Position reconstruction from chemical signals

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Chemotaxis

Many types of cells rely (partially) in their functioning (or survival) on the localisation of a specific location, e.g.

- *Dictyostelium* amoebae hunting for bacterial prey
- Spermatozoa in their search for the ovum
- *E. coli* looking for food (such as glucose)

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Common mechanism for this localisation is the use of chemical attractants or repellents, migration based on this principle known as *chemotaxis* and ubiquitous in biology.

Chemotaxis via spatial sensing

Eukaryotic cells are often large enough to be able measure a chemical gradient along their extent[1].

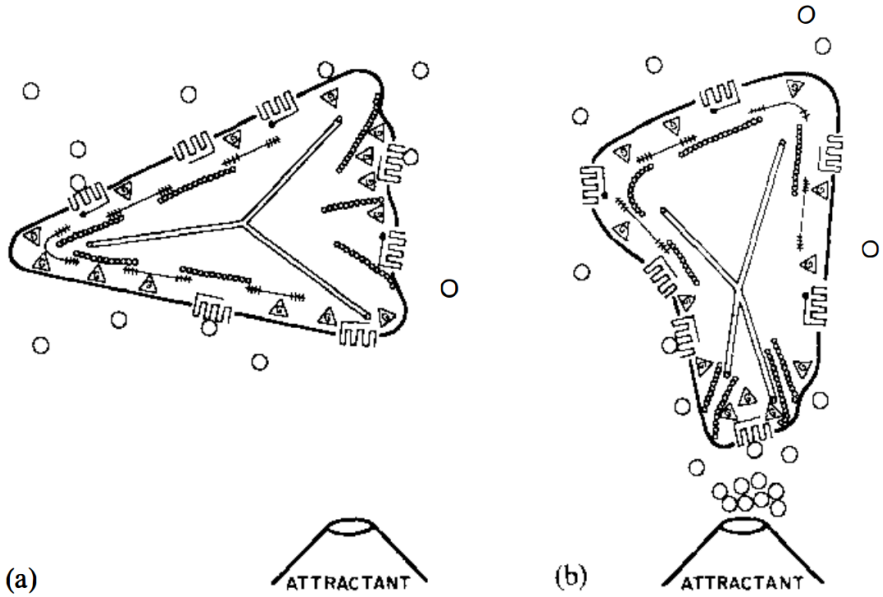
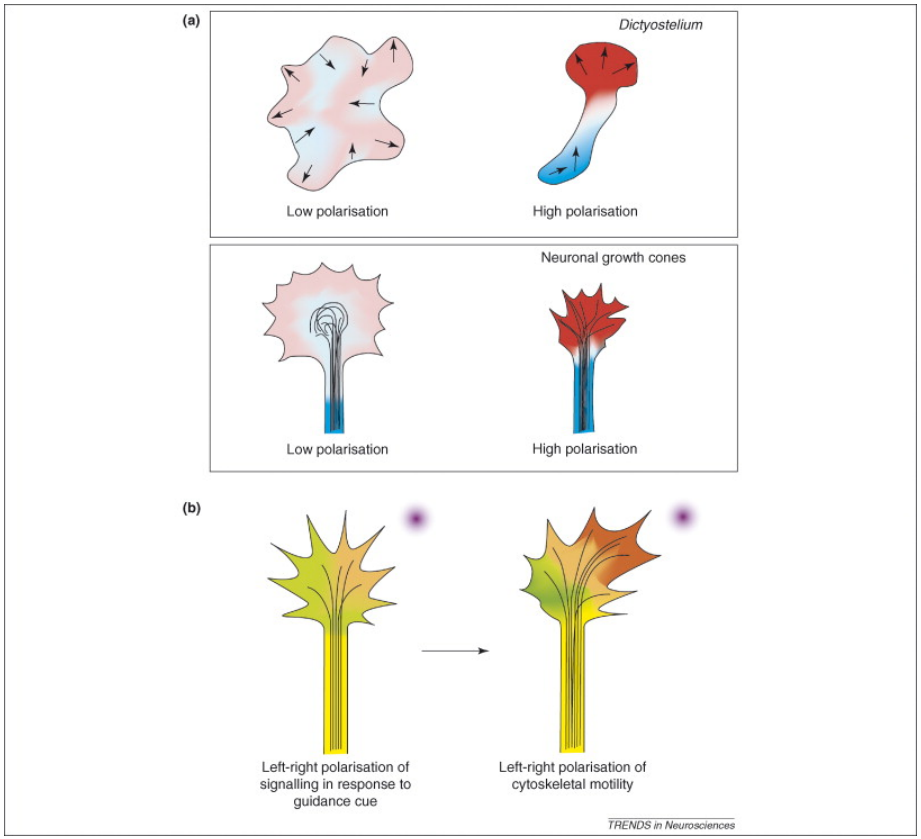


