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Review

Steering yourself by the bootstraps: how cells create their own gradients for chemotaxis

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Chemotaxis, where cell movement is steered by chemical gradients, is a widespread and essential way of organising cell behaviour. But where do the instructions come from – who makes gradients, and how are they controlled? We discuss the emerging concept that chemotactic cells often create attractant gradients at the same time as responding to them. This self-guidance is more robust, works across greater distances, and is more informative about the local environment than passive responses. Several mechanisms can establish autonomous gradients. Best known are self-generated gradients, in which the cells degrade a widespread attractant, but cells also produce repellents and 'relay' by secreting fresh attractant after stimulation. Understanding how cells make and interpret their own chemoattractant gradients is fundamental to understanding the spatial patterns seen in all organisms.

Highlights

Cells can steer themselves by generating their own gradients of attractants or repellents.

Self-steering appears to be used widely throughout biology, but is not always identified.

Self-steering allows cells to obtain information about and interact with their environments.

One form of self-steering – self-generated gradients – yields unusually robust information and allows chemotax over long distances or through complex paths such as mazes.

Chemotaxis and its limitations

Multiple aspects of biology depend on chemotaxis [1]. During normal development, it directs cell movement as embryos grow and become more complex. The formation of normal gonads, for example, requires germ cells to be recruited by chemotaxis from distant sites in the embryo [2]. Similarly, chemotaxis can both cause pathological effects and help treat them. Metastasis, which drives most of the deaths caused by cancer, is often choreographed by chemotaxis [3], and immune cells such as neutrophils use chemotaxis to find and eliminate both pathogens and tumour cells [4].

During chemotaxis, cells interpret gradients of attractant [5,6]. The absolute amount of attractant is not important – the key parameter is the difference in attractant level between the front and the back. This is measured by receptors localised all over the cell's surface, which fall into several classes [7], all of which feature the same two physiological difficulties.

First, the receptors detect attractants over a limited concentration range. When attractant concentrations are too low, few receptors are activated, so the cell cannot detect any signal. Conversely, at high concentrations, receptors are nearly all activated (i.e., the receptors are saturated). In both cases, variations in attractant level between the front and back of the cell cause almost no difference between the receptors at the front and back, so no gradient can be detected. Chemotaxis therefore works well when the attractant gradients occupy a middle ground – a rule of thumb is that their concentrations should lie within about tenfold either side of the dissociation constant (K_d) for the attractant–receptor pair [7] for guidance across significant distances. The correct range ensures that changes in attractant concentration lead to measurable changes in receptor activation across the cell.

Second, cells are usually very small (neutrophils are <10 μm long) and the distances they need to move across can be large. A neutrophil in a linear gradient spanning 1 mm can at best experience

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a 1% change in attractant concentration between its front and back; this is not thought to be enough information for the receptors to interpret which direction the gradient comes from [8,9].

It is not possible to satisfy both the minimum detectable gradient steepness and the maximum attractant concentration over longer distances than this – a cell might read a part of the gradient, but it cannot be guided through the whole path [10]. Either the gradient is too shallow to detect or the receptors are unable to detect the low end or saturated at the high end; no concentration of attractant can serve both functions.

Chemotaxis is often presented as a passive process, with cells attracted along gradients created by external processes in which they play no part. When trying to understand a biological system, such a view presents several problems. It says nothing about how the patterns of attractants are established in space. The creation of this information is an integral part of the biological picture, and by ignoring it we present chemotaxis as a relatively trivial question of interpreting external instructions, rather like painting by numbers. Another issue is that this model of chemotaxis does not allow homeostasis; the cells' responses must be the same, whether one cell or a million follows the gradient [11]. Perhaps the most important problem is that this view is frequently at odds with the facts – there are many examples in real physiology where cells interact with their attractants, but these interactions are often overlooked in passive models of their migratory behaviour.

Below, we discuss three examples where cells create their own chemotactic signals – self-generated gradients, autorepulsion, and relay. We also explain why self-guidance works better than passive response, biological examples where self-guidance is important, and how it can be discovered.

