A Continuous-Time Markov Chain Modeling Cancer-Immune System Interactions

sciendo

CAIM
ISSN 2038-0909

Commun. Appl. Ind. Math. 9 (2), 2018, 106–118 DOI: 10.2478/caim-2018-0018

Research Article

A continuous–time Markov chain modeling cancer–immune system interactions

Diletta Burini[1], Elena De Angelis[2*], Mirosław Lachowicz[3],

[1]Dipartimento di Matematica, Università di Perugia, Perugia, Italy

[2]Dipartimento di Scienze Matematiche "Giuseppe Luigi Lagrange", Politecnico di Torino, Torino, Italy

[3]Institute of Applied Mathematics and Mechanics,
Faculty of Mathematics, Informatics and Mechanics,
University of Warsaw, Warsaw, Poland

[*]Email address for correspondence: elena.deangelis@polito.it

Communicated by Giorgio Fotia

Received on 01 12, 2017. Accepted on 02 2018, 05.

Abstract

In the present paper we propose two mathematical models describing, respectively at the microscopic level and at the mesoscopic level, a system of interacting tumor cells and cells of the immune system. The microscopic model is in terms of a Markov chain defined by the generator, the mesoscopic model is developed in the framework of the kinetic theory of active particles. The main result is to prove the transition from the microscopic to mesoscopic level of description.

Keywords: `Continuous--time Markov chain, Microscopic models, Mesoscopic model, KTAP theory, Cancer cells, Immune system`

AMS subject classification: `60J75, 92D25, 35Q92, 35R09, 37N25, 45K05`

1. Introduction

This paper proposes two mathematical models, describing respectively at the microscopic and at the mesoscopic level a system of interacting tumor cells and cells of the immune system, and the analysis of the transition from the first model to the second one.

The biology of cancer is a vast subject and, as a natural consequence, the literature devoted to the related mathematical models has itself been developing and expanding over the years.

Cancer is a multiscale process in which genetic mutations occurring at a subcellular level manifest themselves as functional changes at the cellular and tissue scale [1]. Cancer is characterized by a group of genetic diseases that cause autonomous and uncontrolled cell proliferation, evasion of cell death, self-construction of oxygen and nutrient supply and spreading of cancerous cells through metastasis (see e.g. [2,3] and references therein). There are many types of genetic variations found in cancer cells, including gene mutations and copy number variations. Genetic and epigenetic alterations can spread through a population of premalignant or cancer cells. Cells become cancerous after mutations accumulate in the various genes that control cell proliferation. The involvement of the immune system in all stages of the tumour life cycle, including prevention, maintenance and response to therapy, is recognized as central to understanding cancer development from a systemic point of view [4].

For most of the human life, the immune system successfully fought cancerous cells, killing them as they developed: that's its job. *Cancer immunology* is the branch of immunology that studies interactions between the immune system and cancer cells. For cancer to develop, the immune system must either be worn out, ineffective, unable to kill cancer cells as fast as they normally develop.

In the formation of cancer, i.e. *carcinogenesis* or *oncogenesis* or *tumorigenesis*, all begin in cells. Cancer starts with changes within the genes of one cell or a small group of cells: different cell interactions are important at different stages of tumour progression. Cell-cell interactions may dominate the early stages.

The present paper aims to describe the interactions between cancer cells and immune system at this stage of the development of the disease.

Two different models, developed at two different scales, will be presented. The first model, see [5], [6] as references, will describe the entire system of a fixed number N of interacting particles at the micro–scale level, in the framework of a Markov process. It can be referred to the description of a branching process of cell division, mutation events and cell death. The second model, see [7–9], describes the system at the mesoscopic level. It is developed in the framework of the kinetic theory of active particles, see [10–12] and references therein, and it describes the progression of the cells, namely the modification of their biological expression and mutation within Darwinian-type selective learning processes.

The main results consists in showing that the solutions of the corresponding nonlinear mesoscopic equation may be approximated by the solutions of the microscopic one, if N is sufficiently large. The paper is organized as follows. Section 2 and section 3 review the general framework leading to the description on the microscopic level and the relative stability. Section 4 contains the main results, dealing with the transition from Micro to Meso scale. Section 5 tackles the problem of reducing the complexity of the system and leads to the description on the mesoscopic level. Section 6 looks at research perspectives.

2. Microscopic scale: individually–based models

In this section we construct the microscopic model in terms of a Markov jump process: we introduce the linear generator that completely describes the evolution of the probability distribution at the microscopic scale that may approximates the solution of the corresponding macroscopic model.

The biological system under consideration is composed of N interacting cells (epithelial, cancer and immune cells) and it is divided into populations. Each cell or *agent* $n \in \{1, 2, ..., N\}$ is characterized by the pair (j_n, u_n), where $j_n \in \mathbb{J}$ defines the population of the n–element and $u_n \in \mathbb{U}$ its biological state (called "*activity*").

Referring to the subpopulations of the system, we assume that $\mathbb{J} = \{0, 1, 2, 3, 4\}$.

$j = 0$: The subpopulation $j = 0$ corresponds to the *reserve* ("Hades"), which consists of cells that have a sort of transient state. This population plays a special role because it does not have a direct biological meaning, but it serves as a container for possible events related to proliferation or destruction phenomena certainly present in the process of interaction between cancer and immune system. We introduce this population because the model is conservative (probabilistic) in nature. We assume that elements of this special population are independent of the biological state. The similar idea appeared in the book [13] (example c-Section 8.1).

$j = 1$: labels epithelial cells, whose function is to feed proliferative phenomena. It is supposed that the organism is a source of this kind of cells, so their quantity can be considered as constant in time. Proliferative events can generate cells with the same phenotype, but also cells with different phenotype toward the onset of cancer cells.

