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# Mathematical models for cell migration: a non-local perspective

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We provide a review of recent advancements in non-local continuous models for migration, mainly from the perspective of its involvement in embryonal development and cancer invasion. Particular emphasis is placed on spatial non-locality occurring in advection terms, used to characterize a cell's motility bias according to its interactions with other cellular and acellular components in its vicinity (e.g. cell–cell and cell–tissue adhesions, non-local chemotaxis), but we also briefly address spatially non-local source terms. Following a short introduction and description of applications, we give a systematic classification of available PDE models with respect to the type of featured non-localities and review some of the mathematical challenges arising from such models, with a focus on analytical aspects.

This article is part of the theme issue 'Multi-scale analysis and modelling of collective migration in biological systems'.

## 1. Introduction

Collective movement arises when individuals correlate their motion with that of others, generating migration at a population level. Paradigms include flocks, swarms and crowds [1], but it also occurs for bacteria [2], embryonic populations, and immune and invading cancer cells [3,4]. Scales span enormous ranges, from a few cells clustered over a few micrometres to millions or billions of organisms distributed over kilometres, e.g. large-scale fish schools [5] and locust swarms [6]. Adoption of theoretical approaches has helped understand these phenomena. *Agent-based modelling* is a popular approach, with its individual-level representation facilitating data fitting. For cell populations, agent-based modelling approaches range greatly in sophistication, including single or multi-site cellular automata [7,8] and descriptions of cells as overlapping spheres [9], deformable ellipsoids [10] or dynamic boundaries [11]. For organisms, collective movement models are often founded on point-based individuals moving with velocities determined by their interactions with neighbours (see the review in [12]).

Despite their many advantages, problems persist with agent-based models (ABMs) that motivate complementary approaches. First, a lack of standard analytical methods leads to heavy reliance on computation which, inevitably, becomes burdensome as population size increases. Second, how should one compare the results emerging following different approaches applied to the same problem, e.g. between a lattice- and off-lattice model used to describe cell sorting behaviour? Precise quantitative matching is clearly unrealistic, so when can one state that two methods generate equivalent behaviour? Third, different implementations of the same method can also generate quantitatively distinct results when applied to the same problem [13]. This typically escalates with the sophistication/detail of the ABM, with variations arising from, say, ambiguously stated assumptions or distinctions in the numerical implementation. Overall, these issues highlight the general challenge of appropriately 'benchmarking' ABMs, and we refer to [14] for a more detailed consideration.

While it would be disingenuous to state that *continuous models* are free from such issues, in principle their solutions are reproducible: well-posed problems generate unique solutions for a given set of initial conditions. Furthermore, with their roots in classical theory, well-developed analytical methods exist that provide generic insights: the analysis necessary to demonstrate the self-organizing capacity of Turing's counterintuitive reaction and diffusion theory of morphogenesis [15] is not restricted to precise reactions, parameters, etc. Phenomenological derivations start with a mass conservation equation, where movement is modelled via stipulating an appropriate *flux*. Coupled to reaction/birth/death processes, governing equations are stated for the key variables (cells, organisms, chemicals, etc.), each represented by continuous density distributions. Models derived in this way typically fall into the class of reaction–diffusion–advection (RDA) equations,

$$\frac{\partial u}{\partial t} = \overbrace{\nabla \cdot (D(\cdot)\nabla u)}^{\text{diffusion}} - \overbrace{\nabla \cdot (\mathbf{a}(\cdot)u)}^{\text{advection}} + \overbrace{f(u,\cdot)}^{\text{reaction}}, \tag{1.1}$$

where $u(x, t)$ denotes the population density at position $x$ at time $t$. Diffusion describes a non-oriented dispersal process, for example due to simple random meandering by individuals, and is characterized by diffusion coefficient $D(\cdot)$. Advection could be passive (e.g. environmental flow) or due to active navigation by individuals, and is described by an advective velocity $\mathbf{a}(\cdot)$. Reaction describes the population birth/death, etc. A vast number of models fall into the above class, including numerous landmark works: textbooks such as [16,17] address several models in this framework. Models of type (1.1) can also be derived as the continuous limiting equation of a biased random walk description for biological particle movement (see [18]).

