POLITECNICO DI TORINO
Repository ISTITUZIONALE

Macroscopic limit of a kinetic model describing the switch in T cell migration modes via binary interactions

Original
Macroscopic limit of a kinetic model describing the switch in T cell migration modes via binary interactions / Estrada-Rodriguez, G., Lorenzi, T.. - In: EUROPEAN JOURNAL OF APPLIED MATHEMATICS. - ISSN 0956-7925. - 34:1(2023), pp. 1-27. [10.1017/S0956792521000358]

Availability:
This version is available at: 11583/2956300 since: 2022-02-25T09:36:29Z

Publisher:
Cambridge University Press

Published
DOI:10.1017/S0956792521000358

Terms of use:

This article is made available under terms and conditions as specified in the corresponding bibliographic description in the repository

Publisher copyright
Cambridge University Press postprint/Author's Accepted Manuscript con licenza CC

This article has been published in a revised form in [Journal] [http://doi.org/XXX]. This version is published under a Creative Commons CC-BY-NC-ND. No commercial re-distribution or re-use allowed. Derivative works cannot be distributed. © copyright holder.

(Article begins on next page)

26 November 2026

arXiv:2008.12105v3 [q-bio.CB] 15 Sep 2021

Macroscopic limit of a kinetic model describing the switch in T cell migration modes via binary interactions

Gissell Estrada-Rodriguez* Tommaso Lorenzi†

Abstract

Experimental results on the immune response to cancer indicate that activation of cytotoxic T lymphocytes (CTLs) through interactions with dendritic cells (DCs) can trigger a change in CTL migration patterns. In particular, while CTLs in the pre-activation state move in a non-local search pattern, the search pattern of activated CTLs is more localised. In this paper, we develop a kinetic model for such a switch in CTL migration modes. The model is formulated as a coupled system of balance equations for the one-particle distribution functions of CTLs in the pre-activation state, activated CTLs and DCs. CTL activation is modelled via binary interactions between CTLs in the pre-activation state and DCs. Moreover, cell motion is represented as a velocity-jump process, with the running time of CTLs in the pre-activation state following a long-tailed distribution, which is consistent with a Lévy walk, and the running time of activated CTLs following a Poisson distribution, which corresponds to Brownian motion. We formally show that the macroscopic limit of the model comprises a coupled system of balance equations for the cell densities whereby activated CTL movement is described via a classical diffusion term, whilst a fractional diffusion term describes the movement of CTLs in the pre-activation state. The modelling approach presented here and its possible generalisations are expected to find applications in the study of the immune response to cancer and in other biological contexts in which switch from non-local to localised migration patterns occurs.

1 Introduction

The interaction between dendritic cells (DCs) and cytotoxic T lymphocytes (CTLs) plays a pivotal role in the immune response to cancer. DCs recognise the antigens expressed by cancer cells and present them to CTLs, which then become selectively activated against those antigens [28, 29]. Growing experimental evidence indicates that activation of CTLs via antigen presentation by DCs can bring about a switch in CTL migration modes [5, 17]. In fact, while CTLs in the pre-activation state move in a non-local search pattern, which enables them to rapidly scan DCs for the presence of possible tumour antigens, the search pattern of activated CTLs is more localised. This allows activated CTLs to stay within a confined area for longer, thus facilitating their encounter with tumour cells expressing the antigens they have been activated against.

Stochastic individual-based models of immune response to cancer taking explicitly into account this difference in movement between CTLs have recently been developed [19, 20]. In these models, cell motion is described as a space-jump process [22]. In particular, CTLs in the pre-activation state undergo a space-jump process consistent with a Lévy walk, whereas a space-jump process corresponding to Brownian motion is used to describe the movement of activated CTLs. Such individual-based models enable representation of biological

*Sorbonne Université, CNRS, Université de Paris, Inria, Laboratoire Jacques-Louis Lions UMR7598, F-75005 Paris, France (estradarodriguez@ljll.math.upmc.fr)

†Department of Mathematical Sciences "G. L. Lagrange", Dipartimento di Eccellenza 2018-2022, Politecnico di Torino, 10129 Torino, Italy (tommaso.lorenzi@polito.it)

processes at the level of single cells and account for possible stochastic variability in cell dynamics, which allow for greater adaptability and higher accuracy in mathematical modelling. However, as the numerical exploration of these models requires large computational times for clinically relevant cell numbers (e.g. cell numbers of orders of magnitude between 10^6 and 10^9 [3]) and the models are not analytically tractable, it is desirable to derive corresponding deterministic continuum models in a suitable limit.

In this paper, integrating the ideas proposed in [19, 20] with the modelling approach presented in [11, 12], we develop a kinetic model for the switch in CTL migration modes that is caused by activation through interactions with DCs. Cells are grouped into three populations: CTLs in the pre-activation state (i.e. inactive CTLs), activated CTLs and DCs. In the model, DCs are assumed to present a given tumour antigen on their surface so that they can activate inactive CTLs by contact. Since the focus of this study is on the mathematical modelling of the change in CTL migration mode upon activation, we do not take into account biological processes involving cell division and death. Furthermore, for simplicity, we do not consider the occurrence of molecular processes leading activated CTLs to re-enter a pre-activation state [30].

The model is formulated as a coupled system of balance equations for the one-particle distribution functions of the three cell populations. CTL activation is modelled as a process of population switching among CTLs induced by binary interactions between inactive CTLs and DCs. Moreover, cell motion is represented as a velocity-jump process [22], with the running time of inactive CTLs following a long-tailed distribution, which is consistent with a Lévy walk [11, 12], and the running time of activated CTLs following a Poisson distribution, which corresponds to Brownian motion. Using a method similar to that previously employed in [11], we formally show that the macroscopic limit of this model comprises a coupled system of balance equations for the cell densities, whereby activated CTL movement is described via a classical diffusion term, whilst a fractional diffusion term describes the movement of CTLs in the pre-activation state.

The paper is organised as follows. In Section 2, we introduce the modelling strategies and the main assumptions used to describe the spatio-temporal dynamics of CTLs and DCs at the scale of single cells, which provide a microscopic representation of the biological system. In Section 3, we present the kinetic model, which constitutes a mesoscopic analogue of the underlying microscopic scale model. In Section 4, we derive the macroscopic limit of a suitably rescaled version of the kinetic model. Section 5 concludes the paper providing a brief overview of possible research perspectives.

2 Description of the system at the microscopic scale

Biological system and cell populations We label the three cell populations by a letter $h \in \{A, D, I\}$, that is, activated CTLs are labelled by $h = A$, DCs are labelled by $h = D$ and inactive CTLs are labelled by $h = I$. We let the total number of cells in the system be denoted by $N = N_D + N_T$, where $N_D \in \mathbb{N}$ is the number of DCs and $N_T \in \mathbb{N}$ is the total number of CTLs. Moreover, we describe the number of inactive and activated CTLs in the system at time $t \in \mathbb{R}_+$ by means of the functions $N_I(t)$ and $N_A(t)$, respectively, with $N_I(t) + N_A(t) = N_T$ for all t.

Mathematical representation of individual cells Every individual cell is modelled as a sphere of diameter $\varrho \in \mathbb{R}_+^*$ and is labelled by an index $i = 1, \ldots, N$. The phase-space state of the i^{th} cell is represented by a pair $(\mathbf{x}_i, \mathbf{v}_i)$, where the vector $\mathbf{x}_i \in \mathbb{R}^n$ describes the position of the centre of the cell and the vector $\mathbf{v}_i \in \mathrm{V} \subset \mathbb{R}^n$, with $\mathrm{V} := \{\mathbf{v}_i \in \mathbb{R}^n : |\mathbf{v}_i| = 1\}$ (i.e. V is the unit n-sphere), represents the direction of the cell velocity. Moreover, the magnitude of the cell velocity is assumed to be constant and is denoted by $c \in \mathbb{R}_+^*$. The value of $n = 1, 2, 3$ depends on the biological scenario under study.

2.1 Description of cell motion

Velocity-jump process We describe the motion of a cell labelled by an index i as a run-and-tumble process with run time $\tau_i \in \mathbb{R}_+^*$ and running probability $\psi(\mathbf{x}_i, \tau_i)$, where $0 < \psi(\cdot,\cdot) \leq 1$ and $\partial_{\tau_i}\psi(\cdot,\cdot) \leq 0$. The running probability $\psi(\mathbf{x}_i, \tau_i)$ correlates with the stopping rate $\beta(\mathbf{x}_i, \tau_i)$ through the relations given by the following definition [11]

$$\psi(\mathbf{x}_i, \tau_i) \coloneqq \exp\left(\int_0^{\tau_i} \beta(\mathbf{x}_i, s)\,\mathrm{d}s\right) \ , \quad \beta = \frac{\varphi}{\psi} \quad \text{with} \quad \varphi := -\partial_{\tau_i}\psi \ . \tag{2.1}$$

Hence, starting at position $\mathbf{x}_i$ at time t, the i^{th} cell will continue moving along a straight path in the direction given by the vector $\mathbf{v}_i$ with constant speed c for a period of time τ_i, after which it may stop with rate $\beta(\mathbf{x}_i, \tau_i)$. The cell will then instantaneously resume moving in a new randomly selected direction given by a vector $\bar{\mathbf{v}}_i$, which is prescribed by a turning kernel $\ell(\mathbf{x}_i, t, \mathbf{v}_i; \bar{\mathbf{v}}_i)$ – i.e. cells undergo a velocity-jump process [22].

Running probability The running probability $\psi(\mathbf{x}_i, \tau_i)$ determines the distribution of the running time τ_i and depends on the way in which the i^{th} cell moves. Note that the running probability is here assumed to be independent from the cell velocity $\mathbf{v}_i$. On the basis of experimental evidence reported in [5, 10], we assume that inactive CTLs move in a non-local search pattern corresponding to trajectories that are characterised by a strong presence of long runs, which enable them to cover larger areas. On the other hand, activated CTLs and DCs[1] move in a more localised search pattern. In particular, building upon the modelling approach presented in [20], we describe the motion of activated CTLs and DCs as a Brownian motion, whereas we let inactive CTLs undergo superdiffusive motion consistent with a Lévy walk, whereby the mean square displacement grows nonlinearly with time. In particular, the mean-square displacement at time t is proportional to $t^{2/\alpha}$, where $\alpha \in (1, 2)$ is the Lévy exponent. We recall that $\alpha = 1$ and $\alpha = 2$ would correspond to ballistic motion (i.e. a form of motion whereby the mean-square displacement at time t is proportional to t^2) and classical diffusion, respectively.

Under these assumptions, if the i^{th} cell belongs to population A or population D, we let the value of the running time τ_i follow a Poisson distribution [23]. Hence, under the additional simplifying assumption that cells in populations A and D are characterised by the same stopping rate, which is assumed to be constant and thus modelled by a parameter $b \in \mathbb{R}_+^*$, we use the following definition of the running probability

$$\psi(\mathbf{x}_i, \tau_i) \equiv \psi(\tau_i) := \exp\left(-b\,\tau_i\right), \quad \varphi(\mathbf{x}_i, \tau_i) \equiv \varphi(\tau_i) := b\,\exp\left(-b\,\tau_i\right) \ . \tag{2.2}$$

On the other hand, if the i^{th} cell belongs to population I, we let the value of the running time τ_i follow a long-tailed distribution, and we define the running probability along the lines of [11] as

$$\psi(\mathbf{x}_i, \tau_i) := \left(\frac{\tau_0(\mathbf{x}_i)}{\tau_0(\mathbf{x}_i) + \tau_i}\right)^{\alpha}, \quad \varphi(\mathbf{x}_i, \tau_i) := \frac{\alpha\,\tau_0(\mathbf{x}_i)^{\alpha}}{(\tau_0(\mathbf{x}_i) + \tau_i)^{\alpha+1}}, \quad \alpha \in (1, 2) \ . \tag{2.3}$$

Here, the function $\tau_0(\mathbf{x}_i) \geq 0$ captures possible spatial inhomogeneities in the running time distribution.

Turning kernel and turning operator We consider the case where the new direction of cell motion given by $\bar{\mathbf{v}}_i$ is symmetrically distributed with respect to the original direction given by $\mathbf{v}_i$ and, therefore, we let the turning kernel $\ell(\mathbf{x}_i, t, \mathbf{v}_i; \bar{\mathbf{v}}_i)$ satisfy the following assumptions [2]

$$\ell(\mathbf{x}_i, t, \mathbf{v}_i; \bar{\mathbf{v}}_i) \equiv \ell(\mathbf{x}_i, t, |\bar{\mathbf{v}}_i - \mathbf{v}_i|) \ , \quad \int_{\mathrm{V}} \ell(\cdot,\cdot,|\mathbf{v}_i - \mathbf{e}_1|)\,\mathrm{d}\mathbf{v}_i = 1 \ , \tag{2.4}$$

[1] We remind the reader that we consider DCs presenting a given tumour antigen on their surface.

where $\mathbf{e}_1 = (1, 0, \ldots, 0) \in \mathbb{R}^n$ is a unit vector.

Moreover, we let the integral operator $\mathcal{T}$ be a turning operator such that for all test functions $\phi(\mathbf{v}_i)$

$$\mathcal{T}[\phi](\cdot, \cdot, \bar{\mathbf{v}}_i) = \int_{\mathrm{V}} \ell(\cdot, \cdot, \mathbf{v}_i; \bar{\mathbf{v}}_i)\phi(\mathbf{v}_i)\, \mathrm{d}\mathbf{v}_i \ , \tag{2.5}$$

where ℓ is the turning kernel defined via (2.4). Since $\displaystyle\int_{\mathrm{V}} \ell(\cdot, \cdot, \cdot; \bar{\mathbf{v}}_i)\, \mathrm{d}\bar{\mathbf{v}}_i = 1$, we have

$$\int_{\mathrm{V}} (\mathbb{1} - \mathcal{T})[\phi](\cdot, \cdot, \bar{\mathbf{v}}_i)\, \mathrm{d}\bar{\mathbf{v}}_i = 0 \ , \tag{2.6}$$

where $\mathbb{1}$ is the identity operator.

