Micro-Macro Derivation of Virus-Chemotaxis Models

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Abstract

This paper deals with the micro-macro derivation of virus models coupled with a reaction diffusion models that generates the dynamics in space of the virus particles. The first part of the presentation focuses, starting from [5, 6] on a survey and a critical analysis of some phenomenological models known in the literature. The second part shows how methods of the kinetic theory can be used to model the dynamics of the system treated in our paper. The third part deals with the derivation of macroscopic models from the underlying description, delivered within a general framework of the kinetic theory.

keywords: Kinetic theory, active particles, cross diffusion, multiscale methods.

1 Aims and plan of the paper

The phenomenological derivation of models of biological tissues can be obtained, at the macroscopic scale, by conservation, or equilibrium, equations that involve locally averaged quantities deemed to describe the state of the system. These structures can be closed by means of heuristic models of the material behavior of the physical system under consideration. Different models correspond to each specific closure that are obtained by material models generally valid only for physical conditions closed to equilibrium, while dynamical models are required to describe physical reality far from equilibrium.

Alternative methods have been developed to tackle the aforementioned conceptual difficulty. Specifically, we refer to the method proposed in [9, 10] where the derivation of reaction-diffusion equations and of the celebrated Keller-Segel model [19, 20] was considered. This derivation is somehow inspired to the
Hilbert’s sixth problem, see [17] which suggests the search of a unified approach to physical theories at all representation scales, see also [16].

In general, the dynamics at the low scale is modeled by the kinetic theory of active particles [3]. This equation is expanded in terms of a small parameter corresponding to the mean distance between pair of particles, which is closed by neglecting the contribution of higher order terms. The macro-scale model is obtained by taking low order terms of the expansion. This method is reviewed in the survey paper [1] mainly devoted to the micro-macro derivation Keller and Segel type models (in short KS model).

In more detail, our paper is devoted to the micro-macro derivation of reaction-diffusion and cross-diffusion models in which a virus model is coupled with a reaction diffusion models that regulate the spatial dynamics of viral particles. This class of models can be defined exotic by a term used to denote models in fields of behavioral sciences, for instance social and economical sciences, namely sciences where individual behaviors have an influence on the mechanical dynamics. Occasionally, the term model in complex environments is used to denote the interaction between a first model, essentially chemotaxis or cross diffusion, with a second (additional) model which describes the external dynamics. The survey [4] reports about a broad variety of this type of models.

In more details on the contents of our paper, Section 2 provides a description and the phenomenological derivation of the aforementioned class of models. Section 3 presents the methodological approach used for the micro-macro derivation. Section 4 shows how the approach can be applied to the derivation of the macroscopic description of the models reported in Section 2. Finally, a critical analysis is presented in the last section looking ahead to research perspectives.

2 Heuristic derivation of cross diffusion of virus models

The class of models presented in this section describes the dynamics of a virus model, where space dynamics is induced by a transport mechanism which is modeled by the action of a reaction-diffusion system. In more details, we consider a classic prototype model for virus dynamics in the spatially homogeneous case derived within a framework of population dynamics [7, 23], which is also known by the acronym SIR [24, 25]. We briefly present the model which has been analytically and computationally studied in [5], where a SIR type model is coupled with a Keller-Segel model.

Let us consider a May-Nowak type model which describes, by a system of ODEs, the dynamics of three components, i.e. the densities of healthy uninfected immune cells \( u = u(t) \), infected immune cells \( v = v(t) \), and virus particles \( w = w(t) \) [24]. The model considers the following heuristic assumptions: Healthy cells are constantly produced by the body at rate \( r \), die at rate \( d_1 u \) and become infected on contact with the virus, at rate \( \beta uv \); Infected cells are produced at rate \( \beta uv \) and die at rate \( d_2 v \); New virus particles are produced at rate \( kv \) and
die at rate $d_3w$. These assumptions lead to the following system of ODEs:

\[
\begin{align*}
\frac{du}{dt} &= -d_1 u - \beta w u + r, \quad t > 0, \\
\frac{dv}{dt} &= -d_2 v + \beta u w, \quad t > 0, \\
\frac{dw}{dt} &= -d_3 w + k v, \quad t > 0.
\end{align*}
\]

