***Mathematical Modelling Of Cell Clustering Due To Chemotaxis***

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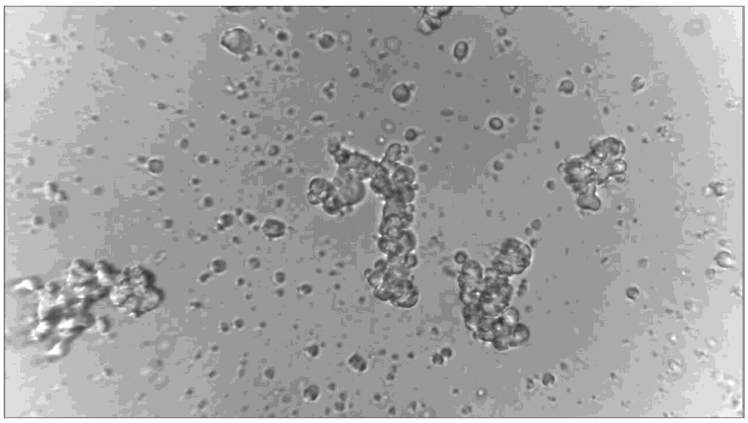
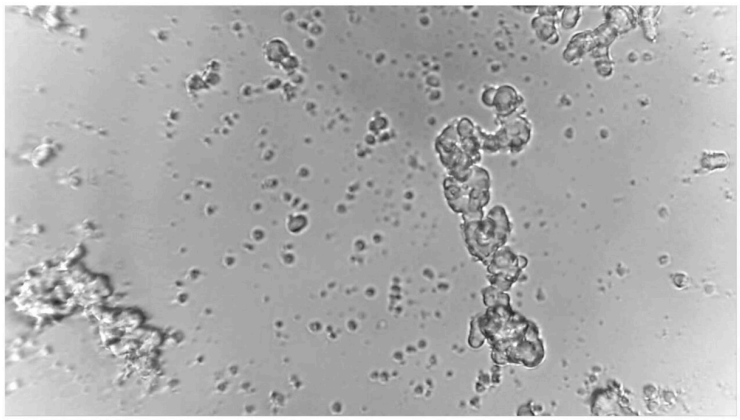
## 1. Introduction

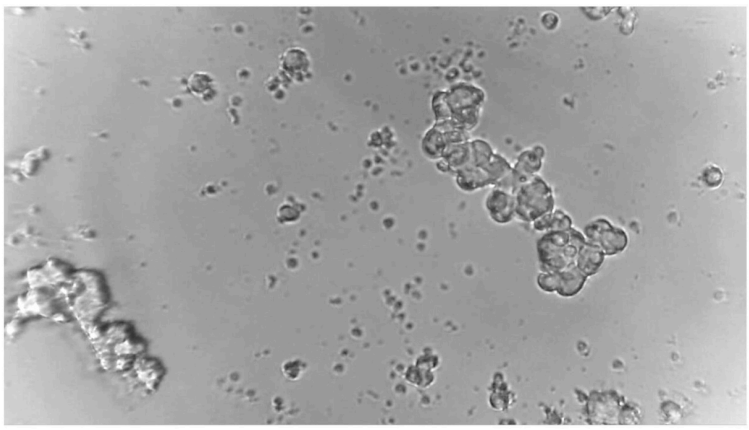
In experimental work it has been observed that cells and clusters of cells, either in vivo or in vitro, can move using the process of chemotaxis where they sense the direction in which the concentration of a chemical is increasing and move towards the region where the concentration is greatest.
Aggregation of cells, either singularly or in small clusters, into large clusters has been reported in the literature. An example of the formation of clusters of pancreatic cells is shown in the Figures below (obtained, with thanks, from The Brighton Centre for Regenerative Medicine, University of Brighton).



Time $t = 0$.



Time $t = 1$.



Time $t = 2$.

Here each figure is a frame taken from a time-lapse video of an experiment to observe the formation of clusters. The times of the frames are given on a linear scale but are otherwise in arbitrary units. The frames from the video show how the cells combine together to form clusters over time. In particular, the video shows how a large number of individual cells can combine together to form a large cluster. The purpose of the research described here is to use mathematical modelling to develop computer simulations of how cells cluster together.
The aim of this research is to develop a mathematical model for simulating how the cells combine together to form clusters, as observed in the above Figure.
The first model developed here assumes that the cells experience a force which is proportional to the gradient of the concentration of a chemical signal in the medium which contains the cells. The standard laws of motion are then used to derive a system of differential equations which can be solved to give the locations of the cells and clusters at any required time.
The subsequent models use more sophisticated mathematics to model the motion of the cells, the spread of the chemical signal and the surrounding fluid.

