A kinetic theory approach for modelling tumour and macrophages heterogeneity and plasticity during cancer progression

R. Eftimie*
University of Dundee, Dundee, DD1 4HN, UK
r.a.eftimie@dundee.ac.uk

L. Gibelli
University of Edinburgh, Edinburgh, EH9 3FB, UK
livio.gibelli@ed.ac.uk

Received 11 September 2019
Revised 17 October 2019
Accepted 29 October 2019
Published 4 May 2020
Communicated by N. Bellomo, F. Brezzi and J. Soler

The heterogeneity and plasticity of macrophages have become a topic of great interest, due to their role in various diseases ranging from cancer to bacterial infections. While initial experimental studies assumed an extreme polarisation situation, with the (anti-tumour) M1 and (pro-tumour) M2 macrophages representing the two extreme cell phenotypes, more recent studies showed a continuum of macrophages polarisation phenotypes. Here, we focus on tumour-macrophage interactions and develop a mathematical model based on kinetic equations for active particles to describe (i) the dynamics of macrophages with a continuum of diverse functional states, ranging from pro-tumour to anti-tumour states; and (ii) the dynamics of tumour cells with a variety of progression (i.e. mutation) states. With the help of this model we show that the growth of solid tumours is associated with an increased clonal heterogeneity, as well as with an increased macrophages phenotypic heterogeneity (caused by a shift from an initial anti-tumour M1-like phenotype to a mixed M1–M2 phenotype). Moreover, we show that the assumption of exponential tumour/immune cell growth leads to an unbounded macrophages growth, which is biologically unrealistic. In contrast, the assumption of logistic tumour/immune cell growth can lead to tumour dormancy (under the control of immune cells), or to tumour growth towards smaller/larger sizes which depend on various model parameters.

*Corresponding author.

This is an Open Access article published by World Scientific Publishing Company. It is distributed under the terms of the Creative Commons Attribution 4.0 (CC BY) License which permits use, distribution and reproduction in any medium, provided the original work is properly cited.
Finally, we show that tumour dormancy is associated with an increase in the clonal heterogeneity of tumour cells and in the phenotypic heterogeneity of macrophages.

**Keywords**: M1 and M2 macrophages; heterogeneous tumour cells; kinetic theory of active particles; collective tumour-macrophage dynamics.

AMS Subject Classification: 34K28, 92B05

1. Introduction

Macrophages are a very important component of the innate immunity, being present in almost all tissues. Cells belonging to the monocyte/macrophage lineage are characterised by heterogeneity and plasticity. The heterogeneity and plasticity of macrophages have become a topic of great interest in immunology, due to the implications to the treatment of various diseases including cancer, bacterial infections, and even liver fibrosis. In solid tumours, between 5–40% of tumour mass is formed of macrophages, and these macrophages are involved in tumour progression and collective migration. The two extreme classes of macrophages are the M1 (or classically activated) cells and the M2 (or alternatively activated) cells, and their nomenclature mirrors the Th1–Th2 paradigm — since the M1 and M2 cell reciprocally engage with the Th1 and Th2 cells. The M1 cells are pro-inflammatory, anti-tumour, have anti-bacterial and anti-viral activity, and can cause tissue damage (see also Fig. 1). The M2 cells are anti-inflammatory, pro-tumour, have anti-parasitic activity and are involved in tissue remodelling (see Fig. 1). Although the view of two extreme classes of macrophages simplifies the understanding of these complex cells, many macrophages express markers of both M1 and M2 differentiation (and therefore can exhibit mixed M1 and M2 activities). Because the majority of experimental studies in the literature do not investigate the differentiation markers (these studies usually look at the total number of macrophages), we are still lacking a full understanding of the role of various types macrophages in different diseases.

Understanding the balance between M1/M2 cells (with their varying polarisation phenotypes) could eventually help predicting the outcome of diseases associated with M1 or M2 immune responses. For example, advanced metastatic tumours have been associated with tumour-infiltrating macrophages that have a M2 phenotype, while early tumours have been associated with macrophages that have a M1 phenotype (see also Fig. 1). In fact, it has been shown that a high M1/M2 ratio was associated with extended survival of some cancer patients. Moreover, the M2 macrophages are involved in the collective migration of tumour cells during tissue invasion and metastasis, through their direct communication with tumour cells via different signalling pathways. Recent studies have suggested immunotherapeutic approaches (e.g. via cytokines such as IFN-γ and receptor-mediated activation signals) to re-polarise the M2 macrophages towards an M1 phenotype with the purpose of treating cancer.

The re-polarisation of M1 and M2 cells to a different phenotype can be influenced by the cytokine environment (cytokines produced by the macrophages them-
Fig. 1. Caricature description of the plasticity and function of macrophages. The macrophages have a continuum of polarisation states between the two extremes: M1 (or classically activated) and M2 (or alternatively activated) cells.

selves, or by other cells such as Th1 and Th2 cells, NK cells or even tumour cells). For example, the exposure of murine macrophages to type-I cytokines (e.g. IFN-γ, IL-12) triggers their polarisation towards M1 cells. In contrast, the exposure of macrophages to type-II cytokines (e.g. IL-4, IL-10, IL-13) triggers their polarisation towards M2 cells.

The outcome of tumour (immuno-)therapies does not depend only on the heterogeneity of tumour-infiltrating macrophages, but also on the clonal heterogeneity of the tumour itself. This intra-tumour heterogeneity is caused not only by genetic and epigenetic instability, but can be caused also by tumour dormancy. Various studies have shown that tumour heterogeneity impacts not only tumour evolution and metastasis, but also drug resistance and immune response.

Therefore, in order to understand and control tumour evolution, it is important to first understand the interplay between the heterogeneity of solid tumours and the heterogeneity of the immune responses (which can be either pro-tumour or anti-tumour).

Mathematical approaches. Over the past decade, various mathematical models have been derived to investigate the interplay between the M1 and M2 macrophages phenotypes in various diseases: from tumour progression, to heart failure, lung infections, healing of bone fractures, or some general inflammatory processes. However, none of these models have investigated the continuum of different polarisation states between the two extremes, M1 and M2, and their role on disease progression.

The kinetic theory of active particles can be used to model and investigate this continuum distribution of different macrophages polarisation states, and the
interactions between macrophages and tumour cells. In fact, kinetic theory models have been used quite often to investigate the competition between tumour and immune cells; see, for example Refs. 3, 5, 8, 10, 11, 12, 34 and the references therein. Some of these models investigated also the interactions between tumour cells and anti-tumour macrophages but the focus was exclusively on the anti-tumour properties of macrophages.

The goal of this study is to develop and assess a model for the kinetic theory of active particles, which considers the dynamics of a macrophage population with a continuum of polarisation states (from the anti-tumour M1 phenotypes to the pro-tumour M2 phenotypes), and its interaction with a clonally-heterogeneous population of tumour cells. To this end, we will consider the following sequential steps that describe the modelling approach of the kinetic theory of active particles (for details see, for example, Refs. 9 and 10):

1. The cells that form the system, which are referred to as active particles, are partitioned into functional subsystems labelled with the subscripts \( i = 1, \ldots, n \). The cell functionality is heterogeneously distributed among active particles, and corresponds to an individual state defined as activity. Hence the state of each functional subsystem is defined by a probability distribution function over the activity variable. The macroscopic quantities, such as density, mean cells’ functionality, and so on, are obtained by moments of the probability distribution functions.

2. Active particles interact within the same functional subsystem as well as with particles of other subsystems. Interactions are modelled by theoretical tools of stochastic games: each player/particle interacts with the collectivity; the outcome of a single interaction event can be known only in probability; the rules of interaction can evolve in time.

3. The evolution of the probability distribution is obtained by a balance of particles (cells) within elementary volumes of the space of microscopic states, the inflow and outflow of particles (cells) being related to the aforementioned interactions.

2. Derivation of the Mathematical Model

To derive the mathematical model, we will go through the details of the steps defined in Sec. 1. For simplicity, in this study, we will ignore the spatial collective movement of macrophages and tumour cells (which will be the subject of a future work), and instead focus only on their temporal and phenotypic dynamics.

Functional subsystems. We first define the following two subsystems: \( i = 1 \): macrophages; \( i = 2 \): tumour cells. For simplicity, we use the same activity variable, \( u \), to describe the functionality of each of the two subsystems:

- For macrophages \( i = 1 \), \( u \in [-1, 1] \) describes the polarisation state of cells. Positive values \( u > 0 \) describe the ability of macrophages to destroy tumour...
cells (i.e. an M1-like phenotype), while negative values ($u < 0$) describe the ability to macrophages to promote tumour progression (i.e. an M2-like phenotype); see also Fig. 2. Thus, variable $u$ models the continuous transition between the two extremes of the macrophages polarisation states.

