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*Research Article*

# Modeling Complex Systems with Particles Refuge by Thermostatted Kinetic Theory Methods

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This paper is concerned with the mathematical modeling of complex systems characterized by particles refuge. Specifically the paper focuses on the derivation and moments analysis of thermostatted kinetic frameworks with conservative and nonconservative interactions for closed and open complex systems at nonequilibrium. Applications and future research perspectives are discussed in the last section of the paper.

## 1. Introduction

The development of nonlinear analysis methods and the strengthening of modern computers have allowed a more accurate description of complex systems in the applied sciences.

The difficulty in modeling complex systems hails from the unexpected behaviors that stem from interactions between the inner elements and the outer environment [1, 2]. These behaviors are not the mere sum of the whole interactions (the system is more than the sum of its component parts) and collective behaviors are also consequence of self-organization [3, 4].

The global collective behaviors that emerge in most complex systems in the applied sciences, such as self-organized biological systems, vehicular traffic, crowd and swarm dynamics, and social and economic systems, are usually in response to external actions. Indeed the environmental action or external agents can affect the whole dynamics and abrupt changes can occur; for example, the behavior pattern carried out by animal swarms can be disturbed by the attack of a predator; tumor growth can be controlled and avoided by the action of an external vaccine at the cellular scale. The interested reader in a deeper understanding of these topics is referred to papers [5–15] and the references cited therein.

In particular complexity arises in biology systems at different levels of organization that range from individual organisms to whole populations; see [16, 17]. Indeed a mutation occurring in particularly fortuitous circumstances can be amplified to the extent that it changes the course of evolution. Moreover the outer environment exerts an action that can influence the whole dynamics far more rapidly than what can be perceived.

Although the environmental action has an outstanding role in the whole dynamics of the system, only a few mathematical models and methods have been developed and used to model open complex systems of the biological and, in general, of the applied sciences systems.

Recently thermostatted kinetic theory for active particles methods have been proposed in [18] for the modeling of complex behaviors occurring in living systems; see also the review paper [19] and the analysis developed in [20, 21]. However, the above-mentioned thermostatted kinetic frameworks seem not suitable for the modeling of proliferative, destructive, and mutative events that occur in biological systems as consequence of the interactions among the constituent elements of the system.

This paper is concerned with a further generalization of the thermostatted kinetic frameworks proposed in paper [22]; the paper deals with the modeling of nonequilibrium complex systems characterized by conservative and nonconservative interactions (including mutative interactions, whose importance has been stressed by most scientists; see [23]) and particles refuge, namely, the capability of some particles to escape the interactions. Moreover the role of external actions or agents at the microscopic scale is taken into

account, generating a more suitable thermostatted kinetic framework for the active particles, which can be proposed for the mathematical modeling of the time evolution of the inner system in the presence of the outer environment (open system).

To the best of our knowledge, the role of particles refuge has not been yet taken into account in thermostatted models; particles refuge is a prerogative of predator-prey models.

In the last three decades, the introduction of prey refuge in predator-prey models has gained much attention; see, among others, the mathematical analysis developed in papers [24–35] and the review paper [36]. In the pertinent literature, prey refuge has been incorporated in predator-prey interactions for considering two types of events: those that protect a constant fraction of prey and those that protect a constant number of prey. The introduction of prey refuge is inserted for modeling the strategies that decrease the predation ability (spatial or temporal refuges, prey aggregations, or reduced search activity by prey). The presence of refuges may affect the coexistence of predators and prey, the stability of equilibrium solutions and could imply the existence of Hopf bifurcations.

The contents of the present paper are outlined as follows. After this introduction, Section 2 presents the mathematical setting of the thermostatted kinetic framework (TKF) for active particles, for the modeling of complex systems with conservative interactions and particles refuge; the systems are composed of a large number of active particles grouped into functional subsystems; the time evolution of each subsystem occurs in the absence of microscopic external actions (closed systems) and is depicted by a distribution function. The derivation of differential equations for the time evolution of the moments and the existence and uniqueness theorem of the mild solution are also performed in this section. Section 3 introduces the TKF for systems with proliferative/destructive and mutative interactions. This section shows how the moments evolution is influenced by these nonconservative interactions. Further generalizations are discussed in Section 4. The derivation of the thermostatted kinetic framework for open systems is presented and discussed in Section 5. Finally, Section 6 concludes the paper with applications and research perspective on the mathematical structures derived in the present paper.

## 2. The TKF with Conservative Interactions and Particles Refuge

This section is meant to derive the thermostatted kinetic framework for the modeling of complex systems subjected to external force fields such that some particles are able to refuge. Specifically the whole system is decomposed into a finite large number $n \in \mathbb{N}$ of particle subsystems such that each subsystem is composed of active particles, which are able to perform the same strategy (functional subsystems). Particles are able to interact with one another and with the particles of the other subsystems. The strategy expressed by the particles is modeled by inserting, into the microscopic state of the particles, a scalar variable $u \in D_u \subseteq \mathbb{R}$, called activity variable. The time evolution of each functional subsystem is depicted by statistical representation, specifically by a distribution function $f_i = f_i(t,u) : [0,\infty) \times D_u \to \mathbb{R}^+$, for $i \in \{1,2,\dots,n\}$.

Let $\mathbf{f}(t,u) = (f_1(t,u), f_2(t,u), \dots, f_n(t,u))$ be the vector function whose $i$th component is the distribution function of the $i$th functional subsystem, and $\widetilde{f}(t,u)$ the function defined as follows:

$$\widetilde{f}(t,u) = \sum_{i=1}^{n} f_i(t,u)\, du. \tag{1}$$

Assuming that $u^p f_i(t,u) \in L^1(D_u)$, the $p$th-order moment of each functional subsystem $f_i$ reads

$$\mathbb{E}_p[f_i](t) = \int_{D_u} u^p f_i(t,u), \quad p \in \mathbb{N}. \tag{2}$$

In general $\mathbb{E}_0[f_i]$ represents the particles density of the $i$th functional subsystem and $\mathbb{E}_2[f_i]$ the related activation energy. In particular the $p$th-order moment of the whole system is obtained by summing the $p$th-order moment of the subsystems:

$$\mathbb{E}_p[\mathbf{f}](t) = \sum_{i=1}^{n} \mathbb{E}_p[f_i](t) = \int_{D_u} u^p \widetilde{f}(t,u), \quad p \in \mathbb{N}. \tag{3}$$

In what follows we assume that the domain $D_u$ is a compact set of $\mathbb{R}$ with respect to the usual topology. Moreover some particles of one or more functional subsystems are able to refuge during the interactions. In particular, for explanation convenience, we assume that some particles of the subsystem with distribution function $f_1(t,u)$ escape the interaction; namely, no refuging particles have microscopic state $u \in R_u \subset D_u$.

For deriving the time evolution equation of each distribution function $f_i$, we need to define the types of interactions. Mutual interactions refer to test particles, whose distribution function is denoted by $f_i(t,u)$, candidate particles (with distribution function denoted by $f_i(t,u_*)$), and field particles (with distribution function denoted by $f_i(t,u^*)$). Candidate particles can acquire in probability the microscopic state of the test particle after interactions with field particles. The possibility of interactions among the particles is measured by introducing the nonnegative function $\eta_{ij}(u_*,u^*) : D_u \times D_u \to \mathbb{R}^+$, which represents the interaction rate between the $u_*$-particle of the subsystem $f_i$ and the $u^*$-particle of the subsystem $f_j$. In particular we model the particles refuge of the functional subsystem $f_1$ by choosing the interaction rate as follows:

$$\eta_{ij}(u_*,u^*) = \begin{cases} \widetilde{\eta}_{ij}(u_*,u^*)\,\chi_{R_u}(u_*)\,\chi_{R_u}(u^*) & \text{if } i=1, j=1, \\ \widetilde{\eta}_{ij}(u_*,u^*)\,\chi_{R_u}(u_*) & \text{if } i=1, j\neq 1, \\ \widetilde{\eta}_{ij}(u_*,u^*)\,\chi_{R_u}(u^*) & \text{if } i\neq 1, j=1, \\ \widetilde{\eta}_{ij}(u_*,u^*) & \text{otherwise,} \end{cases} \tag{4}$$

where $\widetilde{\eta}_{ij}(u_*,u^*) : D_u \times D_u \to \mathbb{R}^+$ and $\chi_{R_u} : R_u \to \{0,1\}$ is the characteristic (indicator) function of $R_u$. The probability

that, after the interaction, the candidate particle undergoes a change in its microscopic state (that of test particle) is measured by introducing the following nonnegative function:

$$\mathscr{A}_{ij}(u_*, u^*, u) : D_u \times D_u \times D_u \longrightarrow \mathbb{R}^+, \tag{5}$$

which is assumed to be a probability density with respect to $u$ and then the following condition holds:

$$\int_{D_u} \mathscr{A}_{ij}(u_*, u^*, u)\, du = 1, \quad \forall u_*, u^* \in D_u. \tag{6}$$