This model has been quite comprehensively understood via a thorough qualitative analysis of corresponding initial value problems (for instance cf. [7, 24]). As it is known, in addition to the infection-free equilibrium $Q_0 := (r, 0, 0)$, if the so-called basic reproduction number $R_0$ is greater than 1, namely $R_0 > 1$ with

\[
R_0 := \frac{\beta kr}{d_1 d_2 d_3},
\]

then, the system shows an additional equilibrium $Q^* := (u^*, v^*, w^*)$, where

\[
u^* := \frac{r}{d_1 R_0}, \quad v^* := \frac{d_1 d_3}{\beta k}(R_0 - 1) \quad \text{and} \quad w^* := \frac{d_1}{\beta}(R_0 - 1).
\]

This equilibrium is globally asymptotically stable and positive defined, whereas if $R_0 \leq 1$ then the infection-free equilibrium $Q_0$ enjoys this property [22].

The space dynamics in the model studied in [5, 6, 13] is modeled by a deterministic reaction diffusion dynamics acting on $u = u(t, x)$, $v = v(t, x)$ and $w = w(t, x)$ which now include space dependence:

\[
\begin{align*}
\frac{\partial u}{\partial t} &= D_u \Delta u - \chi \nabla \cdot (u \nabla v) - d_1 u - \beta u w + r(t, x), \\
\frac{\partial v}{\partial t} &= D_v \Delta v - d_2 v + \beta u w, \\
\frac{\partial w}{\partial t} &= D_w \Delta w - d_3 w + k v,
\end{align*}
\]

where $D_u$, $D_v$ and $D_w$ denote the respective, positive defined, diffusion coefficients and where $\chi$ represents strength and direction of the cross-diffusive interaction, while the parameters $\beta, k, d_1, d_2, d_3$ have been already defined above. The reaction-diffusion action term corresponds to a simplified Keller-Segel chemotaxis system [5].

This model can be viewed as a specific example of interaction between a dynamical system modeled by ODEs and a reaction-diffusion system which creates pattern formation. Further developments may focus on the modeling of the virus dynamics, that might go beyond the limited validity of SIR models, as well as on the modeling space dynamics by selecting cross diffusion-reaction models consistent with the specific biological and physical environment where the dynamics develops.
3 On the micro-macro derivation of virus SIR models in a KS-system

This section presents the micro-macro derivation by an asymptotic expansion somehow inspired to the Hilbert \[10\]. Firstly, we derive a general kinetic model for three interacting population corresponding to the specific case of the SIR model. The derivation of macroscopic equations is treated in the following two subsections. Firstly, we derive a general macroscopic model and then, we show how it can be specifically referred to the virus model under consideration.

3.1 On the derivation of a general kinetic model

This subsection presents the derivation of macroscopic models, by micro-macro decomposition, of linear transport models a binary mixture of self-propelled particles whose state, called microscopic state, is denoted by the variable \((x,v)\), where \(x\) and \(v\) are, respectively, position and velocity. The collective description of a mixture of particles can be encoded in the statistical distribution functions \(f_i = f_i(t,x,v)\), for \(i = 1, 2, 3\). Weighted moments provide, under suitable integrability properties, the calculation of macroscopic variables.

Let us now consider the following class of equations:

\[
\begin{aligned}
(\partial_t + v \cdot \nabla_x) f_1 &= \nu_1 T_1(f_2, f_3)(f_1) + \mu_1 G_1(f_1, f_2, f_3, v), \\
(\partial_t + v \cdot \nabla_x) f_2 &= \nu_2 T_2(f_2) + \mu_2 G_2(f_1, f_2, f_3, v), \\
(\partial_t + v \cdot \nabla_x) f_3 &= \nu_3 T_3(f_3) + \mu_3 G_3(f_1, f_2, f_3, v),
\end{aligned}
\]

(4)

where \(G_1, G_2, G_3\) are interactions terms assumed depending on the quantities \(f_1, f_2, f_3\), while the operator \(T_i(f)\) models the dynamics of biological organisms by a velocity-jump process:

\[
T_i(f) = \int_V \left[ T_i(v^*, v)f(t,x,v^*) - T_i(v, v^*)f(t,x,v) \right] dv^*, \quad i = 1, 2, 3
\]

(5)

where \(T_i(v, v^*)\) is the probability kernel for the new velocity \(v \in V\) assuming that the previous velocity was \(v^*\).