- For tumour cells ($i = 2$), $u \in [0, 1]$ describes the progression state (i.e. it is a measure of the aggressiveness and proliferation ability of tumour cells, as given by genetic cellular alterations). Values $u \approx 0$ correspond to weakly-aggressive tumour cells, and $u \approx 1$ correspond to highly-aggressive tumour cells.

Thus, the state of the two functional subsystems is described by the following probability distribution functions:

- **Macrophages:** $f_1 = f_1(t, u) : [0, T] \times [-1, 1] \rightarrow \mathbb{R}_+$.
- **Tumour cells:** $f_2 = f_2(t, u) : [0, T] \times [0, 1] \rightarrow \mathbb{R}_+$.
Note that we choose finite domains for the variables \( u \) since we assume: (i) a limit for macrophages cellular polarisation (i.e. \( u = -1 \) for fully polarised M2 macrophages and \( u = 1 \) for fully polarised M1 macrophages); (ii) a limit for tumour progression (i.e. \( u = 1 \) corresponds to the most aggressive tumour cell types, with the highest proliferative and metastatic potential).

**Interactions.** It has been shown experimentally that macrophages can have both anti-tumour and pro-tumour effects, depending on their phenotype. Therefore, we will assume that positive values of \( u \) lead to tumour elimination (due to the M1 phenotype of macrophages), while negative values of \( u \) lead to tumour growth (due to the M2 phenotype of macrophages). Moreover, the tumour cells have the ability to reduce the anti-tumour activity of macrophages, by shifting their phenotype from \( u > 0 \) to \( u < 0 \) (note that this is in contrast with the apoptosis effect of tumour cells on some of the adaptive immune cells, such as the T cells). Also, the increase in the number of macrophages is the result of their recruitment to the tissue in response to tumour chemoattractants.

We model the interactions between the macrophages and tumour cells via the following terms:

- *Progression probability density* \( B_{ij}(u_* \rightarrow u) \),
- *proliferative rates* \( \alpha, \beta^f \), and
- *destructive rates* \( \gamma_f \).

Based on the above description, we can formulate the mathematical model as follows:

\[
\begin{align*}
\partial_t f_1(t,u) &= \lambda_1 \int_{-1}^{1} \int_{0}^{1} B_{12}(u_* \rightarrow u | u_*, u^*) f_1(t,u_*) f_2(t,u^*) du^* du_* \\
& - \lambda_1 f_1(t,u) \int_{0}^{1} f_2(t,u^*) du^* - \mu^f f_1(t,u) \\
& + \alpha f_1(t,u) \int_{0}^{1} f_2(t,u^*) du^*, \\
& (2.1a) \\
\partial_t f_2(t,u) &= \lambda_2 \int_{-1}^{0} \int_{0}^{1} B_{21}(u_* \rightarrow u | u_*, u^*) f_1(t,u_*) f_2(t,u_*) du_* du^* \\
& - \lambda_2 f_2(t,u) \int_{-1}^{0} f_1(t,u^*) du^* + \beta^f f_2(t,u) \\
& + \beta f_2(t,u) \int_{-1}^{0} f_1(t,u^*) du^* - \gamma f_2(t,u) \int_{0}^{1} f_1(t,u^*) du^*. \\
& (2.1b)
\end{align*}
\]

The following parameters appear in the above equations:

- \( \lambda_1 = \) re-polarisation rate of \( f_1 \) macrophages. Although this rate depends on the cytokine environment, for simplicity, here we assume that this rate is constant;
- \( \lambda_2 = \) progression rate of \( f_2 \) tumour cells. Throughout this study we assume that this rate is constant;
- \( \alpha = \) proliferation/recruitment rate of macrophages, in response to chemokines secreted by the tumour cells. For simplicity (and since we do not hold enough
information on the possible differences in the proliferation of M1 and M2 macrophages), we assume that $\alpha$ is constant;

- $\mu^d$ = half-life of macrophages. Since during steady state conditions, circulatory monocytes from which macrophages originate have a half-life of one to three days, for simplicity in this study we assume that all macrophages have a similar averaged constant half-life $\mu^d$;

- $\beta$ = proliferation rate of tumour cells, due to interactions between tumours and some external nutrient ($\beta^n$), as well as interactions between tumours and M2 macrophages, i.e. macrophages with activity $u < 0$ ($\beta^f$). Again, for simplicity (and since we could not find information about a possible correlation between the tumour proliferation rate and the progression stage), we assume that these tumour proliferation rates are constant;

- $\gamma$ = destruction rate of tumour cells following interaction with macrophages with M1-like phenotype (i.e. macrophages with activity variable $u > 0$). Again, for simplicity, we assume that the tumour killing rate is constant.

- $B_{12}$ = macrophages polarisation probability density, which is the result of interactions between macrophages and tumour cells. Experimental studies have shown that tumours can switch the macrophages polarisation phenotype: from an initial M1-like phenotype (with $u > 0$) to a M2-like phenotype (with $u < 0$). In this study, we take the approach in Ref. 25 and consider a normalised step function

$$B_{12}(u_\ast \rightarrow u \mid u_\ast, u^\ast) = U[\max(u_\ast - k_1(u^\ast + u_\ast) - \sigma_1, 1), \min(u_\ast - k_1(u^\ast + u_\ast) + \sigma_1, 1)], \quad (2.2)$$

where $U[a, b]$ is the uniform distribution on the interval $[a, b]$. Here, parameter $\sigma_1$ describes the uncertainty of changing macrophages’ polarisation (i.e. phenotype): large $\sigma_1$ means less exact change in polarisation, while small $\sigma_1$ means more exact change in polarisation. We note that $\sigma_1$ depends implicitly on the level of cytokines in the environment. Hence, the function above models the probability for a macrophage with phenotype $u_\ast$ to change its phenotype to $u = u_\ast - k_1(u^\ast + u_\ast)$. Parameter $k_1$ is a measure of the magnitude of polarisation: $k_1 = 0$ no biased polarisation, while $k_1 = 1$ strong biased polarisation following interactions with tumour cells $u^\ast > 0$ (and tumour-produced cytokines). Throughout this study, we consider $k_1 \approx 1$, and thus the new phenotype will be $u \approx -u^\ast \in [-1, 0]$ (provided that $\sigma_1$ is small).

**Remark 2.1.** As observed experimentally, the presence of the tumour always changes the phenotype of macrophages, from an initial M1 phenotype to a later M2 phenotype. Thus, it makes sense to have $u \approx -u^\ast < 0$ in the $B_{12}$ term. This means that more aggressive tumours (i.e. $u^\ast \approx 1$) will lead to macrophages with a full M2 phenotype (i.e. $u \approx -1$) that support tumour progression. On the other hand, less aggressive tumours (i.e. $u^\ast \approx 0$) will lead to macrophages with a less dominant M2 phenotype (i.e. $u \approx 0$).
• $B_{21} = \text{tumour progression probability density, which is the result of interactions between tumours and M2-like macrophages. Experimental studies have shown that tumour-associated macrophages (with an M2-like phenotype) enhance tumour progression through the inflammatory environment they create.}^{21}

We assume again that $B_{21}$ is given by

$$B_{21}(u_* \rightarrow u | u_*, u^*) = U[\max(u_* - k_2(u^* + u_*) - \sigma_2, 0), \min(u_* - k_2(u^* + u_*) + \sigma_2, 1)], \quad (2.3)$$

As before, $U[a, b]$ is the uniform distribution on the interval $[a, b]$. Here, $\sigma_2$ describes the uncertainty of changes in tumour progression. This function models the probability of tumour cells with progression state $u_*$ to evolve into cells with progression state $u = u_* - k_2(u^* + u_*)$ upon interactions with macrophages with phenotype $u^* < 0$ (i.e. M2 cells). As before, $k_2$ is a measure of the progression of tumour cells, and we take $k_2 \approx 1$ which then leads to $u \approx -u^* \in [0, 1]$ (provided that $\sigma_2$ is small). Thus, macrophages with an M2-distinct phenotype (i.e. $u^* \approx -1$) will lead to aggressive tumour cells (with $u \approx 1$).

