

# Generalized hybrid kinetic mathematical model for population dynamics

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**Abstract.** In this paper a generalized kinetic model for the analysis of population dynamics is given. Starting from the classical kinetic model, we propose an integro-differential equation as suitable generalization of known models, aiming to include, as special cases, the most popular models for population dynamics such as the kinetic model for cells competition [2, 4, 5, 6, 7, 9], the master equations model [17, 3, 24, 27], the allergy-immune system competition (CD8T) [25].

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## 1 Introduction

Competition models for population dynamics are typically represented by some non-linear dynamical systems of Lotka-Volterra type and slightly modified versions thereof, such as delay equations, discrete models [1, 2, 3, 4, 6, 7, 8, 11, 12, 14, 15, 16, 18, 19, 20, 21, 22, 23, 26, 28]. Sometime the original Lotka-Volterra equations are modified by introducing some additional parameters aiming to explain some continuously incoming experimental observations and clinical trials. However, by comparing the experimental data with the resulting values of the mathematical models we are forced to notice that there exists some bias between any theoretical model and the experimental data, mostly due to the existence of some uncertainty in the population dynamics. So that we are obliged to take into account also some uncertainty, in the dynamics of populations, by adding some stochastic variables into the classical dynamical models. Because of this, some recent approaches to the population dynamics were built on probabilistic models with stochastic functions/equations. Some of them are simply based on the computation of the distribution/probability function as the solution of a suitable additional (constitutive) equation. Among the many available models and equations it is worth to remind the stochastic type (Ito equation), the probability evolution among discrete states (Master equation) [17, 3, 24, 27], and the hybrid integro-differential kinetic equations [4, 5, 6, 7]. In this case the Boltzmann equations for the computation of the population distribution function are coupled with a non-linear dynamical system of population dynamics. The distribution functions for each

competing population is obtained as solution, of some partial differential equations, depending both on time and on the biological activity at a given macroscopic scale. So that the concept of scale becomes the key point in modelling biological activity.

In the cell populations dynamics and with respect the multiscale approach there exists, and has been deeply investigated [2, 4, 5, 6, 7, 9, 10, 13, 14, 16, 18, 26, 28], at least the two scales model where:

1. The microscopic scale, is the scale where individual cells interact. It is characterized by the evolution on time of the number of cells, and the density of populations are obtained as solution of Volterra type ordinary (nonlinear) differential equations.
2. The macroscopic scale, is the scale where variable sets of activated individuals interact. It is characterized by the evolution of the activity from one state to another. During the evolution the cardinality of the sets is changing, so that we have a well defined distribution density function which describes the activity of cells at a given time. The distribution function is defined as the probability to find a given cell at a time  $t$  and at a specific biological state activity.

From this point of view the competition between populations can be seen both as the transition of cells from one state to another, thus allowing the changing of the distribution function (at a macroscopic state), and as the evolving number density of cells at a microscopic state. With this two scale model, also called hybrid model [4, 5, 6], two set of equations are needed: some suitable partial derivative equations at the macroscopic scale for the computation of the distribution function, which is a function of two variables (time and biological state), and a set of ordinary differential equations at a microscopic scale for the computation of the density number of cell population, which is a function of only one variable (time  $t$ ). Sometimes the transition of the state activity, at a macroscopic scale, is modeled as a stochastic discrete state transition as described by the so-called master equation [17, 3, 27, 24]

In the hybrid system[6, 4, 5, 9] the link between the microscopic and the macroscopic scale is realized by means of a parameter defined by the solution of the partial derivative equations and by the knowledge of the distribution function, to be included as a known function of time into the ordinary Lotka-Volterra type differential equations. In this simple approach this parameter partially explains the uncertainty, due to the evolution of the distribution function and it can be a-priori taken as a stochastic parameter.

In this paper the two scale competition hybrid model [2, 4, 5, 6, 9] is proposed in the framework of hybrid kinetic models. In particular, a model of biological interaction based on scale transition (macro to micro) and transition on the biological states from a stochastic behavior to a deterministic will be discussed. More generally, in order to take into account some of the most popular methods in population dynamics, will be also proposed some suitable generalization of the hybrid model aiming to include, as special cases, the master equation and the immune response.