The derivation of macroscopic models from the kinetic model \[11\], can be obtained in the regime \(\nu_1, \nu_2, \nu_3, \to +\infty\) corresponding to the distance between particles tending to zero. After a dimensionless of the system is obtained, see \[11\], a small parameter \(\varepsilon\) can be chosen, for the parabolic scaling, such that

\[
t \to \varepsilon t, \quad \mu_i = \varepsilon, \quad \nu_i = \frac{1}{\varepsilon^q_i}, \quad q_i \geq 1, \quad i = 1, 2, 3.
\]
Then, the model (4) can be rewritten as follows:

\[
\begin{align*}
(\varepsilon \partial_t + v \cdot \nabla_x) f^j_1 &= \frac{1}{\varepsilon} T_1(f^j_2, f^j_3)(f^j_1) + \varepsilon G_1(f^j_1, f^j_2, f^j_3, v), \\
(\varepsilon \partial_t + v \cdot \nabla_x) f^j_2 &= \frac{1}{\varepsilon} T_2(f^j_2) + \varepsilon G_2(f^j_1, f^j_2, f^j_3, v), \\
(\varepsilon \partial_t + v \cdot \nabla_x) f^j_3 &= \frac{1}{\varepsilon^2} T_3(f^j_3) + \varepsilon G_3(f^j_1, f^j_2, f^j_3, v),
\end{align*}
\]

**Assumption 3.1.** The turning operators $T_1, T_2, T_3$ are supposed to be decomposable as follows:

\[
T_i[f^j_2, f^j_3](g) = T^0_i(g) + \varepsilon^p T^p_i[f^j_2, f^j_3](g), \quad p \geq 1,
\]

where $T^j_i$ for $j = 0, 1$, is given by

\[
T^j_i(g) = \int_V \left[ T^j_i^*(t, x, v^*) - T^j_i(t, x, v) \right] dv^*,
\]

with $T^j_i^* = T^j_i(v^*, v)$ and where the dependence on $f_2, f_3$, of the operator $T_i$ stems from $T^0_i$, while we suppose that $T^0_i$ is independent of $f_2, f_3$, and $T_i$ for $(l = 2, 3)$, is given by

\[
T_i(g) = \int_V \left[ T_i^*(t, x, v^*) - T_i(t, x, v) \right] dv^*.
\]

**Assumption 3.2.** We assume that the turning operators $T_i (i = 1, 2, 3)$ satisfy the following equality:

\[
\int_V T_i(g) dv = \int_V T^0_i(g) dv = \int_V T^1_i[f^j_2, f^j_3](g) dv = 0,
\]

**Assumption 3.3** There exists a bounded velocity distribution $M_j(v) > 0$ (j=2,3) and $M_1(v) > 0$, independent of $t, x$, such that the detailed balance

\[
T^0_i(v, v^*) M_j(v^*) = T^0_i(v^*, v) M_j(v),
\]

and

\[
T_j(v, v^*) M_j(v^*) = T_j(v^*, v) M_j(v),
\]

hold true. Moreover, the flow produced by these equilibrium distributions vanishes, and $M_i$ are normalized

\[
\int_V v M_i(v) dv = 0, \quad \int_V M_i(v) dv = 1 \quad i = 1, 2, 3.
\]

In addition, we assume that the kernels $T_j(v, v^*)$ and $T^0_i(v, v^*)$ are bounded and that there exist constants $\sigma_j > 0$ and $\sigma_1 > 0$, $j = 2, 3$, such that

\[
T_j(v, v^*) \geq \sigma_j M_j(v), \quad T^0_i(v, v^*) \geq \sigma_1 M_1(v),
\]
for all \((v, v^*) \in V \times V, x \in \Omega\) and \(t > 0\).