Remark 2.2. The transition probability densities $B_{12}$ and $B_{21}$ satisfy the following normalisation conditions (for any $u^*, u_*$):

$$\int_{-1}^{1} B_{12}(u_* \rightarrow u | u_*, u^*) du = 1, \quad \int_0^1 B_{21}(u_* \rightarrow u | u_*, u^*) du = 1. \quad (2.4)$$

It is also worth noting that in this paper, attention is restricted to the so-called “linear” interactions, namely interactions which only depend on the microscopic state of the active particles. This assumption leads to a model with quadratic nonlinearities in contrast with the “structural” nonlinearities that arise when the transition probability densities also depend on the probability distribution functions of the interacting active particles. Models with “nonlinear” interactions have been extensively treated in Refs. 7 and 12.

Remark 2.3. These interactions involve the probabilistic assessment of three types of cells (particles): test cells with microscopic (i.e. molecular) state $u$, candidate cells with microscopic state $u_*$, and field cells with microscopic state $u^*$. The candidate cells can acquire, with a certain probability, the microscopic state of the test cells, following an interaction with the field cells. Note that for cells, these proliferative-destructive–progressive interactions usually occur through a variety of molecules (i.e. cytokines, chemokines, growth factors) secreted by the cells themselves. Nevertheless, to keep the model simple, we will assume that these interactions are direct.

3. Results

To start investigating the dynamics of model (2.1a), in Sec. 3.1, we will focus on the steady states and note that this model cannot support nonzero equilibrium distribution functions that are constant over the activity variable. Then, in Sec. 3.2, we will consider a particular case where $\lambda_1 = 0$, and show that the model can
be reduced to a classical Lotka–Volterra-type model whose dynamics is known. In Sec. 3.3, we will perform numerical simulations to support the analytical predictions. Finally, in Sec. 3.4, we will investigate numerically the effect of a logistic tumour and macrophages growth on overall system dynamics.

Throughout this study, the numerical simulations are performed for two different initial conditions:

- Homogeneous macrophages and tumour cells distributions across the phenotype space: \( f_1(0, u) = f_1^*, f_2(0, u) = f_2^* \), with \( \int_{-1}^{1} f_1^* du = \int_{0}^{1} f_2^* du = 1, \forall u \). Thus, we start the simulations when the two populations are composed of cells with all possible phenotypes; see Fig. 3(a).

- Heterogeneous macrophages and tumour cells distributions across the phenotype space: 
  \[
  f_1(0, u) = \frac{1}{\sqrt{2\pi0.001}} \exp\left(-\frac{(u - 0.8)^2}{0.001}\right),
  f_2(0, u) = \frac{1}{\sqrt{2\pi0.001}} \exp\left(-\frac{(u - 0.2)^2}{0.001}\right).
  \]
  Thus, we start the simulations when the two populations are composed of cells with similar phenotypes (i.e. centred around \( u = 0.8 \) for the \( f_1 \) M1-like cells, and around \( u = 0.2 \) for the \( f_2 \) tumour clones); see Fig. 3(b).

The parameter values used for the numerical simulations are shown in Table 1. To obtain some of these values we used the following mouse experimental knowledge:

- It was shown in Ref. 67 that mouse macrophage-like RAW264.7 cells have a doubling time of approximately 35 h when exposed to bacterial lipopolysaccharide (LPS) or mouse recombinant interferon-γ (IFN-γ); and thus acquire an M1-like phenotype (see also Fig. 1). This doubling time translates into a proliferation rate \( \alpha = \ln(2.0)/35 \text{ h} = 0.47/\text{day}. \) In contrast, the unstimulated cells have a
Table 1. Summary of parameter values used throughout the simulations. Whenever there is a range of possible values, in parentheses we show the “baseline” values used for the simulations. Changes from these “baseline” values are listed in the figure captions.

| Parameter | Value | Description |
|-----------|-------|-------------|
| $\lambda_1$ | $10^{-4}$–$10^{-1}$ (0.01) | Re-polarisation rate of $f_1$ macrophages |
| $\lambda_2$ | $10^{-4}$–$10^{-1}$ (0.01) | Progression rate of $f_2$ tumour cells |
| $\alpha$ | 0.47–0.924 (0.7) | Proliferation rate of $f_1$ macrophages |
| $\mu^d$ | 0.099–0.92 (0.4) | Half-life of $f_1$ macrophages |
| $\beta_n$ | 0.043–0.483 (0.1) | Proliferation rate of $f_2$ tumour cells, in response to some external nutrient (e.g. oxygen, glucose, etc.) |
| $\beta_f$ | 0.043–0.483 (0.08) | Proliferation rate of $f_2$ tumour cells, in response to signals generated by M2 macrophages |
| $\gamma$ | 0.17–0.75 (0.5) | Killing rate of tumour cells by M1 macrophages |
| $k_1$ | 1 | Measure of the magnitude of macrophages polarisation (following interactions with tumour cells) |
| $k_2$ | 1 | Measure of the magnitude of tumour progression |
| $\sigma_1$ | 0.5 | Measure of the uncertainty of changes in macrophages polarisation |
| $\sigma_2$ | 0.5 | Measure of the uncertainty of changes in tumour progression |

Doubling time between 18–22h, corresponding to a proliferation rate of $\alpha \in (0.75, 0.924)$/day. Therefore, in this study we choose $\alpha \in (0.47, 0.924)$/day.

- It was suggested in Ref. [31] that murine M1-like macrophages have a half-life between 5–7 days, while M2-like macrophages have a half-life between 18–20 h. This corresponds to a natural death rate $\mu^d$ between $\ln(2.0)/(18 \text{h}) = 0.92$/day and $\ln(2.0)/(7 \text{days}) = 0.099$/day.

- In Ref. [45] murine macrophages were cultured with human castration-refractory prostate cancer (CRPC) cells, and the experiments showed a median percentage phagocytosis (i.e. number of macrophages that express a tumour protein per total number of macrophages) between $\approx 17$–$75\%$. In this study, we consider a killing rate $\gamma \in (0.17, 0.75)$.

- Regarding the proliferation of murine solid tumours (or human solid tumours implanted into mice), which are all infiltrated by macrophages, we note that there is a variety of proliferation rates: from the highly-aggressive B16F10 melanoma that has a doubling time of only 17.2 h [23] to the less aggressive non-small cell lung cancer (NSCLC) that has a median doubling time between $\approx 2.1$–7.9 days [24]. This corresponds to a tumour proliferation rate $\beta \in (0.087, 0.967)$. Since in our study we split the tumour proliferation rate into $\beta_n$ and $\beta_f$, we will assume that each of these rates are half the value of $\beta$: $\beta_n, f \in (0.043, 0.483)$.

3.1. Steady states

The search for equilibrium and local non-equilibrium states is a challenging problem of the kinetic theory of active particles. This topic has been thoroughly investigated, especially in the field of econophysics, sociodynamics and, more recently,
Here, we look for uniform equilibrium distribution functions of the form
\[ f_1(t,u) = f_1^* \]
and
\[ f_2(t,u) = f_2^* . \]
Substituting these values into model (2.1a), we obtain
\[ 0 = \lambda_1 \bar{B}_{12}(u)f_1^* f_2^* - \lambda_1 f_1^* f_2^* - \mu_1^d f_1^* + \alpha f_1^* f_2^* , \]
(3.1a)
\[ 0 = \lambda_2 \bar{B}_{21}(u)f_1^* f_2^* - \lambda_2 f_1^* f_2^* + \beta_1^a f_2^* + \beta_1^f f_2^* f_1^* - \gamma f_1^* f_2^* , \]
(3.1b)
where
\[ \bar{B}_{12}(u) = \int_{-1}^{1} \int_{0}^{1} B_{12}(u_+ \rightarrow u | u_+, u^*) du^* du_+ , \]
(3.2a)
\[ \bar{B}_{21}(u) = \int_{-1}^{0} \int_{0}^{1} B_{21}(u_+ \rightarrow u | u_+, u^*) du^* du_+ . \]
(3.2b)
It is not difficult to prove that \((f_1^*, f_2^*) = (0, 0)\) is a fixed point for the steady state equations (3.2a). In regard to the existence of nonzero fixed points, it is worth noting that \(\bar{B}_{12}(u)\) and \(\bar{B}_{21}(u)\) are not constant functions; see also Fig. 4. Therefore, equilibrium distribution functions which are constant with respect to the activity variable \(u\) do not exist for model (2.1a).