Self-guidance as a driver of form

One approach cells can use to address these issues is self-guidance. This idea emerged from observations in several laboratories where chemotaxis is clearly physiologically important, but there was no obvious source of a gradient. For example, the zebrafish lateral line – a mechanosensory organ that detects water movements – is formed by a group of cells that migrate using chemotaxis, despite no detectable gradient for them to read [12]. Many years' work has led to the conclusion that the primordial group of cells that create this organ make the gradient themselves, at the same time as they move in response to it [13,14]. Similarly, metastatic cancer cells often spread via chemotaxis. It seems unlikely that the patient's body imposes a metastatic cue (which would be extraordinarily maladaptive), but rather that the gradients have been made from ubiquitous, healthy cues by the cancer cells themselves [15].

Mechanisms cells use to generate their own spatial information

Cells can use several different mechanisms to make their own chemotactic cues (Figure 1). Self-generated gradients – a currently popular field – work by local attractant depletion, but numerous other mechanisms have been discovered. We describe two: chemorepulsion and signal relay.

Attractant depletion – 'self-generated gradients'

If a chemoattractant is present everywhere, and a group of cells removes it, then the areas with the highest cell density will inevitably have the lowest local attractant concentration [16]. Groups of cells thus always create gradients directed away from their current positions, a phenomenon called a 'self-generated gradient' [10]. If many cells are present, the number required to degrade the attractant front will migrate away in a dense wave, degrading every trace of attractant in the environment. The cells behind the migrating wave are thus left with no directional cues and can

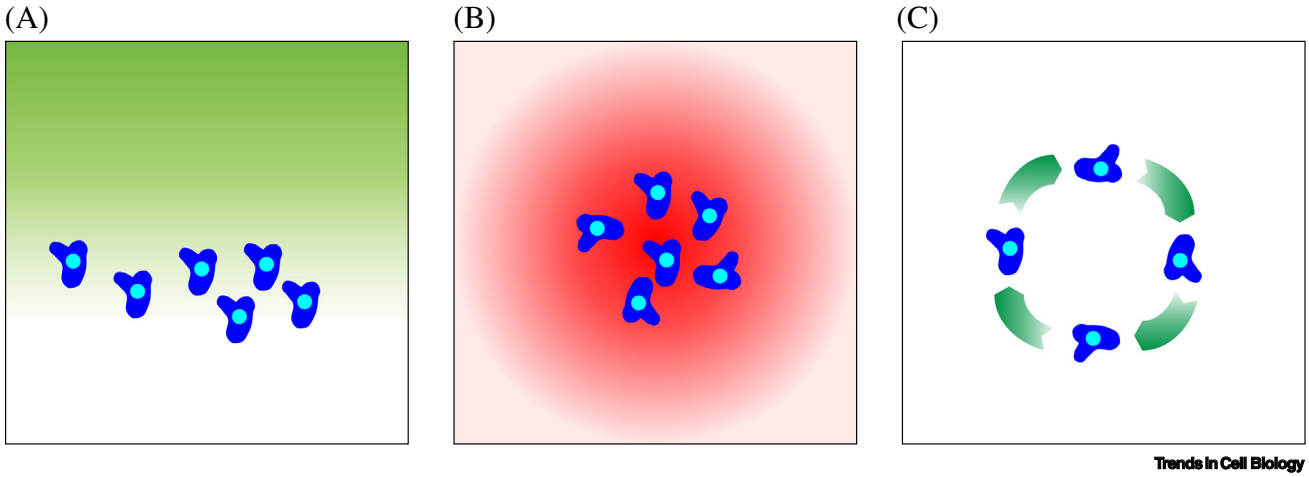

Figure 1. Self-guidance mechanisms used in normal physiology. (A) Self-generated gradient – cells break down an attractive chemical (chemoattractant) to generate an outward-facing gradient. (B) Autorepulsion – cells secrete a repulsive chemical (autorepellent) that drives themselves away from one another. (C) Relay – cells reply to a chemoattractant by producing chemoattractant themselves, as well as migrating towards the source; in the case illustrated, cells cyclically attract one another.