Models in the RDA framework typically have a *local* nature, i.e. terms that depend pointwise. For example, in the well-known Keller–Segel model [19] for chemotaxis, the advection term describes population drift along a local chemoattractant gradient: specifically, $\mathbf{a} = \chi\nabla v$, for some chemoattractant $v$ and function $\chi$. Effectively, cells (or animals) are assumed to detect and migrate in the direction of a local gradient. This is often logical, viewed at a macroscopic level: cells such as leukocytes orient according to the concentration difference of attractant across their body axis, but at the scale of a tissue this can be regarded as a pointwise calculation.

Local assumptions may not, however, always hold or be convenient. Population densities may be high: classical diffusive fluxes (e.g. Fickian) assume diluteness, and at high densities the impact of long-range effects may be important [17]. Moreover, many particles sense the environment over extended regions: filopodia/cytonemes permit cells to detect signals multiple cell diameters away [20]; sensory organs grant organisms highly non-local perception fields (e.g. [21–24]). Approximating information originating over large regions to, say, a local gradient, could clearly be overly reductive. Dispersal distances may also be non-local, for example seeds can be transported significant distances from source while various studies have implicated 'Lévy-type' behaviour in migration paths, where short-range movements are interspersed with occasional long transits (e.g. [25]). Local formulations can also create analytical problems, exemplified in the 'blow-up' phenomena in certain formulations of chemotaxis models (e.g. see [26]). Here, the coupling between a population's pointwise production of its own attractant and movement up the local gradient leads to runaway aggregation and singularity formulation. Such phenomena are powerful indicators of inherent self-organization, yet formation of infinite cell densities is, ultimately, unrealistic.

These considerations and others have led to a range of spatially non-local RDA models, and their modelling and mathematical properties have attracted significant interest. This brief survey focuses on some aspects of modelling through such a framework. Non-locality is, of course, a broad concept and can be included in various ways, for example into any or all of the diffusion, advection or reaction terms. We primarily focus on the use of *non-local advection* models that feature *spatial integral operators* inside advection terms. These have typically been developed to replace the gradient-type terms often used to describe taxis-type movement and, in particular, have come into vogue as a method of modelling collective movement processes in cells and organisms.

## 2. Applications in development and cancer

Non-local advection models have received considerable attention for their capacity to include cell–cell (and cell–matrix) adhesion into models for tissue dynamics. Adhesion occurs when juxtaposing membranes link certain transmembrane adhesion proteins, fastening cells together and forming clusters [27]. Moreover, cell–cell adhesion confers self-organization, with famous studies revealing how mixed cell types can self-rearrange into distinct configurations, implying a capacity to 'recognize' others of same type [28]. The differential adhesion hypothesis (DAH) of Steinberg [29] suggested that distinct adhesion can provide this 'tissue-affinity', with the ratio of self- to cross-adhesion strengths determining the configuration; various experiments corroborate this theory (e.g. [30]).

Models of adhesion should ideally exhibit clustering/sorting, and many ABMs indeed reproduce these phenomena (e.g. [14]). The discrete cell representation is optimal: adhesion easily enters as an attracting force over a range of cell–cell separations, coalescing cells until their compression generates a counteracting repulsion. Incorporating adhesion into continuous models, however, can prove challenging. Attempts starting from an initial discrete random walk process have certainly generated continuous models, yet these can be ill-posed (backward diffusion) or seemingly incapable of displaying more complicated behaviour such as sorting (e.g. [31–33]).

