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Chemotaxis and cross-diffusion models in complex environments: Models and analytic problems toward a multiscale vision

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To the memory of Abdelghani Bellouquid

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This paper proposes a review focused on *exotic* chemotaxis and cross-diffusion models in complex environments. The term *exotic* is used to denote the dynamics of models interacting with a time-evolving external system and, specifically, models derived with the aim of describing the dynamics of living systems. The presentation first, considers the derivation of phenomenological models of chemotaxis and cross-diffusion models with particular attention on nonlinear characteristics. Then, a variety of exotic models is presented with some hints toward the derivation of new models, by accounting for a critical analysis looking ahead to perspectives. The second part of the paper is devoted to a survey of analytical problems concerning the application of models to the study of real world dynamics. Finally, the focus shifts to research perspectives within the framework of a multiscale vision, where different paths are examined to move from the dynamics at the microscopic scale to collective behaviors at the macroscopic scale.

Keywords: Keller–Segel; cross diffusion; multiscale problems; pattern formation; complex interactions; blow-up; well-posedness; micro-macro derivation.

AMS Subject Classification 2020: 35A01, 35B40, 35B44, 35K55, 35K57, 35Q35, 35Q92, 82D99, 91D10

1. Aims and Plan of the Paper

The celebrated Keller–Segel model[153,154] explores, by reaction–diffusion equations, the dynamics of chemotaxis phenomena in a two populations system, where cells (or organisms) interact with a chemoattractant. The applications of this model, as well as of various technical developments to model real biological phenomena, have generated a huge literature on interesting analytic problems focused on the qualitative behaviors of solutions, namely existence of solutions and their asymptotic behaviors.

The qualitative analysis is often focused on the study of stability properties of equilibrium configurations or, in opposite, of blow-up of solutions as it has been reviewed in the surveys[142] and, more recently, in Ref. 19.

The derivation of a broad variety of models, obtained by the classical approach of continuum mechanics, is presented in the survey[136] which is an important reference to scientists interested to chemotaxis phenomena. A useful updating of KS models is delivered in Ref. 11. These models are derived by conservation equations closed by heuristic models suitable to describe the material behavior and the interactions of the two interacting substances. A key problem of the modeling approach consists in inventing heuristic models valid in dynamics far from equilibrium.

A unified approach to the derivation of macroscopic models from the underlying description at the microscopic scale of cells has been proposed in Ref. 51 for models, where the dynamics at the scale of cells is delivered by tools of the kinetic theory for active particles.[15] The dependent variable, which is a probability distribution function over the microscopic state of cells, is expanded in power of a small parameter and if substituted into the differential kinetic model generates a sequence of equations by a technique somehow inspired to the celebrated sixth Hilbert problem.[118,132,234] The authors of Ref. 51 developed their approach, initiated in Ref. 31 for mixtures of interacting cell populations, by using power expansions corresponding both to the parabolic and hyperbolic scaling. The parabolic scaling has been further developed in the survey[52] being specifically applied to the derivation of

cross-diffusion models. The multiscale vision presented in the last part this paper contributes to identify the different paths that lead to derive models.

The recent literature, that includes some papers published after,[19] proposes various studies, where qualitative analysis of Keller–Segel models, as well as of nonlinear cross-diffusion models[151] in complex environments, where this term is used to denote the dynamics of models interacting with a time-evolving external system, for instance, a fluid,[14,188,292,298] or with a transported host, for instance, a virus driven by chemotaxis.[28] Additional examples refer to cross-diffusion models where social interactions[297] are considered, while papers[80,261] give examples of predator–preys models which include complex interactions. The interest in reaction diffusion models in medicine is witnessed in the pioneering book[227] devoted to the modeling of neuro-degenerative diseases.

An interesting variety of papers has been published, but a systematic presentation of these models still needs to be developed. Our paper aims at covering this conceptual gap firstly by presenting a survey of models derived by the phenomenological approach of continuum mechanics, secondly by proposing a forward look at some analytic research perspectives which are brought to the attention of the interested reader to motivate their development, and lastly by a multiscale approach which shows how models can be derived at all scales on the ground of the applications of the same principles in the modeling of interaction.

In more details, the plan of the paper is as follows.

Section 2 is devoted to a concise presentation of the phenomenological derivation of cross-diffusion and chemotaxis models for binary mixtures. In addition, it is shown how models can be written in a dimensionless form and how heuristic models of diffusion can be derived, for instance, flux limited dynamics[30] and fractional diffusion.[34,101] Both topics are briefly presented toward the subsequent derivation of models in complex environments treated in the following sections. The contents of this section has not an immediate connection with the various models presented in Sec. 3, but it may address to possible developments (refinement) of these models.

Section 3 shows how models of cross-diffusion, whose description has been delivered in the preceding section, can be derived for systems in complex environments. This term is used to denote the interaction between a *primary model*, essentially chemotaxis or cross-diffusion, and a *secondary model*, hosted or hosting, deemed to depict some features of the external environment. The interaction dynamics has a reciprocal influence which can create interesting patterns. Various case studies are considered, from the modeling of virus dynamics driven by chemotaxis, to models, where a complex interaction occurs between cross-diffusion and social dynamics.

Section 4 provides a critical analysis and review of classical problems of the qualitative analysis of mathematical problems which appear in the application to real world problems of the various mathematical problems presented in Sec. 3. Specifically, we refer to initial-boundary value problems and related existence and blow-up as well as asymptotic behavior study. We are interested in several cross-diffusion models with novel mathematical structures or new properties. In

particular, we shall focus on qualitatively investigating chemotaxis models for virus infection, haptotaxis models for oncolytic virotherapy, cross-diffusion models for criminal behavior, pursuit-evasion systems for predator–prey interaction and taxis-cascade systems for forager-exploiter interplay, as well as coupled chemotaxis-fluid models.

Section 5 is devoted to research perspectives mainly focused on multiscale methods. Specifically, the derivation of models at all scales based on the same principles and parameters, and on the derivation of macroscopic equations from the underlying description at the microscopic scale and further reasonings on perspectives on modeling topics. These approaches might lead to new classes of models that require further developments of the methods currently used for the qualitative analysis.

2. On the Phenomenological Derivation of Cross-Diffusion Models

This section provides a concise presentation of the mathematical structure of chemotaxis and cross-diffusion models in view of the contents of the next section, where these models are related to a variety of complex environments. Subsequently, it is shown how models can be written in a dimensionless form that is a preliminary to a heuristic interpretation of nonlinearities and non-localization in the diffusion process for the models treated in Sec. 3. The contents do not claim to be exhaustive, but simply an introduction that can be enriched by the literature specialized on this topic, e.g. Ref. 136.

2.1. *Chemotaxis and cross-diffusion models*

Let us consider the cross-diffusion dynamics of two substances diffusing in a three dimensional domain. A quite general structure, which can include a broad variety of models, is as follows:

$$\begin{cases} n_t = \nabla \cdot (k_1(n,m)\nabla n + k_2(n,m)\nabla m) + H(n,m), \\ m_t = \nabla \cdot (k_3(n,m)\nabla n + k_4(n,m)\nabla m) + K(n,m), \end{cases} \tag{2.1}$$

where $n = n(t,x)$ and $m = m(t,x)$ denote the density of the two substances depending on time t and space x. The diffusion terms $k_i = k_i(n,m)$, with $i = 1,2,3,4$ are deemed to model nonlinear diffusion dynamics that might depend on both densities, while the source/sink terms H and K are deemed to model the competition between the two substances.

Chemotaxis models describe the dynamics of the density of cells (or organisms) $n = n(t,x)$ interacting with a chemoattractant $S = S(t,x)$ by the following system:

$$\begin{cases} n_t = \nabla \cdot (k_1(n,S)\nabla n - k_2(n,S)\nabla S) + H(n,S), \\ S_t = \nabla \cdot (k_3(n,S)\nabla S) + K(n,S), \end{cases} \tag{2.2}$$

where the positive definite terms $k_1(n, S)$, $k_2(n, S)$ and $k_3(n, S)$ can depend on n and S, namely on the dependent variables. In addition, H and K model the source terms related to interactions.

Model (2.2) is a generalization of the well-known Keller–Segel (KS) model[153,154] where the diffusion coefficient k_3 is constant, in this case model (2.2) reduces to

$$\begin{cases} n_t = \nabla \cdot (k_1(n, S)\nabla n - k_2(n, S)\nabla S) + H(n, S), \\ S_t = k_3\, \Delta S + K(n, S). \end{cases} \tag{2.3}$$

Structure (2.2) is quite general as it includes several models that describe the movement of cells by chemotaxis and diffusion. These models are obtained by a specialization of the form of the various terms on the right-hand side of (2.2). The shape of $k_1(n, S)$, which describes the diffusivity of the cells, can depend nonlinearly on the cell density n. For example, in the model studied in Ref. 162, it is supposed that k_1 increases with increasing cell density according to the phenomenological model $k_1 = k_1(n) = n^r$ for $r \geq 0$. However, in several applications the diffusion coefficient k_1 is simply supposed to be constant.

In several models, the term $k_2(n, S)$ has the form $n\,\chi(S)$, where χ collects the properties of the chemotactic sensitivity. In its simplest form, χ is independent of chemoattractant concentration,[189] that is $\chi(S) = \alpha$, where α is constant. When $\chi(S)$ is not constant, sensitivity of chemoattractant is usually assumed to be decreasing with increasing concentration of the chemoattractant,[153,154] namely $\chi(S) = \frac{\alpha}{S}$, which is usually known as logarithmic sensitivity. This assumes that the cell's response refers to a single substrate of attractant which does not diffuse. A revised chemotactic coefficient form to model the action of cell-surface receptors has been proposed in Ref. 166 as follows:

$$\chi(S) = \alpha \frac{K_d}{(K_d + S)^2},$$

where K_d is constant (the receptor-ligand binding dissociation constant).

The source terms $H(n, S)$ and $K(n, S)$ describe proliferation/death of cells and chemoattractant production/degradation, respectively. The simplest model has no proliferation/death of cells, i.e. $H(n, S) = 0$, while the production and degradation of the chemoattractant depending on n and S as follows:

$$K(n, S) = an - bS,$$

for some constants a, $b \geq 0$. If H is not zero, a possible (logistic) model is

$$H(n, S) = rn(N - n),$$

with r and N both non-negative constants.[189]

The interested reader can find in the Lecture Notes[151] an excellent survey of entropy methods devoted to the qualitative analysis of solutions to initial-boundary value problems.

A detailed and deep report on the phenomenological derivation of models has been developed in the already cited survey[136] which reports about a broad variety of different KS-models as summarized in Table 1 of the same paper, where various models are directly related to phenomenological assumptions on the interactions within the binary mixture. In addition, this paper also shows some analytic results focusing on the existence of solutions and the stability of steady states. However, the modeling approach should, as we shall see, refer to multiscale frameworks, where interactions should refer to biological theories rather than to phenomenological conjectures, and the derivation of macroscopic should be developed from the underlying description at the micro-scale by methods somehow inspired to the celebrated Hilbert sixth problem,[132] see also Ref. 118.

2.2. *Using dimensionless variables*

The qualitative analysis of the physical properties models can take advantage of a dimensionless setting, where both dependent and independent variables are referred to limit quantities that are peculiar of each specific system under consideration. Therefore, writing a model in dimensionless form needs to be adapted to each case study. However, some rules can be given for the general structure (2.1) under the following technical assumptions:

(i) Both independent and depended variables are labeled by the subscript "r", namely t_r, x_r and n_r, m_r, while dimensionless quantities are not labeled.
(ii) A characteristic linear space dimension ℓ can be defined for all linear components of x.
(iii) Each dimensional variable n_r and m_r has an upper bound, n_M and m_M, respectively, with $\frac{n_M}{m_M} = \mu$ related to either full packaging or saturations.
(iv) The diffusion coefficients $k_i(n_r, m_r)$ can be written as follows $c_i\, \kappa_i(n, m)$, where c_i is a dimensional constant and κ_i is a dimensionless function of n and m.
(v) Similarly, the source terms $H(n_r, m_r)$ and $K(n_r, m_r)$ can be written as $h_0 h(n, m)$ and $s_0 S(n, m)$, where h_0 and s_0 are dimensional constants and h and S are functions of dimensionless variables.
(vi) A critical time T_c can be defined by making equal to one the first coefficient of the first diffusion term:

$$\frac{T_c k_1}{\ell^2} = 1 \Rightarrow T_c = \frac{\ell^2}{k_1}\cdot \tag{2.4}$$

Bearing, in the mind all above assumptions, we first rewrite Eq. (2.1) by using the new notations for the case with dimensions

$$\begin{cases} \partial_{t_r} n_r = \nabla_{x_r} \cdot (c_1\kappa_1(n, m)\nabla_{x_r} n_r + c_2\kappa_2(n, m)\nabla_{x_r} m_r) + h_0 h(n, m), \\ \partial_{t_r} m_r = \nabla_{x_r} \cdot (c_3\kappa_3(n, m)\nabla_{x_r} n_r + c_4\kappa_4(n, m)\nabla_{x_r} m_r) + s_0 S(n, m). \end{cases} \tag{2.5}$$

Subsequently, by letting

$$\eta_i = \frac{c_i}{c_1}, \quad \mu_n = \frac{h_0}{c_1}, \quad \mu_m = \frac{s_0}{c_1},$$

it yields

$$\begin{cases} n_t = \nabla \cdot (\kappa_1(n,m)\nabla n + \eta_2\kappa_2(n,m)\nabla m) + \mu_n h(n,m), \\ m_t = \nabla \cdot (\eta_3\kappa_3(n,m)\nabla n + \eta_4\kappa_4(n,m)\nabla m) + \mu_m S(n,m). \end{cases} \tag{2.6}$$

The dimensionless structure (2.6) contributes to a deeper understanding about nonlinear features of diffusion that depend on the specific physical features of the system under consideration. A specialized study of nonlinearities is postponed to the next section focusing on specific models. However, some general concepts can be anticipated focusing on density dependent nonlinearities by some reasonings somehow inspired in Ref. 52.

We refer to diffusion dynamics related to a generic substance whose dimensionless density is denoted by $\rho = \rho(t,x)$ with values in $[0,1]$, while multi-component models can be seen as an extension of these. Our reasonings refer to the following types of nonlinearity: density dependent, gradient dependent, and fractional diffusion. This features in the modeling of diffusion are important for particles that have a significant size that generates a packing density, which motivates the use of dimensionless quantities, specifically $\rho \in [0,1]$. Then, as observed in Ref. 52, the shape of a generic diffusion coefficient can be modeled as follows:

$$\kappa(\rho) = \rho^{\alpha}(1-\rho)^{\beta}, \quad \alpha, \beta > 0, \tag{2.7}$$

so that $\kappa(0) = \kappa(1) = 0$.

It has been argued, see Refs. 17 and 18, that particles are sensitive to local gradients rather than local density only. This conjecture essentially means that living diffusive particles perceive a density higher (lower) than the real one in the presence of positive (negative) gradients. Models of this type have been applied in crowd dynamics[24] and appears to be consistent in the case of a broad variety of self-propelled particles. In the one-dimensional setting, a simple model, see Ref. 52, accounting for this flux-saturation is as follows:

$$\begin{cases} \partial_x\rho \geq 0 : \partial_t\rho = (2\rho-1)\partial_x\rho + \partial_x\left(\rho(1-\rho)\dfrac{(\partial_x\rho)^2}{1+(\partial_x\rho)^2}\right), \\ \partial_x\rho < 0 : \partial_t\rho = (2\rho-1)\partial_x\rho - \partial_x\left(\rho^2\dfrac{(\partial_x\rho)^2}{1+(\partial_x\rho)^2}\right). \end{cases} \tag{2.8}$$

A prototype of this mechanism is proposed in Refs. 10, 55, 56, 57 as follows:

$$\partial_t\rho = \nu\partial_x\left(\frac{|\rho|\partial_x\rho^m}{\sqrt{1+\frac{\nu^2}{c^2}|\partial_x\rho^m|^2}}\right), \quad \nu, c > 0, \quad m \geq 1, \tag{2.9}$$

which combines flux-saturation effects together with those of porous media flow, in one space dimension.

Some applications to tumor evolution and dynamics based on systems with flux-saturated and porous media mechanisms with biochemical and bio-mechanical (reactions) interactions can be seen in Refs. 46, 82 and 269. The derivation is obtained by using optimal transport theory accounting for a dynamics, where the propagation speed of discontinuous interfaces is generically bounded by c.

We also mention that fractional models can be used to account for nonlocal features of diffusion dynamics. An example, specifically applied to Keller–Segel models, has been given in Ref. 34, see also Ref. 101. Fractional diffusion, see Ref. 54, has been recently studied in the case of free boundary problems.[86]

2.3. *Cross-diffusion by nonlocal source terms*

Cross-diffusion can be driven, as shown in Ref. 35, by cross source terms generated by nonlocal interactions. The derivation is referred to the original SIR model by Kermack and McKendrick, see Ref. 212 which describes the dynamics of three compartments of a population classified as

$$\text{susceptible} \ \rightarrow \ \text{infected} \ \rightarrow \text{removed individuals.}$$

The size of the populations is given by u, v and R, respectively. The model is as follows:

$$\begin{cases} u_t = -\beta uv - d_1 u, \\ v_t = \beta uv - d_2 v, \\ R_t = kv - d_3 R, \end{cases} \tag{2.10}$$

where the first two equations, in this simple model, can be treated separately, as R can be deduced from the dynamics of the first two equations. In this case the infection rate depends on βuv, differently from the ratio of infected cells βuw that appears in the May-Nowak model (3.1), treated later in Sec. 3, as the role of w in (3.1) is different from that of R in this Eq. (2.10).

This subsection reports some reasonings on nonlocal interactions. In details, we consider an integro-differential approach that incorporates non-local interactions by the term βuv which can be modified as follows

$$\beta uv \rightarrow u(t,x) \int_\Omega \beta(x,y) v(t,y) dy, \tag{2.11}$$

where Ω is the support of β and v, essentially it correspond to the sensitivity domain. This assumption on the modeling of interactions is the key toward the derivation of the Kermack–McKendrick model. The review[131] reports about a broad variety of models of infectious diseases. Equation (2.11) defines a nonlocal source term, while transport terms consider the speed of propagation of each component. The

framework is as follows:

$$\begin{cases} u_t(t,x) - \Delta(c_u(x)u(t,x)) \\ \quad = -u(t,x)\displaystyle\int_\Omega \beta(t,\tau,x,y)v(t,y)dy - d_1 u(t,x), \\ v_t(t,y) - \Delta(c_v(x)v(t,x)) \\ \quad = u(t,x)\displaystyle\int_\Omega \beta(t,\tau,x,y)v(t,y)dy - d_2 v(t,y). \end{cases} \tag{2.12}$$

This model refers to the structured population approach,[212] where τ represents and models the time of exposure or relaxation of the infectious process, which can induce a convolution term also in time (in that case, $v(t,x)$ must be replaced by $v(\tau,x)$ and an extra integral in τ will represent the interaction in time) and not only in space in terms of the β kernel. This represents the influence of interactions in a spatial environment and a possible memory-time term in the evolution of populations.

The model may be viewed as a case study focused on a simple assumption on non-local interaction term that generate a drift for diffusion. The interested reader can rapidly figure out some technical developments motivated by applications on collective dynamics including those reviewed in Ref. 35, where a detailed study of propagation speeds has been developed.

Further generalization of model (2.12) can be also identified by considering different aspects of nonlinear diffusion when c_u and c_v depend on u and v. More general aspects of nonlocal interactions can be found, focusing on the characterization of Ω in hydrodynamical models of crowd dynamics,[12,13] where the shape of depends on the local velocity direction, e.g. it is a sector of circle with axis in the direction of the velocity. Further refinements can be developed by the literature on swarm dynamics,[29] where the size of Ω is referred to a critical density ρ_c by the following relation:

$$\rho_c = \int_\Omega \rho(t,x)dx, \tag{2.13}$$

where $\Omega = \Omega(t,x)$ which can be computed under suitable assumptions on the shape (not the size) of Ω.

2.4. *Additional reasonings on modeling*

The various examples, presented in the preceding subsections are mainly focused on different ways of modeling nonlinear diffusion phenomena, but the presentation does not cover the whole variety of conceivable models that generally depend on the specific physical-biological phenomena under consideration. However, a detailed

study of nonlinear diffusion goes beyond the aims of our paper, which is devoted to the study of cross-diffusion and reaction–diffusion models in complex environments. We refer also to previously published surveys[11,19,136] to bring a more extended presentation of models to the interested reader.

In addition, we should mention that an important topic to be considered in the qualitative and computational analysis of the mathematical problem is the complex interaction between diffusion dynamics and stability problem. This class of problems has been generated by the intuition by Turing[266] who observed that even if the dynamical system corresponding to the source term shows stability properties, these can be lost under a diffusive action, see also Ref. 217, as shown, for instance, in Ref. 224.

More in general, a detailed study of specific features of interactions at the microscale can suggest some technical developments of KS-type models. As possible examples, selected among various biological phenomena. We mention, in view of Sec. 3, indirect attractant production,[145] signal-dependent motilities,[245] attraction repulsion dynamics,[175] tissue remodeling,[205] and various others reported in Ref. 136.

3. Chemotaxis and Cross-Diffusion Models in Complex Environments

The term *exotic models* is used occasionally to denote models in various fields of behavioral sciences, for instance social and economics sciences with the idea of including individual behaviors that have an influence on the mechanical dynamics which, in turn may have some influence on the behavioral dynamics. These models are treated in our survey that goes beyond the study of biological and mechanical systems.

Indeed, this section investigates how the modeling approach can be applied to a variety of complex systems, where the collective dynamics of interacting entities can be modeled within the framework of mathematical structures corresponding to that of cross-diffusion in general and, in particular, to Keller–Segel type models. Examples, considered in the following, refer, for instance, to the competition between criminality and security forces, or predators–prey systems chasing for food.

Furthermore, this section presents a variety of *models in a dynamical environments*, where this term is used to denote the interaction between a *first model* with a *second* (*additional*) *model* which describes the dynamics of the external environment where the first model live. At first, one or both models can be exotic in the sense described above, which has suggested the term *models in exotic environment.*

There are countless examples, of great mathematical and application relevance, in which small variations in the environment (ecological, political decisions, biomedical or bio-mechanical inputs, etc.) can cause a huge change in the architecture (interactions, stability, asymptotic behavior) of the initial model. We are interested

to case studies, where one of the two models corresponds to reaction–diffusion dynamics.