only move randomly. This yields a highly robust mechanism for creating spatial information, and additionally for recruiting specific numbers of cells. Cells continue to act as an attractant sink as they move, so the members of the leading wave maintain a very steep localised gradient around themselves, continuously guiding them towards areas they have not visited [10]. This makes self-generated gradients suitable for long-range migration, able to direct movement over distances that are much too long to navigate by simple chemotaxis. As discussed earlier, static gradients over long distances become unreadable. In self-generated chemotaxis, because the gradient is constantly reformed by the leading group of cells, it is always focused on where these cells are and can be maintained as long as fresh attractant is available to be degraded. Self-generated gradients also cope with saturating concentrations of attractant. These completely block simple chemotaxis, because no gradient can be read if receptors at both ends of the cells are saturated. In self-generated gradients, an excess of attractant just causes a delay to the migratory response [17]; the cells initially cannot migrate, but continually break down the attractant until its concentration is low enough that a readable gradient is formed [10]. Similarly, if there are not enough cells in the leading wave to break down all the attractant they encounter, then they leave attractant behind them, which attracts more cells to the wave. Most remarkably, self-generated chemotaxis allows cells to navigate through complex topologies like mazes [18].

Cells can deplete chemoattractants using several mechanisms. The simplest is enzymatic breakdown. Some metastatic cancers follow gradients of lysophosphatidic acid (LPA) they have themselves created using the cell-surface enzyme lipid phosphate phosphatase 3 (LPP3) [17,19]. Similarly, the chemotactic model organism *Dictyostelium discoideum* locally degrades both of its principal attractants (cAMP and folic acid) using membrane-bound enzymes (cAMP phosphodiesterase [20] and folate deaminase [21], respectively). Bacteria can create the same type of patterns by consuming local nutrients; this has the useful result of driving them towards areas with untapped resources [22]. Attractant may also be removed locally using dedicated scavenger receptors, which bind and internalise attractant without connecting to downstream signalling pathways [23]. The developing zebrafish lateral line is established by a thin stripe of the chemoattractant CXCL12a. A mechanically connected group of cells navigates along this stripe; cells expressing the signalling receptor CXCR4 are located at the front of the group, and cells with the scavenger receptor CXCR7/ACKR3 are positioned the rear [12]. Thus, the group

is constantly presented with higher CXCL12a at its front than its rear. Growth factors are active at much lower concentrations than chemokines. This means cells responding to growth factors can combine both functions in the same protein, because receptors such as the epidermal growth factor (EGF) receptor both communicate stimulatory signals to the cytoplasm and also endocytose and destroy their ligand EGF. This allows breast cancer cells to migrate using self-generated EGF gradients [24].

Autorepellents

A related way that cells can steer themselves away from a group occurs when they produce their own repellents. In one medically important example, the amoebic dysentery pathogen, *Entamoeba histolytica*, produces ethanol during growth; ethanol is also a strong chemorepellent [25]. This sets up a gradient that drives amoebas out of the gut lumen and into the host. At a bulk level, this is very similar to local attractant degradation, steering cells away from the centre of larger populations. However, autorepellents cannot create a leading wave; differences in the way cells respond to receptor saturation effects destabilise the migratory front and make it spread, rather than maintaining a peak of cell density [8]. Autorepellents have been observed in a number of different single-cell species, including *Helicobacter* quorum sensing [26] and *D. discoideum* colony dispersal [27], and may also mediate immune cell dispersal in humans [28], but are in general less frequently observed than self-generated gradients.

Autocrine signalling and relay

Chemotaxing cells can also produce their own attractants, a process known as 'autocrine signalling'. This opens up an additional set of feedback mechanisms that can create new information, independently or together with attractant breakdown. In cancer, the phospholipase autotaxin can produce LPA [29], which is a potent chemoattractant, and a number of immune cell types produce chemokines that they themselves respond to chemotactically. Autocrine signalling can even lead to incorrect identification of chemoattractants (Box 1).

If cells constantly produce and respond to attractants, this leads to simple clumping. However, if cells respond to a chemoattractant by triggering a pulse of new secretion of the same attractant, after a delay, the results are different and can be complex and unpredictable. This process, which has been called 'relay' [30], allows signals to propagate from cell to cell, with each sensing (and responding to) the attractant release from the last. Cells can use relay to orchestrate the aggregation of a dispersed population of cells on-site. Neutrophils, as the first responders of the innate immune system, use it to arrange inflammation at sites of infection [31]. Starving *Dictyostelium* amoebas transition from solitary unicells to multicellular bodies, using both chemotaxis towards and relay of cAMP. Both mechanisms are described in detail below. In

Box 1. Is growth factor chemotaxis really a complex self-guidance?