### 3.2. Reduction to the classical Lotka–Volterra model

If we assume that \(\lambda_1 = 0\), Eqs. (2.1a) simplify to the classical Lotka–Volterra model when the initial distribution of macrophages is uniform. Indeed, by integrating Eq. (2.1a) in \([-1,1]\) and Eq. (2.1b) in \([0,1]\), the following equations for the population densities are obtained:
\[ \frac{dn_1}{dt} = n_1(\alpha n_2 - \mu_1^d) , \]
(3.3a)
\[ \frac{dn_2}{dt} = n_2(\beta_1^a + \beta_1^f n_1^(-) - \gamma n_1^+) , \]
(3.3b)
It is clear that, when \( \lambda_1 = 0 \), if \( n_1^{(-)}(0) = n_1^{(+)}(0) \) then \( n_1^{(-)}(t) = n_1^{(+)}(t) = n_1/2 \). Accordingly, we have

\[
\frac{dn_1}{dt} = n_1(\alpha n_2 - \mu d), \quad (3.5a)
\]

\[
\frac{dn_2}{dt} = n_2 \left[ \beta n + \frac{(\beta f - \gamma)}{2} n_1 \right]. \quad (3.5b)
\]

It is worth noting that this Lotka–Volterra-type dynamical system admits also a nonzero (co-existence) fixed point \( (n_1^*, n_2^*) = (\frac{\beta f}{2}, \frac{\gamma}{2}) \) (in addition to the trivial fixed point \( (n_1^n, n_2^n) = (0, 0) \)).

If we consider separately the dynamics of \( n_1^+ \) and \( n_1^- \), we can re-write Eqs. \((3.5a)\) as

\[
\frac{dn_1^+}{dt} = n_1^+ (\alpha n_2 - \mu d), \quad (3.6a)
\]

\[
\frac{dn_1^-}{dt} = n_1^- (\alpha n_2 - \mu d), \quad (3.6b)
\]

\[
\frac{dn_2}{dt} = n_2 (\beta n + \beta f n_1^- - \gamma n_1^+), \quad (3.6c)
\]

where adding Eqs. \((3.6a)\) and \((3.6b)\) leads to Eq. \((3.3a)\). This ODE model exhibits three fixed points: the trivial point \( (n_1^{+,*}, n_1^{-, *}, n_2^*) = (0, 0, 0) \), the semi-trivial point \( (n_1^{+,*}, n_1^{-, *}, n_2^*) = (\frac{\beta f}{\gamma}, 0, \frac{\gamma}{\alpha}) \), and the coexistence point \( (n_1^{+,*}, n_1^{-, *}, n_2^*) = (n_1^{+,*}, n_1^{-, *}, \frac{\beta f}{\alpha}) \) with \( \gamma n_1^{+,*} = \beta n + \beta f n_1^{-,*} \). We note that there exist an infinite number of coexistence points, for any combination of \( n_1^{+,*} > 0 \) and \( n_1^{-,*} > 0 \) that satisfies the above equation. We also note that the semi-trivial fixed point corresponds to the case of a tumour containing exclusively M1-like macrophages (i.e. \( n_1^{+,*} > 0 \) and \( n_1^{-,*} = 0 \)), which is not biologically realistic as the tumour-associated macrophages usually have a M2-like phenotype \( 22 \) (although it is possible to have mixed M1 and M2 phenotypes). For this reason, in Sec. \( 3.3 \) we will discuss a generalisation of models \((2.1a)\) and \((3.6a)\), which can exhibit also states that have coexistent M2-like cells and tumour cells.

**Remark 3.1.** The reduction of kinetic models for tumour-immune interactions to classical Lotka–Volterra ODE models is common in the literature. For example, Ref. [16] showed that a generic kinetic model for the evolution of the tumour-immune interactions (first introduced in Ref. [30]) can be reduced to a system of two coupled local ODEs. In Ref. [16] the authors also extended their reduced ODE model by
assuming a saturated killing of tumour cells by the immune cells (using Holling-type and Ivlev-type interaction terms).

### 3.3. Numerical simulations

Numerical solutions of model \((2.1a)\) are obtained by discretising the distribution functions on uniform grids. This yields a system of ordinary differential equations which are numerically solved by a first-order explicit Euler scheme. Integrals on the right-hand side of Eqs. \((2.1a)\) are computed by means of the midpoint quadrature formula. The solution provides the distribution functions \(f_i(t^n, u_j), i = 1, 2,\) and related moments at different times \(t^n\) and activity discrete points \(u_j\).

We start the numerical investigation into the dynamics of the kinetic model \((2.1a)\) by comparing the cases (a) \(\lambda_1 = 0\) (when the model can be reduced to Eqs. \((3.5a)\)) and (b) \(\lambda_1 > 0\). Figure 5(a) shows numerical solutions of the kinetic model \((2.1a)\) in the \((n_1, n_2) = \left(\int_1^0 f_1(t, u) du, \int_0^1 f_2(t, u) du\right)\) space, for \(\lambda_1 = 0\) and for different initial conditions (where the distribution functions of macrophages and tumour cells are taken to be uniform). As expected, the system dynamics leads to periodic orbits around the fixed point \((n_1^*, n_2^*) = \left(\frac{2\beta n^*}{\gamma - \beta f}, \frac{\mu d^*}{\alpha}\right)\) that exists

Fig. 5. (Color online) (a) Numerical solution of the reduced model, Eqs. \((3.5a)\), for different initial conditions (ICs) denoted by black solid circles. The light-blue solid circle denotes the unstable (co-existence) fixed point around which the limit cycle exists. The initial distribution functions of macrophages and tumour cells are taken to be uniform (see Fig. 5(a)). Here, \(\lambda_1 = 0\). (b) Numerical solution of the kinetic model, Eqs. \((2.1a)\), for different values of \(\lambda_1\). The initial condition is denoted by the black solid circle. Distribution functions of macrophages and tumour cells are uniform (see Fig. 5(a)). Here, \(\lambda_1\) is increased from 0 → 0.01 → 0.1. All other parameters are: \(\lambda_2 = 0.01,\) \(\alpha = 0.7,\) \(\mu^* = 0.4,\) \(\beta^* = 0.1,\) \(\beta f = 0.08\) (i.e. the baseline values from Table 1).
for $\lambda_1 = 0$. In fact, the solution trajectories eventually approach infinity — as it will be seen more clearly in the next figures.

Next, we investigate the time-dynamics of model (2.1a) in the activity space, for the baseline parameter values summarised in Table 1. In Fig. 6(a), we consider initial

Fig. 6. (a) Baseline dynamics of model (2.1a) when we use homogeneous initial conditions (ICs) as in Fig. 3(a). (b) Baseline dynamics of model (2.1a) when we use heterogeneous initial conditions (ICs) as in Fig. 3(b). (i) Time evolution for the macrophages and tumour population averaged densities $n_1$ and $n_2$. (ii) Distribution of macrophages population $f_1(t, u)$, at different time steps: $t = 0, 100, 200, 300$ and $400$ (as well as $t = 800$ for the heterogeneous ICs). (iii) Distribution of tumour population $f_2(t, u)$, at different time steps: $t = 0, t = 100, t = 200, t = 300$ and $t = 400$ (as well as $t = 800$ for the heterogeneous ICs).
conditions that are homogeneous distributions (as in Fig. 3(a)), while in Fig. 6(b), we assume initial conditions that are heterogeneous distributions (as in Fig. 4(b)). Both types of initial conditions lead to a time-periodicity in tumour–immune interactions, and for very large times the macrophage population will eventually grow unbounded (see Figs. 5(i)). Moreover, the evolution of the tumour leads to a particular cell distribution over the activity space, which is independent of the initial conditions: all macrophages eventually acquire phenotypes $u < 0.5$ (see Figs. 5(ii)), and all tumour cells acquire mutations $u \in [0, 1]$ with slightly more cells having mutations $u = 0.5$ (see Figs. 5(iii)).

Note that the large growth in macrophage population, which is triggered by a relatively high proliferation rate, is not biologically realistic in the context of solid tumours. Next, we investigate the effect of decreasing macrophages’ proliferation rate $\alpha$ and increasing their death rate $\mu^d$. Figure 7 shows the dynamics of model (2.1a) for $\alpha = 0.5$ and $\alpha = 0.05$, while $\mu^d = 0.9$. Even in this case the macrophage population eventually grows unbounded, triggered by a significant growth in the tumour population.

