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Introduction

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Multi-scale analysis and modelling of collective migration in biological systems

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Collective migration has become a paradigm for emergent behaviour in systems of moving and interacting individual units resulting in coherent motion. In biology, these units are cells or organisms. Collective cell migration is important in embryonic development, where it underlies tissue and organ formation, as well as pathological processes, such as cancer invasion and metastasis. In animal groups, collective movements may enhance individuals' decisions and facilitate navigation through complex environments and access to food resources. Mathematical models can extract unifying principles behind the diverse manifestations of collective migration. In biology, with a few exceptions, collective migration typically occurs at a 'mesoscopic scale' where the number of units ranges from only a few dozen to a few thousands, in contrast to the large systems treated by statistical mechanics. Recent developments in multi-scale analysis have allowed linkage of mesoscopic to micro- and macroscopic scales, and for different biological systems. The articles in this theme issue on 'Multi-scale analysis and modelling of collective migration' compile a range of mathematical modelling ideas and multi-scale methods for the analysis of collective migration. These approaches (i) uncover new unifying organization principles of collective behaviour, (ii) shed light on the transition from single to collective migration, and (iii) allow us to define similarities and differences of collective behaviour in groups of cells and organisms. As a common theme, self-organized collective migration is the result of ecological and evolutionary constraints both at the cell and organismic levels. Thereby, the rules governing physiological collective behaviours also underlie pathological processes, albeit with different upstream inputs and consequences for the group.

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

1. Introduction

Collective migration, the coordinated movement of groups of biological units, is observed across a multitude of scales in living systems (figure 1). At the cellular scale, it plays an essential role in biological development and the progression of cancer [2–4]. In particular, the collective migration of cohesive cell groups is observed during embryogenesis and is key to the formation of complex tissues and organs. Here, multicellular dynamics form the basis of epithelia, vascular and neuronal structures, with very different resulting shapes and functions. Similar collective cell behaviour is displayed by many invasive cancer types,

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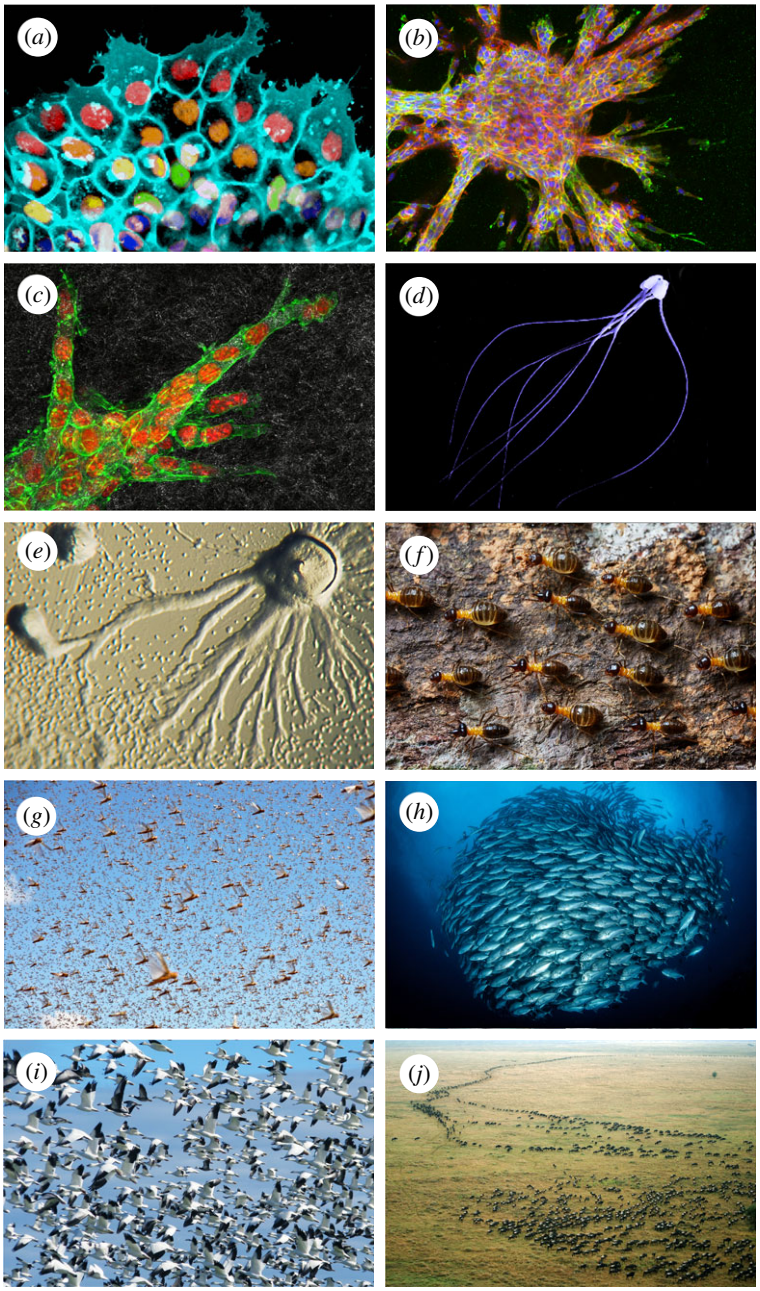