Figure 3 Diagram of chemotactically sensitive cell. (A) Cell locomoting in a uniform concentration of chemoattractant. The leading edge of the cell and the direction of locomotion are to the right. (B) Same cell shortly after release of concentrated chemoattractant from the micropipet in the lower portion of diagram. Shown are attractant molecules (○); receptors (⊔); modified receptors (⊔); G proteins (△); actin filaments (∞∞∞∞∞∞∞∞); myosin filaments (⊣⊢); microtubules (═).

[1] P. N. Devreotes and S. H. Zigmond. "Chemotaxis in Eukaryotic Cells: A Focus on Leukocytes and Dictyostelium". In: *Annual Review of Cell Biology* 4.1 (1988), pp. 649–686.

Chemotaxis via spatial sensing

Chemical cue leads to polarisation of cell which can induce directed motion/growth.[2]



[2] D. Mortimer et al. "Growth cone chemotaxis". In: *Trends in Neurosciences* 31.2 (2008), pp. 90–98.

Chemotaxis via other mechanisms

Not all cells can use their spatial extent to find concentration gradients, e.g. prokaryotic cells. Different strategies such as the famous tumble and swim strategy of *E. coli* (biased random walk).

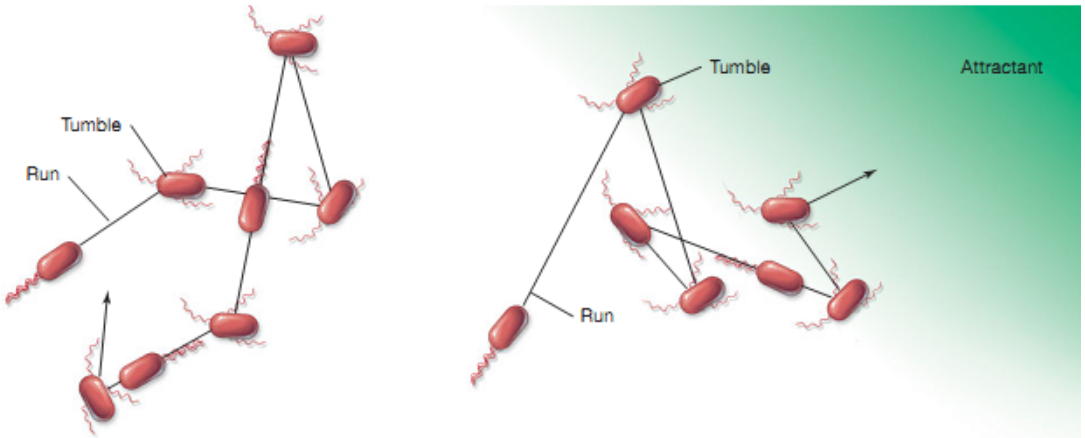


Photo by Goetingen Project iGem 2012 / CC BY

Berg & Purcell limits to chemical sensing

Mathematical modelling in the context of chemotaxis been studied over the past decades. One of the most noteworthy contributions made by Berg & Purcell[3] which concerns chemical concentration detection and uncertainty related to these measurements.

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They consider a spherical cell with N absorbing patches in a spherically homogeneous steady state diffusive concentration field.