We should emphasise that changes in other parameter values lead to tumour–immune behaviours similar to those in Fig. 7 — not shown here. For example,
increasing the tumour-killing rate $\gamma$ (e.g. to $\gamma = 0.75$) leads to macrophage oscillations with increased amplitude, as in Fig. 7(i). Decreasing the transition rates $\lambda_{1,2}$ (e.g. to $\lambda_1 = 0.001, \lambda_2 = 0.0001$) leads to a very slow growth in the amplitude of macrophage oscillations; but eventually the amplitude of oscillations will approach infinity.

Remark 3.2. These numerical results suggest that the non-negative solutions for model (2.1b) with exponential tumour/macrophages growth and with the initial conditions $f_{1,2}(0, u) = f_{1,2}^0(u)$ described at the beginning of Sec. 3 exists only locally. Note that the local existence of non-negative solutions for the kinetic model (2.1a) can be proved analytically by taking the same approach as in Ref. 4. Alternatively, if we re-write the averaged density model (3.3a) as (3.6a), then, local existence and uniqueness of non-negative solutions for this ODE can be shown using the classical Picard–Lindelöf existence theorem and Gronwall’s inequality. Finally, we note in Eqs. (3.6a)–(3.6b) that as soon as $n_2(t) > \mu_d/\alpha$, the macrophages will grow unbounded (i.e. $n_1^+ \to \infty$ as $t \to \infty$), which explains the above numerical results. On the other hand, if $n_1^+ \approx 0$ (by choosing a very small $\alpha$, such that $n_2 < \mu_d/\alpha$), then the tumour cells will grow unbounded (i.e. $n_2(t) \to \infty$ as $t \to \infty$). Therefore, the blow-up in the solutions of model (3.3a) (as well as the original model (2.1a) — see the numerical simulations in Figs. 6(i) and 7) can be triggered by both the uncontrolled growth of macrophages as well as the uncontrolled growth of tumour cells.

3.4. Logistic tumour and macrophages growth

Next, we modify model (2.1a) to incorporate a logistic growth of tumour cells caused by the availability of resources, as observed in many experimental and clinical studies that emphasise the slow-down in tumour growth at large volumes. We also assume a logistic growth of macrophages, since experimental studies have shown that macrophages growth curves displays an initial exponential growth phase followed by a stationary phase. Moreover, very large macrophage populations secrete large amounts of cytokines that could eventually kill the patient (e.g. by triggering the cytokine storm syndrome). The carrying capacities for the $f_1$ and $f_2$ cell populations, namely $K_1$ and $K_2$, are assumed to satisfy the relation $K_1 = 0.4K_2$ (since up to 40% of tumour mass can be formed of macrophages). Thus, the new model with logistic cell growth is given by the following equations:

$$
\partial_t f_1(t, u) = \lambda_1 \int_{-1}^{1} \int_0^1 \mathcal{B}_{12}(u_\ast \to u \mid u_\ast, u_\ast') f_1(t, u) f_2(t, u') du' du_\ast \\
- \lambda_1 f_1(t, u) \int_0^1 f_2(t, u') du' - \mu_d f_1(t, u) \\
+ \alpha f_1(t, u) \left(1 - \frac{\int_{-1}^{1} f_1(t, u') du'}{K_1} \right) \int_0^1 f_2(t, u') du',
$$

(3.7a)
A kinetic theory approach for modelling tumour and macrophages heterogeneity 675

\[ \partial_t f_2(t, u) = \lambda_2 \int_{-1}^{0} B_{21}(u_s \rightarrow u | u_s, u^*) f_1(t, u^*) f_2(t, u_s) du_s du^* \]

\[ - \lambda_2 f_2(t, u) \int_{-1}^{0} f_1(t, u^*) du^* - \gamma f_2(t, u) \int_{0}^{1} f_1(t, u^*) du^* \]

\[ + f_2(t, u) \left( \beta^n + \beta^f \int_{-1}^{0} f_1(t, u^*) du^* \right) \left( 1 - \frac{\int_{0}^{1} f_2(t, u^*) du^*}{K_2} \right). \]  

\[ (3.7b) \]

**Remark 3.3.** The above kinetic system can be reduced to the following equations for the averaged cell population densities:

\[ \frac{dn_1}{dt} = \alpha n_1 \left( 1 - \frac{n_1}{K_1} \right) n_2 - \mu^d n_1, \quad (3.8a) \]

\[ \frac{dn_2}{dt} = n_2 \beta^n + \beta^f n_1^+ \left( 1 - \frac{n_2}{K_2} \right) - \gamma n_2 n_1^+, \quad (3.8b) \]

where \( n_1^+, n_1 \) and \( n_2 \) are defined by Eqs. (3.6a). If we further split Eq. (3.8b) into two separate equations for \( n_1^+ \) and \( n_1^- \) (with \( n_1^+ + n_1^- = n_1 \)) we have

\[ \frac{dn_1^+}{dt} = \alpha n_1^+ \left( 1 - \frac{n_1^+ + n_1^-}{K_1} \right) n_2 - \mu^d n_1^+, \quad (3.9a) \]

\[ \frac{dn_1^-}{dt} = \alpha n_1^- \left( 1 - \frac{n_1^+ + n_1^-}{K_1} \right) n_2 - \mu^d n_1^-, \quad (3.9b) \]

\[ \frac{dn_2}{dt} = n_2 (\beta^n + \beta^f n_1^-) \left( 1 - \frac{n_2}{K_2} \right) - \gamma n_2 n_1^+, \quad (3.9c) \]

This model admits five fixed points: the trivial state \( (n_1^{+,*}, n_1^{-,*}, n_2) = (0, 0, 0) \), a semi-trivial tumour-only state \( (n_1^{+,*}, n_1^{-,*}, n_2) = (0, 0, K_2) \), a semi-trivial state with M2 cells infiltrating the tumour

\[ (n_1^{+,*}, n_1^{-,*}, n_2) = \left( 0, \frac{K_1(\alpha K_2 - \mu^d)}{\alpha}, K_2 \right) \]

that exists for \( \alpha K_2 > \mu^d \), a semi-trivial state with M1 cells infiltrating the tumour

\[ (n_1^{+,*}, n_1^{-,*}, n_2) = \left( N_1^{+,*}, 0, \frac{\beta^n - \gamma N_1^{+,*}}{\beta^n} K_2 \right) \]

with

\[ N_1^{+,*} = -(K_1 \gamma - \beta^n)/(2\beta^n) + (1/2\beta^n) \sqrt{(1 - \beta^2)^2 + 4\mu^d \beta^n K_1 \gamma \alpha}, \]

and a tumour-macrophages coexistent state \( (n_1^{+,*} > 0, n_1^{-,*} > 0, n_2 > 0) \). The existence of so many steady states suggests that model (3.9a) can exhibit more complex dynamics, with solutions approaching or moving away from these states, depending on their stability (note that for the parameter values discussed in this
study — see Table 1 — the coexistence state is stable while the other states are unstable.

Moreover, it can be easily seen that the solutions of (3.9a) stay within the non-negative octant $D_+ = \{0 \leq n_1^+ \leq K_1, 0 \leq n_1^- \leq K_1, 0 \leq n_2 \leq K_2\}$, and thus the trajectories are always bounded.

Model (3.7a) is discretised using the same numerical method described in the previous section. Here, we focus only on the case of heterogeneous initial cell distributions (as in Fig. 3(b)), since this case describes the more realistic situation where the initial tumour does not contain too many mutations.

Figure 8 shows a few examples of tumour dynamics as we vary different model parameters. We note in particular the dormant tumour behaviour displayed in panels (a)–(c): the tumour size does not grow significantly while the tumour cells increase their clonal heterogeneity; see the $n_2$ curve for (a) $t \in (300, 650)$, (b) $t \in (400, 1000)$ and (c) $t \in (150, 300)$. This result is consistent with various experimental observations of tumour phenotype plasticity during dormancy, where the accumulation of tumour mutations leads to immune escape. The tumour-macrophages dynamics in Figs. 8(a)–8(c) shows that the tumour is controlled at very small sizes (i.e. $n_2 \approx 1$ in panels (a) and (b) and $n_2 \approx 2$ in panel (c)) by a much larger macrophage population. This macrophage population is formed of a mixed M1–M2 phenotype, although the macrophages $f_1(t, u)$ with an extreme M2-phenotype, i.e. with $u \in [-1, -0.75]$, have a much lower density compared with those macrophages with $u > -0.75$ (see Fig. 8(a)(ii) for $t = 400$ and $t = 600$). The tumour relapse in panel (a) is associated with a large density of macrophages with extreme M2 phenotype (see Fig. 8(a)(ii) for $t = 800$). Moreover, at this stage, the tumour density is almost homogeneously distributed over the activity interval $[0, 1]$, meaning that the tumour is formed of equal densities of cells with all possible clonal mutations.