The interaction of the dynamics of the two systems has a reciprocal influence which can create interesting patterns. In some cases, for instance models of social dynamics, the two models interact without distinguishing the role of internal or external models. The role of the external action is, in some models, simply modeled by a source term depending only on the variables modeling the state of two or more interacting sub-systems. Therefore, the dynamics is described by a system of partial differential equations corresponding to the interacting sub-systems.

The next subsections present a selection of different classes of models, consistent with the aforementioned description, which are derived by the phenomenological approach developed at the macroscopic scale. The presentation in each section follows the same path for each case study. Firstly, a phenomenological description is presented for the specific class of systems under consideration, subsequently a general model is derived, and finally a critical analysis is proposed focusing on the specific features of nonlinear diffusion which appear in the model.

A preliminary study focused on possible generalizations of models is proposed in each subsection leaving to the interested reader the effective development according to their own research project. In some cases, for instance the derivation of urban criminality models, we present exotic models in view of analytic studies proposed in Sec. 4. However, we also show how the modeling can be further developed to the study of their interactions with additional social dynamics, so that the models conform to what we have defined as models in exotic environments.

The derivation of models requires a detailed analysis of individual-based interactions across the populations involved in the dynamics. These interactions occur at the micro-scale, while the derivation of models treated in this paper is at the macroscopic scale. Therefore, local averaging techniques are necessary to make consistent the micro-scale with the related macro-scale. This is a delicate issue which is critically analyzed in the last section of our paper within the framework of a multiscale vision.

3.1. *Virus dynamics driven by chemotaxis interactions*

The class of models presented in this subsection describes the virus dynamics to account for space evolution by a transport mechanism which can be modeled by reaction–diffusion system or, more in general, by a cross-diffusion system. As an example we consider a classic prototype model for virus behavior in the spatially homogeneous case derived within a framework of population dynamics.[47,199] This type of models is also known with the acronym SIR.[200,212]

In more details, we refer here to the particular case known as the May-Nowak model which describes 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 $w = w(t)$, by the following dynamical system:

$$\begin{cases} u_t = -d_1 u - \beta uw + \lambda, & t > 0, \\ v_t = -d_2 v + \beta uw, & t > 0, \\ w_t = -d_3 w + kv, & t > 0. \end{cases} \tag{3.1}$$

The model has been derived under the following phenomenological assumptions[28]:

(1) Healthy cells are constantly produced by the body at rate λ, die at rate $d_1 u$ and become infected on contact with the virus, at rate βuw.
(2) Infected cells are produced at rate βuw and die at rate $d_2 v$.
(3) New virus particles are produced at rate kv and die at rate $d_3 w$.
(4) λ is a source term.

This model has been quite comprehensively understood via a thorough qualitative analysis of corresponding initial value problems (for instance cf. Refs. 47 and 200). As it is known, in addition to the infection-free equilibrium $Q_0 := (\frac{\lambda}{d_1}, 0, 0)$, if the so-called *basic reproduction number*:

$$R_0 := \frac{\beta k \lambda}{d_1 d_2 d_3},$$

is greater than 1. Then, the system shows an additional equilibrium

$$Q^* := (u^*, v^*, w^*),$$

where

$$u^* := \frac{\lambda}{d_1}\frac{1}{R_0}, \quad v^* := \frac{d_1 d_3}{\beta k}(R_0 - 1) \quad \text{and} \quad w^* := \frac{d_1}{\beta}(R_0 - 1). \tag{3.2}$$

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, see Ref. 160.

The mathematical model studied in Ref. 28, 32, 108 describes the space dynamics, viewed as space formation, by a virus model over which a deterministic reaction-diffusion dynamics acts over the three components $u = u(t, x)$, $v = v(t, x)$ and $w = w(t, x)$, which now depend on time and space and the source term λ may, in general, depend on time and space.

The mathematical model is as follows:

$$\begin{cases} u_t = D_u \Delta u - \chi \nabla \cdot (u \nabla v) - d_1 u - \beta uw + \lambda(t, x), \\ v_t = D_v \Delta v - d_2 v + \beta uw, \\ w_t = D_w \Delta w - d_3 w + kv, \end{cases} \tag{3.3}$$

where D_u, D_v and D_w denote the respective diffusion coefficients, henceforth considered fixed and positive, and where χ represents the strength and direction of the cross-diffusive interaction, while the parameters β, 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.[28] The modeling approach of Ref. 237 is followed for the migration mechanisms.

It is noteworthy that an explicit equation for a chemical chemokine is excluded, with the density distribution of infected cells providing a proxy for its distribution; such simplifications are commonly employed in Keller–Segel-based models for immune dynamics, e.g. see Ref. 204.

This model is quite simple, however, it can inspire some developments to take into account specific features of the physical reality of interest in applications. For instance, one can consider further developments of modeling of the virus dynamics to go beyond the limited validity of SIR models, as well as modeling space dynamics by more realistic cross-diffusion models.

Concerning the first topic, the virus model reported in (3.1) is just one of the possible examples, while the dynamics can refer to different types of dynamical systems. For instance, delay-distributed virus dynamics models,[99] infection model with multi-target cells,[100] or even models with progression, mutations, and selection dynamics.[117]

An additional biological component that appears to be interesting to explore is the inclusion of the space dynamics in the virus evolution models of COVID-19,[37,187] which can be treated according to the framework reviewed in this paper. However, the modeling should go beyond the simplicity of SIR models as enlightened in Ref. 191 and cited bibliography therein, see Refs. 67, 68 and 141. The conceptual difficulties to model epidemics in the case of pandemics are properly enlightened in Ref. 221.

The modeling approach developed in Ref. 20 accounts for the above hints in two steps within a multiscale framework. Firstly, by modeling the contagion dynamics, somehow related to the so-called *social distance*, across individuals carriers of two micro-scale variables, i.e. the virus load and the immune defense ability corresponding to the micro-scale within the hosting individuals. Later, in the modeling of the dynamics of the virus, competition develops within the host, generally in the lung, where space dynamics can be modeled by reaction–diffusion, as already done in a different context.[93]

Indeed, it is a complex environment where the contagion dynamics begins its evolution within the host. The two systems are coupled as the contagion probability depends on the virus load of the interacting individuals.

Concerning the second topic, it is plain that modeling the space dynamics should be referred to each case study under consideration. This means, at least, accounting for nonlinearity in diffusion and selecting the most appropriate cross-diffusion model. The examples of nonlinearities in Sec. 2 might contribute to focus on the most appropriate selection of the diffusion model which depends also on the type of the virus object of the modeling approach.[98] In addition, heterogeneous environments might be considered in the diffusion model to account for preferred diffusion directions.

3.2. *On the modeling of oncolytic viruses*

An additional class of models, which definitely deserves attention, is somehow related to virus dynamics, but it refers to more complex biological environments. We can consider different therapies by active virus induced by modeling approaches developed in Ref. 6 focused on the so-called *oncolytic viruses* that can replicate selectively within cancer cells and attack them up to destruction.

In mode details, the authors derive a moving boundary model based on coupled systems of partial differential equations both at the macro-scale (tissue-scale) and at the micro-scale (cell-scale).[6] These equations are connected through a double feedback link. One of the interesting aspect of this model is that it is effectively multiscale as biological reality requires.

The model proposed in Ref. 6 describes, at the macroscopic scale, the dynamic interactions between four macro-scale components moving on a domain $\Omega(t)$, which evolves with time, contained in a cube Y of dimension $n \in \{2, 3\}$. These components are the density of uninfected cancer cells $u(t, x)$, the density of infected cancer cells $w(t, x)$, the density of Extracellular Matrix (ECM) $v(t, x)$ and the density of the oncolytic virus particles $z(t, x)$, with $x \in \Omega(t)$ and $t > 0$. In its general form, the model reads as follows:

$$\begin{cases} u_t = D_u \Delta u - \xi_u \nabla \cdot (u \nabla v) + \mu_u u(1-u) - \rho_u uz, \\ v_t = -v(\alpha_u u + \alpha_w w) + \mu_v v(1-v), \\ w_t = D_w \Delta w - \xi_w \nabla \cdot (w \nabla v) + \rho_w uz - \delta_w w, \\ z_t = D_z \Delta z - \xi_z \nabla \cdot (u \nabla v) + \beta w - \delta_z z - \rho_z uz, \end{cases} \tag{3.4}$$

where $D_u, D_w, D_z, \xi_u, \alpha_u$ and α_w are positive defined parameters, while ξ_w, μ_u, $\mu_v, \rho_u, \rho_w, \rho_z, \beta, \delta_w$ and δ_z are non-negative constants.

Here, the underlying modeling assumptions are that the uninfected/infected cancer cells move randomly with diffusion coefficients D_u, D_w, which of course can be restated with some of the nonlinear terms mentioned in Sec. 2, directly toward the ECM gradients with haptotactic coefficients ξ_u, ξ_w, respectively. At the same time, uninfected cells proliferate logistically at rate μ_u and become infected due to the contact with oncolytic viruses at rate ρ_u, while infected cells die at rate δ_w and proliferating at rate ρ_z. The equation on v describes the remodeling of the ECM as the difference between the logistically growth of its components at rate μ_v and their degradation by uninfected and infected cells at rates α and β, respectively. Finally, the oncolytic virus cells diffuse at rate D_z and direct their movement toward regions of higher ECM densities with a ECM-OV-taxis rate given by ξ_z. These virus particles also proliferate at rate β, die at rate d_z, while are reduced when they infect at a rate ρ_z.

On the other hand, the space dynamics of the system at the microscopic scale is described by a coupled system of reaction–diffusion equations modeling the spatio-temporal evolution of suitable degrading enzymes, namely the urokinase

plasminogen activator (uPA), plasminogen activator inhibitor (PAI-1), and plasmin within a microscopic domain εY, and then the derived microscopic model is coupled with the macro-scale system (3.4) via a "top-down" and "bottom-up" links; we refer to Ref. 6, see also Ref. 263, for more details.

An additional example is the macro-scale model proposed in Ref. 170, where a haptotactic cross-diffusion system was derived as a model for oncolytic therapy by a virus, which describes the influence of the extracellular matrix taxis over the tumor-oncolytic virus interaction in the form of haptotaxis of both cancer cells and oncolytic virus toward higher ECM densities. More precisely, the mathematical approach in Ref. 170 suggests the following model:

$$\begin{cases} u_t = D_u \Delta u - \xi_u \nabla \cdot (u \nabla v) + \mu_u u(1 - u^r) - \dfrac{\rho_u u z}{k_u + \theta u}, \\ v_t = -v(\alpha_u u + \alpha_w w) + \mu_v v(1 - v), \\ w_t = D_w \Delta w - \xi_w \nabla \cdot (w \nabla v) + \dfrac{\rho u z}{k_u + \theta u} - \delta_w w, \\ z_t = D_z \Delta z - \xi_z \nabla \cdot (z \nabla v) + \gamma w - \delta_z v - \dfrac{\rho u z}{k_u + \theta u}. \end{cases} \tag{3.5}$$

Herein, compared to the macroscopic system (3.4), the production term cv has been replaced by $\frac{cv}{k_c + \theta c}$ of Beddington–deAngelis type $k_c, \theta > 0$ while the proliferating term $\mu_u u(1 - u)$ is adjusted to $\mu_u u(1 - u^r)$ with a positive parameter $r > 0$.

3.3. *Cross-diffusion in criminality models*

An interesting application, somehow referred to the framework defined in Sec. 3.2, is the derivation of models of criminality invasion by reaction–diffusion equations. This approach was introduced in the pioneering paper[231] by an interdisciplinary team of authors referring specifically to the area of Los Angeles. In more details, we consider the following model:

$$\begin{cases} u_t = \nabla \cdot \left(D(u, v) \nabla u - 2 \dfrac{u}{v} \nabla v \right) - uv + B_1(u, v), \\ v_t = \eta \, \Delta u - v + uv + B_2(u, v), \end{cases} \tag{3.6}$$

where $u = u(t, x)$ denotes the density of *offending criminals* at time t and position x, while $v = v(t, x)$ is the *attractiveness field*, which models how desirable any given site x is a target for criminal activity at a given time t. $D = D(u, v)$ is diffusion, while $B_1 = B_1(u, v)$ and $B_2 = B_2(u, v)$ are external sources, and $0 < \eta < 1$ is a constant parameter. In general, D might be nonlinearly depending on u and v thus generating nonlinear diffusion, while H and K might depend on the localization in the territory. An example of models with nonlinear diffusion, which appears when interacting individuals want to avoid competition, was proposed in Ref. 222. This is accomplished by allowing the diffusion rate D to depend on u only which leads

to the following model:

$$\begin{cases} u_t = \nabla \cdot \left(u^{m-1} \nabla u - 2 \dfrac{u}{v} \nabla v \right) - uv + B_1(u, v), \\ \\ v_t = \eta \, \Delta v - v + uv + B_2(u, v), \end{cases} \tag{3.7}$$

where $m > 1$ is a given parameter. We can see that the only difference with respect to system (3.6) is in the term that describes the diffusion of criminals, namely the diffusion term $\nabla \cdot (u^{m-1} \nabla u)$, which is an equation of the porous mean type.

The derivation of (3.6) was obtained by averaging technique of an agent-based model based on three fundamental concepts:

(1) The so-called *routine activity approach*,[81] namely the assumption that the two primary factors for a crime to occur are the following: a motivated offender and an opportunity that might even include a victim and a lack of a capable guardian.
(2) The *repeat and near-repeat victimization effect*,[150] which is based on empirical observations that elevated risk of burglary, at the same location as well as neighboring locations, follows an initial incident separated by a short time duration.
(3) The *broken-windows theory*,[155] namely a criminology theory stating that crime is emitted from disorder and is the final result of a long chain of events, which make crime more likely to lead to more crime.

Let us focus on some specific assumptions which lead to the model:

- The agent-based model describes the dynamics of criminal agents moving in a two-dimensional rectangular lattice with spacing ℓ. Each criminal, in a fixed location $x = (i, j)$ that is taken between times t and $t + \Delta t$, may burglarize the house in position x with probability: $P(t, x) = 1 - e^{-v(t,x)\Delta t}$, which corresponds to the assumption that the crime probability P follows a Poisson process with a mathematical expectation given by v. This assumption implies that the number of crime is given by uv.
- After a burglary crime, it is supposed that the corresponding criminal agent exits from the lattice at that time, but if the criminal does not choose to commit a crime, he moves to neighboring locations following a random walk process described by the following probability of movement from position x to location y:

$$R(t, x \to y) = \frac{v(t, y)}{\sum_{z \sim x} v(t, z)},$$

  where the notation $z \sim x$ denotes all of the sites near location x.
- Criminals are also generated at each position x at rate Γ. The attractiveness field v is decomposed into baseline attractiveness v^0 (which is a static component) and dynamic attractiveness $v = v(t, x)$, namely $v(t, x) = v^0 + v(t, x)$.

- The diffusion term $\eta\Delta v$ in the equation for v incorporates the near-repeat victimization and broken windows effects. The assumption that criminal agents move toward high concentrations of the attractiveness value, giving rise to the taxis term $-\nabla\cdot(2\frac{u}{v}\nabla v)$ in the first equation. Finally, the external function H introduces criminal agents into the system and the attractiveness differences between neighborhoods at the beginning are modeled by K.
- The dynamic of attractiveness is ruled by a heuristic model that corresponds to the aforementioned repeat, and near-repeat, victimization as well as to the broken-windows sociological effects. First, repeat victimization is modeled by the assumption that crime increases the dynamic field, thus when a house is burglarized, v is increased by a quantity θ.
- The near-repeat victimization and broken windows effects are modeled by allowing v to spread from position x to its neighbors, this implies that the dynamics by which the attractiveness v diffuse is driven by a weighted averaging procedure between the actual location x and its neighbors. These correspond to the following model:

$$v(t+\Delta t,x)=\left[(1-\eta)v(t,x)+\frac{\eta}{s}\sum_{y\sim x}v(t,y)\right](1-\omega\Delta t)+\theta E(t,x), \tag{3.8}$$

where $0<\eta<1$ was defined referring to Eq. (3.6), s is the coordination number (i.e. the number of locations near site x which equal to four in the case of a square lattice), ω is a time scale which control the time which separates two successive burglary events, and $E(t,x)$ is the number of burglary crimes at site x occurred between times t and $t+\Delta t$.

According to the above assumptions, the macroscopic model (3.6) can be derived as a continuum limit of the above agent-based model. Detailed calculations, which are not repeated here, can be found in Ref. 239.

This class of models has attracted the attention of applied mathematicians either referring to the qualitative analysis of solutions or focusing on further developments of models, for instance, see Refs. 35 and 36 and related qualitative analysis, as well as models on the complex interaction between law breakers and security forces,[22] where methods of statistical mechanics were developed to account for the heterogeneity within the interacting groups. Analytic problems will be more treated in Sec. 4, here we mention, without claim of completeness, some papers on the qualitative analysis of solutions in Ref. 128 on the study of the role of the source terms. In more details, the stability of spike solutions is treated in Ref. 192, a detailed study on the dynamics of diffusion in Ref. 222, while pattern formation mainly focuses in Ref. 229.

Technical developments of this model can be implemented by focusing on the characterization of the diffusion terms, which should account both of nonlinearity whenever it might depend on the local density and of asymmetries related to the

local shapes of the distribution of the population in the territory. As a possible example in this context, consider the case of nonlocal diffusion treated in Sec. 2.3. These developments should be, however, related to well-defined case studies.

The methodological approach can be made more general to tackle the modeling of social systems somewhat different, or richer, than those of the original paper which, however, has the merit of providing an interesting conceptual basis for the modeling of a broad variety of social systems. For instance, a modeling approach to describe the distribution of homeless citizens in the geographical area of Los Angeles has been proposed in Ref. 176. Indeed, it is a crucial social problem to be tackled at the administrative-political level without forgetting that mathematical modeling and simulations can contribute, as shown in Ref. 176, to decision makers. As a matter of fact, mathematicians are becoming aware of the need of studying social problems, see Ref. 232 as an example.

Models described in this subsection can be identified as *exotic* models as interactions are modeled by heuristic interpretation within the broad framework of behavioral dynamics. Looking ahead to research perspectives, an important development would be dealing with the modeling approach within the more general framework of *modeling in complex environments*, by inserting the criminality dynamics within the environment of social dynamics. Indeed, the need of accounting for a broad variety of social dynamics can be discovered even by the pioneering literature, for instance Ref. 81, while the kinetic theory approach has already accounted for this important feature in accounting of the role of wealth distribution which, as shown in Ref. 27, can generate not only opposition to governments but also the onset of extreme radicalization.

A formal framework can be obtained by adding to system (3.6) the dynamics of an additional variable $\mathbf{w} = \{w_i, \ldots, w_n\}$, where w_i corresponds to the fraction of individuals of a certain population, while w_1 and w_n correspond, respectively, to the fraction of individuals in the lowest and highest state labeled by $i = 1$ and $i = n$. The formal structure deemed to provide the framework of models is then defined by a system of three equations of the type:

$$\begin{cases} u_t = \nabla \cdot \left(D(u,v)\nabla v - 2\,\dfrac{u}{v}\,\nabla v \right) - uv + H(u,v), \\ v_t = \eta\,\Delta v - v + uv + K(u,v), \\ \mathbf{w}_t = \mathcal{S}[v, \mathbf{w}], \end{cases} \tag{3.9}$$

where the vector operator $\mathcal{S}$ models the overall social dynamics based on the social policy applied by the local government over v and $\mathbf{w}$.

Analogous reasonings have been proposed within the framework of the modeling of the complex interaction between security forces and criminality,[22] where the source of criminality is related to unfear distribution of wealth that can generate a source of criminality induced by unfear social conditions.

3.4. *Cross-diffusion mediated by social and biological interactions*

We consider models, where two, or more, different populations compete to chase the same source, distributed in space, which may depend on the size of the two interaction populations. These undergo a cross-diffusion dynamics somehow promoted by the said source. Otherwise, in more general cases, the dynamics of the source can be modeled by an additional equation linked to that of the two populations.

This topic is of interest in ecology as it allows to investigate the dynamics of pattern formation of two or more populations which compete for the source. An important reference for this topic is the paper,[239] where the authors consider different social interactions and show how the dynamics, under suitable assumptions on the modeling of interaction, can evolve in time and space toward a unique pattern. Firstly, we consider a model in the contexts of predator–prey systems,[265] which describes the so-called *pursuit-evasion dynamics*. Subsequently, we consider more general cases that are described by the so-called *taxis-cascade systems*. Finally, we show how analogous structures can be used for the competition between cell populations in the case of search available sources necessary to proliferate, we refer specifically to the next paragraph titled "*In host biological dynamics and cancer modeling*".

• *Pursuit-evasion dynamics*

We consider the aforementioned dynamics referring to Ref. 265. The model can be written as follows:

$$\begin{cases} u_t = D_1 \Delta u - \chi_1 \nabla \cdot (u \nabla v) + f(u, v), \\ v_t = D_2 \Delta v + \chi_2 \nabla \cdot (v \nabla u) + g(u, v), \end{cases} \tag{3.10}$$

with positive parameters D_1, D_2, χ_1, χ_2 and local kinetics functions f and g, and with $u = u(t, x)$ and $v = v(t, x)$ representing the population densities of predators and preys, respectively.

Food distribution $c = c(t, x)$ might supposed to be constant in time $c \cong c_0(x)$, then model (3.10) simplifies as follows:

$$\begin{cases} u_t = D_1 \Delta u - \chi_1 \nabla \cdot (u \nabla c_0) + f(u, v; c_0), \\ v_t = D_2 \Delta v + \chi_2 \nabla \cdot (v \nabla u) + g(u, v; c_0). \end{cases} \tag{3.11}$$

Various additional modifications are known referring, for instance, to predator–prey models, see Refs. 80 and 261. See also Ref. 246 accounting for different strategies. This model (3.10) can be defined *exotic* according to the definition given in the introduction to this present section. We are interested in understanding how far this class of models can be further developed to describe different types of social interactions. Some technical developments, known in the literature, are presented in the following.

• *Taxis-cascade systems*

We consider a class of models, where space dynamics of the two populations is modeled by reaction–diffusion equations chasing a source that depends on the space availability of food, which diffuses being somehow reduced by the action of the two populations, namely *foragers* that search for food directly, and *scroungers*, (say *exploiters*), in the search the food by following the foragers, namely exploiting forager aggregations. The dynamics of food interacts with that of the first two populations. A quite general model is as follows:

$$\begin{cases} u_t = \Delta u - \chi_1 \nabla \cdot (u \nabla w) + f(u, v, w), \\ v_t = \Delta v - \chi_2 \nabla \cdot (v \nabla u) + g(u, v, w), \\ w_t = \Delta w - \lambda(u + v)w - \mu w + r(w), \end{cases} \tag{3.12}$$

where $u = u(t, x)$, $v = v(t, x)$, and $w = w(t, x)$ are, respectively, the dimensionless densities of foragers, scroungers, and food, while $f(u, v, w)$ and $g(u, v, w)$ are source terms acting across the first two populations, while $r(w)$ is the inner source of the third population. Dimensionless variables are used as in the calculations of Appendix annex to Ref. 239, somehow analogous to those in Sec. 2. In particular, the dimensionless parameters χ_1 and χ_2 are taxis parameters of foragers and exploiters, while λ is the per-capita consumption rate and μ is the decay rate of the prey. This framework defines the so-called *taxis-cascade systems*.