## 2 Hybrid kinetic model for the tumor-immune system competition

The hybrid kinetic model is based on a two scale approach to the analysis of competition between two populations, such as cancer cells and immune system. In the biological competition, we can roughly identify at least two scale at a macroscopic and microscopic level respectively. In the microscopic scale single cells interact with the remaining so that this scale is characterized by the evolution on time of the number of cells modeled by some nonlinear ordinary differential equations (like Lotka-Volterra equations).

At a macroscopic scale the competition between two populations is studied by analyzing the time variation of some probability density distributions. This function defines the probability to find at a time  $t$  a cell with a given biological state. The state transition is due to the encounters with other cells. These functions can be obtained by solving a set of nonlinear partial differential equations when the state transition is continuously depending on time or by ordinary equations when the time steps are sampled, as in the so-called master equations.

In the first case, one of the most popular model for cells competition is the kinetic model which is shortly summarized as follows.

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

$$(2.1) \quad \mu = \mu[f_i(t, u)] \quad , \quad (\mu[f_i(t, u)] : \mathbb{R}_+ \rightarrow \mathbb{R}_+).$$

**Definition 2.1** (Density distribution function). The description of the overall distribution over the microscopic state within each populations is given by the density distribution function:

$$(2.2) \quad f_i = f_i(t, u), \quad (f_i(t, u) : [0, T] \times D_u \rightarrow \mathbb{R}_+, \quad D_u \subseteq \mathbb{R})$$

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  $[u, u + du]$ :

$$(2.3) \quad d\mu = f_i(t, u) du .$$

Moreover, it is

$$(2.4) \quad \forall i, \quad \forall t \geq 0 : f_i(t, u) \geq 0 \quad , \quad \int_{D_u} f_i(t, u) du = 1 \quad .$$

In this section we consider 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 is referred to a specific

case where the second population attempts to learn about a first population which escapes by modifying its appearance. Specifically, the hybrid evolution equations can be formally written as follows [4, 5, 6];

$$(2.5) \quad \begin{cases} \frac{dn_i}{dt} = G_i(n_1, n_2; \mu[f]) , \\ \frac{\partial f_i}{\partial t} = \mathcal{A}_i[f], \end{cases}$$

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, (2.5) denotes an hybrid system of a deterministic system coupled with a microscopic system statistically described by the kinetic theory approach. In the following the evolution of density distribution will be taken within the kinetic theory (Boltzmann-like equations).

The derivation of (2.5)<sub>2</sub> can be obtained by starting from a detailed analysis of microscopic interactions. Specifically, let us consider binary interactions 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 modeling of microscopic interactions is supposed to lead to the following quantities:

**Definition 2.2** (Encounter rate). The encounter rate is a parameter which depends for each pair of interacting populations on a suitable average of the relative velocity  $\eta_{ij}$ , with  $i, j = 1, 2$ .

**Definition 2.3** (Transition density function). The transition density function is the function  $\varphi_{ij}(u_*, u^*, u)$  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

$$(2.6) \quad \forall i, j, \quad \forall u_*, u^* : \int_{D_u} \varphi_{ij}(u_*, u^*, u) du = 1 \quad , \quad \varphi_{ij}(u_*, u^*, u) > 0$$

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

$$(2.7) \quad \forall u_*, u^* : \int_{D_u} \varphi_{ij}(u_*, u^*, u) du = 0 \iff \varphi_{ij}(u_*, u^*, u) = 0.$$

The state transition

$$u_* \xrightarrow{u^*} u$$

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

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

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

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

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 other particles of its own population. Instead, the individuals of the  $j$ -th population change its state only due to the interaction with the other  $i$ -th population. They do not interfere 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 particle both from its own  $j$ -th population and from the  $i$ -th population so that

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

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

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

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

$$(2.8) \quad \varphi_{ij}(u_*, u^*, u) = 0 \quad , \quad (i = j) .$$

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 [4, 5, 6, 7, 9], it yields the following class of evolution equations:

$$(2.9) \quad \boxed{\begin{aligned} \frac{\partial f_i}{\partial t}(t, u) &= \sum_{j=1}^2 \int_{D_u \times D_u} \eta_{ij} \varphi_{ij}(u_*, u^*, u) f_i(t, u_*) f_j(t, u^*) du_* du^* \\ &- f_i(t, u) \sum_{j=1}^2 \int_{D_u} \eta_{ij} f_j(t, u^*) du^* , \end{aligned}} \quad (i = 1, 2)$$

which can be formally written as (2.5)<sub>2</sub>.