Setting

$$\Gamma_{ij} = \Gamma_{ij}(u_*, u^*, u) = \eta_{ij}(u_*, u^*)\, \mathscr{A}_{ij}(u_*, u^*, u), \tag{7}$$

bearing all the above in mind and summing up with respect to all candidate and field particles we obtain the following operator $\mathscr{G}_i[\mathbf{f}] = \mathscr{G}_i[\mathbf{f}](t,u)$ which models the gain of test particles into the $i$th functional subsystem:

$$\begin{aligned}\mathscr{G}_i[\mathbf{f}] &= \sum_{j=1}^{n} \int_{D_u \times D_u} \Gamma_{ij}\, f_i(t, u_*)\, f_j(t, u^*)\, du_* du^* \\ &= \int_{D_u \times R_u} \tilde{\eta}_{i1}(u_*, u^*)\, \mathscr{A}_{i1}(u_*, u^*, u)\, f_i(t, u_*) \\ &\qquad \times f_1(t, u^*)\, du_* du^* \\ &\quad + \sum_{j=2}^{n} \int_{D_u \times D_u} \Gamma_{ij}\, f_i(t, u_*)\, f_j(t, u^*)\, du_* du^*.\end{aligned} \tag{8}$$

Similarly, the loss of test cells into the $i$th functional subsystem is modeled by the operator $\mathscr{L}_i[\mathbf{f}] = \mathscr{L}_i[\mathbf{f}](t,u)$ that reads

$$\begin{aligned}\mathscr{L}_i[\mathbf{f}] &= f_i(t,u) \sum_{j=1}^{n} \int_{D_u} \eta_{ij}(u, u^*)\, f_j(t, u^*)\, du^* \\ &= f_i(t,u) \left( \int_{R_u} \tilde{\eta}_{i1}(u, u^*)\, f_1(t, u^*)\, du^* \right. \\ &\qquad \left. + \sum_{j=2}^{n} \int_{D_u} \eta_{ij}(u, u^*)\, f_j(t, u^*)\, du^* \right).\end{aligned} \tag{9}$$

We now assume that the system is closed from the microscopic point of view and in nonequilibrium conditions; namely, there is an external force field $F_i = F_i(u) : D_u \to \mathbb{R}^+$, for $i \in \{1, 2, \ldots, n\}$, at macroscopic scale. Bearing all the above in mind, the thermostatted kinetic framework with particles refuge for closed systems is obtained by balancing the inlet and the outlet flow of particles into the volume of the microscopic states. The framework is a system of $n$ kinetic equations coupled with the Gaussian isokinetic thermostat, whose $i$th equation reads

$$\partial_t f_i + \partial_u (F_i f_i) - \mathscr{T}_i[F_i, \mathbf{f}] = \mathscr{J}_i[\mathbf{f}] = \mathscr{G}_i[\mathbf{f}] - \mathscr{L}_i[\mathbf{f}], \tag{10}$$

where $\mathscr{T}_i[F_i, \mathbf{f}] = \mathscr{T}_i[F_i, \mathbf{f}](t,u)$ is the thermostatted term, which reads

$$\mathscr{T}_i[F_i, \mathbf{f}](t,u) = \partial_u \left( u F_i(u) \left( \int_{D_u} u \tilde{f}(t,u)\, du \right) f_i(t,u) \right). \tag{11}$$

The thermostatted term is a damping operator that is adjusted so as to control the evolution of lower $p$th order moments (in general the $p = 1$ and $p = 2$ moments). This term is based on Gauss principle of the least constrain; see [37–41].

*Remark 1.* It is worth stressing that the thermostatted term (11) can be written as function of the $p = 1$st-order moment as follows:

$$\mathscr{T}_i[F_i, \mathbf{f}](t,u) = \partial_u \left( u F_i(u)\, \mathbb{E}_1[\mathbf{f}](t)\, f_i(t,u) \right). \tag{12}$$

This is a further source of nonlinearities.

The depicted thermostatted kinetic framework (10) is quite general and can be exploited to originate specific models for complex systems with particles refuge by acting on the specific forms of the interaction rate $\eta_{ij}$, the probability density $\mathscr{A}_{ij}$, and the external force $F_i$.

It is worth stressing that particles refuge defined in the present paper can also be introduced in the thermostatted frameworks developed and analyzed in the paper [22] and in the $p$-thermostatted framework proposed in the paper [42]. In the latter case the thermostatted term reads

$$\mathscr{T}_i[F_i, \mathbf{f}](t,u) = \partial_u \left( u F_i(u)\, \mathbb{E}_{p-1}[\mathbf{f}](t)\, f_i(t,u) \right). \tag{13}$$

*2.1. Preliminary Investigations.* This section deals with analytical results on the mathematical framework (10) related to the moment evolutions.

*Definition 2.* Let $F_i = F_i(u)$, $u \in D_u$, be an external force field differentiable with respect to $u$; $\eta_{ij}(u_1, u_2) : D_u \times D_u \to \mathbb{R}^+$ the interaction rate between the $i$th and $j$th functional subsystems; $\Gamma_{ij}(u_1, u_2, u) : D_u \times D_u \times D_u \to \mathbb{R}^+$, for $i, j \in \{1, 2, \ldots, n\}$, the function defined in (7); $\mathscr{A}_{ij}(u_1, u_2, u) : D_u \times D_u \times D_u \to \mathbb{R}^+$ the probability density satisfying the property (6). A vector function $\mathbf{f}(t,u)$, whose $i$th component is the distribution function of the $i$th functional subsystem $f_i = f_i(t,u) : [0, \infty) \times D_u \to \mathbb{R}^+$, is said to be solution of the model (10) if

(i) $f_i(t,u) \in C([0,\infty), L^1(D_u))$;

(ii) $f_i(t,u)$ is differentiable with respect to the variables $t$ and $u$;

(iii) $u f_i(t,u)$ is an integrable function with respect to the elementary measure $du$;

(iv) $\Gamma_{ij}(u_1, u_2, u) f_i(t, u_1) f_j(t, u_2)$ is an integrable function with respect to the elementary measure $du_1 du_2$;

(v) $\eta_{ij}(u_1, u_2) f_j(t, u_2)$ is an integrable function with respect to the elementary measure $du_2$;

(vi) $f_i(t,u) = 0$ as $(t,u) \in [0,\infty) \times \partial D_u$;

(vii) $f_i$ satisfies (10) for all $(t,u) \in [0,\infty) \times D_u$.

*Assumption 3.* We assume that $F_i(u) = F$ and $\tilde{\eta}_{ij}(u_*, u^*) = \tilde{\eta}$ are nonnegative constants.

*Assumption 4.* We assume that $\mathscr{A}_{ij}(u_*, u^*, u) : D_u \times D_u \times D_u \to \mathbb{R}^+$ is an even nonnegative function on $D_u = [-a, a]$, with $a > 0$.

*Assumption 5.* We assume that $\mathscr{A}_{ij}(u_*, u^*, u) : D_u \times D_u \times D_u \to \mathbb{R}^+$ satisfies the following property:

$$\int_{D_u} u^2 \mathscr{A}_{ij}(u_*, u^*, u)\, du = u_*^2, \quad \forall u_*, u^* \in D_u. \tag{14}$$

The following result holds true.