The solution of the initial-boundary problems can be focused on the study of spatiotemporal patterns somehow related to the benefit of individuals according to conditions under which either strategy leads to enhanced success. In practice, success can be referred directly to the net food consumption.

This class of models offers the conceptual framework for the derivation of a broad variety of social dynamics. A preliminary step toward this objective requires an overlook at possible technical developments of (3.12). For instance:

• Models of source terms h_u and h_v might include dependence also on c;

• Diffusion might be nonlinear by coefficients depending on the variables of the system, in general $D_u = D_u(u, v, w)$, $D_v = D_v(u, v, w)$, and $D_w = D_w(u, v, w)$.

So that a more general model writes as follows:

$$\begin{cases} u_t = \nabla(D_u(u, v, w)\nabla u) - \chi_1 \nabla \cdot (u \nabla w) + h_u(u, v, w), \\ v_t = \nabla(D_v(u, v, w)\nabla v) - \chi_2 \nabla \cdot (v \nabla u) + h_v(u, v, w), \\ w_t = \nabla(D_w(u, v, w)\nabla w) - \lambda(u + v)w - \mu w + r(w). \end{cases} \tag{3.13}$$

Nonlinear diffusion models can be further specialized by accounting, in the diffusion coefficient, for the *perceived density*, see Sec. 2, which is higher (lower) in the presence of positive (negative) gradients. Flux-saturated terms can be inserted, as we have seen, once the model is written in a dimensionless form. On the other hand, a simplification corresponds to the pursuit-evasion dynamics (3.10).

In addition, let us mention that this structure provides a framework which goes beyond the ecological framework, for instance looking at different types of social dynamics that have been treated by different types of kinetic theory approach.[91] For instance, opinion formation[90,111] or competition of firms over the source of international markets.[23]

A challenging key perspective to further modeling developments consists in linking the social dynamics reviewed in this subsection, to other interactive dynamics that can have an important influence over the first dynamics. For instance, welfare policy that might be fair, or even, unfair[176] up to presenting dishonest features.[112,213,226]

Specifically, we refer to models derived within the framework of the kinetic theory of active particles,[21] see Refs. 22 and 27, where it is shown that unfair societies enhance either extreme radicalization or criminality. These kinetic approaches provide a detailed description of interactions that can lead, by averaging techniques or asymptotic limits, to the continuum description by PDEs.

Models, derived by the kinetic theory approach, in social dynamics show that internal variables are necessary to account for the heterogeneous behavior of individuals,[53] which should be also taken into account at the micro-scale as heterogeneity. This is an important feature in behavioral sciences and, specifically, in economics,[85] where social dynamics and economics interact.

• *In host biological dynamics and cancer modeling*

Reaction–diffusion equations have been developed to model pattern formation in cancer biology. The physical-biological reality is highly complex as it includes mutations and selection followed by proliferative and/or destructive events related to the interaction between tumor cells and immune cells,[122,285] see also Refs. 83 and 194 for the biology of the immune competition, as well as some pioneering interpretations developed in Ref. 33.

A useful source is Ref. 281, where a variety of models are reported. Our subsection, which is focused on modeling, takes advantage of the excellent survey,[281] see also Refs. 205 and 206

$$\begin{cases} u_t = \Delta u - \chi \nabla \cdot (u \nabla v) - \xi \nabla \cdot (u \nabla w) + \mu u(r - u - w), \\ v_t = \dfrac{1}{\sigma} \Delta u - \dfrac{1}{\sigma}(v - u), \\ w_t = -vw + \eta w(1 - u - w), \end{cases} \tag{3.14}$$

where

— $u = u(t, x)$, $v = v(t, x)$, and $w = w(t, x)$ are the model variables corresponding to the density of cancer cells, the concentration of the Matrix-Degrading Enzyme (MDE), and the concentration of the Extracellular Matrix (ECM), respectively.

— The independent variables are time t and space $x \in \Omega$, where Ω is a bounded domain with regular surface $\partial\Omega$ so that the outward normal derivative on $\partial\Omega$ can be defined for the statement of the boundary value problems.

Concerning the biological meaning of the parameters and source terms in the model:

— χ and ξ measure the chemotactic and haptotactic sensitivities, respectively.
— The term $\mu(r - u - w)$ implies that in the absence of the ECM, cancer cells proliferate according to a standard logistic law.
— $\eta > 0$ models the ability of the ECM to remodel back to a healthy level as a coefficient to the term $w(1 - u - w)$.
— The scaling parameter σ takes value in the interval $[0, 1]$, where the limit values $\sigma = 0$ and $\sigma = 1$, define two biological limit behaviors, namely $\sigma = 0$ indicates that the diffusion of the enzyme is much faster in comparison to that of cancer cells,[74] which may also follow an approach of the quasi-steady-state approximation frequently used to study minimal chemotaxis systems.

The interest to this topic has motivated the growth of a vast literature, for instance see the pioneering articles[73,74] on cancer invasion and modeling angiogenesis and,[113–116] where some perspective ideas were posed on the evolutionary features of cancer phenomena. These concepts have been recently treated within the framework of multiscale approaches.[228]

Some selected examples from the literature refer to the study of the remodeling dynamics,[244] cancer invasion,[9,137,236] cell motility, moving boundary problems and multiscale problems,[7,238] as well as[97] that includes modeling of aggregation and proliferation. Also for this class of models, various authors enlighten the need of improving the modeling of the diffusion coefficient. Indeed, it is correctly observed in Ref. 281 that it should not be confined to one component only of the multiphase flow, but it depends on the local density of all components. We do agree with this remark that is consistent with the contents of Sec. 2 of this paper.

Actually, all authors who have tackled this challenging topic agree on the need of multiscale methods[209] as the parameters of the macro-scale dynamics depend on the interactions at the low scale of cells. However, this requires deriving models at the macro-scale from the underlying description at the low scale within the multiscale vision,[132] see for instance Refs. 198 and 203, focused on showing how models of cell mobility lead to a macro-scale description of the collective behavior. Various papers have been developed on this topic, which has a similar impact to all models presented in this section. The literature will be object of critical reasonings in the last section of our paper.

3.5. *Cross-diffusion models within a fluid*

An interesting class of models, where the cross-diffusion-reaction dynamics interacts with an external environment, refers to the interaction within a fluid, specifically

to biological fluids.[133] This type of models was already treated in Ref. 19 focusing also on the micro-macro derivation.[14]

However, it is worth returning to this topic as various concepts of the original model have been recently used to model pattern formations developed within a fluid. Bearing this motivation in the mind let us very rapidly report about a general mathematical structure underlying this class of modes that consists in the following set of equations:

$$\begin{cases} n_t + u \cdot \nabla n = \delta \Delta n - \nabla \cdot (n\chi(c) \cdot \nabla c), \\ c_t + u \cdot \nabla c = \mu \Delta c - k(c)n, \\ u_t = F[u, n, c], \\ \nabla \cdot u = 0, \end{cases} \tag{3.15}$$

where the dependent variables are $n = n(t, x)$, $c = c(t, x)$, and $u = u(t, x)$, corresponding, respectively, to number density, chemical concentration, and velocity field. In addition, F represents the motion of the fluid, by the nonlinear incompressible Navier–Stokes equation:

$$F[u, n, c] = -u \cdot \nabla u - \nabla p + \nu \Delta u - n \nabla \phi, \tag{3.16}$$

where $p = p(t, x)$ is the local pressure in the fluid. Or by the incompressible Stokes equations:

$$F[u, n, c] = -\nabla p + \nu \Delta u - n \nabla \phi, \tag{3.17}$$

where the positive constants δ, μ, and ν correspond to diffusion coefficients for the cells, chemical and fluid; $\chi(u)$ is the chemotactic sensitivity; and $k(u)$ is the consumption rate of the chemical by the cells. Moreover, $\phi = \phi(x)$ is a given potential function accounting the effects of external forces such as gravity. This linear term can be replaced by a nonlinear term that contemplates self-interaction effects between individuals and involves the speed of the external fluid through a commutator, see for example Ref. 215 and the references therein. It can be noticed from (3.15)–(3.17) that chemotaxis and fluid are coupled through both the transport of the cells and the chemical action of the fluid $u \cdot \nabla n$, $u \cdot \nabla c$, and by the external force $-n\nabla\phi$ exerted on the fluid by the cells.

It should be mentioned that some similar models describing different phenomena of chemotaxis in fluids have been considered in the literature. Including chemotaxis-fluid models presented first in Refs. 92, 138 and 267, to describe the behavior of oxygen-taxis bacteria swimming in an incompressible fluid, and developed later by various authors.[77,311] Models can also account for additional technical features, for instance logistic sources,[165] boundary sources,[45] and subcritical sensitivity.[275]

Recent research activity on cross-diffusion models was focused on chemotaxis-fluid systems of migrating entities in different situations. These include *transport of bacteria in fluids*,[138] while *coral broadcast spawning* phenomena studied in Ref. 157 (see also Ref. 158). Broadcast spawning is a fertilization strategy by which many

aquatic animals release sperm and egg gametes, some of which will become fertilized (the larva) and start a new colony.

The mathematical model proposed in Ref. 157 is as follows:

$$\begin{cases} \rho_t + \mathbf{u} \cdot \nabla \rho = \Delta \rho - \chi \nabla \cdot (\rho \nabla c) - \varepsilon \rho^q, \\ \Delta c + \rho = 0, \end{cases} \tag{3.18}$$

where $\rho = \rho(t, x)$ stands for the density of both sperms and egg gametes, $c = c(t, x)$ is the concentration of the signal released by the eggs, $\mathbf{u} = \mathbf{u}(t, x)$ is a given fluid vector field that is independent of the local density ρ and is divergence free, χ is a positive chemotactic sensitivity coefficient, and $q \geq 1$, $0 < \varepsilon \ll 1$ are constant parameters.

This model was derived under the assumption that the densities of sperm and egg gametes are identical and shows the sperm chemotactic movement toward the higher densities of the chemical released by the eggs. The second term on the left-hand side of the first equation, $\mathbf{u} \cdot \nabla \rho$, describes the tendency of ρ to transport through the fluid, while the first two terms in the right, i.e.

$$\Delta \rho - \chi \nabla \cdot (\rho \nabla c),$$

are the same as in the KS model (2.2) (with $k_1 = 1$ and $k_2 = \chi \rho$). This assumes that the chemotactic movement is directly along the signal gradient. The term $-\varepsilon \rho^q$ in the equation for ρ models the fertilization process, ε is a small parameter that controls the strength of the fertilization. The equation for c corresponds to an approximation to that of the KS system based on the assumption that the chemical diffusion is faster than the diffusion of egg gamete densities.

The two component model (3.18) relies on the simplifying assumption that the fluid velocity field is known. This assumes that the chemical concentration remains unaffected by the fluid motion. If $\mathbf{u}$ is unknown, then one possible model is obtained by assuming that the fluid vector field is modeled through the incompressible Navier–Stokes equations. This leads to the following Keller–Segel–Navier–Stokes type model[102]

$$\begin{cases} \rho_t + \mathbf{u} \cdot \nabla \rho = \Delta \rho - \chi \nabla \cdot (\rho \nabla c) - \varepsilon \rho^2, \\ c_t + \mathbf{u} \cdot \nabla c = \Delta c - c + \rho, \\ \mathbf{u}_t + \tau (\mathbf{u} \cdot \nabla) \mathbf{u} = \nu \Delta \mathbf{u} - \nabla p - \rho \nabla \phi, \\ \nabla \cdot \mathbf{u} = 0, \end{cases} \tag{3.19}$$

where $p = p(t, x)$ is the pressure of the fluid, $\phi = \phi(t, x)$ is a given gravitational potential, and $\tau = 0$ or 1. The case $\tau = 0$ corresponds to a Keller–Segel–Stokes type model where the fluid field $\mathbf{u}$ is modeled through Stokes equations, this is the case for example when the fluid flow is slow compared with the movement of the sperm and egg (see Ref. 102), while $\tau = 1$ corresponds to the full Navier–Stokes case.

Here, in comparison to (3.18), the term $\mathbf{u}\cdot\nabla c$, in the second equation, models the transport of chemical substances, and $-\rho\nabla\phi$, in the third equation, is an external force exerted on the fluid by egg gametes and is modeling the buoyancy effects of the cells on the fluid field $\mathbf{u}$ through the gravitational potential ϕ.

The two models, which have been outlined above, rely on the hypothesis that the densities of sperm and egg gametes are identical. A refinement in this direction has been proposed in Ref. 103, where the density ρ has been splitting to $\rho = n+m$, where n and m denote the population densities of sperms and egg gametes, respectively, which leads to the following four-component chemotaxis-Navier–Stokes model:

$$\begin{cases} n_t + \mathbf{u}\cdot\nabla n = \Delta n - \chi\nabla\cdot(n\nabla c) - nm, \\ c_t + \mathbf{u}\cdot\nabla c = \Delta c - c + m, \\ m_t + \mathbf{u}\cdot\nabla m = \Delta m - nm, \\ \mathbf{u}_t + \tau(\mathbf{u}\cdot\nabla)\mathbf{u} = \nu\Delta\mathbf{u} - \nabla p - (n+m)\nabla\phi, \\ \nabla\cdot\mathbf{u} = 0. \end{cases} \tag{3.20}$$

In comparison to (3.19), now the egg gamete population is not affected by the chemotaxis, but rather its dynamics is determined only by diffusion, fluid transport and degradation upon interactions with sperms. However, the term $-\varepsilon\rho^2$ in the first equation of (3.19) has been replaced by $-nm$, modeling a respective dependence between the egg gametes and the sperm population.

A natural approach to incorporate such a change consists in allowing the sensitivity coefficient χ to be a matrix-valued quantity, denoted here by S, which leads to a model with

$$n_t + \mathbf{u}\cdot\nabla n = \Delta n - \nabla\cdot(S(x,n,c)n\nabla c) - nm, \tag{3.21}$$

deemed to replace the first equation in (3.20).

At first, sensitivity tensor $S(x,n,c)$ might be nonlinear depending on both n and c and possibly may take values that are matrices with nontrivial entries. In the simplest case S is constant, for instance in the two-dimensional case a possible model is the following[311]:

$$S = \begin{pmatrix} 0 & 1 \\ -1 & 0 \end{pmatrix}.$$

More general models can be obtained within a multiscale framework, where models are derived by micro-macro asymptotic methods as shown in Refs. 14 and 89 which are somehow inspired, as mentioned, by the celebrated sixth Hilbert problem.

Finally, let us emphasize that both the derivation of models and the related qualitative analysis of mathematical problems must consider the qualitative analysis of the solutions to the hydrodynamic equations. The interactions between agents/individuals and the surrounding fluid pose new challenges related to the aggregation, fragmentation or clustering (crowds, flocking and swarming included)

of the particles or agents, but it also affects the feedback to the fluid causing temperature, pressure or local turbulence gradients.

Furthermore, the interactions between both systems lead to new challenges both in the field of modeling and in mathematical analysis, where new non-Newtonian non-local transport (possibly limited to a domain of sensitivity and influence of the environment) and nonlinear diffusion terms appear. In fact, this is a research field of great interest to scientists active in applied mathematics, as is also attested in recent literature, see Refs. 50, 106, 147, 215, 233 and the references therein as possible examples.

3.6. *Critical analysis and modeling perspectives*

A variety of models have been presented in the frameworks that we have specified in the introduction to this section such as *exotic* and *in complex environments*. The presentation includes a selection of models corresponding to different classes of social-biological dynamics, where reaction–diffusion and cross-diffusion dynamics plays a key role either as internal or external system.

The models presented in this section have been extracted from the existing literature in view of the review of the analytic contributions to the qualitative analysis of mathematical problems. Their structure includes diffusion and interactions terms linking the dynamics of each component of the system to the others. Possible modeling extensions to other cases and developments of models have been reported in each subsection.

Focusing on the diffusion and interaction terms, the contents of Sec. 2 have shown that the interpretation of the physics of each case study may demand a deep analysis of the nonlinear features of each term. Both nonlinear and nonlocal diffusion should be considered. For instance diffusion may depend on the local density and density gradients, see Eq. (2.8), while interactions that generate source or sink terms are generally nonlocal, see Eq. (2.11). Indeed, nonlinear and nonlocal features are typical of living systems, as each individual entity feels at some distance the presence of the other entities that are in certain sensitivity domain. Therefore, perceived quantities differ from the local ones. Actually, nonlinear and nonlocal interactions are often related.

The study of human crowds[12] and animal swarms[25] has provided a detailed analysis of this key aspect of modeling nonlinear and nonlocal interactions in collective motion. Some of the ideas of Refs. 12 and 25 can be transferred to models at the macroscopic scale, such as those presented in this section, where the phenomenological modeling approach should introduce the concept of perceived quantities to the entities in the elementary volume dx in localized in x of the physical space.

These reasonings naturally lead to a multiscale vision necessary in the modeling approach. This topic is treated in Sec. 5. Therefore, the mathematical results of the qualitative analysis of mathematical problems, which is treated in Sec. 4, can look at research perspectives taking advantage of the review of each class of models

already introduced, the different nonlinearities mentioned above in a consistent way with a multiscale vision.

This process will allow the coupling of different evolutionary processes, which can even refer to dynamics at different scales, which constitutes an interesting perspective towards the derivation of new classes of models.

4. A Review and Critical Analysis of Mathematical Problems

This section provides a survey of analytic results concerning the qualitative study of the solutions to mathematical problems, typically initial-boundary value problems. We specifically refer to existence of solutions, their regularity properties and stability. The study of blow-up of solutions is a challenging feature of the said qualitative analysis. The presentation is subdivided into subsections somehow related to the index followed in Sec. 3.

4.1. *Virus propagation via chemotaxis*

As mentioned in Sec. 3, in order to describe the hotspot phenomena of virus infection experimentally observed in Ref. 121, we consider the initial-boundary problem:

$$\begin{cases} u_t = D_u\Delta u - \chi\nabla\cdot(u\nabla v) - u - uw + \lambda, & x\in\Omega,\ \ t>0,\\ v_t = D_v\Delta v - v + uw, & x\in\Omega,\ \ t>0,\\ w_t = D_w\Delta w - w + v, & x\in\Omega,\ \ t>0,\\ \dfrac{\partial u}{\partial\nu} = \dfrac{\partial v}{\partial\nu} = \dfrac{\partial w}{\partial\nu} = 0, & x\in\partial\Omega,\ \ t>0,\\ u(x,0)=u_0(x),\quad v(x,0)=v_0(x),\quad w(x,0)=w_0(x), & x\in\Omega, \end{cases} \tag{4.1}$$

for the three unknown variables $u = u(x,t)$, $v = v(x,t)$ and $w = w(x,t)$, respectively corresponding to the densities of healthy uninfected cells, infected cells and virus particles at position x and time t, where D_u, D_v and D_w denote the respective diffusion coefficients and λ is the birth rate of healthy cells, and where χ measures the strength of the cross-diffusive interaction.

In contrast to the classical Keller–Segel model with linear production of chemotactic signal, the attractant production term in (4.1) is in a superlinear manner of uw, which coupled with the destabilizing chemotaxis mechanism increases the tendency toward blow-up of solutions and gives rise to considerable challenges in establishing global existence theory. Nevertheless, for any choice of initial data fulfilling

$$\begin{cases} u_0\in C^0(\overline{\Omega}), \quad u_0\geq 0 \text{ in } \Omega,\\ v_0\in W^{1,q}(\Omega), \quad v_0\geq 0 \text{ in } \Omega,\\ w_0\in C^0(\overline{\Omega}), \quad w_0\geq 0 \text{ in } \Omega, \end{cases} \tag{4.2}$$

with some $q > n$, it is possible to identify a smallness condition on $|\chi|$ that warrants global existence of a classical solution.

Theorem 4.1. (Ref. 28) *Let $n \geq 1$ and $\Omega \subset \mathbb{R}^n$ be a bounded domain with smooth boundary, and let $D_u > 0, D_v > 0, D_w > 0$ and $\lambda > 0$. Then for all u_0, v_0 and w_0 fulfilling* (4.2) *with some $q > n$, there exist $\chi_0 > 0$ with the property that whenever $\chi \in \mathbb{R}$ is such that*

$$|\chi| \leq \chi_0, \tag{4.3}$$

the problem (4.1) *possesses a globally defined classical solution which is non-negative in $\Omega \times (0, \infty)$ as well as uniformly bounded with respect to the norm in $L^\infty(\Omega) \times W^{1,q}(\Omega) \times L^\infty(\Omega)$ for all $t > 0$.*

Proof. The proof is based on a self-map argument.