Given that \(L_j = T_j(j = 2, 3)\) and \(L_1 = T_1^0\). Technical calculations yields the following Lemma:

**Lemma 1** Suppose that Assumptions 3.3 holds. Then, for \(i = 1, 2, 3\), the following properties of the operators \(L_1, L_2\) and \(L_3\) hold:

i) The operator \(L_i\) is self-adjoint in the space \(L^2\left(V, \frac{dv}{M_i}\right)\).

ii) For \(f \in L^2\), the equation \(L_i(g) = f\) has a unique solution \(g \in L^2\left(V, \frac{dv}{M_i}\right)\),

which satisfies

\[
\int_V g(v) dv = 0 \quad \text{if and only if} \quad \int_V f(v) dv = 0 .
\]

iii) The equation \(L_i(g) = v M_i(v)\) has a unique solution that we call \(\theta_i(v)\).

iv) The kernel of \(L_i\) is \(N(L_i) = \text{vect}(M_i(v))\).

### 3.2 Derivation of a general macroscopic models

A system coupling a hydrodynamic part with a kinetic part of the distribution functions, is derived in this subsection. Then it is proved that such a system is equivalent to the two scale kinetic equation (6). This new formulation provides the basis for the derivation of the general model we are looking for.

In the remainder, the integral with respect to the variable \(v\) will be denoted by \(\langle \cdot \rangle\). This notation is used also for any argument within \(\langle \rangle\). In addition, let us denote by \(f = (f_1, f_2, f_3)\) the solution of (6), where \(f\) is decomposed as follows:

\[
f_1^\varepsilon(t, x, v) = \sum_{i=0}^{q_1+1} \varepsilon^i g_i(t, x, v) + O(\varepsilon^{q_1+2}),
\]

(15)

\[
f_2^\varepsilon(t, x, v) = \sum_{j=0}^{q_2+1} \varepsilon^j h_j(t, x, v) + O(\varepsilon^{q_2+2}).
\]

(16)

and

\[
f_3^\varepsilon(t, x, v) = \sum_{l=0}^{q_3+1} \varepsilon^l k_l(t, x, v) + O(\varepsilon^{q_3+2}).
\]

(17)

In order to develop asymptotic analysis of Eq. (6), additional assumptions on the operator \(T_1^1\) and the interaction terms \(G_i(i = 1, 2, 3)\) are needed.
Assumption 3.4. We assume that the turning operator $T^1_i$ and the interaction terms $G^i_i(i = 1, 2, 3)$ satisfy the following asymptotic behavior as:

$$T^1_i[f^i_2, f^i_3](g) = T^1_i[h_0, k_0](g)$$

$$+ \sum_{m=1}^{q_1+1-p} \varepsilon^m R^m_i[h_0, ..., h_j, k_0, ..., k_l](g)$$

$$+ O(\varepsilon^{q_1+2-p}), \forall p \leq q_1, \forall g, h_j, k_l,$$

$$T^1_i[f^i_2, f^i_3](g) = T^1_i[h_0, k_0](g) + O(\varepsilon), \forall p > q_1, \forall g,$$

for $j = 0, 1, ..., q_2 + 1$ and $l = 0, 1, ..., q_3 + 1$.

Then, (10) rapidly yields:

$$\int_V R^m_i[h_0, ..., h_j, k_0, ..., k_l](\varphi)dv = 0, \forall \varphi.$$  

(19)

and

$$G^i(g + \varepsilon \hat{g}, h + \varepsilon \hat{h}, k + \varepsilon \hat{k}, v) = G^i(g, h, k, v) + O(\varepsilon), \forall g, \hat{g}, h, \hat{h}, k, \hat{k}$$  

(20)

for $i = 1, 2, 3$.

Then, the first terms of Hilbert expansion of equal order in $\varepsilon^i$, $\varepsilon^j$ and $\varepsilon^l$ for $i = 0, 1, ..., q_1 + 1$, $j = 0, 1, ..., q_2 + 1$ and $l = 0, 1, ..., q_3 + 1$ are:

$$\varepsilon^0:

\begin{align*}
T^0_1(g_0) &= 0, \\
T^0_2(h_0) &= 0, \\
T^0_3(k_0) &= 0,
\end{align*}$$  

(21)

$$\varepsilon^1:

\begin{align*}
T^0_1(g_1) &= \delta_{q_1, 1} v \cdot \nabla g_0 - \delta_{q_1, 1} T^1_1[h_0, k_0](g_0), \\
T^0_2(h_1) &= \delta_{q_2, 1} v \cdot \nabla h_0, \\
T^0_3(k_1) &= \delta_{q_3, 1} v \cdot \nabla k_0,
\end{align*}$$  

