Notes complementing custom code for generating the ‘M’ swarming metric.

Chemotaxis refers to directed cell movement driven by individual cellular responses to a biochemical gradient. Chemotaxis is a critical driver of an array of physiological processes; it plays a crucial role in embryonic development, directing migratory behaviour of cells in growing tissues [1], formation of new capillaries to sites of ischaemia via angiogenesis [2], and orchestrates cell dynamics in wound healing [3, 4]. In addition, the progressive directed clustering of immune cells based on chemotaxis, which we term chemotactic swarming, has been observed during responses to injury where neutrophils swarm to sites of inflammation [5],

Developments in live-cell imaging techniques increasingly allow for precise localisation of individual cells, their movements and interactions to be captured [6–9]. As such, a significant amount of imaging data capturing cell motility is becoming available. Probing this data to detect the presence of chemotactic swarming presents a unique challenge, due to the fact that visualising a chemoattractant gradients in conjunction with cell movements is very difficult, particularly without disturbing the underlying dynamics. New statistical approaches need to be developed to detect and characterise chemotactic swarming using cell position data.

Recently, methods from spatial statistics have been applied to pathological samples of different solid tumours, finding that spatial association between particular immune cells and tumour cells is positively correlated with increased patient survival [10–13]. There is therefore significant interest in investigating the interplay between immune cells capable of destroying cancer cells, such as cytotoxic T cells, and tumours. Importantly, if T cells exhibited chemotactic swarming in their interactions with tumour cells, secreting a chemoattractant to draw other neighbouring T cells towards the tumour, this could substantially increase the number of T cells in contact with the tumour, theoretically increasing the likelihood of mounting a successful immune response and eliminating all cancer cells.

In this paper we set out a method for detecting and characterising chemotactic swarming in agent-based processes. We develop our methodology for motile agents in two dimensions, but our methodology can be extended to 3D processes. Our approach is motivated by an attempt to detect chemotactic swarming in T cell-tumour interactions, with the system geometry used reflecting experiments where the spatiotemporal positioning of T cells surrounding a tumour can be captured. We expect that our approach will generalise to the analysis of other biological systems.

Our approach assumes that the evolution of agent density is well modelled by the Fokker-Planck equation. The Fokker-Planck equation is a generalised advection-diffusion type PDE that allows for spatial and temporal dependence with respect to drift and diffusivity terms [14–16]. Fokker-Planck type equations provide close approximation of

the evolution of cell density in individual-based models (IBMs) of cell movement [17–26].

A popular and well studied continuum model of chemotaxis is the Keller-Segal type model, which uses coupled Fokker-Planck type equations for cell position and chemokine concentration [16, 27–29]. Recently, statistical approaches for analysing experimental data from cell-based experiments for Keller-Segal model selection have been developed [30]. A significant contribution to statistical analysis of cell-based experiments, this approach is apparently limited by significant computational costs [30]. Furthermore, this approach is parametric, constraining its applicability to the analysis of biological processes with theoretically sound underlying PDE models.

In this paper, we present a general framework for the analysis of chemotactic swarming in agent-based processes. Similarly to [31], we utilise a novel combination of techniques, using spatial statistics to analyse the positional data generated by agent-based processes, and functional data analysis to interpret the functional time series produced. Our methodology involves adapting Ripley's K function from spatial statistics, [32–35], to analyse the distribution of agents around an area of interest, e.g. a tumour. The empirical estimates for these K-type functions, which we refer to as "well" K functions, can then be used to generate a functional time series, and hence be modelled using functional linear models [36–38]. Our approach is non-parametric in the sense that while we assume that agent density is modelled by the Fokker-Planck equation, we make no assumptions as to the form of the drift and diffusivity coefficients. In addition, our approach has minimal computational cost.

The rest of the paper is organised as follows. In Section 2 we provide some background and notational definitions relating to agent-based processes. In Section 3 we define agent density and the associated Fokker-Planck equation for polar co-ordinates. In Section 4 we introduce "well" K functions, the main objects of study in this paper, and outline our method for using these functions to estimate the drift and diffusivity functions for the Fokker-Planck equation of agent density. In Section 5 we define well L functions, and an associated metric of chemotactic swarming. In Section 6 we introduce an off-lattice random walk model for chemotactic swarming, and use simulations of these models to demonstrate the performance of our approach.