(i) We start from the local existence: There exist $T_{\max} \in (0, \infty]$ and a uniquely determined triple of non-negative functions u, v and w such that (u, v, w) is a classical solution of (4.1) in $\Omega \times (0, T_{\max})$, and such that

$$\text{if } T_{\max} < \infty, \quad \text{then } \limsup_{t \nearrow T_{\max}} \{\|u(\cdot,t)\|_{L^\infty(\Omega)} + \|v(\cdot,t)\|_{W^{1,q}(\Omega)} + \|w(\cdot,t)\|_{L^\infty(\Omega)}\} = \infty. \tag{4.4}$$

(ii) Working on the second equation in (4.1) and invoking parabolic smoothing properties, we claim that there exists $K_1 > 0$ with the following property: If for some $\chi \in \mathbb{R}$, $M > 0$ and $N > 0$ there exists $T \in (0, T_{\max})$ such that the solution of (4.1) satisfies the following inequalities:

$$\|u(\cdot,t)\|_{L^\infty(\Omega)} \leq M \quad \text{and} \quad \|w(\cdot,t)\|_{L^\infty(\Omega)} \leq N \quad \text{for all } t \in (0,T), \tag{4.5}$$

then

$$\|\nabla v(\cdot,t)\|_{L^q(\Omega)} \leq K_1 \cdot (MN^\theta + 1) \quad \text{for all } t \in (0,T),$$
$$\text{with } \theta := \frac{q-1}{q} \in (0,1). \tag{4.6}$$

(iii) Again according to smoothing properties of the Neumann heat semigroup $(e^{\sigma\Delta})_{\sigma \geq 0}$, we infer from the third equation that the above estimate can be transformed into a corresponding pointwise upper inequality for w. More precisely, we have: One can find $K_2 > 0$ such that if $\chi \in \mathbb{R}, M > 0$ and $N > 0$ are such that (4.5) holds for the solution of (4.1) with some $T \in (0, T_{\max})$, then

$$\|w(\cdot,t)\|_{L^\infty(\Omega)} \leq K_2 \cdot (MN^\theta + 1) \quad \text{for all } t \in (0,T). \tag{4.7}$$

(iv) In the same manner as above, we can further conclude that there exists $K_3 > 0$ such that if $\chi \in \mathbb{R}, M > 0$ and $N > 0$ are such that (4.5) holds for the solution

of (4.1) with some $T \in (0, T_{\max})$, then

$$\|u(\cdot,t)\|_{L^\infty(\Omega)} \le K_3 \cdot \{(M^2 N^\theta + 1)|\chi| + 1\} \quad \text{for all } t \in (0,T). \tag{4.8}$$

(v) Closing the loop. Using the fact that $\theta < 1$ and invoking the estimates (4.7) and (4.8), by first choosing the number M suitably large and then N appropriately large and finally $\chi_0 >$ sufficiently small, we obtain that

$$\|u(\cdot,t)\|_{L^\infty(\Omega)} \le M \quad \text{and} \quad \|w(\cdot,t)\|_{L^\infty(\Omega)} \le N \quad \text{for all } t \in (0,T_{\max}). \tag{4.9}$$

This along with (4.6) and (4.4) implies that $T_{\max} = \infty$. □

Let us furthermore mention that by constructing genuine Lyapunov functionals for (4.1), it is possible to make sure that when $|\chi|$ is suitably small, the above global classical solution will stabilize either to the infection-free equilibrium $(\lambda, 0, 0)$ or to the coexistence state $(1, \lambda - 1, \lambda - 1)$, depending on whether $\lambda < 1$ or $\lambda > 1$.[28]

On the other hand, some numerical simulations documented in Refs. 28 and 237 indicate that the model (4.1) can indeed depict chemotaxis-induced aggregation of cells, in the form of blow-up, even for $\lambda < 1$, provided that $\chi > 0$ is suitably large. In order to suitably simplify (4.1) so as to become accessible to analytical approaches capable of investigating such singular structure formation in (4.1), we observe that the migration speed of cells is significantly enhanced upon infection, which is supported by the experimental findings reported in Ref. 306, according to which infected cells secrete some effector interacting with host proteins that regulate motility of cells, and thus this effector actually promotes motility of infected cells and accelerates the spread of infection. In light of this and classical parabolic–elliptic model limit procedures in Keller–Segel systems,[146,212] we shall perform a quasi-equilibrium approximation to the equation describing the evolution of infected cells in subsequently concentrating on the simplified parabolic–elliptic–parabolic version of (4.1) given by

$$\begin{cases} u_t = D_u \Delta u - \chi \nabla \cdot (u \nabla v) - u - uw + \lambda, & x \in \Omega,\ t > 0, \\ 0 = D_v \Delta v - v + uw, & x \in \Omega,\ t > 0, \\ w_t = D_w \Delta w - w + v, & x \in \Omega,\ t > 0, \\ \dfrac{\partial u}{\partial \nu} = \dfrac{\partial v}{\partial \nu} = \dfrac{\partial w}{\partial \nu} = 0, & x \in \partial\Omega,\ t > 0, \\ u(x,0) = u_0(x), \quad w(x,0) = w_0(x), & x \in \Omega, \end{cases} \tag{4.10}$$

in a ball $\Omega = B_R(0) \subset \mathbb{R}^n$ with $n \in \{2,3\}$ and $R > 0$. Here the initial data are assumed to satisfy

$$\begin{cases} u_0 \in C^0(\overline{\Omega}) & \text{is radially symmetric and non-negative,} \quad \text{and} \\ w_0 \in C^0(\overline{\Omega}) & \text{is radially symmetric and positive in } \overline{\Omega}. \end{cases} \tag{4.11}$$

Within this framework, the following result confirms that finite-time blow-up of solutions indeed occurs for some initial data, which indeed may be viewed as reflecting essential aspects of the hot-spot formation phenomena observed in Ref. 121.

Theorem 4.2. (Ref. 258) *Let $\Omega = B_R(0) \subset \mathbb{R}^n$ with $n \in \{2, 3\}$ and some $R > 0$, and suppose that $D_u > 0, D_v > 0, D_w > 0$ and $\lambda > 0$. Then given any radially symmetric and positive $w_0 \in C^0(\overline{\Omega})$, for each $m > 0$ one can find $r_\star = r_\star(m, w_0) \in (0, R)$ and $\chi_\star = \chi_\star(m, w_0) > 0$ such that whenever $\chi > \chi_\star$ and $u_0 \in C^0(\overline{\Omega})$ is a radially symmetric and non-negative function fulfilling*

$$\int_\Omega u_0 \leq m \tag{4.12}$$

and

$$\int_{B_{r_\star}(0)} u_0 \geq \frac{m}{2}, \tag{4.13}$$

the problem (4.10) *possesses a classical solution which blows up in finite time*; *more precisely*: *There exist $T \in (0, \infty)$ and uniquely determined non-negative functions u, v and w such that (u, v, w) solves* (4.10) *in the classical sense in $\Omega \times (0, T)$, but that*

$$\limsup_{t \nearrow T} \|u(\cdot, t)\|_{L^\infty(\Omega)} = \infty. \tag{4.14}$$

Proof. We only sketch the main steps.

(i) Let $T_{\max}$ denote the maximal time for the local existence, let $p \in (\frac{n}{2}, \frac{n}{n-2})$, and suppose that

$$\ell \leq w_0(x) \leq L \quad \text{for all } x \in \Omega, \tag{4.15}$$

with some positive parameters ℓ and L. Then there exist $t_\star = t_\star(m, L, p) > 0$ and $M = M(m, L, p) > 0$ with the property that whenever $\chi > 0$, we have

$$\int_\Omega u(\cdot, t) \leq 2m \quad \text{for all } t \in (0, \min\{t_\star, T_{\max}\}), \tag{4.16}$$

$$\frac{\ell}{2} \leq \|w(\cdot, t)\|_{L^\infty(\Omega)} \leq 2L \quad \text{for all } t \in (0, \min\{t_\star, T_{\max}\}), \tag{4.17}$$

$$\|v(\cdot, t)\|_{L^p(\Omega)} \leq M \quad \text{for all } t \in (0, \min\{t_\star, T_{\max}\}). \tag{4.18}$$

(ii) We introduce the mass accumulation function

$$z(s, t) := \frac{1}{n|B_1(0)|} \int_{B_{\sqrt[n]{s}}(0)} u(x, t)dx, \quad s \in [0, R^n], \quad t \in [0, T_{\max}) \tag{4.19}$$

and derive that

$$z_t = n^2 D_u s^{2-\frac{2}{n}} z_{ss} + \frac{\chi}{D_v|B_1(0)|} \cdot z_s \cdot \int_{B_{s^{1/n}}(0)} u(\cdot,t)w(\cdot,t) - \frac{\alpha\chi}{D_v|B_1(0)|} \cdot z_s \cdot \int_{B_{s^{1/n}}(0)} v(\cdot,t) + \frac{1}{n|B_1(0)|} \int_{B_{s^{1/n}}(0)} (\lambda - u(\cdot,t) - u(\cdot,t)w(\cdot,t)) \tag{4.20}$$

in $(0,R^n)\times(0,T_{\max})$.

(iii) Relying on (4.16)–(4.18), we suitably estimate the nonlocal contributions to (4.20) to obtain that for any given $\varepsilon>0$, there exist positive constants $t_{\star\star}=t_{\star\star}(m,\ell,L,\varepsilon)$, $\gamma_1=\gamma_1(\ell)$, $\gamma_2=\gamma_2(m,L,\varepsilon)$ and $\gamma_3=\gamma_3(L)$ such that the function z introduced in (4.19) satisfies

$$z_t \geq n^2 D_u s^{2-\frac{2}{n}} z_{ss} + \gamma_1\chi z z_s - \gamma_2\chi s^{\frac{2}{n}-\varepsilon} z_s - \gamma_3 z \tag{4.21}$$

in $(0,R^n)\times(0,\min\{t_{\star\star},T_{\max}\})$.

(iv) Let $\varepsilon\in(0,\frac{2}{n}]$, then a testing procedure on (4.21) results in that for any choice of $s_0\in(0,R^n)$,

$$\begin{aligned}\frac{d}{dt}\int_0^{s_0}(s_0-s)z(s,t)ds \geq\ & -2n(n-1)D_u\int_0^{s_0} s^{1-\frac{1}{n}} z(s,t)ds \\ & + \frac{\gamma_1\chi}{2}\int_0^{s_0} z^2(s,t)ds - \gamma_2\chi\int_0^{s_0} s^{\frac{2}{n}-\varepsilon} z(s,t)ds \\ & - \gamma_3\int_0^{s_0}(s_0-s)z(s,t)ds \end{aligned} \tag{4.22}$$

for all $t\in(0,\min\{t_{\star\star},T_{\max}\})$.

(v) Appropriate interpolation next turns (4.22) into the following quadratically forced autonomous ODI

$$\begin{aligned}\frac{d}{dt}\int_0^{s_0}(s_0-s)z(s,t)ds \geq\ & \Gamma_1\cdot\frac{\chi}{s_0^3}\cdot\left\{\int_0^{s_0}(s_0-s)z(s,t)ds\right\}^2 \\ & - \Gamma_2\cdot\int_0^{s_0}(s_0-s)z(s,t)ds \\ & - \Gamma_3\cdot\frac{s_0^{3-\frac{2}{n}}}{\chi} - \Gamma_4\cdot\chi\cdot s_0^{\frac{n+4}{n}-2\varepsilon}, \end{aligned} \tag{4.23}$$

valid with some positive constants $\Gamma_i, i\in\{1,2,3,4\}$, and for all $t\in(0,\min\{t_{\star\star\star},T_{\max}\})$ and any $s_0\in(0,R^n)$.

(vi) We are now in a position to claim the following: There exist $r_0=r_0(m,\ell,L)\in(0,R)$ and $\chi_0=\chi_0(m,\ell,L)>0$ with the property that if $\chi>\chi_0$, and if u_0

additionally satisfies

$$\int_{B_{r_0}(0)} u_0 \geq \frac{m}{2}, \tag{4.24}$$

then $T_{\max} < \infty$.

To verify this, firstly take s_0 small, then χ_0 large and finally $r_0 := (\frac{s_0}{2})^{\frac{1}{n}}$, then we necessarily have $T_{\max} \leq t_{\star\star}$.

In fact, assuming on the contrary that $T_{\max} > t_{\star\star}$ we would obtain from (4.23) that

$$y(t) := \int_0^{s_0} (s_0 - s) z(s,t) ds, \quad t \in [0, T_{\max}),$$

was well defined on $[0, t_{\star\star}]$ with

$$y'(t) \geq \frac{\Gamma_1 \chi}{s_0^3} y^2(t) - \Gamma_2 y(t) - \frac{\Gamma_3 s_0^{3-\frac{2}{n}}}{\chi} - \Gamma_4 \chi s_0^{\frac{n+4}{n}-2\varepsilon} \quad \text{for all } t \in (0, t_{\star\star}).$$

However, for the above choice of s_0, χ_0 and r_0, a careful analysis of this differential inequality will lead to the absurd conclusion that $t_{\star\star} \leq \frac{t_{\star\star}}{2}$ and thereby shows that actually we must indeed have had $T_{\max} \leq t_{\star\star}$. □

We remark that most available blow-up proofs for radial solutions to classical parabolic–elliptic Keller–Segel systems[38,146,195] quite strongly rely on fairly fragile structural properties of cross-diffusive interaction which most commonly disappear upon extending the model. In the above proof, this is reflected in the appearance of a nonlocal nonlinearity in the crucial destabilizing contribution to the parabolic equation (4.20).

An appropriate control of nonlocal terms seems to form a main challenge not only in the understanding of (4.1), but also in a corresponding blow-up analysis of more general classes of more complex extensions of Keller–Segel systems.

We finally mention that for some relatives of (4.1), involving certain regularizing mechanisms such as saturation in cross-diffusion or signal production, results on blow-up prevention for widely arbitrary initial data can be found in Refs. 32, 108, 144, 207 and 299.

4.2. *A haptotaxis model for oncolytic virotherapy*

Oncolytic virotherapy involves the use of genetically-engineered replication-competent viruses that selectively infect cancer cells, replicate inside them, and eventually cause their death; upon lysis of a tumor cell, lots of new viruses are released, and they continue to attack adjacent tumor cells. However, the efficacy of this novel therapy is restricted by physical barriers such as the extracellular matrix (ECM). In order to theoretically understand the interaction between uninfected cancer cells, infected cancer cells, extracellular matrix (ECM) and oncolytic virus, represented by population densities denoted by $u = u(x,t)$, $w = w(x,t)$, $v = v(x,t)$ and $z = z(x,t)$, respectively, Alzahrani *et al.* in Ref. 6 originally proposed the

following haptotaxis system:

$$\begin{cases} u_t = D_u\Delta u - \xi_u\nabla\cdot(u\nabla v) + \mu_u u(1-u) - \rho_u uz, & x\in\Omega,\ t>0,\\ v_t = -(\alpha_u u + \alpha_w w)v + \mu_v v(1-v), & x\in\Omega,\ t>0,\\ w_t = D_w\Delta w - \xi_w\nabla\cdot(w\nabla v) - \delta_w w + \rho_w uz, & x\in\Omega,\ t>0,\\ z_t = D_z\Delta z - \delta_z z - \rho_z uz + \beta w, & x\in\Omega,\ t>0,\\ (D_u\nabla u - \xi_u u\nabla v)\cdot\nu = (D_w\nabla w - \xi_w w\nabla v)\\ \quad\cdot\nu = \dfrac{\partial z}{\partial\nu} = 0, & x\in\partial\Omega,\ t>0,\\ u(x,0)=u_0(x),\quad v(x,0)=v_0(x),\\ w(x,0)=w_0(x),\quad z(x,0)=z_0(x), & x\in\Omega, \end{cases} \tag{4.25}$$

in a bounded domain $\Omega\subset\mathbb{R}^n$ with smooth boundary, where $D_u, D_w, D_z, \xi_u, \alpha_u$ and α_w are positive parameters and $\xi_w, \mu_u, \mu_v, \rho_u, \rho_w, \rho_z, \beta, \delta_w$ and δ_z are non-negative constants. In addition to apparent random motion and zero-order interaction terms, in (4.25) it is assumed that cancer cells can bias their movement toward regions of higher ECM densities. Besides possibly including two simultaneous haptotaxis processes, as its obviously most striking feature the model (4.25) includes the zero-order superlinear production term $\rho_w uz$, which seems to constitute a substantial difference to most of the haptotaxis systems that have been thoroughly studied in the literature,[177,244,296,321] and thus already issues from basic solvability theory become challenging. Our considerations in this regard will be based on the fundamental observation that the system (4.25) formerly enjoys an energy-like structure associated with the evolution of the functional

$$\begin{aligned}\mathcal{F}(t) := A\int_\Omega \{u(\cdot,t)\ln u(\cdot,t) - u(\cdot,t)\} + 2\int_\Omega |\nabla\sqrt{v(\cdot,t)}|^2\\ + B\int_\Omega \{w(\cdot,t)\ln w(\cdot,t) - w(\cdot,t)\} + \frac{1}{2}\int_\Omega z^2(\cdot,t), \quad t>0,\end{aligned}$$

with suitable $A>0$ and $B>0$, where it will turn out that through a correspondingly dissipated quantity due to virus diffusion, the last summand herein can be used to appropriately cope with the superlinear contribution induced by the presence of the crucial superlinear production term $\rho_w uz$ in (4.25) in low-dimensional settings. As a consequence, implying $L\log L$ estimates for both u and w will thereafter form a starting point for the derivation of higher regularity properties, and hence for the global extension of local-in-time solutions existing due to standard theory.

Indeed, under the assumption that

$$\begin{cases} u_0, v_0 \text{ and } w_0 \text{ are non-negative functions from } C^{2+\vartheta}(\overline{\Omega}) \text{ for some } \vartheta>0,\\ \text{with } u_0\not\equiv 0,\quad w_0\not\equiv 0,\quad z_0\not\equiv 0,\quad \sqrt{v_0}\in C^1(\overline{\Omega})\\ \text{and}\quad \dfrac{\partial u_0}{\partial\nu} = \dfrac{\partial v_0}{\partial\nu} = \dfrac{\partial w_0}{\partial\nu} = \dfrac{\partial z_0}{\partial\nu} = 0 \quad \text{on } \partial\Omega, \end{cases} \tag{4.26}$$

the following can be derived by pursuing this basic strategy.

Theorem 4.3. (Ref. 247) *Let $n \leq 2$ and $\Omega \subset \mathbb{R}^n$ be a bounded domain with smooth boundary, and suppose that*

$$D_u, D_w, D_z, \xi_u, \alpha_u \quad \text{and} \quad \alpha_w \text{ are positive,}$$

and that

$$\xi_w, \mu_u, \mu_v, \rho_u, \rho_w, \rho_z, \beta, \delta_w \quad \text{and} \quad \delta_z \text{ are non-negative,}$$

where

$$\rho_u + \rho_z > 0 \quad \text{if } \rho_w > 0.$$

Then for any choice of u_0, v_0, w_0 and z_0 fulfilling (4.26), *one can find $(u, v, w, z) \in (C^{2,1}(\overline{\Omega} \times [0, \infty)))^4$ such that u, w and z are positive and v is non-negative in $\overline{\Omega} \times (0, \infty)$, and that (u, v, w, z) solves* (4.25) *in the classical sense.*

We underline that by including the borderline case $\mu_u = 0$, Theorem 4.3 does not require the presence of a genuine quadratic degradation term in the first equation from (4.25). For a modified model in which also the fourth equation from (4.25) incorporates some haptotactic cross-diffusion, a result on global classical solvability in one-dimensional domains has been derived in Ref. 243; under the additional assumption that the first equation from (4.25) includes a super-quadratic type damping term or that the nonlinear infection term $\rho_w uz$ therein is replaced by the approximately linear Beddington–deAngelis type infection term, global existence and boundedness of classical solutions in a two-dimensional setting is asserted in Ref. 170.

Results on global solvability in three-dimensional versions of (4.25), partially within suitably generalized solution frameworks, have recently been obtained in Refs. 219 and 242. In order to further capture some qualitative properties of system (4.25), in the following we shall consider the prototypical version thereof given by

$$\begin{cases} u_t = \Delta u - \nabla \cdot (u \nabla v) - \rho uz, & x \in \Omega, \ t > 0, \\ v_t = -(u + w)v, & x \in \Omega, \ t > 0, \\ w_t = D_w \Delta w - w + uz, & x \in \Omega, \ t > 0, \\ z_t = D_z \Delta z - z - uz + \beta w, & x \in \Omega, \ t > 0, \\ (\nabla u - u \nabla v) \cdot \nu = \dfrac{\partial w}{\partial \nu} = \dfrac{\partial z}{\partial \nu} = 0, & x \in \partial\Omega, \ t > 0, \\ u(x, 0) = u_0(x), \quad v(x, 0) = v_0(x), & \\ w(x, 0) = w_0(x), \quad z(x, 0) = z_0(x), & x \in \Omega, \end{cases} \tag{4.27}$$

in a smoothly bounded domain $\Omega \subset \mathbb{R}^2$, with positive parameters β, D_w and D_z, and with a given number $\rho \geq 0$. Theorem 4.3 clearly rules out any occurrence of explosions within finite time. As for the possibility of infinite-time blow-up, however, it will turn out that at least in the simple case when $\rho = 0$, there exists a genuine critical mass phenomenon. To describe this in more detail, we first make sure that

whenever the virus replication rate satisfies $\beta > 1$, for all initial distributions with the total mass in their first component exceeding a certain value, the corresponding solution must become unbounded in the large time limit. This is reflected in the following statement in which, as throughout the sequel, for $\varphi \in L^1(\Omega)$ we abbreviate $\overline{\varphi} := \frac{1}{|\Omega|}\int_\Omega \varphi$.

Theorem 4.4. (Ref. 248) *Assume that $\rho = 0$. Let $\Omega \subset \mathbb{R}^2$ be a bounded domain with smooth boundary, let $\beta > 1$, and suppose that u_0, v_0, w_0 and z_0 satisfy* (4.26) *with*

$$\overline{u_0} > \frac{1}{\beta - 1}. \tag{4.28}$$

Then the global classical solution $(u, v, w, z) \in (C^{2,1}(\overline{\Omega} \times [0, \infty)))^4$ of (4.27) *from Theorem* 4.3 *above satisfies*

$$\limsup_{t\to\infty}\{\|u(\cdot,t)\|_{L^\infty(\Omega)} + \|w(\cdot,t)\|_{L^\infty(\Omega)} + \|z(\cdot,t)\|_{L^\infty(\Omega)}\} = \infty. \tag{4.29}$$

Proof. The proof is based on a contradiction argument by supposing, to the contrary, that

$$\sup_{t>0}\{\|u(\cdot,t)\|_{L^\infty(\Omega)} + \|w(\cdot,t)\|_{L^\infty(\Omega)} + \|z(\cdot,t)\|_{L^\infty(\Omega)}\} < \infty, \tag{4.30}$$

and then it proceeds in six main steps.