Figure 1. Collective migration in biological systems. (*a*) Collectively migrating neural crest cells in *Xenopus* embryos; membrane in cyan, nucleus pseudocoloured to distinguish leader (red) and trailing (blue) cells, photograph by Roberto Mayor; (*b*) E-cadherin negative MMT cells invading three-dimensional fibrillar collagen, photograph by Olga Ilina and Peter Friedl; (*c*) collective migration of cancer cells *in vitro* (red, nuclei; green, cytoskeleton; grey, collagen), photograph by Antoine Khalil and Peter Friedl; (*d*) electronmicrograph showing the aggregate formed by seven sperm cells of the dear mouse (*Peromyscus maniculatus*), modified from [1]; (*e*) collective migration and aggregation by chemotaxis in the social amoeba *Dictyostelium discoideum*; (*f*) a colony of termites (*Nasutitermes* sp.) on a march for food, following, and leaving, trail pheromones, photograph by Paul Bertner; (*g*) a migratory swarm of locusts (*Schistocerca gregaria*) in Isalo National Park, photograph by Tiphaine Desjardin; (*h*) a school of bigeye trevally (*Caranx sexfasciatus*), photograph by Ludovic Galko-Rundgren; (*i*) a flock of greater snow goose (*Chen caerulescens atlantica*), photograph by Will MacGregor; (*j*) the great wildebeest migration in the Serengeti National Park (*Connochaetes gnou*), photograph by Pete Aighton. (Online version in colour.)

where detrimental tissue disruption and collective metastasis consequently arise [5]. Collective migration at the organismic scale is observed in animal species that typically move over long distances and in a periodic manner implying a regular return to the region of departure [6]. The Natal sardine run is, without any doubt, one of the most spectacular examples of collective migration observed in the wild [7]. It is the second most important animal migration on the planet after that of wildebeest in the Serengeti [8], and it takes place every year from the beginning of May to the end of July along the east coast of South Africa. Millions of sardines (*Sardina pilchardus*) leave the cold waters of the Cape region to go up north, following the 'Benguela' stream, which moves up along the coast, to join more temperate waters. Schools of sardines can reach sizes of more than 7 km length, 1.5 km width and 30 m depth. Collective migrations may be seasonal, but also irruptive and linked to the particular context. Thus, in locusts (*Schistocerca gregaria*), individual insects adapt their physiology, morphology and behaviour to gregarious life when environmental conditions (rain, abundance of food) become favourable and when their density exceeds the threshold of about 65 winged adults per square

metre [9–11]. The adults gather in gigantic swarms of several million insects, which can travel thousands of kilometres, fall on the crops and devastate everything on their path. That was one of the largest outbreaks of the last century and it is an ongoing problem in East Africa.

In each of these scenarios, collective movements require a tight behavioural coordination of individual units, based on the direct, proximate or indirect, mid- or long-range exchange of information between the units [12–15]. Information exchange then influences the behaviour of other individuals of the group at a later point in time, in support of collective coordination or dispersion. Physical and mechanical interactions are also involved in coordinated movements at the cellular level in combination with topographic cues [16,17]. The fine decoding of the mechanisms governing such collective phenomena has been facilitated by the development of new tracking techniques making it possible to reconstruct with an increasing level of precision the trajectories of cells and organisms in moving groups and over increasingly long periods of time [18–21]. High-precision tracking combined with mathematical modelling has enabled us to understand how the non-trivial properties of collective dynamics emerge at the macroscopic scale from the combined interactions between the units at the microscopic level [12,22,23]. For a long time, conceptually similar research fields evolved independently, i.e. theorizing on how individual behaviour influences collective migration [24–28] or identifying similar collective phases in migrating lymphocyte clusters and fish schools [27,29,30]. Recent developments in parameterization, modelling and multi-scale analysis now permit us to extract common principles as well as differences between these phenomena at cellular and organismic levels.

The overarching goal of this theme issue is to bring together biologists, physicians, physicists and mathematicians in order to meet this challenge. The articles span central facets of studying collective migration phenomena in both cellular and behavioural biology. This includes methodological advances in data analysis to reconstruct the physical and biological interactions between units; integrating strategies to parameterize and quantify the collective dynamics of cells, tissues and animal groups; and the development of discrete and continuous mathematical models of collective migration. It is our intention that this issue will become a resource for scientists wishing to learn about the methods and techniques used to investigate collective migration in biological systems, to identify the similarities and differences in the coordination mechanisms at work at the cellular and organismic levels, and to shape future interdisciplinary research agendas.

