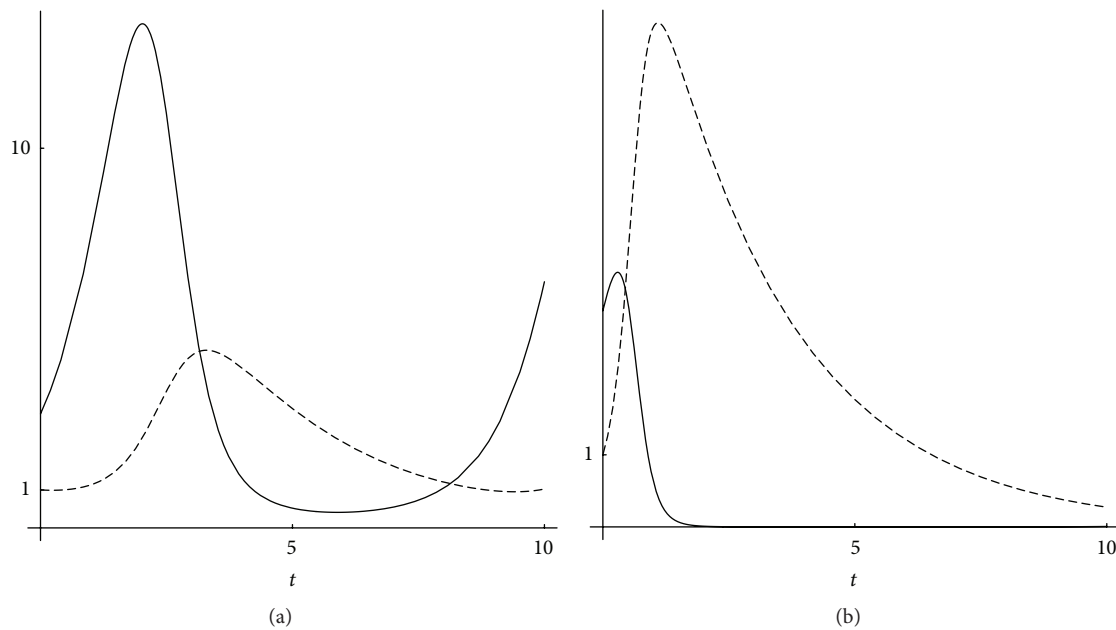


FIGURE 2: Numerical solution of  $n_1(t)$  (plain) and  $n_2(t)$  (dashed) of the system (85) with initial conditions  $n_1(0) = 3, n_2(0) = 1$ , for  $t \leq 10$  and parameters  $\alpha = 1.636, \beta = 0.3743$  ((a) with parameters  $\gamma = 0.1, p = 0.01$ ) and ((b) with parameters  $\gamma = 0.9, p = 0.9$ ).

tends to zero in a short time, while the second population grows very fast and becomes the prevalent population in Figure 2(b).

**6. Conclusion**

In this paper, the hybrid competition model has been solved under some assumptions on the transition density. In the simple case of Lotka-Volterra, the numerical solution gives

some significant and realistic insights on the evolution of competing populations.

**References**

[1] N. Bellomo, *Modeling Complex Living Systems—Kinetic Theory and Stochastic Game Approach*, Springer, Boston, Mass, USA, 2008.

- [2] A. Bellouquid and M. Delitala, *Mathematical Modeling of Complex Biological Systems. A Kinetic Theory Approach*, Springer, Boston, Mass, USA, 2006.
- [3] C. Bianca and N. Bellomo, *Towards a Mathematical Theory of Multiscale Complex Biological Systems*, World Scientific, Singapore, 2010.
- [4] C. Cattani and A. Ciancio, “Qualitative analysis of second-order models of tumor-immune system competition,” *Mathematical and Computer Modelling*, vol. 47, no. 11-12, pp. 1339–1355, 2008.
- [5] C. Cattani and A. Ciancio, “Hybrid two scales mathematical tools for active particles modelling complex systems with learning hiding dynamics,” *Mathematical Models and Methods in Applied Sciences*, vol. 17, no. 2, pp. 171–187, 2007.
- [6] C. Cattani and A. Ciancio, “Separable transition density in the hybrid model for tumor-immune system competition,” *Computational and Mathematical Methods in Medicine*, vol. 2012, Article ID 610124, 6 pages, 2012.
- [7] D. Abrams, “The evolution of predator-prey systems: theory and evidence,” *Annual Review of Ecology, Evolution, and Systematics*, vol. 31, Article ID 79105, 2000.
- [8] H. P. de Vladar and J. A. González, “Dynamic response of cancer under the influence of immunological activity and therapy,” *Journal of Theoretical Biology*, vol. 227, no. 3, pp. 335–348, 2004.
- [9] A. d’Onofrio, “A general framework for modeling tumor-immune system competition and immunotherapy: mathematical analysis and biomedical inferences,” *Physica D*, vol. 208, no. 3-4, pp. 220–235, 2005.
- [10] A. d’Onofrio, “Metamodeling tumor-immune system interaction, tumor evasion and immunotherapy,” *Mathematical and Computer Modelling*, vol. 47, no. 5-6, pp. 614–637, 2008.
- [11] U. Forý’s, “Marchuk’s model of immune system dynamics with application to tumor growth,” *Journal of Theoretical Medicine*, vol. 4, no. 1, pp. 85–93, 2002.
- [12] M. Galach, “Dynamics of the tumor-immune system competition—the effect of time delay,” *International Journal of Applied Mathematics and Computer Science*, vol. 13, no. 3, pp. 395–406, 2003.
- [13] R. A. Gatenby, T. L. Vincent, and R. J. Gillies, “Evolutionary dynamics in carcinogenesis,” *Mathematical Models & Methods in Applied Sciences*, vol. 15, no. 11, pp. 1619–1638, 2005.
- [14] S. A. Gourley and Y. Kuang, “A stage structured predator-prey model and its dependence on maturation delay and death rate,” *Journal of Mathematical Biology*, vol. 49, no. 2, pp. 188–200, 2004.
- [15] M. Kolev, “A mathematical model of cellular immune response to leukemia,” *Mathematical and Computer Modelling*, vol. 41, no. 10, pp. 1071–1081, 2005.
- [16] V. A. Kuznetsov, I. A. Makalkin, M. A. Taylor, and A. S. Perelson, “Nonlinear dynamics of immunogenic tumors: parameter estimation and global bifurcation analysis,” *Bulletin of Mathematical Biology*, vol. 56, no. 2, pp. 295–321, 1994.
- [17] N. V. Stepanova, “Course of the immune reaction during the development of a malignant tumour,” *Biophysics*, vol. 24, no. 5, pp. 917–923, 1979.
- [18] O. Sotolongo-Costa, L. Morales Molina, D. Rodríguez Perez, J. C. Antoranz, and M. Chacón Reyes, “Behavior of tumors under nonstationary therapy,” *Physica D*, vol. 178, no. 3-4, pp. 242–253, 2003.
- [19] T. E. Wheldon, *Mathematical Models in Cancer Research*, Hilger, Boston, Mass, USA, 1988.
- [20] H. R. Thieme, *Mathematics in Population Biology*, Princeton, NJ, USA, 2003.



# Hindawi

Submit your manuscripts at  
<http://www.hindawi.com>