However, if we compare the tumour dynamics in panels (a) and (b) we note that even when the tumour is controlled at smaller sizes (as in panel (b)) there is a mixed phenotype of M1 and M2 macrophages infiltrating the tumours. Nevertheless, the level of $f_1(800, u)$ in panel (a)(ii) is much higher than the level of $f_1(800, u)$ in panel (b)(ii). This, together with the higher $\gamma$ values in sub-panels (b), explains the lower tumour sizes in these sub-panels.

Another aspect that we investigated in Fig. 8(e) is the effect of decreasing the transition rates $\lambda_1$ (for macrophage re-polarisation) and $\lambda_2$ (for tumour clonal mutation). We note that lower $\lambda_{1,2}$ rates could allow the M1 macrophages to keep the tumour under control at very small sizes for a very large time: $n_2 \approx 0.6$ for $t \in (600, 1600)$.

Note that all simulations in Fig. 8 were performed under the assumption that the tumour carrying capacity is small, i.e. $K_2 = 40$ (and correspondingly the carrying capacity of tumour-infiltrating macrophages is small $K_1 = 40\%$, $K_2 = 10$). This describes the growth of small avascular tumours up to the point where they deplete the environment from nutrients and to continue growing they need to induce
Fig. 8. (a) Baseline dynamics for the logistic kinetic model (3.7a): (i) Time-evolution of the activity-averaged solutions \( n_1(t) = \int_{-1}^{1} f_1(t,u)du \) and \( n_2(t) = \int_{0}^{1} f_2(t,u)du \) for the baseline parameter values shown in Table 1. Sub-panels (ii) and (iii) show the probability distribution of macrophage \( f_1 \) and tumour \( f_2 \) sub-populations over the activity space \( u \), at five different time steps. (b) Dynamics of model (3.7a) when we increase the rate at which M1-macrophages kill tumour cells: \( \gamma = 0.5 \rightarrow \gamma = 0.75 \); Sub-panel (i) shows the time-evolution of the activity-averaged solutions \( n_1 \) and \( n_2 \), while sub-panels (ii) and (iii) show the probability distribution of macrophage \( f_1 \) and tumour \( f_2 \) sub-populations over the activity space \( u \), at five different time steps. (c) Time-evolution of \( n_1 \) and \( n_2 \) as we decrease the proliferation rate of macrophages to \( \alpha = 0.5 \) and increase the half-life of macrophages to \( \mu^f = 0.9 \). (d) Time-evolution of \( n_1 \) and \( n_2 \) as we decrease \( \alpha \) even further to \( \alpha = 0.05 \). (e) Time-evolution of \( n_1 \) and \( n_2 \) as we decrease the transition rates \( \lambda_1 = 0.01 \rightarrow \lambda_1 = 0.001 \) and \( \lambda_2 = 0.01 \rightarrow 0.0001 \). For all these simulations we consider \( K_1 = 10 \), \( K_2 = 40 \) (corresponding to some small tumour volumes) and all other parameter values as in Table 1.
Table 2. Summary of tumour and macrophages populations dynamics, for the models with exponential and logistic cells growth.

| Type          | Parameter(s) | Description                                                                 |
|---------------|--------------|-----------------------------------------------------------------------------|
| Exponential   | $\lambda_1$  | $\lambda_1 = 0$: Oscillatory dynamics                                      |
|               |              | $\lambda_1 > 0$: Unbounded growth of macrophages and tumour cells           |
| Logistic      | $\alpha$     | $\alpha$ “high”: Dormant tumour: increased tumour clonal phenotypic heterogeneity and increased macrophages phenotypic heterogeneity |
|               |              | $\alpha$ “low”: Growing tumour                                             |

Understanding the collective dynamics of solid tumours, many of which being infiltrated with large macrophage populations that have different phenotypes and functions, is an important step in the future development of new anti-cancer therapies. To shed some light on the evolution of such solid tumours, in this study, we derived a new kinetic model for active particles that focuses on the interactions between a heterogeneous population of macrophages and a heterogeneous population of tumour cells. While there are many other kinetic models for tumour-immune interactions (see, for example, Refs. [12, 16, 30, 34], the majority of those models are quite generic, being formulated as general competition models. In this study, we aimed to derive a new model based on latest experimental studies regarding the dynamics of macrophages with different phenotypes (anti-tumour M1 and pro-tumour M2) and their specific interactions with the tumour cells. The main results have been summarised in Table 2.

We started our investigation into the dynamics of this new kinetic model by showing that it cannot display phenotypically/clonally homogeneous steady states (Fig. 4). The model could be reduced to the classical Lotka–Volterra model when assuming an initial uniform macrophage phenotype distribution and no macrophages re-polarisation (i.e. $\lambda_1 = 0$). And as expected, the reduced model exhibited an oscillatory dynamics (Fig. 5). The introduction of macrophages re-polarisation ($\lambda_1 > 0$) combined with an exponential cell growth (for macrophages and tumour cells) led to an unbounded growth of macrophages, which then triggered the growth of tumour population (see Fig. 6). For very low macrophage proliferation rates ($\alpha = 0.05$ in Fig. 7) one could see an initial unbounded tumor growth, which triggers an unbounded macrophages growth.

To avoid this unrealistic unbounded growth of macrophages, and to incorporate the phenomenological observation that tumour growth slows down at large sizes [35, 36] we then assumed logistic cell growth. This led to dormant tumour angiogenesis. However, increasing the tumour carrying capacity to $K_2 = 400$ leads to dynamics similar to the one in Fig. 8 — not shown here.

All these numerical results confirm that in the presence of a logistic growth, the non-negative solutions for model (3.7a) exist globally in time, as mentioned at the end of Remark 3.3.

4. Summary and Discussion

Understanding the collective dynamics of solid tumours, many of which being infiltrated with large macrophage populations that have different phenotypes and functions, is an important step in the future development of new anti-cancer therapies. To shed some light on the evolution of such solid tumours, in this study, we derived a new kinetic model for active particles that focuses on the interactions between a heterogeneous population of macrophages and a heterogeneous population of tumour cells. While there are many other kinetic models for tumour-immune interactions (see, for example, Refs. [12, 16, 30, 34], the majority of those models are quite generic, being formulated as general competition models. In this study, we aimed to derive a new model based on latest experimental studies regarding the dynamics of macrophages with different phenotypes (anti-tumour M1 and pro-tumour M2) and their specific interactions with the tumour cells. The main results have been summarised in Table 2.
dynamics (see Figs. 8(a)–8(c)), during which the tumour cells increased their clonal heterogeneity (see Fig. 8). This simulation result is consistent with various experimental studies, which emphasise the divergence in tumour clones during dormancy. Understanding tumour dormancy is important because it can lead to further tumour relapse and possible patient death (in Ref. 56, the authors noted that more than 60% of all deaths from breast cancer take place after the five-year survival mark, which implies that dormancy might play an important role on patient survival). In our study, the tumour-dormant behaviour was mediated by the immune cells (i.e. M1-like cells), and was also characterised by a re-polarisation of M1 macrophages towards an M2 phenotype. And when the density of macrophages with the extreme M2-phenotype (i.e. $u \approx -1$) increased significantly, this was associated with a tumour relapse.

Note that for large phagocytosis rates $\gamma$, it is possible that the tumour is controlled at relatively small values also in the presence of macrophages with M2-phenotype (see Fig. 8(b)). This result could explain some of the contradictory experimental studies in the literature regarding the contribution of M1 versus M2 macrophages to patient survival time. For example, in Ref. 46, the authors observed that increased M1 macrophage densities inside tumour islets and stroma were associated with improved survival, but the M2 macrophage densities (even if they were higher than the M1 densities inside tumour islets and stroma) were not associated with patients survival time. In Ref. 51, the authors observed increased patient survival following the infiltration of tumour islets with M1 cells (as well as relatively large numbers of M2 cells). Extended survival was also observed for large densities of M1 and M2 cells in the tumour stroma. On the other hand, in Ref. 52, the authors suggested that while high infiltration of M1 macrophages inside tumour islets was indeed associated with increased overall survival, high infiltration of M2 macrophages (inside islets and stroma) was associated with reduced overall survival. Therefore, there is still quite a lot of debate on the pro-tumour/anti-tumour roles of M1 and M2 cells infiltrating the tumours, and our study (Fig. 8) suggests that the rates at which these cells eliminate or support tumour growth might lead to improved or reduced patient survival.