**Lemma 6.** *Let $p$ be an odd number and assume that Assumptions 3 and 4 hold. Let $\mathbf{f}$ be a nonnegative solution of the thermostatted kinetic framework with particles refuge* (10). *Then the pth-order moment $\mathbb{E}_p[\mathbf{f}] = \mathbb{E}_p[\mathbf{f}](t)$ of $\mathbf{f}$ satisfies the following ordinary differential equation:*

$$\frac{d}{dt}\mathbb{E}_p[\mathbf{f}] = -\mathbb{E}_p[\mathbf{f}]\left(pF\mathbb{E}_1[\mathbf{f}] + \tilde{\eta}\mathbb{R}_0[\mathbf{f}]\right) + pF\mathbb{E}_{p-1}[\mathbf{f}], \tag{15}$$

*where*

$$\mathbb{R}_0[\mathbf{f}] = \mathbb{R}_0[\mathbf{f}](t) = \int_{R_u} f_1(t,u)\, du + \sum_{j=2}^{n} \mathbb{E}_0\left[f_j\right]. \tag{16}$$

*Moreover if $\mathbb{E}_p[\mathbf{f}]$ is initially bounded, it remains bounded for all $t > 0$.*

*Proof.* The interaction operator $\mathscr{J}_i[\mathbf{f}]$ can be written as follows:

$$\mathscr{J}_i[\mathbf{f}](t,u) = \mathscr{G}_i[\mathbf{f}](t,u) - \tilde{\eta} f_i(t,u)\, \mathbb{R}_0[\mathbf{f}], \tag{17}$$

where $\mathbb{R}_0[\mathbf{f}]$ is given by formula (16).

Multiplying both sides of (10) by $u^p$ and integrating over $D_u$, we have

$$\int_{D_u} u^p\, \mathscr{J}_i[\mathbf{f}](t,u)\, du = 0 - \tilde{\eta}\mathbb{R}_0[\mathbf{f}]\, \mathbb{E}_p\left[f_i\right]. \tag{18}$$

Summing up with respect to $i$, we obtain

$$\sum_{i=1}^{n} \int_{D_u} u^p\, \mathscr{J}_i[\mathbf{f}](t,u)\, du = -\tilde{\eta}\mathbb{R}_0[\mathbf{f}]\, \mathbb{E}_p[\mathbf{f}]. \tag{19}$$

Performing integration by parts on the second and third terms of the left hand side of (10) and summing up with respect to $i$, we have

$$\begin{aligned} &\sum_{i=1}^{n} \int_{D_u} u^p \partial_u\left(\left(1 - u\, \mathbb{E}_1[\mathbf{f}](t)\right) f_i(t,u)\right) du \\ &\quad = \mathbb{E}_1[\mathbf{f}](t)\, \mathbb{E}_p[\mathbf{f}](t) - \mathbb{E}_{p-1}[\mathbf{f}](t), \end{aligned} \tag{20}$$

and the proof is gained. □

*Remark 7.* Setting $p = 1$ in formula (15), the 1st-order moment $\mathbb{E}_1[\mathbf{f}] = \mathbb{E}_1[\mathbf{f}](t)$, which is part of the thermostat operator (11), is solution of the following Riccati nonlinear ordinary differential equation:

$$\frac{d}{dt}\mathbb{E}_1[\mathbf{f}] = F\left[\mathbb{E}_0[\mathbf{f}] - \left(\mathbb{E}_1[\mathbf{f}]\right)^2\right] - \tilde{\eta}\mathbb{R}_0[\mathbf{f}]\, \mathbb{E}_1[\mathbf{f}]. \tag{21}$$

Equation (21) admits a unique solution when an initial condition is assigned; then it is possible to obtain an explicit formula for $\mathbb{E}_1[\mathbf{f}](t)$; see [20].

*2.2. Existence of Mild Solutions.* The possibility to obtain an explicit formula for $\mathbb{E}_1[\mathbf{f}](t)$ allows introducing the notion of mild solution for the relative abstract Cauchy problem of the thermostatted kinetic framework with particles refuge (10) and performing the mathematical analysis developed in paper [43] regarding the existence and uniqueness of the mild solution.

Let $\mathbf{f}_0(u) : D_u \to (\mathbb{R}^+)^n$ be a $L^1$-integrable vector function on $D_u$ such that $\|\mathbf{f}_0\|_{L^1(D_u)} \in \mathbb{R}$. The Cauchy problem for the thermostatted framework (10) reads

$$\begin{aligned} \Psi_{\mathbf{F}}[\mathbf{f}](t,u) &= \mathbf{J}[\mathbf{f}](t,u), \\ \mathbf{f}(0,u) &= \mathbf{f}_0(u), \end{aligned} \tag{22}$$

where $\Psi_{\mathbf{F}}[\mathbf{f}]$ is the following operator:

$$\begin{aligned} &\Psi_{\mathbf{F}}[\mathbf{f}](t,u) \\ &\quad = \partial_t \mathbf{f}(t,u) + \partial_u\left(\mathbf{F}\left(1 - u \int_{D_u} u\tilde{f}(t,u)\, du\right)\mathbf{f}(t,u)\right), \end{aligned} \tag{23}$$

with $\mathbf{J}[\mathbf{f}] = (\mathscr{J}_1[\mathbf{f}], \mathscr{J}_2[\mathbf{f}], \ldots, \mathscr{J}_n[\mathbf{f}])$ and $\mathbf{F} = (F, F, \ldots, F) \in \mathbb{R}^n$. Bearing all the above in mind, the thermostatted framework in vectorial form can be rewritten as follows:

$$\begin{aligned} &\partial_t \mathbf{f}(t,u) + \mathbf{F}\left(1 - u\mathbb{E}_1[\mathbf{f}]\right)\partial_u \mathbf{f}(t,u) \\ &\quad + \left(\eta\mathbb{E}_0[\mathbf{f}] - \mathbf{F}\mathbb{E}_1[\mathbf{f}]\right)\mathbf{f}(t,u) = \mathbf{G}[\mathbf{f}](t,u), \end{aligned} \tag{24}$$

where $\mathbf{G}[\mathbf{f}] = (\mathscr{G}_1[\mathbf{f}], \mathscr{G}_2[\mathbf{f}], \ldots, \mathscr{G}_n[\mathbf{f}])$. By applying the following transformations:

$$\begin{aligned} \mathbf{c}_t(u) &= ue^{-\mathbf{a}(t)} + \mathbf{F}e^{-\mathbf{a}(t)} \int_0^t e^{\mathbf{a}(v)} dv, \\ \mathbf{a}(t) &= \mathbf{F}\int_0^t \mathbb{E}_1[\mathbf{f}](v)\, dv, \end{aligned} \tag{25}$$

we have

$$\partial_t \mathbf{f}_{\mathbf{c}}(t,u) + \left(\eta\mathbb{E}_0[\mathbf{f}] - \mathbf{F}\mathbb{E}_1[\mathbf{f}]\right)\mathbf{f}_{\mathbf{c}}(t,u) = \mathbf{G}_{\mathbf{c}}[\mathbf{f}](t,u), \tag{26}$$

with $\mathbf{f}_{\mathbf{c}}(t,u) = \mathbf{f}(t, \mathbf{c}_t(u))$ and $\mathbf{G}_{\mathbf{c}}[\mathbf{f}](t) = \mathbf{G}[\mathbf{f}](t, \mathbf{c}_t(u))$. Set

$$\mathbf{s}(t) = \int_0^t \left(\eta\, \mathbb{E}_0[\mathbf{f}] - \mathbf{F}\mathbb{E}_1[\mathbf{f}](u)\right) du. \tag{27}$$