Phenomenological approaches founded on non-local concepts appear to be more successful. Such models capture cell–neighbour interactions through the proposed movement of cells according to the density of others in their vicinity. An early model of this type was proposed in [34], although subsequent analysis focused on a localized form derived under expansion. The non-local model for adhesion proposed in [35] was explored regarding its ability to recapitulate the sorting behaviour predicted by the DAH, and its relative success has led to various extensions: [36] performed a more comprehensive analysis; [37,38] replaced the overly reductive linear diffusion terms with nonlinear forms, generating the sharp cell boundaries often observed experimentally; [39] extended to more general cell–cell contact phenomena, for example allowing repulsive interactions as found in Ephephrin interactions [40]; the model of [41] has been extended to allow dynamic adhesion regulation.

Typical applications lie in morphogenesis and cancer. The former has witnessed non-local advection models used to

**Table 1.** Non-local modifications of the gradient operator applied to a function $v$ (or $v = (v_1, v_2)$).

| integral operator | examples | references |
|---|---|---|
| is placed before $\nabla$ | $(J \star v_1)\nabla v_2$ | [58] |
| is placed inside $\nabla$ | $\nabla(J \star v)$ | [65] |
| replaces $\nabla$ | $\mathcal{A}_r v(x) = \frac{1}{r}\fint_{B_r} v(x+\xi)\frac{\xi}{\lvert\xi\rvert}F_r(\lvert\xi\rvert)\,\mathrm{d}\xi$ | adhesion velocity [35,66] |
| | $\mathring{\nabla}_r v(x) = \frac{n}{r}\fint_{S_r} v(x+\xi)\xi\,d_{S_r}$ | non-local chemotaxis [67,68] |
| is applied to $\nabla$ | $\mathcal{T}_r\nabla v(x) = \frac{1}{r}\int_0^1\fint_{B_r}(\nabla v(x+s\xi)\cdot\xi)\frac{\xi}{\lvert\xi\rvert}F_r(\lvert\xi\rvert)\,d\xi\,\mathrm{d}s$ | [69] |
| | $\mathcal{S}_r\nabla v(x) = \frac{n}{r}\int_0^1\fint_{S_r}(\nabla v(x+s\xi)\cdot\xi)\xi\,d_{S_r}\mathrm{d}s$ | [69] |

describe somitogenesis [42], mesenchymal condensation in early limb development [43,44], neuronal positioning in early brain development [45,46] and zebrafish gastrulation [41]. Notably, many of these studies integrate modelling with experimental data. The formulation of non-local advection models for cancer invasion has addressed the question of how cell–cell and cell–matrix adhesion interact with other mechanisms to facilitate cancer invasion, e.g. [47–53]. As one example, the study of [51] recapitulates various observed tumour infiltrative patterns, as well as the characteristic morphologies of ductal carcinomas and fibroadenomas. Other cellular applications of non-local advection models include the interactions between liver hepatocyte and stellate cells for *in vitro* culture systems [54]. Non-local models of cell migration and spread including adhesion have also been extended to account for further structure, such as cellular age and the level of bound receptors; see [51,52,55,56]. Including variables characterizing subcellular dynamics opens the way for multiscality.

Non-local advection models have also been applied extensively to problems of animal movement, particularly animal swarming/flocking behaviour. The pioneering model of [57] featured a non-local advection based on a convolution, modelling the attracting and repelling interactions between neighbouring swarm members. This model has sparked various extensions and significant analysis, for example see [58–63]. In the context of swarming, hyperbolic approaches have been developed in which non-local interactions are included in the turning behaviour of swarm members, allowing extensions to orientation alignment (see the review in [64]). Non-local advection models have also been used to incorporate perceptual range into the model [23,24], i.e. animal movement according to information drawn from potentially large regions of their environment.