One class of self-generated gradient was controversial when published, but seems more clear-cut in the light of recent work. Zicha and Dunn [55] analysed cells migrating up different growth factor gradients. They found that while sarcoma cells moved significantly up-gradient, they steered more strongly towards one another than the growth factors that were thought to be steering them. A mathematical analysis of the cells' tracks concluded that cells were chemotactic, but attracted to an attractant they themselves made (i.e., an autocrine attractant) in response to the growth factors. Chemotaxis towards the growth factor itself was either absent or swamped by the autocrine attractant.

This work emphasises a fundamental problem with measuring chemotaxis – even with the best, direct-view chambers, migration up a gradient could indicate a small bias in some other migration process, rather than simple chemotaxis. One of the chief challenges for the field will be to separate primary chemotaxis, in which attractant gradients directly drive migration, from secondary processes like this.

each case, the cells also degrade the relayed attractant, allowing them to relay a signal without saturating areas of high-cell density and opening up the ability to use self-generated gradients and relay together.

What do cells gain by making their own gradients?

One of the biggest surprises from recent work is how differently cells behave when they respond to self-generated, rather than imposed gradients, even if the ligand is the same. They instinctively seem similar, but the biological outcomes are not [8]. One constant feature is self-organisation, making guidance cues responsive to the current positions and numbers of cells and allowing groups of cells to emphasise or ignore different stimuli as the response evolves.

Making gradients steepest near the responding cells

Self-generated chemotactic gradients are limited by the same biophysical issues described earlier for simple gradients. As potential paths get longer, gradients must be spread further so they become shallower. However, the self-generated gradients can use a clever mechanism to extend their range. If cells are clustered in one location, there is no need for the gradient to cover the whole path. In self-generated chemotaxis, the cells focus the gradient on wherever they are; the gradient can always be steep, and the level of receptor occupancy ideal, because the cells create it themselves [8]. This also means that the information provided by the gradient has a clear (and unusually dynamic) meaning. Up-gradient represents places the cell group has not reached, whereas down-gradient indicates places it has already visited.

This is particularly clear with self-generated gradients generated by breaking down an attractant, because they often cause cells to collect in a coherent wave. This means the local gradient can be extremely steep, because the cells are collected in a small area. It also allows cells to chemotax over large distances – the cells can travel in a wave, with saturating chemoattractant ahead of them and zero behind them wherever they go; the wave is self-maintaining, so it can travel continuously through distances many times larger than are possible with fixed gradients.

Refining external information

In this review, as in most of the literature, self-guidance mechanisms are mostly described as a way to create chemoattractant gradients where none exist before. However, existing information – for example, shallow gradients or attractant sinks – can bias self-guided responses. The information the cells respond to is self-made, but it reflects what was in the environment before. For example, an even field of *Dictyostelium* cells can convert a high-concentration, linear gradient of attractant (very hard to read accurately) into a near-exponential pattern that is much easier to interpret [10]. The cells react to the gradient they have made, but the overall direction is specified externally. This important gradient refinement mechanism may be one reason why self-generated gradients were not discovered sooner – the cells appear to respond to what they were given, though the real attractant profiles are radically different.

Exploring complex environments and mazes

One consequence of self-generated gradients was initially unexpected, but has wide-ranging implications – they allow cells to obtain information about their environment, even some distance away, without physically visiting it [18,24]. Gradients are created as attractant diffuses to replace what the cells have broken down. The directions of gradients depend on the geometry of the local environment – where nearby is there a supply of new attractant, and which directions are

blocked? Impermeable structures such as basement membranes prevent attractant diffusion, so cells move away from them, but gaps in barriers become extremely attractive.

Mazes – deliberately tortuous paths made in cell-scale microfluidic devices – give a remarkable demonstration of cells' ability to sense information at a distance using self-generated gradients [18]. Mazes start with a homogeneous high level of chemoattractant, but cells break it down as they enter. This means that cells can identify which branches of a maze connect to an outside reservoir ('correct' branches) because fresh attractant diffuses in from them. Branches that are not connected ('wrong' branches) have no attractant supply, so their gradients are weaker. Given a choice, cells can often read which branch is correct from the steeper gradient. Figure 2 shows cell mazes containing chemotactic pancreatic cancer cells (Figure 2A) and *Dictyostelium* (Figure 2B) – it is apparent that most cells can sense and avoid blind branches without ever migrating into them.