**2. Simple Model**
Assume that a cell can be represented as a rigid circle, and as the motion is so slow (typically over hours) assume that other than providing drag, the motion of the surrounding liquid can be neglected. Assume that all cells have the same uniform thickness and density so that their mass is proportional to the square of their radii. Hence if $\mathbf{x}_i(t)$ denotes the location of the $i^{\text{th}}$ cell or cluster at time $t$ then

$$m\frac{d^2\mathbf{x}_i}{dt^2} + \lambda\frac{d\mathbf{x}_i}{dt} = \mathbf{F}_i$$

The force $\mathbf{F}_i$ is assumed to be proportional to the gradient in the concentration of a chemical that attracts the cells. That is,

$$\mathbf{F}_i = k\ \nabla c$$

where $c$ satisifes

$$\frac{\partial c}{\partial t} = \mu\,\nabla^2 c.$$

If the chemical is being secreted by more than one cell, the total concentration is the sum of the contributions from all of the emitting cells

$$c(x,y,t) = \sum_{j=1}^{N} c_j(x,y,t).$$

The concentration $c_j$ of the chemical released by the $j^{\text{th}}$ cell at release time $t_j$ is given by

$$c_j(x,y,t) = \begin{cases} \dfrac{A_j}{\mu(t-t_j)}\exp\left(-\dfrac{(x-x_{j0})^2+(y-y_{j0})^2}{4\mu(t-t_j)}\right) & t > t_j \\ 0 & t \le t_j. \end{cases}$$

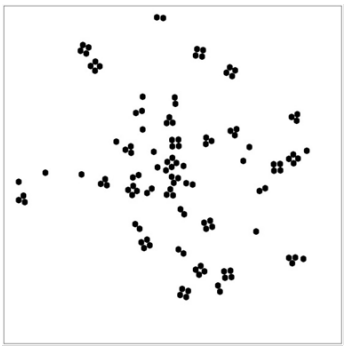
Hence the equation of motion for the $i^{\text{th}}$ cell or cluster is

$$m\frac{d^2\mathbf{x}_i}{dt^2} + \lambda\frac{d\mathbf{x}_i}{dt} = k\sum_{j=1}^{N}\nabla c_j(x_i,\, y_i,\, t)$$

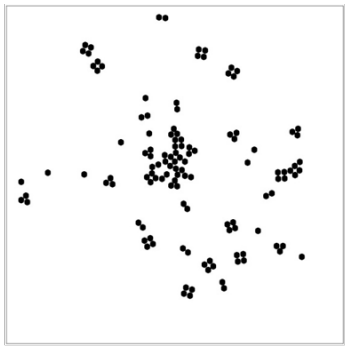
which gives a system of $N$ second order differential equations (or $2N$ first order differential equations) to solve. In the work presented here an adaptive 4th order Runge-Kutta method has been used (see Atkinson 1989 for the details of the Runge-Kutta scheme).
If the cells all have radius $R$ then two cells will have collided if

$$\left|\mathbf{x}_i - \mathbf{x}_j\right| \leq 2R.$$

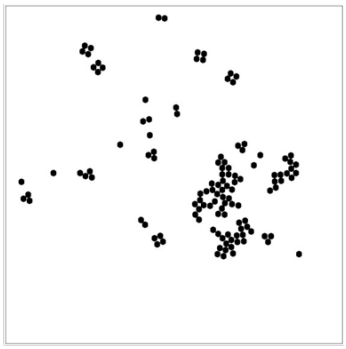
After two (or more) cells have collided they form a cluster. Assume that the relative positions of cells in a cluster are fixed. That is, they move as a single rigid body. The total force acting on a cluster due to the chemical signal is simply the sum of the forces acting on each individual cell. When two (or more) cells or clusters collide, the velocity of the new larger cluster is given by the conservation of momentum.
The Figure below shows the results of simulation cell clustering over time due to chemotaxis for an example with 123 cells in 50 initial small clusters.