Finally, we recall that in n-dimensions the surface area of the unit sphere V is

$$|\mathrm{V}| = \begin{cases} \dfrac{2\pi^{n/2}}{\Gamma\left(\frac{n}{2}\right)} \ , & \text{for } n \text{ even}, \\ \dfrac{\pi^{n/2}}{\Gamma\left(\frac{n}{2} + 1\right)} \ , & \text{for } n \text{ odd} \end{cases} \tag{2.7}$$

where $\Gamma(\cdot)$ is the Gamma function, and we also recall some useful properties of the spectrum of the turning operator $\mathcal{T}$ [2]:

Lemma 1. *If the turning kernel $\ell(\cdot, \cdot, |\bar{\mathbf{v}}_i - \mathbf{v}_i|)$ is continuous, then $\mathcal{T}$ is a symmetric compact operator. In particular, there exists an orthonormal basis of $L^2(\mathrm{V})$ consisting of eigenfunctions $\{\phi_k,\ k \geq 0\}$ of $\mathcal{T}$. Using the notation $\mathbf{v}_i = (v_0^i, v_1^i, \ldots, v_{n-1}^i) \in \mathrm{V}$, we have:*

$$\phi_0(\mathbf{v}_i) = \frac{1}{|\mathrm{V}|} \quad \textit{is an eigenfunction associated with the eigenvalue} \quad \iota_0 = 1,$$

$$\phi_1^j(\mathbf{v}_i) = \frac{n v_j^i}{|\mathrm{V}|} \quad \textit{are eigenfunctions associated with the eigenvalue}$$

$$\iota_1 = \int_{\mathrm{V}} \ell(\cdot, \cdot, |\bar{\mathbf{v}}_i - \mathbf{e}|)\bar{v}_1^i\, \mathrm{d}\bar{\mathbf{v}}_i < 1, \tag{2.8}$$

where $\mathbf{e} = (1, 1, \ldots, 1) \in \mathbb{R}^n$ is the vector with all components equal to 1. Moreover, any function $p_i \in L^2(\mathbb{R}^n \times \mathbb{R}_+ \times \mathrm{V})$ admits a unique decomposition of the form

$$p_i = \frac{1}{|\mathrm{V}|}\left(\rho_i + n\mathbf{v}_i \cdot w_i\right) + \hat{z}, \tag{2.9}$$

where $\hat{z}$ is orthogonal to all linear polynomials in $\mathbf{v}_i$,

$$\rho_i(\mathbf{x}_i, t) = \int_{\mathrm{V}} p_i(\mathbf{x}_i, t, \mathbf{v}_i)\phi_0(\mathbf{v}_i)\, \mathrm{d}\mathbf{v}_i, \quad w_i^j(\mathbf{x}_i, t) = \int_{\mathrm{V}} p_i(\mathbf{x}_i, t, \mathbf{v}_i)\phi_1^j(\mathbf{v}_i)\, \mathrm{d}\mathbf{v}_i,$$

and $w_i = (w_0^i, \ldots, w_{n-1}^i)$.

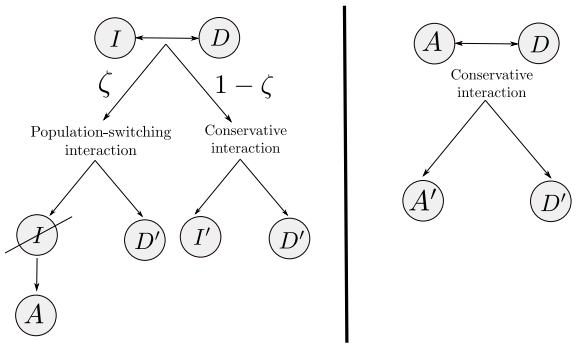


Figure 1: Schematics of cell-cell interactions corresponding to Assumptions 1 and 2. Prime symbols indicate a change in cell velocity upon interaction.

2.2 Description of the interactions between cells

Building on previous work on individual-based models of interaction dynamics between DCs and CTLs [19, 20], we consider only the effects of binary cell-cell interactions, thus neglecting interactions that involve more than two cells.

Moreover, given that the focus of this work is on modelling the switch in T cell migration modes mediated by interactions between inactive CTLs and DCs, we explicitly model the effects of interactions between cells of population I and cells of population D, while for simplicity, we neglect the effects of intrapopulation cell-cell interactions and interactions between cells of population I and cells of population A.

Furthermore, the spatial dynamics of DCs are primarily affected by interactions with inactive CTLs [6, 14, 26]. Hence, for simplicity, we explicitly model the effect of interactions between cells of population D and cells of population A on the motion of A cells, while we neglect the effect of these interactions on the motion of D cells, since we take it to be negligible compared to that of interactions with cells of population I.

On the basis of these considerations, we incorporate into the model only the effects of interactions between pairs of cells that are summarised by the schematics in Figure 1, which correspond to the following definitions and assumptions.

Definition 1. (Conservative interactions) *Conservative interactions are those that preserve the number of cells in every population and only modify the velocity of the cells according to* (2.11)*. Otherwise, the interaction is a population-switching interaction.*

Definition 2. (Population-switching interactions) *Population-switching interactions are those that lead a cell to enter a different population. These interactions are destructive for the original population of the cell and creative for the population in which the cell will be upon interaction.*

Assumption 1 (**Interactions between inactive CTLs and DCs).** We model activation of CTLs upon interaction with DCs by assuming that, when a cell in population I interacts with a cell in population D, the I cell switches from population I to population A (i.e. the interaction is population-switching in the sense of Definition 2) with probability $\zeta \in (0, 1)$. For simplicity, we assume that the I cell enters population A without changing its velocity. If activation does not occur, event that happens with probability $1 - \zeta$, the I cell remains in the same population (i.e. the interaction is conservative in the sense of Definition 1) and acquires the post-interaction velocity defined via (2.11). Upon interaction, the D cell always acquires a post-interaction velocity defined as in (2.11).

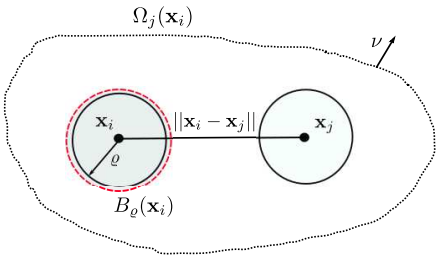


Figure 2: Schematics of the interaction domain defined in (2.10).

Assumption 2 (Interactions between activated CTLs and DCs). We assume that when a cell in population A interacts with a cell in population D, the A cell remains in the same population and acquires the post-interaction velocity defined via (2.11), and the interaction is conservative in the sense of Definition 1. As explained above, we do not take into account the effect of interactions between cells of population D and cells of population A on the motion of the D cells.

We allow interactions between a cell i in the phase-space state $(\mathbf{x}_i, \mathbf{v}_i)$ and a cell j in the phase-space state $(\mathbf{x}_j, \mathbf{v}_j)$ to occur when the cell j is in the domain of interaction of the cell i, which is defined as the set

$$\Omega_j(\mathbf{x}_i) := \{\mathbf{x}_j \in \mathbb{R}^n : |\mathbf{x}_i - \mathbf{x}_j| \geq \varrho\} \equiv \mathbb{R}^n \setminus \mathrm{B}_\varrho(\mathbf{x}_i) \ , \tag{2.10}$$

where $\mathrm{B}_\varrho(\mathbf{x}_i)$ denotes the ball of radius ϱ centred at $\mathbf{x}_i$. If a cell i acquires a new velocity upon interaction with a cell j, the new velocity is defined, for simplicity, as the following post-interaction velocity

$$\mathbf{v}_i' = \mathbf{v}_i - 2\,(\mathbf{v}_i \cdot \nu)\,\nu \quad \text{with} \quad \nu := \frac{\mathbf{x}_i - \mathbf{x}_j}{|\mathbf{x}_i - \mathbf{x}_j|} \ , \tag{2.11}$$

where ν is the normal vector at the point of interaction (i.e. ν is the unit normal that points outward from $\Omega_j(\mathbf{x}_i)$ and inward to $\mathrm{B}_\varrho(\mathbf{x}_i)$) [7].

Remark 1. *Definition* (2.11) *relies on the observation that, although binary collisions between cells are not elastic in nature, they may result in cell outgoing trajectories compatible with those observed in elastic collisions [1, 18].*

3 Mesoscopic scale model

In this section, we derive the mesoscopic scale model corresponding to the microscopic scale description presented in Section 2, which comprises a system of transport equations for the one-particle distribution functions of inactive CTLs, activated CTLs and DCs.

3.1 Preliminaries, assumptions and notation

The state of the system at time t is described by the N-particle distribution function [7, 27]

$$f^N\left(\mathbf{x}_1, \ldots, \mathbf{x}_N, t, \mathbf{v}_1, \ldots, \mathbf{v}_N, \tau_1, \ldots, \tau_N\right).$$

In the case where cell dynamics at the microscopic scale obey the rules presented in Section 2, the evolution of f^N is governed by the following transport equation [16]

$$\partial_t f^N + \sum_{i=1}^{N} \Big(\partial_{\tau_i} f^N + c\, \mathbf{v}_i \cdot \nabla_{\mathbf{x}_i} f^N \Big) = -\sum_{i=1}^{N} \beta\, f^N \tag{3.1}$$

posed on $\Omega^N \times \mathbb{R}_+^* \times \mathrm{V}^N \times \mathbb{R}_+^{*N}$, with

$$\Omega^N := \{(\mathbf{x}_1, ..., \mathbf{x}_N) \in \mathbb{R}^{n\times N} : \ |\mathbf{x}_i - \mathbf{x}_j| \geq \varrho \ \forall i, j\} \ .$$

We consider the transport equation (3.1) subject to smooth, compactly supported initial conditions at $t = 0$, boundary conditions corresponding to elastic interactions on $\partial\Omega^N$, and suitable Dirichlet boundary conditions at $\tau_i = 0$ linked to the running probability ψ for $i = 1, \ldots, N$. In the mathematical framework given by (3.1), the probability of finding at position $\mathbf{x}_1$ and at time t the cell labelled by the index 1 that is moving in direction $\mathbf{v}_1$ for a period of time τ_1 is related to the one-particle marginal

$$f(\mathbf{x}_1, t, \mathbf{v}_1, \tau_1) = \frac{1}{|\mathrm{V}|^{N-1}} \int_{[0,t]^{N-1}} \int_{\Omega_{N-1}(\mathbf{x}_1)} \int_{\mathrm{V}^{N-1}} f^N(\mathbf{x}_1, \ldots, \mathbf{x}_N, t, \mathbf{v}_1, \ldots, \mathbf{v}_N, \tau_1, \ldots, \tau_N) \\ \times \mathrm{d}\mathbf{v}_2\, \mathrm{d}\mathbf{x}_2\, \mathrm{d}\tau_2 \ldots \mathrm{d}\mathbf{v}_N\, \mathrm{d}\mathbf{x}_N\, \mathrm{d}\tau_N \ .$$

Here, $|\mathrm{V}|$ denotes the surface area of the unit sphere V and $\Omega_{N-1}(\mathbf{x}_1) \coloneqq \{(\mathbf{x}_2, \ldots, \mathbf{x}_N) \in \mathbb{R}^{n\times N-1} : (\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_N) \in \Omega^N\}$.

A comprehensive description of cell dynamics would in principle require considering possible interactions between all cells. However, as mentioned earlier, building on previous work on the mathematical modelling of the interaction dynamics between DCs and CTLs [19, 20], we consider only the effect of binary cell-cell interactions, thus neglecting interactions that involve more than two cells. Therefore, as per the scaling and assumptions introduced in Section 4.1, which are similar to those typically considered in low-density regimes [7, 22, 27], we truncate the hierarchy of equations corresponding to (3.1) at the second order by integrating out cells $3, \ldots, N$ from the N-particle distribution function $f^N(\mathbf{x}_1, \ldots, \mathbf{x}_N, t, \mathbf{v}_1, \ldots, \mathbf{v}_N, \tau_1, \ldots, \tau_N)$.

Two-particle distribution functions Let $f_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k, \tau_h, \tau_k)$ with $h, k \in \{A, D, I\}$ and $k \neq h$ denote the two-particle distribution function associated with:

- a cell of population h in the generic phase-space state $(\mathbf{x}_h, \mathbf{v}_h) \in \mathbb{R}^n \times \mathrm{V}$, with generic run time $\tau_h \in [0, t]$ and stopping rate $\beta_h(\mathbf{x}_h, \tau_h)$ defined via (2.1);
- a cell of population k in the generic phase-space state $(\mathbf{x}_k, \mathbf{v}_k) \in \mathbb{R}^n \times \mathrm{V}$, with generic run time $\tau_k \in [0, t]$ and stopping rate $\beta_k(\mathbf{x}_k, \tau_k)$ defined via (2.1).

Truncating the hierarchy of equations corresponding to (3.1) at the second order, we obtain the following transport equation for $f_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k, \tau_h, \tau_k)$

$$(\partial_t + \partial_{\tau_h} + \partial_{\tau_k} + c\, \mathbf{v}_h \cdot \nabla_{\mathbf{x}_h} + c\, \mathbf{v}_k \cdot \nabla_{\mathbf{x}_k}) f_{hk} = -(\beta_h + \beta_k) f_{hk} \tag{3.2}$$

posed on $\Omega^2 \times \mathbb{R}_+ \times \mathrm{V}^2 \times \mathbb{R}_+^{*2}$, with

$$\Omega^2 := \{(\mathbf{x}_h, \mathbf{x}_k) \in \mathbb{R}^{n\times 2} : \ |\mathbf{x}_h - \mathbf{x}_k| \geq \varrho \ \ \forall h, k\} \ . \tag{3.3}$$

This equation is subject to a smooth, compactly supported initial condition at $t = 0$, specular reflective boundary conditions corresponding to elastic interactions on $\partial\Omega^2$, and with boundary conditions at $\tau_k = 0$ and $\tau_h = 0$ given by

$$\begin{aligned} f_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k, \tau_h, \tau_k = 0) &= \mathcal{T} \int_0^t \beta_k f_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k, \tau_h, \tau_k)\, \mathrm{d}\tau_k \ , \\ f_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k, \tau_h = 0, \tau_k) &= \mathcal{T} \int_0^t \beta_h f_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k, \tau_h, \tau_k)\, \mathrm{d}\tau_h \ . \end{aligned} \tag{3.4}$$

One-particle distribution functions Given the two-particle distribution function

$$\tilde{\tilde{f}}_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k) := \int_0^t \int_0^t f_{hk}\, \mathrm{d}\tau_h\, \mathrm{d}\tau_k \ , \tag{3.5}$$

the one-particle distribution function of population h is given by

$$p_h(\mathbf{x}_h, t, \mathbf{v}_h) := \frac{1}{|\mathrm{V}|} \int_{\Omega_k(\mathbf{x}_h)} \int_{\mathrm{V}} \tilde{\tilde{f}}_{hk}\, \mathrm{d}\mathbf{v}_k\, \mathrm{d}\mathbf{x}_k \ , \tag{3.6}$$

with the set $\Omega_k(\mathbf{x}_h)$ defined via (2.10). The function $p_h(\mathbf{x}_h, t, \mathbf{v}_h)$ describes the density of cells of population h which at position $\mathbf{x}_h$ and time t move with velocity $\mathbf{v}_h$ (*i.e.* the quantity $p_h(\mathbf{x}_h, t, \mathbf{v}_h)\, \mathrm{d}\mathbf{v}_h\, \mathrm{d}\mathbf{x}_h$ is the number of cells of population h in the volume element $\mathrm{d}\mathbf{v}_h\, \mathrm{d}\mathbf{x}_h$ centred at the point $(\mathbf{x}_h, \mathbf{v}_h)$ of the phase space). Moreover, we will consider the weighted two-particle distribution function given by

$$\tilde{\tilde{f}}^{\beta_z}_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k) := \int_0^t \int_0^t \beta_z\ f_{hk}\, \mathrm{d}\tau_h\, \mathrm{d}\tau_k \ , \quad z \in \{h, k\} \ , \tag{3.7}$$

and the weighted one-particle distribution function given by

$$p_h^{\beta_h}(\mathbf{x}_h, t, \mathbf{v}_h) := \frac{1}{|\mathrm{V}|} \int_{\Omega_k(\mathbf{x}_h)} \int_{\mathrm{V}} \tilde{\tilde{f}}^{\beta_h}_{hk}\, \mathrm{d}\mathbf{v}_k\, \mathrm{d}\mathbf{x}_k \ . \tag{3.8}$$

Here $|\mathrm{V}|$ denotes the surface area of the unit sphere V.