$j = 2$: The subpopulation $j = 2$ is of cancer cells, generated from the population $j = 1$, that have acquired the ability of suppressing the immune reaction. During the multistep development of human tumors, various biological capabilities, i.e. *hallmark capabilities*, are acquired by the tumor cells, [14]. The transition from population $j = 1$ to population $j = 2$ can be understood as the transition of the epithelial cells to the first hallmarks of cancer.

$j = 3$: The subpopulation $j = 3$ is of the innate immune system cells which have the ability to acquire, by a learning process, the capacity of contrasting the development of cancer cells.

$j = 4$: labels immune cells generated from the population $j = 3$, which have acquired the ability of contrasting the development of cancer cells of the population $j = 2$.

Referring to the biological state or activity, we refer to a discrete representation of this variable: $\mathbb{U} = \{u_1, \dots, u_i, \dots, u_r\}$, with $u_1 = 0$, $u_r = 1$, and $u_i < u_{i+1}$, for $i = 1, \dots, r-1$. We assume that it is heterogeneously distributed and that increasing values of the activity correspond to an increasing ability of each population to express its biological function.

Following the general framework, [6], [5], we consider the Markov chain setting, because the model refers to the probabilities on the discrete set. The corresponding *modified Liouville equations* describes

the evolution of probability, with microscopic representation of the system of N interacting agents. The linear generator, defining the modified Liouville equation, completely describes the time evolution of the probability at the micro-scale.

Let consider the n_1–agent which changes its population and/or its activity at random times due to the interaction with the n_2–agent. In the case of proliferative interactions we consider interactions between two agents n_2 and n_3 that give rise a new agent n_1: a shifting from $j = 0$ to $j_{n_1} \neq 0$.

The rate of interaction between two agents: The agent of j_{n_1}–th population with activity u_{n_1} and the agent of j_{n_2} population with activity u_{n_2} is given by function $a = a((j_{n_1}, u_{n_1}), (j_{n_2}, u_{n_2}))$ such that

$$0 \leq a\Big((j_{n_1}, u_{n_1}), (j_{n_2}, u_{n_2})\Big)\,, \tag{1}$$

for all $j_{n_1}, j_{n_2} \in \mathbb{J}$ and all $u_{n_1}, u_{n_2} \in \mathbb{U}$.

The transition into k–th population with activity v of an agent of j_{n_1}–th population with activity u_{n_1}, due to the interaction with agent of j_{n_2} population with activities u_{n_2} is defined by the function A such that

$$A = A\Big((k, v); (j_{n_1}, u_{n_1}), (j_{n_2}, u_{n_2})\Big) \geq 0\,, \tag{2}$$

for all $k, j_{n_1}, j_{n_2} \in \mathbb{J}$ and all $v, u_{n_1}, u_{n_2} \in \mathbb{U}$,

$$\sum_{k\in\mathbb{J}} \sum_{v\in\mathbb{U}} A\Big((k, v)\,;\, (j_{n_1}, u_{n_1}), (j_{n_2}, u_{n_2})\Big) = 1\,, \tag{3}$$

for all $j_{n_1}, j_{n_2} \in \mathbb{J}$ and all $u_{n_1}, u_{n_2} \in \mathbb{U}$ such that

$$a\Big(\,(j_{n_1}\,,\, u_{n_1}), (j_{n_2}, u_{n_2})\,\Big) > 0\,.$$

As we stated before, it is quite natural to assume that if $j_{n_k} = 0$ than the corresponding function do not depend on u_{n_k}: the agents in the reserve are not characterized by any activity.

The (microscopic) stochastic model is completely determined by the functions a and A. Different choices of the functions give rise to different microscopic stochastic models (Markov chains).

Let system be initially distributed according to the probability $\overset{\circ}{f}{}^N \in l^{(N)}$, where $l^{(N)} = \mathbb{R}^{2N}$ is the standard setting

$$\|f\|_N = \sum_{j_1\in\mathbb{J}} \sum_{u_1\in\mathbb{U}} \cdots \sum_{j_N\in\mathbb{J}} \sum_{u_N\in\mathbb{U}} \Big|f\Big((j_1, u_1), \ldots, (j_N, u_N)\Big)\Big|\,.$$

Time evolution is described by the following linear equation — the modified Liouville equation:

$$\frac{\mathrm{d}}{\mathrm{d}\,t} f^N = \Lambda_N f^N\,; \qquad f^N\Big|_{t=0} = \overset{\circ}{f}{}^N\,, \tag{4}$$

where Λ_N is the generator,

$$\begin{aligned}
&\Lambda_N f^N\Big((j_1, u_1), (j_2, u_2), ..., (j_N, u_N)\Big) \\
&= \tfrac{1}{N} \sum_{\substack{n_1, n_2 \\ n_1 \neq n_2}} \Bigg(\sum_{k\in\mathbb{J}} \sum_{v\in\mathbb{U}} A\big((j_{n_1}, u_{n_1}); (k, v), (j_{n_2}, u_{n_2})\big) a\big((k, v), (j_{n_2}, u_{n_2})\big) \\
&\times f^N\Big((j_1, u_1), \ldots, (j_{n_1-1}, u_{n_1-1}), (k, v), (j_{n_1+1}, u_{n_1+1}), \ldots, (j_N, u_N)\Big) \\
&- a\big((j_{n_1}, u_{n_1}), (j_{n_2}, u_{n_2})\big) f^N\big((j_1, u_1), \ldots, (j_N, u_N)\big)\Bigg)\,.
\end{aligned}$$

The operator Λ_N is the difference between the *gain* and *loss* term, where

- the *gain term* that is the term describing changes from state (k, v) of the n–agent into state (j_n, u_n) due to interaction with the m agent with state (j_m, u_m);
- the *loss term* that is the term describing changes from state (j_n, u_n) of the n–agent into another state due to the interaction with the m agent with state (j_m, u_m).