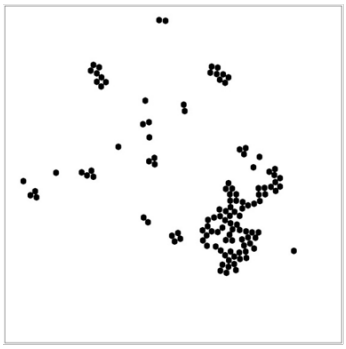
$t = 0$



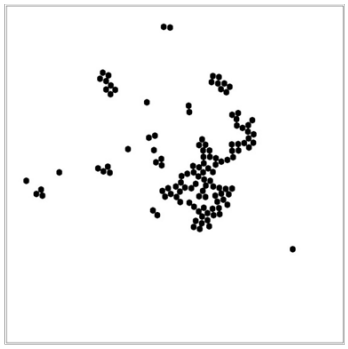
$t = 1$



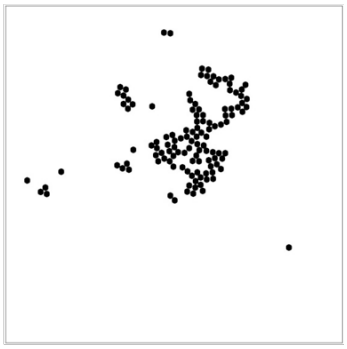
$t = 2$



$t = 3$



$t = 4$



$t = 5$

**3. Computational Models.**

This section presents the more sophisticated computational models that have been developed for simulating cell motion due to chemotaxis. The first subsection presents the fluid flow part which is the same for all the models developed here. The later subsections present the different methods for modelling the spread of the chemical signal, and the resulting forces acting on the cells.

**3.1 Boundary Element Method For Modelling The Fluid Motion.**

Let $\Omega_F$ denote the fluid filled region exterior to the cells and let $\Omega_i$ and $\Gamma_i$ denote the interior and boundary of the $i^{\text{th}}$ cell respectively. As the work presented here is going to use a Stokes flow model for the fluid flow, let $\Gamma_0$ denote the outer boundary to the fluid domain that is needed to avoid the problems associated with Stokes paradox which states that it is impossible to an non-zero boundary condition for a flow in an infinite two-dimensional fluid (see Lighthill 1986 for example). Finally let $\Gamma$ be the union of $\Gamma_0$ and all of the cell boundaries $\Gamma_i$.

Let $\boldsymbol{x}_i$, $\boldsymbol{v}_i$ and $\boldsymbol{a}_i$ denote the location, velocity and acceleration of the centre of mass of the $i^{\text{th}}$ cell, and let $\theta_i$ and $\omega_i$ denote the rotation and angular velocity of the $i^{\text{th}}$ cell about its centre of mass.

Assume that the Reynolds number of the flow is small enough that at each instant the flow can be represented as Stokes flow:

$$-\nabla p + \mu \nabla^2 \boldsymbol{u} = \boldsymbol{0}$$
$$\nabla \cdot \boldsymbol{u} = 0$$

where $p$ is the fluid pressure, $\boldsymbol{u}$ is the fluid velocity and $\mu$ is the dynamic viscosity. The boundary conditions for the flow are

$$\boldsymbol{u}(\boldsymbol{x}) = \boldsymbol{v}_i + \omega_i J\,(\boldsymbol{x} - \boldsymbol{x}_i) \quad \boldsymbol{x} \in \Gamma_i$$

$$\boldsymbol{u}(\boldsymbol{x}) = \boldsymbol{0} \qquad \boldsymbol{x} \in \Gamma_0$$

Where

$J = \begin{bmatrix} 0 & 1 \\ -1 & 0 \end{bmatrix}$.

The flow of the fluid can be formulated as the boundary integral equation (Pozrikidis 1992)

$$\oint_{\Gamma} \left( T(\boldsymbol{x}, \boldsymbol{x}_0)\, \boldsymbol{u}(\boldsymbol{x}) - G(\boldsymbol{x}, \boldsymbol{x}_0)\, \boldsymbol{f}_h(\boldsymbol{x}) \right) d\Gamma_{\boldsymbol{x}} = \begin{cases} \boldsymbol{u}(\boldsymbol{x}_0) & \boldsymbol{x}_0 \in \Omega_F \\ \frac{1}{2}\boldsymbol{u}(\boldsymbol{x}_0) & \boldsymbol{x}_0 \in \Gamma \\ \boldsymbol{0} & \text{otherwise} \end{cases}$$

where

$$T_{ij}(\boldsymbol{x}, \boldsymbol{x}0) = -\frac{\boldsymbol{r} \cdot \boldsymbol{n}}{\pi r^4}\, r_i\, r_j$$

$$G_{ij}(\boldsymbol{x}, \boldsymbol{x}_0) = \frac{1}{4\pi\mu} \left( -\delta_{ij} \ln(r) + \frac{r_i\, r_j}{r^2} \right)$$