Agent-based processes in polar coordinates around a well

We consider systems of agents (e.g. cells, animals, robots) that change their position over time, and analyse their arrangements around some local region in space which we refer to as a "well". We are interested in establishing whether agents are attracted or repulsed from this well. With a particular focus on the analysis of experimental data in which agent positions may only be available within a bounded region we define an observation region, $R \subseteq \mathbb{R}^d$, in which agents are observed and outside of which agent positions are not recorded. As such, for any given time t, the realisation of the dynamic agent-based process results in a spatial point pattern within R. Let $X(t)$ be the spatial co-ordinate data for agents at a given time t, such that $X(t) = \{x_1, x_2, ..., x_{n(t)}\}$, with x_j being the spatial co-ordinates of the j^{th} agent, and $n(t)$ being the total number of agents occurring within the observation region R at time t. Likewise, let the time points at which observations of an agent-based process occur be given as $\boldsymbol{T} = \{t_1, t_2, ..., t_N\}$, with N giving the total number of time points observed.

For simplicity we focus on the case in which the number of agents within R, $n(t)$, does not change with time. However, one can envisage cases where the number of agents does change with time, either via birth-death processes, or via agents entering or leaving R from the boundaries. We deal with these cases in later sections.

We continue by considering the following idealised spatial geometry for such agent-based processes. Let $B \subseteq R$ be the well of attraction/repulsion. For simplicity we continue by working in 2D with the assumption that $R \subseteq \mathbb{R}^2$ is circular with radius r_R, and also that B is a circle with radius r_B, with B occurring at the centre of R. Let $A \subseteq R$ denote the region in R outside of B, i.e. A is the annulus $A = R - B$. We let $r_A = r_R - r_B$. We also assume that the distribution of agents in R is isotropic, i.e. that agents are distributed uniformly with respect to direction from the centre of R. We note that this framework allows for the case in which B is a point, rather than a circular region, i.e. setting $r_B = 0$.

The expected population-level behaviour of agents can be described using the first spatial moment defined in [39–41]. We use planar polar coordinates, (r, θ), and since we assume that the distribution of agents within R is isotropic we can describe the density of agents independently of θ.

We define the density of agents as

$$\lambda(r,t) = \lim_{dr \to 0} \frac{\mathbb{E}[Y(dr,t)]}{|dr|}, \qquad 0 \leq r \leq r_R$$

with dr defining a small annulus r from B, $|dr|$ giving the volume of dr, and $Y(dr,t)$ giving the number of agents within dr at time t, and $\mathbb{E}[\cdot]$ denoting expectation.

Using the common continuum model for cell movement [16, 27–30], we assume that the evolution of $\lambda(r,t)$ is governed by the Fokker-Planck equation,

$$\frac{\partial \lambda}{\partial t} = -\nabla \cdot (\mathbf{f}\lambda) + \nabla \cdot (\mathbf{D}\nabla\lambda). \tag{1}$$

Working in polar coordinates, and using the assumption of isotropy, we have

$$\frac{\partial \lambda}{\partial t} = \frac{1}{r}\frac{\partial}{\partial r}\Big(r\Big(-f(r,t)\lambda(r,t) + D(r,t)\lambda'(r,t)\Big)\Big) \tag{2}$$

where $f(r,t)$ is the drift term, $D(r,t)$ the diffusivity term, and $\lambda'(r,t) = \frac{\partial \lambda}{\partial r}$.

If the movement of agents positioned at an arbitrary distance r from B is unbiased for a given time t, with no attraction or repulsion exerted on agents, then we will have $f(r,t) = 0$. If there is attraction of agents towards B at some r value then $f(r,t) < 0$ for a given t. If agents are repulsed from B then $f(r,t) > 0$. The diffusivity term D gives a measure of the stochastic component of agent motility.

We note that agent based processes may evolve in this geometry in such a way that agent behaviour within B is of no interest. I.e. we are only interested in the behaviour of agents outside of B within A. For example, an agent-based process might evolve such that agents that reach or enter B stop moving and as such their behaviour and distribution within B is of no interest. In such circumstances the range of r values analysed can be truncated accordingly, for example, $r \in [r_B, r_R]$, for the procedures demonstrated in the following sections.

Classification of clustering, chemotactic clustering, and chemotactic swarming

In the analysis of cell motility terms are often used interchangeably to describe cell aggregation. We here attempt to formally define several terms relating to agent aggregation in a fixed region of space, B.

Clustering: An agent-based process exhibits clustering during its evolution if, for some subset of time, the expected number of agents within B is increasing, and that

this increase would occur for the given time period even if agent density decreased across the boundary of B.