Transition from $k = 0$ into $j \neq 0$ means a birth of an individual of the population j whereas transition from $k \neq 0$ into $j = 0$ means a death of an individual of the population k.

We neglect the possibility of transition from $k = 0$ into $j = 0$ in the sense that the corresponding a vanishes.

The Cauchy Problem (4) has the unique solution given by the formula

$$f^N(t) = e^{t\Lambda_N} \overset{\circ}{f}{}^N$$

in $l^{(N)}$ for all $t \geq 0$. Furthermore, standard arguments show that the solution is nonnegative for nonnegative initial data and the $l^{(N)}$–norm is preserved

$$\|f^N(t)\|_N = \|\overset{\circ}{f}{}^N\|_N = 1\,, \qquad \text{for } t > 0\,. \tag{5}$$

From this, $\left(e^{t\Lambda_N}\right)_{t\geq 0}$ is a group of Markov operators on the discrete space.

We consider symmetric functions, that is

$$f^N\Big((j_1, u_1), \ldots, (j_N, u_N)\Big) = f^N\Big((j_{r_1}, u_{r_1}), \ldots, (j_{r_N}, u_{r_N})\Big)\,, \tag{6}$$

for all j_1,...,$j_N \in \mathbb{J}$, all u_1,...,$u_N \in \mathbb{U}$, and for any permutation $\{r_1, \ldots, r_N\}$ of the set $\{1, \ldots, N\}$.

We introduce the s–agent marginal probability $(1 \leq s < N)$

$$\begin{aligned} &f^{N,s}\Big((j_1, u_1), \ldots, (j_s, u_s)\Big) = \\ &= \sum_{j_{s+1}\in\mathbb{J}} \sum_{u_{s+1}\in\mathbb{U}} \cdots \sum_{j_N\in\mathbb{J}} \sum_{u_N\in\mathbb{U}} f^N\Big((j_1, u_1), \ldots, (j_N, u_N)\Big)\,, \end{aligned} \tag{7}$$

where $f^{N,N} = f^N$ and $f^{N,s'} \equiv 0$ if $s' > N$.

The function f^N satisfies Eq. (4) if and only if $f^{N,s}$ satisfy the following finite hierarchy of equations

$$\frac{d}{dt} f^{N,s} = \frac{s}{N}\Lambda_s f^{N,s} + \frac{N-s}{N}\Theta_{s+1} f^{N,s+1}\,, \tag{8}$$

for $s = 1, 2, \ldots, N$, where

$$\begin{aligned} &(\Theta_{s+1} f)\Big((j_1, u_1), \ldots, (j_s, u_s)\Big) = \\ &= \sum_{n=1}^{s} \Bigg(\sum_{k\in\mathbb{J}} \sum_{v\in\mathbb{U}} \sum_{l\in\mathbb{J}} \sum_{w\in\mathbb{U}} A\Big((j_n, u_n); (k, v), (l, w)\Big) a\Big((k, v), (l, w)\Big) \\ &\times f\Big((j_1, u_1), \ldots, (j_{n-1}, u_{n-1}), (k, v), (j_{n+1}, u_{n+1}), \ldots, (j_s, u_s), (l, w)\Big) \\ &- \sum_{k\in\mathbb{J}} \sum_{v\in\mathbb{U}} a\Big((j_n, u_n), (k, v)\Big) f\Big((j_1, u_1), \ldots, (j_s, u_s), (k, v)\Big) \Bigg)\,, \end{aligned}$$

Taking sufficiently large N we may expect that the solution of the finite hierarchy (8) approximates the solution of the following infinite hierarchy of equations

$$\frac{d}{dt} f^s = \Theta_{s+1} f^{s+1}\,, \qquad s = 1, 2, \ldots\,. \tag{9}$$

The integral versions of hierarchies (8) and (9) read

$$f^{N,s}(t) = F^{N,s} + \tfrac{s}{N}\int_0^t \Lambda_s f^{N,s}(t_1)\,\mathrm{d}t_1 + \\ + \tfrac{N-s}{N}\int_0^t \Theta_{s+1} f^{N,s+1}(t_1)\,\mathrm{d}t_1\,, \qquad s = 1,\dots,N\,, \tag{10}$$

and

$$f^{s}(t) = F^{s} + \int_0^t \Theta_{s+1} f^{s+1}(t_1)\,\mathrm{d}t_1\,, \qquad s = 1,2,\dots\,, \tag{11}$$

respectively.

The details of such an approach may be found in [5].

3. Stability

Although the linear (microscopic) model Eq. (4) is quite complex, its stability analysis usually (in some cases) can be easier than the analysis of the corresponding bilinear (mesoscopic) model Eq. (36). On may apply the general theory of continuous Markov chains or e.g. the Lasota–Yorke theorem, see [15,16] (and references therein) in one of its version.