## 2.1 Coupling with ordinary differential equations for cells competition

From the solution of this system one can define a parameter (or a set of parameters) which define the time evolving distance between the distributions. These parameters

characterize the microscopic scale, typically represented by a nonlinear ordinary differential system for the competition of two populations (Lotka-Volterra and similar ones).

In the case of tumor cells immune system it has been considered only one parameter which has been taken as representative of [6, 4, 5] a stochastic process. The 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 or similar more realistic competition models (see e.g. [1, 14, 11, 12, 15, 16, 18, 19, 20, 21, 22, 23, 28, 26, 8])

$$(2.10) \quad \begin{cases} \frac{dn_i}{dt} = G_i(n_1, n_2; \mu[f]) , \\ \frac{\partial f_i}{\partial t} = \mathcal{A}_i[f], \end{cases}$$

For the Volterra equations we have

$$(2.11) \quad \begin{cases} \frac{dN}{dt} = aN - \mu(f)NP \\ \frac{dP}{dt} = bP - cNP \\ \frac{\partial f_i}{\partial t} = \mathcal{A}_i[f] \quad , \quad (i = 1, 2) . \end{cases}$$

### 3 Allergy-immune system competition: primary *CD8T* cell immune response

Another example of biological competition and population dynamics can be found in the immune response to a pathogen encounter. The primary *CD8 T*-cell response is biologically modeled by an initial increasing of cells followed by a relaxation. From mathematical point of view the immune response can be modeled by an hybrid system of three nonlinear ordinary differential equations coupled with a linear partial differential equation [25], as follows.

Let  $f(t, u)$  be the number of effector cells at time  $t$  and age  $u$ ,  $\rho(u)$  the cell division rate and  $d(u)$  the death rate of effector cells at the age  $u$ , the partial differential equation for  $f(t, u)$  is [25]

$$(3.1) \quad \boxed{\frac{\partial}{\partial t} f(t, u) + \frac{\partial}{\partial u} f(t, u) = [d(u) - \rho(u)] f(t, u)}$$

In the immune response the density  $f(t, u)$  is coupled with a set of nonlinear ordinary differential equations for the number  $N(t)$  of *T*-cells at time  $t$  and the number of pathogens  $P(t)$ . However, it should be noticed from Eq. (3.1) that also in this case likewise the kinetic equations the macroscopic behavior is described by a density

distribution function  $f(t, u)$  which is a solution of a linear equation. When  $f(t, u)$  is independent on the activity variable  $u$ , then from (3.1) we re-obtain the simplest equation for modeling population dynamics which is the Malthus equation. From this we can assume, and it will be shown in the following sections, that population dynamics, at a macroscopic scale should be based on the same model which describes the evolving density distribution. In other words the equation from where to obtain the density distribution function must be the same for almost all kind of population dynamics models.

## 4 Master equation

As another example of population dynamics, let us consider in this section another equation which is used for discrete population dynamics and in presence of some stochastic behavior. Let us consider a biological system which is characterized by a discrete finite set of phenomenological states  $\sigma_i$ ,  $i = 1, \dots, n < \infty$ . Each state is characterized by the probability  $f_i$  that the system falls into that state, at a given time  $t$ . The transition from one state into another is given a-priori and is characterized by a given transition matrix  $w_{ik}$ ,  $i, k = 1, \dots, n < \infty$ . So that the master equations can be written as follows [3, 17, 27]

$$(4.1) \quad \boxed{\frac{d}{dt}f_i(t) = \sum_{k=1, \dots, n} w_{ik}f_k(t) \quad , \quad i = 1, \dots, n}$$

with

$$\sum_{k=1, \dots, n} w_{ik} = 0 \quad \forall i .$$

Thus we get the more familiar form of the master equations

$$(4.2) \quad \frac{d}{dt}f_i(t) = \sum_{\substack{k=1, \dots, n \\ k \neq i}} w_{ik}f_k(t) - w_{ki}f_i(t) \quad i = 1, \dots, n$$

The master equation is a system of first order differential equations for the probability distribution of state transition. The transition matrix  $w_{ik}$  is a constant matrix, but in the more general not stationary case we can assume that it is time depending. This equation has been successfully applied to the investigation of granular media and cells transition [3]. The simplest stationary case is described by a set of linear differential equations which can be easily solved.