(i) Under the change of variables determined by

$$a := ue^{-v}, \tag{4.31}$$

we obtain equivalence of (4.27) to

$$\begin{cases} a_t = e^{-v}\nabla\cdot(e^v\nabla a) + a(ae^v + w)v, & x \in \Omega,\ \ t > 0, \\ \dfrac{\partial a}{\partial \nu} = 0, & x \in \partial\Omega,\ \ t > 0, \\ a(x,0) = u_0(x)e^{-v_0(x)}, & x \in \Omega, \end{cases} \tag{4.32}$$

coupled to the respective sub-problem for (v, w, z). An application of a standard testing procedure leads to

$$\int_0^\infty \int_\Omega |\nabla a|^2 < \infty \tag{4.33}$$

and

$$\int_0^\infty \|a(\cdot,t) - \overline{a(\cdot,t)}\|^2_{L^2(\Omega)}dt < \infty. \tag{4.34}$$

(ii) In order to improve the above very weak decay information, we employ a second testing procedure by multiplying the first equation in (4.32) by $e^v a_t$ to

infer that

$$\int_0^\infty \int_\Omega a_t^2 < \infty \tag{4.35}$$

and

$$\sup_{t>0} \int_\Omega |\nabla a(\cdot,t)|^2 < \infty. \tag{4.36}$$

(iii) By means of a compactness argument we then assert that

$$a(\cdot,t) - \overline{a(\cdot,t)} \to 0 \quad \text{in } L^2(\Omega) \quad \text{as } t \to \infty. \tag{4.37}$$

(iv) Using (4.37) we next deduce that

$$v(\cdot,t) \to 0 \quad \text{in } L^1(\Omega) \quad \text{as } t \to \infty. \tag{4.38}$$

(v) Combining (4.37), (4.38) with (4.31) we obtain that

$$u(\cdot,t) \to \overline{u_0} \quad \text{in } L^1(\Omega) \quad \text{as } t \to \infty. \tag{4.39}$$

(vi) Relying on (4.39), we finally show that there exist $b > 0, t_0 > 0$ and $C > 0$ such that

$$\frac{d}{dt}\left\{\int_\Omega \ln w + b\int_\Omega \ln z\right\} \geq C \quad \text{for all } t > t_0, \tag{4.40}$$

which implies

$$\int_\Omega \ln w(\cdot,t) + b\int_\Omega \ln z(\cdot,t) \to \infty \quad \text{as } t \to \infty.$$

This contradicts the boundedness properties of w and z particularly assumed in (4.30). □

To confirm that the mass level appearing in (4.28) indeed is critical with regard to the unboundedness feature in Theorem 4.4, based on the use of comparison arguments globally bounded classical solutions (u, v, w, z) of (4.27) were constructed in Ref. 248 whenever $\rho = 0$, $v_0 \equiv 0$ and

$$\overline{u_0} \equiv \frac{1}{|\Omega|}\int_\Omega u_0 < \frac{1}{(\beta-1)_+}. \tag{4.41}$$

The above results indicate that the virus production rate β plays a crucial role in determining the behavior of solutions. In fact, the following result reveals that whenever $\beta < 1$, the population density of uninfected tumor cells has a pointwise lower bound.

Theorem 4.5. (Ref. 251) *Let $\Omega \subset \mathbb{R}^2$ be a bounded domain with smooth boundary, let $\rho \geq 0$, and suppose that*

$$\beta \in (0,1). \tag{4.42}$$

Then there exists $C = C(\beta, \Omega) > 0$ *with the property that whenever* u_0, v_0, w_0 *and* z_0 *satisfy* (4.26), *for the solution of* (4.27) *we have*

$$u(x,t) \geq \big\{ \inf_{y\in\Omega} u_0(y)\big\} \cdot \exp\{-\|v_0\|_{L^\infty(\Omega)} - C\|w_0\|_{L^2(\Omega)} - C\|z_0\|_{L^\infty(\Omega)}\big\} \tag{4.43}$$

for all $x \in \Omega$ *and* $t > 0$.

Proof. We again only outline the main ideas.

(i) Using the key assumption (4.42), we integrate the third and fourth equations in (4.27) over Ω to obtain

$$\int_\Omega w(\cdot,t) \leq \left\{ \int_\Omega w_0 + \int_\Omega z_0 \right\} \cdot e^{-(1-\beta)t} \quad \text{for all } t > 0 \tag{4.44}$$

and

$$\int_\Omega z(\cdot,t) \leq \left\{ \int_\Omega w_0 + \int_\Omega z_0 \right\} \cdot e^{-(1-\beta)t} \quad \text{for all } t > 0. \tag{4.45}$$

(ii) For suitable $b > 0$, the functional

$$\mathcal{F}(t) := \frac{1}{2}\int_\Omega w^2(\cdot,t) + \int_\Omega w(\cdot,t)z(\cdot,t) + \frac{b}{2}\int_\Omega z^2(\cdot,t), \quad t \geq 0, \tag{4.46}$$

satisfies

$$\mathcal{F}'(t) + \mathcal{F}(t) \leq c_1 \cdot \left\{ \int_\Omega w(\cdot,t) \right\}^2 \quad \text{for all } t > 0 \tag{4.47}$$

with some $c_1 > 0$.

(iii) From (i) and (ii) we infer that

$$\|w(\cdot,t)\|_{L^2(\Omega)} \leq C \cdot \{\|w_0\|_{L^2(\Omega)} + \|z_0\|_{L^2(\Omega)}\} \cdot e^{-\gamma t} \quad \text{for all } t > 0 \tag{4.48}$$

with some $\gamma > 0$.

(iv) Using (4.48) and in view of well-known parabolic smoothing properties we see that

$$\|z(\cdot,t)\|_{L^\infty(\Omega)} \leq C \cdot \{\|w_0\|_{L^2(\Omega)} + \|z_0\|_{L^\infty(\Omega)}\} \cdot e^{-\gamma t} \quad \text{for all } t > 0. \tag{4.49}$$

(v) Again, employing the variable transformation

$$a(x,t) := u(x,t)e^{-v(x,t)}, \quad x \in \overline{\Omega}, \ \ t \geq 0,$$

we see that

$$a_t = e^{-v}\nabla \cdot (e^v \nabla a) - a v_t - \rho a z \quad \text{for all } x \in \Omega \quad \text{and} \quad t > 0.$$

Working on this equation and relying on (4.49), we can construct an appropriate subsolution and finally we obtain

$$u(x,t) \geq \inf_{y\in\Omega}\{u_0(y)e^{-v_0(y)}\} \cdot \exp\{-C \cdot \{\|w_0\|_{L^2(\Omega)} + \|z_0\|_{L^\infty(\Omega)}\}\} \qquad (4.50)$$

for all $x \in \Omega$ and $t > 0$. □

Under the additional assumption that $u_0 > 0$, (4.43) ensures the existence of some $C > 0$ such that

$$u(x,t) \geq C \quad \text{for all } x \in \Omega \quad \text{and} \quad t > 0,$$

which in turn entails that

$$v(\cdot,t) \to 0 \quad \text{in } L^\infty(\Omega) \quad \text{as } t \to \infty.$$

Using this information as a starting point, upon employing a bootstrap argument we can obtain the following.

Theorem 4.6. (Ref. 249) *Let $\Omega \subset \mathbb{R}^2$ be a bounded domain with smooth boundary, let $\rho \geq 0$, and let*

$$\beta \in (0,1).$$

Then for any choice of (u_0, v_0, w_0, z_0) fulfilling (4.26) with $u_0 > 0$, the solution (u, v, w, z) of (4.27) is bounded in the sense that

$$\sup_{t>0}\{\|u(\cdot,t)\|_{L^\infty(\Omega)} + \|v(\cdot,t)\|_{L^\infty(\Omega)} + \|w(\cdot,t)\|_{L^\infty(\Omega)} + \|z(\cdot,t)\|_{L^\infty(\Omega)}\} < \infty,$$

and apart from that there exists $u_\infty > 0$ such that

$$u(\cdot,t) \to u_\infty \quad \text{in } L^p(\Omega) \quad \text{for all } p \geq 1$$

as well as

$$(v(\cdot,t), w(\cdot,t), z(\cdot,t)) \to (0,0,0) \quad \text{in } (L^\infty(\Omega))^3 \quad \text{as } t \to \infty.$$

In the case $\beta > 1$, the dynamical features of (4.27) seem only partially explored in any planar domain. In fact, it remains an open question whether the solution must be unbounded for large initial data if (4.28) holds in the case $\rho > 0$. After all, the less ambitious question whether one can find at least *some* nontrivial bounded solution in the presence of such supercritical virus production rates can be answered in the affirmative. By designing a suitably arranged self-map type reasoning, which presupposes a certain assumption on smallness and decay of z within an appropriate time interval, it is possible to make sure that z will maintain such a property on the whole time interval, thus implying the following.

Theorem 4.7. (Ref. 250) *Let $\Omega \subset \mathbb{R}^2$ be a bounded domain with smooth boundary, and let $\beta > 0$ and $\gamma \in (0, \frac{1}{(\beta-1)_+})$. Then for each $M > 0$ one can find*

$\varepsilon = \varepsilon(\beta, \gamma, M) > 0$ with the property that whenever $\rho \geq 0$ and u_0, v_0, w_0 and z_0 are such that (4.26) *holds and that*

$$\|u_0 - \gamma\|_{L^\infty(\Omega)} < \varepsilon \quad \textit{and} \quad \|v_0\|_{L^\infty(\Omega)} < \varepsilon$$

as well as

$$\|w_0\|_{L^\infty(\Omega)} < \min\left\{\frac{\varepsilon}{\rho}, M\right\} \quad \textit{and} \quad \|z_0\|_{L^\infty(\Omega)} < \min\left\{\frac{\varepsilon}{\rho}, M\right\},$$

there exists $u_\infty > 0$ such that solution of (4.27) *satisfies*

$$(u(\cdot,t), v(\cdot,t), w(\cdot,t), z(\cdot,t)) \to (u_\infty, 0, 0, 0) \quad \textit{in } (L^\infty(\Omega))^4 \quad \textit{as } t \to \infty.$$

Moreover, in the particular case when $\rho = 0$ we have $u_\infty = \overline{u_0}$, so that for any $\gamma \in (0, \frac{1}{(\beta-1)_+})$ the corresponding steady state solution $(\gamma, 0, 0, 0)$ of (4.27) *is asymptotically stable with respect to the norm in $(L^\infty(\Omega))^4$ in the above sense.*

Before closing this subsection we note that the author in Ref. 76 discussed the boundedness and stabilization of smooth solutions to a variant of (4.27) with an additional quadratic damping term in the first equation.

4.3. *Cross-diffusion models for criminal behavior*

As already addressed in Sec. 3, in order to describe the spatio-temporal evolution of urban crime let us consider the taxis-type cross-diffusion system given by

$$\begin{cases} u_t = \Delta u - \chi \nabla \cdot \left(\dfrac{u}{v} \nabla v\right) - uv + B_1(x,t), \\ v_t = \Delta v - v + uv + B_2(x,t), \end{cases} \tag{4.51}$$

with the positive parameter χ and with given source functions B_1 and B_2; for the particular value $\chi = 2$, this precisely coincides with the model proposed in Refs. 230 and 231, where $u(x,t)$ stands for the density of criminal agents and $v(x,t)$ the attractiveness value. Comprehensive studies on related stationary systems[36,58,120,161,192,264] strongly support the conjecture that systems of this form should be capable of generating spatially structured behavior, and to thereby adequately describe the formation of crime hotspots encountered in reality. Mathematically, the coupling of singular chemotaxis sensitivities with the additional zero-order nonlinearities uv forms a main obstacle in qualitative analysis of the full evolution system (4.51), even in low-dimensional situations. Accordingly, we will first concentrate on the spatially one-dimensional version of system (4.51) and under mild assumptions on χ, B_1 and B_2, and thus we shall first consider the initial-boundary value problem

$$\begin{cases} u_t = \Delta u - \chi \nabla \cdot \left(\dfrac{u}{v} \nabla v\right) - uv + B_1(x,t), & x \in \Omega, \ t > 0, \\ v_t = \Delta v - v + uv + B_2(x,t), & x \in \Omega, \ t > 0, \\ u_x = v_x = 0, & x \in \partial\Omega, \ t > 0, \\ u(x,0) = u_0(x), \quad v(x,0) = v_0(x), & x \in \Omega \end{cases} \tag{4.52}$$

in a bounded open interval $\Omega \subset \mathbb{R}$. Moreover, throughout this subsection we assume that

$$\begin{cases} B_1 \quad \text{and} \quad B_2 \text{ are non-negative and bounded functions} \\ \text{belonging to } C^{\vartheta}(\overline{\Omega} \times [0,\infty)) \text{ for some } \vartheta \in (0,1), \end{cases} \tag{4.53}$$

and that

$$\begin{cases} u_0 \in C^0(\overline{\Omega}) \quad \text{is non-negative, and that} \\ v_0 \in W^{1,\infty}(\Omega) \quad \text{is positive in } \overline{\Omega}. \end{cases} \tag{4.54}$$

In this general framework, more comprehensive than that addressed in a precedent one-dimensional study,[272] for arbitrary $\chi > 0$ the problem (4.52)–(4.54) is globally solvable in the classical sense.

Theorem 4.8. (Ref. 223) (a) *Let $\chi > 0$ and let B_1 and B_2 satisfy* (4.53). *Then for any given u_0 and v_0 fulfilling* (4.54), *the problem* (4.52) *admits a global classical solution (u, v) which for each $r > 1$ is uniquely determined by the inclusions*

$$\begin{cases} u \in C^0(\overline{\Omega} \times [0,\infty)) \cap C^{2,1}(\overline{\Omega} \times (0,\infty)), \\ v \in C^0([0,\infty); W^{1,r}(\Omega)) \cap C^{2,1}(\overline{\Omega} \times (0,\infty)), \end{cases} \tag{4.55}$$

and which is such that $u, v > 0$ in $\overline{\Omega} \times [0,\infty)$.

(b) *Under the additional assumption that*

$$\inf_{t>0} \int_{\Omega} B_2(x,t)dx > 0, \tag{4.56}$$

there exists $C > 0$ such that the solution (u, v) satisfies

$$u(x,t) \le C \quad \textit{for all } x \in \Omega \quad \textit{and} \quad t > 0, \tag{4.57}$$

and

$$\frac{1}{C} \le v(x,t) \le C \quad \textit{for all } x \in \Omega \quad \textit{and} \quad t > 0. \tag{4.58}$$

Proof. (i) The local solution can readily be constructed in $\Omega \times (0, T_{\max})$, with $T_{\max} \in (0,\infty]$ having the property that

either $T_{\max} < \infty$, or for all $r > 1$

$$\limsup_{t \nearrow T_{\max}} \left\{ \|u(\cdot,t)\|_{L^\infty(\Omega)} + \left\| \frac{1}{v(\cdot,t)} \right\|_{L^\infty(\Omega)} + \|v_x(\cdot,t)\|_{L^r(\Omega)} \right\} = \infty. \tag{4.59}$$

Moreover, for any given $T \in (0, T_{\max})$ there exists $c_1(T) > 0$ satisfying

$$\int_{\Omega} u(x,t) \le c_1(T) \quad \text{for all } x \in \Omega \quad \text{and} \quad t \in (0,T) \tag{4.60}$$

and

$$\int_{\Omega} v(x,t) \le c_1(T) \quad \text{for all } x \in \Omega \quad \text{and} \quad t \in (0,T). \tag{4.61}$$

(ii) A well-known pointwise positivity property of the Neumann heat semigroup $(e^{t\Delta})_{t\geq 0}$ on the bounded real interval yields the existence of $c_2(T) > 0$ such that

$$v(x,t) \geq c_2(T) \quad \text{for all } x \in \Omega \quad \text{and} \quad t \in (0,T). \tag{4.62}$$

(iii) A simple testing procedure along with (4.61) shows that for any $q \in (0,1)$, there holds

$$\int_t^{t+\tau} \int_\Omega v^{q-2} v_x^2 \leq c_3(T) \quad \text{for all } t \in (0, T-\tau)$$

with some $c_3(T) > 0$, where $\tau := \min\{1, \frac{1}{3}T_{\max}\}$. This along with an interpolation results in the existence of $c_4(T) > 0$ such that given $r \in (1,3)$, we have

$$\int_t^{t+\tau} \int_\Omega v^r \leq c_4(T) \quad \text{for all } t \in (0, T-\tau). \tag{4.63}$$

(iv) On the basis of (4.52) and in view of (4.63), a delicate analysis of the key functional $\int_\Omega u^p v^q$ leads to the following fundamental estimate:

Let $p \in (0,1)$ be such that $p < \frac{1}{\chi^2}$ and suppose that $q \in (q^-(p), q^+(p))$ with

$$q^\pm(p) := \frac{1-p}{2}(1 \pm \sqrt{1-p\chi^2}), \tag{4.64}$$

then we have

$$\int_t^{t+\tau} \int_\Omega u^{p-2} v^q u_x^2 \leq c_5(T) \quad \text{for all } t \in (0, T-\tau) \tag{4.65}$$

and

$$\int_t^{t+\tau} \int_\Omega u^p v^{q-2} v_x^2 \leq c_5(T) \quad \text{for all } t \in (0, T-\tau) \tag{4.66}$$

with some $c_5(T) > 0$.

(v) An interpolation in conjunction with (4.62), (4.60) and (4.65) entails the existence of $c_6(T) > 0$ with the property that for $p \in (0,1)$ satisfying $p < \frac{1}{\chi^2}$, we obtain

$$\int_t^{t+\tau} \int_\Omega u^{p+2} \leq c_6(T) \quad \text{for all } t \in (0, T-\tau). \tag{4.67}$$

(vi) Using known smoothing properties of the Neumann heat semigroup and invoking (4.67) to deal with the nonlinear production $+uv$ in (4.52), we see that let $r \in (1, \frac{3}{2})$ be such that $r < 1 + \frac{1}{2\chi^2}$, then we have

$$\|v_x(\cdot,t)\|_{L^r(\Omega)} \leq c_7(T) \quad \text{for all } t \in (0,T) \tag{4.68}$$

with some $c_7(T) > 0$.

(vii) In light of (4.68) and (4.62) and regularization estimates for the heat equation, we have the following: Let $\gamma \in (0, \frac{1}{3})$ be such that $\gamma < \frac{1}{1+2\chi^2}$, then we have

$$\|u(\cdot,t)\|_{C^\gamma(\overline{\Omega})} \leq c_8(T) \quad \text{for all } t \in (0,T) \tag{4.69}$$

with some $c_8(T) > 0$. This along with (4.68) and (4.62) proves (i).

Under the additional assumption (4.56), the above bounds $c_i(T)$ $(i = 1, \dots, 8)$ can actually be refined to be independent of T, and thereby also the assertion in (b) can be obtained. □

Beyond this basic statement, the approach described above can be further developed so as to additionally provide information on the qualitative behavior of the obtained solutions in cases when the external sources B_1 and B_2 undergo certain types of stabilization. In fact, whenever χ belongs to a suitable range including the physical case $\chi = 2$, the large time behavior of the solution constructed in (i) of Theorem 4.8 can be described quite comprehensively.

Theorem 4.9. (Ref. 223) *Let* $\chi \in (0, \frac{\sqrt{6\sqrt{3}+9}}{2})$, *and suppose that* B_1 *and* B_2 *are such that beyond* (4.53), *we also have*

$$\int_0^\infty \int_\Omega B_1 < \infty \tag{4.70}$$

and

$$B_2(\cdot, t) \to B_{2,\infty} \quad a.e.\ in\ \Omega \quad as\ t \to \infty, \tag{4.71}$$

with some $0 \not\equiv B_{2,\infty} \in L^1(\Omega)$. *Then for each* u_0 *and* v_0 *satisfying* (4.54), *the corresponding solution* (u, v) *of* (4.52) *has the properties that*

$$u(\cdot, t) \to 0 \quad in\ L^\infty(\Omega) \quad as\ t \to \infty, \tag{4.72}$$

and

$$v(\cdot, t) \to v_\infty \quad in\ L^\infty(\Omega) \quad as\ t \to \infty, \tag{4.73}$$

where v_∞ *denotes the solution to the boundary value problem*

$$\begin{cases} -\partial_{xx} v_\infty + v_\infty = B_{2,\infty}, & x \in \Omega, \\ \partial_x v_\infty = 0 & x \in \partial\Omega. \end{cases} \tag{4.74}$$

Proof. Under the assumptions (4.70) and (4.71), one readily verifies (4.72). However, the proof of the convergence for the solution component v is quite technical. The main ideas can be outlined as follows.

(i) Using the assumptions (4.70) and (4.71), we firstly improve the estimates (4.65) and (4.66) to obtain $c_1 > 0$ such that

$$\int_t^{t+1} \int_\Omega u^{p-2} v^q u_x^2 \le c_1 \quad \text{and} \quad \int_t^{t+1} \int_\Omega u^p v^{q-2} v_x^2 \le c_1 \quad \text{for all } t > 0,$$

which implies the existence of $c_2 > 0$ satisfying

$$\int_t^{t+1} \int_\Omega \left[\left(u^{\frac{p}{2}} v^{\frac{q}{2}} \right)_x \right]^2 \le c_2 \quad \text{for all } t > 0. \tag{4.75}$$

(ii) Relying on (4.75), we can achieve the following crucial estimate:
Suppose that there exists $r_\star \geq 1$ such that

$$\sup_{t>0} \int_\Omega v^{r_\star}(\cdot,t) < \infty, \tag{4.76}$$

let $p \in (0,1)$ be such that $p < \frac{1}{\chi^2}$, and with $q^{\pm}(p)$ defined in (4.64) let $q \in (q^-(p), q^+(p))$ satisfies

$$\frac{q}{p} \leq \frac{p+1}{1-p} \cdot r_\star, \tag{4.77}$$

then there exists $c_3 > 0$ such that

$$\int_t^{t+1} \int_\Omega u v^{\frac{q}{p}} \leq c_3 \quad \text{for all } t > 0. \tag{4.78}$$

Writing $r := \frac{q}{p}$, this along with the fact that

$$\frac{1}{r}\frac{d}{dt}\int_\Omega v^r + (r-1)\int_\Omega v^{r-2} v_x^2 + \int_\Omega v^r = \int_\Omega u v^r + \int_\Omega B_2 v^{r-1} \quad \text{for all } t > 0$$

yields

$$\int_\Omega v^{\frac{q}{p}}(\cdot,t) \leq c_4 \quad \text{for all } t > 0 \tag{4.79}$$

with some $c_4 > 0$.