Let $T > 0$ be fixed. The integral form of (24) for $t \in [0, T]$ and $u \in D_u$ reads

$$\mathbf{f_c}(t,u) = e^{-\mathbf{s}(u)}\,\mathbf{f_c}(0,u) + e^{-\mathbf{s}(u)}\int_0^t e^{\mathbf{s}(\tau)}\,\mathbf{G_c}[\mathbf{f}](\tau,u)\,d\tau \tag{28}$$

and then

$$\begin{aligned}\mathbf{f}(t,u) &= e^{-\mathbf{s}(u)}\mathbf{f}_0\left(\mathbf{c}_t^{-1}(u)\right)\\ &\quad + e^{-\mathbf{s}(u)}\int_0^t e^{\mathbf{s}(\tau)}\mathbf{G}[\mathbf{f}]\left(\tau,\mathbf{c}_\tau\circ\mathbf{c}_t^{-1}(u)\right)d\tau.\end{aligned} \tag{29}$$

*Definition 8.* Let $\mathbf{f}_0(u) : D_u \to (\mathbb{R}^+)^n$ be a $L^1$-integrable function on $D_u$ such that $\mathbb{E}_0[\mathbf{f}_0] = 1$. A nonnegative vector function $\mathbf{f}$ is said to be a mild solution to the Cauchy problem (22) if $\mathbf{f}(t,u) \in [C([0,\infty), L^1(D_u))]^n$ and $\mathbf{f}$ satisfies (29).

The following result holds true.

**Theorem 9.** *Assume that Assumptions 3, 4, and 5 hold. Let $\mathbf{f}_0(u)$ be the initial vector function such that $\mathbb{E}_0[\mathbf{f}_0] = 1$. Then the Cauchy problem* (22) *admits a unique globally in time mild solution. Furthermore $\mathbb{E}_0[\mathbf{f}] = \mathbb{E}_2[\mathbf{f}] = 1$.*

*Proof.* The proof of the theorem follows by integration along the characteristic curves and the definition and analysis of successive approximations sequences; see [20]. □

*Remark 10.* Theorem 9 states that the introduction of the thermostatted term guarantees the conservation of the $\mathbb{E}_0[\mathbf{f}]$ and $\mathbb{E}_2[\mathbf{f}]$ moments, namely, the density and the activation energy of the system.

## 3. The TKF with Nonconservative Interactions and Particles Refuge

This section deals with the derivation and analysis of the TKF with particles refuge and nonconservative interactions, namely, interactions that modify the number of particles. Nonconservative interactions include proliferative, destructive, and mutative events. These interactions are typical of the biological systems; indeed proliferative/destructive events occur when cells start to duplicate or are eliminated/inhibited by the immune system; mutative events are the result of genetic mutations.

Following [17, 44] and references cited therein, the role of proliferative and/or destructive interactions during particle refuge is modeled by the following operator:

$$\mathcal{N}_i[\mathbf{f}] = f_i(t,u)\sum_{j=1}^n\int_{D_u}\alpha_{ij}(u,u^*)\,f_j(t,u^*)\,du^*, \tag{30}$$

where

$$\alpha_{ij}(u,u^*) = \eta_{ij}(u,u^*)\,\mu_{ij}(u,u^*), \tag{31}$$

with $\mu_{ij}(u_*,u^*)$ being the net proliferation rate. In particular for the particles refuge case, the operator (30) reads

$$\begin{aligned}\mathcal{N}_i[\mathbf{f}] = f_i(t,u)\Bigg(&\int_{R_u}\widetilde{\eta}_{ij}(u,u^*)\,\mu_{ij}(u,u^*)\,f_1(t,u^*)\,du^*\\ &+\sum_{j=2}^n\int_{D_u}\alpha_{ij}(u,u^*)\,f_j(t,u^*)\,du^*\Bigg).\end{aligned} \tag{32}$$

Moreover the role of mutative events is modeled by the following operator:

$$\begin{aligned}\mathcal{M}_i[\mathbf{f}] = &\sum_{h=1}^n\sum_{k=1}^n\int_{D_u\times D_u}\beta_{hk}^i(u_*,u^*,u)\\ &\times f_h(t,u_*)\,f_k(t,u^*)\,du_*du^*,\end{aligned} \tag{33}$$

where

$$\beta_{hk}^i(u_*,u^*,u) = \eta_{hk}(u_*,u^*)\,\varphi_{hk}^i(u_*,u^*,u), \tag{34}$$

with $\varphi_{hk}^i(u_*,u^*,u)$ being the net proliferation rate into the $i$th functional subsystem, due to interactions that occur with rate $\eta_{hk}$, of the candidate $h$-particle, with state $u_*$, and the field $k$-particle, with state $u^*$. In particular in the case of particles refuge, the operator (33) reads

$$\begin{aligned}\mathcal{M}_i[\mathbf{f}] = &\int_{R_u\times R_u}\widetilde{\eta}_{11}(u_*,u^*)\,\varphi_{11}^i(u_*,u^*,u)\\ &\times f_1(t,u_*)\,f_1(t,u^*)\,du_*du^*\\ &+\sum_{k=2}^n\int_{R_u\times D_u}\widetilde{\eta}_{1k}(u_*,u^*)\,\varphi_{1k}^i(u_*,u^*,u)\\ &\times f_1(t,u_*)\,f_k(t,u^*)\,du_*du^*\\ &+\sum_{h=2}^n\int_{D_u\times R_u}\widetilde{\eta}_{h1}(u_*,u^*)\,\varphi_{h1}^i(u_*,u^*,u)\,f_h(t,u_*)\\ &\times f_1(t,u^*)\,du_*du^*\\ &+\sum_{h=2}^n\sum_{k=2}^n\int_{D_u\times D_u}\beta_{hk}^i(u_*,u^*,u)\,f_h(t,u_*)\\ &\times f_k(t,u^*)\,du_*du^*.\end{aligned} \tag{35}$$

Assuming that the system is closed and in nonequilibrium conditions, the $i$th equation of the thermostatted kinetic framework with particles refuge for closed systems and with nonconservative interactions thus reads

$$\begin{aligned}\partial_t f_i + \partial_u(F_i f_i) - \mathcal{T}_i[F_i,\mathbf{f}] &= J_i[\mathbf{f}]\\ &= \mathcal{G}_i[\mathbf{f}] - \mathcal{L}_i[\mathbf{f}] + \mathcal{N}_i[\mathbf{f}] + \mathcal{M}_i[\mathbf{f}],\end{aligned} \tag{36}$$

where the meaning of each operator can be recovered from the previous section.

*3.1. Evolution of Moments.* This section is concerned with a preliminary analysis of the thermostatted framework (36).

*Definition 11.* Let $F_i = F_i(u)$, $u \in D_u$, be an external force field differentiable with respect to $u$; $\eta_{ij}(u_1, u_2) : D_u \times D_u \to \mathbb{R}^+$ the interaction rate among the subsystems; $\Gamma_{ij}(u_1, u_2, u) : D_u \times D_u \times D_u \to \mathbb{R}^+$, for $i, j \in \{1, 2, \ldots, n\}$, the function defined in (7); $\alpha_{ij}(u_1, u_2) : D_u \times D_u \to \mathbb{R}^+$ the function defined in (31); $\beta^i_{hk}(u_1, u_2, u) : D_u \times D_u \times D_u \to \mathbb{R}^+$ the function defined in (34), for $i, h, k \in \{1, 2, \ldots, n\}$; $\mathscr{A}_{ij}(u_1, u_2, u) : D_u \times D_u \times D_u \to \mathbb{R}^+$ the probability density. A vector function $\mathbf{f}(t, u)$, whose $i$th component is the distribution function of the $i$th functional subsystem $f_i = f_i(t, u) : [0, \infty) \times D_u \to \mathbb{R}^+$, is said to be solution of model (36) if the conditions (i), (ii), (iii), (iv), and (v) of Definition 2 and the following further conditions hold:

(vi) $\alpha_{ij}(u_1, u_2)\ f_j(t, u_2)$ is an integrable function with respect to the elementary measure $du_2$;

(vii) $\beta^i_{hk}(u_1, u_2, u) f_h(t, u_1) f_k(t, u_2)$ is an integrable function with respect to the elementary measure $du_1 du_2$;

(viii) $f_i(t, u) = 0$ as $(t, u) \in [0, \infty) \times \partial D_u$;

(ix) $f_i$ satisfies (36) for all $(t, u) \in [0, \infty) \times D_u$.