These mazes are of course artificial; they do not look like anything physiological. However, the problems they pose are just like the problems real cells encounter throughout their life cycles. Examples like a neutrophil in a blood vessel, a germ cell in an embryo, or a neurite in a developing brain all face the same problem – how to find a target (an infection, the gonad, and a target for synapsis, respectively) robustly, despite the complex organisation and signalling

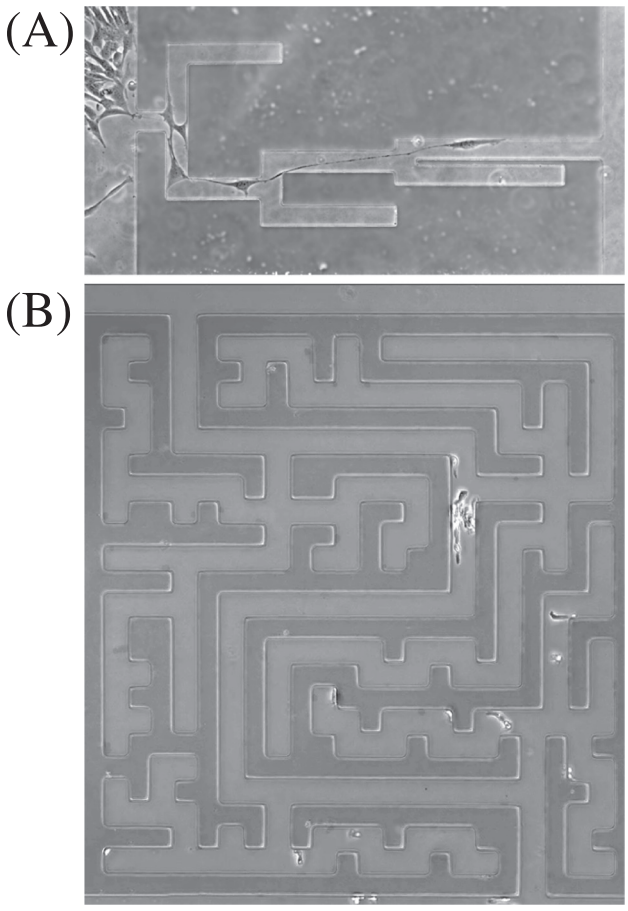

Figure 2. Solving mazes using self-generated gradients. (A) Pancreatic ductal adenocarcinoma and (B) *Dictyostelium* cells navigating complex mazes using self-generated gradients. The attractant concentrations are initially constant throughout the mazes. From Tweedy *et al.* [18].

noise within an organism. Self-generated chemotaxis is a strong approach to answering such problems.

Positional information need not just be blind versus open ends, as in the mazes. The chemical composition of the environment can change self-generated gradients by changing how fresh ligand diffuses into areas after cells have depleted it. For example, all chemokines bind strongly, but reversibly, to the extracellular matrix, altering their effective diffusivity. Different chemokines have different affinities for matrix, so their diffusion is impeded differentially. This means cells could use self-generated gradients to probe the composition of the local matrix as well as the physical shape of the surrounding space.

Physiological examples of self-guidance

Self-generated gradients have been observed in a range of biological conditions, though there are undoubtedly many more to find. They were first identified in bacteria, through 'Adler rings' [32]. Bacteria chemotax towards foods such as sugars and amino acids, while depleting them as they eat. A colony plated on a single food source expands outwards, in a weirdly discrete ring (Figure 3A), driven by chemotaxis. Outside the ring the food is plentiful; inside it is completely depleted. On complex media, multiple rings are formed, each corresponding to a specific nutrient. The most attractive sugar forms the outermost ring; cells behind that respond to the next most attractive, forming a second, inner ring and so on [32].

The zebrafish lateral line, discussed earlier, is a clear example in developmental neurobiology, but the underlying mechanism is general (Figure 3C). Another case is incompletely explained – during *Drosophila* embryogenesis, the gonad is formed separately from the germ cells, which must migrate through the embryo to find their home. An agent presumed to be a phospholipid similar to LPA is clearly important, but is not yet identified [33]. It is transduced by the TRE1 receptor [34] and broken down by the Wunen and Wunen2 gene products, which closely resemble the lipid phosphate phosphodiesterases that break down LPA in mammals [35,36]. Without them, the germ cells fail to find the gonad (Figure 3B), and the fly is sterile. Mammalian germ cells also need to migrate to the gonads during embryogenesis, so here again the underlying mechanism is likely conserved – but the details are yet to emerge.

