Position determination by a single cell using chemical sensing

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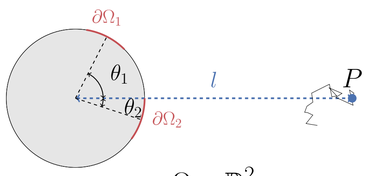
The big question

Can a single cell determine the position of a source of diffusing particles?

Motivation

Cells like spermatozoa or neural axons have to be able to find targets over a large range of length scales. The process of chemoreception could serve as a mean for cells to direct their movement through a medium. Many studies since the seminal paper by Berg and Purcell [1] have looked into mathematical models and limitations of chemotaxis. Literature, however, overlooks the actual influence of the position of the source relative to the cell and the question whether directional information can be extracted from diffusing molecules.

A toy problem



$\Omega = \mathbb{R}^2$

We consider a steady source P of diffusing particles with diffusion constant D a distance l away from a (spherical) cell with radius R in the domain $\Omega = \mathbb{R}^d$, $d \geq 2$. The cell has two (small) receptors $\partial\Omega_{1,2}$ on the surface of the cell $\partial\Omega$ which absorb the particles, whilst the rest of $\partial\Omega$ reflects the particle. Let $\varepsilon = |\partial\Omega_{1,2}| \,/\, |\partial\Omega| \ll 1$.

Of main interest are the splitting probabilities $p_1(P)$ and $p_2(P)$ of starting from P and first hitting $\partial\Omega_1$ or $\partial\Omega_2$ respectively.

Simulation of Brownian motion in an unbounded domain

We non-dimensionalise the problem such that $R = 1$ and $D = 1$. Now the only parameters left are that of the cell receptors ε, θ_1 and θ_2 and separation distance between cell and source L.

For simulation purposes we apply the Euler scheme with time step Δt to the Brownian motion SDE for the position $X(t)$ to get

$$X(t + \Delta t) = X(t) + \sqrt{2D\Delta t}\zeta, \qquad (1)$$

where $\zeta \sim \mathcal{N}_d(0, \mathbb{I})$. However:

- A severe time step constraint is imposed by the receptors, $\Delta t = \mathcal{O}(\varepsilon)$, to correctly resolve the cell.
- Particles can make large excursions before absorption, see Figure 1. If $d \geq 3$ it can wander around forever without absorption.

Naive simulations with small holes are therefore (too) expensive.

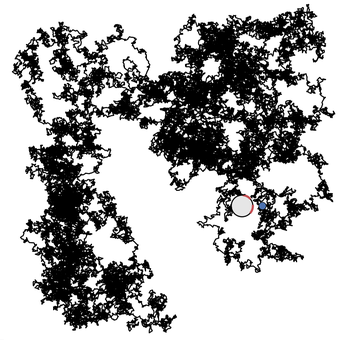


Figure 1 : Large detour of a Brownian particle starting at $L = 2$ to the cell with receptors of size $\varepsilon = 0.1$.

First-passage properties

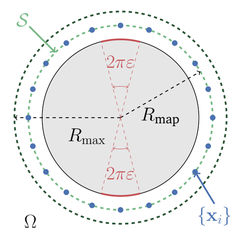
Ideally we want to focus on what happens when particles are close to the cell. To this end we use the first-passage properties of a Brownian particle externally to a sphere [2] to refine our efforts to an annulus of size $\mathcal{O}(\varepsilon)$ around the cell. We draw a protective sphere $\mathcal{S}$ of radius R_{map} around the cell. The first-passage results then yield $p_{\text{map}}(\mathbf{y}, \mathbf{x}, \mathcal{S})$, the probability to first hit $\mathbf{x} \in \mathcal{S}$ starting from $\mathbf{y}$ externally to $\mathcal{S}$.

We can then use this mapping to $\mathcal{S}$ and conditional probability to write

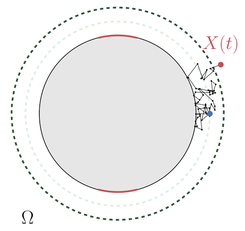
$$p_{1,2}(P) = \int_{\mathcal{S}} p_{\text{map}}(P, \mathbf{x}, \mathcal{S}) p_{1,2}(\mathbf{x}) \, \mathrm{d}\mathbf{x}. \qquad (2)$$

If $d = 2$ note that the integrand in (2) is periodic. As a result we can numerically approximate the integral very accurately by the trapezoidal rule using few points on $\mathcal{S}$. This reduces the computation of $p_{1,2}$ for *any* P outside $\mathcal{S}$ to the computation of $p_{1,2}$ for a small set of $\{\mathbf{x}_i\} \subset \mathcal{S}$.

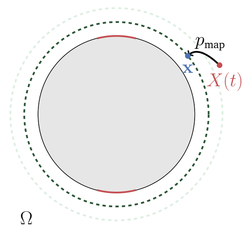
Efficient simulation on Ω



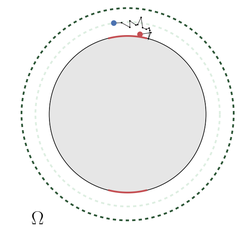
i) Start Brownian particles at discrete set $\{\mathbf{x}_i\} \subset \mathcal{S}$. Use (1) until *ii)* or *iv)*.



ii) Particle leaves protective annulus, i.e. $\|X(t)\|_2 \geq R_{\text{max}}$. Use *iii)*.



iii) Map particle back to protective annulus by sampling a position $\mathbf{x}$ from $p_{\text{map}}(X(t), \mathbf{x}, \mathcal{S})$. Use (1) until *ii)* or *iv)*.



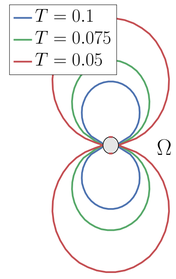
iv) Particle hits the cell at $\partial\Omega_{1,2}$ and is thus removed and we retrieve the exit position.

Sensitivity regions

Suppose that a cell can compare the influx of molecules between the two holes. The relevant measure in that case is the relative influx

$$r(P) = \frac{|p_1(P) - p_2(P)|}{p_1(P) + p_2(P)}.$$

Assuming cells cannot distinguish arbitrary relative fluxes we set a threshold value T such that if $r(P) < T$ the cell is blind to the source P.



Sensitivity regions for $\varepsilon = 0.1$ and antipodal receptors. If P outside the shown curves, the cell is blind to its position. Note that the size of the regions is of the order of a few cell lengths only.

Conclusions and outlook

Simulations using the new technique seem to suggest that under the current model long range sensing is prohibited. Future research will use the computational approach and narrow escape theory to further explore the actual reconstruction of source positions from influx of molecules. We will also look at the extension to different geometries.

References

1. Berg, H. C. & Purcell, E. M. Physics of chemoreception. *Biophysical journal* **20**, 193–219 (1977).
2. Redner, S. *A Guide to First-Passage Processes* (Cambridge University Press, 2001).

Acknowledgements

C. B. was supported by a Clarendon & New College scholarship.

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