(iii) Based on a recursive argument connecting (4.76)–(4.79), we can find that when $\chi \in (0, \frac{\sqrt{6\sqrt{3}+9}}{2})$, there exist $c_5 > 0$ and an increasing real number sequence $(r_k)_{k\in\mathbb{N}}$ with $r_k \to +\infty$ such that

$$\int_\Omega v^{r_k}(\cdot,t) \leq c_5 \quad \text{for all } t > 0. \tag{4.80}$$

(iv) It is easily checked that the assumption (4.70) warrants that $\int_0^\infty \int_\Omega uv < \infty$ and hence

$$\int_t^{t+1} \int_\Omega uv \to 0 \quad \text{as } t \to \infty. \tag{4.81}$$

In conjunction with (4.75), (4.80) and the Gagliardo–Nirenberg inequality, this reveals that when $\chi \in (0, \frac{\sqrt{6\sqrt{3}+9}}{2})$, for all $p \in (0, \frac{1}{3})$ with $p < \frac{1}{\chi^2}$, we have

$$\int_t^{t+1} \int_\Omega (uv)^{p+2} \to 0 \quad \text{as } t \to \infty. \tag{4.82}$$

Relying on this, we can further derive the Hölder regularity of v; namely, there exist $\gamma \in (0,1)$ and $c_6 > 0$ such that

$$\|v(\cdot,t)\|_{C^\gamma(\overline{\Omega})} \leq c_6 \quad \text{for all } t > 1. \tag{4.83}$$

(v) Thanks to (4.83) and the assumption (4.71), by means of a straightforward testing process it can be shown that

$$v(\cdot,t) \to v_\infty \quad \text{in } L^2(\Omega) \quad \text{as } t \to \infty. \tag{4.84}$$

Together with (4.83), through a compactness-based argument this entails (4.73). □

In corresponding multi-dimensional settings, available results seem rather limited so far: In Ref. 291, certain renormalized solutions are constructed in two-dimensional radially symmetric frameworks; findings on global classical solvability in two-dimensional domains so far rely on the condition $\chi < 1$,[107] or on suitable smallness assumptions on $B_1, \nabla\sqrt{B_2}, u_0$ and $\nabla\sqrt{v_0}$ as well as certain positivity requirements on B_2 and v_0.[252] A result on generalized solvability in a variant of (4.51) involving logistic-type growth limitations has been derived in Ref. 128, and a further study has shown that suitably strong porous medium-type diffusion enhancement can enforce boundedness of solutions.[222]

A very interesting alternative approach has very recently been developed in Ref. 1, where by means of a comparison-based argument a result on boundedness in a fairly general class of taxis-type cross-diffusion systems involving singular sensitivities such as in (4.51) is derived, and where, as particular consequences, global boundedness in variants of (4.51) accounting for certain saturated signal production mechanisms has been obtained even in domains of arbitrary dimension.

4.4. *Pursuit-evasion interaction*

To describe pursuit-evasion dynamics, e.g. in contexts of predator–prey systems, the authors in Ref. 265 proposed the doubly tactic cross-diffusion system

$$\begin{cases} u_t = D_1\Delta u - \chi_1\nabla\cdot(u\nabla v) + f(u,v), \\ v_t = D_2\Delta v + \chi_2\nabla\cdot(v\nabla u) + g(u,v), \end{cases} \tag{4.85}$$

with positive parameters D_1, D_2, χ_1, χ_2 and local kinetics functions f and g, and with $u = u(x,t)$ and $v = v(x,t)$ representing the population densities of predators and preys, respectively. Numerical simulations and formal linearized analysis in Ref. 265 and in closely-related literature[119,268,308] indicate that the simultaneous presence of two taxis terms may have considerable effects on solution behavior, e.g. by generating new types of propagating waves.

Unlike in cases of triangular cross-diffusive chemotaxis systems, such as those discussed in previous sections, the use of scalar parabolic techniques seems rather limited for the analysis of (4.85). In order to nevertheless create an analytical approach capable of establishing a basic theory of global solvability and of addressing some aspects of qualitative behavior, we first focus on the simplest

version of (4.85) which yet captures the most essential features of (4.85), and hence consider the one-dimensional initial-boundary value problem

$$\begin{cases} u_t = D_1 u_{xx} - \chi_1 (u v_x)_x, & x \in \Omega, \ \ t > 0, \\ v_t = D_2 v_{xx} + \chi_2 (v u_x)_x, & x \in \Omega, \ \ t > 0, \\ u_x = v_x = 0, & x \in \partial\Omega, \ \ t > 0, \\ u(x,0) = u_0(x), \quad v(x,0) = v_0(x), & x \in \Omega, \end{cases} \tag{4.86}$$

in an open bounded interval $\Omega \subset \mathbb{R}$, where D_1, D_1, χ_1 and χ_2 are positive parameters.

Within an appropriately generalized framework of solvability, we plan to construct global solutions to (4.86) through a suitable approximation procedure. Here the ambition to retain some crucial system-inherent structural properties of (4.86) (cf. the discussion below) also at the approximate level brings about several constraints, the simultaneous fulfillment of which seems widely impossible in contexts of straightforward regularization approaches such as those pursued in numerous related taxis-type problems of triangular type. Our strategy will therefore be built on the use of a fourth-order approximation, at its core involving artificial thin-film type degenerate operators in order to preserve nonnegativity. To describe this essential part of our approach in more detail, and to formulate our main results obtained on the basis thereof, with parameters $n > 0, m \in (0,n), \alpha > 0$ and $\beta > 0$ to be specified below and for $\varepsilon \in (0,1)$, let us consider the regularized versions of (4.86) given by

$$\begin{cases} u_{\varepsilon t} = -\varepsilon \left(\dfrac{u_\varepsilon^n}{u_\varepsilon^{n-m} + \varepsilon} u_{\varepsilon xxx} \right)_x + \varepsilon^\beta (u_\varepsilon^{-\alpha} u_{\varepsilon x})_x + D_1 u_{\varepsilon xx} \\ \qquad - \chi_1 \left(\dfrac{u_\varepsilon^{n-m+1}}{u_\varepsilon^{n-m} + \varepsilon} v_{\varepsilon x} \right)_x, & x \in \Omega, \ \ t > 0, \\ v_{\varepsilon t} = -\varepsilon \left(\dfrac{v_\varepsilon^n}{v_\varepsilon^{n-m} + \varepsilon} v_{\varepsilon xxx} \right)_x + \varepsilon^\beta (v_\varepsilon^{-\alpha} v_{\varepsilon x})_x + D_2 v_{\varepsilon xx} \\ \qquad + \chi_2 \left(\dfrac{v_\varepsilon^{n-m+1}}{v_\varepsilon^{n-m} + \varepsilon} u_{\varepsilon x} \right)_x, & x \in \Omega, \ \ t > 0, \\ u_{\varepsilon x} = u_{\varepsilon xxx} = v_{\varepsilon x} = v_{\varepsilon xxx} = 0, & x \in \partial\Omega, \ \ t > 0, \\ u_\varepsilon(x,0) = u_{0\varepsilon}(x), \quad v_\varepsilon(x,0) = v_{0\varepsilon}(x), & x \in \Omega, \end{cases} \tag{4.87}$$

where the second-order diffusion operators of fast-diffusion type will be used to control some ill-signed contributions which due to the presence of the fourth-order thin-film-like diffusion arise in the justification of entropy inequalities at approximate levels. As for the initial data used herein, given $\{u_0, v_0\} \subset W^{1,2}(\Omega)$ such that

$u_0 > 0$ and $v_0 > 0$ in $\overline{\Omega}$, we fix families $(u_{0\varepsilon})_{\varepsilon\in(0,1)}$ and $(v_{0\varepsilon})_{\varepsilon\in(0,1)}$ such that

$$\begin{cases} u_{0\varepsilon} \in C^5(\overline{\Omega}) \text{ and } v_{0\varepsilon} \in C^5(\overline{\Omega}) \text{ satisfy } u_{0\varepsilon} > 0 \text{ and } v_{0\varepsilon} > 0 \text{ in } \overline{\Omega} \text{ for all } \varepsilon \in (0,1) \\ \text{and } u_{0\varepsilon x} = u_{0\varepsilon xxx} = v_{0\varepsilon x} = v_{0\varepsilon xxx} = 0 \text{ on } \partial\Omega \text{ for all } \varepsilon \in (0,1), \text{ that} \\ \displaystyle\int_\Omega u_{0\varepsilon} = \int_\Omega u_0 \quad \text{and} \quad \int_\Omega v_{0\varepsilon} = \int_\Omega v_0 \quad \text{for all } \varepsilon \in (0,1), \quad \text{and that} \\ u_{0\varepsilon} \to u_0 \text{ and } v_{0\varepsilon} \to v_0 \text{ in } W^{1,2}(\Omega) \text{ as } \varepsilon \searrow 0, \end{cases} \tag{4.88}$$

and as shown in Ref. 259, each of the problems (4.87) then indeed admits globally defined smooth solutions for which u_ε and v_ε are positive in $\overline{\Omega} \times [0,\infty))$.

Now a first requirement to be adequately coped with stems from the observation that, formally, smooth positive solutions to (4.86) enjoy the Lyapunov-type inequality

$$\frac{d}{dt}\left\{\chi_2 \int_\Omega u\ln u + \chi_1 \int_\Omega v \ln v\right\} + \chi_2 D_1 \int_\Omega \frac{u_x^2}{u} + \chi_1 D_2 \int_\Omega \frac{v_x^2}{v} = 0. \tag{4.89}$$

Here a crucial question in the course of our existence analysis for (4.86) will be how far the approximation given as (4.87) is consistent with the above identity. Fortunately, under suitable restrictions on m, n, α and β, this property can be adequately retained by the approximation.

Lemma 4.1. (Ref. 259) *Let $n > \frac{7}{2}$, $m \in (\frac{1}{2}, 2]$ and $\alpha \in (0, \frac{1}{2})$ be such that $\alpha \geq 4-n$, and let $\beta > 0$. For $\varepsilon \in (0,1)$, define*

$$\begin{aligned} \mathcal{E}_\varepsilon(t) := {} & \chi_2 \int_\Omega u_\varepsilon(\cdot,t)\ln u_\varepsilon(\cdot,t) + \chi_1 \int_\Omega v_\varepsilon(\cdot,t)\ln v_\varepsilon(\cdot,t) \\ & + \frac{\chi_2 \varepsilon}{(n-m)(n-m-1)} \int_\Omega \frac{1}{u_\varepsilon^{n-m-1}(\cdot,t)} \\ & + \frac{\chi_1 \varepsilon}{(n-m)(n-m-1)} \int_\Omega \frac{1}{v_\varepsilon^{n-m-1}(\cdot,t)}, \quad t \geq 0, \end{aligned} \tag{4.90}$$

and

$$\begin{aligned} \mathcal{D}_\varepsilon(t) := {} & \chi_2 D_1 \int_\Omega \frac{u_{\varepsilon x}^2(\cdot,t)}{u_\varepsilon(\cdot,t)} + \chi_1 D_2 \int_\Omega \frac{v_{\varepsilon x}^2(\cdot,t)}{v_\varepsilon(\cdot,t)} \\ & + \chi_2 D_1 \varepsilon \int_\Omega u_\varepsilon^{-n+m-1}(\cdot,t) u_{\varepsilon x}^2(\cdot,t) + \chi_1 D_2 \varepsilon \int_\Omega v_\varepsilon^{-n+m-1}(\cdot,t) v_{\varepsilon x}^2(\cdot,t) \\ & + A \cdot \left\{ \chi_2 \varepsilon \int_\Omega u_\varepsilon^{m-1}(\cdot,t) u_{\varepsilon xx}^2(\cdot,t) + \chi_1 \varepsilon \int_\Omega v_\varepsilon^{m-1}(\cdot,t) v_{\varepsilon xx}^2(\cdot,t) \right\}, \end{aligned} \tag{4.91}$$

for $t > 0$, with $A := \min\{1, \frac{2m-1}{2-m}\}$. Then

$$\mathcal{E}_\varepsilon'(t) \leq -\mathcal{D}_\varepsilon(t) \quad \textit{for all } t > 0 \textit{ and any } \varepsilon \in (0,1). \tag{4.92}$$

Our formulation of our main results on global solvability in (4.86) is now prepared by the following.

Definition 4.1. Let $D_1 > 0, D_2 > 0$, $\chi_1 > 0$ and $\chi_2 > 0$, and suppose that $u_0 \in L^1(\Omega)$ and $v_0 \in L^1(\Omega)$ are non-negative. Then if u and v are non-negative functions defined a.e. in $\Omega \times (0,\infty)$ which are such that

$$u, v, u_x, v_x, uv_x \quad \text{and} \quad vu_x \quad \text{belong to } L^1_{\rm loc}(\overline{\Omega} \times [0,\infty)),$$

then (u, v) will be called a *global weak solution* of (4.86) if for all $\varphi \in C_0^\infty(\overline{\Omega} \times [0,\infty))$, the identities

$$-\int_0^\infty \int_\Omega u\varphi_t - \int_\Omega u_0\varphi(\cdot,0) = -D_1 \int_0^\infty \int_\Omega u_x\varphi_x + \chi_1 \int_0^\infty \int_\Omega uv_x\varphi_x$$

and

$$-\int_0^\infty \int_\Omega v\varphi_t - \int_\Omega v_0\varphi(\cdot,0) = -D_2 \int_0^\infty \int_\Omega v_x\varphi_x - \chi_2 \int_0^\infty \int_\Omega vu_x\varphi_x$$

hold.

Relying on Lemma 4.1 as a starting point to establish ε-independent *a priori* estimates for smooth solutions of (4.87), such a weak solution to the original problem (4.86) can indeed be constructed.

Theorem 4.10. (Ref. 259) *Let $\Omega \subset \mathbb{R}$ be a bounded open interval, and let $D_1 > 0, D_2 > 0$, $\chi_1 > 0$ and $\chi_2 > 0$. Then for any choice of $u_0 \in W^{1,2}(\Omega)$ and $v_0 \in W^{1,2}(\Omega)$ satisfying $u_0 > 0$ and $v_0 > 0$ in $\overline{\Omega}$, in the sense of Definition* 4.1 *the problem* (4.86) *possesses a global weak solution which has the additional properties that*

$$\{u, v\} \subset C^0_w([0,\infty); L^1(\Omega)) \cap L^3_{\rm loc}(\overline{\Omega} \times [0,\infty)) \cap L^{\frac{3}{2}}_{\rm loc}([0,\infty); W^{1,\frac{3}{2}}(\Omega)) \cap L^\infty((0,\infty); L\log L(\Omega)), \tag{4.93}$$

where for intervals $J \subset \mathbb{R}$, as usual $C^0_w(J; L^1(\Omega))$ denotes the space of $L^1(\Omega)$-valued functions on J which are continuous with respect to the weak topology in $L^1(\Omega)$. Moreover, given families $(u_{0\varepsilon})_{\varepsilon\in(0,1)}$ and $(v_{0\varepsilon})_{\varepsilon\in(0,1)}$ fulfilling (4.88), *and parameters $n > \frac{7}{2}$, $m \in (\frac{1}{2}, 2]$, $\alpha \in (0, \frac{1}{2})$ and $\beta > 0$ such that $\alpha \geq 4 - n$, one can find $(\varepsilon_j)_{j\in\mathbb{N}} \subset (0,1)$ such that $\varepsilon_j \searrow 0$ as $j \to \infty$, and such that for the solutions $(u_\varepsilon, v_\varepsilon)$ of* (4.87) *we have $u_\varepsilon \to u$ as well as $v_\varepsilon \to v$ a.e. in $\Omega \times (0,\infty)$ as $\varepsilon = \varepsilon_j \searrow 0$.*

Now due to the presence of doubly cross-diffusive interaction in (4.86), it is unclear whether the solutions gained above enjoy regularity properties beyond those listed above, especially in cases when χ_1 and χ_2 and the initial data are unfavorably large. Nevertheless, the basic dissipation process implicitly expressed through (4.89) indicates a certain global relaxation property at least in a suitable weak sense: In fact, a second formally present fundamental gradient structure, now corresponding to a *conditional* entropy inequality of the form

$$\frac{d}{dt}\mathcal{F}(t) + \left\{\frac{1}{K} - K\mathcal{F}(t)\right\} \cdot \left\{\int_\Omega \frac{u_{xx}^2}{u} + \int_\Omega \frac{v_{xx}^2}{v}\right\} \leq 0, \tag{4.94}$$

where

$$\mathcal{F}(t) := \chi_2 \int_\Omega \frac{u_x^2}{u} + \chi_1 \int_\Omega \frac{v_x^2}{v}$$

with suitably chosen $K > 0$, suggests that the weak decay information on the dissipation rate in (4.89) can actually be turned into genuine decay.

To verify this at a level of rigorous analysis, it seems necessary to adequately cope with the key question is how far (4.94) can be further developed so as to become genuinely justifiable for solutions to (4.87). Fortunately, upon suitable adjustment of the auxiliary parameter m in (4.87) compatible with the requirements from Theorem 4.10, a modified variant of $\mathcal{F}$ from (4.94) will indeed satisfy a conditional entropy inequality of the above flavor.

Lemma 4.2. (Ref. 259) *Let $n > \frac{7}{2}$, $m \in (n-2, n-1)$, $\alpha \in (0, \frac{1}{2})$ and $\beta > 0$ be such that*

$$m \geq 2, \tag{4.95}$$

that

$$\alpha \geq 4 - n \quad \text{and} \quad \alpha > \frac{n-m-1}{2}, \tag{4.96}$$

and that

$$\beta < \frac{\alpha}{n-m}. \tag{4.97}$$

Then there exist $K > 0$ and $\varepsilon_{\star\star} \in (0,1)$ such that for any choice of $\varepsilon \in (0, \varepsilon_{\star\star})$, writing

$$\mathcal{F}_\varepsilon(t) := \chi_2 \int_\Omega \psi_\varepsilon(u_\varepsilon(\cdot,t)) u_{\varepsilon x}^2(\cdot,t) + \chi_1 \int_\Omega \psi_\varepsilon(v_\varepsilon(\cdot,t)) v_{\varepsilon x}^2(\cdot,t), \quad t \geq 0, \tag{4.98}$$

with

$$\psi_\varepsilon(s) := \frac{1}{s} + \frac{\varepsilon}{s^{n-m+1}}, \quad s > 0, \tag{4.99}$$

we have

$$\mathcal{F}_\varepsilon'(t) + \left\{ \frac{1}{K} - K\mathcal{F}_\varepsilon^{\frac{m+2}{2}}(t) - K\mathcal{F}_\varepsilon(t) \right\} \cdot \left\{ \int_\Omega \frac{u_{\varepsilon xx}^2}{u_\varepsilon} + \int_\Omega \frac{v_{\varepsilon xx}^2}{v_\varepsilon} \right\} \leq 0 \quad \text{for all } t > 0. \tag{4.100}$$

Making appropriate use of the latter finally leads to the following.

Theorem 4.11. (Ref. 259) *Let $n \in (\frac{7}{2}, 4)$ and $m = 2$, and let $\alpha \in (0, \frac{1}{2})$ and $\beta > 0$ be such that $\alpha \geq 4 - n, \alpha > \frac{n-3}{2}$ and $\beta < \frac{\alpha}{n-2}$. Then if $\Omega \subset \mathbb{R}$ is a bounded open interval, D_1, D_2, χ_1 and χ_2 are positive and $u_0 \in W^{1,2}(\Omega)$ and $v_0 \in W^{1,2}(\Omega)$ are such that $u_0 > 0$ and $v_0 > 0$ in $\overline{\Omega}$, and if $(u_{0\varepsilon})_{\varepsilon \in (0,1)}$ and $(v_{0\varepsilon})_{\varepsilon \in (0,1)}$ satisfy* (4.88), *then the global weak solution (u,v) of* (4.86) *obtained in Theorem* 4.4 *has the additional properties that there exist $T > 0$ and $C > 0$ such that*

$$\|u(\cdot,t)\|_{L^\infty(\Omega)} + \|v(\cdot,t)\|_{L^\infty(\Omega)} \leq C \quad \text{for all } t > T, \tag{4.101}$$

and that (u,v) *stabilizes toward* $(\overline{u}_0,\overline{v}_0)$ *in the sense that*

$$u(\cdot,t)\to\overline{u}_0 \quad \textit{in } L^\infty(\Omega) \quad \textit{and} \quad v(\cdot,t)\to\overline{v}_0 \textit{ in } L^\infty(\Omega) \quad \textit{as } t\to\infty. \tag{4.102}$$

We underline that Theorem 4.11 does not require any restriction on the size of the initial data, nor on the tactic parameters χ_1 and χ_2; especially, the above thereby covers situations in which the cross-diffusive interplay in (4.85) considerably overbalances the action of diffusion for small times.

Let us next consider some cases in which tactic pursuit-evasion is coupled to classical Lotka-Volterra kinetics. Specifically, we shall consider the fully cross-diffusive predator–prey system

$$\begin{cases} u_t = D_1 u_{xx} - \chi_1 (uv_x)_x + u(\lambda_1 - u + a_1 v), \\ v_t = D_2 v_{xx} + \chi_2 (vu_x)_x + v(\lambda_2 - v - a_2 u), \end{cases} \tag{4.103}$$

along with the corresponding regularized variants, as for $\varepsilon\in(0,1)$ given by

$$\begin{cases} u_{\varepsilon t} = -\varepsilon \left(\dfrac{u_\varepsilon^4}{u_\varepsilon^{4-n_1}+\varepsilon} u_{\varepsilon xxx} \right)_x + \varepsilon^{\frac{\alpha}{2}} (u_\varepsilon^{-\alpha} u_{\varepsilon x})_x + D_1 u_{\varepsilon xx} - \chi_1 \\ \qquad \times \left(\dfrac{u_\varepsilon^{5-n_1}}{u_\varepsilon^{4-n_1}+\varepsilon} v_{\varepsilon x} \right)_x + \dfrac{3u_\varepsilon^3}{3u_\varepsilon^2+\varepsilon} \cdot (\lambda_1 - u_\varepsilon + a_1 v_\varepsilon), \\ v_{\varepsilon t} = -\varepsilon \left(\dfrac{v_\varepsilon^4}{v_\varepsilon^{4-n_2}+\varepsilon} v_{\varepsilon xxx} \right)_x + \varepsilon^{\frac{\alpha}{2}} (v_\varepsilon^{-\alpha} v_{\varepsilon x})_x + D_2 v_{\varepsilon xx} + \chi_2 \left(\dfrac{v_\varepsilon^{5-n_2}}{v_\varepsilon^{4-n_2}} + \varepsilon u_{\varepsilon x} \right)_x \\ \qquad + \dfrac{3v_\varepsilon^3}{3v_\varepsilon^2+\varepsilon} \cdot (\lambda_2 - v_\varepsilon - a_2 u_\varepsilon), \end{cases} \tag{4.104}$$

in an open bounded interval as the spatial domain. Here, for $i\in\{1,2\}$ the parameters D_i, a_i, λ_i and χ_i are positive, and the free parameters $\alpha\in(0,\frac{1}{2}]$, $n_1>0$ and $n_2>0$ are to be suitably specified. Although an introduction both of similar thin-film-type fourth-order diffusion operators and of corresponding second-order fast diffusion corrections has already been carried out in Ref. 259, an essential difference in the present situation consists in the circumstance that the parameters n_1 and n_2, which may be viewed as measuring a certain intermediate-scale degeneracy of the considered fourth-order diffusion mechanisms, will be allowed to attain different values here: While global existence will merely require that $n_i\in[1,2]$ for $i\in\{1,2\}$, the qualitative analysis will rely on the specific choices $(n_1,n_2)=(2,2)$ and $(n_1,n_2)=(2,1)$, respectively, depending on the parameter setting dictated by the Lotka-Volterra interaction in (4.103).