If agent density is governed by Eq (1) clustering implies that we have $\frac{\partial \xi}{\partial t} > 0$ for a given time period and that this relation holds independently of $\frac{\partial \lambda}{\partial r}|_{r=0}$. In particular, we have $\frac{\partial \xi}{\partial t} > 0$ even if $\frac{\partial \lambda}{\partial r}|_{r=0} \leq 0$.

Clustering implies that the expected number of agents within B increases with time even when random motility of agents would normally lead to a decrease in agent density in B.

Clustering can be further characterised using the following definitions:

Non-biased clustering: An agent-based process exhibits non-biased clustering during its evolution if, for some subset of time, the process exhibits clustering as defined above and agent movements not being biased to move towards B.

If agent density is governed by Eq (1) non-biased clustering implies that $f(r,t) = 0$ for all r during the period in which the process exhibits clustering.

Non-biased clustering may occur, for instance, because agents that are performing a non-biased search arrest and cease to move when in contact with B, leading to the aggregation of agents around B.

Attractive clustering: An agent-based process exhibits attractive clustering during its evolution if, for some subset of time, the process exhibits clustering **and** movements of agents for some subset of r are biased to move towards B.

If agent density is governed by Eq (1) attractive clustering implies that $f(r,t) < 0$ for some subset of r values during the period in which the process exhibits clustering.

Repulsive clustering: An agent-based process exhibits repulsive clustering during its evolution if, for some subset of time, the process exhibits clustering as defined above and agents for some subset of r are biased to move away from B.

If agent density is governed by Eq (1) non-biased clustering implies that $f(r,t) > 0$ for some subset of r values during the period in which the process exhibits clustering.

Repulsive clustering may occur, for instance, because agents searching for B arrest and cease to move when in contact with B, leading to the aggregation of agents around B, but are also repulsed from B for some range of r values due to some protective repellant created from some source within B that biases neighbouring agents to move away from B.

A process may exhibit attractive clustering and repulsive clustering.

Swarming: An agent-based process exhibits swarming during its evolution if, for some subset of time, the process exhibits attractive clustering **and** the strength of this attraction is positively associated with the number of agents within B during some preceding subset of time.

We produce a mathematical definition of swarming under a set of assumptions regarding the evolution of the agent-based process that we outline below. For agents to attract other agents the must produce some "signal" (we assume there is only one type of signal for simplicity). Let $\zeta(r,t)$ give the "concentration" of the signal for a given r at time t. We continue by assuming that f is dependent on $\zeta(r,t)$, though we note that taking motivation from Keller-Segal models of chemotaxis f may be dependent on the gradient of the concentration, $\frac{\partial \zeta}{\partial r} = \zeta'(r,t)$ [29]. Let $\varphi(r,t,s)$ give the contribution of signal produced at B at time s to $\zeta(r,t)$, i.e. the contribution to concentration of signal at position r at time t. Furthermore, let $\zeta_0(r,t)$ give the contribution of any initially present signal to $\zeta(r,t)$. We can write

$$\zeta(r,t) = \zeta_0(r,t) + \int_0^t \varphi(r,t,s)ds. \tag{3}$$

We note that we assume that ζ, and thus $\zeta_0(r,t)$ and $\varphi(r,t,s)$, are non-negative functions.

For simplicity we continue with the assumption that agents produce signal at the edge of B a constant rate at any time in which they are within B. One could imagine a case in which the amount of signal produced by an agent was dependent on how long an agent had been within B, e.g. an agent might take time to increase production of a signal to a maximal level and might also eventually burn out and produce less signal or stop all together.

Swarming thus implies that $\varphi(r,t,s)$ is dependent on $\xi(s)$ such that $\varphi(r,t,s) = \varphi(r,t,s,\xi(s))$, and in particular $\frac{\partial \varphi}{\partial \xi} \geq 0$, for a given subset of time during the evolution of the process. This in turn implies that the concentration $\zeta(r,t)$ is positively associated with previous values of $\xi(s)$ for some subset of $s \leq t$ during this period. A process thus exhibits swarming if the above associations hold and that furthermore we have $f(r,t)$ being negatively associated with ξ for some subset of $s \leq t$. This implies that agents produce a signal that increases attraction of agents towards B.