(22)
The first equation of (21) implies that
\[
\begin{align*}
T_1^0(g_2) &= \delta_{q_1,1} (\partial_t g_0 + v \cdot \nabla_x g_1) - \delta_{p,2} T_1^1[h_0, k_0](g_0) - \delta_{p,1} T_1^1[h_0, k_0](g_1) \\
&\quad + \delta_{q_1,2} v \cdot \nabla_x g_0 - \delta_{p,1} R_1^1[h_0, ..., h_j, k_0, ..., k_l](g_0) \\
&\quad - \delta_{q_1,1} G_1(g_0, h_0, k_0, v), \quad \forall p \leq q_1, \\
T_2^0(g_2) &= \delta_{q_1,1} (\partial_t g_0 + v \cdot \nabla_x g_1) - \delta_{p,2} T_1^1[h_0, k_0](g_0) \\
&\quad + \delta_{p,2} v \cdot \nabla_x g_0 - \delta_{q_1,1} G_1(g_0, h_0, k_0, v), \quad \forall p > q_1, \\
T_3^0(g_2) &= \delta_{q_1,1} (\partial_t k_0 + v \cdot \nabla_x k_1) + \delta_{q_1,2} v \cdot \nabla_x k_0 \\
&\quad - \delta_{q_1,1} G_3(g_0, h_0, k_0).
\end{align*}
\]

Further calculations yield:
\[
\begin{align*}
T_1^0(g_{q_1+1}) &= \partial_t g_0 + v \cdot \nabla_x g_1 - \sum_{m=1}^{q_1+1-p} \left[ \delta_{p,q_1+1-m} T_1^1[h_0, k_0](g_m) \
&\quad - \sum_{i=1}^{q_1-p-m} \delta_{p,q_1-m-i} R_1^1[h_0, ..., h_j, k_0, ..., k_l](g_m) \right] \\
&\quad - G_1(g_0, h_0, k_0, v) \\
&\quad - \sum_{i=1}^{q_1+1-p} \delta_{p,q_1+1-i} R_1^1[h_0, ..., h_j, k_0, ..., k_l](g_0), \quad \forall p \leq q_1, \\
T_1^0(g_{q_1+1}) &= \partial_t g_0 + v \cdot \nabla_x g_1 - G_1(g_0, h_0, k_0, v) \\
&\quad - \delta_{p,q_1+1} T_1^1[h_0, k_0](g_0),
\end{align*}
\]

and
\[
\begin{align*}
\varepsilon^{q_2+1} : T_2(h_{q_1+1}) &= \partial_t h_0 + v \cdot \nabla_x h_1 - G_2(g_0, h_0, k_0, v), \\
\varepsilon^{q_3+1} : T_3(k_{q_1+1}) &= \partial_t k_0 + v \cdot \nabla_x k_1 - G_3(g_0, h_0, k_0, v),
\end{align*}
\]

where \(\delta_{a,b}\) stands for the Kronecker delta.

The first equation of (21) implies that
\[
\begin{align*}
g_0 &\in \text{vect}(M_1(v)), \quad h_0 \in \text{vect}(M_2(v)), \quad \text{and} \quad k_0 \in \text{vect}(M_3(v)).
\end{align*}
\]

Therefore \(\exists c(t, x), \exists s(t, x), \exists u(t, x)\) such that
\[
\begin{align*}
g_0(t, x, v) &= M_1(v) c(t, x), \\
h_0(t, x, v) &= M_2(v) s(t, x) \quad \text{and} \quad k_0(t, x, v) = M_3(v) u(t, x).
\end{align*}
\]
Using (13), (10), (19) and (26)-(28), denoting by

\[
g_1 = \delta_{q_1,1}(T_0^{q_1})^{-1}(v \cdot \nabla_x g_0) - \delta_{p,1}(T_0^{p})^{-1}(T_1^p[h_0](g_0)),
\]

\[
h_1 = \delta_{q_2,1}T_2^{-1}(v \cdot \nabla_x h_0),
\]

\[
k_1 = \delta_{q_3,1}T_3^{-1}(v \cdot \nabla_x k_0).
\]