3.2 Derivation of a system of transport equations

Transport equations for two-particle distribution functions The dynamics of the two-particle distribution functions f_{ID} and f_{AD} are governed by the following specific forms of transport equation (3.2)

$$(\partial_t + \partial_{\tau_I} + \partial_{\tau_D} + c\, \mathbf{v}_I \cdot \nabla_{\mathbf{x}_I} + c\, \mathbf{v}_D \cdot \nabla_{\mathbf{x}_D}) f_{ID} = -(\beta_I + \beta_D) f_{ID} \ , \tag{3.9}$$

$$(\partial_t + \partial_{\tau_A} + \partial_{\tau_D} + c\, \mathbf{v}_A \cdot \nabla_{\mathbf{x}_A} + c\, \mathbf{v}_D \cdot \nabla_{\mathbf{x}_D}) f_{AD} = -(\beta_A + \beta_D) f_{AD} \ , \tag{3.10}$$

which are posed on $\Omega^2 \times \mathbb{R}_+^* \times \mathrm{V}^2 \times \mathbb{R}_+^{*2}$. The boundary conditions at $\tau_A = 0,\ \tau_D = 0$ and $\tau_I = 0$ are analogous to (3.4). Starting from transport equations (3.9)-(3.10) and using the method employed in [11], it is possible to show (see Appendix A) that the two-particle distribution functions $\tilde{\tilde{f}}_{ID}$ and $\tilde{\tilde{f}}_{AD}$ given by (3.5) satisfy the following transport equations

$$(\partial_t + c\, \mathbf{v}_I \cdot \nabla_{\mathbf{x}_I} + c\, \mathbf{v}_D \cdot \nabla_{\mathbf{x}_D}) \tilde{\tilde{f}}_{ID} = -\,(\mathbb{1} - \mathcal{T}_I)[\tilde{\tilde{f}}^{\beta_I}_{ID}] - (\mathbb{1} - \mathcal{T}_D)[\tilde{\tilde{f}}^{\beta_D}_{ID}] \ , \tag{3.11}$$

$$(\partial_t + c\, \mathbf{v}_A \cdot \nabla_{\mathbf{x}_A} + c\, \mathbf{v}_D \cdot \nabla_{\mathbf{x}_D}) \tilde{\tilde{f}}_{AD} = -\,(\mathbb{1} - \mathcal{T}_A)[\tilde{\tilde{f}}^{\beta_A}_{AD}] - (\mathbb{1} - \mathcal{T}_D)[\tilde{\tilde{f}}^{\beta_D}_{AD}] \ , \tag{3.12}$$

posed on $\Omega^2 \times \mathbb{R}_+^* \times \mathrm{V}^2$. Here, $\mathcal{T}_I$, $\mathcal{T}_D$ and $\mathcal{T}_A$ are the turning operators defined via (2.5), and $\tilde{\tilde{f}}_{hk}^{\beta_h}$ and $\tilde{\tilde{f}}_{hk}^{\beta_k}$ are the weighted two-particle distribution functions given by (3.7).

Remark 2. *Notice that the equation describing the evolution of the one-particle distribution function p_D will be derived from the transport equation* (3.11) *for the two-particle distribution function $\tilde{\tilde{f}}_{ID}$ by integrating the variables corresponding to the I cell, and using the interaction rules described in Assumption 1.*

Transport equation for p_h Starting from transport equation (3.2) and building upon the method presented in [11], it is possible to show (see Appendix B) that the one-particle distribution function $p_h(\mathbf{x}_h, t, \mathbf{v}_h)$ given by (3.6) satisfies the following transport equation

$$\partial_t p_h + c\,\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h} p_h = -(\mathbb{1} - \mathcal{T}_h)[p_h^{\beta_h}] + \mathcal{Q}_{hk}, \quad \mathbf{x}_h \in \mathbb{R}^n, t \in \mathbb{R}_+, \mathbf{v}_h \in \mathrm{V}\ . \tag{3.13}$$

Here, the turning operator $\mathcal{T}_h$ is defined via (2.5), the weighted one-particle distribution function $p_h^{\beta_h}(\mathbf{x}_h, t, \mathbf{v}_h)$ is given by (3.8) and

$$\mathcal{Q}_{hk}(\mathbf{x}_h, t, \mathbf{v}_h) := \frac{c}{|\mathrm{V}|} \int_{\partial \mathrm{B}_\varrho(\mathbf{x}_h)} \int_{\mathrm{V}} \nu \cdot (\mathbf{v}_h - \mathbf{v}_k) \tilde{\tilde{f}}_{hk}\, \mathrm{d}\mathbf{v}_k\, \mathrm{d}\sigma\ . \tag{3.14}$$

In (3.14), ν is the unit normal defined in (2.11) and $\mathrm{d}\sigma$ denotes the surface element.

The first term on the right-hand side of transport equation (3.13) represents the rate of change of the one-particle distribution function due to cell movement, while the term $\mathcal{Q}_{hk}$ is the rate of change due to interactions between cells. The specific forms of these terms depend, respectively, on the way in which cells move and the interactions they undergo, as discussed in the remainder of this section.

Expressions for $p_h^{\beta_h}$ The specific form of the first term on the right-hand side of transport equation (3.13) depends on the expression for $p_h^{\beta_h}$ which, in turn, will depend on the definition of the stopping rate β_h.

When cells move in a local search pattern (i.e. for $h = A$ and $h = D$), the stopping rate β_h is defined via (2.1) and (2.2). In this case, inserting the definition of β_h into (3.8) yields

$$p_h^{\beta_h}(\mathbf{x}_h, t, \mathbf{v}_h) = b\, p_h(\mathbf{x}_h, t, \mathbf{v}_h)\ . \tag{3.15}$$

On the other hand, when cells move in a non-local search pattern (i.e. for $h = I$), the stopping rate β_h is defined via (2.1) and (2.3). In this case, it is possible to show (see Appendix C) that

$$p_h^{\beta_h}(\mathbf{x}_h, t, \mathbf{v}_h) = \mathcal{B}[p_h](\mathbf{x}_h, t, \mathbf{v}_h)\ , \tag{3.16}$$

where $\mathcal{B}$ is a convolution operator such that

$$\mathcal{B}[p_h](\mathbf{x}_h, t, \mathbf{v}_h) = \int_0^t B(\mathbf{x}_h, t-s) p(\mathbf{x}_h - (c\mathbf{v}_h + b)(t-s), s, \mathbf{v}_h)\, \mathrm{d}s\ , \tag{3.17}$$

with B being defined through its Laplace transform in time $\hat{B}$ as

$$\hat{B}(\mathbf{x}_h, \lambda + b + c\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h}) = \frac{\hat{\varphi}_h(\mathbf{x}_h, \lambda + b + c\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h})}{\hat{\psi}_h(\mathbf{x}_h, \lambda + b + c\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h})}\ . \tag{3.18}$$

Here, λ is the Laplace variable, $\hat{\varphi}_h$ and $\hat{\psi}_h$ are the Laplace transforms in τ_h of the functions φ_h and ψ_h defined via (2.3), and the parameter b is defined via (2.2).

Expressions for $\mathcal{Q}_{hk}$ Following [11, 13], we first note that when a cell in the phase-space state $(\mathbf{x}_h, \mathbf{v}_h)$ interacts with a cell in the phase-space state $(\mathbf{x}_k, \mathbf{v}_k)$ we have $|\mathbf{x}_h - \mathbf{x}_k| = \varrho$. Hence, the normal vector at the point of physical contact between the interacting cells, $\nu \in \mathrm{V}$, defined via (2.11) can be written as $\nu = (\mathbf{x}_h - \mathbf{x}_k)/\varrho$, that is, $\mathbf{x}_k = \mathbf{x}_h - \nu\varrho$. As a result, using the fact that $\mathrm{B}_\varrho = \varrho\mathrm{V}$ along with the change of variable $\nu \mapsto -\nu$, we rewrite (3.14) as

$$\begin{aligned}\mathcal{Q}_{hk}(\mathbf{x}_h, t, \mathbf{v}_h) :=& \frac{c}{|\mathrm{V}|}\int_{\partial \mathrm{B}_\varrho(\mathbf{x}_h)}\int_{\mathrm{V}} \nu\cdot(\mathbf{v}_h - \mathbf{v}_k)\tilde{\tilde{f}}_{hk}\,\mathrm{d}\mathbf{v}_k\,\mathrm{d}\sigma \\ =& -\frac{c}{|\mathrm{V}|}\varrho^{n-1}\int_{\mathrm{V}}\int_{\mathrm{V}} \nu\cdot(\mathbf{v}_h - \mathbf{v}_k)\tilde{\tilde{f}}_{hk}(\mathbf{x}_h, \mathbf{x}_h + \nu\varrho, t, \mathbf{v}_h, \mathbf{v}_k)\,\mathrm{d}\mathbf{v}_k\,\mathrm{d}\nu\ . \end{aligned} \tag{3.19}$$

Following [11], we also note that $\mathrm{V} \equiv \mathrm{V}^+_{hk} \cup \mathrm{V}^-_{hk}$ with

$$\begin{aligned}\mathrm{V}^+_{hk} &\coloneqq \{\nu \in \mathrm{V} : \nu\cdot(\mathbf{v}_h - \mathbf{v}_k) > 0\}\ , \\ \mathrm{V}^-_{hk} &\coloneqq \{\nu \in \mathrm{V} : \nu\cdot(\mathbf{v}_h - \mathbf{v}_k) < 0\} \equiv \{-\nu \in \mathrm{V} : \nu\cdot(\mathbf{v}_h - \mathbf{v}_k) > 0\}\ . \end{aligned} \tag{3.20}$$

Therefore, a cell moving in direction $\mathbf{v}_h$ and a cell moving in direction $\mathbf{v}_k$ will move toward each other if $\nu \in \mathrm{V}^+$ and away from each other if $\nu \in \mathrm{V}^-$.

Under Assumptions 1-2, denoting the post-interaction directions corresponding to $\mathbf{v}_h$ and $\mathbf{v}_k$ by $\mathbf{v}'_h$ and $\mathbf{v}'_k$, which are defined via (2.11), we consider two different types of interactions between cells:

- conservative interactions (*cf.* Definition 1), between a cell of population h and a cell of population k, whereby both cells remain in their original populations upon interaction and acquire the post-interaction velocities;

- population-switching interactions (*cf.* Definition 2), between a cell in population h and a cell in population k, whereby the h cell switches from its original population to a different one upon interaction.

From (3.19), we define the rate of change of the one-particle distribution function $p_h(\mathbf{x}_h, t, \mathbf{v}_h)$ due to conservative interactions as

$$\begin{aligned}\mathcal{K}_{hk}(\mathbf{x}_h, t, \mathbf{v}_h) :=& -\frac{c}{|\mathrm{V}|}\varrho^{n-1}\,N_k(t)\Big[\int_{\mathrm{V}^+_{hk}}\int_{\mathrm{V}} \nu\cdot(\mathbf{v}_h - \mathbf{v}_k)\tilde{\tilde{f}}_{hk}(\mathbf{x}_h, \mathbf{x}_h + \nu\varrho, t, \mathbf{v}_h, \mathbf{v}_k)\,\mathrm{d}\mathbf{v}_k\,\mathrm{d}\nu \\ &+ \int_{\mathrm{V}^-_{hk}}\int_{\mathrm{V}} \nu\cdot(\mathbf{v}_h - \mathbf{v}_k)\tilde{\tilde{f}}_{hk}(\mathbf{x}_h, \mathbf{x}_h + \nu\varrho, t, \mathbf{v}_h, \mathbf{v}_k)\,\mathrm{d}\mathbf{v}_k\,\mathrm{d}\nu\Big] \\ =& \frac{c}{|\mathrm{V}|}\varrho^{n-1}\,N_k(t)\int_{\mathrm{V}^+_{hk}}\int_{\mathrm{V}} \nu\cdot(\mathbf{v}_h - \mathbf{v}_k)\Big[\tilde{\tilde{f}}_{hk}(\mathbf{x}_h, \mathbf{x}_h - \nu\varrho, t, \mathbf{v}'_h, \mathbf{v}'_k) \\ &- \tilde{\tilde{f}}_{hk}(\mathbf{x}_h, \mathbf{x}_h + \nu\varrho, t, \mathbf{v}_h, \mathbf{v}_k)\Big]\,\mathrm{d}\mathbf{v}_k\,\mathrm{d}\nu\ , \end{aligned} \tag{3.21}$$

with $N_k(t)$ being the number of cells in population k at time t. The second equality in (3.21) is obtained by using the normal vector $-\nu$ and the post-interaction directions $\mathbf{v}'_h$ and $\mathbf{v}'_k$ in $\tilde{\tilde{f}}_{hk}$ over the set V^-_{hk}. Notice that the following property holds

$$\int_{\mathrm{V}} \mathcal{K}_{hk}(\cdot, \cdot, \mathbf{v}_h)\,\mathrm{d}\mathbf{v}_h = 0\ , \tag{3.22}$$

which ensures that the density of cells in population h will be preserved in the course of such interactions.