Based on this type of approach, for any choice of the system parameters and arbitrarily large positive initial data from H^1, not only a result on global existence of weak solutions has recently been asserted in Ref. 260; apart from that, it is also concluded there that in both cases $\lambda_2 > a_2\lambda_1$ and $\lambda_2 \le a_2\lambda_1$, the respectively obtained spatially homogeneous coexistence and prey-extinction states retain their

global asymptotic stability properties known from the ODE case when $\chi_1 = \chi_2 = D_1 = D_2 = 0$, provided that both tactic sensitivities χ_1 and χ_2 are suitably small.

For the associated multi-dimensional model

$$\begin{cases} u_t = D_1 \Delta u - \chi_1 \nabla \cdot (u \nabla v) + u(\lambda_1 - u + a_1 v), \\ v_t = D_2 \Delta v + \chi_2 \nabla \cdot (v \nabla u) + v(\lambda_2 - v - a_2 u), \end{cases} \tag{4.105}$$

in a smoothly bounded domain $\Omega \subset \mathbb{R}^n$, $n \in \{1, 2, 3\}$, stability properties of the corresponding spatially homogeneous states $(u_\star, v_\star)$ have recently been described in Ref. 109: As shown there, namely, for arbitrarily large $\chi_1 > 0$ and $\chi_2 > 0$ it is possible to find $\delta > 0$ such that if $u_0, v_0 \in W^{2,2}(\Omega)$ are non-negative fulfilling $\partial_\nu u_0 = \partial_\nu v_0 = 0$ and $\|u_0 - u_\star\|_{W^{2,2}(\Omega)} + \|v_0 - v_\star\|_{W^{2,2}(\Omega)}\| < \delta$, then there exists a global classical solution (u, v) of (4.105) that stabilizes to $(u_\star, v_\star)$ exponentially for the case $\lambda_2 \neq \lambda_1 a_2$ or algebraically for the case $\lambda_2 = \lambda_1 a_2$. The key idea for the proof is to derive *a priori* estimates through identifying certain entropy-like features, similar to those of $\mathcal{F}$ in (4.94) being conditional in the sense of relying on smallness of deviation from the corresponding target state, of the functional

$$\begin{aligned} \mathcal{F}(t) := A_1 \int_\Omega (u - u_\star)^2 + B_1 \int_\Omega |\nabla u|^2 + C_1 \int_\Omega |\Delta u|^2 \\ + A_2 \int_\Omega (v - v_\star)^2 + B_2 \int_\Omega |\nabla c|^2 + C_2 \int_\Omega |\Delta v|^2, \quad t > 0, \end{aligned}$$

with suitable positive parameters A_1, A_2, B_1, B_2, C_1 and C_2.

4.5. *Taxis-cascade systems*

Social interactions in mixed-species groups might be complex. For instance, predator–prey systems may be influenced by so-called forager-exploiter interaction that involves two species: "Foragers", regarded as members of a first population, follow a direct strategy of searching for food by biasing their migration upward gradients of the food concentration, whereas "exploiters", as the individuals of a second population, pursue a more indirect strategy for finding food by tracking the first population and moving toward regions of higher forager population densities. In this regard, the macroscopic formation of shearwater flocks through attraction to kittiwake foragers in Alaska serves as a paradigmatic example.[140]

As a macroscopic model for the spatio-temporal evolution of the population densities $u = u(x, t)$ and $v = v(x, t)$ of foragers and scroungers in such contexts, along with the food density $w = w(x, t)$ as a third unknown variable, the authors in Ref. 239 proposed the taxis-cascade system

$$\begin{cases} u_t = \Delta u - \chi_1 \nabla \cdot (u \nabla w), \\ v_t = \Delta v - \chi_2 \nabla \cdot (v \nabla u), \\ w_t = d \Delta w - \lambda(u + v) w - \mu w + r, \end{cases} \tag{4.106}$$

with positive parameters χ_1, χ_2, d and λ, and with $\mu \geq 0$ and $r \geq 0$. Besides supposing that foragers and scroungers as well as the food resources undergo random diffusion, the model assumes the latter to be consumed by both foragers and scroungers upon contact, to spontaneously decay, and to possibly have an external supply or a growth source.

The coupling of two taxis mechanisms in a consecutive manner in (4.106) leads to an apparent lack of any favorable energy structure, which gives rise to a considerable mathematical challenge in its qualitative analysis; in fact, the numerical experiments reported in Ref. 239 indicate quite a complex dynamics of (4.106) even in one-dimensional frameworks. Therefore, our first goal is to develop an analytical approach which enables us to assert global existence of bounded classical solutions for widely arbitrary initial data in the one-dimensional version of (4.106).

To this end, in a bounded open interval $\Omega \subset \mathbb{R}$ let us consider the initial-boundary value problem for (4.106) given by

$$\begin{cases} u_t = u_{xx} - \chi_1 (u w_x)_x, & x \in \Omega, \ t > 0, \\ v_t = v_{xx} - \chi_2 (v u_x)_x, & x \in \Omega, \ t > 0, \\ w_t = d w_{xx} - \lambda (u+v) w - \mu w + r, & x \in \Omega, \ t > 0, \\ u_x = v_x = w_x = 0, & x \in \partial\Omega, \ t > 0, \\ u(x,0) = u_0(x), \quad v(x,0) = v_0(x), \quad w(x,0) = w_0(x), & x \in \Omega, \end{cases} \tag{4.107}$$

where the initial data are such that

$$\begin{cases} u_0 \in W^{1,\infty}(\Omega) \text{ is non-negative with } u_0 \not\equiv 0, \\ v_0 \in W^{1,\infty}(\Omega) \text{ is non-negative with } v_0 \not\equiv 0, \quad \text{and that} \\ w_0 \in W^{1,\infty}(\Omega) \text{ is positive in } \overline{\Omega}. \end{cases} \tag{4.108}$$

We then, firstly, have the following global solvability result.

Theorem 4.12. (Ref. 246) *Let $\Omega \subset \mathbb{R}$ be a bounded open interval, and let $\chi_1, \chi_2, d, \lambda$ and μ be positive and r be non-negative. Then for any choice of (u_0, v_0, w_0) fulfilling* (4.108)*, the problem* (4.107) *possesses a global classical solution (u, v, w) which is uniquely determined by the properties that*

$$u, v \text{ and } w \text{ belong to } C^0([0,\infty); W^{1,2}(\Omega)) \cap C^{2,1}(\overline{\Omega} \times (0,\infty)), \tag{4.109}$$

and which is such that $u > 0$ and $v > 0$ in $\overline{\Omega} \times (0,\infty)$ as well as $w > 0$ in $\overline{\Omega} \times [0,\infty)$. Moreover, this solution is bounded in the sense that there exists $C > 0$ such that

$$\|u(\cdot,t)\|_{W^{1,2}(\Omega)} + \|v(\cdot,t)\|_{W^{1,2}(\Omega)} + \|w(\cdot,t)\|_{W^{1,2}(\Omega)} \leq C \quad \text{for all } t > 0. \tag{4.110}$$

Proof. From standard theory on parabolic systems we can infer the local existence in $\Omega \times (0, T_{\max})$ with some $T_{\max} \in (0, \infty]$, along with the extensibility information

that

$$\text{if } T_{\max} < \infty, \quad \text{then}$$

$$\limsup_{t \nearrow T_{\max}} \{\|u(\cdot,t)\|_{W^{1,2}(\Omega)} + \|v(\cdot,t)\|_{W^{1,2}(\Omega)} + \|w(\cdot,t)\|_{W^{1,2}(\Omega)}\} = \infty. \quad (4.111)$$

In light of this, in order to claim that $T_{\max} = \infty$, we need to establish the *a priori* estimates of u, v and w in the norm of $W^{1,2}(\Omega)$ for all $t \in (0, T_{\max})$, and the proof proceeds in the following sequence of steps.

(i) By the maximum principle,

$$\|w(\cdot,t)\|_{L^\infty(\Omega)} \le \frac{r}{\mu} + \|w_0\|_{L^\infty(\Omega)} e^{-\mu t} \quad \text{for all } t \in (0, T_{\max}). \quad (4.112)$$

(ii) Using smoothing properties of the Neumann heat semigroup together with (4.112) we obtain $\alpha_1 > 0$ such that for all $M > 0$ and any $q > 1$ one can find $K_1(M,q) > 0$ with the property that whenever u_0, v_0 and w_0 satisfy (4.108) as well as

$$\int_\Omega u_0 + \int_\Omega v_0 \le M, \quad (4.113)$$

there exists $C_1 = C_1(u_0, v_0, w_0) > 0$ such that

$$\|w_x(\cdot,t)\|_{L^q(\Omega)} \le K_1(M,q) + C_1 e^{-\alpha_1 t} \quad \text{for all } t \in (0, T_{\max}). \quad (4.114)$$

(iii) Relying on (4.114) with $q = 2$, a standard test procedure yields the existence of $\alpha_2 > 0, \alpha_3 > 0, K_2(M) > 0, K_3(M) > 0, C_2 = C_2(u_0, v_0, w_0) > 0$ and $C_3 = C_3(u_0, v_0, w_0) > 0$ satisfying

$$\int_\Omega u^2(\cdot,t) \le K_2(M)\overline{u_0}^2 + C_2 e^{-\alpha_2 t} \quad \text{for all } t \in (0, T_{\max}) \quad (4.115)$$

and

$$\int_t^{t+\tau} \int_\Omega u_x^2 \le K_3(M)\overline{u_0}^2 + C_3 e^{-\alpha_3 t} \quad \text{for all } t \in (0, T_{\max} - \tau), \quad (4.116)$$

where $\tau := \min\{1, \frac{1}{2} T_{\max}\}$, and where again $\overline{u_0} = \frac{1}{|\Omega|}\int_\Omega u_0$.

(iv) Employing heat semigroup estimates to further improve the regularity of u, in view of (4.115) and (4.114), we obtain that

$$\|u(\cdot,t)\|_{L^\infty(\Omega)} \le K_4(M)\overline{u_0} + C_4 e^{-\alpha_4 t} \quad \text{for all } t \in (0, T_{\max}) \quad (4.117)$$

with some $\alpha_4 > 0, K_4(M) > 0$ and $C_4 = C_4(u_0, v_0, w_0) > 0$.

(v) Another straightforward testing procedure along with (4.116) yields the existence of $\alpha_5 > 0, K_5(M) > 0$ and $C_5 = C_5(u_0, v_0, w_0) > 0$ such that

$$\int_t^{t+\tau} \int_\Omega \frac{v_x^2}{(v+1)^2} \le K_5(M) + C_5 e^{-\alpha_5 t} \quad \text{for all } t \in (0, T_{\max} - \tau). \quad (4.118)$$

(vi) A simple interpolation together with the above estimate readily shows that

$$\int_t^{t+\tau}\int_\Omega v^2 \le K_6(M) + C_6 e^{-\alpha_6 t} \quad \text{for all } t \in (0, T_{\max}-\tau), \tag{4.119}$$

with some $\alpha_6 > 0, K_6(M) > 0$ and $C_6 = C_6(u_0, v_0, w_0) > 0$.

(vii) By (4.115), (4.119) and (4.112), a further testing process entails the existence of $\alpha_7 > 0, K_7(M) > 0$ and $C_7 = C_7(u_0, v_0, w_0) > 0$ with the property that

$$\int_t^{t+\tau}\int_\Omega w_{xx}^2 \le \frac{K_7(M)}{\tau} + C_7 e^{-\alpha_7 t} \quad \text{for all } t \in (0, T_{\max}-\tau). \tag{4.120}$$

(viii) With the help of (4.117) and (4.120), a higher-order testing process yields the existence of $\alpha_8 > 0, \alpha_9 > 0, K_8(M) > 0, K_9(M) > 0, C_8 = C_8(u_0, v_0, w_0) > 0$ and $C_9 = C_9(u_0, v_0, w_0) > 0$ fulfilling

$$\int_\Omega u_x^2(\cdot,t) \le \frac{K_8(M)}{\tau^2} + C_8 e^{-\alpha_8 t} \quad \text{for all } t \in (0, T_{\max}) \tag{4.121}$$

and

$$\int_t^{t+\tau}\int_\Omega u_{xx}^2 \le \frac{K_9(M)}{\tau^2} + C_9 e^{-\alpha_9 t} \quad \text{for all } t \in (0, T_{\max}-\tau). \tag{4.122}$$

(ix) Performing another testing procedure in conjunction with (4.121), we see that

$$\int_\Omega v^4(\cdot,t) \le \frac{K_{10}(M)\overline{v}_0^4}{\tau^{10}} + C_{10} e^{-\alpha_{10} t} \quad \text{for all } t \in (0, T_{\max}) \tag{4.123}$$

with some $\alpha_{10} > 0, K_{10}(M) > 0$ and $C_{10} = C_{10}(u_0, v_0, w_0) > 0$.

(x) In light of (4.121) and (4.123), a semigroup-based argument similar to that from (iv) implies the existence of $\alpha_{11} > 0, K_{11}(M) > 0$ and $C_{11} = C_{11}(u_0, v_0, w_0) > 0$ such that

$$\|v(\cdot,t)\|_{L^\infty(\Omega)} \le \frac{K_{11}(M)\overline{v}_0}{\tau^{\frac{7}{2}}} + C_{11} e^{-\alpha_{11} t} \quad \text{for all } t \in (0, T_{\max}). \tag{4.124}$$

(xi) Using (4.124) and (4.122) and proceeding as in (viii), we see that

$$\int_\Omega v_x^2(\cdot,t) \le \frac{K_{12}(M)}{\tau^{10}} + C_{12} e^{-\alpha_{12} t} \quad \text{for all } t \in (0, T_{\max}) \tag{4.125}$$

with some $\alpha_{12} > 0, K_{12}(M) > 0$ and $C_{12} = C_{12}(u_0, v_0, w_0) > 0$. Along with (4.121), (4.117), (4.124), (4.112) and (4.114), this completes the proof. □

Now a linear stability analysis performed in Ref. 239 predicts that as long as either the average population of foragers or that of scroungers is suitably small, the two populations as well as food will eventually be homogenously distributed over the spatial habitat. Fortunately, a rigorous nonlinear analysis can confirm this prophecy, and a key observation in this context is contained in the following identification of a conditional entropy structure, relying on a smallness hypothesis on $\min\{\overline{u_0}, \overline{v}_0\}$.

Lemma 4.3. (Ref. 246) *Let $M > 0$. Then there exists $\delta(M) > 0$ such that if u_0, v_0 and w_0 are such that if beyond* (4.108) *and* (4.130) *we have*

$$\left\{\int_\Omega u_0\right\} \cdot \left\{\int_\Omega v_0\right\}^2 \leq \delta(M), \tag{4.126}$$

then it is possible to find $b = b(u_0, v_0, w_0) > 0$ and $t_0 = t_0(u_0, v_0, w_0) > 0$ with the property that

$$\mathcal{F}(t) := \int_\Omega u(\cdot,t)\ln\frac{u(\cdot,t)}{\overline{u_0}} + b\int_\Omega v(\cdot,t)\ln\frac{v(\cdot,t)}{\overline{v}_0} + \frac{\chi_1}{2\lambda}\int_\Omega \frac{w_x^2(\cdot,t)}{w(\cdot,t)}, \quad t > 0 \tag{4.127}$$

and

$$\mathcal{D}(t) := \frac{1}{2}\int_\Omega \frac{u_x^2(\cdot,t)}{u(\cdot,t)} + \frac{b}{2}\int_\Omega \frac{v_x^2(\cdot,t)}{v(\cdot,t)} + \frac{\chi_1\mu}{4\lambda}\int_\Omega \frac{w_x^2(\cdot,t)}{w(\cdot,t)}, \quad t > 0, \tag{4.128}$$

satisfy

$$\mathcal{F}'(t) \leq -\mathcal{D}(t) \quad \text{for all } t > t_0. \tag{4.129}$$

Built on this core ingredient, the following can be obtained.

Theorem 4.13. (Ref. 246) *Suppose that $\Omega \subset \mathbb{R}$ is a bounded open interval, that $\chi_1, \chi_2, d, \lambda$ and μ are positive, and that $r \geq 0$. Then for all $M > 0$ one can find $\varepsilon(M) > 0$ with the property that whenever u_0, v_0 and w_0 are such that besides* (4.108) *we have*

$$\int_\Omega u_0 + \int_\Omega v_0 \leq M \tag{4.130}$$

as well as

$$\int_\Omega u_0 \leq \varepsilon(M) \quad \text{or} \quad \int_\Omega v_0 \leq \varepsilon(M), \tag{4.131}$$

there exist $C = C(u_0, v_0, w_0) > 0$ and $\alpha = \alpha(u_0, v_0, w_0) > 0$ such that the solution (u, v, w) of (4.107) *satisfies*

$$\begin{aligned}&\|u(\cdot,t) - \overline{u_0}\|_{L^\infty(\Omega)} + \|v(\cdot,t) - \overline{v}_0\|_{L^\infty(\Omega)} + \|w(\cdot,t) - w_\star\|_{L^\infty(\Omega)}\\ &\quad \leq Ce^{-\alpha t} \quad \text{for all } t > 0,\end{aligned} \tag{4.132}$$

where $w_\star$ is the non-negative constant given by

$$w_\star := \frac{r}{\lambda(\overline{u_0} + \overline{v}_0) + \mu}. \tag{4.133}$$

In multi-dimensional cases, global existence of certain generalized solutions to the Neumann initial-boundary problem associated with (4.106) has been asserted under an explicit smallness condition on w_0 and r in Ref. 297. Beyond this, the recent literature discusses global existence of generalized solutions or classical solutions, partially even with further information on asymptotic behavior, for some higher-dimensional variants of (4.106) with additional super-quadratic zero-order

degradation terms[42,171,271,310] or with weakened taxis sensitivities[65,185] or enhanced diffusivities,[270] or also with a regularized consumption term.[186] Moreover, radially symmetric renormalized solution to a variant of (4.106) with singular tactic sensitivities was obtained in Ref. 60.

4.6. *Chemotaxis-fluid models*

The analysis of chemotaxis-fluid systems has received considerable interest during the past few years. Motivated and influenced both by corresponding developments in the biomathematical modeling[14,92,267] and by simulation-based and rigorous findings identifying nontrivial effects of fluid interaction on taxis systems,[104,127,157–159,188,267] the literature meanwhile contains a noticeable variety of approaches capable not only of establishing basic existence theories, but also of describing some qualitative facets.

Stimulated by the considerations in Refs. 92 and 267, and hence guided by the ambition to describe pattern formation in populations of aerobic bacteria interacting with their flowing environment via transport and buoyancy, a first class of models thoroughly discussed contains the chemotaxis-consumption system coupled to the (Navier-)Stokes equations

$$\begin{cases} n_t + u \cdot \nabla n = \Delta n^m - \nabla \cdot (n \nabla c), & x \in \Omega, \ t > 0, \\ c_t + u \cdot \nabla c = \Delta c - nc, & x \in \Omega, \ t > 0, \\ u_t + \kappa (u \cdot \nabla) u = \Delta u + \nabla P + n \nabla \Phi, \quad \nabla \cdot u = 0, & x \in \Omega, \ t > 0, \\ (n^m \nabla n - n \nabla c) \cdot \nu = \nabla c \cdot \nu = 0, \quad u = 0, & x \in \partial\Omega, \ t > 0, \\ n(x,0) = n_0(x), \quad c(x,0) = c_0(x), \quad u(x,0) = u_0(x), & x \in \Omega \end{cases} \tag{4.134}$$

posed in a smoothly bounded domain $\Omega \subset \mathbb{R}^N$ or also $\Omega = \mathbb{R}^N$, $N \in \{2,3\}$, as its most prototypical representative. With early key contributions going back to Refs. 71, 95, problems of this and closely related forms have been the object of various studies concerned with issues of global solvability both in classes of bounded solutions, or at least solutions locally bounded in $\overline{\Omega} \times [0,\infty)$, when either $N = 2$,[2,70,87,94,129,257,274,288,295,305,312] or $N = 3$ and $\kappa = 0$,[78,96,168,216,255,273,277,290,294,322] or $N = 3$ and additional smallness conditions are imposed,[95,163] and moreover also in classes of weak solutions, possibly exhibiting partially singular behavior, when $N = 3$ and $\kappa = 1$.[165,291]

In fact, a first parallel to the taxis-free situation of the pure Navier–Stokes system[110,286] is drawn by the following observation concerned with global smooth solvability and exponentially fast stabilization of solutions emanating from data suitably close to homogeneous states in the linear diffusion case when $m = 1$.

Theorem 4.14. (Ref. 62) *Let $N \in \{2,3\}$ and $\Omega \subset \mathbb{R}^N$ be a smoothly bounded domain, let $\kappa = 1$, $m = 1$ and $\Phi \in W^{2,\infty}(\Omega)$, and let $p \in (\frac{N}{2}, \infty), q \in (N, \infty)$ and*

$\mu > 0$. Then there exists $\eta > 0$ such that whenever $0 \leq n_0 \in C^0(\overline{\Omega})$, $0 \leq c_0 \in W^{1,\infty}(\Omega)$ and $u_0 \in W^{2,2}(\Omega;\mathbb{R}^3) \cap W_0^{1,2}(\Omega) \cap L^2_\sigma(\Omega)$ are such that

$$\overline{n}_0 = \frac{1}{|\Omega|}\int_\Omega n_0 = \mu$$

and

$$\max\{\|n_0 - \overline{n}_0\|_{L^p(\Omega)}, \|c_0\|_{L^\infty(\Omega)}, \|u_0\|_{L^N(\Omega)}\} \leq \eta,$$

the problem (4.143) *possesses a global classical solution (n, c, u, P), with*

$$\begin{cases} n \in C^0(\overline{\Omega}\times[0,\infty)) \cap C^{2,1}(\overline{\Omega}\times(0,\infty)), \\ c \in \bigcap_{q>3} C^0([0,\infty); W^{1,q}(\Omega)) \cap C^{2,1}(\overline{\Omega}\times(0,\infty)), \\ u \in \bigcup_{\vartheta\in(\frac{3}{4},1)} C^0([0,\infty); D(A^\vartheta)) \cap C^{2,1}(\overline{\Omega}\times(0,\infty);\mathbb{R}^3) \quad \text{and} \\ P \in C^{1,0}(\Omega\times(0,\infty)), \end{cases} \tag{4.135}$$

which satisfies

$$\|n(\cdot,t) - \overline{n}_0\|_{L^\infty(\Omega)} + \|c(\cdot,t)\|_{W^{1,\infty}(\Omega)} + \|u(\cdot,t)\|_{L^\infty(\Omega)} \leq Ce^{-\beta t} \quad \text{for all } t > 0$$

with some $C > 0$ and $\beta > 0$.