## 3. Classes of non-local models for cell migration

We can extend (1.1) to a general RDA equation of the form (3.1), describing the evolution of a subpopulation density $u_i$ as a part of an ensemble $u = (u_1, \ldots, u_n)$ of $n \in \mathbb{N}$ components representing cell densities, densities of a surrounding fibrous environment (e.g. natural or artificial tissue), concentrations of nutrients and chemical signals, etc.:

$$\partial_t u_i = \nabla\cdot(a_{i0}(u)\nabla u_i) - \nabla\cdot\left(\sum_{j=1}^{m-1} a_{ij}(u)\nabla b_{ij}(u)\right) + a_{im}(u). \tag{3.1}$$

Here, $\nabla = \nabla_x$ is the spatial gradient, $m \in \mathbb{N}$, and the coefficients have the following meaning: $a_{i0}(u)$ is the diffusion coefficient (normally non-negative), $a_{ij}(u)$ and $b_{ij}(u)$ for $j \in \{1, \ldots, m-1\}$ describe tactic sensitivities and signal functions, respectively, and, finally, $a_{im}(u)$ is the reaction-interaction term. As previously remarked, non-locality can be introduced in multiple ways into such partial differential equations (PDEs). Often, it takes the form of an integral operator with respect to time $t$ and/or position $x$ in a spatial set $O \subset \mathbb{R}^d$, $d \in \mathbb{N}$, but other independent variables (e.g. orientation/speed or age/phenotype/individual state, etc.) can also be involved. A typical spatial non-local operator can be described as follows:

$$\mathcal{I}v(x) := \int_O J(x,y)v(y)\,\mathrm{d}y,$$

where $J$ is some kernel defined in $O \times O$. If, for instance, $O = \mathbb{R}^d$ and $J = J(x-y)$, then the so-called convolution notation is used

$$\mathcal{I}v = J \star v.$$

It can be seen e.g. as the combined ability (over the whole spatial region $O$) of some extracellular trait (mediated by a density distribution function $J$) and some quantity $v$ (density/volume fraction/etc.) to determine the cell density at a specific location $x$.

Non-localities of orders zero, one or two can be distinguished according to whether a coefficient function, a first- or a second-order differential operator is replaced by a non-local one. For example, a zero-order non-locality is present if an $a_{ij}$ is made dependent upon $\mathcal{I}u$. Moreover, non-locality can be introduced into the reaction, taxis or diffusion terms, leading to another possible classification. In the subsequent text, we address these and other possibilities in more detail.

### (a) Spatial non-locality in advection terms

There are (at least) four ways to include a non-locality into the advective flux; see table 1.

Hereafter, $B_r$ and $S_r$ denote the open $d$-dimensional ball and the $(d-1)$-dimensional sphere, respectively, which are centred at the origin and have radius $r$, termed the sensing radius. The operator $\fint$ denotes the usual averaging over the set upon which the integration takes place. For the precise mathematical formulations consult the references in table 1. Constructions in lines 1 and 2 in the table can be viewed as zero-order non-localities. The former describes, e.g. the situation of long-range interactions of individuals having density $v_1$ with their environment containing a signal of concentration $v_2$ (think of cells extending protrusions towards sites with higher concentrations of some chemoattractant, i.e. directing themselves towards the gradient of such concentrations). If the chemical signal itself is assumed to move much faster than the cells—

which is often the case—then $v_2$ can actually be expressed as a function of $v_1$, possibly in a non-local way, too, thus leading to a flux of the form $(J_1 \star v_1)\nabla(J_2 \star v_1)$, as e.g. in [58]. This corresponds to direct, long-range intraspecific interactions. Line 2 in table 1 refers e.g. to the case of individuals (cells, ants, …) moving in a collective way, thereby perceiving and correspondingly adapting to regions with large crowd density.[1] Concerning the remaining lines of table 1, an operator $\mathcal{M} \in \{\mathcal{A}_r, \mathring{\nabla}_r, \mathcal{T}_r\nabla, \mathcal{S}_r\nabla\}$ can be used to include a non-locality of first order. A basic model example of the latter case is given by a system of two equations

$$\partial_t u_1 = \nabla \cdot (a_{10}(u)\nabla u_1 - a_{11}(u)\mathcal{M}(b_{11}(u))) + a_{12}(u) \tag{3.2a}$$

and

$$\partial_t u_2 = a_{20}\Delta u_2 + a_{21}(u), \tag{3.2b}$$

equipped with suitable initial and boundary conditions. It can describe growth and motility of a single-cell population of density $u_1$ biased by intra- and interspecies interactions and/or a signal concentration $u_2$. The latter is either a diffusing chemoattractant/-repellent if $a_{20} > 0$, or, if $a_{20} = 0$, an insoluble cue—usually a non-diffusing polymeric matrix such as tissue fibres. Further components can be included into the system, e.g. other cell populations and other soluble/insoluble signals.