Moreover, based on (3.19) and (3.21), we define the rate of change of the one-particle distribution function $p_h(\mathbf{x}_h, t, \mathbf{v}_h)$ due to population-switching interactions leading the cell to leave population h as

$$\mathcal{J}_{hk}(\mathbf{x}_h, t, \mathbf{v}_h) := -\frac{c}{|\mathrm{V}|}\, \varrho^{n-1}\, N_k(t) \int_{\mathrm{V}^+_{hk}} \int_{\mathrm{V}} \nu \cdot (\mathbf{v}_h - \mathbf{v}_k)\, \tilde{\tilde{f}}_{hk}(\mathbf{x}_h, \mathbf{x}_h + \nu\varrho, t, \mathbf{v}_h, \mathbf{v}_k)\, \mathrm{d}\mathbf{v}_k\, \mathrm{d}\nu\ . \tag{3.23}$$

Analogously, we define the rate of change of $p_h(\mathbf{x}_h, t, \mathbf{v}_h)$ due to population-switching interactions leading a cell to leave a generic population $l \neq h$ and enter population h as

$$\begin{aligned}\mathcal{J}^h_{lk}(\mathbf{x}_h, t, \mathbf{v}_h) :=& \frac{c}{|\mathrm{V}|}\, \varrho^{n-1}\, N_k(t) \int_{\Omega_l(\mathbf{x}_k)} \int_{\mathrm{V}} \delta(\mathbf{x}_l - \mathbf{x}_h)\, \delta(\mathbf{v}_l - \mathbf{v}_h) \\ &\times \int_{\mathrm{V}^+_{lk}} \int_{\mathrm{V}} \nu \cdot (\mathbf{v}_l - \mathbf{v}_k) \tilde{\tilde{f}}_{lk}(\mathbf{x}_l, \mathbf{x}_l + \nu\varrho, t, \mathbf{v}_l, \mathbf{v}_k)\, \mathrm{d}\mathbf{v}_k\, \mathrm{d}\nu\, \mathrm{d}\mathbf{v}_l\, \mathrm{d}\mathbf{x}_l\ ,\end{aligned} \tag{3.24}$$

with $\delta(\mathbf{z} - \mathbf{z}^*)$ being the Dirac delta distribution centred at $\mathbf{z}^*$. Definition (3.24) ensures that the density of cells that leave population l due to such interactions will appear in population h. In fact, we have

$$\mathcal{J}^h_{lk}(\mathbf{x}_h, t, \mathbf{v}_h) = -\int_{\Omega_l(\mathbf{x}_k)} \int_{\mathrm{V}} \delta(\mathbf{x}_l - \mathbf{x}_h) \delta(\mathbf{v}_l - \mathbf{v}_h) \mathcal{J}_{lk}(\mathbf{x}_l, t, \mathbf{v}_l)\, \mathrm{d}\mathbf{v}_l\, \mathrm{d}\mathbf{x}_l\ .$$

In summary, the term $\mathcal{Q}_{hk}$ in transport equation (3.13) is defined in terms of (3.21)-(3.24) in different possible ways depending on the cell-cell interactions that are considered.

Under Assumptions 1-2 and definitions (3.21), (3.23) and (3.24), the rates of change of the one-particle distribution functions $p_I(\mathbf{x}_I, t, \mathbf{v}_I)$, $p_A(\mathbf{x}_A, t, \mathbf{v}_A)$ and $p_D(\mathbf{x}_D, t, \mathbf{v}_D)$ due to cell-cell interactions will be, respectively,

$$\mathcal{Q}_{ID}(\mathbf{x}_I, t, \mathbf{v}_I) = (1-\zeta)\mathcal{K}_{ID}(\mathbf{x}_I, t, \mathbf{v}_I) + \zeta \mathcal{J}_{ID}(\mathbf{x}_I, t, \mathbf{v}_I)\ , \tag{3.25}$$

$$\mathcal{Q}_{AD}(\mathbf{x}_A, t, \mathbf{v}_A) = \mathcal{K}_{AD}(\mathbf{x}_A, t, \mathbf{v}_A) + \zeta\, \mathcal{J}^A_{ID}(\mathbf{x}_A, t, \mathbf{v}_A)\ , \tag{3.26}$$

$$\mathcal{Q}_{DI}(\mathbf{x}_D, t, \mathbf{v}_D) = \mathcal{K}_{DI}(\mathbf{x}_D, t, \mathbf{v}_D)\ . \tag{3.27}$$

Substituting (3.15), (3.16) and (3.25)-(3.27) into transport equation (3.13), we obtain the following transport equations for $p_I(\mathbf{x}_I, t, \mathbf{v}_I)$, $p_A(\mathbf{x}_A, t, \mathbf{v}_A)$ and $p_D(\mathbf{x}_D, t, \mathbf{v}_D)$:

$$\begin{aligned}\partial_t p_I + c\, \mathbf{v}_I \cdot \nabla_{\mathbf{x}_I} p_I =& \underbrace{-(\mathbb{1} - \mathcal{T}_I)\mathcal{B}[p_I]}_{\text{cell motion}} + \underbrace{(1-\zeta)\mathcal{K}_{ID}}_{\text{interactions}} \\ &\underbrace{+\zeta \mathcal{J}_{ID}}_{\substack{\text{outflow due}\\ \text{to activation}}}, \qquad \mathbf{x}_I \in \mathbb{R}^n, t \in \mathbb{R}^*_+, \mathbf{v}_I \in \mathrm{V}\ ,\end{aligned} \tag{3.28}$$

$$\begin{aligned}\partial_t p_A + c\, \mathbf{v}_A \cdot \nabla_{\mathbf{x}_A} p_A =& \underbrace{-b\,(\mathbb{1} - \mathcal{T}_A)[p_A]}_{\text{cell motion}} + \underbrace{\mathcal{K}_{AD}}_{\text{interactions}} \\ &\underbrace{+\zeta\, \mathcal{J}^A_{ID}}_{\substack{\text{inflow due}\\ \text{to activation}}}, \qquad \mathbf{x}_A \in \mathbb{R}^n, t \in \mathbb{R}^*_+, \mathbf{v}_A \in \mathrm{V}\ ,\end{aligned} \tag{3.29}$$

$$\begin{aligned}\partial_t p_D + c\mathbf{v}_D \cdot \nabla_{\mathbf{x}_D} p_D =& \underbrace{-b\,(\mathbb{1} - \mathcal{T}_D)[p_D]}_{\text{cell motion}} \\ &\underbrace{+\mathcal{K}_{DI}}_{\text{interactions}}, \qquad \mathbf{x}_D \in \mathbb{R}^n, t \in \mathbb{R}^*_+, \mathbf{v}_D \in \mathrm{V}\ .\end{aligned} \tag{3.30}$$

The terms on the right-hand sides of (3.28)-(3.30) represent the rate of change of the one-particle distributions due to the biophysical phenomena specified below each term.

4 Macroscopic scale model

In this section, we derive a macroscopic system of equations corresponding to the mescoscopic scale model given by transport equations (3.28)-(3.30). Such a model consists of a coupled system of balance equations for the macroscopic densities of inactive CTLs, activated CTLs and DCs.

4.1 Preliminaries, assumptions and notation

Scaling We assume the mean run time $\bar{\tau}$ to be small compared to the characteristic temporal scale for the dynamics of the macroscopic cell densities, which is represented by the parameter $T \in \mathbb{R}_+^*$, i.e. we make the assumption

$$\frac{\bar{\tau}}{T} =: \varepsilon \ll 1 \ .$$

Moreover, we let $X \in \mathbb{R}_+^*$ represent the characteristic spatial scale for the dynamics of the macroscopic cell densities and introduce the rescaled quantities

$$\hat{t} = \frac{t}{T}, \quad \hat{\mathbf{x}} = \frac{\mathbf{x}}{X}, \quad \hat{\tau} = \frac{\bar{\tau}}{T}, \quad \hat{c} = c\,\frac{T}{X} \ .$$

As similarly done in [2, 11], in order to obtain a mathematical model for the dynamics of the cells at the macroscopic scale, we consider the scaling

$$(\mathbf{x}, t, c, \tau) \mapsto (\hat{\mathbf{x}}/\varepsilon, \hat{t}/\varepsilon, \hat{c}/\varepsilon^{\gamma}, \hat{\tau}/\varepsilon^{\mu}) \ , \tag{4.1}$$

with

$$\gamma, \mu \in \mathbb{R}_+^* \ , \quad \gamma < 1 \quad \text{and} \quad \mu > 1 - \gamma \ . \tag{4.2}$$

Throughout the rest of the paper, we will drop the carets from (4.1) and we will study two-dimensional cell dynamics (i.e. we assume $n = 2$).

Furthermore, noting that the diameter of the cells is small compared to the characteristic spatial scale for the dynamics of the macroscopic cell densities, and considering a biological scenario where the number of cells in the system is large and activation of CTL occurs with a small probability ζ, we assume

$$\varrho = \varepsilon^{\xi} \ , \quad N_I(t) \equiv \varepsilon^{-\vartheta}, \quad N_D = \varepsilon^{-\vartheta} \ , \quad \zeta = \varepsilon^{\kappa} \ , \quad \xi, \vartheta, \kappa \in \mathbb{R}_+^* \ . \tag{4.3}$$

In particular, we will be focussing on a biological scenario corresponding to the following assumptions

$$\gamma := \frac{1}{2} \ , \quad \xi - \vartheta := 1 - \frac{\gamma}{\alpha - 1} \quad \text{and} \quad \kappa = -(\xi - \vartheta) + \frac{3}{2} > 0 \ . \tag{4.4}$$

Notice that $\xi - \vartheta < 0$ when $\alpha < 3/2$. In the case where cells follow a Brownian motion (i.e. for $h = A$ and $h = D$) we have $\alpha = 2$ and, therefore, $\xi - \vartheta = 1 - \gamma = 1/2$. Under scaling (4.1) definitions (2.3) become

$$\psi^{\varepsilon}(\mathbf{x}_i, \tau_i) = \Big(\frac{\varepsilon^{\mu}\tau_0(\mathbf{x}_i)}{\varepsilon^{\mu}\tau_0(\mathbf{x}_i) + \tau_i}\Big)^{\alpha} \ , \quad \varphi^{\varepsilon}(\mathbf{x}_i, \tau_i) := \frac{\alpha\,\varepsilon^{\mu}\,\tau_0(\mathbf{x}_i)^{\alpha}}{(\varepsilon^{\mu}\,\tau_0(\mathbf{x}_i) + \tau_i)^{\alpha+1}}, \quad \alpha \in (1, 2) \ . \tag{4.5}$$

Moreover, under assumption (4.3) on ϱ we have

$$\tilde{\tilde{f}}_{hk}(\mathbf{x}_h, \mathbf{x}_h \pm \nu\rho, t, \mathbf{v}_h, \mathbf{v}_k) \equiv \tilde{\tilde{f}}_{hk}(\mathbf{x}_h, \mathbf{x}_h \pm \varepsilon^{\xi}\nu, t, \mathbf{v}_h, \mathbf{v}_k) \ . \tag{4.6}$$

"Molecular chaos" assumption Considering a biological scenario where cell densities are sufficiently low, we assume the velocities of any two cells which are about to interact to be uncorrelated – *i.e.* we make the so-called "molecular chaos" assumption, which holds at low densities and is commonly used in kinetic theory [7, 22, 27]. Under this assumption, the two-particle distribution function $\tilde{\tilde{f}}_{hk}(\mathbf{x}_h, \mathbf{x}_h \pm \varepsilon^{\xi}\nu, t, \mathbf{v}_h, \mathbf{v}_k)$ can be approximately expressed as the product of the corresponding one-particle distribution functions, that is,

$$\tilde{\tilde{f}}_{hk}(\mathbf{x}_h, \mathbf{x}_h \pm \varepsilon^{\xi}\nu, t, \mathbf{v}_h, \mathbf{v}_k) = p_h^{\varepsilon}(\mathbf{x}_h, t, \mathbf{v}_h)\, p_k^{\varepsilon}(\mathbf{x}_h, t, \mathbf{v}_k) + \mathcal{O}(\varepsilon^{\xi}) \ . \tag{4.7}$$

We draw the attention of the reader to the fact that, throughout the rest of the paper, superscript and subscript related to the scaling should not be confused with the index of another cell population.

Under scaling (4.1) and assumptions (4.3), using (4.6), (4.7) and assuming $n = 2$, the interaction terms defined via (3.21), (3.23) and (3.24) read as

$$\begin{aligned}\mathcal{K}_{hk}^{\varepsilon}(\mathbf{x}_h, t, \mathbf{v}_h) = \frac{1}{|\mathrm{V}|}\varepsilon^{\xi-\vartheta-\gamma}\, c \int_{\mathrm{V}_{hk}^{+}} \int_{\mathrm{V}} \nu \cdot (\mathbf{v}_h - \mathbf{v}_k) \Big[p_h^{\varepsilon}(\mathbf{x}_h, t, \mathbf{v}_h')p_k^{\varepsilon}(\mathbf{x}_h, t, \mathbf{v}_k') \\ - p_h^{\varepsilon}(\mathbf{x}_h, t, \mathbf{v}_h)p_k^{\varepsilon}(\mathbf{x}_h, t, \mathbf{v}_k) \Big] \, \mathrm{d}\mathbf{v}_k \, \mathrm{d}\nu \ ,\end{aligned} \tag{4.8}$$

$$\mathcal{J}_{hk}^{\varepsilon}(\mathbf{x}_h, t, \mathbf{v}_h) = -\frac{1}{|\mathrm{V}|}\varepsilon^{\xi-\vartheta-\gamma}\, c \int_{\mathrm{V}_{hk}^{+}} \int_{\mathrm{V}} \nu \cdot (\mathbf{v}_h - \mathbf{v}_k)\, p_h^{\varepsilon}(\mathbf{x}_h, t, \mathbf{v}_h)p_k^{\varepsilon}(\mathbf{x}_h, t, \mathbf{v}_k) \, \mathrm{d}\mathbf{v}_k \, \mathrm{d}\nu \tag{4.9}$$

and

$$\begin{aligned}{}_{\varepsilon}\mathcal{J}_{lk}^{h}(\mathbf{x}_h, t, \mathbf{v}_h) =& \frac{1}{|\mathrm{V}|}\, \varepsilon^{\xi-\vartheta-\gamma}\, c \int_{\Omega_l(\mathbf{x}_k)} \int_{\mathrm{V}} \delta(\mathbf{x}_l - \mathbf{x}_h)\, \delta(\mathbf{v}_l - \mathbf{v}_h) \\ & \times \int_{\mathrm{V}_{lk}^{+}} \int_{\mathrm{V}} \nu \cdot (\mathbf{v}_l - \mathbf{v}_k) p_l^{\varepsilon}(\mathbf{x}_l, t, \mathbf{v}_l)p_k^{\varepsilon}(\mathbf{x}_l, t, \mathbf{v}_k) \, \mathrm{d}\mathbf{v}_k \, \mathrm{d}\nu \, \mathrm{d}\mathbf{v}_l \, \mathrm{d}\mathbf{x}_l \ .\end{aligned} \tag{4.10}$$

Expansion of p_h^{ε} and macroscopic cell quantities Exploiting the results established by Lemma 1 in the case where $n = 2$, we expand the one-particle distribution function p_h^{ε} in terms of its zeroth moment ρ_h^{ε} (i.e. the macroscopic cell density) and its first moment w_h^{ε} (i.e. the local macroscopic direction of cell motion). This is possible because, as one can see from the right-hand side of transport equation (4.13), the interaction terms are of higher order in ε (*cf.* the scaling used in (4.8)-(4.10)) and, therefore, we can write

$$p_h^{\varepsilon}(\mathbf{x}_h, t, \mathbf{v}_h) = \frac{1}{|\mathrm{V}|}\Big(\rho_h^{\varepsilon}(\mathbf{x}_h, t) + \varepsilon^{\gamma}\, 2\, \mathbf{v}_h \cdot w_h^{\varepsilon}(\mathbf{x}_h, t)\Big) + o(\varepsilon^{\gamma}) \ , \quad h \in \{A, D, I\} \ , \tag{4.11}$$

where

$$\rho_h^{\varepsilon}(\mathbf{x}_h, t) := \int_{\mathrm{V}} p_h^{\varepsilon}(\mathbf{x}_h, t, \mathbf{v}_h) \, \mathrm{d}\mathbf{v}_h \ , \quad w_h^{\varepsilon}(\mathbf{x}_h, t) := \frac{1}{\varepsilon^{\gamma}} \int_{\mathrm{V}} \mathbf{v}_h \, p_h^{\varepsilon}(\mathbf{x}_h, t, \mathbf{v}_h) \, \mathrm{d}\mathbf{v}_h \ . \tag{4.12}$$

We refer the reader to [23, 24] and the seminal work [2] for a complete derivation in the case of no interactions and to [11, 13] for the case of velocity jump models with interacting particles. The appropriate choice of scaling for the local macroscopic direction of motion is found by first inserting (4.11) into (4.13) and then integrating over V in order to obtain a suitable macroscopic equation (see transport equation (4.19)).