For large-data solutions in three-dimensional domains and for the full Navier–Stokes model determined by the selection $\kappa = 1$, the by now most comprehensive theory seems available in the case of linear diffusion obtained on letting $m = 1$, with global existence results being available also within a considerably wider range of m. To describe some developments in this context, for definiteness let us assume that the gravitational potential in (4.134) satisfies

$$\Phi \in W^{2,\infty}(\Omega), \tag{4.136}$$

and that initial data be such that

$$\begin{cases} n_0 \in L\log L(\Omega) & \text{is non-negative with } n_0 \not\equiv 0, \\ c_0 \in L^\infty(\Omega) & \text{is non-negative and such that } \sqrt{c_0} \in W^{1,2}(\Omega), \quad \text{and} \\ u_0 \in L^2_\sigma(\Omega), \end{cases} \tag{4.137}$$

where $L^2_\sigma(\Omega) := \{\varphi \in L^2(\Omega) \mid \nabla\cdot\varphi = 0\}$ denotes the space of all solenoidal vector in $L^2(\Omega)$.

We first specify our notion of solvability in the following quite natural definition.

Definition 4.2. By a global weak solution of (4.134) we mean a triple (n, c, u) of functions

$$n \in L^1_{\rm loc}(\overline{\Omega}\times[0,\infty)), \quad c \in L^1_{\rm loc}([0,\infty); W^{1,1}(\Omega)), \quad u \in L^1_{\rm loc}([0,\infty); W_0^{1,1}(\Omega);\mathbb{R}^3),$$

such that $n \geq 0$ and $c \geq 0$ a.e. in $\Omega\times(0,\infty)$,

$$nc \in L^1_{\rm loc}(\overline{\Omega}\times[0,\infty)), \quad u\otimes u \in L^1_{\rm loc}(\overline{\Omega}\times[0,\infty);\mathbb{R}^{3\times 3}),$$

$$\nabla n^m, \quad n\nabla c, \quad nu, \quad cu \in L^1_{\rm loc}(\overline{\Omega}\times[0,\infty);\mathbb{R}^3),$$

that $\nabla \cdot u = 0$ a.e. in $\Omega \times (0,\infty)$, and that

$$-\int_0^\infty \int_\Omega n\phi_t - \int_\Omega n_0\phi(\cdot,0) = -\int_0^\infty \int_\Omega \nabla n^m \cdot \nabla\phi + \int_0^\infty \int_\Omega n\nabla c \cdot \nabla\phi + \int_0^\infty \int_\Omega nu \cdot \nabla\phi$$

for all $\phi \in C_0^\infty(\overline{\Omega} \times [0,\infty))$,

$$-\int_0^\infty \int_\Omega c\phi_t - \int_\Omega c_0\phi(\cdot,0) = -\int_0^\infty \int_\Omega \nabla c \cdot \nabla\phi - \int_0^\infty \int_\Omega nc\phi + \int_0^\infty \int_\Omega cu \cdot \nabla\phi$$

for all $\phi \in C_0^\infty(\overline{\Omega} \times [0,\infty))$ as well as

$$-\int_0^\infty \int_\Omega u \cdot \phi_t - \int_\Omega u_0 \cdot \phi(\cdot,0) = -\int_0^\infty \int_\Omega \nabla u \cdot \nabla\phi + \int_0^\infty \int_\Omega u \otimes u \cdot \nabla\phi + \int_0^\infty \int_\Omega n\nabla\Phi \cdot \phi$$

for all $\phi \in C_0^\infty(\Omega \times [0,\infty); \mathbb{R}^3)$ satisfying $\nabla \cdot \phi \equiv 0$.

In order to construct such a solution, with families of appropriately approximate initial data $n_{0\varepsilon}, c_{0\varepsilon}$ and $u_{0\varepsilon}$, $\varepsilon \in (0,1)$, we introduce the regularized problems

$$\begin{cases} \partial_t n_\varepsilon + u_\varepsilon \cdot \nabla n_\varepsilon = \Delta(n_\varepsilon + \varepsilon)^m - \nabla \cdot (n_\varepsilon F_\varepsilon'(n_\varepsilon)\nabla c_\varepsilon), & x \in \Omega,\ t > 0, \\ \partial_t c_\varepsilon + u_\varepsilon \cdot \nabla c_\varepsilon = \Delta c_\varepsilon - F_\varepsilon(n_\varepsilon)c_\varepsilon, & x \in \Omega,\ t > 0, \\ \partial_t u_\varepsilon + (Y_\varepsilon u_\varepsilon \cdot \nabla)u_\varepsilon = \Delta u_\varepsilon + \nabla P_\varepsilon + n_\varepsilon \nabla\Phi, & x \in \Omega,\ t > 0, \\ \nabla \cdot u_\varepsilon = 0, & x \in \Omega,\ t > 0, \\ \dfrac{\partial n_\varepsilon}{\partial \nu} = \dfrac{\partial c_\varepsilon}{\partial \nu} = 0, \quad u_\varepsilon = 0, & x \in \partial\Omega,\ t > 0, \\ n_\varepsilon(x,0) = n_{0\varepsilon}(x), \quad c_\varepsilon(x,0) = c_{0\varepsilon}(x), \quad u_\varepsilon(x,0) = u_{0\varepsilon}(x), & x \in \Omega, \end{cases} \tag{4.138}$$

where

$$F_\varepsilon(s) := \frac{1}{\varepsilon}\ln(1+\varepsilon s) \quad \text{for } s \geq 0, \tag{4.139}$$

and where we use the standard Yosida approximation Y_ε defined by

$$Y_\varepsilon v := (1+\varepsilon A)^{-1} v \quad \text{for } v \in L^2_\sigma(\Omega). \tag{4.140}$$

Here, by A we mean the realization of the Stokes operator $-\mathcal{P}\Delta$ in $L^2_\sigma(\Omega)$, with domain $D(A) = W^{2,2}(\Omega) \cap W_0^{1,2}(\Omega) \cap L^2_\sigma(\Omega)$, and where $\mathcal{P}$ denotes the Helmholtz projection in $L^2(\Omega)$. It is well known that A is self-adjoint and positive due to the fact that Ω is bounded, and hence in particular possesses fractional powers A^α for arbitrary $\alpha \in \mathbb{R}$.

Due to the regularization of taxis and nonlinear convection expressed in (4.139) and (4.140), it can be shown that for each $\varepsilon \in (0,1)$, (4.138) admits a globally

defined smooth solution[291]; an observation of crucial importance for a corresponding limit passage consists in the detection of a quasi-entropy structure: In fact, there exist $\kappa > 0$ and $K > 0$ such that for all $\varepsilon \in (0,1)$ and for all $t > 0$, the solution of (4.138) satisfies

$$\frac{d}{dt}\left\{\int_\Omega n_\varepsilon \ln n_\varepsilon + \int_\Omega |\nabla\sqrt{c_\varepsilon}|^2 + \kappa\int_\Omega |u_\varepsilon|^2\right\} + \frac{1}{K}\left\{\int_\Omega n_\varepsilon^{m-2}|\nabla n_\varepsilon|^2 + \int_\Omega \frac{|D^2 c_\varepsilon|^2}{c_\varepsilon} + \int_\Omega \frac{|\nabla c_\varepsilon|^4}{c_\varepsilon^3} + \int_\Omega |\nabla u_\varepsilon|^2\right\} \le K. \tag{4.141}$$

The following consequence is built on this cornerstone.

Theorem 4.15. (Refs. 291, 315) *Let $\Omega \subset \mathbb{R}^3$ be a bounded convex domain with smooth boundary, let $m > \frac{2}{3}$, and assume* (4.136). *Then for all n_0, c_0 and u_0 fulfilling* (4.137), *there exists a global weak solution of the problem* (4.134) *in the sense of Definition* 4.2. *This solution can be obtained as the limit of smooth solutions to the regularized problems* (4.138).

Beyond this, in the linear diffusion case $m = 1$ the above global weak solution actually enjoys certain further regularity properties, and asymptotically behaves in a diffusion-dominated manner previously known from two-dimensional analogues.[289,314]

Theorem 4.16. (Ref. 292) *Suppose that $\Omega \subset \mathbb{R}^3$ is a smoothly bounded convex domain, let $m = 1$, and let* (4.136) *and* (4.137) *hold. Then there exists $T_0 > 0$ such that the solution (n, c, u) of* (4.134) *from Theorem* 4.15 *satisfies*

$$(n, c, u) \in C^{2,1}(\overline{\Omega} \times [T_0, \infty); \mathbb{R}^5)$$

and

$$(n(\cdot,t), c(\cdot,t), u(\cdot,t)) \to (\overline{n}_0, 0, 0) \quad \text{in } L^\infty(\Omega;\mathbb{R}^5) \quad \text{as } t \to \infty.$$

Finally, based on an analysis of

$$y_\varepsilon(t) := \int_\Omega n_\varepsilon^p(\cdot,t) + \int_\Omega |\nabla c_\varepsilon(\cdot,t)|^{2p} + \int_\Omega |A^{\frac{\alpha}{2}} u_\varepsilon(\cdot,t)|^2, \quad t \ge 0, \quad \varepsilon \in (0,1), \tag{4.142}$$

for suitably chosen $p > 1$ and $\alpha \in (0,1)$, it is possible to make sure that (4.134) with $m = 1$ in fact even enjoys a property of generic smoothness in the style of Leray's celebrated structure theorem for the three-dimensional Navier–Stokes system[167]:

Theorem 4.17. (Ref. 301) *Assume that $\Omega \subset \mathbb{R}^3$ is a bounded convex domain with smooth boundary and that $m = 1$, and let* (4.136) *and* (4.137) *be valid. Then* (4.134) *has a global weak energy solution that is smooth throughout $\overline{\Omega} \times E$, where E denotes a countable union of open intervals which is such that $|(0,\infty)\backslash E| = 0$.*

Another quite thoroughly investigated branch in this field consists of models that involve similar types of fluid coupling in contexts of chemotaxis systems which, contrary to (4.134) account for signal production through cells in the style of the corresponding attractant evolution mechanisms covered by classical Keller–Segel systems.[153] In the analysis of the accordingly obtained prototypical model

$$\begin{cases} n_t + u \cdot \nabla n = \nabla \cdot (D(n)\nabla n) - \nabla \cdot (nS(n)\nabla c), & x \in \Omega, \ t > 0, \\ c_t + u \cdot \nabla c = \Delta c - c + n, & x \in \Omega, t > 0, \\ u_t + \kappa(u \cdot \nabla)u = \Delta u + \nabla P + n\nabla\Phi, \quad \nabla \cdot u = 0, & x \in \Omega, \ t > 0, \\ (D(n)\nabla n - nS(n)\nabla c) \cdot \nu = \nabla c \cdot \nu = 0, \quad u = 0, & x \in \partial\Omega, \ t > 0, \\ n(x,0) = n_0(x), \quad c(x,0) = c_0(x), \quad u(x,0) = u_0(x), & x \in \Omega, \end{cases} \tag{4.143}$$

beyond establishing results on global existence of small-data solutions[59,163,313] a key problem appears to consist in determining how far fluid interaction may lead to substantial differences in comparison to the correspondingly unperturbed fluid-free system, where a natural focus is on issues related to the occurrence of blow-up. Indeed, while the knowledge concerning associated dichotomies has been fairly comprehensive for quite a while already,[79,256,287] for (4.143) the picture seems much less complete in this regard; in particular, it has not fully been clarified yet how far in N-dimensional domains the asymptotic behavior

$$\frac{S(n)}{D(n)} \sim n^{\frac{2}{N}-1}, \quad n \simeq \infty, \tag{4.144}$$

retains its critical character known from the fluid free case.

For the precise case of porous medium type diffusion, that is, with

$$D(n) = n^m, \quad n \geq 0, \quad (m > 0) \tag{4.145}$$

and under the assumption that $S \in C^2([0,\infty))$ satisfies

$$|S(n)| \leq \frac{S_0}{(n+1)^\alpha} \quad \text{for all } n \geq 0 \tag{4.146}$$

with some $S_0 > 0$ and $\alpha > 0$, the following recent contribution provides some essential progress for the full Keller–Segel–Navier–Stokes version of (4.143) that is well compatible with (4.144) in this respect (cf. also Refs. 152, 181, 183, 169, 275, 316).

Theorem 4.18. (Refs. 40 and 41) *Let $\Omega \subset \mathbb{R}^3$ be a bounded domain with smooth boundary, let $\kappa = 1$ and $\Phi \in W^{2,\infty}(\Omega)$, and suppose that* (4.145) *and* (4.146) *hold with some $m \geq 1, S_0 > 0$ and $\alpha > 0$ satisfying*

$$m + \alpha > \frac{4}{3}.$$

Then for any $n_0 \in \bigcup_{\gamma\in(0,1)} C^\gamma(\overline{\Omega})$, $c_0 \in W^{1,\infty}(\Omega)$ and $u_0 \in W^{2,2}(\Omega;\mathbb{R}^3) \cap W_0^{1,2}(\Omega) \cap L^2_\sigma(\Omega)$ fulfilling $0 \leq n_0 \not\equiv 0$ and $0 \leq c_0 \not\equiv 0$, the problem (4.143)

admits at least one global very weak solution (n, c, u) *in the sense of Definition* 2.2 *from Ref.* 41. *In particular, this solution satisfies*

$$n \in L^{2(m+\alpha)-\frac{4}{3}}_{\rm loc}(\overline{\Omega} \times [0,\infty)), \quad c \in L^2_{\rm loc}([0,\infty); W^{1,2}(\Omega)),$$
$$u \in L^2_{\rm loc}([0,\infty); W^{1,2}_0(\Omega; \mathbb{R}^3))$$

and

$$\int_\Omega n(\cdot,t) = n_0 \quad \textit{for a.e. } t > 0.$$

Under a slightly stronger assumption involving the condition $m + 2\alpha > \frac{5}{3}$, genuine weak solutions enjoying even more regularity features can be constructed.[41]

In the simplified Stokes variant of (4.143), even boundedness can be obtained under an essentially optimal assumption on subcriticality of taxis related to diffusion (see also the precedent in Ref. 211).

Theorem 4.19. (Refs. 61, 280, 293, 304) *Suppose that* $\Omega \subset \mathbb{R}^3$ *is a bounded domain with smooth boundary, that* $\Phi \in W^{2,\infty}(\Omega)$, *and that* $D \in C^2([0,\infty))$ *and* $S \in C^2([0,\infty))$ *are such that* $D > 0$ *in* $[0,\infty)$, *and that*

$$k n^{m_0-1} \le D(n) \le K n^{m-1} \quad \textit{for all } n > 1 \tag{4.147}$$

as well as

$$\frac{|S(n)|}{D(n)} \le K_{SD}\, n^{\alpha-1} \quad \textit{for all } n > 1 \tag{4.148}$$

with some $m_0 \in \mathbb{R}, m \ge m_0$, $k > 0, K > 0$, $K_{SD} > 0$ *and* $\alpha < \frac{2}{3}$. *Then for any choice of* $0 \le n_0 \in C^0(\overline{\Omega})$, $0 \le c_0 \in W^{1,\infty}(\Omega)$ *and* $u_0 \in W^{2,2}(\Omega; \mathbb{R}^3) \cap W^{1,2}_0(\Omega) \cap L^2_\sigma(\Omega)$ *one can find functions* n, c, u *and* P *fulfilling* (4.135) *as well as* $n \ge 0$ *and* $c \ge 0$ *in* $\Omega \times (0,\infty)$, *and which are such that* (n, c, u, P) *forms a classical solution of* (4.143). *Moreover,*

$$\sup_{t>0}\{\|n(\cdot,t)\|_{L^\infty(\Omega)} + \|c(\cdot,t)\|_{W^{1,\infty}(\Omega)} + \|A^\vartheta u(\cdot,t)\|_{L^2(\Omega)}\} < \infty \quad \textit{for all } \vartheta \in \left(\frac{3}{4}, 1\right), \tag{4.149}$$

where for $\vartheta > 0$, A^ϑ *denotes the fractional power of the Stokes operator* A *in its domain* $D(A) = W^{2,2}(\Omega; \mathbb{R}^3) \cap W^{1,2}_0(\Omega) \cap L^2_\sigma(\Omega)$.

Comparably optimal statements, partially even up to the detection of critical mass phenomena, have been derived at least for some subclasses of (4.143) in two-dimensional domains, asserting global boundedness even for the corresponding full Navier–Stokes version.[148,173,174,279,282,302,318]

Let us finally mention that considerable recent progress in various directions related to (4.134) and (4.143) addresses chemotaxis-fluid systems toward various

research directions. For instance:

— Under alternative types of boundary conditions.[48,49,210,262,283,309]
— Models of further influences which can be described by logistic-type proliferation terms.[102,105,164,193,197,218,253,254,276,284,298,307]
— Signal-dependent and especially singular sensitivity functions.[2,39,43,44,182,278,307]
— Gradient-dependent migration rates.[149,178,240,241,303,323]
— More complex chemotaxis-fluid models involving couplings to additional components.[63,64,139,143,172,178–180,184,317,319,320]

5. Modeling Toward a Multiscale Vision

The contents of this paper have been devoted to a review and critical analysis on the derivation of a variety of models, which we have called *exotic reaction–diffusion models*, and on the analytical results related to mathematical problems generated by the application of these models to the dynamics of real world systems.

This final section is devoted to propose some research perspectives focused on deriving more advanced or even new model classes, thus going beyond those presented in Secs. 2 and 3. It is hoped that these new models will open up exciting new research perspectives. The presentation is based on key concepts, by looking forward from those we have inserted in the preceding sections, while the analytical formalization to effective research programs is left to the initiative of the interested reader.

The selection of models, considered in the preceding sections, has been obtained by the classical derivation at the macroscopic scale. *Id est*, by equilibrium and/or conservation equations generally referred to the macroscopic scale. These equations generate non-complete systems that can be closed by adding further equations corresponding to material models, which provide a phenomenological interpretation of physical reality. In most cases, these material models are valid at equilibrium, but their validity far from these conditions deserves a critical analysis. The sixth Hilbert problem[118,132] has already posed, at the beginning of the past century, the need of a unified multiscale modeling approach also with the aim of tackling the aforementioned problem.

Exotic models, treated in our paper, present additional difficulties as they correspond, in most (all) cases, to the living matter. Therefore, as observed by various authors, background field theories, which are valid to the inter matter, are not valid in the case of living systems.[123,124,130,190] Therefore novel approaches should be developed within the aforementioned Hilbert's multiscale vision.

The first step toward this challenging objective is the scaling problem corresponding to a derivation approach, based on the same principles, at the two scales microscopic and macroscopic, with an intermediate statistical description that may be inspired by the classical kinetic theory of diluted gases.[69] See, referring to classical particles, the derivation theory proposed in Ref. 225. Indeed, the key problem of all reasonings in the following is the so-called scaling problem focused on the

selection of the modeling scale among the micro-scale (individual based), mesoscopic scale (kinetic), and macro-scale (hydrodynamical).

The selection of the representation and modeling scale should consider that models at each scale presents consistency features, but also pitfalls. For instance, the number of interacting entities in several systems is not large enough to justify not only the continuous approximation by models at the macroscopic scale, but also the continuous approximation, in the kinetic theory approach, of the probability distribution over the microscopic state. On the other hand, the derivation of models at the microscopic scale requires the identification of the individual entities and leads to excessively large nonlinear dynamical systems.

An additional difficulty is that the state, at each scale, of living systems is not simply defined by mechanical variables,[46] but also by additional internal variables which model the biological and/or social state of the interacting entities.[17,82,84,156] The said internal variables are not, in most cases, equally shared by all entities composing a living system. Then, heterogeneity should be considered by statistical distributions. In addition, models should also consider how interactions modify the said distributions.

The mathematical approach to modeling collective motion of large systems of interacting entities, such as behavioral crowds[12] and behavioral swarms,[26] indicates the first step to account for the aforementioned reasonings consists in deriving models based on the same physical principles at each scale. This approach implies that modeling interactions at the micro-scale leads to implement the pseudo Newtonian framework which generates models of the collective dynamics of all entities. In addition, models of micro-scale interactions interactions naturally lead to the derivation of models by the kinetic theory approach. These concepts can be transferred to the derivation of models straightforwardly at the macro-scale by inserting in the model suitable micro-scale variable and by considering their dynamic linked to that of all dependent variable. In this case, the overall continuum system can be treated by a mixture of subsystems each of them characterized by different properties modeled by the aforementioned parameter.

A further topic concerning multiscale approaches is the derivation of macroscopic models from the underlying models delivered by the kinetic theory of active particles. The equations of kinetic models can be written in dimensionless form which extracts a small parameter, say ε, related to the mean distance between active particles. Then, methods inspired to the Hilbert approach lead to expansion of the dependent variables in power of this parameter. Substituting this expansion into the equations of the model and equating the terms with the same power of ε might lead to deriving the terms of the power expansion. This method is presented in Ref. 52, where various technical difficulties are critically analyzed.

Applications on the micro-macro derivation have been developed in biology[17,18]; in the derivation of models with nonlinear diffusion,[51] in crowd dynamics[13] for a specific model,[16] synchronization[208,214] and swarms.[5,25,66,106] This research line has

been promoted by the pioneering papers[72,88,134,196,201,202,220] up to recent results which include various features of nonlinear diffusion already treated in Sec. 2. In more details, the perturbation technique proposed in Ref. 201 has given an important trace to several papers as reviewed in Ref. 18. Interesting results can be obtained by averaging approaches applied to stochastic particles methods.[4,125,126]

Furthermore, we propose a reflection on the place that deep learning techniques should occupy in this work scheme in connection with multiscale models, mainly in problems originating in the biomedical field. In particular, discerning which is the good ε scale in relation to the possible and diverse choices of the parameters, analyzing their sensitivity in the model, or the correct simplification or interpretation of nonlinearities is an interesting point of connection between multiscale models and deep learning process.[3]

This combination allows to exploit the underlying physics to restrict the design spaces and the limits of scale on neural networks or dense graphs, as well as the identification of the dynamics of the system. Furthermore, numerical methods adapted to multiscale kinetic systems, such as Monte Carlo methods or particle methods, can help to improve deep learning techniques in relation to multiscale models.

The micro-macro derivation reviewed in this section has the merit of linking macroscopic models and related parameters to the dynamics at the micro-scale, where parameters are supposed to be valid also far from equilibrium. Therefore, however without forgetting the challenging analytic difficulties that the aforementioned methods involve, we suggest revisiting the models presented in Sec. 3 within a multiscale vision that arguably may lead to new class of models which would require further development of the presently know tools used in the qualitative analysis reviewed in our paper.

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