Chemotaxis: Active attractant degradation enables optimal maze navigation

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Summary

How signals coordinate and direct chemotaxis is actively investigated. A new study shows how dynamic alteration of chemo-attractant flux by chemo-taxing cells provides an efficient way to solve complex navigational tasks including finding the optimal path through a complex maze.

Short- and long-range organised cell movements are known to play key roles in many aspects of embryonic development and critical processes in adult life such as wound healing, tissue regeneration and the functioning of the immune system. The mechanism that direct and coordinate these directed movement responses are widely investigated. Chemotaxis, the process where cells move up or down gradients of attractants or repellents, respectively, is one of the best understood mechanism of directed cell migration, with chemo-attraction being most widely studied [1]. In eukaryotes chemo-taxing cells measure gradients over their length, polarise and move up or down the gradients in response.

In many cases, these attractants are being actively inactivated through receptor-mediated internalisation and or enzymatic degradation by the responding cells. The inactivation of the ligand
leads to a cell density-dependent dynamic alteration of the local attractant concentration profiles, which results in the self-generation of gradients that can direct the motion of the migrating cells [2]. This concept has been well established in the chemotactic amoeba *Dictyostelium discoideum*, where it was used in the identification of 3'-5' cyclic AMP (cAMP), one of the first chemo-attractants to be identified [3]. *Dictyostelium* cells secrete a highly active cAMP phosphodiesterase that very rapidly degrades cAMP to inactive 5'-AMP. When *Dictyostelium* cells are deposited on a surface containing a uniform concentration of cAMP, they start to degrade cAMP creating an outward-directed concentration gradient, which they then follow resulting in radial outward migration [4]. This assay was part of the original identification of cAMP as a chemo-attractant. In more modern microfluidic versions of this experiment a microfluidic channel connects a cell loading reservoir with an attractant reservoir [5]. Diffusion of the attractant in the channel sets up a concentration gradient, which when left long enough will form a linear concentration gradient of attractant, which entices the cells to migrate into the channel.

Tweedey et al. have now taken these observations a step further and show that this dynamic interaction between an attractant signal and density-dependent degradation by responding cells can be used by populations of cells to solve much more complex navigational tasks such as finding the optimal path through a maze [6]. This is done through an effective combination of microfluidic-based experimental designs, where chemo-attractant flux and complexity of path options can be carefully controlled and chemotaxis of populations of cells can be tested, in combination with detailed mathematical modelling of these systems (Fig. 1). They first confirm that in simple imposed gradient cells move more efficiently over longer distances if they can degrade the chemo-attractant, comparing the response of *Dictyostelium* cells in gradients of cAMP and the non-degradable cAMP analogue (Sp-cAMPS). A critical feature is that cAMP degradation sharpens the gradient as the cells move, resulting in a more efficient clustering of cells in the migration front. Next, they demonstrate that cells can use this mechanism to make an informed choice when encountering a bifurcation in two channels, one providing access to a reservoir of limited size and the other to a reservoir of very
much larger size (Fig. 1). Due to the faster effective depletion of the attractant in the small reservoir channel, compared to the much slower depletion of the large reservoir channel, the chemo-attractant gradient will be steeper in the larger reservoir channel, resulting in more effective migration into that channel. This principle can be used to make decisions on the path ahead and to solve a maze by finding the shortest path between an entry point and an exit point providing an unlimited supply of chemo-attractant.

To solve a maze, cells have make a series of choices at a succession of bifurcation points (Fig. 1). The combined efficiency of making the right decision at every point will determine how many cells will find the exit of the maze in a reasonable time. Tweedy et al. show that, as expected, this efficiency is largely governed by the relative size of the reservoirs ahead at every decision point. Mazes with highly branched shorter dead-end channels can be solved more effectively. The findings are clearly presented in experimental data both with Dictyostelium and mouse pancreatic cancer cells that respond to the small diffusible chemo-attractants cAMP and LPA respectively, as well as, in detailed computational simulations that provide an excellent mapping of the experimental results. The simulations further show that efficiency is not only determined by the size of the reservoir, but that there is a trade-off between the speed of cell movement and the diffusion of the attractant. As expected, slow-moving cells responding to a highly diffusible attractant give the most accurate results, since this will create the highest attractant flux resulting in the cells effectively being able to “look” further ahead before making a decision at a bifurcation. Together, these results give some interesting novel insights on how a relatively simple mechanism based on chemotaxis and dynamic attractant modulation can be used to solve complex navigational problems such as solving a maze.

A number of interesting points arise from these findings. The active gradient shaping mechanism is self-limiting. Cells in the wake of the front see less steep gradients at lower concentrations, they migrate less efficiently and are left behind. Eventually the thinning of the front will result in the active attractant flux modulation coming to a halt. In some biological scenarios this may be
beneficial, i.e. a group of pioneer cells laying out an efficient route, leaving cells behind that could fulfil some important function, like keeping a supply line going or forming the corner stones of a connected network. Examples of this are the migration of streams of cranial neural crest and the laying down of the peripheral nervous system by these cells or the formation of the lateral line organ in the fish [7, 8]. In other cases, it might be advantageous to keep all the cells together as a moving front. Intercellular interactions that favour clustering of cells, like cell-cell contact dependent cell polarisation or secretion of self-attractants, would result in stream formation and enhance the effectiveness of collective migration [9]. These mechanisms affect the migratory response of the cells; however, if the signal synthesis itself was also dynamic, even more interesting possibilities arise. Excitable reaction-diffusion systems such as the Belousov-Zhabothinsky reaction are be very good at solving mazes [10]. An excitation front initiated at the entrance of a maze and propagates in all directions and probes all possible solutions simultaneously. By recording the emerging pattern of wave propagation and by following back the first waves to emerge at the exit will allow the establishment of the shortest path of a maze of any complexity. Therefore by combining these two principles- active signal amplification and relay and local signal modulation- moving cells can solve very complex patterning issues very robustly, as exemplified by Dictyostelium aggregation, which is mediated by periodic cAMP wave propagation which guiding chemotaxis, where cAMP degradation plays a key role in both processes [11]. A second well known example is the formation of complex tube like structures in the Physarum plasmodium that connects multiple food sources through an optimal path, the formation of which is mediated through a combination of internal peristaltic wave propagation and flow dependent pruning of branches [12]. It is likely that these clearly very powerful and abundant principles will have found important implementations in many other biological systems and contexts.
References


Figure 1: Cell mediated attractant degradation enables a population of chemotaxing cells to navigate along an optimal path through a network of successive bifurcating open and closed channels. Left panel shows a schematic of a series of bifurcating channels, some of which are dead ended, that connect a cell loading compartment (cell containing bottom horizontal channel) with an attractant source (top horizontal channel). Attractant (purple depicts high concentration) diffuses from the source and is degraded (white depicts low concentration) by the migrating cells. The 3, 10 and 15 minute columns show a comparison between an experiment of Dictyostelium cells migrating through a series of two successive bifurcations (three top row panels) and corresponding computer simulations of the experiment (three bottom row panels) from the maze shown in the left panel.

Figure courtesy of Dr Luke Tweedy