$\boldsymbol{r} = \boldsymbol{x} - \boldsymbol{x}_0,\ r = |\boldsymbol{r}|,\ \boldsymbol{n}$ is the unit normal to Γ and $\delta_{ij}$ is the Kronecker delta function. Since the fluid velocity $\boldsymbol{u}$ is known on the whole of the boundary Γ, this gives a first-kind Fredholm integral equation to solve for the hydrodynamic surface forces $\boldsymbol{f}_h$. These are the hydrodynamic forces which act on the surfaces of the cells. The next section will consider the forces due to chemotaxis.

**3.2 The Convection-Diffusion Equation For Modelling The Chemical Signal.**

When a moving cell secrets the chemical signal into the (moving) surrounding fluid the concentrations $c$ can be modelling using

$$\frac{\partial c}{\partial t} = \nabla \cdot (D(\boldsymbol{x}, t) \nabla c) - \nabla \cdot (c\ \boldsymbol{u}) + F(\boldsymbol{x}, t)$$

where $D$ is the diffusion constant and $\boldsymbol{u}$ the velocity of the fluid. This is solved on the whole domain Ω with

$$D(\boldsymbol{x}, t) = \begin{cases} D_f & \boldsymbol{x} \in \Omega_F \\ D_c & \boldsymbol{x} \in \Omega_i. \end{cases}$$

Here $F(\boldsymbol{x}, t)$ is a source term that can be used to simulate a cell manufacturing the chemical signal. Hence if cell 1 is producing the chemical signal at the rate $R$ for the first $t_1$ units of time then

$$F(x, t) = \begin{cases} R & x \in \Omega_1 \text{ and } t \le t_1 \\ \\ 0 & \text{otherwise.} \end{cases}$$

Applying the finite element method to solve this equation leads to (see Zienkiewicz and Taylor 1989 for details of the finite element method)

$$M\dot{\boldsymbol{c}} = K(t)\, \boldsymbol{c} + \boldsymbol{F}(t)$$

where

$$M_{ij} = \int_{\Omega} \phi_i(\boldsymbol{x}) \phi_j(\boldsymbol{x})\ d\boldsymbol{x}$$

$$K_{ij}(t) = \int_{\Omega} \left( D(\boldsymbol{x}, t)\, \nabla\phi_j(\boldsymbol{x}) - \phi_j(\boldsymbol{x}) \boldsymbol{u}(\boldsymbol{x}, t) \right) \cdot \nabla\phi_i(\boldsymbol{x})\, d\boldsymbol{x}$$

$$F_i(t) = \int_{\Omega} F(\boldsymbol{x}, t) \phi_i(\boldsymbol{x})\ d\boldsymbol{x}.$$

Here $\boldsymbol{c}$ denotes the vector of nodal values of the concentration and an overdot denotes differentiation with respect to time. The main drawback of this method is that $K(t)$ will need to be recalculated at every time-step which adds considerably to the computational cost of this method.

### 3.3 Simplified Model Of The Spread Of The Chemical

To avoid the computational cost of having to solve the convection-diffusion equation, an alternative model is where the spread of the chemical is modelled using the linear diffusion equation

$$\frac{\partial c}{\partial t} = D \ \nabla^2 c$$

and move the solution with the cell that is secreting the chemical. Numerical results show that this is an acceptable approximation.

For a circular cell it is possible to find an exact solution to the diffusion equation for the concentrations. If the location of the cell secreting the chemical is $(x_1(t), y_1(t))$ then the concentration of the chemical is given by

$$c(x,y,t) = \frac{c_0}{\mu(t-t_0)} \exp\left( -\frac{\big(x - x_1(t)\big)^2 + \big(y - y_1(t)\big)^2}{4\mu(t-t_0)} \right)$$

where $c_0$ is a constant that controls the magnitude of the concentrations and $t_0$ is a small parameter to avoid computational problems when $t = 0$. However, this method can only be applied when the cell secreting the chemical is circular. A method that can be used for cells with other shapes is currently under development.