## 5 Generalized model

In order to extend the previously considered models to a more general set of equations we will focus only on the macroscopic scale. In fact, at the microscopic scale the competition of single individuals can be still considered within the framework of Volterra equations and its generalization. Instead at the macroscopic scale we will try to take into account some uncertainty of the evolving distribution functions which

lead us to consider some stochastic equations. This generalization is done in a such a way that the above models can be obtained from the general scheme by some simplifying hypotheses. In particular, it is expected that the master equations representing transition from discrete phases, the competition of immune system and pathogene agents, and the kinetic equations for continuous transition of states will be recovered from the general equations.

By modeling the competition of populations we should start again from the idea that this can be modeled at different scales. Cells of different populations are characterized by biological functions heterogeneously distributed and they are represented by some probability distribution.

The interacting system is still characterized at a macroscopic scale by a density distribution functions  $f_i(t, u)$  which describes the cells activity during the interaction-proliferation.

At this level the distribution of cells fulfill some partial differential equations taken from the classical kinetic theory. In this case we have the following theorem.

**Theorem 5.1** (Generalized equations for the density distribution function). *The more general model of  $n$  interacting populations, each one represented by a density distribution function consists in a nonlinear system of partial differential equations:*

$$(5.1) \quad \frac{\partial f_i}{\partial t}(t, u) + k(t, u) \frac{\partial f_i}{\partial u}(t, u) = \lambda \sum_{j=1}^n \int_{D_u \times D_u} \eta_{ij} \varphi_{ij}(u_*, u^*, u) f_i(t, u_*) f_j(t, u^*) du_* du^* - f_i(t, u) \left[ \sum_{i=1}^n w_{ik} - \delta_{ki} \sum_{j=1}^n \int_{D_u} \eta_{ij} f_j(t, u^*) du^* \right],$$

with  $i = 1, \dots, n$ .

*Proof.* In the special case  $k(t, u) = 0$ ,  $w_{ik} = 0$  and  $\lambda = 1$ ,  $n = 2$  we have the classical kinetic system, already studied in [2, 4, 5, 6, 7, 9] for the tumor-immune system competition (5.1)

$$(5.2) \quad \frac{\partial f_i}{\partial t}(t, u) = \sum_{j=1}^2 \int_{D_u \times D_u} \eta_{ij} \varphi_{ij}(u_*, u^*, u) f_i(t, u_*) f_j(t, u^*) du_* du^* - f_i(t, u) \sum_{j=1}^2 \int_{D_u} \eta_{ij} f_j(t, u^*) du^*, \quad (i = 1, 2)$$

While for  $k(t, u) = 1$ ,  $\lambda = 0$  and the  $\sum_{j=1}^2 \int_{D_u} \eta_{ij} f_j(t, u^*) du^* = 0$  and  $w_{11} = \rho(u)$ ,  $w_{22} = -d(u)$ ,  $w_{12} = w_{21} = 0$  we obtain the equation proposed by Terry et Al. [25] for the primary CD8T cell immune response (3.1)

$$(5.3) \quad \frac{\partial f_i}{\partial t}(t, u) + \frac{\partial f_i}{\partial u}(t, u) = f_i(t, u)[d(u) - \rho(u)], \quad (i = 1, 2)$$



It should be noticed that as independent parameters Terry et Al. proposed  $\tau$ , i.e. the age, instead of the activity parameter  $u$ .

When the distribution depends on time only, we can have from the above system the master equations [3, 17, 27]: for  $k(t, u) = 0$ ,  $\lambda = 0$ ,  $\frac{\partial f_i}{\partial u} = 0$  and

$$\sum_{j=1}^2 \int_{D_u} \eta_{ij} f_j(t, u^*) du^* = 0,$$

we have

$$(5.4) \quad \frac{df_i}{dt} = \sum_{k=1}^n w_{ik} f_k(t), \quad (i = 1, \dots, n)$$

so that the above equations are also a natural generalization of the master equations (4.1) as time evolution of probability.  $\square$

There follows that the equations (5.1) should be considered as the more general set of equations describing the population dynamics at a macroscopic scale. From these equations we can obtain the density distribution function, in the more general case.

## Conclusions

In this paper a generalized kinetic model for the investigation of population dynamics at the macroscopic scale has been given. It has been also shown that some of the most popular classical models of cells competition such as the master equation and the immune response can be easily obtained from the generalized equations.

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