4.2 Derivation of a macroscopic scale system

Transport equation for p_h^ε Under scaling (4.1) and assumptions (4.3), using (4.6), (4.7) and assuming $n = 2$, we rewrite transport equation (3.13) for the one-particle distribution function $p_h(\mathbf{x}_h, t, \mathbf{v}_h)$ as

$$\varepsilon \partial_t p_h^\varepsilon + \varepsilon^{1-\gamma} c\, \mathbf{v}_h \cdot \nabla_{\mathbf{x}_h} p_h^\varepsilon = -(\mathbb{1} - \mathcal{T}_h)[{}_\varepsilon p_h^{\beta_h}] + \mathcal{Q}_{hk}^\varepsilon \ , \tag{4.13}$$

where $\mathcal{Q}_{hk}^\varepsilon$ is defined in terms of $\mathcal{K}_{hk}^\varepsilon$, $\mathcal{J}_{hk}^\varepsilon$ and ${}_\varepsilon\mathcal{J}_{lk}^h$ as per (3.25)-(3.27), that is,

$$\mathcal{Q}_{ID}^\varepsilon(\mathbf{x}_I, t, \mathbf{v}_I) = (1 - \varepsilon^\kappa)\mathcal{K}_{ID}^\varepsilon(\mathbf{x}_I, t, \mathbf{v}_I) + \varepsilon^\kappa \mathcal{J}_{ID}^\varepsilon(\mathbf{x}_I, t, \mathbf{v}_I) \ , \tag{4.14}$$

$$\mathcal{Q}_{AD}^\varepsilon(\mathbf{x}_A, t, \mathbf{v}_A) = \mathcal{K}_{AD}^\varepsilon(\mathbf{x}_A, t, \mathbf{v}_A) + \varepsilon^\kappa\, {}_\varepsilon\mathcal{J}_{ID}^A(\mathbf{x}_A, t, \mathbf{v}_A) \tag{4.15}$$

and

$$\mathcal{Q}_{DI}^\varepsilon(\mathbf{x}_D, t, \mathbf{v}_D) = \mathcal{K}_{DI}^\varepsilon(\mathbf{x}_D, t, \mathbf{v}_D) \ . \tag{4.16}$$

We recall that in the case where cells move in a local search pattern (i.e. for $h = A$ and $h = D$), β_h is defined via (2.1) and (2.2), and thus ${}_\varepsilon p_h^{\beta_h}(\mathbf{x}_h, t, \mathbf{v}_h)$ is given as in (3.15). On the other hand, in the case where cells move in a non-local search pattern (i.e. for $h = I$), β_h is defined via (2.1) and (2.3), and thus ${}_\varepsilon p_h^{\beta_h}(\mathbf{x}_h, t, \mathbf{v}_h)$ is given by (3.16) with

$$\mathcal{B}^\varepsilon[p_h^\varepsilon](\mathbf{x}_h, t, \mathbf{v}_h) = \int_0^t B^\varepsilon(\mathbf{x}_h, t-s) p_h^\varepsilon(\mathbf{x}_h - (c\mathbf{v}_h + b)(t-s), s)\, \mathrm{d}s \ .$$

As before, B^ε is defined through its Laplace transform in time $\hat{B}^\varepsilon$ and, in particular, under assumptions (4.2), we make the approximation

$$\hat{B}^\varepsilon(\mathbf{x}_h, \varepsilon\lambda + \varepsilon^\mu b + \varepsilon^{1-\gamma} c\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h}) \simeq \hat{B}^\varepsilon(\mathbf{x}_h, \varepsilon^{1-\gamma} c\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h}) \ .$$

Using the properties of the Laplace transform of a convolution, we write

$$\int_0^t B^\varepsilon(\mathbf{x}_h, t-s) p_h^\varepsilon(\mathbf{x}_h - (c\mathbf{v}_h + b)(t-s), s, \mathbf{v}_h)\, \mathrm{d}s \simeq \hat{B}^\varepsilon(\mathbf{x}_h, \varepsilon^{1-\gamma} c\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h}) p_h^\varepsilon(\mathbf{x}_h, t, \mathbf{v}_h) \ ,$$

with

$$\hat{B}^\varepsilon(\mathbf{x}_h, \varepsilon^{1-\gamma} c\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h}) = \frac{\hat{\varphi}_h^\varepsilon(\mathbf{x}_h, \varepsilon^{1-\gamma} c\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h})}{\hat{\psi}_h^\varepsilon(\mathbf{x}_h, \varepsilon^{1-\gamma} c\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h})} \ . \tag{4.17}$$

Analogous calculations are fully detailed in Appendix C. Substituting the expressions of $\hat{\varphi}_h^\varepsilon$ and $\hat{\psi}_h^\varepsilon$ into (4.17), calculations similar to those carried out in [11, 12] allow one to show that

$$\begin{aligned} \hat{B}^\varepsilon(\mathbf{x}_h, \varepsilon^{1-\gamma} c\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h}) &= \frac{\alpha - 1}{d_\varepsilon} - \frac{\varepsilon^{1-\gamma}}{2-\alpha} c\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h} \\ &\quad - d_\varepsilon^{\alpha-2} \varepsilon^{(1-\gamma)(\alpha-1)} (c\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h})^{\alpha-1} (\alpha-1)^2 \Gamma(-\alpha+1) + \mathcal{O}(d_\varepsilon^{\alpha-1}\lambda^\alpha) \ . \end{aligned} \tag{4.18}$$

In (4.18), $d_\varepsilon(\mathbf{x}_h) := \tau_0(\mathbf{x}_h)\, \varepsilon^\mu$, where $\tau_0(\mathbf{x}_h)$ is defined via (2.3).

Transport equations for ρ_I^ε, ρ_A^ε and ρ_D^ε Integrating both sides of transport equation (4.13) with respect to $\mathbf{v}_h$ over the set V and using the fact that the turning operator $\mathcal{T}_h$ satisfies (2.6), we find that the macroscopic cell density $\rho_h^\varepsilon(\mathbf{x}_h, t)$ given by (4.12) satisfies the following transport equation

$$\partial_t \rho_h^\varepsilon + 2c\, \nabla_{\mathbf{x}_h} \cdot w_h^\varepsilon = \varepsilon^{-1} \int_{\mathrm{V}} \mathcal{Q}_{hk}^\varepsilon \, \mathrm{d}\mathbf{v}_h \ , \quad \mathbf{x}_h \in \mathbb{R}^n, t \in \mathbb{R}_+^* \ . \tag{4.19}$$

Moreover, substituting the expressions for $p_h^\varepsilon(\mathbf{x}_h, t, \mathbf{v}_h)$ and $p_k^\varepsilon(\mathbf{x}_h, t, \mathbf{v}_k)$ given by (4.11) into the definitions of $\mathcal{K}_{hk}^\varepsilon$, $\mathcal{J}_{hk}^\varepsilon$ and ${}_\varepsilon\mathcal{J}_{hk}^l$ given by (4.8)-(4.10) we find

$$\int_{\mathrm{V}} \mathcal{K}_{hk}^\varepsilon(\mathbf{x}_h, t, \mathbf{v}_h) \, \mathrm{d}\mathbf{v}_h = 0 \tag{4.20}$$

and, neglecting higher order terms, we also obtain

$$\int_{\mathrm{V}} \mathcal{J}_{hk}^\varepsilon(\mathbf{x}_h, t, \mathbf{v}_h) \, \mathrm{d}\mathbf{v}_h = -\varepsilon^{\xi-\vartheta-\gamma}\, c\, M\, \rho_h^\varepsilon \rho_k^\varepsilon \ , \quad \int_{\mathrm{V}} {}_\varepsilon\mathcal{J}_{lk}^h(\mathbf{x}_h, t, \mathbf{v}_h) \, \mathrm{d}\mathbf{v}_h = \varepsilon^{\xi-\vartheta-\gamma}\, c\, M\, \rho_l^\varepsilon \rho_k^\varepsilon \ , \tag{4.21}$$

where M is given by

$$M := \frac{1}{|\mathrm{V}|^3} \int_{\mathrm{V}} \int_{\mathrm{V}} \int_{\mathrm{V}_{hk}^+} \nu \cdot (\mathbf{v}_h - \mathbf{v}_k) \, \mathrm{d}\nu \, \mathrm{d}\mathbf{v}_h \, \mathrm{d}\mathbf{v}_k \ , \quad h, k \in \{A, D, I\},\ h \neq k \ . \tag{4.22}$$

Notice that relation (4.20) is obtained using property (3.22).

In conclusion, using (4.20) and (4.21) along with (4.14)-(4.16), from transport equation (4.19) we obtain the following equations for the macroscopic cell densities $\rho_I^\varepsilon(\mathbf{x}_I, t)$, $\rho_A^\varepsilon(\mathbf{x}_A, t)$ and $\rho_D^\varepsilon(\mathbf{x}_D, t)$:

$$\partial_t \rho_I^\varepsilon + 2c\, \nabla_{\mathbf{x}_I} \cdot w_I^\varepsilon = -\, c\, M\, \rho_I^\varepsilon \rho_D^\varepsilon \ , \qquad \mathbf{x}_I \in \mathbb{R}^2, t \in \mathbb{R}_+^* \ , \tag{4.23}$$

$$\partial_t \rho_A^\varepsilon + 2c\, \nabla_{\mathbf{x}_A} \cdot w_A^\varepsilon = \, c\, M\, \rho_I^\varepsilon \rho_D^\varepsilon \ , \qquad \mathbf{x}_A \in \mathbb{R}^2, t \in \mathbb{R}_+^* \ , \tag{4.24}$$

$$\partial_t \rho_D^\varepsilon + 2c\, \nabla_{\mathbf{x}_D} \cdot w_D^\varepsilon = 0 \ , \qquad \mathbf{x}_D \in \mathbb{R}^2, t \in \mathbb{R}_+^* \ . \tag{4.25}$$

Here, we have used the scaling relations in (4.4) for the parameter κ. On the right hand side of (4.23) we have the density of cells that are leaving the state I (due to interactions with cells in the population D) and are appearing in the new state A in (4.24).

Transport equations for w_I^ε, w_A^ε and w_D^ε Multiplying both sides of transport equation (4.13) by $\mathbf{v}_h$ and then integrating both sides of the resulting equation with respect to $\mathbf{v}_h$ over the set V, we find that the local macroscopic direction of cell motion $w_h^\varepsilon(\mathbf{x}_h, t)$ given by (4.12) satisfies the following transport equation

$$\begin{aligned} \varepsilon^{1+\gamma} 2\partial_t w_h^\varepsilon + \varepsilon^{1-\gamma} c \nabla_{\mathbf{x}_h} \int_{\mathrm{V}} \mathbf{v}_h \otimes \mathbf{v}_h \, p_h^\varepsilon \, \mathrm{d}\mathbf{v}_h = &- \int_{\mathrm{V}} \mathbf{v}_h (\mathbb{1} - \mathcal{T}_h)[{}_\varepsilon p_h^{\beta_h}] \, \mathrm{d}\mathbf{v}_h \\ &+ \int_{\mathrm{V}} \mathbf{v}_h \, \mathcal{Q}_{hk}^\varepsilon \, \mathrm{d}\mathbf{v}_h \ . \end{aligned} \tag{4.26}$$

In the case where β_h is defined via (2.1) and (2.2), using (4.11), (3.15) and the properties of the turning operator $\mathcal{T}_h$ established by Lemma 1 we find that the first term on the right-hand side of (4.26) is given by

$$\int_{\mathrm{V}} \mathbf{v}_h (\mathbb{1} - \mathcal{T}_h)[{}_\varepsilon p_h^{\beta_h}] \, \mathrm{d}\mathbf{v}_h = \frac{2\varepsilon^\gamma}{|\mathrm{V}|} b(1 - \iota_1) w_h^\varepsilon \ . \tag{4.27}$$

Here, $\iota_1(\mathbf{x}_h,t)$ is the first non-zero eigenvalue of the turning operator $\mathcal{T}_h$, which is given by (2.8). On the other hand, when β_h is defined via (2.1) and (2.3), using (4.11), (3.16) and the properties of the turning operator $\mathcal{T}_h$ established by Lemma 1, it was proved in [12] that the following approximate expression of the first term on the right-hand side of (4.26) holds

$$\int_{\mathrm{V}} \mathbf{v}_h(\mathbb{1}-\mathcal{T}_h)[{}_\varepsilon p_h^{\beta_h}]\,\mathrm{d}\mathbf{v}_h = \varepsilon^{1-\frac{\gamma}{\alpha-1}}\Big(g_\alpha \nabla^{\alpha-1}\rho_h^\varepsilon - \frac{2(\alpha-1)}{\tau_0|\mathrm{V}|}(\iota_1-1)w_h^\varepsilon\Big) + \text{l.o.t.}\,, \tag{4.28}$$

where

$$g_\alpha(\mathbf{x}_h,t) := \frac{\pi\tau_0^{\alpha-2}(1-\alpha)^2c^{\alpha-1}}{\sin(\pi\alpha)\Gamma(\alpha)}\Big(\frac{4\iota_1-|\mathrm{V}|}{|\mathrm{V}|}\Big) \quad \text{for} \quad \Gamma(-\alpha+1) = \frac{\pi}{\sin(\pi\alpha)\Gamma(\alpha)}\,. \tag{4.29}$$

Notice that $g_\alpha(\cdot,\cdot)>0$ since $\sin(\pi\alpha)<0$ for $\alpha\in(1,2)$ and $4\iota_1-|\mathrm{V}|<0$ by using (2.7) for $n=2$ and recalling that $\iota_1<1$.