A non-local chemotaxis model was introduced in [68] and further studied in [67,70–72]. Such settings can be derived from position- or velocity-jump processes under adequate assumptions, e.g. constant $r$ for shrinking spatial mesh size or non-local sensing introducing a bias of higher order with respect to $r$. This leads to the operator $\nabla_r$ in the advection term. Cell–cell and/or cell–tissue interactions are usually characterized by a so-called adhesion operator $\mathcal{A}_r$ involving a suitable function $F_r$. The latter represents the distance-dependent magnitude of the interaction force. We refer to [35,70,72] and references therein for formal deductions of such models. Other versions characterizing the non-local space–time dynamics of one or several interacting species (cell populations, soluble and insoluble signals) have also been addressed [35,47,49,73].

Very recently, a model class was introduced [69], which uses $\mathcal{T}_r\nabla$ (resp. $\mathcal{S}_r\nabla$) rather than $\mathcal{A}_r$ (resp. $\mathring{\nabla}_r$). There, it was pointed out that on the one hand

$$\mathcal{A}_r u = \mathcal{T}_r(\nabla u),\ \mathring{\nabla}_r u = \mathcal{S}_r(\nabla u)$$
$$\text{in } \Omega_r := (x \in \Omega : \operatorname{dist}(x, \partial\Omega) > r),$$

whereas, on the other hand, e.g. for $\Omega = (-1, 1)$ and $u \equiv 1$ in $\Omega$

$$\mathcal{T}_r(u') \equiv 0 \equiv u', \quad \int_{-1}^{1} |\mathcal{A}_r u|\, \mathrm{d}x = 1 \ \text{ for } r \in (0, 1). \tag{3.3}$$

In [69], $\Omega_r$ was termed *domain of restricted sensing* since there cells *a priori* cannot directly perceive signals from outside the domain of interest $\Omega$. For $r \to 0$, it tends to cover the whole of $\Omega$. By contrast, a cell inside the $r$-thick boundary layer $\Omega \setminus \Omega_r$ can potentially reach beyond $\partial\Omega$. Of course, if $r$ is larger than the diameter of $\Omega$, then each cell can do that. However, if the population is kept in a Petri dish or it is confined within comparatively hard barriers, e.g. bone material, then the cell flux through the boundary $\partial\Omega$ vanishes. This leads to cell densities such as $u$ from above. As (3.3) shows, in such cases the outputs under operators $\mathcal{A}_r$ and $\mathcal{T}_r\nabla$ are equal in $\Omega_r$, but may disagree substantially inside $\Omega \setminus \Omega_r$ even for very small $r$. In the case of impenetrable boundaries and $r$ close to zero, the study in [69] supports the idea that cells actively adjust their movement after suitably sampling signal gradients rather than densities. We refer to that reference for a detailed discussion.

Other continuous models have been obtained by starting from a particle description, e.g. accounting for long-range attraction and short-range repulsion between individuals in a population alongside Brownian dispersal. In the limit of sufficiently large populations these lead to nonlinear PDEs for one-component models [65,74] containing, for instance, a degenerate diffusion $a_{10}(u) = u$ as well as an operator $\mathcal{J}$ in the advection. Further models in this category have been proposed in [75,76]. Models accounting for cell interactions with attraction or repulsion have also been studied in [37,38]. A related approach [77] employs an off-lattice ABM and derives a continuum approximation able to account for correlations between moving cells. A mean-field approximation of the evolution equations obtained for one- and two-cell density functions starting from Langevin equations for cell movement leads to a PDE akin to the more common adhesion models from above. Models with similar mathematical structure are also used to describe crowd dynamics, flocking or swarming, often referred to as self-organization models; see [78–80] and references therein.