While some of the model parameters listed in Table 1 were obtained from the published biological literature, we need to emphasise that there is a lot of variability in these parameters. For example, the proliferation ($\alpha$) and death rates of macrophages ($\mu^d$) overlap over a large interval, which leads to the possibility of having $\alpha \leq \mu^d$ or $\alpha \geq \mu^d$. Also the proliferation rates of the tumour cells ($\beta^{n,f}$) or the rates at which the M1-like macrophages can kill tumour cells ($\gamma$) can vary over large intervals, depending on the tumour cell lines. For the baseline values listed in Table 1, we chose arbitrary values from the middle of the parameter ranges. A more rigorous approach for parameter identification would have been to fit the models (2.1a) and (3.7a) to a published dataset for tumour growth in the presence/absence of macrophages with different phenotypes. Unfortunately, we are not aware of any experimental/clinical studies that quantify (through time series data)
not only tumour volume growth but also the evolution of macrophage populations with intermediate phenotypes (although there are some studies that quantify tumour growth in the presence of macrophages with extreme M1 and M2 phenotypes, also quantified in terms of their percentages on days 7 and 14 after tumour injection\cite{1}). This lack of experimental data makes it difficult to parametrise kinetic mathematical models for active particles (as opposed to simpler ODE models that were parametrised with the tumour/macrophages data from Ref. \cite{1} see Ref. \cite{2}). For this reason, the purpose of this current study was not to make quantitative predictions, but to try to obtain a better understanding of the qualitative dynamics exhibited by models (2.1a) and (3.7a).

Previous experimental studies have shown a co-migration of tumour cells and macrophages during the invasion and metastasis process\cite{2,20}. Therefore, future work will focus on generalising these kinetic models to incorporate also the collective spatial movement of both macrophages and tumour cells, as a results of cell–cell communication via different signalling pathways.

Acknowledgments

R. E. was partially supported by an Engineering and Physical Sciences Research Council (UK) First Grant (EP/K033689/1). L. G. was financially supported by the UK’s Engineering and Physical Sciences Research Council (EPSRC) via Grant Nos. EP/N016602/1 and EP/R007438/1.

References

1. V. Aristov, Biological systems as nonequilibrium structures described by kinetic methods, *Res. Phys.* 13 (2019) 102232.
2. V. Aristov, Methods of kinetic theory in problems of econophysics, in *AIP Conf. Proc.*, Vol. 2132 (AIP Publishing, 2019), p. 190004.
3. L. Arlotti, A. Gamba and M. Lachowicz, A kinetic model of tumour/immune system cellular interactions, *J. Theor. Med.* 4 (2002) 39–50.
4. L. Arlotti and M. Lachowicz, Qualitative analysis of a nonlinear integrodifferential equation modelling tumour-host dynamics, *Math. Comput. Model.* 23 (1996) 11–29.
5. N. Bellomo, A. Bellouquid, L. Gibelli and N. Outada, *A Quest Towards a Mathematical Theory of Living Systems* (Birkhäuser, 2017).
6. N. Bellomo, P. Degond and E. Tadmor (eds.), *Active Particles*, Vol. 1 (Birkhäuser, 2017).
7. N. Bellomo, P. Degond and E. Tadmor (eds.), *Active Particles*, Vol. 2 (Birkhäuser, 2019).
8. N. Bellomo and G. Forni, Dynamics of tumour interaction with the host immune system, *Math. Comput. Model.* 20 (1994) 107–122.
9. N. Bellomo, D. Knopoff and J. Soler, On the difficult interplay between life, “complexity”, and mathematical sciences, *Math. Models Methods Appl. Sci.* 23 (2013) 1861–1913.
10. N. Bellomo, N. Li and P. Maini, On the foundations of cancer modelling: Selected topics, speculations, and perspectives, *Math. Models Methods Appl. Sci.* 18 (2008) 593–646.
A kinetic theory approach for modelling tumour and macrophages heterogeneity

11. A. Bellouquid, E. D. Angelis and D. Knopoff, From the modelling of the immune hallmarks of cancer to a black swan in biology, *Math. Models Methods Appl. Sci.* **23** (2013) 949–978.
12. A. Bellouquid and M. Delitala, *Mathematical Modelling of Complex Biological Systems* (Birkhäuser, 2006).
13. M. Benoit, B. Desnue and J.-L. Mege, Macrophage polarisation in bacterial infections, *J. Immunol.* **181** (2008) 3733–3739.
14. S. Benzekry, C. Lamont, A. Beheshti, A. Tracz, J. Ebos, L. Hlatky and P. Hahnfeldt, Classical mathematical models for description and prediction of experimental tumour growth, *PLoS Comput. Biol.* **10** (2014) e1003800.
15. R. Burrell, N. McGranahan, J. Bartek and C. Swanton, The causes and consequences of genetic heterogeneity in cancer evolution, *Nature* **501** (2013) 338–345.
16. G. Caraffini, M. Iori and S. Olivieri, Prey–predator models in the analysis of tumour–immune system interaction, *Riv. Mat. Univ. Parma* **3** (2000) 321–340.
17. D. Caswell and C. Swanton, The role of tumour heterogeneity and clonal cooperativity in metastasis, immune evasion and clinical outcome, *BMC Med.* **15** (2017) 133.
18. P. Chen, Y. Huang, R. Bong, Y. Ding, N. Song, X. Wang, X. Song and Y. Luo, Tumour-associated macrophages promote angiogenesis and melanoma growth via adrenomedullin in a paracrine and autocrine manner, *Clin. Cancer Res.* **17** (2011) 7230–7239.
19. V. Chitu, Y. Yeung, W. Yu, S. Nandi and E. Stanley, Measurement of macrophage growth and differentiation, *Curr. Protoc. Immunol.* (2011) 1–26.
20. J. Condeelis and J. Pollard, Macrophages: Obligate partner for tumour cell migration, invasion, and metastasis, *Cell* **124** (2006) 263–266.
21. M. Coscia, E. Quaglino, M. Iezzi, C. Curcio, F. Pantaleoni, C. Riganti, I. Holen, H. Mönkkönen, M. Boccardo, G. Forni, P. Musiani, A. Bosia, F. Cavollo and M. Masaia, Zoledronic acid repolarises tumour-associated macrophages and inhibits mammary carcinogenesis by targeting the mevalonate pathway, *J. Cell Mol. Med.* **14** (2010) 2803–2815.
22. C. Danciu, A. Falamas, C. Dehelean, C. Stoica, H. Radeke, L. Barbu-Tudoran, F. Bojin, S. Cinta-Pinzaru and M. Munteanu, A characterisation of four B16 murine melanoma cell sublines molecular fingerprint and proliferation behaviour, *Cancer Cell Int.* **13** (2013) 75.
23. N. den Breems and R. Eftimie, The re-polarisation of M2 and M1 macrophages and its role on cancer outcomes, *J. Theor. Biol.* **390** (2016) 23–39.
24. R. Eftimie and H. Hamam, Modelling and investigation of the CD4⁺ T cells — Macrophages paradox in melanoma immunotherapies, *J. Theor. Biol.* **420** (2016) 82–104.
25. E. Geigant, K. Ladizhansky and A. Mogilner, An integrodifferential model for orientational distributions of F-actin in cells, *SIAM. J. Appl. Math.* **59** (1998) 787–809.
26. S. Goswami, E. Sahai, J. Wyckoff, M. Cammer, D. Cox, F. Pixley, E. Stanley, J. Segall and J. Condeelis, Macrophages promote the invasion of breast carcinoma cells via a colony-stimulating factor-1/epidermal growth factor paracrine loop, *Cancer Res.* **65** (2005) 5278–5283.
27. W. Hao, L. Schlesinger and A. Friedman, Modeling granulomas in response to infection in the lung, *PLoS One* **11** (2016) e0148738.
28. M. Heusinkveld and S. van der Burg, Identification and manipulation of tumour associated macrophages in human cancers, *J. Trans. Med.* **9** (2011) 216.
29. V. Huber, S. Fais, M. Iero, L. Lugini, P. Canese, P. Squarcina, A. Zaccheddu, M. Colone, G. Arancia, M. Gentile, E. Seregni, R. Valenti, G. Ballabio, F. Belli,
E. Leo, G. Parmiani and L. Rivoltini, Human colorectal cancer cells induce T-cell death through release of proapoptotic microvesicles: Role in immune escape, *Gastroenterology* 128 (2005) 1796–1804.