Moreover, as similarly done in [11], using the fact that $(\cdot)':\mathrm{V}\mapsto\mathrm{V}$ is a bijection and $\mathbf{v}_h'\cdot\nu=-\mathbf{v}_h\cdot\nu$, whence $\nu\cdot(\mathbf{v}_h-\mathbf{v}_k)=-\nu\cdot(\mathbf{v}_h'-\mathbf{v}_k')$, we find

$$\begin{aligned}
&\int_{\mathrm{V}}\mathbf{v}_h\,\mathcal{K}_{hk}^\varepsilon\,\mathrm{d}\mathbf{v}_h\\
&\quad=\frac{1}{|\mathrm{V}|}\varepsilon^{\xi-\vartheta-\gamma}\,c\,\Big(\int_{\mathrm{V}}\int_{\mathrm{V}}\int_{\mathrm{V}^+_{hk}}\mathbf{v}_h\,p_h^\varepsilon(\mathbf{x}_h,t,\mathbf{v}_h')p_k^\varepsilon(\mathbf{x}_h,t,\mathbf{v}_k')\nu\cdot(\mathbf{v}_h-\mathbf{v}_k)\,\mathrm{d}\nu\,\mathrm{d}\mathbf{v}_k\,\mathrm{d}\mathbf{v}_h\\
&\quad-\int_{\mathrm{V}}\int_{\mathrm{V}}\int_{\mathrm{V}^+_{hk}}\mathbf{v}_h\,p_h^\varepsilon(\mathbf{x}_h,t,\mathbf{v}_h)p_k^\varepsilon(\mathbf{x}_h,t,\mathbf{v}_k)\nu\cdot(\mathbf{v}_h-\mathbf{v}_k)\,\mathrm{d}\nu\,\mathrm{d}\mathbf{v}_k\,\mathrm{d}\mathbf{v}_h\Big)\\
&\quad=-\frac{1}{|\mathrm{V}|}\varepsilon^{\xi-\vartheta-\gamma}\,c\int_{\mathrm{V}}\int_{\mathrm{V}}\int_{\mathrm{V}^+_{hk}}(\mathbf{v}_h')'p_h^\varepsilon(\mathbf{x}_h,t,\mathbf{v}_h')p_k^\varepsilon(\mathbf{x}_h,t,\mathbf{v}_k')\nu\cdot(\mathbf{v}_h'-\mathbf{v}_k')\,\mathrm{d}\nu\,\mathrm{d}\mathbf{v}_h'\,\mathrm{d}\mathbf{v}_k'\\
&\qquad-\int_{\mathrm{V}}\int_{\mathrm{V}}\int_{\mathrm{V}^+_{hk}}\mathbf{v}_h p_h^\varepsilon(\mathbf{x}_h,t,\mathbf{v}_h)p_k^\varepsilon(\mathbf{x}_h,t,\mathbf{v}_k)\nu\cdot(\mathbf{v}_h-\mathbf{v}_k)\,\mathrm{d}\nu\,\mathrm{d}\mathbf{v}_h\,\mathrm{d}\mathbf{v}_k\\
&\quad=\frac{1}{|\mathrm{V}|}\varepsilon^{\xi-\vartheta-\gamma}\,c\int_{\mathrm{V}}\int_{\mathrm{V}}\int_{\mathrm{V}^+_{hk}}(\mathbf{v}_h'-\mathbf{v}_h)p_h^\varepsilon(\mathbf{x}_h,t,\mathbf{v}_h)p_k^\varepsilon(\mathbf{x}_h,t,\mathbf{v}_k)\nu\cdot(\mathbf{v}_h-\mathbf{v}_k)\,\mathrm{d}\nu\,\mathrm{d}\mathbf{v}_h\,\mathrm{d}\mathbf{v}_k\\
&\quad=-\frac{1}{|\mathrm{V}|}\varepsilon^{\xi-\vartheta-\gamma}\,c\,\frac{4}{3}\int_{\mathrm{V}}\int_{\mathrm{V}}|\mathbf{v}_h-\mathbf{v}_k|\,\mathbf{v}_h\,p_h^\varepsilon(\mathbf{x}_h,t,\mathbf{v}_h)\,p_k^\varepsilon(\mathbf{x}_h,t,\mathbf{v}_k)\,\mathrm{d}\mathbf{v}_h\,\mathrm{d}\mathbf{v}_k\,.
\end{aligned}\tag{4.30}$$

The last equality in (4.30) is obtained using the fact that $\mathbf{v}_h'-\mathbf{v}_h=-2(\mathbf{v}_h\cdot\nu)\nu$. Substituting the expressions for $p_h^\varepsilon(\mathbf{x}_h,t,\mathbf{v}_h)$ and $p_k^\varepsilon(\mathbf{x}_h,t,\mathbf{v}_k)$ given by (4.11) into (4.30) and into definitions (4.9) and (4.10) of $\mathcal{J}_{hk}^\varepsilon$ and ${}_\varepsilon\mathcal{J}_{lk}^h$, neglecting higher order terms we find

$$\int_{\mathrm{V}}\mathbf{v}_h\,\mathcal{K}_{hk}^\varepsilon\,\mathrm{d}\mathbf{v}_h = -\varepsilon^{\xi-\vartheta}\,c\,\frac{8}{3}\,\frac{1}{|\mathrm{V}|^3}\,q_h\,\rho_k^\varepsilon w_h^\varepsilon\,, \tag{4.31}$$

and

$$\int_{\mathrm{V}}\mathbf{v}_h\,\mathcal{J}_{hk}^\varepsilon\,\mathrm{d}\mathbf{v}_h = -\frac{\varepsilon^{\xi-\vartheta}2c}{|\mathrm{V}|^2}\tilde{q}_h\rho_k^\varepsilon w_h^\varepsilon\,,\quad \int_{\mathrm{V}}\mathbf{v}_h\,{}_\varepsilon\mathcal{J}_{lk}^h\,\mathrm{d}\mathbf{v}_h = \frac{\varepsilon^{\xi-\vartheta}2c}{|\mathrm{V}|^2}\tilde{q}_h\rho_k^\varepsilon w_h^\varepsilon\,, \tag{4.32}$$

where q_h and $\tilde{q}_h$ are defined as

$$q_h := \int_{\mathrm{V}}|\mathbf{v}_h-\mathbf{v}_k|\,\mathrm{d}\mathbf{v}\,,\quad \tilde{q}_h := \int_{\mathrm{V}^+_{hk}}|\nu||\mathbf{v}_h-\mathbf{v}_k|\,\mathrm{d}\nu\,,\quad h\in\{A,D,I\}\,. \tag{4.33}$$

Finally, substituting the expression of $p_h^\varepsilon(\mathbf{x}_h, t, \mathbf{v}_h)$ into the second term on the left-hand side of (4.26) and neglecting higher order terms yields

$$c\,\nabla_{\mathbf{x}_h}\int_{\mathrm{V}}\mathbf{v}_h\otimes\mathbf{v}_h\,p_h^\varepsilon\,\mathrm{d}\mathbf{v}_h = C_h\,\nabla_{\mathbf{x}_h}\rho_h^\varepsilon\ , \tag{4.34}$$

with C_h being defined as

$$C_h := \frac{c}{|\mathrm{V}|}\int_{\mathrm{V}}\mathbf{v}_h\otimes\mathbf{v}_h\,\mathrm{d}\mathbf{v}_h\ , \quad h\in\{A,D,I\}\ . \tag{4.35}$$

In conclusion, using (3.15) and (3.16), (4.31), (4.32) and (4.34) along with (4.14)-(4.16), from transport equation (4.26) we obtain the following transport equations for the local macroscopic directions of cell motion $w_I^\varepsilon(\mathbf{x}_I,t)$, $w_A^\varepsilon(\mathbf{x}_A,t)$ and $w_D^\varepsilon(\mathbf{x}_D,t)$:

$$\begin{aligned}\varepsilon^{1+\gamma}2\partial_t w_I^\varepsilon + \varepsilon^{1-\gamma}C_I\,\nabla_{\mathbf{x}_I}\rho_I^\varepsilon = -\varepsilon^{1-\frac{\gamma}{\alpha-1}}\left(g_\alpha\nabla^{\alpha-1}\rho_I^\varepsilon - \frac{2(\alpha-1)}{\tau_0|\mathrm{V}|}(\iota_1-1)w_I^\varepsilon\right)\\ -\varepsilon^{\xi-\vartheta}\,c\left((1-\varepsilon^\kappa)\frac{8}{3}\frac{1}{|\mathrm{V}|^3}q_I\,\rho_D^\varepsilon w_I^\varepsilon + \frac{2c}{|\mathrm{V}|^2}\tilde{q}_I\rho_D^\varepsilon w_I^\varepsilon\right)\ ,\quad \mathbf{x}_I\in\mathbb{R}^2, t\in\mathbb{R}_+^*\ ,\end{aligned} \tag{4.36}$$

$$\begin{aligned}\varepsilon^{1+\gamma}2\partial_t w_A^\varepsilon + \varepsilon^{1-\gamma}C_A\,\nabla_{\mathbf{x}_A}\rho_A^\varepsilon = -\frac{2\varepsilon^\gamma}{|\mathrm{V}|}b(1-\iota_1)w_A^\varepsilon\\ -\varepsilon^{\xi-\vartheta}\,c\left(\frac{8}{3}\frac{1}{|\mathrm{V}|^3}q_A\,\rho_D^\varepsilon w_A^\varepsilon - \frac{2c}{|\mathrm{V}|^2}\tilde{q}_A\rho_D^\varepsilon w_A^\varepsilon\right)\ ,\quad \mathbf{x}_A\in\mathbb{R}^2, t\in\mathbb{R}_+^*\ ,\end{aligned} \tag{4.37}$$

and

$$\begin{aligned}\varepsilon^{\gamma+1}2\partial_t w_D^\varepsilon + \varepsilon^{1-\gamma}C_D\,\nabla_{\mathbf{x}_D}\rho_D^\varepsilon = -\frac{2\varepsilon^\gamma}{|\mathrm{V}|}b(\iota_1-1)w_D^\varepsilon\\ -\varepsilon^{\xi-\vartheta}\,c\,\frac{8}{3}\frac{1}{|\mathrm{V}|^3}q_D\,\rho_I^\varepsilon w_D^\varepsilon\ ,\quad \mathbf{x}_D\in\mathbb{R}^2, t\in\mathbb{R}_+^*\ .\end{aligned} \tag{4.38}$$

Macroscopic scale model Noting that $1-\dfrac{\gamma}{\alpha-1} < 1-\gamma$ since $\alpha\in(1,2)$ and using assumptions (4.4) for the scaling parameters, letting $\varepsilon\to 0$ in (4.36)-(4.38) we formally find the following expressions for the leading-order terms $w_I(\mathbf{x},t)$, $w_A(\mathbf{x},t)$ and $w_D(\mathbf{x},t)$ of the asymptotic expansions for the local macroscopic directions of cell motion $w_{I\varepsilon}(\mathbf{x},t)$, $w_{A\varepsilon}(\mathbf{x},t)$ and $w_{D\varepsilon}(\mathbf{x},t)$:

- From (4.36) and choosing the scaling parameters as $1-\frac{\gamma}{\alpha-1} = \xi-\vartheta$ we have

$$w_I = -\frac{g_\alpha}{H_I}\nabla_{\mathbf{x}}^{\alpha-1}\rho_I\ ,\quad \text{where}\quad H_I := \frac{2(\alpha-1)(1-\iota_1)}{\tau_0|\mathrm{V}|} + \frac{8c}{|3\mathrm{V}|^3}q_I\rho_D > 0\ . \tag{4.39}$$

- From (4.37) and choosing $\xi-\vartheta=\gamma$ in agreement with (4.4), we obtain

$$w_A = -\frac{C_A}{H_A}\nabla_{\mathbf{x}}\rho_A\ ,\quad \text{where}\quad H_A := \frac{2b}{|\mathrm{V}|}(1-\iota_1) + \frac{8c}{3|\mathrm{V}|^3}q_A\rho_D > 0\ . \tag{4.40}$$

- Finally, using the same scaling rules as in the previous case we obtain from (4.38)

$$w_D = -\frac{C_D}{H_D}\nabla_{\mathbf{x}}\rho_D\ ,\quad \text{where}\quad H_D := \frac{2b}{|\mathrm{V}|}(1-\iota_1) + \frac{8c}{3|\mathrm{V}|^3}q_D\rho_I > 0\ . \tag{4.41}$$

Furthermore, under assumptions (4.4), letting $\varepsilon \to 0$ in (4.23)-(4.25) and using(4.39)-(4.41), we formally obtain the following balance equations for the leading-order terms $\rho_I(\mathbf{x},t)$, $\rho_A(\mathbf{x},t)$ and $\rho_D(\mathbf{x},t)$ of the asymptotic expansions for the macroscopic cell densities $\rho_I^\varepsilon(\mathbf{x},t)$, $\rho_A^\varepsilon(\mathbf{x},t)$ and $\rho_D^\varepsilon(\mathbf{x},t)$

$$\partial_t \rho_I - \nabla_{\mathbf{x}} \cdot \left(D_I \, \nabla_{\mathbf{x}}^{\alpha-1} \rho_I \right) = -a \, \rho_I \, \rho_D \ , \quad \alpha \in (1,2) \ , \qquad \mathbf{x} \in \mathbb{R}^2, t \in \mathbb{R}_+^* \ , \tag{4.42}$$

$$\partial_t \rho_A - \nabla_{\mathbf{x}} \cdot \left(D_A \, \nabla_{\mathbf{x}} \rho_A \right) = a \, \rho_I \, \rho_D \ , \qquad \mathbf{x} \in \mathbb{R}^2, t \in \mathbb{R}_+^* \ , \tag{4.43}$$

$$\partial_t \rho_D - \nabla_{\mathbf{x}} \cdot \left(D_D \, \nabla_{\mathbf{x}} \rho_D \right) = 0 \ , \qquad \mathbf{x} \in \mathbb{R}^2, t \in \mathbb{R}_+^* \ , \tag{4.44}$$

where

$$D_I := \frac{2\,c\,g_\alpha}{H_I}, \quad D_A := \frac{2\,c\,C_A}{H_A}, \quad D_D := \frac{2\,c\,C_D}{H_D}, \quad a := c\,M.$$

Remark 3. *Notice that the the functions D_I, D_A and D_D are strictly positive. Moreover, the dependence of these functions on the cell densities follows from conservative interactions between cells of different populations, while population-switching interactions do not affect their values.*

Considerations on the macroscopic scale model (4.42)-(4.44) The functions $\rho_I(\mathbf{x},t)$, $\rho_A(\mathbf{x},t)$ and $\rho_D(\mathbf{x},t)$ model, respectively, the density of CTLs in the pre-activation state, activated CTLs and DCs presenting a tumour antigen on their surface at position $\mathbf{x}$ and time t. The spatio-temporal coevolution of CTLs and DCs is modelled through the coupled system of balance equations (4.42)-(4.44), which governs the dynamics of the cell density functions.