## (b) Further types of spatial or other non-locality

Replacing the usual Laplace operator in a diffusion term with a fractional Laplacian (e.g. [81]) is another way of including spatial non-locality within motility terms and exemplifies a second-order non-locality. Such models account for dispersal of individuals performing Lévy flights rather than Brownian motion, cf. §1. Systems describing competition between locally and non-locally dispersing populations were developed and studied in [82,83].

Non-localities introduced into reaction-interaction terms can still affect cell motion, albeit indirectly. Indeed, cell proliferation and decay (alongside intra- and interspecific interactions) lead to local changes in densities, which flows into the density-dependent coefficients. From a modelling perspective, this accounts for population pressure, competition for resources, cooperation in signal transmission, differentiation, and/or tissue degradation, etc. But even when motion coefficients do not depend on the population density, local versus non-local source terms may lead to different overall evolution; see the discussion below. In a broader framework, classical reaction terms in population dynamics have been introduced in [84,85] and they are local. For the emergence and evolution of a single biological species, the typical choice is

$$a(u) = \mu u^\alpha (1 - u) - \gamma u. \tag{3.4}$$

For $\alpha = 1$, growth is proportional to the population density and limited by competition for available resources. The case $\alpha > 1$ accounts for advantages of clustering together or organizing in groups. This applies to cells [86], but also to sexual reproduction (case $\alpha = 2$) or swarming of animals.

Individuals, of course, typically perceive information related to occupancy, biochemical cues, etc. within a neighbourhood centred on their current position. Thus, local terms like (3.4) have been recently replaced by non-local ones. The best known example of the resulting equation is

$$\partial_t u = \Delta u + \mu u^\alpha (1 - J \star u^\beta) - \gamma u, \tag{3.5}$$

where $J$ is a kernel as above, and $\alpha, \beta, \mu, \gamma$ are constants. Here, the non-locality is of order zero. Similar reaction terms have

been used, e.g. to describe natural selection of tumour cells leading to the emergence of therapy-resistant clones [87,88]. Further examples of non-local source terms, not necessarily connected to biological applications, are of the form $a(u) = f(u) + I(g(u))$, where $I(\zeta) := \int_\mathcal{O} \zeta(y, t)\,\mathrm{d}y$, e.g. [89–91]. In a biological context such terms can account for both local and non-local interactions between cells and their surroundings. We refer to [92,93] for a rich variety of non-local reaction models in engineering and biology.

Several model classes have also been developed featuring integral terms that describe non-locality with respect to one or several other variables, including age, phenotype, internal cell state, velocity, etc. They include the large class of structured population models [94], as well as kinetic transport equations (KTEs) (and in particular the so-called kinetic theory of active particles framework; see [95,96] and references therein). Under appropriate conditions, models with spatial non-locality can be (formally) derived from KTEs, e.g. [68,97].

## 4. Local versus non-local models: mathematical aspects

This section briefly discusses relevant qualitative results. We focus on analysis pertaining to just two model classes: equations featuring non-local reaction and local diffusion, e.g. (3.5), and settings that involve a first-order non-locality to model a process such as adhesion or non-local chemotaxis (cf. §3a). Our motivation for this focus is as follows. On the one hand, the most straightforward way of accounting for non-locality is via a zeroth order in the source terms.[2] Thus, understanding and overcoming challenges met when analysing such equations is essential for developing a general mathematical theory applicable to non-local problems. Consequently, the basic representative of the class, equation (3.5), has received significant attention by analysts. While models involving first-order non-localities have received considerably less study, they are particularly relevant for applications, particularly in the context of collective motion phenomena (cf. §2).