*Assumption 12.* In what follows we assume that $F_i = F$, $\tilde{\eta}_{ij} = \tilde{\eta}$, $\mu_{ij} = \mu$, and $\varphi^i_{hk} = \varphi$ are constants and $\mathscr{A}_{ij}$ is an even function with respect to $u \in D_u$, where $D_u = [-a, a]$ with $a > 0$.

*Remark 13.* Under Assumption 12, if we also assume for computational convenience that $F_i = 0$, integrating the left and right hand sides of (36) with respect to $u$, we obtain the following equation:

$$\partial_t \left(\mathbb{E}_0 [f_i]\right) = \tilde{\eta}\mu \mathbb{E}_0 [f_i] \left[ \int_{R_u} f_1 (t, u)\, du + \sum_{j=2}^{n} \mathbb{E}_0 [f_j] \right] + 2a\beta \sum_{h=1}^{n} \sum_{k=1}^{n} \mathbb{E}_0 [f_h] \mathbb{E}_0 [f_k], \tag{37}$$

which shows that the evolution of the density $\mathbb{E}_0[f_i]$ of the $i$th functional subsystem depends on the distribution function $f_1(t, u)$ of the nonrefuging particles. In particular the above equation can be rewritten as follows:

$$\partial_t \left(\mathbb{E}_0 [f_i]\right) = \eta\mu \mathbb{E}_0 [f_i] \left[ \left(\mathbb{E}_0 [f_1] - \tilde{\mathbb{E}}_0 [f_1]\right) + \sum_{j=2}^{n} \mathbb{E}_0 [f_j] \right] + 2a\beta \sum_{h=1}^{n} \sum_{k=1}^{n} \mathbb{E}_0 [f_h] \mathbb{E}_0 [f_k], \tag{38}$$

where

$$\tilde{\mathbb{E}}_0 [f_1] = \int_{D_u \setminus R_u} f_1 (t, u)\, du \tag{39}$$

is the density of the particles of the functional subsystem $f_1$ that have refuged. Moreover

$$\begin{aligned} &\sum_{h=1}^{n} \sum_{k=1}^{n} \mathbb{E}_0 [f_h] \mathbb{E}_0 [f_k] \\ &\quad = \left(\mathbb{E}_0 [f_1] - \tilde{\mathbb{E}}_0 [f_1]\right) \\ &\qquad \times \left( \left(\mathbb{E}_0 [f_1] - \tilde{\mathbb{E}}_0 [f_1]\right) + 2 \sum_{k=2}^{n} \mathbb{E}_0 [f_k] \right) \\ &\qquad + \sum_{h=2}^{n} \sum_{k=2}^{n} \mathbb{E}_0 [f_h] \mathbb{E}_0 [f_k]. \end{aligned} \tag{40}$$

Therefore the differential equation for the density $\mathbb{E}_0[f_i]$ of the $i$th functional subsystem reads

$$\begin{aligned} \partial_t \left(\mathbb{E}_0 [f_i]\right) &= \eta\mu \mathbb{E}_0 [f_i] \left[ \left(\mathbb{E}_0 [f_1] - \tilde{\mathbb{E}}_0 [f_1]\right) + \sum_{j=2}^{n} \mathbb{E}_0 [f_j] \right] \\ &\quad + 2a\beta \left(\mathbb{E}_0 [f_1] - \tilde{\mathbb{E}}_0 [f_1]\right) \\ &\quad \times \left( \left(\mathbb{E}_0 [f_1] - \tilde{\mathbb{E}}_0 [f_1]\right) + 2 \sum_{k=2}^{n} \mathbb{E}_0 [f_k] \right) \\ &\quad + 2a\beta \sum_{h=2}^{n} \sum_{k=2}^{n} \mathbb{E}_0 [f_h] \mathbb{E}_0 [f_k]. \end{aligned} \tag{41}$$

The following result holds true.

**Theorem 14.** *Let $p$ be an odd number and assume that Assumption 12 holds. If there exists a nonnegative solution $\mathbf{f}$ of the thermostatted kinetic framework with particles refuge and nonconservative interactions* (36)*, then the $p$th-order moment $\mathbb{E}_p[\mathbf{f}] = \mathbb{E}_p[\mathbf{f}](t)$ is solution of the following ordinary differential equation:*

$$\begin{aligned} &\frac{d}{dt} \mathbb{E}_p [\mathbf{f}] \\ &\quad = -\mathbb{E}_p [\mathbf{f}] \left( pF\mathbb{E}_1 [\mathbf{f}] + \tilde{\eta} (1 - \mu) \mathbb{R}_0 [\mathbf{f}] \right) + pF\mathbb{E}_{p-1} [\mathbf{f}], \end{aligned} \tag{42}$$

*where $\mathbb{R}_0[\mathbf{f}]$ is given by formula* (16).

*Proof.* The interaction operator $J_i[\mathbf{f}]$ can be written as follows:

$$\begin{aligned} &J_i [\mathbf{f}] (t, u) \\ &\quad = \mathscr{G}_i [\mathbf{f}] (t, u) - \tilde{\eta} (1 - \mu) f_i (t, u) \mathbb{R}_0 [\mathbf{f}] + \eta\varphi m (t), \end{aligned} \tag{43}$$

where

$$m(t) = \left(\int_{R_u} f_1(t,u_*)\,du_*\right)^2 + 2\left(\int_{R_u} f_1(t,u_*)\,du_*\right)\sum_{k=2}^{n}\mathbb{E}_0[f_k] + \sum_{h=2}^{n}\sum_{k=2}^{n}\mathbb{E}_0[f_h]\,\mathbb{E}_0[f_k]. \tag{44}$$

Multiplying both sides of $J_i[\mathbf{f}]$ by $u^p$ and integrating over $D_u$, we have

$$\int_{D_u} uJ_i[\mathbf{f}](t,u)\,du = 0 - \tilde{\eta}(1-\mu)\,\mathbb{R}_0[\mathbf{f}]\int_{D_u} uf_i(t,u)\,du + 0. \tag{45}$$

Summing up with respect to $i$, we obtain

$$\sum_{i=1}^{n}\int_{D_u} u^p\mathcal{J}_i[\mathbf{f}](t,u)\,du = -\tilde{\eta}(1-\mu)\,\mathbb{R}_0[\mathbf{f}]\,\mathbb{E}_p[\mathbf{f}], \tag{46}$$

and bearing Lemma 6 in mind, we obtain the proof. □

*Remark 15.* Setting $p = 1$ in the differential equation (42), the 1st-order moment $\mathbb{E}_1[\mathbf{f}] = \mathbb{E}_1[\mathbf{f}](t)$ of $\mathbf{f}$ satisfies the following Riccati nonlinear ordinary differential equation:

$$\frac{d}{dt}\mathbb{E}_1[\mathbf{f}] = F\left[\mathbb{E}_0[\mathbf{f}] - (\mathbb{E}_1[\mathbf{f}])^2\right] - \tilde{\eta}(1-\mu)\,\mathbb{R}_0[\mathbf{f}]\,\mathbb{E}_1[\mathbf{f}]. \tag{47}$$

As (47) states, the time evolution of $\mathbb{E}_1[\mathbf{f}]$ does not depend on the mutative interactions when $\varphi^i_{hk}$ is constant. If $\varphi^i_{hk} = \varphi^i_{hk}(u)$ (namely, it does not depend on $u_*$ and $u^*$), the evolution equation of $\mathbb{E}_1[\mathbf{f}]$ reads

$$\frac{d}{dt}\mathbb{E}_1[\mathbf{f}] = F\left[\mathbb{E}_0[\mathbf{f}] - (\mathbb{E}_1[\mathbf{f}])^2\right] - \tilde{\eta}(1-\mu)\,\mathbb{R}_0[\mathbf{f}]\,\mathbb{E}_1[\mathbf{f}] + \eta\varphi s(t), \tag{48}$$

where

$$s(t) = \left(\int_{R_u} f_1(t,u_*)\,du_*\right)^2 \times \sum_{i=1}^{n}\zeta^i_{11} + 2\int_{R_u} f_1(t,u_*)\,du_*\sum_{i=1}^{n}\sum_{k=2}^{n}\zeta^i_{1k}\mathbb{E}_0[f_k] + \sum_{i=1}^{n}\sum_{h=2}^{n}\sum_{k=2}^{n}\zeta^i_{hk}\mathbb{E}_0[f_h]\,\mathbb{E}_0[f_k], \tag{49}$$

$$\zeta^i_{hk} = \int_{D_u} u\varphi^i_{hk}(u)\,du. \tag{50}$$

Obviously, if $\varphi^i_{hk}(u)$ is an even function with respect to $u$, then $s(t) = 0$ and (48) does not depend on the mutative term again.