Assume that A and a satisfies the following condition, cf. [17,18]:

Assumption 3.1. *There is $(j,u) \in \mathbb{J}\times\mathbb{U}$ such that for each pair $(k_1,v_1) \in \mathbb{J}\times\mathbb{U}$ and $(k_2,v_2) \in \mathbb{J}\times\mathbb{U}$ we have*

$$A\Big((j,u);(k_1,v_1),(k_2,v_2)\Big) > 0\,, \qquad a\Big((k_2,v_2),(k_2,v_2)\Big) > 0\,.$$

We say that a stochastic semigroup $T = T(t)$ on $l^{(N)}$ is asymptotically stable if there exists a probability f_* on $\mathbb{J}\times\mathbb{U}$ such

$$\lim_{t\to\infty} \|T(t)f - f_*\|_N = 0 \qquad \text{for all probabilities } f\,. \tag{12}$$

We have ([17,18])

Theorem 3.1. *Let (1), (2), (3) together with Assumption 3.1 be satisfied. Then the semigroup $e^{t\Lambda_N}$ is asymptotically stable.*

Proof. Let $a_+ = \frac{N-1}{2}\max a$. We rewrite Eq. (4) in the form

$$\frac{\mathrm{d}}{\mathrm{d}\,t} f^N = \Gamma_N f^N - a_+ f^N\,, \tag{13}$$

where Γ_N is a positive operator. Then

$$e^{t\,\Lambda_N}\,\overset{\circ}{f}{}^N = e^{-a_+\,t} e^{t\,\Gamma_N}\,\overset{\circ}{f}{}^N\,, \tag{14}$$

The semigroup $e^{t\,\Lambda_N}$ is asymptotically stable iff the operator $e^{t_0\,\Lambda_N}$, for some $t_0 > 0$, is asymptotically stable as the operator defining a discrete dynamical system, cf. [15,16]. We may consider e.g. $t_0 = 1$.

Let $n \geq 1$, we have

$$e^{n\,\Lambda_N}\,\overset{\circ}{f}{}^N = e^{\Lambda_N} e^{(n-1)\,\Lambda_N}\,\overset{\circ}{f}{}^N\,. \tag{15}$$

We note that $\hat{f}^N = e^{(n-1)\,\Lambda_N}\,\overset{\circ}{f}{}^N$ is a probability. On the other hand

$$e^{\Lambda_N}\hat{f}^N = e^{-a_+} e^{\Gamma_N}\hat{f}^N \geq e^{-a_+}\frac{1}{N!}\Gamma_N^N \hat{f}^N \geq \mathfrak{c}_N\,\|\hat{f}^N\|_N\,, \tag{16}$$

for any probability $\overset{\circ}{f}{}^N$, where $\mathfrak{c}_N$ is a positive (>0) constant (that depends on N and a_+).

Because $\|\hat{f}^N\| = 1$ we obtain

$$e^{n\,\Lambda_N}\,\overset{\circ}{f}{}^N \geq \mathfrak{c}_N\,, \tag{17}$$

for any $n \geq 1$ and any probability $\overset{\circ}{f}{}^N$.

Therefore a lower function for the semigroup $e^{t\Lambda_N}$ exists and the semigroup is stable — cf. [15,16]. □

4. Micro — Meso links

In order to derive the nonlinear equations resulting in the limit $N \to \infty$ i.e. at the mesoscopic level, from Eq. (4) the approach of [5] (c.f. [6,17,18]) may be used.

We assume that the process starts with a factorized probability

$$\overset{\circ}{f}{}^N = \overset{\circ}{f}{}^{N\otimes} := \underbrace{\overset{\circ}{f}\otimes\ldots\otimes\overset{\circ}{f}}_{N\times}, \tag{18}$$

where

$$\underbrace{\overset{\circ}{f}\otimes\ldots\otimes\overset{\circ}{f}}_{N\times}\Big((j_1,u_1),\ldots,(j_N,u_N)\Big) = \prod_{n=1}^{N}\overset{\circ}{f}\,(j_n,u_n),$$

i.e. N-fold outer product of the probability $\overset{\circ}{f}$.

In the limit $N\to\infty$, the (linear) modified Liouville equation (4) yields, [5], a nonlinear Boltzmann–like integro–differential equation that can be related to the mesoscopic description. In fact we may see that the propagation of chaos is held and the solution $f^s(t)$ to Eq. (11) is the s-product of solution $f(t)$ of the following nonlinear kinetic equation, see [5],

$$\frac{d}{dt}f(t,j,u) = G[f](t,j,u) - f(t,j,u)Lf(t,j,u)\,, \qquad (j,u)\in\mathbb{J}\times\mathbb{U}\,, \tag{19}$$

where G is the *gain term*,

$$G[f](t,j,u) = \\ = \sum_{k\in\mathbb{J}}\sum_{v\in\mathbb{U}}\sum_{l\in\mathbb{J}}\sum_{w\in\mathbb{U}} A\big((j,u);(k,v),(l,w)\big)a\big((k,v),(l,w)\big)f\big(t,(k,v)\big)f\big(t,(l,w)\big)\,,$$

and fLf is the *loss term*,

$$Lf\big(t,(j,u)\big) = \sum_{k\in\mathbb{J}}\sum_{v\in\mathbb{U}} a\big((j,u),(k,v)\big)f\big(t,(k,v)\big)\,.$$

By ref. [5] we have

Corollary 4.1. *Let Assumptions (1), (2), (3) be satisfied and $\overset{\circ}{f}$ be a probability on $\mathbb{J}\times\mathbb{U}$. Then, for each $T>0$, there exists an admissible hierarchy $\{f^s\}_{s=1,2,\ldots}$ such that*

(i) it is a unique solution of Eq. (11) with factorized initial data (18),
(ii) $f^s(t)$ is factorized,

$$f^s(t) = \Big(f(t)\Big)^{s\otimes}\,, \tag{20}$$

for all $0<t\leq T$ and $s=1,2,\ldots$, where $f(t)$ is the unique solution in $l^{(1)}$ of Eq. (19) with the initial datum $\overset{\circ}{f}$.