### (a) Analysis of models with spatial non-localities in reaction terms

The analysis of reaction–diffusion equations featuring non-localities in source terms is highly challenging, in large part down to classical techniques that rely on comparison principles being no longer valid. A general theory seems presently out of reach, since the analysis heavily depends on the exact form of involved non-locality, where key features of the corresponding settings are revealed, e.g. [89–91]. If one includes a parameter where, as it is formally sent to zero, the non-local equation becomes local, then one can expect that results for the local equation can be suitably generalized to the non-local setting. As for the corresponding local case, studies of general non-local models such as (3.5) include results on global well-posedness, blow-up and stationary solutions. Specific solutions, such as stationary, radially symmetric, travelling wave solutions, or monotone wavefronts have also received attention owing to their relevance in applications.

To exemplify, consider the relatively well-understood non-local Fisher–KPP equation (3.5) for the case $\gamma = 0$. For $J \equiv 1$, which corresponds to the situation of blind competition, and with general $\alpha$, $\beta \geq 1$, a global bounded solution has been shown to exist both for bounded and unbounded domains [98,99]. When the kernel $J$ is replaced by the Dirac delta function, (3.5) reduces to a classical, local reaction–diffusion equation. There, results on global well-posedness, asymptotic stability of non-trivial stationary solutions, as well as other solution behaviours such as hair-trigger effect,[3] extinction and quenching, have been intensively investigated, e.g. [84,100,101]. If instead $J > 0$ in a ball of positive radius, then the non-locality can have a profound impact. For instance, the constant solution $u \equiv 1$ can lose the stability of the corresponding local case with a periodic-in-space stationary solution bifurcating from it [102–104]. This phenomenon has been observed in the study of travelling wave solutions, and numerically tested for the time-dependent version in [97]. On the other hand, if $J$ has an everywhere-positive Fourier transform or if it approximates the Dirac delta function, then there are travelling waves connecting $u = 0$ and $u = 1$ for $\alpha = 1$ (see [105]), and [97] shows that for $1 \leq \alpha < 1 + 2\beta/N$ the hair-trigger effect appears, while for large $\mu$ values $u = 1$ can indeed become unstable and Turing patterns occur [106]. Similar results have been obtained for the bistable case [107]. As observed in [97], the concrete solution behaviour, in particular with respect to pattern formation, depends strongly on the shape of the interaction kernel. Even for (3.5) the integral kernel must be fixed to study in detail long-time behaviour. For systems of PDEs with non-localities in the reaction terms the situation is even more complicated and, to our knowledge, there has been no breakthrough in the study of behaviour in this context.

### (b) Analysis of models with spatial non-localities in advection terms

The rigorous analysis of local RDA systems has enjoyed great popularity over recent decades. The Keller–Segel systems are among the best studied [26,108,109], a model class corresponding to $\mathcal{M} = \nabla$ in (3.2). By contrast, only a few studies consider problems including one of the four non-local operators introduced in table 1 that lead to first-order non-localities. At a general level, combining local diffusion with non-local advection appears to preclude the existence of an energy functional satisfying a precise dissipation identity, as known for various formulations of local Keller–Segel model and providing a key for their analysis. Owing to this drawback, only settings where the non-local advection is effectively dominated by diffusion have been investigated so far. This is generally the case when the operators $\mathcal{A}_r$ or $\mathring{\nabla}_r$ are involved, since they replace a differential operator by an integral one, leading to an increase (rather than a decrease) in regularity. In the absence of other effects this allows well-posedness to be established. Moreover, it turns out that the uniform boundedness of solutions can be guaranteed under quite general assumptions, including even cases where the corresponding local system exhibits finite time blow-up. Even situations in which $a_{10} - a_{11}\partial_{u_1} b_{11}$ is somewhere negative can be covered. In the corresponding local setting this implies negative self-diffusion and, generally, non-existence of solutions. A detailed analysis of a non-local chemotaxis system was carried out in [67]. Several studies, in particular [52,66,73,110–112], address equations or systems featuring the adhesion operator $\mathcal{A}_r$ or its extension to a possibly unbounded sensing region [113]. Some works

exploit specific solutions that are particularly relevant for applications, including steady states and their stability, existence of travelling waves, etc.; see [114] and [67,70,110,111,115] for models with $\mathring{\nabla}_r$ and $\mathcal{A}_r$, respectively.