It is worth stressing that, in the general case $\varphi^i_{hk} = \varphi^i_{hk}(u_*, u^*, u)$, the differential equation fulfilled by $\mathbb{E}_p[\mathbf{f}](t)$ depends on the following quantity:

$$\sum_{i=1}^{n}\int_{D_u} u^p\varphi^i_{hk}(u_*, u^*, u)\,du, \tag{51}$$

for which, in general, is not possible to give an explicit formula.

As already mentioned, the possibility to obtain an explicit formula for $\mathbb{E}_1[\mathbf{f}](t)$ solution of the differential equation (47) allows defining the mild solution of the relative abstract Cauchy problem. However, in the nonconservative interactions case, global existence may not occur and the proof of the global existence depends casewise. This is a work in progress and results will be reported in due course.

## 4. Particles Refuge in Functional Subsystems

For concluding the discussion on the introduction of particles refuge in thermostatted kinetic models for closed systems, this section is concerned with the derivation of the thermostatted kinetic framework that generalizes the thermostatted kinetic framework (36) when more than one functional subsystem contains particles refuge. Specifically we define the following sets:

$$\begin{aligned}\mathcal{R} &= \{j \in \{1,2,\ldots,n\} : f_j(t,u) \text{ has particles refuge in } D_u\},\\ \mathcal{S} &= \{j \in \{1,2,\ldots,n\} : f_j(t,u) \text{ has not particles refuge in } D_u\}.\end{aligned} \tag{52}$$

Therefore the relative interaction rate $\eta_{ij}$ defined in (4) now reads

$$\eta_{ij}(u_*, u^*) = \begin{cases}\tilde{\eta}_{ij}(u_*, u^*)\,\chi_{R^i_u}(u_*)\,\chi_{R^j_u}(u^*) & \text{if } i \in \mathcal{R}, j \in \mathcal{R},\\ \tilde{\eta}_{ij}(u_*, u^*)\,\chi_{R^j_u}(u_*) & \text{if } i \in \mathcal{R}, j \in \mathcal{S},\\ \tilde{\eta}_{ij}(u_*, u^*)\,\chi_{R^i_u}(u^*) & \text{if } i \in \mathcal{S}, j \in \mathcal{R},\\ \tilde{\eta}_{ij}(u_*, u^*) & \text{otherwise,}\end{cases} \tag{53}$$

where $R^h_u$ denotes the domain of the nonrefuging particles of the $h$th functional subsystem.

Bearing all the above in mind, we can split the operators in the right hand side of (36) as follows: the gain particles operator reads

$$\begin{aligned}\mathscr{G}_i[\mathbf{f}] &= \sum_{j\in\mathscr{R}}\int_{\widetilde{D}_u^i\times R_u^j}\widetilde{\eta}_{ij}(u_*,u^*)\mathscr{A}_{ij}(u_*,u^*,u)\\ &\qquad\times f_i(t,u_*)f_j(t,u^*)\,du_*du^*\\ &\quad+\sum_{j\in\mathscr{S}}\int_{D_u\times D_u}\Gamma_{ij}f_i(t,u_*)f_j(t,u^*)\,du_*du^*,\end{aligned}\tag{54}$$

where

$$\widetilde{D}_u^i=\begin{cases}D_u & \text{if the } i\text{th subsystem has no particles refuge,}\\ R_u^i & \text{if the } i\text{th subsystem has particles refuge.}\end{cases}\tag{55}$$

The lost particles operator is splitted as follows:

$$\mathscr{L}_i[\mathbf{f}]=f_i(t,u)\left(\sum_{j\in\mathscr{R}}\int_{R_u^j}\widetilde{\eta}_{ij}(u,u^*)f_j(t,u^*)\,du^*+\sum_{j\in\mathscr{S}}\int_{D_u}\eta_{ij}(u,u^*)f_j(t,u^*)\,du^*\right).\tag{56}$$

The proliferative operator reads

$$\begin{aligned}\mathscr{N}_i[\mathbf{f}] &= f_i(t,u)\sum_{j\in\mathscr{R}}\int_{D_u\times R_u^j}\widetilde{\eta}_{ij}(u_*,u^*)\mu_{ij}(u_*,u^*)\\ &\qquad\times f_j(t,u^*)\,du_*du^*\\ &\quad+f_i(t,u)\sum_{j\in\mathscr{S}}\int_{D_u\times D_u}\alpha_{ij}(u_*,u^*)\\ &\qquad\times f_j(t,u^*)\,du_*du^*,\end{aligned}\tag{57}$$

and finally the mutative operator is written as follows:

$$\begin{aligned}\mathscr{M}_i[\mathbf{f}] &= \sum_{h=1}^{n}\sum_{k=1}^{m}\int_{\widetilde{D}_u^h\times\widetilde{D}_u^k}\beta_{hk}^i(u_*,u^*,u)f_h(t,u_*)\\ &\qquad\times f_k(t,u^*)\,du_*du^*.\end{aligned}\tag{58}$$

## 5. The TKF for Open Systems with Particles Refuge

The mathematical structures dealt with the previous sections are meaningful for complex biological systems with particles refuge subjected to external force fields at the macroscopic scale but in the absence of interactions with the outer environment at the microscopic scale. Modeling external actions at the microscopic scale means representing the outer system as functional subsystems with distribution function denoted by $g_{ir}=g_{ir}(t,v):[0,\infty[\times D_u\to\mathbb{R}^+$; see [45]. Specifically the $i$th functional subsystem interacts with the $r$th external agent, for $r\in\{1,2,\ldots,m\}$. Therefore, the external agent is regarded as a specific functional subsystem with the ability to interact with active particles of the inner system and has the ability to modify the state $u$ of the system by a particular action related to the variable $v\in D_u$. This system is known as *open system*.

*Assumption 16.* It is assumed that the action $g_{ir}(t,v)$ is factorized as follows:

$$g_{ir}(t,v)=\epsilon_{ir}(t)\varrho_r(v),\quad v\in D_u,\tag{59}$$

where the term $\epsilon_{ir}=\epsilon_{ir}(t)$ is the intensity that depends on time, by which the agent acts on the system, and $\varrho_r(v)$ is the probability function associated with the variable $v$.