As a by–product, we obtain the existence (and uniqueness) of solutions to Eq. (19).

We may now state the theorem (cf. [5]) that defines the links between the solutions to Eq. (4) and to Eq. (19) or, in other words, that defines the transition from the microscopic level to the mesoscopic level.

Theorem 4.1. *Let Assumptions (1), (2), (3) be satisfied and* $\overset{\circ}{f}$ *be a probability on* $\mathbb{J}\times\mathbb{U}$*. Then, for each* $T>0$*, there exists* N_0 *such that for* $N\geq N_0$

$$\sup_{t\in[0,T]}\|f^{N,1}-f\|_{l^{(1)}}\leq\frac{c}{N^{\zeta}}\,, \tag{21}$$

where $f^N\in l^{(N)}$ *is the unique non–negative solution of Eq. (4) corresponding to the initial datum (18);* $f\in l^{(1)}$ *is the unique non–negative solution of Eq. (19) corresponding to the initial datum* $\overset{\circ}{f}$*; and* ζ*,* c *are positive constants that depend on* T*.*

Proof. See [5]. □

Theorem states that the solution to the (nonlinear) mesoscopic equation (36) may be approximated by the solutions of the (linear) microscopic equation (4), with properly chosen A and a, if both N and M are sufficiently large. Approximation may be realized by many possible microscopic equations (various A and a may taken into account).

If, on the other hand, N is not large, then the linear equation (4) related to the microscopic description, and the nonlinear equation (36) at the mesoscopic scale, may independently play important roles in the mathematical description of the complex processes, presumably giving different results. In such a case one may expect that the microscopic model gives results that are closer to reality.

5. Mesoscopic model

In this section we present a mesoscopic approach to the problem of the modeling Darwinian mutations and selection processes, [8,9]. The overall state of the system is described by the *discrete distribution function*

$$f(t,j,u),\quad j\in\mathbb{J},\quad u\in\mathbb{U} \tag{22}$$

which represents the number of agents (cells) from population j that, at time t, have the state u. As before it is natural to assume that if $j=0$ then f is independent of u, i.e.

$$f(t,0,u)=f(t,0)\qquad\forall\, t\geq 0,\quad\forall\, u\in\mathbb{U}\,.$$

The quantity,

$$n(t,j)=\sum_{u\in\mathbb{U}}f(t,j,u),\quad j\in\mathbb{J}, \tag{23}$$

gives the number of agents (cells) that, at time t, are in the j-th population; while the total number of cells at time t is normalized

$$\sum_{j\in\mathbb{J}}n(t,j)=1\quad\forall t\geq 0\,. \tag{24}$$

This latter condition is due to the role of population $j=0$, indeed its presence allows the conservation of the probability distributions.

This representation is consistent with the heterogeneous behavior of cells and with the need of reducing the large number of components.

The mathematical structure for such a system should describe the evolution in time of the probability functions $f(t, j, u)$. It is obtained by equating the variation rate of agents, in the corresponding state u of functional subsystem j, with the difference between the inlet and outlet fluxes from this state. In this way, the balance equation can be summarized as follows:

$$\frac{d}{dt} f(t, j, u) = T[f](t, j, u) + P[f](t, j, u)\,, \tag{25}$$

where T and P are suitable operators acting over the whole set of probability densities. Specifically,

- $P[f](t, j, u)$ denotes the gain, at time t, into the state u of the population j, due to proliferative events;
- $T[f](t, j, u)$ is the term modeling the other types of interactions, including the net flux, at time t, into the state u of the population j, due to interactions that only modify the micro–state, and/or the transition to the population $j = 0$, i.e. the loss, at time t, in the state u of the population j, due to destructive events. This term may also include the natural relaxation of the immune system at time t and in the state u of the population j, to a given healthy state.

This requires the modeling of interactions at the cellular level to compute the balance of agents in the elementary volume of the space of the microscopic states. If the f's are known, the overall behavior of the system is properly described not only by moments, but also by the distribution of biological activity of cells. Accordingly all emerging behaviors are put in evidence.

Let us now consider the problem of modeling a multicellular system consistently with the representation that has been given above. The guidelines to pursue such objective are the following:

i. Interactions involve not only immediate neighbors (short range interactions) but also the distant ones (long range interactions). In fact, living systems communicate each other directly or through media. Consequently, each agent interacts with all the others in a domain whose elements are able to communicate.
ii. Each cell plays a game with the surrounding cells lying in its interaction domain. This game modifies the state of the agents, while the strategy it expresses can also be modified by the shape of the heterogeneous distribution of the interacting cells. In some cases generates net proliferative and/or destructive events.
iii. Interactions are complex, namely the output of the game is not the linear superposition of its separated interactions, but a complex combination whose form depends on the strategy that all agents can develop.
iv. The output of the game can also generate, in the proliferative process, agents with a different structure (for instance, entities with a different phenotype).
v. The following agents play the game: *candidate*, whose distribution function is $f(t, k, v)$ and which interacts with field agents; *field*, whose distribution function is $f(t, l, w)$ and *test*, whose distribution function is $f(t, j, u)$. Candidate agents may acquire, in probability, the state of the test ones by interaction with the field agents.

Some guidelines toward the modeling of the quantities related to the interaction terms are suggested here in view of the derivation of the specific model proposed in this paper. A useful reference is that offered by the mathematical approach to the theory of evolution presented in [19]. In order to simplify the notation, let us denote by the abbreviation (j, u)–agent the meaning of cell belonging to the j–th population with state u.