The calculations of \(g_{q_1+1}, h_{q_2+1},\) and \(k_{q_3+1}\) are obtained from the solvability conditions at \(O(\varepsilon^{q_1+1}), O(\varepsilon^{q_2+1})\) and \(O(\varepsilon^{q_3+1})\), which are given by the following:

\[
\int_V \left( \partial_t g_0 + v \cdot \nabla_x g_1 - \sum_{m=1}^{q_1-p} \delta_{p,q_1+1-m}T_1^m[h_0,k_0](g_m) - \sum_{i=1}^{q_1-p} \delta_{p,q_1+1-m}R_1^m[h_0,\ldots,h_j,k_0,\ldots,k_i](g_m) - G_1(g_0,h_0,k_0,v) - G_2(g_0,h_0,k_0,v) \right) dv = 0,
\]

\[
\forall p \leq q_1,
\]

\[
\int_V \left( \partial_t g_0 + v \cdot \nabla_x g_1 - G_1(g_0,h_0,k_0,v) - \delta_{p,q_1+1}T_1^p[h_0,k_0](g_0) \right) dv = 0,
\]

\[
\forall p > q_1,
\]

and

\[
\int_V \left( \partial_t h_0 + v \cdot \nabla_x h_1 - G_2(g_0,h_0,k_0,v) \right) dv = 0,
\]

\[
\int_V \left( \partial_t k_0 + v \cdot \nabla_x k_1 - G_3(g_0,h_0,k_0,v) \right) dv = 0,
\]

Using (13), (10), (19) and (26)-(28), denoting by \(\langle \cdot, \cdot \rangle\) the integral with respect to the variables \(v\), shows that the system (29)-(30) can be rewritten as follows:

\[
\begin{align*}
\partial_t c + \delta_{q_1,1} \langle v \cdot \nabla_x (T_0^{q_1})^{-1}(vM_1 \cdot \nabla_x c) \rangle & - \delta_{p,1} \langle (T_0^{q_1})^{-1}(T_1^p[M_2s,M_3u](M_1c)) \rangle \\
& - \langle G_1(M_1c,M_2s,M_3u,v) \rangle = 0,
\end{align*}
\]

\[
\begin{align*}
\partial_t s + \delta_{q_2,1} \langle v \cdot \nabla_x T_2^{-1}(vM_2 \cdot \nabla_x s) \rangle & - \langle G_2(M_1c,M_2s,M_3u,v) \rangle = 0,
\end{align*}
\]

\[
\begin{align*}
\partial_t u + \delta_{q_3,1} \langle v \cdot \nabla_x T_3^{-1}(vM_3 \cdot \nabla_x u) \rangle & - \langle G_3(M_1c,M_2s,M_3u,v) \rangle = 0.
\end{align*}
\]

As \(T_1^q, T_2^q\) and \(T_3^q\) are self-adjoint operators in \(L^2(D_v,\frac{dv}{M_1(v)})\), \(L^2(D_v,\frac{dv}{M_2(v)})\)
and $L^2\left(D_v, \frac{dv}{M_1(v)}\right)$, one has the following computations:

\[
\langle v \cdot \nabla x \left(T^0_1\right)^{-1}(vM_1 \cdot \nabla_x c) \rangle = \text{div}_x \left( \langle v \otimes \theta_1(v) \rangle \cdot \nabla_x c \right),
\]

\[
\langle v \cdot \nabla x T_2^{-1}(vM_2 \cdot \nabla x s) \rangle = \text{div}_x \left( \langle v \otimes \theta_2(v) \rangle \cdot \nabla x s \right),
\]

\[
\langle v \cdot \nabla x T_3^{-1}(vM_3 \cdot \nabla x u) \rangle = \text{div}_x \left( \langle v \otimes \theta_3(v) \rangle \cdot \nabla x u \right),
\]

and

\[
\langle v \cdot \nabla x \left(T^0_1\right)^{-1}T_1^{-1}[M_2s, M_3u](M_1c) \rangle = \text{div}_x \left( \frac{\theta_1(v)}{M_1(v)} cT^0_1[M_2s, M_3u](M_1) \right),
\]

where $\theta_1$ and $\theta_2$ are given in Lemma 2.