The mathematical model defined by (4.42)-(4.44) provides a macroscopic description of cell dynamics that takes explicitly into account the effects of cell-cell interactions and the characteristics of cell motion that are encapsulated in the parameters c (i.e. the magnitude of the cell velocity, which is assumed to be constant), α (i.e. the characteristic exponent of the long-tailed distribution followed by the running time of CTLs in the pre-activation state) and b (i.e. the characteristic exponent of the Poisson distribution followed by the running time of activated CTLs and DCs).

This model effectively captures the fact that interactions between DCs presenting a tumour antigen on their surface and CTLs in the pre-activation state lead to CTL activation. In particular, the term on the right-hand side of (4.42) models the decay in the density of CTLs in the pre-activation state at position $\mathbf{x}$ and time t due to contact interactions with DCs which result in CTL activation, while the term on the right-hand side of (4.43) models the corresponding growth in the density of activated CTLs. As one would expect, these two terms differ only in their signs and are proportional to the product between the cell density functions $\rho_I(\mathbf{x},t)$ and $\rho_D(\mathbf{x},t)$. The factor of proportionality a increases with the value of the parameter c. This is coherent with the observation that higher cell motilities may increase the encounter rate of CTLs in the pre-activation state with DCs.

The model captures also the fact that CTLs in the pre-activation state move in a non-local search pattern, while the search pattern of activated CTLs is more localised. In fact, the rate of change of the density of CTLs in the pre-activation state due to cell movement (i.e. the second term on the left-hand side of (4.42)) is a fractional diffusion term, while that of the density of activated CTLs (i.e. the second term on the left-hand side of (4.43)) is a classical diffusion term. The function modelling the diffusivity of CTLs in the pre-activation state (i.e. the function D_I) and the function modelling the diffusivity of activated CTLs (i.e. the function D_A) are proportional to the parameter c. This is coherent with the observation that, *ceteris paribus*, a higher magnitude of the cell velocity correlates with a higher cell motility. Both D_I and D_A are monotonically decreasing functions of the cell density function $\rho_D(\mathbf{x},t)$, which means that, all else being equal, the higher the density of DCs at a given position, the lower the diffusivity of CTLs. This reflects the fact that higher densities of DCs will make it

more likely that interactions between CTLs and DCs occur and, since these interactions force CTLs to change their direction of movement at the mesoscopic scale, this will ultimately result in a lower cell diffusivity at the macroscopic scale. Moreover, D_A is an increasing function of b. This is coherent with the fact that larger values of this parameter correspond to larger mean values of the cell running times.

The fact that the right-hand side of (4.44) is zero translates in mathematical terms the idea that we are not taking into account the effects of division and death of DCs. Moreover, coherently with the fact that the motion of DCs is here described as a Brownian motion, the rate of change of the density of DCs due to cell movement (i.e. the second term on the left-hand side of (4.44)) is a classical diffusion term. Considerations analogous to those made above about the dependence of the function D_A on the parameters c and b apply to the function modelling the diffusivity of DCs (i.e. the function D_D) as well. Furthermore, considerations similar to those made above about the dependence of D_I on the density function $\rho_D(\mathbf{x}, t)$ hold for the dependence of D_D on the density function $\rho_I(\mathbf{x}, t)$.

5 Research perspectives

The modelling approach for the switch between cell migration modes presented here could be generalised by including additional cellular phenomena involved in the immune response to cancer, and considering other aspects of immune cell movement as well. For the case of movement in bacteria, a recent work in this direction is [25], where the switch in type of movement, i.e. the switch between Lévy and Brownian strategies, was determined by chemical pathways internal to the bacteria.

With reference to the mathematical modelling of the immune response to cancer, a natural generalisation would be to include a population of cancer cells and allow activated CTLs to induce death in cancer cells via binary interactions. Moreover, the recognition phase of the adaptive immune response to cancer could be modelled by splitting the population of DCs into a subpopulation of cells with no tumour antigens on their surface and a subpopulation of cells presenting some antigen – which would move in a non-local and in a more localised search pattern, respectively [10] – and letting DCs switch from one subpopulation to the other via binary interactions with cancer cells [28, 29]. The strategy we have used here to model non-conservative cell-cell interactions may prove useful to the development of both generalisations of our modelling approach.

In regard to the mathematical modelling of other aspects of immune cell movement, our modelling approach could be extended to represent other switches in T cell migration patterns observed in the immune response to different pathogens, which are driven by possible chemotactic cues and by the conditions of the surrounding microenvironment [17]. Moreover, further generalisations of the modelling approach could be developed in relation to experimental results indicating that T cells can also undergo subdiffusive [32] and fully ballistic [31] migration.

In general, it would be interesting to apply the modelling approach presented in this paper and its possible developments to other biological and ecological contexts whereby switch from non-local to localised migration patterns has been reported [4, 8, 9, 15, 21].

We conclude by remarking that, as previously noted, although they may result in cell outgoing trajectories compatible with those observed in elastic collisions, binary collisions between cells are not elastic in nature. Hence, it will be necessary to go beyond the definition of post-collision velocities used here in order to have a more biophysically faithful representation of cell-cell interactions. This is beyond the scope of the present work, which is primarily focused on modelling the switch in T cell migration modes mediated by interactions between inactive CTLs and DCs. Moreover, the formal approach employed in this article to derive a macroscopic limit of the mesoscopic model relies on the assumption that cell densities are sufficiently low so that cell velocities can be assumed to be uncorrelated. As such, it may lead to an inaccurate mean field representation of the dynamics of the underlying biological system in cases where cell densities are not sufficiently low, or cell-cell interactions introduce a stronger correlation between cell velocities. Therefore, another fruitful avenue of research would lie

in extending this formal approach to these more complex cases by identifying alternative ways of obtaining a closed system of coupled equations for the macroscopic cell densities starting from the corresponding kinetic model.

A Derivation of transport equations (3.11)-(3.12)

Using the method presented in [11], we show how to derive a transport equation for the two-particle distribution function $\tilde{\tilde{f}}_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k)$ starting from transport equation (3.2) for the two-particle distribution function $f_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k, \tau_h, \tau_k)$.

We first introduce the notation

$$\tilde{f}_{\tau_h}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k, \tau_h) := \int_0^t f_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k, \tau_h, \tau_k)\, \mathrm{d}\tau_k \ ,$$

and

$$\tilde{f}_{\tau_k}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k, \tau_k) := \int_0^t f_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k, \tau_h, \tau_k)\, \mathrm{d}\tau_h \ ,$$

and then note that, when β_h and β_k are given by (2.1) with ψ_h and ψ_k defined via (2.2) or (2.3), the solutions of (3.2) subject to the initial and boundary conditions considered here are such that $\tilde{f}_{\tau_h}$ decays monotonically as τ_h increases, and $\tilde{f}_{\tau_k}$ exhibits an analogous behaviour. Hence, integrating (3.2) with respect to (τ_h, τ_k) over $(0,t)^2$ with t large enough so that $\tilde{f}_{\tau_h}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k, \tau_h = t)$ is negligible compared to $\tilde{f}^0_{\tau_h}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k)$ and $\tilde{f}_{\tau_k}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k, \tau_k = t)$ is negligible compared to $\tilde{f}^0_{\tau_k}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k)$, with

$$\tilde{f}^0_{\tau_h}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k) := \tilde{f}_{\tau_h}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k, \tau_h = 0)$$

and

$$\tilde{f}^0_{\tau_k}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k) := \tilde{f}_{\tau_k}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k, \tau_k = 0) \ ,$$

we obtain the following transport equation for $\tilde{\tilde{f}}_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k)$

$$(\partial_t + c\,\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h} + c\,\mathbf{v}_k \cdot \nabla_{\mathbf{x}_k})\tilde{\tilde{f}}_{hk} = -\int_0^t \int_0^t (\beta_h + \beta_k) f_{hk}\, \mathrm{d}\tau_h\, \mathrm{d}\tau_k + \tilde{f}^0_{\tau_h} + \tilde{f}^0_{\tau_k} \ ,$$

which can be rewritten as

$$(\partial_t + c\,\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h} + c\,\mathbf{v}_k \cdot \nabla_{\mathbf{x}_k})\tilde{\tilde{f}}_{hk} = -\tilde{\tilde{f}}^{\beta_h}_{hk} - \tilde{\tilde{f}}^{\beta_k}_{hk} + \tilde{f}^0_{\tau_h} + \tilde{f}^0_{\tau_k} \ , \tag{A.1}$$

with $\tilde{\tilde{f}}^{\beta_h}_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k)$ and $\tilde{\tilde{f}}^{\beta_k}_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k)$ given by (3.7).

When cell movement at the microscopic scale obeys the rules presented in Section 2, we have

$$\tilde{f}^0_{\tau_h} = \mathcal{T}_h[\tilde{\tilde{f}}^{\beta_h}_{hk}] \quad \text{and} \quad \tilde{f}^0_{\tau_k} = \mathcal{T}_k[\tilde{\tilde{f}}^{\beta_k}_{hk}] \ , \tag{A.2}$$

with the turning operators $\mathcal{T}_h$ and $\mathcal{T}_k$ being defined via (2.5). The first two terms on the right-hand side of (A.1) describe the density of cells that stop with rates β_h, β_k. The initial conditions at $\tau_h = 0$ and $\tau_k = 0$ (i.e. at the beginning of a new run phase) given by (A.2) describes how the cells will resume their motion in a new direction dictated by the turning operators $\mathcal{T}_h$ and $\mathcal{T}_k$, respectively.

Substituting the expressions for $\tilde{f}^0_{\tau_h}$ and $\tilde{f}^0_{\tau_k}$ given by (A.2) into transport equation (A.1) yields

$$\begin{aligned}(\partial_t + c\,\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h} + c\,\mathbf{v}_k \cdot \nabla_{\mathbf{x}_k})\tilde{\tilde{f}}_{hk} = &-(\mathbb{1} - \mathcal{T}_h)[\tilde{\tilde{f}}^{\beta_h}_{hk}] \\ &- (\mathbb{1} - \mathcal{T}_k)[\tilde{\tilde{f}}^{\beta_k}_{hk}] \ , \quad (\mathbf{x}_h, \mathbf{x}_k) \in \Omega^2, t \in \mathbb{R}_+, (\mathbf{v}_h, \mathbf{v}_k) \in \mathrm{V}^2 \ .\end{aligned} \tag{A.3}$$

Remark 4. *Since we consider transport equation* (3.2) *complemented with a smooth, compactly supported initial condition, the initial condition for transport equation* (A.3) *will be a smooth, compactly supported function as well. Therefore, the two-particle distribution function* $\tilde{\tilde{f}}_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k)$ *will have compact support on* $\Omega^2 \times \mathrm{V}^2$ *for all* $t \in \mathbb{R}_+^*$.

B Derivation of the equation for the one-particle distribution

Transport equation (3.13) for the one-particle distribution function $p_h(\mathbf{x}_h, t, \mathbf{v}_h)$ can derived from transport equation (A.3) for the two-particle distribution function $\tilde{\tilde{f}}_{hk}(\mathbf{x}_h, \mathbf{x}_k, t, \mathbf{v}_h, \mathbf{v}_k)$ in six steps as previously done in [11].

(I) We integrate transport equation (A.3) with respect to $(\mathbf{x}_k, \mathbf{v}_k)$ over the set $\Omega_k(\mathbf{x}_h) \times \mathrm{V}$ and multiply both sides of the resulting equation by $|\mathrm{V}|^{-1}$ to obtain

$$\begin{aligned} |\mathrm{V}|^{-1} \int_{\Omega_k(\mathbf{x}_h)} \int_{\mathrm{V}} (\partial_t + c\,\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h} + c\,\mathbf{v}_k \cdot \nabla_{\mathbf{x}_k}) \tilde{\tilde{f}}_{hk} \,\mathrm{d}\mathbf{v}_k \,\mathrm{d}\mathbf{x}_k = \\ - |\mathrm{V}|^{-1} \int_{\Omega_k(\mathbf{x}_h)} \int_{\mathrm{V}} (\mathbb{1} - \mathcal{T}_h)[\tilde{\tilde{f}}_{hk}^{\beta_h}] \,\mathrm{d}\mathbf{v}_k \,\mathrm{d}\mathbf{x}_k \\ - |\mathrm{V}|^{-1} \int_{\Omega_k(\mathbf{x}_h)} \int_{\mathrm{V}} (\mathbb{1} - \mathcal{T}_k)[\tilde{\tilde{f}}_{hk}^{\beta_k}] \,\mathrm{d}\mathbf{v}_k \,\mathrm{d}\mathbf{x}_k \ . \end{aligned} \tag{B.1}$$

(II) Using the fact that p_h is given by (3.6) and integrals with respect to $\mathbf{x}_k$ and $\mathbf{v}_k$ commute, we rewrite the first term on the left-hand side of (B.1) as

$$|\mathrm{V}|^{-1} \partial_t \int_{\Omega_k(\mathbf{x}_h)} \int_{\mathrm{V}} \tilde{\tilde{f}}_{hk} \,\mathrm{d}\mathbf{v}_k \,\mathrm{d}\mathbf{x}_k = \partial_t p_h \ .$$

(III) Using Reynold's transport theorem in the variable $\mathbf{x}_h$, we rewrite the second term on the left-hand side of (B.1) as

$$\begin{aligned} |\mathrm{V}|^{-1} c \int_{\Omega_k(\mathbf{x}_h)} \int_{\mathrm{V}} (\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h}) \tilde{\tilde{f}}_{hk} \,\mathrm{d}\mathbf{v}_k \,\mathrm{d}\mathbf{x}_k = |\mathrm{V}|^{-1} c\,\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h} p_h \\ - |\mathrm{V}|^{-1} c \int_{\partial \mathrm{B}_\varrho(\mathbf{x}_h)} \int_{\mathrm{V}} (\mathbf{v}_h \cdot \nu) \tilde{\tilde{f}}_{hk} \,\mathrm{d}\mathbf{v}_k \,\mathrm{d}\sigma \ . \end{aligned}$$

Here, ν is the unit normal to $\partial\Omega_k(\mathbf{x}_h)$ that points outward from $\Omega_k(\mathbf{x}_h)$ and inward to $\mathrm{B}_\varrho(\mathbf{x}_i)$, and $\mathrm{d}\sigma$ denotes the surface element.