2. Methods and key issues

The general methodology used to study collective migration operates at two levels, to monitor and quantify (i) the behaviours of individual units and, in parallel, (ii) the collective organization and behaviours of the group, and then connect both levels at different scales (micro, individual; meso, group; and macro, whole population), by means of mathematical models [12,14,22,31–37]. Third, environmental heterogeneity guides and modulates the structures, dynamics and forms of collective behaviours [38,39]. Consequently, the experimental work performed under laboratory-controlled conditions has to make it possible to identify and quantify the biological and physical interactions between units on the one hand and between units and the substrate on the other (i.e. the extracellular matrix in the case of cells, or the environment in case of animals), as well as the effects of these interactions on the behaviour of the units. To quantify such behaviour, the set of successive units' positions is recorded during a given period of time, usually at discrete time steps. Where possible, observations and measurements on individual and collective scales are also recorded in homogeneous environments, to decouple the modulation effects of these environmental parameters on individual interactions [40]. For studying collective movements of animal groups, experimental interventions include, for instance, precisely controlling temperature, brightness and humidity of the experimental room [41]. For monitoring cell groups, experimental variables include group size (from cell doublets to whole tissues and organisms spanning thousands of cells), chemical signals providing directionality (chemokines, cytokines), geometry (two-dimensional, three-dimensional), topology (linear, random), mechanical properties (stiffness, plasticity) and molecular organization of the extracellular environment [38]. From these experimental data, one can then reconstruct the trajectories of all units in a group and calculate different quantities, such as their instantaneous velocity and acceleration in response to directive cues present in the environment, as well as the group cohesion and polarization and, finally, reconstruct and model the functional form of interactions on an individual scale (e.g. [42,43] in this issue).

Understanding the non-trivial properties of collective dynamics that emerge at the macroscopic scale from interactions between units at the microscopic level requires the construction and use of mathematical models. The main function of a model is to predict or reproduce experimental results, including how individuals combine the information about the behaviour of their neighbours with environmental cues to coordinate their own motion and make collective decisions. Precise mathematical modelling (which is definitely not just fitting) is recognized as a major and often essential element of all research work in modern biology and especially in the research area of collective behaviour in biological systems (e.g. [12,44]. A model helps to identify the most important processes at play in the system. Thus, a model retains only a few, but highly characteristic and decisive, components of the real system. The model should consider as few parameters as possible so that, if a key component is missing in the model, it should be possible to extract particular experimental parameters that would invalidate the model. This strongly suggests that the retained minimal parameters jointly comprise and govern the key mechanisms underlying collective organization and decision-making. The qualitative and quantitative agreement between the model's predictions and experimental data contribute to our understanding of a system. A model failing at predicting or reproducing qualitatively or quantitatively (to some extent) basic experimental results is a sure sign that our understanding of the system is incomplete at best. In an iterative manner, new experiments are also commonly designed to try to put a model at fault, in order to test its domain of applicability/validity, and to find the minimal set of components that must be integrated to improve the model.

On the other hand, if the mathematical model is able to reproduce the experimental behaviour of interest in a satisfactory way, then one can modify the parameters to investigate what would happen in an experiment if a biological modification is introduced, prior to performing the experiments. Restricted to the collective dynamics this theme issue is focusing on, a key question one can ask the model aims at understanding how many changes at the individual level one should introduce in order to control the collective behaviour in the desired manner, how many leaders are necessary to control a group of uninformed followers, and how versatile and adjustable should the leadership role be to guarantee a collectively robust system.

Over the past years, a multitude of mathematical models for studying collective migration have been developed and are presented in this theme issue. Many of these models are derived from physical systems and adapted for the study of collective biological migration. For example, the cellular Potts model for interacting cell systems has been derived from a large-Q Potts model of interacting spins on a crystalline lattice, and the lattice-gas cellular automaton models for migrating cell populations have been adopted from lattice-gas models for incompressible fluids [45,46].

An important difference between living and non-living systems is the presence of stable heterogeneity in biological systems. For example, cells can differ strongly in speed and/or adhesivity. Therefore, it is important to quantify dynamic heterogeneity in experiments and in models. Only recently, mathematical models for collective dynamics have been developed to analyse the effects of heterogeneity [47].

To accommodate the increasing need of complexity and heterogeneity, various modelling and simulation platforms for the study of patterning and migration in multicellular systems have been introduced [48–50]. It will be important to make use of these platforms for the study of collective migration. Moreover, they might trigger the development of modelling and simulation platforms for animal populations too.

3. Overview of contributed papers

(a) Mathematical models and multi-scale analysis

After celebrated papers on collective migration of animal groups [51–55], the number of modelling approaches used to also describe the collective dynamics of biological cells has expanded considerably. Mathematical models look at collective phenomena from different levels: from the microscopic scale, e.g. by lattice-based and/or agent-based models, from the mesoscopic scale, e.g. by kinetic models, and from the macroscopic scale by systems of partial differential equations. From the mathematical point of view, such a burst of models operating at different scales has brought the need of connecting the models, highlighting not only similarities and differences, but also of clarifying how, in the various models, information at the smaller scale can be transferred to the larger scale. This requires the use and development of proper multi-scale methods [56]. Instead, staying on the same modelling level calls for a systematic comparison of different models and for the study of how different model terms affect the collective behaviour of the aggregates.