This mathematical definition of swarming allows for $f(r,t)$ to be dependent on $\xi(s)$ at earlier times, incorporating the fact that there may be some time delay or lag between a signal being released from agents at B and the detection and reaction to this signal by agents outside of B. Furthermore, the generality of φ also allows for the scenario in which the concentration released by ξ can be modified by the agent density $\lambda(r,t)$, such as may occur in chemotaxis with the consumption of chemokine by agents.

As such, swarming implies that attraction of agents towards B is agent dependent with agents attracting one another to move towards B.

Chemotactic clustering and **chemotactic swarming** are subsets of attractive clustering and swarming where the bias in agent movements is generated by the diffusion of a biochemical signal from B in an agent-independent fashion for chemotactic clustering, and/or from the agents within B in the case of chemotactic swarming.

We note that the diffusivity, $D(r,t)$, may be dependent on r, and in particular may depend on the level of "signal" in a similar fashion to $f(r,t)$. This may influence the rate at which agents come into contact with B. However, since changes in $D(r,t)$ have no impact on directionality of cell movement we do not consider this term in the above definitions in this context. We also note that while the above definitions have been made in relation to agent dynamics around a fixed point, these definitions can be expanded to consider movements around a moving region of interest.

Well K functions for agent-based processes

Under the above framework and categorization of agent aggregation around a well, inferring and classifying the type and strength of aggregation can be achieved by estimating $f(r,t)$ from the available agent positions. In order to do so, we here introduce what we refer to as "well K functions". K functions are a summary spatial statistic used for detecting and characterising the deviation of spatial point patterns from complete spatial randomness [32,34,35]. We adapt them here for the analysis of correlation between agent position within A and the edge of the well of attraction, B.

We here consider the case where the number of agents within R is constant. The cases where the number of agents is not constant is dealt with in appendix A.

To proceed we define

$$\begin{aligned} \lambda_R &= \frac{\mathrm{E}[\text{Number of agents in R}]}{|R|} \\ &= \frac{2\pi}{|R|}\int_0^{\tau_R} s\lambda(s,t)d, \end{aligned} \tag{4}$$

with $|R|$ giving the volume of R. We define well K functions as follows:

$$\begin{aligned} K(r,t) &= \frac{1}{\lambda_R}\mathbb{E}[\text{Number of agents within } r \text{ of the origin at time } t] \\ &= \frac{2\pi}{\lambda_R}\int_0^r s\lambda(s,t)ds, \quad 0 \leq r \leq r_R. \end{aligned} \tag{5}$$

For each time point t_i we can use the associated spatial point pattern X_i to produce an empirical $\hat{K}(r,t_i)$ function as an estimate of $K(r,t_i)$. Due to the discrete time nature of observations, we instead express $\hat{K}(r,t_i)$ as $\hat{K}_i(r)$. We define $\hat{K}_i(r)$ as

$$\hat{K}_i(r) = \frac{|R|}{N}\sum_{k=1}^{n_i}\mathbb{1}(\delta(k) \leq r), \quad 0 \leq r \leq r_R, \tag{6}$$

where N is the number of agents in R, $\delta(k)$ is the r coordinate of the k^{th} agent in R giving the distance of the agent from the origin, and $\mathbb{1}(\cdot)$ is the indicator function. Since our analysis of agents is limited to the behaviour of agents within R we do not require an edge correction term in Eq (6) as is typical when producing K function estimates in spatial statistics; see [35].

Well L functions and a metric of chemotactic swarming

Analogous to spatial statistics we can transform well K functions to produce well L functions that are visually easier to interpret. Such well L functions can then be used to produce a what we refer to as a swarming metric, giving a single value that measures the level of agent aggregation.

$$L(r,t) = \sqrt{\frac{K(r,t)}{\pi}}, \quad 0 \leq r \leq r_R. \tag{7}$$

The theoretical well K function associated with uniform distribution of agents within R is $K(r) = \pi r^2$, making the associated theoretical L function $L(r) = r$. As such, as is the case in spatial statistics, well L functions are visually easier to interpret than well K functions, especially for smaller r values. Empirical $\hat{L}_i(r)$ functions are produced using $\hat{K}_i(r)$ in Eq (10).

Well L functions can be used to produce a simple metric of aggregation as detailed below. By all producing a time series of this metric we are able to demonstrate how the distribution of agents changes with time in a simple and easily visualisable manner. We define this metric as $M(t)$, and refer to it as the swarming metric due to its capacity to analyse the changing agent distribution with time.

The metric $M(t)$ is produced by comparing empirical $\hat{L}_i(r)$ functions against idealised L functions associated with a "perfectly" aggregated distribution, uniformly distributed agents within A, and a "perfectly" dispersed distribution.