- $\alpha\big((j, u), (k, v)\big)$ and $\lambda\big((j, u), (k, v)\big)$ are the encounter rates between the (j, u)–candidate with the (k, v)–field. It is assumed, according to [20], that it depends on the ability of interacting cells to recognize each other based on the distance between their states $|u - v|$.

- $\mathcal{B}\big((j,u);(j,v),(l,w)\big)$ is the transition probability that the (j,v)–candidate falls into the state u of the same population after an interaction with a (l,w)–field:

$$\sum_{j\in\mathbb{J}}\sum_{u\in\mathbb{U}}\mathcal{B}\Big((j,u);(j,v),(l,w)\Big)=1\,.$$

  For instance, it can be assumed that the activity variable has a trend toward an increase of progression that depends on the state of the interacting cells and on the overall action of the system.
- $\Lambda\big((j,u);(k,v),(l,w)\big)$ models the net proliferation rate into the (j,u)–state, due to interactions, occurring with rate $\lambda\big((k,v),(l,w)\big)$ between the (k,v)–candidate the (l,w)–field. Interactions can induce net proliferative events, which may generate, although with small probability, a daughter cell that presents genetic modifications with respect to the mother cell.

In some cases, these different cells represent the first mutation toward the onset of cancer cells. If these cells have the ability to overcome the immune defense, then further mutations can occur [21] toward progression [22] and hallmarks of cancer [14]. The modeling approach is based on the idea that these mutations occur with higher probability when progression increases. The general framework is that of mutations and Darwinian selection [19,23].

Remark 5.1. More general models can be obtained by assuming that the encounter rate α depends nonlinearly on the distribution functions over the microscopic states, i.e. α is an operator over f [8]. For example, a source of nonlinearity arises from the idea that two subsystems with close distributions are *affine* and hence interact with higher frequency. Thus, a dependence of $\alpha\big((k,v),(l,w)\big)$ on the *affinity distance* between the interacting agents distribution functions can be considered [8].

It is now possible to specify the terms appearing in the right–hand side of Eq. (25) and relate it with Eq. (19)

$$A\big((j,u);(j,v),(l,w)\big)=\mathcal{B}\big((j,u);(j,v),(l,w)\big)\,, \tag{26}$$

for any $k\neq 0$ and any $l\neq 0$,

$$a\big((k,v),(l,w)\big)=\alpha\big((k,v),(l,w)\big)\,, \tag{27}$$

for any $k\neq 0$ and any $l\neq 0$, and

$$a\big((k,v),(l,w)\big)=\alpha\big((k,v),(l,w)\big)=0\qquad\text{if}\quad l=0\,. \tag{28}$$

Moreover

$$A\big((j,u);(0,v),(l,w)\big)=\Lambda\big((j,u);(0,v),(l,w)\big)=\delta_{jl}\Lambda_0(u,w)\,, \tag{29}$$

where

$$\sum_{u\in\mathbb{U}}\Lambda_0(u,w)=1\qquad\forall\, w\in\mathbb{U}\,.$$

Finally

$$a\big((0,v),(l,w)\big)=\lambda\big((0,v),(l,w)\big)\,, \tag{30}$$

for all $l\neq 0$, is independent on $v\in\mathbb{U}$.

Eqs.(26)-(30) define the relationship between the microscopic and mesoscopic models. Their spirit lies in the fact that the interaction and destruction terms are treated as a one part. In other words the play between two object may either create a change of state or destruction of an agent.

Under some restrictive assumption, one may also consider a model in which the interactions which change only the state and the ones generating the destructions are separated, and are respectively denoted as conservative term and the destructive term.

We decompose the set $\big(\mathbb{J}\times\mathbb{U}\big)^2$ into the set defining the interactions that change only the state and only create destruction (shifting to $j=0$), respectively,

$$\big(\mathbb{J}\times\mathbb{U}\big)^2 \supseteq \mathbf{U}_C\cup\mathbf{U}_D\,,\qquad \mathbf{U}_C\cap\mathbf{U}_D=\emptyset\,, \tag{31}$$

and non of the sets $\mathbf{U}_C$ and $\mathbf{U}_D$ is empty.

We assume that

$$a\big((k,v),(l,w)\big)=0\,,\qquad \forall\,\big((k,v),(l,w)\big)\in\big(\mathbb{J}\times\mathbb{U}\big)^2\setminus\big(\mathbf{U}_C\cup\mathbf{U}_D\big)\,,$$

that means the interactions may either change the state (i.e. referring to $\mathbf{U}_C$) or create destruction (i.e. referring to $\mathbf{U}_D$).

The balance equation can now be summarized as follows:

$$\frac{d}{dt}f(t,j,u)=C[f](t,j,u)+P[f](t,j,u)+D[f](t,j,u), \tag{32}$$

where C, P, D are suitable operators acting over the whole set of probability densities. Specifically,