Let $\varrho=\{\varrho_1,\varrho_2,\ldots,\varrho_m\}$ be the vector whose components are the $m$ distribution functions associated with the external agents. Thus the $i$th equation of the thermostatted mathematical framework, with particle refuge and nonconservative interactions, for open systems reads

$$\begin{aligned}&\partial_t f_i(t,u)+\partial_u\left(F_i(u)\left(1-u\int_{D_u}u\widetilde{f}(t,u)\,du\right)f_i(t,u)\right)\\ &\quad=\mathscr{Z}_i[\mathbf{f},\varrho](t,u),\end{aligned}\tag{60}$$

with

$$\mathscr{Z}_i[\mathbf{f},\varrho](t,u)=J_i[\mathbf{f}](t,u)+Q_i[\mathbf{f},\varrho](t,u),\tag{61}$$

where the operator $J_i[\mathbf{f}](t,u)$ reads

$$\begin{aligned}J_i[\mathbf{f}](t,u) &= \mathscr{G}_i[\mathbf{f}](t,u)-\mathscr{L}_i[\mathbf{f}](t,u)\\ &\qquad+\mathscr{N}_i[\mathbf{f}](t,u)+\mathscr{M}_i[\mathbf{f}](t,u),\end{aligned}\tag{62}$$

and the meaning of each operator can be recovered by the previous sections, and consider

$$\begin{aligned}Q_i[\mathbf{f},\varrho](t,u) &= \sum_{r=1}^{m}\epsilon_{ir}(t)\int_{\widetilde{D}_u^i\times D_u}\eta_{ir}^e(u_*,v^*)\mathscr{B}_{ir}(u_*,v^*,u)\\ &\qquad\times f_i(t,u_*)\varrho_r(v^*)\,du_*dv^*\\ &\quad-f_i(t,u)\sum_{r=1}^{m}\epsilon_{ir}(t)\int_{D_u}\eta_{ir}^e(u,v^*)\varrho_r(v^*)\,dv^*.\end{aligned}\tag{63}$$

The terms of the operator $Q_i[\mathbf{f},\varrho](t,u)$ have the following meanings:

(i) $\eta_{ir}^e(u_*,v^*)$ is the inner-outer encounter rate between the $r$th external agent, with state $v^*$, and the active (candidate) particle of the $i$th population, with state $u_*$. According to the role of particles refuge, the inner-outer encounter rate reads

$$\eta_{ir}^e(u_*,v^*)=\begin{cases}\widetilde{\eta}_{ir}^e(u_*,v^*)\chi_{R_u^i}(u_*) & \text{if } i\in\mathscr{R},\\ \widetilde{\eta}_{ir}^e(u_*,v^*) & \text{otherwise.}\end{cases}\tag{64}$$

(ii) $\mathscr{B}_{ir}(u_*, v^*, u)$ is the inner-outer transition probability density which describes the probability density that a candidate particle of the $i$th population, with state $u_*$, falls into the state $u$ after an interaction with the $r$th external agent whose state is $v^*$.

The density $\mathscr{B}_{ir}$ satisfies, for all $r \in \{1, 2, \ldots, m\}$ and $i \in \{1, 2, \ldots, n\}$, the following condition:

$$\int_{D_u} \mathscr{B}_{ir}(u_*, v^*, u)\, du = 1, \quad \forall u_*, v^* \in D_u. \tag{65}$$

It is worth noting that the thermostatted framework (60) is not autonomous; indeed the time variable is explicitly inserted by the intensity function $\epsilon_{ir} = \epsilon_{ir}(t)$.

*5.1. On the Evolution of Moments.* This section is meant to derive evolution equations for the moments of the solution of the thermostatted framework (60).

*Definition 17.* Let $F_i = F_i(u)$, $u \in D_u$, be an external force field differentiable with respect to $u$; $\eta_{ij}(u_1, u_2)$, $\eta^e_{ir}(u_1, u_2) : D_u \times D_u \to \mathbb{R}^+$ the inner-inner and inner-outer interaction rate among the subsystems, for $i, j \in \{1, 2, \ldots, n\}$ and $r \in \{1, 2, \ldots, m\}$; $\Gamma_{ij}(u_1, u_2, u) : D_u \times D_u \times D_u \to \mathbb{R}^+$, for $i, j \in \{1, 2, \ldots, n\}$, the function defined in (7); $\alpha_{ij}(u_1, u_2) : D_u \times D_u \to \mathbb{R}^+$ the function defined in (31); $\beta^i_{hk}(u_1, u_2, u) : D_u \times D_u \times D_u \to \mathbb{R}^+$ the function defined in (34), for $i, h, k \in \{1, 2, \ldots, n\}$; $\mathscr{A}_{ij}(u_1, u_2, u) : D_u \times D_u \times D_u \to \mathbb{R}^+$ the inner-inner probability density; $\mathscr{B}_{ir}(u_1, u_2, u)$ the inner-outer probability density; $g_{ir} = g_{ir}(t, v) = \epsilon_{ir}(t)\varrho_r(v) : [0, \infty[ \times D_u \to \mathbb{R}^+$ the distribution function of the external actions.

A vector function $\mathbf{f}(t, u)$, whose $i$th component is the distribution function of the $i$th functional subsystem $f_i = f_i(t, u) : [0, \infty) \times D_u \to \mathbb{R}^+$, is said to be solution of model (60) if the conditions (i), (ii), (iii), (iv), and (v) of Definition 2 and the conditions (vi), (vii), (viii), and (ix) of Definition 11 hold, and

(x) $\eta^e_{ir}(u, u_2)\varrho_r(u_2)$ is an integrable function with respect to the elementary measure $du_2$;

(xi) $f_i$ satisfies (60) for all $(t, u) \in [0, \infty) \times D_u$.

*Assumption 18.* In what follows we assume that $F_i = F$, $\tilde{\eta}_{ij} = \tilde{\eta}$, $\mu_{ij} = \mu$, $\varphi^i_{hk} = \varphi$, and $\tilde{\eta}^e_{ir} = \tilde{\eta}^e$ are constants and $\mathscr{A}_{ij}$ and $\mathscr{B}_{ir}$ are even functions with respect to $u \in D_u$, where $D_u = [-a, a]$ with $a > 0$. The following result holds true.

**Theorem 19.** *Assume that Assumption 18 holds. If there exists a nonnegative solution* $\mathbf{f}$ *of the thermostatted kinetic framework with particles refuge and nonconservative interactions* (60), *then the 1st-order moment* $\mathbb{E}_1[\mathbf{f}] = \mathbb{E}_1[\mathbf{f}](t)$ *is solution of the following Riccati nonlinear ordinary differential equation:*

$$\begin{aligned}\frac{d}{dt}\mathbb{E}_1[\mathbf{f}] &= F\left[\mathbb{E}_0[\mathbf{f}] - (\mathbb{E}_1[\mathbf{f}])^2\right] \\ &\quad + \left[\tilde{\eta}(\mu - 1)\mathbb{R}_0[\mathbf{f}] - \tilde{\eta}^e\delta_i(t)\right]\mathbb{E}_1[\mathbf{f}],\end{aligned} \tag{66}$$

*where*

$$\delta_i(t) = \sum_{r=1}^{m} \epsilon_{ir}(t) \int_{D_u} \varrho_r(v^*)\, dv^*. \tag{67}$$

*Proof.* The interaction operator $\mathscr{Z}_i[\mathbf{f}, \varrho](t, u)$ can be written as follows:

$$\begin{aligned}\mathscr{Z}_i[\mathbf{f}, \varrho](t, u) &= \mathscr{G}_i[\mathbf{f}](t, u) - \tilde{\eta}(1 - \mu) f_i(t, u)\mathbb{R}_0[\mathbf{f}] \\ &\quad + \tilde{\eta}\varphi m(t) + \mathscr{G}^e_i[\mathbf{f}](t, u) - \tilde{\eta}^e f_i(t, u)\delta_i(t),\end{aligned} \tag{68}$$

where

$$\begin{aligned}\mathscr{G}^e_i[\mathbf{f}](t, u) &= \tilde{\eta}^e \sum_{r=1}^{m} \epsilon_{ir}(t) \int_{D_u \times D_u} \mathscr{B}_{ir}(u_*, v^*, u) \\ &\quad \times f_i(t, u_*)\varrho_r(v^*)\, du_* dv^*, \\ \delta_i(t) &= \sum_{r=1}^{m} \epsilon_{ir}(t) \int_{D_u} \varrho_r(v^*)\, dv^*.\end{aligned} \tag{69}$$

Multiplying both sides of $\mathscr{Z}_i[\mathbf{f}, \varrho]$ by $u$ and integrating over $D_u$, we have

$$\begin{aligned}\int_{D_u} u\mathscr{Z}_i[\mathbf{f}, \varrho](t, u)\, du &= 0 - \tilde{\eta}(1 - \mu)\mathbb{R}_0[\mathbf{f}] \\ &\quad \times \int_{D_u} u f_i(t, u)\, du + 0 + 0 - \tilde{\eta}^e\delta_i(t) \\ &\quad \times \int_{D_u} u f_i(t, u)\, du.\end{aligned} \tag{70}$$