If we have a given number of agents, n, in R, then to be perfectly aggregated they must all be localised to the origin, i.e they are all localised to $r = 0$. The L function associated with this distribution of agents is

$$L_S(r) = r_R, \quad 0 \leq r \leq r_R. \tag{8}$$

The perfectly dispersed configuration of agents will consist of agents being localised on the outer edge of R, with $r = r_R$. The associated L function for this distribution of

agents is

$$L_D(r) = \begin{cases} 0 & \text{if } 0 \leq r < r_R \\ r_R & \text{if } r = r_R \end{cases}$$

The swarming metric $M(t)$ can then be produced for a given time point t by transforming the associated well $L(r,t)$ function as follows:

$$M(t) = \frac{2}{r_R^2} \int_0^{r_R} \big(L(s,t) - s\big) ds. \tag{9}$$

As such, $M(t)$ has a range of $[-1,1]$, with -1 being equivalent to agents being perfectly dispersed, and 1 being equivalent to agents being perfectly aggregated at the origin. The empirical metric $\hat{M}_i$ is produced using $\hat{L}_i(r)$ in Eq (9).

As noted previously, we may only be interested in the distribution of agents with respect to their position in relation to B. In particular, we may only be concerned with the distribution of agents within A around B, and the total number of agents that are within B. That is, how agents are distributed within B is of no interest. For instance, if agents stop moving when they reach or enter B, then the distribution of agents within B may not be of importance for analysis.

In these contexts our definitions for uniform distribution of agents, perfectly aggregated distribution of agents, and perfectly dispersed distribution of agents need to be adjusted. Specifically, we take a uniform distribution of agents to mean that agents are distributed uniformly within A, rather than within R. We take the perfectly aggregated distribution of agents to mean that all agents are within B such that $r < r_B$ for each agent's position, but make no specifications regarding their distribution within B. The perfectly dispersed distribution of agents remains the same, i.e. that all agents are located on the edge of R (i.e. the outer edge of A), with $r = rR$.

We adjust our definition of L accordingly, setting

$$L(r,t) = \sqrt{\frac{\frac{r_R^2 - r_B^2}{r_R^2} K(r,t) + \pi r_B^2}{\pi}} - r_B, \quad r_B \leq r \leq r_R. \tag{10}$$

Note that we have truncated the range of r values for which the new L function is defined to $r \in [r_B, r_R]$.

The theoretical well L function associated with uniform distribution of agents within A is

$$L(r) = r - r_B, \quad r_B \leq r \leq r_R. \tag{11}$$

The L function associated with the perfectly aggregated distribution of agents is

$$L_S(r) = r_A, \quad r_B \leq r \leq r_R. \tag{12}$$

The L function associated with the perfectly dispersed distribution of agents is

$$L_D(r) = \begin{cases} 0 & \text{if } r_B \leq r < r_R \\ r_A & \text{if } r = r_R \end{cases}$$

References

1. Schumacher LJ, Kulesa PM, McLennan R, Baker RE, Maini PK. Multidisciplinary approaches to understanding collective cell migration in developmental biology. Open biology. 2016;6(6):160056.

2. Lamalice L, Le Boeuf F, Huot J. Endothelial cell migration during angiogenesis. Circulation research. 2007;100(6):782–794.

3. Gillitzer R, Goebeler M. Chemokines in cutaneous wound healing. Journal of leukocyte biology. 2001;69(4):513–521.

4. Callaghan T, Khain E, Sander LM, Ziff RM. A stochastic model for wound healing. Journal of statistical physics. 2006;122(5):909–924.

5. Dianqing W. Signaling mechanisms for regulation of chemotaxis. Cell research. 2005;15(1):52.

6. Chtanova T, Schaeffer M, Han SJ, van Dooren GG, Nollmann M, Herzmark P, et al. Dynamics of neutrophil migration in lymph nodes during infection. Immunity. 2008;29(3):487–496.

7. Ng LG, Qin JS, Roediger B, Wang Y, Jain R, Cavanagh LL, et al. Visualizing the neutrophil response to sterile tissue injury in mouse dermis reveals a three-phase cascade of events. Journal of Investigative Dermatology. 2011;131(10):2058–2068.

8. Meijering E, Dzyubachyk O, Smal I, et al. Methods for cell and particle tracking. Methods Enzymol. 2012;504(9):183–200.