### 3.4 Time Integration Methods

Using either of the above methods the chemotaxis force acting on the surface of the cell are given by

$$\oint_{\Gamma_i} k_i \, c(\boldsymbol{x}, t) \ \boldsymbol{n} \ d\Gamma_{\boldsymbol{x}}$$

where $\boldsymbol{n}$ is the unit normal vector acting outwards from the cell interior and $k_i$ is a constant that controls how strongly the $i^{\text{th}}$ cell reacts to the chemical signal. Hence the total force and torque acting on the cell is the sum of the hydrodynamic forces and the chemotaxis forces given by

$$\boldsymbol{f}_i = \oint_{\Gamma_i} (\boldsymbol{f}_h + k_i \, c(\boldsymbol{x}, t)\boldsymbol{n}) \, d\Gamma_i.$$

$$\tau_i = \oint_{\Gamma_i} (\boldsymbol{f}_h + k_i \, c(\boldsymbol{x}, t)\boldsymbol{n}) \, J \, (\boldsymbol{x} - \boldsymbol{x}_i) \, d\Gamma_i$$

The equations of motion for the cells are now given by

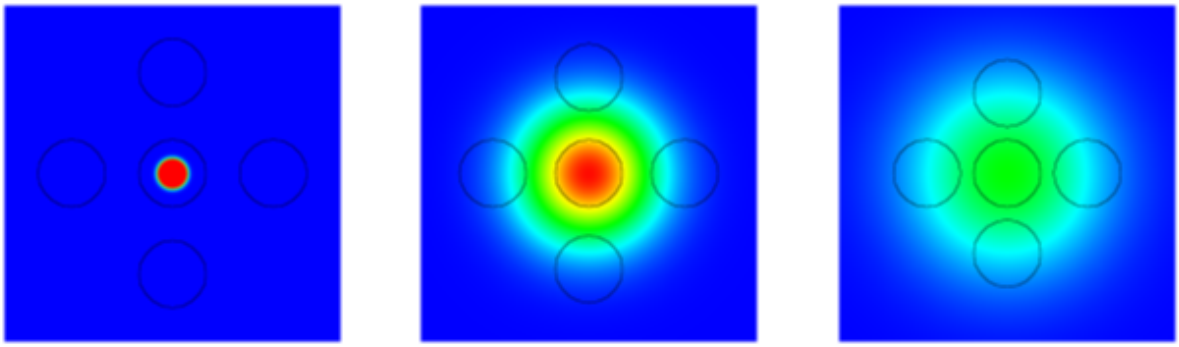
$$\frac{d\boldsymbol{v}_i}{dt} = \frac{1}{m_i} \boldsymbol{f}_i \qquad \frac{d\omega_i}{dt} = \frac{1}{I_i} \tau_i$$

$$\frac{d\boldsymbol{x}_i}{dt} = \boldsymbol{v}_i \qquad \frac{d\theta_i}{dt} = \omega_i.$$

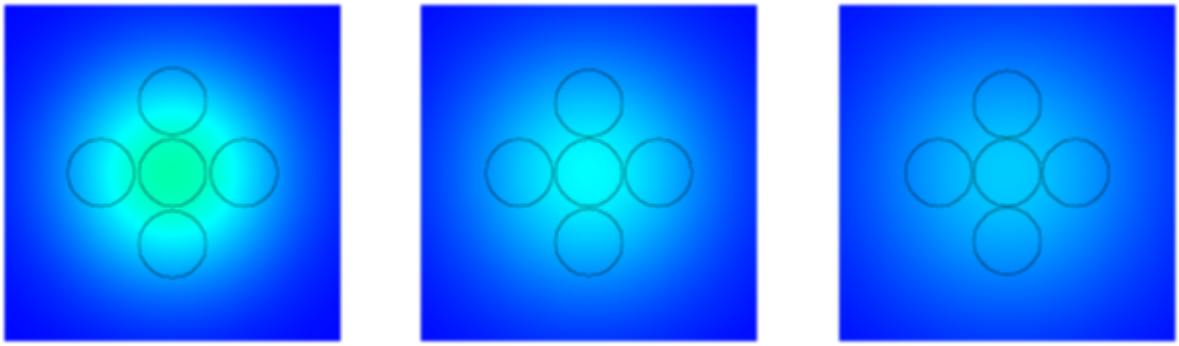
These can be integrated through time using a fourth order Runge-Kutta scheme.

### 3.5 Numerical Results.

The test problem below shows the motion of four cells towards a central cell that is secreting the chemical signal. In the diagrams, blue denotes regions where the chemical concentration is low and red denotes regions where the concentration is high.