Therefore, the macroscopic model \((31)\) can be written as follows:

\[
\begin{cases}
\partial_t c + \text{div}_x \left( \delta_{p_1} c \alpha(s, u) - \delta_{q_1} D_c \cdot \nabla_x c \right) - H_1(c, s, u) = 0, \\
\partial_t s - \delta_{q_2} \text{div}_x (D_s \cdot \nabla x s) - H_2(c, s, u) = 0, \\
\partial_t u - \delta_{q_3} \text{div}_x (D_u \cdot \nabla x u) - H_3(c, s, u) = 0,
\end{cases}
\]

where $D_c, D_s, D_u, \alpha$ are given, respectively, by

\[
D_c = -\int_V v \otimes \theta_1(v) dv, \quad D_s = -\int_V v \otimes \theta_2(v) dv, \quad D_u = -\int_V v \otimes \theta_3(v) dv,
\]

and

\[
\alpha(s, u) = -\int_V \frac{\theta_1(v)}{M_1(v)} T_1^1[M_2s, M_3u](M_1c) dv,
\]

while $H_i(c, s, u), (i=1,2,3)$ are given by:

\[
H_i(c, s, u) = \int_V G_i(M_1c, M_2s, M_3u, v) dv.
\]

### 3.3 Derivation of virus models with in a Keller-Segel system

More in detail, let us consider the following kernels:

\[
T^0_1(v, v^*) = \sigma_1 M_1(v), \quad T_2(v, v^*) = \sigma_2 M_2(v), \quad T_3(v, v^*) = \sigma_3 M_3(v),
\]

with $\sigma_1, \sigma_2, \sigma_3 > 0$.

Hence, the leading turning operators $T_j$ ($j=2,3$) and $T^0_1$ can be viewed as relaxation operators:

\[
T^0_j(g) = -\sigma_j \left(g - M_j(g)\right),
\]

while $H_i(c, s, u), (i=1,2,3)$ are given by:

\[
H_i(c, s, u) = \int_V G_i(M_1c, M_2s, M_3u, v) dv.
\]
\[ T_2(g) = -\sigma_2 \left( g - M_2(g) \right), \]
\[ T_2(g) = -\sigma_2 \left( g - M_2(g) \right), \]
\[ T_3(g) = -\sigma_3 \left( g - M_3(g) \right), \]

Moreover, \( \theta_1, \theta_2, \) and \( \theta_3 \) are given by
\[ \theta_1(v) = -\frac{1}{\sigma_1} v M_1(v), \quad \theta_2(v) = -\frac{1}{\sigma_2} v M_2(v), \quad \text{and} \quad \theta_3(v) = -\frac{1}{\sigma_3} v M_3(v), \]
while \( \alpha \), are defined by (34)–(35), and are computed as follows:
\[ \alpha(s, u) = \frac{1}{\sigma_1} \int_V v T_1^1 (M_2 s, M_3 u)(M_1(v)) dv, \]

The diffusion tensors \( D_c, D_s, \) and \( D_u \) are given by
\[ D_c = \frac{1}{\sigma_1} \int_V v \otimes v M_1(v) dv, \quad \text{and} \quad D_s = \frac{1}{\sigma_2} \int_V v \otimes v M_2(v) dv, \]
\[ D_u = \frac{1}{\sigma_3} \int_V v \otimes v M_3(v) dv, \]
while \( H_1, H_2, H_3 \) are still given by (35).

Let us now consider that \( q_1 = q_2 = q_3 = 2 \) and \( p = 2 \), then from (32) one has the following macro-scale type models up to \( \varepsilon \):
\[
\begin{align*}
\frac{dc}{dt} &= H_1(c, s, u), \\
\frac{ds}{dt} &= H_2(c, s, u), \\
\frac{du}{dt} &= H_3(c, s, u).
\end{align*}
\]