9. Tong PL, Roediger B, Kolesnikoff N, Biro M, Tay SS, Jain R, et al. The skin immune atlas: three-dimensional analysis of cutaneous leukocyte subsets by multiphoton microscopy. Journal of Investigative Dermatology. 2015;135(1):84–93.
10. Heindl A, Nawaz S, Yuan Y. Mapping spatial heterogeneity in the tumor microenvironment: a new era for digital pathology. Laboratory investigation. 2015;95(4):377.
11. Nawaz S, Yuan Y. Computational pathology: Exploring the spatial dimension of tumor ecology. Cancer letters. 2016;380(1):296–303.

12. Carstens JL, de Sampaio PC, Yang D, Barua S, Wang H, Rao A, et al. Spatial computation of intratumoral T cells correlates with survival of patients with pancreatic cancer. Nature Communications. 2017;8.

13. Barua S, Fang P, Sharma A, Fujimoto J, Wistuba I, Rao AU, et al. Spatial interaction of tumor cells and regulatory T cells correlates with survival in non-small cell lung cancer. Lung Cancer. 2018;117:73–79.

14. Risken H. Fokker-planck equation. In: The Fokker-Planck Equation. Springer; 1996. p. 63–95.

15. Codling EA, Plank MJ, Benhamou S. Random walk models in biology. Journal of the Royal Society Interface. 2008;5(25):813–834.

16. Chavanis PH. Nonlinear mean field Fokker-Planck equations. Application to the chemotaxis of biological populations. The European Physical Journal B. 2008;62(2):179–208.

17. Alber M, Chen N, Lushnikov PM, Newman SA. Continuous macroscopic limit of a discrete stochastic model for interaction of living cells. Physical review letters. 2007;99(16):168102.

18. Lushnikov PM, Chen N, Alber M. Macroscopic dynamics of biological cells interacting via chemotaxis and direct contact. Physical Review E. 2008;78(6):061904.

19. Binder BJ, Landman KA. Exclusion processes on a growing domain. Journal of theoretical biology. 2009;259(3):541–551.

20. Bruna M, Chapman SJ. Excluded-volume effects in the diffusion of hard spheres. Physical Review E. 2012;85(1):011103.

21. Yates CA, Baker RE, Erban R, Maini PK. Going from microscopic to macroscopic on nonuniform growing domains. Physical Review E. 2012;86(2):021921.

22. Hywood JD, Landman KA. Biased random walks, partial differential equations and update schemes. The ANZIAM Journal. 2013;55(2):93–108.

23. Middleton AM, Fleck C, Grima R. A continuum approximation to an off-lattice individual-cell based model of cell migration and adhesion. Journal of theoretical biology. 2014;359:220–232.

24. Dyson L, Baker RE. The importance of volume exclusion in modelling cellular migration. Journal of mathematical biology. 2015;71(3):691–711.

25. Irons C, Plank MJ, Simpson MJ. Lattice-free models of directed cell motility. Physica A: Statistical Mechanics and its Applications. 2016;442:110–121.

26. Matsiaka OM, Penington CJ, Baker RE, Simpson MJ. Continuum approximations for lattice-free multi-species models of collective cell migration. Journal of theoretical biology. 2017;422:1–11.

27. Keller EF, Segel LA. Initiation of slime mold aggregation viewed as an instability. Journal of Theoretical Biology. 1970;26(3):399–415.

28. Keller EF, Segel LA. Model for chemotaxis. Journal of theoretical biology. 1971;30(2):225–234.

29. Hillen T, Painter KJ. A user's guide to PDE models for chemotaxis. Journal of mathematical biology. 2009;58(1-2):183.

30. Ferguson EA, Matthiopoulos J, Insall RH, Husmeier D. Statistical inference of the mechanisms driving collective cell movement. Journal of the Royal Statistical Society: Series C (Applied Statistics). 2017;66(4):869–890.

31. Hywood JD, Read MN, Rice G. Statistical analysis of spatially homogeneous dynamic agent-based processes using functional time series analysis. Spatial Statistics. 2016;17:199–219.

32. Ripley BD. Modelling spatial patterns. Journal of the Royal Statistical Society Series B (Methodological). 1977;39(2):172–212.

33. Ripley BD. Statistical inference for spatial processes. Cambridge university press; 1991.

34. Diggle PJ. Statistical analysis of spatial point patterns. Hodder Arnold; 2003.

35. Diggle PJ. Statistical analysis of spatial and spatio-temporal point patterns. CRC Press; 2013.