The most natural approach to describe the coordination of collective movements in groups of cells and organisms is the one that describes the behaviour of the single agents using individual-based or agent-based models. Such approaches can be split into two classes depending on whether a discrete lattice is used to describe space or not. Cellular and lattice-gas cellular automaton models are examples of on-lattice models [34]. Though on- and off-lattice models operate at the same spatial scale, the fact that space is described in different ways might lead to artefacts that need to be quantified. So, it is natural to ask whether such models yield similar results and to what extent. This is the aim of the contribution by Nava-Sedeño *et al.* [57]. Defining prototypic on- and off-lattice models of polar and apolar alignment, they show how to obtain an on-lattice from an off-lattice model for collective migration based on velocity alignment. For the purposes mentioned above, the macroscopic limits derived from the two model approaches are also compared, highlighting similarities and differences.

An important off-lattice model class for the study of collective migration is based on the idea of self-propelled particles (SPP), which describe autonomous agents converting energy from the environment into directed or persistent motion. Interacting SPP display fascinating collective phenomena. One of the most remarkable examples is the possibility of long-range orientational order in two-dimensional SPP models with continuum symmetry. The Mermin–Wagner theorem states that equilibrium systems with these characteristics cannot exhibit long-range order [58]. However, SPP with continuum symmetry and moving in a two-dimensional space, being out of equilibrium systems, can develop long-range orientational order, as shown for the first time in the seminal work by Vicsek *et al.* [54]. In this model, the velocity alignment of self-propelled agents is key for achieving different modes of collective migration. Meanwhile, various types of polar (ferromagnetic) and apolar (nematic) alignment have been studied with on- and off-lattice models [59–61]. In their paper, Bernardi and Scianna [62] address the collective dynamics in groups of moving animals with a 'deterministic SPP approach'. They use a similar modelling approach as in the contribution by Colombi *et al.* [63] that focuses on a cellular system. The migration of the population is described by a set of first-order ordinary differential equations for the animal positions, which can be formally derived from a second-order Newtonian approach under the assumption of an over-damped velocity response. Extending existing discrete models for collective migration that typically assume the constant speed of individual migration, the model by Bernardi & Scianna describes animals moving with changing speed and orientation, where the individual orientation response results from a set of behavioural stimuli. Model simulations capture different types of collective migration patterns depending on the particular choice of attractive, repulsive and alignment behavioural stimuli. The inclusion of an escape stimulus into the model allows the study of various hunting scenarios in a predator–prey system.

In agent-based and cellular automata models, it is straightforward to study the collective behaviours of cells or animals emerging from interactions with their spatial neighbours [27,64–67]. In fact, individual dynamics in such models explicitly take into account the interaction of particles located at different points in space. This is not the case in kinetic and continuous (e.g. reaction–diffusion) models that typically only represent reaction/interaction terms evaluated at the same space point. To deal with collective behaviours in

partial differential equation models that require us to take into account point-to-point interactions, one can include non-local operators over the region sensed by the individual that is characterized by a finite range and, e.g. a visual angle. The contribution by Chen *et al*. [68] summarizes how classical reaction–diffusion–transport models need to be transformed in order to take non-local effects into account. Modelling non-locality usually involves the introduction of convolutional operators in space. The focus of this contribution is to study the effect of the transport term that is typically in charge of modelling taxis-type migration phenomena. In fact, the literature has so far mainly focused on the transport aspect, though in principle a similar approach could be extended to other model components, to include non-local effects on growth and death. Moreover, the contribution also includes a discussion on how macroscopic reaction–diffusion–transport models can be obtained from microscopic individual-based models.

With a similar philosophy, in kinetic models, the tactic and kinetic responses of test individuals as a consequence of the non-local sensing of the surrounding environment and of the presence and behaviour of other individuals is considered by introducing non-local collision (or rather, interaction) operators [69–72]. In the kinetic framework, continuous models are recovered by diffusive or hydrodynamic limits, introducing, respectively, a parabolic or hyperbolic scaling of the kinetic model [71,73]. We mention that similar non-local operators should also be present in agent-based models when, in addition to other organisms, the individual needs to sense the environment for other important cues, typically chemo-attractants and substrate properties, which are usually described by continuous variables. In this theme issue, this feature is for instance present in the contribution of Colombi *et al*. [63] dealing with the migration of neural crest cells forming the posterior lateral line (PLL) of the zebrafish, which is a biological model system allowing the study of collective cell migration in embryonic development and pathological situations. PLL development involves the formation of a primordial cell cluster which collectively moves within the animal myoseptum. This process depends on the activity of specific diffusive chemicals, which trigger collective chemotactic cell migration and patterning. In this case, a multi-scale hybrid model is defined that integrates a discrete model for the cellular level and a continuous reaction–diffusion model for the molecular scale. With respect to previous mathematical models for PLL formation, the model developed by Colombi *et al*. [63] includes more molecular details, in particular, the two chemo-attractants FGF10 and SDF1a. Numerical model simulations can reproduce not only PLL development of wild-type embryos but also several pathological conditions induced by the fragmentation of the primordial cell cluster.