In cancer, most mortality is caused by metastasis, in which cells migrate out from the tumour and into the rest of the patient's body. However, this leads to a slightly unexpected question – how do the cells know where 'out' is? Random migration is ineffective for moving cells between tissues. There must be a steering signal – and in many cases, this signal is a self-generated gradient.

Multiple types of cancer spread using self-guidance. One clear example is melanoma. Essentially all melanomas above a certain thickness spread via the bloodstream [37]. Muinonen-Martin *et al.* [15] showed that they are attracted from the tumour by a gradient created when a widely present chemoattractant is locally broken down (Figure 3D,E). Multiple cultured melanoma lines were chemotactic towards LPA; all also expressed a cell-surface enzyme, LPP3, that breaks down LPA outside the cell [17]. When the tumour reaches a defined thickness, it breaks down LPA faster than it can be replenished, so a gradient is established that drives cells outwards from the tumour. A second, more complex self-guidance mechanism is established by the interaction between breast cancer cells and macrophages [38,39]. Each secretes an attractant for the other, with cancer cells secreting colony stimulating factor 1 (CSF-1) and macrophages producing EGF,

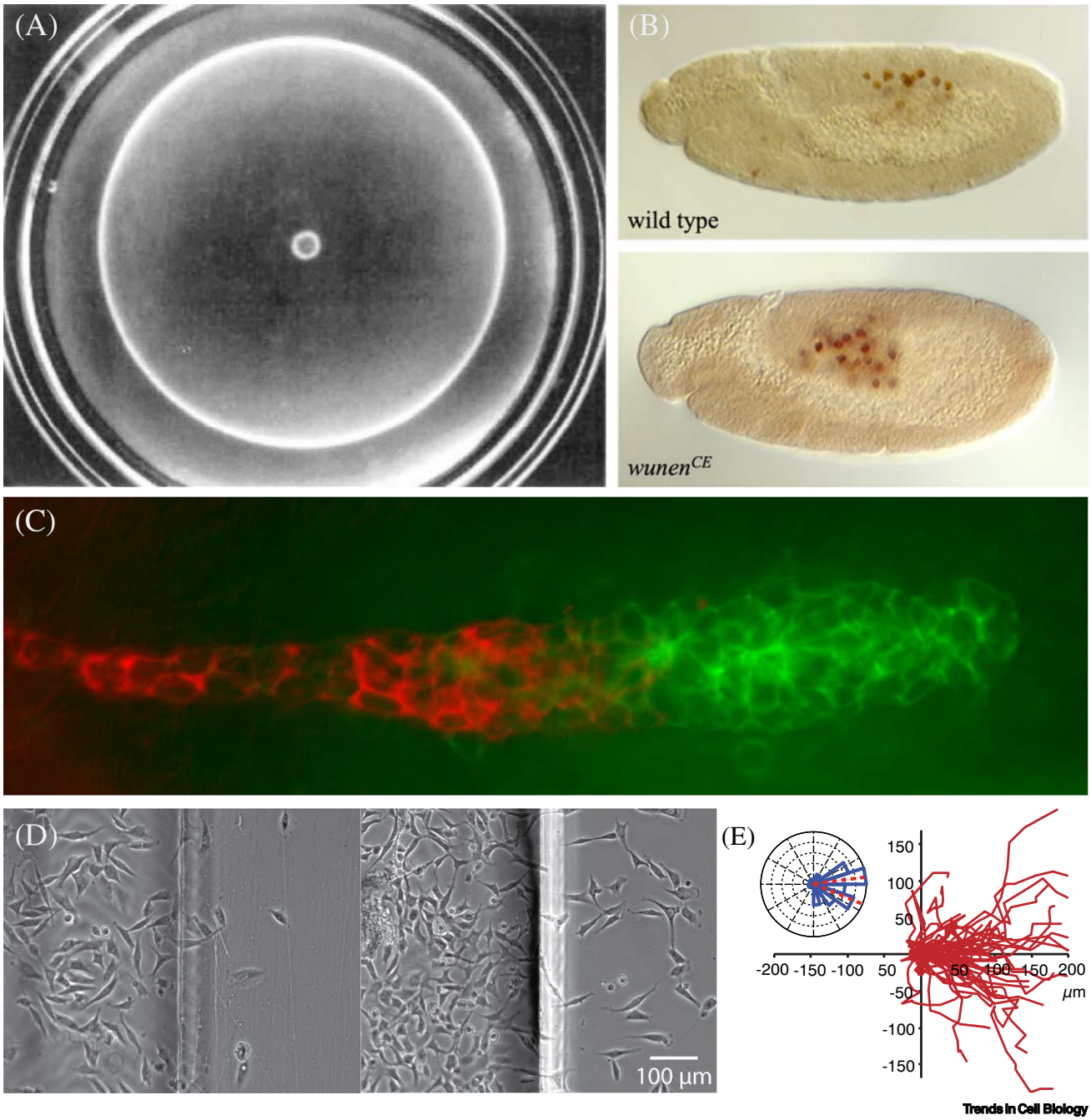

Figure 3. Examples of known physiological self-generated gradients. (A) Adler rings (from Budrene and Berg [47]); (B) germ cells (dark brown) migrating to the *Drosophila* gonad (adapted with permission from Starz-Gaiano *et al.* [56]); (C) zebrafish lateral line progenitor showing CXCR7 in red and CXCR4 in green (from D. Dalle Nogare, unpublished, similar to Dalle Nogare *et al.* [54]); (D,E) cancer (melanoma cells, images taken 12 h apart and visualised as rose and spider plots; from Muinonen-Martin *et al.* [15]).

setting up a paracrine loop that again draws cells out of the tumour and into the bloodstream. This provides a convolved version of simple chemoattractant relay, which uses positive feedback to generate new positional information.

Leukotriene B4 and neutrophil swarming

Even simple examples of chemotaxis can behave in an extremely complex way as gradients become self-generated. The cells both move in response to the gradient and generate it, causing feedback loops that defy intuitive understanding. Thus, chemotactic mammalian neutrophils – the rapidly moving attack dogs of the immune system, which respond to multiple attractants – have very complex responses indeed. Neutrophils have not so far been explicitly shown to generate gradients by attractant breakdown. However, their surfaces are densely coated with proteases [40] and other enzymes that break down known attractants [41], so attractant breakdown and self-generated gradients are near-certain. They efficiently break down the stereotypical attractant formyl peptide (fMLP), for example, implying that chemotaxis towards fMLP is reinforced by self-generated gradients [42].