(IV) Since $\tilde{\tilde{f}}_{hk}$ has compact support on $\Omega^2 \times \mathrm{V}^2$ (*vid.* Remark 4), we use the divergence theorem and rewrite the third term on the left-hand side of (B.1) as

$$|\mathrm{V}|^{-1} c \int_{\Omega_k(\mathbf{x}_h)} \int_{\mathrm{V}} (\mathbf{v}_k \cdot \nabla_{\mathbf{x}_k}) \tilde{\tilde{f}}_{hk} \,\mathrm{d}\mathbf{v}_k \,\mathrm{d}\mathbf{x}_k = |\mathrm{V}|^{-1} c \int_{\partial \mathrm{B}_\varrho(\mathbf{x}_h)} \int_{\mathrm{V}} (\mathbf{v}_k \cdot \nu) \tilde{\tilde{f}}_{hk} \,\mathrm{d}\mathbf{v}_k \,\mathrm{d}\sigma \ .$$

(V) Changing order of integration, we rewrite the first term on the right-hand side of (B.1) as

$$-|\mathrm{V}|^{-1} \int_{\Omega_k(\mathbf{x}_h)} \int_{\mathrm{V}} (\mathbb{1} - \mathcal{T}_h)[\tilde{\tilde{f}}_{hk}^{\beta_h}] \,\mathrm{d}\mathbf{v}_k \,\mathrm{d}\mathbf{x}_k = -(\mathbb{1} - \mathcal{T}_h)[p_h^{\beta_h}] \ ,$$

with $p_h^{\beta_h}(\mathbf{x}_h, t, \mathbf{v}_h)$ given by (3.8).

(VI) Since $\mathcal{T}_k$ satisfies (2.6), the second term on the right-hand side of (B.1) is identically zero.

Taken together, the results obtained in Steps **(I)**-**(VI)** allow one to conclude that the one-particle distribution function $p_h(\mathbf{x}_h, t, \mathbf{v}_h)$ satisfies the following transport equation

$$\partial_t p_h + c\,\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h} p_h = -(\mathbb{1} - \mathcal{T}_h)[p_h^{\beta_h}] + \mathcal{Q}_{hk}, \quad \mathbf{x}_h \in \mathbb{R}^n, t \in \mathbb{R}_+, \mathbf{v}_h \in \mathrm{V}\ , \tag{B.2}$$

with the weighted one-particle distribution function $p_h^{\beta_h}(\mathbf{x}_h, t, \mathbf{v}_h)$ being given by (3.8) and the term $\mathcal{Q}_{hk}(\mathbf{x}_h, t, \mathbf{v}_h)$ being defined according to (3.14).

C Derivation of the non-local trajectory term

In the case where β_h is defined via (2.1) and (2.3) (i.e. for $h = I$) and β_k is defined via (2.1) and (2.2) (i.e. for $k = D$), applying the method of characteristics to (3.2) and using the fact that $\dfrac{\psi_k(\cdot, \tau_k)}{\psi_k(\cdot, \tau_k - \tau_h)} = e^{-b\tau_h}$ one finds [11]

$$f_{hk} = f_{hk}(\mathbf{x}_h - c\,\mathbf{v}_h\tau_h, \mathbf{x}_k - c\mathbf{v}_k\tau_h, t - \tau_h, \mathbf{v}_h, \mathbf{v}_k, \tau_h = 0, \tau_k - \tau_h)\,\psi_h(\mathbf{x}_h, \tau_h)\,e^{-b\tau_h}\ . \tag{C.1}$$

Introducing the notation

$$\bar{f}^0_{hk} := \int_{\Omega_k(\mathbf{x}_h)} \int_{\mathrm{V}} \int_0^t f_{hk}(\cdot, \mathbf{x}_k - c\mathbf{v}_k\tau_h, \cdot, \cdot, \mathbf{v}_k, \tau_h = 0, \tau_k - \tau_h)\,\mathrm{d}\tau_k\,\mathrm{d}\mathbf{v}_k\,\mathrm{d}\mathbf{x}_k$$

and substituting (C.1) into (3.8) gives

$$\begin{aligned} p_h^{\beta_h}(\mathbf{x}_h, t, \mathbf{v}_h) &= \frac{1}{|\mathrm{V}|}\int_0^t \frac{\varphi_h(\mathbf{x}_h, \tau_h)}{\psi_h(\mathbf{x}_h, \tau_h)} \int_{\Omega_k(\mathbf{x}_h)} \int_{\mathrm{V}} \int_0^t f_{hk}\,\mathrm{d}\tau_k\,\mathrm{d}\mathbf{v}_k\,\mathrm{d}\mathbf{x}_k\,\mathrm{d}\tau_h \\ &= \frac{1}{|\mathrm{V}|}\int_0^t \varphi_h(\mathbf{x}_h, \tau_h) e^{-b\tau_h} \bar{f}^0_{hk}(\mathbf{x}_h - c\,\mathbf{v}_h\tau_h, t - \tau_h, \mathbf{v}_h)\,\mathrm{d}\tau_h \\ &= \frac{1}{|\mathrm{V}|}\int_0^t \varphi_h(\mathbf{x}_h, t - s) e^{-(t-s)(b + c\,\mathbf{v}_h\cdot\nabla_{\mathbf{x}_h})} \bar{f}^0_{hk}(\mathbf{x}_h, s, \mathbf{v}_h)\,\mathrm{d}s\ . \end{aligned} \tag{C.2}$$

The last equality in (C.2) is obtained using the change of variables $s = t - \tau_h$ along with the following Taylor expansion

$$\begin{aligned} e^{-(t-s)c\mathbf{v}\cdot\nabla} f(\mathbf{x}) &= \sum_{m=0}^{\infty} \frac{(-(t-s)\,c\,\mathbf{v}\cdot\nabla)^m}{m!} f(\mathbf{x}) \\ &= \sum_{m=0}^{\infty} \frac{1}{m!}(-(t-s)\,c\,\mathbf{v})^m \nabla^m f(\mathbf{x}) = f(\mathbf{x} - (t-s)\,c\,\mathbf{v})\ . \end{aligned}$$

Hence, the Laplace transform in time of $p_h^{\beta_h}(\mathbf{x}_h, t, \mathbf{v}_h)$ is

$$\hat{p}_h^{\beta_h}(\mathbf{x}_h, \lambda, \mathbf{v}_h) = \frac{1}{|\mathrm{V}|}\hat{\varphi}_h(\mathbf{x}_h, \lambda + b + c\,\mathbf{v}_h\cdot\nabla_{\mathbf{x}_h})\hat{\bar{f}}^0_{hk}(\mathbf{x}_h, \lambda, \mathbf{v}_h)\ . \tag{C.3}$$

Here, λ is the Laplace variable, and $\hat{\varphi}_h$ and $\hat{\bar{f}}^0_{hk}$ are the Laplace transforms in time of the functions φ_h and $\bar{f}^0_{hk}$. Moreover, substituting (C.1) into (3.6) and computing the Laplace transform in time yields

$$\hat{p}_h(\mathbf{x}_h, \lambda, \mathbf{v}_h) = \frac{1}{|\mathrm{V}|}\hat{\psi}_h(\mathbf{x}_h, \lambda + b + c\,\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h})\hat{\bar{f}}^0_{hk}(\mathbf{x}_h, \lambda, \mathbf{v}_h) \ ,$$

with $\hat{\psi}_h$ being the Laplace transform of the function ψ_h. The latter equation gives

$$\hat{\bar{f}}^0_{hk}(\mathbf{x}_h, \lambda, \mathbf{v}_h) = |\mathrm{V}| \, \frac{\hat{p}_h(\mathbf{x}_h, \lambda, \mathbf{v}_h)}{\hat{\psi}_h(\mathbf{x}_h, \lambda + b + c\,\mathbf{v}_h \cdot \nabla_{\mathbf{x}_h})}.$$

Substituting such an expression for $\hat{\bar{f}}^0_{hk}$ into (C.3) ones sees that (C.2) can be written as

$$p_h^{\beta_h}(\mathbf{x}_h, t, \mathbf{v}_h) = \mathcal{B}[p_h](\mathbf{x}_h, t, \mathbf{v}_h)$$

with the integral operator $\mathcal{B}$ being defined according to (3.17).

References

[1] Guenter Albrecht-Buehler. The phagokinetic tracks of 3T3 cells. *Cell*, 11(2):395–404, 1977.

[2] Wolgang Alt. Biased random walk models for chemotaxis and related diffusion approximations. *Journal of Mathematical Biology*, 9(2):147–177, 1980.

[3] Elham Azizi, Ambrose J Carr, George Plitas, Andrew E Cornish, Catherine Konopacki, Sandhya Prabhakaran, Juozas Nainys, Kenmin Wu, Vaidotas Kiseliovas, Manu Setty, et al. Single-cell map of diverse immune phenotypes in the breast tumor microenvironment. *Cell*, 174(5):1293–1308, 2018.

[4] Frederic Bartumeus, Francesc Peters, Salvador Pueyo, Celia Marrasé, and Jordi Catalan. Helical Lévy walks: adjusting searching statistics to resource availability in microzooplankton. *Proceedings of the National Academy of Sciences*, 100(22):12771–12775, 2003.

[5] Alexandre Boissonnas, Luc Fetler, Ingrid S Zeelenberg, Stéphanie Hugues, and Sebastian Amigorena. In vivo imaging of cytotoxic T cell infiltration and elimination of a solid tumor. *The Journal of Experimental Medicine*, 204(2):345–356, 2007.

[6] Philippe Bousso. T-cell activation by dendritic cells in the lymph node: lessons from the movies. *Nature Reviews Immunology*, 8(9):675–684, 2008.

[7] Carlo Cercignani, Reinhard Illner, and Mario Pulvirenti. *The mathematical theory of dilute gases*, volume 106. Springer Science & Business Media, 2013.

[8] Monique de Jager, Frederic Bartumeus, Andrea Kölzsch, Franz J Weissing, Geerten M Hengeveld, Bart A Nolet, Peter MJ Herman, and Johan van de Koppel. How superdiffusion gets arrested: ecological encounters explain shift from Lévy to Brownian movement. *Proceedings of the Royal Society B: Biological Sciences*, 281(1774):20132605, 2014.

[9] HJ De Knegt, GM Hengeveld, F Van Langevelde, WF De Boer, and KP Kirkman. Patch density determines movement patterns and foraging efficiency of large herbivores. *Behavioral Ecology*, 18(6):1065–1072, 2007.

[10] John J Engelhardt, Bijan Boldajipour, Peter Beemiller, Priya Pandurangi, Caitlin Sorensen, Zena Werb, Mikala Egeblad, and Matthew F Krummel. Marginating dendritic cells of the tumor microenvironment cross-present tumor antigens and stably engage tumor-specific T cells. *Cancer Cell*, 21(3):402–417, 2012.

[11] Gissell Estrada-Rodriguez and Heiko Gimperlein. Interacting particles with Lévy strategies: limits of transport equations for swarm robotic systems. *SIAM Journal on Applied Mathematics*, 80(1):476–498, 2020.

[12] Gissell Estrada-Rodriguez, Heiko Gimperlein, and Kevin J Painter. Fractional Patlak–Keller–Segel equations for chemotactic superdiffusion. *SIAM Journal on Applied Mathematics*, 78(2):1155–1173, 2018.

[13] Benjamin Franz, Jake P Taylor-King, Christian Yates, and Radek Erban. Hard-sphere interactions in velocity-jump models. *Physical Review E*, 94(1):012129, 2016.

[14] Alycia Gardner and Brian Ruffell. Dendritic cells and cancer immunity. *Trends in Immunology*, 37(12):855–865, 2016.

[15] Nicolas E Humphries, Nuno Queiroz, Jennifer RM Dyer, Nicolas G Pade, Michael K Musyl, Kurt M Schaefer, Daniel W Fuller, Juerg M Brunnschweiler, Thomas K Doyle, Jonathan DR Houghton, et al. Environmental context explains Lévy and Brownian movement patterns of marine predators. *Nature*, 465(7301):1066–1069, 2010.

[16] Earle H Kennard et al. *Kinetic theory of gases*, volume 287. McGraw-hill New York, 1938.

[17] Matthew F Krummel, Frederic Bartumeus, and Audrey Gérard. T cell migration, search strategies and mechanisms. *Nature Reviews Immunology*, 16(3):193, 2016.

[18] Jakob Löber, Falko Ziebert, and Igor S Aranson. Collisions of deformable cells lead to collective migration. *Scientific Reports*, 5(1):1–7, 2015.

[19] Fiona R Macfarlane, Mark AJ Chaplain, and Tommaso Lorenzi. A stochastic individual-based model to explore the role of spatial interactions and antigen recognition in the immune response against solid tumours. *Journal of Theoretical Biology*, 480:43–55, 2019.

[20] Fiona R Macfarlane, Tommaso Lorenzi, and Mark AJ Chaplain. Modelling the immune response to cancer: an individual-based approach accounting for the difference in movement between inactive and activated T cells. *Bulletin of Mathematical Biology*, 80(6):1539–1562, 2018.

[21] Bart A Nolet and Wolf M Mooij. Search paths of swans foraging on spatially autocorrelated tubers. *Journal of Animal Ecology*, pages 451–462, 2002.

[22] Hans G Othmer, Steven R Dunbar, and Wolfgang Alt. Models of dispersal in biological systems. *Journal of Mathematical Biology*, 26(3):263–298, 1988.

[23] Hans G Othmer and Thomas Hillen. The diffusion limit of transport equations derived from velocity-jump processes. *SIAM Journal on Applied Mathematics*, 61(3):751–775, 2000.

[24] Hans G Othmer, Philip K Maini, and James D Murray. *Experimental and theoretical advances in biological pattern formation*, volume 259. Springer Science & Business Media, 2012.

[25] Benoît Perthame, Weiran Sun, and Min Tang. The fractional diffusion limit of a kinetic model with biochemical pathway. *Zeitschrift für angewandte Mathematik und Physik*, 69(3):67, 2018.

[26] Tobias Rothoeft, Sandra Balkow, Mathias Krummen, Stefan Beissert, Georg Varga, Karin Loser, Pia Oberbanscheidt, Frank van den Boom, and Stephan Grabbe. Structure and duration of contact between dendritic cells and T cells are controlled by T cell activation state. *European Journal of Immunology*, 36(12):3105–3117, 2006.

[27] Cédric Villani. A review of mathematical topics in collisional kinetic theory. *Handbook of mathematical fluid dynamics*, 1(71-305):3–8, 2002.

[28] Alex D Waldman, Jill M Fritz, and Michael J Lenardo. A guide to cancer immunotherapy: from T cell basic science to clinical practice. *Nature Reviews Immunology*, pages 1–18, 2020.

[29] Stefanie K Wculek, Francisco J Cueto, Adriana M Mujal, Ignacio Melero, Matthew F Krummel, and David Sancho. Dendritic cells in cancer immunology and immunotherapy. *Nature Reviews Immunology*, pages 1–18, 2019.

[30] E John Wherry and Makoto Kurachi. Molecular and cellular insights into T cell exhaustion. *Nature Reviews Immunology*, 15(8):486–499, 2015.

[31] Colleen M Witt, Subhadip Raychaudhuri, Brian Schaefer, Arup K Chakraborty, and Ellen A Robey. Directed migration of positively selected thymocytes visualized in real time. *PLOS Biolology*, 3(6):e160, 2005.

[32] Tim Worbs, Thorsten R Mempel, Jasmin Bölter, Ulrich H von Andrian, and Reinhold Förster. CCR7 ligands stimulate the intranodal motility of T lymphocytes in vivo. *The Journal of Experimental Medicine*, 204(3):489–495, 2007.