The role of the terms \( H_1(c, s, u), H_2(c, s, u), \) and \( H_3(c, s, u) \) in (35) consists in modeling the interaction between the for quantities of the mixture. For example, by choosing:
\[
\begin{align*}
G_1(f_1, f_2, f_3, v) &= -\frac{d_1}{|V|} \frac{f_1}{M_1} - \frac{\beta}{|V|} \frac{f_1}{M_1} \frac{f_3}{M_3} + \frac{1}{|V|} r, \\
G_2(f_1, f_2, f_3, v) &= -\frac{d_2}{|V|} \frac{f_2}{M_2} + \frac{\beta}{|V|} \frac{f_1}{M_1} \frac{f_3}{M_3}, \\
G_3(f_1, f_2, f_3, v) &= -\frac{d_3}{|V|} \frac{f_3}{M_3} + \frac{k}{|V|} \frac{f_2}{M_2}.
\end{align*}
\]
Therefore, the macroscopic model [44] writes:

\[
\begin{align*}
\frac{dc}{dt} &= -d_1 c - \beta c u + r, \\
\frac{ds}{dt} &= -d_2 s + \beta c u, \\
\frac{du}{dt} &= -d_3 u + k s.
\end{align*}
\] (48)

- Let us also consider that \( q_1 = q_2 = q_3 = 1 \), \( p = 1 \), and the following choice:

\[
T_1^1[f_2, f_3] = K_{\frac{f_2}{M_2}}(v, v^*) \cdot \nabla_x f_2 M_2,
\] (49)

where \( K_{\frac{f_2}{M_2}}(v, v^*) \) is a vector valued function satisfying the following:

\[
K_{S + \varepsilon \frac{f_2}{M_2}} = K_S + O(\varepsilon), \quad \text{as} \quad \varepsilon \to 0.
\] (50)

Then \( T_1^1 \) satisfies [43], and leads to the following:

\[
T_1^1[M_2 s, M_3 u](M_1) = \psi(v, s) \cdot \nabla_x s,
\]

where

\[
\psi(v, s) = \int_V \left( K_s(v, v^*)M_2(v^*) - K_s(v^*, v)M_2(v) \right) dv^*.
\] (51)

Finally, \( \alpha(s) \), defined in [41], is given by \( \alpha(s) = \chi(s) \cdot \nabla_x s \), where the chemotactic sensitivity \( \chi(s) \) is given by the matrix

\[
\chi(s) = \frac{1}{\sigma_1} \int_V v \otimes \psi(v, s) dv.
\] (52)

Therefore, the macroscopic model [52] can be written as follows:

\[
\begin{align*}
\partial_t c + \text{div}_x \left( c \chi(s) \cdot \nabla_x s - (D_c \cdot \nabla_x c) \right) &= H_1(c, s, u), \\
\partial_t s - \text{div}_x (D_s \cdot \nabla_x s) &= H_2(c, s, u), \\
\partial_t u - \text{div}_x (D_u \cdot \nabla_x u) &= H_3(c, s, u).
\end{align*}
\] (53)

Supposing that the \( G_i(i = 1, 2, 3) \), are given by [43]-[47], yields the following macroscopic model [53]:

\[
\begin{align*}
\partial_t c + \text{div}_x \left( c \chi(s) \cdot \nabla_x s - (D_c \cdot \nabla_x c) \right) &= -d_1 c - \beta c u + r, \\
\partial_t s - \text{div}_x (D_s \cdot \nabla_x s) &= -d_2 s + \beta c u, \\
\partial_t u - \text{div}_x (D_u \cdot \nabla_x u) &= -d_3 u + k s,
\end{align*}
\] (54)

where the \( D_c, D_s, D_u \), and \( \chi(s) \) are given by [42]-[44] and [52].
4 Critical analysis and perspectives

We trust that the micro-macro derivation developed in our paper, can be further extended to a variety of exotic models including models of the dynamics of different types of virus. This subsection simply introduces this topic which will be developed in a well defined research program. Indeed, the complexity of the dynamics may substantially increase thus requiring nontrivial developments of the approach. In more details on virus dynamics, possible developments might account for delay-distributed dynamics [11], infection model with multi-target cells [12], stochastic models which include selective progression [13]. In addition, the recent Covid-19 virus pandemic has generated a huge number of models that can be viewed as a technical development of SIR type models. The research article [14] is one of the first contributions to this topic. Subsequently, it has been followed by various papers which have gone beyond the framework of compartmental models accounting for multiscale features and of the immune competition inside the lung [2], transport dynamics [8], contagion in crowds [21], and various others.

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