Neutrophils also clearly use attractant relay [43]. When they respond to chemotactic signals (such as formylated peptides, complement fragments, or chemokines such as CXCL8/interleukin-8), they simultaneously migrate and secrete a signalling lipid, leukotriene B4 (LTB4), which is a strong attractant [44]. Inhibition of either production or responses to LTB4 causes a marked decrease in the efficiency of fMLP chemotaxis [43], showing that the measured behaviour is a combination of external and self-generated responses.

LTB4 may also drive neutrophils to release their own LTB4. This relay causes the neutrophils to attract one another, driving them together into groups known as 'swarms' [31]. The wave behaviour seen in *Dictyostelium* (see below) does not occur in neutrophils, perhaps because their responses are too complex to behave synchronously, but the end result is similar – a homogeneous initial layer of cells rapidly form into large clumps.

Combinations of self-steering mechanisms

Dictyostelium is a social amoeba that depends on chemotaxis throughout its life cycle. This has made it a strongly favoured model organism for analysis of chemotactic mechanisms [7]. In most experimental geometries, chemotaxis is portrayed as passive, towards sources of the small molecules cAMP or folate. However, this is misleading – the cells express potent cAMP- and folate-metabolising enzymes on their outer membranes, so the cells rapidly break down and reshape externally imposed gradients. This has provided a solution to an old problem – how can cells respond efficiently to linear gradients? One would expect the response at the high end of the gradient to be far weaker, because the gradient is a much smaller proportion of the background attractant concentration, yet *Dictyostelium* read linear gradients efficiently. However, modelling the effects of the enzymes shows that the cells remodel the linear gradient into a near-exponential, making it easy to read at all points [10]. The breakdown of folate and cAMP also allows cells to chemotax even when there is initially no gradient to read; so-called 'one-spot' assays, in which the attractants are initially homogeneous but a local spot of cells causes a gradient to be formed, have been widely used for their ease of set up [45].