Overall, operators $\mathring{\nabla}_r$ and $\mathcal{A}_r$ form a powerful alternative to the local gradient, particularly as they allow modelling a broader range of aggregative mechanisms without fear of potential blow-up. Moreover, as formal Taylor expansions performed in [116] and [47], respectively, indicate, $\mathring{\nabla}_r$ and $\mathcal{A}_r$ approach the local gradient $\nabla u$ for some fixed smooth $u$ and vanishing $r$. In [67], the question was therefore raised concerning convergence of solutions to a family of non-local chemotaxis systems as $r \to 0$. This corresponds to the sensing region of a cell almost shrinking to its respective position, i.e. the sensing is effectively local. However, as the example from §4a indicates, blow-up may appear in the gradient limit on the boundary of the spatial domain. Using $\mathcal{T}_r\nabla$ or $\mathcal{S}_r\nabla$ instead excludes this undesired effect. These operators are, however, computed based on the gradient and they are closer to it both quantitatively and qualitatively. Consequently, the domination of diffusion over advection demands much stronger conditions on coefficients $a_{ij}$ and $b_{ij}$. Suitable conditions have been found and existence and rigorous convergence (of a subsequence) of solutions proved in [69].

The issue of connecting spatially local and non-local models acting on the same (macroscopic) scale has also been addressed, e.g. in [58] (upon performing an adequate scaling) and, as mentioned above, in [47,116] upon Taylor approximations (for small $r$) of functions inside the non-local operators. Those deductions are, however, formal, whereas [69] provides a rigorous approach.

## 5. Outlook

Several challenges arise in connection with non-local models, some of which we already mentioned. Here, we focus on models for cell migration, but most mathematical issues also apply to systems of this type characterizing other real-world phenomena.

From the *modelling* viewpoint, the settings can be extended to account for various aspects of cell migration and growth. For instance, tumour heterogeneity can be with respect to cell phenotypes, motility, treatment response, etc.; each of these is influenced by the composition of the tumour microenvironment, which in turn is dynamically modified by the cells, according to their population behaviour. This results in ODE–PDE systems with intricate couplings and nonlinearities, even if only spatial non-locality is considered. Including several populations of cells structured by further variables, as addressed at the end of §3b, leads to multiscale descriptions, involving hyperbolic and/or parabolic PDEs with various non-localities. The latter can also occur in a pure macroscopic framework with only spatial non-locality. When the cell densities evolve in a bounded domain one has to provide adequate boundary conditions. Depending on the complexity of the system accounting for interactions of cells between themselves and their surroundings, deriving them together with the population-level dynamics is often non-trivial and calls for a careful modelling starting on lower scales and performing appropriate upscalings. Connections between local and non-local settings retain their relevance also in this context. From the *numerical* viewpoint, non-local models present significant challenges: integrating across a non-local region carries a substantial extra burden over classical local RDA models, compounded as one moves into higher (e.g. three) dimensions. Numerically efficient techniques can be developed (e.g. [36,47]), although they typically rely on, e.g., convenient boundary conditions or static sensing regions. Continued development of efficient methodologies is therefore a must for further, more intricate applications.

From an *analytical* viewpoint, it is desirable to support initially formal deductions by performing a rigorous limit procedure wherever it is possible. Notwithstanding, qualitative properties, such as the well-posedness, the long-time behaviour including the possibility of a blow-up, the limit behaviour with respect to some vanishing parameter, etc. need to be addressed for the resulting models. Overall, these key aspects have remained open for many cell migration models, and that includes even local, single-scale ones. Introducing a non-locality into a well-understood local model can lead to additional challenges since it breaks the original structure; see the discussions in §4.

Data accessibility. This article has no additional data.

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## Endnotes

[1]Thereby, $J \star v$ can be seen to represent the average density felt by the individual.

[2]In this review, we use the standard designations 'reaction' and 'source' for all terms containing zero-order derivatives.

[3]Meaning that an initially very small cell density can evolve in the long term into a cell mass completely filling the space, i.e. at maximum density.

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