30. M. Iori, G. Nespi and G. Spiga, Analysis of a kinetic cellular model for tumour–immune system interactions, *Math. Comput. Model.* 29 (1999) 117–129.

31. P. Italiani and D. Boraschi, From monocytes to M1/M2 macrophages: Phenotypical versus functional differentiation, *Front. Immunol.* 5 (2014) 1–22.

32. J. Jackute, M. Zemaitis, D. Pranys, B. Sitkauskiene, S. Miliauskas, S. Vaitkiene and R. Sakalauskas, Distribution of M1 and M2 macrophages in tumour islets and stroma in relation to prognosis of non-small cell lung cancer, *BMC Immunol.* 19 (2018) 3.

33. D. Knighton, D. Ausprunk, D. Tapper and J. Folkman, Avascular and vascular phases of tumour growth in the chick embryo, *Br. J. Cancer* 35 (1977) 347–356.

34. M. Kolev, Mathematical modelling of the competition between tumour and immune system considering the role of antibodies, *Math. Comput. Model.* 37 (2003) 1143–1152.

35. A. Laird, Dynamics of tumor growth, *Br. J. Cancer* 18 (1964) 490–502.

36. A. Laird, Dynamics of relative growth, *Growth* 29 (1965) 249–263.

37. J. Lan, L. Sun, F. Xu, L. Liu, F. Hu, D. S. Abd, Z. Hou, W. Wu, X. Luo, J. Wang, X. Yuan, J. Hu and G. Wang, M2 macrophage-derived exosomes promote cell migration and invasion in colon cancer, *Cancer Res.* 79 (2019) 146–158.

38. H.-W. Lee, H.-J. Choi, S.-J. Ha, K.-T. Lee and Y.-G. Kwon, Recruitment of monocytes/macrophages in different tumor microenvironments, *BBA Rev. Cancer* 1835 (2013) 170–179.

39. Y. Louzoun, C. Xue, G. Lesinski and A. Friedman, A mathematical model for pancreatic cancer growth and treatments, *J. Theor. Biol.* 351 (2014) 74–82.

40. S. Mahajan, C. Decker, E. Mellins and R. Facio, Macrophage dependent pathways modulate the pathogenesis of cytokine storm syndrome, *J. Immunol.* 200 (2018) 42.18–42.18.

41. G. Malbacher, L. Curtis, J. Lowengrub and H. Frieboes, Mathematical modelling of tumour-associated macrophage interactions with the cancer microenvironment, *J. Immunother. Cancer* 6 (2018) 10.

42. A. Mantovani, A. Sica, Macrophage polarisation comes of age, *Immunity* 23 (2005) 344–346.

43. A. Mantovani, S. Sozzani, M. Locati, P. Allavena and A. Sica, Macrophage polarization: Tumor-associated macrophages as a paradigm for polarized M2 mononuclear phagocytes, *Trends Immunol.* 23 (2002) 549–555.

44. S. Marino, N. Clifone, J. Mattila, J. Linderman, J. Flynn and D. Kirschner, Macrophage polarisation drives granuloma outcome during *mycobacterium tuberculosis* infection, *Infect. Immun.* 83 (2015) 324–338.

45. D. Martinez-Marin, C. Jarvis, T. Nelius and S. Filleur, Assessment of phagocytic activity in live macrophages-tumour cells co-cultures by Confocal and Nomarski microscopy, *Biol. Meth. Protocols* 2 (2017) 1–7.

46. J. Ma, L. Liu, G. Che, N. Yu, F. Dai and Z. You, The M1 form of tumour-associated macrophages in non-small cell lung cancer is positively associated with survival time, *BMC Cancer* 10 (2010) 112.

47. N. McGranahan and C. Swanton, Clonal heterogeneity and tumour evolution: Past, present, and the future, *Cell* 168 (2017) 613–628.

48. J. Mège, V. Mehraj and C. Capo, Macrophage polarisation and bacterial infection, *Curr. Opin. Infect. Dis.* 24 (2011) 230–234.

49. C. Mills, M1 and M2 macrophages: Oracles of health and disease, *Crit. Rev. Immunol.* 32 (2012) 463–488.
50. D. Mosser and J. Edwards, Exploring the full spectrum of macrophage activation, *Nat. Rev. Immunol.* 8 (2008) 958–969.
51. C. Ohri, A. Shikotra, R. Green, D. Waller and P. Bradding, Macrophages within NSCLC tumour islets are predominantly of a cytotoxic M1 phenotype associated with extended survival, *Eur. Respir. J.* 33 (2009) 118–126.
52. S. Ostrand-Rosenberg, Immune surveillance: A balance between pro-tumour and anti-tumour immunity, *Curr. Opin. Genet. Dev.* 18 (2008) 11–18.
53. L. Perko, *Differential Equations and Dynamical Systems* (Springer, 2001).
54. B. Qian and J. Pollard, Macrophage diversity enhances tumour progression and metastasis, *Cell* 141 (2010) 39–51.
55. A. Sica, P. Larghi, A. Mancino, L. Rubino, C. Porta, M. Totaro, M. Rimoldi, S. Biswas, P. Allavena and A. Mantovani, Macrophage polarisation in tumour progression, *Semin. Cancer Biol.* 18 (2008) 349–355.
56. M. Sosa, P. Bragado and J. Aguirre-Ghiso, Mechanisms of disseminated cancer cell dormancy: An awakening field, *Nat. Rev. Cancer* 14 (2014) 611–622.
57. S. Sousa, R. Brion, M. Lintunen, P. Kronqvist, J. Sandholm, J. Mönkkönen, P.-L. Kelokumpu-Lehtinen, S. Lauttia, O. Tynninen, H. Joensuu, D. Heymann and J. Määttä, Human breast cancer cells educate macrophages toward the M2 activation status, *Breast Cancer Res.* 17 (2015) 101.
58. F. Tacke and H. Zimmermann, Macrophage heterogeneity in liver injury and fibrosis, *J. Hepatol.* 60 (2014) 1090–1096.
59. M. Torres, J. Wang, P. Yannie, S. Gosh, R. Segal and A. Reynolds, Identifying important parameters in the inflammatory process with a mathematical model of immune cell influx and macrophage polarisation, *PLoS Comput. Biol.* 15 (2019) e1007172.
60. I. Trejo, H. Kojouharov and B. Chen-Charpentier, Modelling the macrophage-mediated inflammation involved in the bone fracture healing process, *Math. Comput. Appl.* 24 (2019) 12.
61. Y. Wang, T. Yang, Y. Ma, G. Halade, J. Zhang, M. Lindsey and Y.-F. Jin, Mathematical modelling and stability analysis of macrophage activation in left ventricular remodelling post-myocardial infarction, *BMC Genom.* 13 (2012) S21.
62. H. Yamaji, T. Iizasa, E. Koh, M. Suzuki, M. Otsuji, H. Chang, S. Motohashi, S. Yokoi, K. Hiroshima, M. Tagawa, T. Nakayama and T. Fujisawa, Correlation between interleukin 6 production and tumour proliferation in non-small cell lung cancer, *Cancer Immunol. Immunother.* 53 (2004) 786–792.
63. X. Yang, X. Liang, M. Zheng and Y. Tang, Cellular phenotype plasticity in cancer dormancy and metastasis, *Front. Oncol.* 8 (2018) 505.
64. J. Yang, L. Zhang, C. Yu, X.-F. Yang and H. Wang, Monocyte and macrophage differentiation: Circulation inflammatory monocyte as biomarker for inflammatory disease, *Biomark Res.* 2 (2014) 1–9.
65. J. Yokota, Tumour progression and metastasis, *Carcinogenesis* 21 (2000) 497–503.
66. M. Zhang, Y. He, X. Sun, Q. Li, W. Wang, A. Zhao and W. Di, A high M1/M2 ratio of tumour-associated macrophages is associated with extended survival in ovarian cancer patients, *J. Ovarian Res.* 7 (2014) 19.
67. J. Zhuang and G. Wogan, Growth and viability of macrophages continuously stimulated to produce nitric oxide, *Proc. Natl. Acad. Sci. USA* 94 (1997) 11875–11880.