Dictyostelium also uses attractant relay. Cells respond to sources of cAMP by chemotaxis. A short while after responding, they also secrete a short pulse of their own cAMP. This causes coordinated waves of cAMP and cell migration to pass through cell monolayers (shown in detail in Video S1 in the supplemental information online) as cells first move towards a cAMP source, then become the source themselves. These waves are arranged either in concentric circles or spirals, with cells mainly (but not always [46]) migrating inwards towards the centre – causing

large numbers of individuals to coalesce into the multicellular aggregates that define *Dictyostelium*'s form following starvation.

Bacteria, too, can combine self-steering mechanisms. *Escherichia coli* make patterns of extraordinary beauty and complexity by combining the self-generated nutrient gradients (described earlier) that lead to Adler rings with autocrine secretion of attractants such as aspartate [47].

Modelling self-generated signals

Self-generated signals resist traditional biochemical analysis. They are unstable and evanescent, dissipating if cells are removed [17] and changing constantly through diffusion. Cells alter the attractiveness of their surroundings. This in turn directs their movement, which changes the place they affect, and so on. The results of such complex feedback between cells and environment are hard to predict intuitively, making experimental analysis difficult. Further, the changes that occur when cellular enzymes affect attractants are often hard to follow. For example, fluorescent ligands do not help; there are fluorescent versions of ligands such as LPA and cAMP, but the fluorescence does not change after LPP3 and phosphodiesterase inactivate them. Imaginative experiments can show whether cells have in the past experienced gradients [13,14,16], but they show cells' history, rather than the current state and how it is evolving. One of the best ways of understanding self-guidance has therefore been mathematical modelling [11], predicting the behaviours of cells that are implied by any particular mechanical hypothesis, underpinned by experimental validation.

Biological pattern formation has been investigated using mathematics since Alan Turing's foundational work [48] showed that various morphogen patterns could spontaneously, robustly arise from specified reaction–diffusion dynamics and stochastic fluctuations. In the 1990s, bacterial chemotaxis was demonstrated to drive the formation of spot, ring, and stripe patterns strongly reminiscent of Turing's original work [49], with mathematical models of such chemotactic pattern forming appearing around the same time [50].

More recently, the power of computational modelling has become apparent. It can provide an excellent means of exploring complex systems, able to predict counterintuitive results, as well as to suggest experiments that can validate or falsify the mechanistic assumptions made. This cross-disciplinary approach has illuminated, among many others, how changing neural crest cell identity informs migration during development [51], and predicted single-cell behaviours in models of relay [52,53] and attractant depletion [10,54]. Simulations are essential to microfluidic experiments, in particular the mazes described earlier [18,24]. Computational power continues to increase, and with it the scale of the questions we can ask increases. Given its importance in this emerging field, we hope that the connections between experimental and computational biology grow stronger and yet more informative.

Concluding remarks

Self-steering allows cells to achieve more than they ever could by simple chemotaxis alone. It allows cells to participate actively in a physiological system, integrating information about their locations with the strength or direction of the signalling gradients. This means they can be more robust, can steer their migration over longer distances, and can obtain surprisingly complex information about the structure of their environments. At the moment, self-steering has only been reported in a small subset of cases, generally where chemotaxis plays a fundamental role in our understanding of the cells' physiology. However, it has not been tested for most cells and most attractants. Given its advantages to the cells that use it, it seems likely that self-steering will be far more widespread than is currently known (see Outstanding questions).

Outstanding questions

Above all, which known physiological examples of chemotaxis involve self-steering, and which ones demonstrably do not?

For each example that may involve self-steering, what is the mechanism by which cells shape gradients? In particular, what are the enzymes that break down chemoattractants in cells that use self-generated gradients?

Is it possible to measure self-steering directly, or must we continue to rely on indirect experiments and mathematical modelling?

What other information can cells obtain using self-steering mechanisms? And what patterns can they make?

Is neuronal migration self-steered? Its complexity suggests it, but no examples have yet been described.

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Declaration of interests

The authors declare no competing interests.

Supplemental information

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