- $C[f](t,j,u)$ denotes the net flux, at time t, into the state u of the population j, due to "conservative" interactions that only modify the micro–state;
- $P[f](t,j,u)$ denotes the gain, at time t, into the state u of the population j, due to proliferative events;
- $D[f](t,j,u)$ denotes the loss, at time t, in the state u of the population j, due to destructive events;

and

- $\alpha_C\big((k,v),(l,w)\big)=a\big((k,v),(l,w)\big)\chi\Big(\big((k,v),(l,w)\big)\in\mathbf{U}_C\Big)$ and $\alpha_D\big((k,v),(l,w)\big)=a\big((k,v),(l,w)\big)\chi\Big(\big((k,v),(l,w)\big)\in\mathbf{U}_D\Big)$ in the "conservative" or destructive interactions, respectively, are the encounter rates between the (k,v)–candidate with the (l,w)–field.
- $\mathfrak{B}\big((j,u);(j,v),(l,w)\big)$, $j=1,2,3,4$, is the transition probability that the (j,v)–candidate falls into the state u of the same population after an interaction with a (l,w)–field:
$$\sum_{u\in\mathbb{U}}\mathfrak{B}\big((j,u);(j,v),(l,w)=1\,,$$
for any $\big((j,v),(l,w)\big)\in\mathbf{U}_C$.
- $\Lambda\big((j,u);(j,v),(l,w)\big)$ models the net proliferation rate into the (j,u)–state, due to interactions, occurring with rate $\lambda\big((j,v),(l,w)\big)$ between the (j,v)–candidate the (l,w)–field. Interactions can induce net proliferative events, which may generate, although with small probability, a daughter cell that presents genetic modifications with respect to the mother cell.
- $\nu\big(0;(k,v),(l,w)\big)=A\big(0;(k,v),(l,w)\big)=\frac{\delta_{j0}}{|\mathbb{U}|}$ models the net destruction rate into the (k,v)–state, due to interactions, occurring with rate $\alpha_D\big((k,v),(l,w)\big)$ between the (k,v)–candidate and the (l,w)–field, where $\big((k,v),(l,w)\big)\in\mathbf{U}_D$. Interactions can induce net destructive events in the sense that the immune system has the ability to kill a cancer cell.

It is now possible to specify the terms appearing in the right–hand side of the evolution equation (32):

$$\begin{aligned}&C[f](t,j,u)\;=\\&=\sum_{l=1}^{4}\sum_{v\in\mathbb{U}}\sum_{w\in\mathbb{U}}\mathfrak{B}\big((j,u);(j,v),(l,w)\big)\alpha_C\big((j,v),(l,w)\big)\,f(t,j,v)\,f(t,l,w)\\&-f(t,j,u)\sum_{k\in\mathbb{J}}\sum_{v\in\mathbb{U}}\alpha_C\big((j,u),(k,v)\big)\,f(t,k,v)\,,\end{aligned} \tag{33}$$

for $j = 1, 2, 3, 4\,,\ u \in \mathbb{U}\,;$

$$
\begin{aligned}
&P[f](t,j,u) \;= \\
&= \sum_{l\in\mathbb{J}} \sum_{v\in\mathbb{U}} \sum_{w\in\mathbb{U}} \Lambda\big((j,u);(j,v),(l,w)\big)\, \lambda\big((j,v),(l,w)\big)\; f(t,j,v)\, f(t,l,w) \\
&- f(t,j,u) \sum_{k\in\mathbb{J}} \sum_{v\in\mathbb{U}} \lambda\big((j,u),(k,v)\big)\, f(t,k,v)\,,
\end{aligned}
\tag{34}
$$

for $j = 1, 2, 3, 4\,,\ u \in \mathbb{U}\,;$

$$
\begin{aligned}
&D[f](t,j,u) \;= \\
&= \sum_{k,l\in\mathbb{J}} \sum_{v,w\in\mathbb{U}} \nu\big(0;(k,v),(l,w)\big)\, \alpha_D\big((k,v),(l,w)\big)\; f(t,k,v)\, f(t,l,w) \\
&- f(t,j,u) \sum_{k\in\mathbb{J}} \sum_{v\in\mathbb{U}} \alpha_D\big((j.u),(k,v)\big)\, f(t,k,v)
\end{aligned}
\tag{35}
$$

for $j = 0,\ u \in \mathbb{U}$.

The general class of bilinear systems of Boltzmann–like integro–differential equations describes the dynamics of elements undergoing kinetic binary interactions — see [6,24]. This type of equations can model interactions between pairs of elements of various populations at the mesoscopic scale.

The general mesoscopic model, Eq. (25), in a compact form reads

$$
\frac{d}{dt} f(t,j,u) = \mathcal{A}[f](t,j,u)\,, \quad j \in \mathbb{J}\,, \quad u \in \mathbb{U}\,.
\tag{36}
$$

Theorem 5.1. *Consider the IVP* (36) *with* $\overset{\circ}{f} \in l^{(1)}_{+}$. *Assume that conditions Eqs.* (1) – (3) *are satisfied. Then there exists a unique solution* $f = f(t)$ *in* $l^{(1)}$ *of the the IVP for Eq.* (36), *for any* $t > 0$. *Moreover, if* $\overset{\circ}{f}$ *is a probability then* $f(t)$ *is a probability for any* $t > 0$.

The conditions assure that the operator appearing at the right hand side of (36) is Lipschitz continuous in $l^{(1)}$ which proves the existence of a unique solution local in time. Positivity follows in a standard way. This together with the conservative properties leads to the global existence result. Finally the $l^{(1)}$–norm is conserved.

6. Research perspectives

In this paper we have linked two classes of models, developed respectively at the micro and at the meso scale. We have proved that the solutions of the corresponding nonlinear mesoscopic equation may be approximated by the solutions of the microscopic one, if N is sufficiently large.