Another feature that can help classifying models for collective migration is whether they are deterministic or stochastic. Certainly, the former is a strongly simplifying assumption. Stochasticity is present in all behaviours of living organisms and cells. Cell and animal collective movement is no exception. Stochasticity might have a strong effect on the overall behaviour of the aggregate leading to what is called intrinsic noise at the group level. Theory predicts that the strength of intrinsic noise is not a constant but often depends on the collective state of the group. For this reason, it is also called a state-dependent noise or a multiplicative noise. This effect is discussed in the contribution of Jhawar & Guttal [74]. By characterizing the role of stochasticity directly from high-resolution time-series data of collective dynamics, they argue that the group-level noise may encode important information about the underlying processes at the individual scale.

The difficult step in every model is usually to pass from qualitative to quantitative validation. Luckily, the recent development of new tracking techniques allows the provision, in principle, of large and accurate data sets that can be used for this purpose. Unfortunately, so far data are only available for a few systems. In this respect, the contribution by Escobedo *et al*. [43] presents a general method to extract interaction functions between individuals that are required to achieve collective migration. The method is then specifically applied to characterize social interactions in two species of shoaling fish, the rummy-nose tetra (*Hemigrammus rhodostomus*) and the zebrafish (*Danio rerio*), which both exhibit burst-and-coast motion. In principle, the method can be extended to other systems when data becomes available.

(b) Collective migration at the cellular level

The collective migration of cells as a cohesive group depends on both the interaction between neighbouring cells through mechanical cell–cell junctions and/or chemical information exchange [75]. Intercellular junctions can be weak and transient, as in swarming leucocytes or neural crest cells, or very tight and cohesive, as in moving epithelia or contracting muscle [76]. As a result of collective organization and dynamics, cells move as sheets, strands, clusters or ducts rather than individually, and use similar actin- and myosin-mediated protrusions. In the end, collective polarization, force generation and cell decision-making eventually result in complex tissue organization.

(i) Embryonic development

The migration of neural crest cells in the developing embryo has provided a rich resource for understanding the balance between adhesive and chemical signal integration between cells moving as a loose collective. In their contribution, Shellard & Mayor [77] provide an overview on how moving cells integrate mechanical cell–cell coupling, based on cell–cell adhesion provided by cadherin molecules, that is counteracted by cell repulsion mediated by ephrins and semaphorins surface receptors (similarly to what is done in the contribution by Colombi *et al*. [63] mentioned above). Accordingly, a balance of adhesion and repulsion is critical in mediating cell alignment and group coordination. They further demonstrate the importance of chemotactic cell-to-cell signalling, which directs weakly adherent cells to align with neighbours and move along the joint trail. To recapitulate these principles, they summarize how computational modelling using Boïds, which simulates the flocking behaviour of birds [78], and robotics' algorithms to simulate the swarm intelligence [79] have contributed to identifying collective behaviours in the developing embryo as a self-organizing system.

In contrast to the developing embryo, sperm cell migration occurs in a fluid within body cavities, without direct adhesive sperm cell interaction. While only a single sperm cell will eventually fertilize the egg, the long-distance travelling of sperm cells towards the egg has recently been identified as collective dynamics. Schoeller *et al*. [80] here summarize quantitative

analyses on multicellular sperm dynamics, including wavelike patterns, multicellular coordination and directionality. Besides experimental observations, they describe mechanistic models that link the motion of individual sperm cells and their flagella to observed collective dynamics. As an emerging principle, multicellular coordination largely depends on the synchronization of the sperms' flagellae. Lastly, they discuss the importance of mucus, which provides a viscous extracellular environment for sperm propagation and multicellular coordination. Thus, as in multicellular organisms, an interplay between intercellular coordination and an integrating extracellular substrate jointly coordinate collective motion.

The development of a tree-like structure of epithelial branches is the central building block of several epithelial organs, including lungs, kidneys and the mammary gland. Their function is the secretion or absorption of molecules, coupled to a guiding tube-like duct structure for transport. Rens *et al.* [81] summarize the cellular mechanisms of branching morphogenesis, which include directed collective cell migration, oriented cell division, cell shape changes, cell differentiation and cell competition. Thereby, the moving epithelium interacts and is guided by the surrounding mesenchymal tissues, which ultimately dictates the geometry and function of the resulting organ. To extract the basic mechanism of autonomous branching morphogenesis, Rens *et al.* propose a simple mechanism, which is mediated by collective movement in the absence of proliferation and cross-talk with the surrounding mesenchymal tissue. Using combined cellular Potts and partial differential equation modelling, they show that cell-autonomous autocrine secretion of a morphogen (transforming growth factor-β, TGF-β) inhibits the formation of cell protrusions, which then leads to curvature-dependent inhibition of sprouting and duct formation. The outcome is consistent with the experimentally observed tissue geometry-dependent determination of the branching sites, and it suffices for the formation of self-avoiding branching structures.