Summing up with respect to $i$, we obtain

$$\begin{aligned}&\sum_{i=1}^{n} \int_{D_u} u\, \mathscr{Z}_i[\mathbf{f}, \varrho](t, u)\, du \\ &\quad = \left[\tilde{\eta}(\mu - 1)\mathbb{R}_0[\mathbf{f}] - \tilde{\eta}^e\delta_i(t)\right]\mathbb{E}_1[\mathbf{f}],\end{aligned} \tag{71}$$

and the proof is gained. □

It is worth stressing that, as in the previous sections, if $p$ is an odd number, we are able to obtain the differential equation for the $\mathbb{E}_p[\mathbf{f}] = \mathbb{E}_p[\mathbf{f}](t)$ moment. Specifically for open systems, the moment $\mathbb{E}_p[\mathbf{f}]$ is solution of the following ordinary differential equation:

$$\begin{aligned}\frac{d}{dt}\mathbb{E}_p[\mathbf{f}] &= -\mathbb{E}_p[\mathbf{f}]\left(pF\mathbb{E}_1[\mathbf{f}] + \tilde{\eta}(\mu - 1)\mathbb{R}_0[\mathbf{f}]\right. \\ &\quad \left. -\tilde{\eta}^e\delta_i(t)\right) + pF\mathbb{E}_{p-1}[\mathbf{f}].\end{aligned} \tag{72}$$

It is easy to show that, if $\mathbb{E}_p[\mathbf{f}]$ is initially bounded, it remains bounded for all $t > 0$.

## 6. Concluding Remarks and Applications

The goal of this paper is the derivation of mathematical frameworks for the modeling of complex biological system with particles refuge and characterization of proliferative and mutative interactions. Moreover the roles of external actions acting on the system at the macroscopic and microscopic scales have been taken into account. These actions can refer to the action of the external environment or agents. The mathematical frameworks proposed in the present paper also refer to complex systems characterized by nonequilibrium circumstances (due to the actions of external macroscopic force fields) and particles that escape from interactions (particle refuge).

The evolution equation satisfied by moments of the solution belongs to the class of linear differential equations (for $p \neq 1$ odd number) and Riccati differential equations (for $p = 1$). As known, the general form of the Riccati differential equation reads

$$y'(t) + a(t)\, y(t) + b(t)\, y^2(t) + c(t) = 0, \tag{73}$$

which is a nonlinear ordinary differential equation, where $a(t)$, $b(t)$, and $c(t)$ are continuous functions defined on a subset of $\mathbb{R}^+$. The analytical method for solving Riccati equations of the form (73) is based on the knowledge of a particular solution. Indeed, let $\overline{y}(t)$ be a known solution of (73); then the general integral of (73) can be obtained as follows:

$$y(t) = \overline{y}(t) + \frac{1}{z(t)}, \tag{74}$$

with $z(t)$ being the general integral of the following first-order linear ordinary differential equation:

$$z'(t) - \left[a(t) + 2b(t)\,\overline{y}(t)\right] z(t) = b(t), \tag{75}$$

whose general integral reads

$$\begin{aligned} z(t) = {} & \exp\left(\int \left[a(t) + 2b(t)\,\overline{y}(t)\right] dt\right) \\ & \times \left(k + \int b(t) \exp\left(-\int \left[a(t) + 2b(t)\,\overline{y}(t)\right] dt\right) dt\right). \end{aligned} \tag{76}$$

Therefore we are able to obtain an explicit formula of the moments when a specific complex system is modeled, considering, as particular solution can be taken, the critical point of the framework, which is in particular a constant solution; see [21].

Differential equations fulfilled by moments with order of an even number $p$ have not been derived in the present paper. Indeed, following the same strategy performed in the whole paper, we are not able to give an explicit formula to the following integrals:

$$\int_{D_u} u^p \mathscr{A}_{ij}(u_*, u^*, u)\, du, \qquad \int_{D_u} u^p \mathscr{B}_{ik}(u_*, u^*, u)\, du, \tag{77}$$

without adding further assumptions on the terms of the thermostatted framework.

As already mentioned, applications of the particles refuge introduction refer to the modeling of complex biological systems, especially to the tumor escape during tumor-immune system competition; see, among others, papers [46–51]. As known, tumor escape occurs when the immune system response completely fails to control the tumor progression; the process results in the selection of tumor cell variants that are able to resist, avoid, or suppress the antitumor immune response, leading to the escape phase. During the escape phase, the immune system is no longer able to contain tumor progression, and a progressively growing tumor results; see, among others, papers [52, 53] and the references cited therein.

Research perspectives include the modeling of space dynamics [54] and the introduction of stochastic terms that model jump processes in the activity and/or in the velocity variable. Specifically in velocity-jump processes discontinuous changes in the speed or direction of an individual are generated by a Poisson process; see paper [55] and the references section. In particular the resulting thermostatted kinetic framework for each functional subsystem reads

$$\begin{aligned} & \partial_t f_i + \partial_u \left(F_i(u)\left(1 - u\int_{D_u} u\widetilde{f}(t,u)\, du\right) f_i(t,u)\right) \\ & \quad = \mathscr{X}_i[\mathbf{f}, \varrho] + \mathscr{U}_i[f_i], \end{aligned} \tag{78}$$

where the operator $\mathscr{U}_i[f_i]$, which is responsible for the modeling by an activity-jump process, is written as follows:

$$\begin{aligned} & \mathscr{U}_i[f_i](t,u) \\ & \quad = \varpi_i \int_{D_u} \left[U_i(u^*, u)\, f_i(t, u^*) - U_i(u, u^*)\, f_i(t,u)\right] du^*, \end{aligned} \tag{79}$$

with $\varpi_i$ being turning time and $U_i(u^*, u)$ the turning kernel which gives, for each functional subsystem, the probability that the activity $u^* \in D_u$ jumps into the activity $u \in D_u$ if a jump occurs; the interaction frequency is defined as follows:

$$\nu_i(u) = \int_{D_u} U_i(u^*, u)\, dv^*. \tag{80}$$

A further research perspective consists in the formal derivation of macroscopic equations by means of asymptotic limits. Specifically these limits are obtained by employing the mathematical methods developed in papers [8, 56–59] that use parabolic and/or hyperbolic scaling; see also the book [17]. Macroscopic equations are of great interest for the mathematical modeling at tissue scale. Indeed, they allow a complete micro/macrodescription [60]. This is part of the multiscale problem, which consists in linking the mathematical models derived at different scales; the interested reader is referred to the book [17].

The mathematical frameworks proposed in this paper established also interesting future research directions regarding the derivation of theoretical results. Indeed it is missing the proof of the existence and uniqueness of mild solution

for the nonconservative thermostatted Cauchy problems. Moreover the existence of solutions to the stationary problem is missing. Stationary solutions $f = f(u)$ satisfy the following system of thermostatted kinetic equations:

$$\partial_u \left(F_i(u) f_i(u)\right) - \mathcal{T}_i \left[F_i, \mathbf{f}\right](u) = \mathcal{Z}_i \left[\mathbf{f}, \varrho\right](u), \qquad (81)$$

where the meaning of each term can be recovered by the previous sections.

In this context, stationary solutions model nonequilibrium steady states. A nonequilibrium steady state is reached when the system is driven by external forces in a stationary nonequilibrium state where its properties do not change with time. The interested reader is referred to papers [19, 61–63] and the references cited therein.

It is worth stressing that most of the complex biological systems are such that the interaction rate, the proliferative/destructive rate, the mutative rate, and the probability density are conditioned by the distribution functions of the functional subsystems and/or low-order moments. This is the case of the nonlinear interactions. However, the analysis of thermostatted kinetic models which include nonlinear interactions is still a hard open problem and a few number of contributions can be found in the pertinent literature; see [64].

## Conflict of Interests

The author declares that there is no conflict of interests regarding the publication of this paper.

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