A challenging open problem would be development of a theory of macroscopic limits corresponding to the microscopic or mesoscopic models. It would lead to the full scale description of the process in question. One may observe that except some particular cases — see [17,25] and references therein — that generally could be quite complex. The main question is what we are going to consider as a basic scale. If one accepts the models on macroscopic scale, for which generally the identification of parameters is easier — we may construct a class of the corresponding microscopic or macroscopic models. Then with the presence of experimental data on microscopic or mesoscopic scale we may choose a proper one among the classes. The mathematical framework of such approach was proposed in series of works — see [6,17,25]. An alternative but much difficult approach could be the modeling on microscopic (or mesoscopic) scale and finding a corresponding macroscopic limit (a kind of "*hydrodynamic limit*"). This is a challenging problem because of the difficulties both on the level of modeling at the agent–based scale and mathematical difficulties. On the mathematical level the starting point could be an identification of the equilibria for the models on microscopic and mesoscopic scales. In some cases — see [17] — it is

possible (and relatively easy), but in the general case it seems to be a difficult question. Using standard tools in the present paper we show that such an identification is possible under however rather strong assumptions — see Section 3. It can be treated as a preliminary step towards the general description of mathematical relationships between microscopic, mesoscopic and macroscopic scales.

Acknowledgements

M. Lachowicz was supported by the National Science Centre Poland Grant 2017/25/B/ST1/00051.

References

1. A. R. A. Anderson and P. K. Maini, Special issue: Mathematical oncology, *Bull. Math. Biol.*, vol. 280, pp. 945–953, 2018.
2. P. M. Altrock, L. L. Liu, and F. Michor, The mathematics of cancer: integrating quantitative models, *Nat. Rev. Cancer*, vol. 15, pp. 730–745, 2015.
3. M. P. Little, Cancer models, genomic instability and somatic cellular darwinian evolution, *Biology Direct*, vol. 5, pp. 1–19, 2010.
4. A. Konstorum, A. T. Vella, A. J. Adler, and R. C. Laubenbacher, Addressing current challenges in cancer immunotherapy with mathematical and computational modelling, *J. R. Soc. Interface*, vol. 14, p. 20170150, 2017.
5. M. Lachowicz, Individually–based Markov processes modeling nonlinear systems in mathematical biology, *Nonlinear Anal. Real World Appl.*, vol. 12, pp. 2396–2407, 2011.
6. J. Banasiak and M. Lachowicz, *Methods of small parameter in mathematical biology.* Basel: Birkhäuser, 2014.
7. N. Bellomo, A. Bellouquid, and E. De Angelis, The modelling of immune competition by generalised kinetic (boltzmann) models: review and research perspectives, *Math. Comput. Modelling*, vol. 37, pp. 65–86, 2003.
8. A. Bellouquid, E. De Angelis, and D. Knopoff, From the modeling of the immune hallmarks of cancer to a black swan in biology, *Math. Models Methods Appl. Sci.*, vol. 23, pp. 949–978, 2013.
9. E. De Angelis, On the mathematical theory of post-darwinian mutations, selection, and evolution, *Math. Models Methods Appl. Sci*, vol. 24, pp. 2723–2742, 2014.
10. N. Bellomo, *Modeling Complex Living Systems - A Kinetic Theory and Stochastic Game Approach.* Basel: Birkhäuser, 2008.
11. N. Bellomo, A. Bellouquid, L. Gibelli, and N. Outada, *A Quest Towards a Mathematical Theory of Living Systems.* Basel: Birkhäauser, 2017.
12. N. Bellomo, P. Degond, and E. Tadmor, eds., *Active Particles Volume 1 - Advances in Theory, Models, and Applications.* Basel: Birkhäauser, 2017.
13. A. D. Wentzell, *A course in the theory of stochastic processes.* McGraw-Hill International, 1981.
14. D. Hanahan and R. A. Weinberg, Hallmarks of cancer: The next generation, *Cell*, vol. 44, pp. 646–674, 2011.
15. A. Lasota and J. A. Yorke, Exact dynamical systems and the frobenius–perron operator, *Trans. Amer. Math. Soc.*, vol. 273, pp. 375–384, 1982.
16. R. Rudnicki, Models of population dynamics and their applications in genetics, in *From genetics to mathematics* (M.Lachowicz and J. Miękisz, eds.), pp. 103–147, New Jersey: World Sci., 2009.
17. M. Lachowicz, A class of microscopic individual models corresponding to the macroscopic logistic growth, *Math. Methods Appl. Sci.*, vol. 41, pp. 8446–8454, 2018.
18. M. Lachowicz, A class of individual–based models, *BIOMATH*, vol. 7, p. 1804127, 2018.
19. N. Bellomo and B. Carbonaro, Toward a mathematical theory of living system focusing on developmental biology and evolution: A review and prospectives, *Physics of Life Reviews*, vol. 8, pp. 1–18, 2011.

20. S. De Lillo and N. Bellomo, On the modeling of collective learning dynamics, *Appl. Math. Lett.*, vol. 24, pp. 1861–1866, 2011.
21. F. Michor, Y. Iwasa, and M. A. Nowak, Dynamics of cancer progression, *Nature Reviews Cancer*, vol. 4, pp. 197–205, 2004.
22. P. C. Nowell, Tumor progression: a brief historical perspective, *Seminars in Cancer Biology*, vol. 12, pp. 261–266, 2002.
23. R. A. Gatenby and T. L. Vincent, Evolutionary model of carcinogenesis, *Cancer Research*, vol. 63, pp. 6212–1620, 2003.
24. L. Arlotti, N. Bellomo, and M. Lachowicz, Kinetic equations modelling population dynamics, *Transport Theory Statist. Phys.*, vol. 29, pp. 125–139, 2000.
25. M. Lachowicz, Links between microscopic and macroscopic descriptions, in *Lecture Notes Math. 1940, Multiscale Problems in the Life Sciences. From Microscopic to Macroscopic* (J. Banasiak, V. Capasso, M. A. J. Chaplain, M. Lachowicz, and J. Miękisz, eds.), pp. 201–268, Berlin: Springer, 2008.