(ii) Cancer invasion and wound healing

Collective cell migration also plays a major role in wound repair and cancer invasion. It may lead to the formation of cell clusters, i.e. 'multicellular structures' that enable cells to better respond to chemical and physical cues, when compared with isolated cells. In particular, epithelial cells heal wounds via the migration of large sheets of cells with tight intercellular connections. Various mathematical models have been suggested that allow mechanistic insights which will benefit the clinical understanding of wound healing [82]. Moreover, cancer invasion is a hallmark of cancer progression [83]. Increasing evidence indicates that metastasis is driven by collective cell migration, where clusters of metastatic cells invade collectively into the vasculature and lymphatic system of cancer patients [5]. Meanwhile, mathematical models have been established to analyse potential mechanisms of invasion with a focus on glioma invasion [84].

The contribution by Kim *et al.* [85] focuses on glioblastoma multiforme (GBM) which is the most aggressive and malignant brain tumour. GBM is characterized by aggressive proliferation and cellular infiltration of healthy brain tissue. The primary treatment option is surgery followed by chemoradiation. Unfortunately, recurrence of the tumour is almost sure to occur within a rather short time span, the causes of which are largely unknown. It has been speculated that surgery-mediated effects could play a major role. Kim *et al.* [85] define a mathematical model to study the implications of surgery on the dynamics of reactive astrocytes in the tumour microenvironment and test the following hypothesis: astrocyte injury from surgery induces a transition of reactive astrocytes into a stem cell-like phenotype which secretes the chemokine Cxcl5. This signal in turn promotes GBM proliferation and migration through the miR-451-LKB1-AMPK-OCT1-mTor signalling pathway, which is known to regulate GBM proliferation and invasion. The resulting multi-scale mathematical model couples a differential equation model for the signalling pathway and a reaction–diffusion model for glucose, oxygen and the chemokine with a force-based model for the dynamics of tumour cells and astrocytes after surgery. The model shows how variations in glucose availability significantly affect the activity of signalling molecules and, in turn, lead to critical cell migration. The model also predicts that microsurgery of a primary tumour can induce phenotypical changes in reactive astrocytes and stem cell-like astrocytes promoting tumour cell proliferation and migration. Moreover, a novel anti-tumour strategy based on Cxcl5-targeting drugs was tested with the help of the model. It shows that the optimal use of anti-Cxcl5 drugs may slow down tumour growth and prevent cell invasion and recurrence.

The contribution of Vishwakarma *et al.* [86] studies the dynamics of collective cell migration during epithelial wound closure which bear similarities with a jamming–unjamming transition in dense granular matter [87,88]. In this process, cells known as 'leader cells' migrate at the tips of cellular cohorts and provide directional cues to the followers. Interfacial geometry and bulk mechanical activity play an important role in regulating leader cell-mediated migration and subsequent collective migration. As cell density increases, the spatial distribution of velocities and forces becomes more homogeneous. Vishwakarma *et al.* [86] suggest the four-point susceptibility to characterize the dynamic heterogeneity of the cell population. This susceptibility has been previously introduced to quantify correlations between relaxation processes at different points in non-biological systems. It is shown that varying the susceptibility, by changing cell density, alters the number of leader cells at the wound margin. At a low heterogeneity level, wound closure is delayed, with decreased persistence, reduced coordination and disruptive leader–follower interactions. Finally, a microscopic characterization of cell-substrate adhesions illustrates how heterogeneity influences orientations of focal adhesions, i.e. affecting coordinated cell movements. Together, these results demonstrate the importance of the newly defined four-point susceptibility as readout of dynamic heterogeneity in epithelial wound healing.

(c) Collective migration at the organismic level

From the point of view of collective migration of animal groups, a previous theme issue of the *Philosophical Transactions* has already been devoted to behavioural ecology and movement ecology [89]. For this reason, this theme issue is not intended to cover the whole range of collective migration phenomena observed in groups of organisms. In fact, the examples discussed here concern more specifically the experimental analyses of behavioural interactions that take place at the individual scale and their impact on collective behaviour. In this respect, today, behavioural biologists have access to large volumes of data that make it possible to

precisely measure social interactions involved in the coordination of collective movements in animal groups, thanks to methods such as those presented by Escobedo *et al*. [43] in their article. Therefore, by systematically applying such methods it becomes possible to build a map of the different forms of social interactions used by different species to coordinate their movements when travelling in groups, according to their mode of propulsion, the shape of their body, their sensory and cognitive modalities and their living environment. Establishing such a map could bring important insights about the impact of these parameters on the various forms of social interactions, and in particular, the effect of an explicit alignment on the direction of movement of neighbours as observed in the rummy-nose tetra (*Hemigrammus rhodostomus*) [42] or a simple combination of long-range attraction and short-range repulsion as observed in the mosquitofish (*Gambusia holbrooki*) [90]. This information is crucial to understand the evolution of coordination mechanisms in moving animal groups.