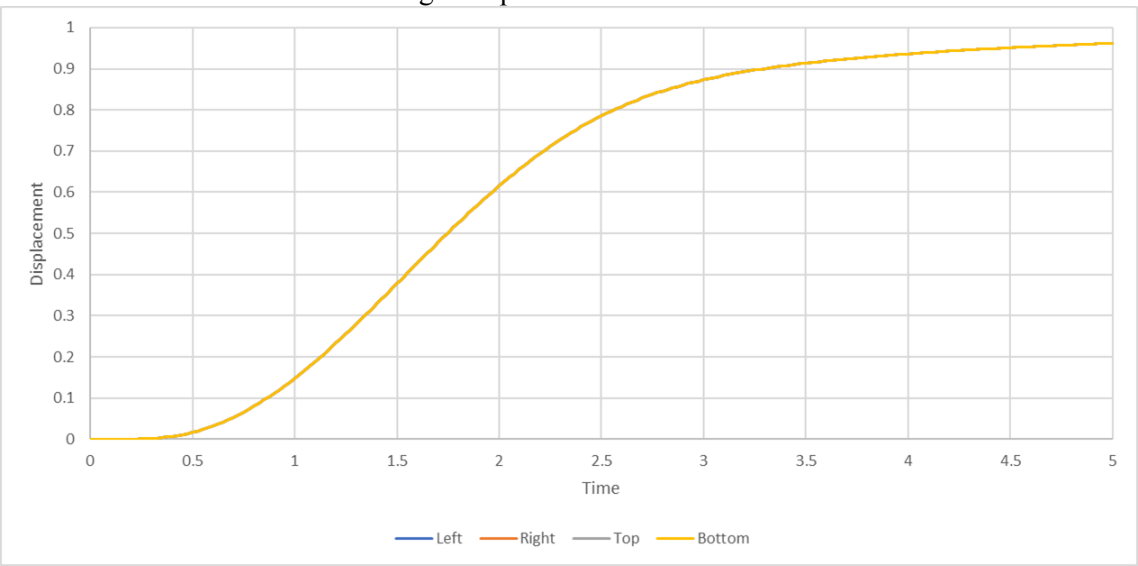


t=0 t=1 t=2



t=3 t=4 t=5

As expected, the four outer cells move symmetrically towards the central cell which is secreting the chemical. The Figure below shows the distance that each of the four outer cells move towards the central cell. The four curves are superimposed, demonstrating the expected symmetry of the results and that the numerical simulation is behaving as expected.




## 4. Conclusions And Future Work

The simple rigid particle model is very good for seeing how a large number of cells can form clusters due to chemotaxis. However, this model has limited scope in terms of the fluid mechanics and cell/cluster geometries. The boundary integral method is an effective way of modelling the motion of biological cells moving in a viscous fluid and does not have the same geometrical limitations as the rigid particle model. The convection-diffusion equation can be used to model the spread of the chemical signal through the fluid, but it needs to be solved numerically using the finite element method (or similar) which is computationally very expensive. Avoiding the use of the finite element method

considerably reduces the computational cost, but possibly at the cost of losing some of the information about how the chemical signal spreads out.
A method for modelling how a cell which is not circular manufactures the chemical is currently under development, based on an integral representation of the initial chemical concentrations. A model of how two cells collide needs to be developed. The early stages of the collision has similarities to the way in which two liquid droplets coalesce. However, in the later stages the two cells remain separate and the material in their interiors does not combine in the say way that the liquid in two droplets combines.

**Publications.**

Harris P. J.: A simple mathematical model of cell clustering by chemotaxis. *Mathematical Biosciences*, **294**, 62 - 70, (2017).
Harris P. J.: Modelling the motion of clusters of cells in a viscous fluid using the boundary integral method. *Mathematical Biosciences*, **360**, 141 - 152, (2018)
Harris P. J.: A combined boundary element and finite element model of cell motion due to chemotaxis. In *Integral Methods In Science and Engineering: Analytic Treatment and Numerical Approximations*, Ed. C. Constanda and P. J. Harris, 163 - 172, (2019).

**Other References.**

Atkinson, K. E.: *An introduction to numerical analysis, 2nd Edition*. John Wiley and Sons, New York, (1989)
Lighthill, M. J.: *An informal introduction to theoretical fluid mechanics*. Clarendon Press, Oxford. (1986).
Pozrikidis, C.: *Boundary Integral and Singularity Methods for Linearized Viscous Flow*. Cambridge Texts in Applied Mathematics, Cambridge University Press, (1992).
Zienkiewicz, O. C. and Taylor R.L.: *The Finite Element Method, fourth Edition*. McGraw-Hill Book Company Europe, London, (1989).