Social interactions between organisms do not only allow the coordination of individuals' actions, but also they endow a group with emergent properties such as the ability to efficiently escape predator attacks and navigate up noisy and weak thermal or resource gradients, even if no individual is capable of estimating the local gradient. The animal group as a whole thus functions as an integrated self-organizing sensor network, which significantly increases the range of effective perception of individuals [91]. It is also well-known that collective foraging based on indirect interactions in social or pre-social insects or based on long-range direct interactions in vertebrates improves the detection and exploitation of food sources. In their article, Ding *et al*. [92] investigate the foraging strategies in *Caenorhabditis elegans*, a 1 mm long nematode which has very limited sensory modalities and very short-range social interactions. By combining a computational model and experiments carried out on two strains of *C. elegans*, one social and the other solitary, they show that very simple social interactions such as the detection by an individual of a nearby worm allows the social phenotype to detect more efficiently patchy food sources in the environment.

These results suggest that the amount of social information needed by each individual to ensure the coordination of collective actions is limited. Still, this question remains widely debated. In the case of starlings (*Sturnus vulgaris*), previous studies have suggested that each bird within a flock interacts on average with a limited number of neighbours (typically seven) rather than with all neighbours within a fixed metric distance [93]. However, several recent studies suggest that, in fish, each individual in a school would collect only a limited amount of information on its environment thus avoiding cognitive saturation [94–96]. In animal groups, it is particularly difficult to design experiments to investigate such complex issues. In this respect, the results reported in the article by Jayles *et al*. [97] provide some elements to answer these questions. Using an artificial sensory device that filters out and adapts the amount of information delivered in real time to the participants in simple segregation task experiments with human groups, it is shown that the amount of information collected at the individual scale deeply affects the collective separation dynamics. However, they also show that each individual must only acquire a minimum amount of information on their first seven nearest neighbours to get an optimal level of segregation. In fact, the results show that the acquisition of additional information by individuals does not improve the collective performance of the group.

4. A path forward: integration of the concepts and methods in future research

Collective migration phenomena observed in cells and animal groups share many similarities and their comparative study enriches both cellular and behavioural biology. It is, therefore, not surprising that not only the questions addressed, but also the concepts and tools used to study and understand these phenomena, are rather similar in these research fields.

Thus, in addition to the common use of tracking, trajectory analysis and modelling techniques, certain concepts and processes stemming from the analysis of collective behaviour in social insects such as *stigmergy* have been successfully applied to the description of the mechanisms underlying collective cell migration. Stigmergy is a process by which social insects such as ants or termites coordinate their foraging and nest-building activities through indirect interactions by depositing pheromone trails on the ground or impregnating building materials with chemical compounds [98,99]. These chemical traces constitute sources of information and stimulation that, once perceived by other insects, trigger the execution of specific behaviours leading to the self-organization of the activities in a colony [100]. It has been shown that the self-organized multicellular behaviours that occur during the collective migration of the social bacterium *Myxococcus xanthus* over a surface-solidified nutrient are coordinated, at least in part, through stigmergic processes [101]. Indeed, the components of the extracellular matrix and the furrows produced by vanguard cells facilitate and guide subsequent cellular movements. This process leads to the formation of trails that physically confine cells and facilitate their motility, which further reinforce and deepen the furrows, leading to the continued maintenance of the trail network. A similar mechanism has also been described in *Pseudomonas aeruginosa* that coordinates the expansion of its interstitial biofilms through the creation and remodelling of an interconnected network within a semisolid substratum [15]. Thus, stigmergy appears as an important self-organizing principle in biological systems. The study of collective cell migration could, therefore, benefit from the numerous experimental and modelling studies that have been carried out on stigmergic processes in social insects over the past 30 years [102–107].

The last decade has also seen further improvement in our comprehension of coordination processes and the way information pervades biological systems during collective motion, which has led to the development of new common research themes. One concept that has united several works in recent years is that of criticality [108,109]. An increasing number of works have indeed shown that biological systems such as collectives of cells, swarms of insects, flocks of birds and herds of sheep behave as though they are near the 'critical point' of a phase transition, like correlated spins in a magnet on the verge of ordering [110–115]. In flocks of starlings, for example, one can observe 'scale-free correlations', which occur on all possible length scales in the flock [116]. This hallmark of criticality is characterized by the fact that the velocity fluctuations of two distant birds mutually influence each other. The same property has been recently discovered in the self-organized aggregation of the social amoeba *Dictyostelium discoideum* in

response to starvation [114]. In this species the local coupling between cells via cAMP secretion is tuned to a critical value, resulting in emergent long-range communication between cells that span the whole group independently of its size. Here, criticality brings some adaptive advantage allowing cells to act as a single, coherent unit and to make informed decisions to achieve optimal aggregate sizes for the most effective spore dispersal. Criticality also endows a group of cells or organisms with an extreme sensitivity to changes in the behaviour of a small number of individuals within the group [117]. Thanks to the social interactions, the reaction of these individuals can spread to all the other group members, allowing them to react more efficiently to external disturbances such as a predator attack. In sheep, it has been shown that the intensity with which individuals imitate each other (i.e. the strength of the coupling between sheep) leads a flock to be in a critical state, while optimizing two conflicting needs at the individual scale: the need to explore the maximum area of space to avoid inter-individual competition when foraging and the need to keep contact with the other group members to ensure cohesion and protection in case of danger [113]. These few examples suggest that natural selection operates not only on the particular form of social interactions but also on their intensity so that groups of cells or organisms have collective adaptive capabilities. Future work should focus on confirming these collective properties in a larger number of biological systems.

Selection processes also drive cancer progression and support cancer cell heterogeneity, a hallmark of cancer. So far, cancer evolution and collective migration have been studied separately [118]. It will be interesting to include mutations and selection in mathematical models for collective cell migration that will shed light on the evolution of collective cancer cell migration.

Originally, the study of collective migration has focused on the implications of inter-individual interactions. More recently, the importance of the non-cellular environment has been studied in cellular systems. In a recent paper [119], the physical geometry and available space (confinement) have been identified as key regulators forcing cells together, irrespective of their cell–cell adhesion properties. Whereas highly adhesive epithelial cells retain strict cell–cell interactions and migrate with strong neighbour correlation (like a solid-like state), decreasing cell–cell adhesion provides increasing degrees of freedom with diminishing intercellular coordination until near-complete independence of individual movements is reached in the cell group (active fluid). This transition reflects a fundamental building principle to physically control unjamming transitions and cancer cell invasion irrespective of the composition and stability of cell–cell junctions. The new study highlights the importance of the non-cellular microenvironment while previous work focused on the role of cell–cell interactions. Beyond cancer cell invasion, jamming–unjamming transitions are likely to shed light on the mechanisms of multicellular cooperation and collective behaviours in a range of cell models, as well as animal migration and coordination such as those described in ants and sheep [120–122].

5. Conclusion

One of the key properties of life is that it can switch between gas-, fluid- and solid-like states: cells or organisms move independently (gas state), form lose connections and migrate collectively (fluid state), or aggregate into immobile sheets and clusters (solid or jammed state). In the devastating example of malignant tumours, cells switch from a solid-like state to an invasive fluid or gas state, ultimately leading to deadly metastases. What are the decision-making mechanisms that underlie these transitions? Since the celebrated paper by Vicsek *et al.* [54], who suggested alignment interaction as a simple organization principle of collective migration, we have seen major progress in the study of collective phenomena. This theme issue highlights important developments: quantitative mathematical models and new multi-scale methods for their analysis have been introduced and new organization principles have been suggested.

A general tendency is that models become more and more individualized and heterogeneity and variability is considered more and more in various model extensions. Though some models presented in this theme issue take into account the variability of response to environmental cues, very little has been done in coupling the individual behaviour to the internal mechanisms determining that behaviour and the related stochastic response. In the context of cell migration, emerging questions focus on how the expression of a protein and the triggering of certain pathways determine the collective behaviour and, in particular, discriminate between an individual and a social behaviour, between a leading role and a follower role. Studying such questions would require nesting a microscopic model into an individual-based model with the ability to include the possibility that not all individuals may respond in the same way to the same environmental cues, introducing further stochastic aspects.

The presence of anomalous diffusion behaviour at the single-cell level with the transition from random walks to Levi's walks [123] and their social control by the group is also an interesting subject that deserves to be addressed in the future.

In this respect, also in view of applications to crowd and traffic management, what has been learned by studying the behaviour of cell and animal groups can be transferred to human groups, in particular by using the same research methods (e.g. [124,125]).

Looking at animals and cells from a modelling perspective highlights similarities but also important differences. Better knowledge about collective decision-making in cell populations is highly relevant for medical applications. New cancer therapy ideas will benefit from new insights into the control of collective migration that are also relevant for optimizing wound healing and regeneration since the controlled switching between single and collective migration is a key ingredient in these systems. New insights into collective behaviour will also be important for tissue engineering and optimization of organoid systems, and for explaining collective polarity, cell sorting and lumen formation. To this end, better knowledge of both single-cell behaviours and the resulting effects on the organism will identify currently unappreciated types of indirect and long-range information exchange beyond juxtacrine cellular mechano-coupling, which underlie collective coordination, including the deposition of information in tissues (chemical memory), swarm intelligence and jamming transitions [87,88].

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