- Derive estimates for the rms fractional error of the background concentration.
- Use this to look at species hypothesised using temporal mechanisms, e.g. swimming *E. coli.*
- Spatial gradients however completely absent from the discussion. (No localised source)

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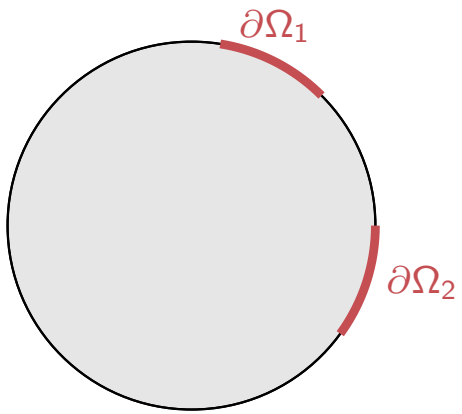
Introducing the toy problem

Same setting as Berg & Purcell, a single cell in an unbounded medium Ω with absorbing patches $\partial\Omega_i$ depicting the receptors on the surface of the cell, through which particles leave the domain Ω.



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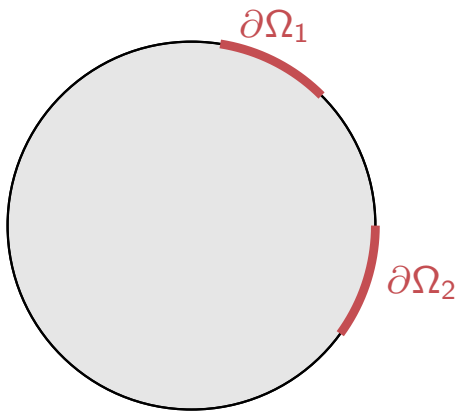

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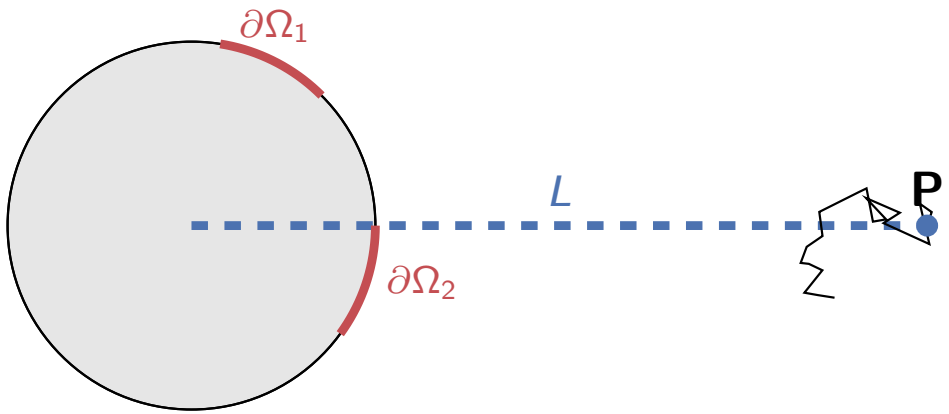

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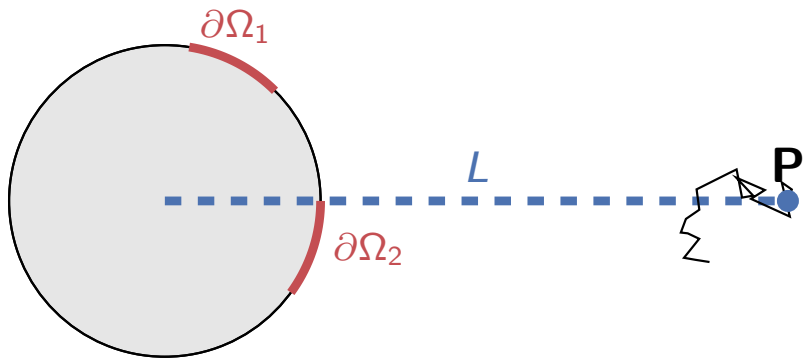
Important is that we do not consider a fully absorbing cell as is often seen in literature.

However, we now consider a localised source of chemicals at location **P**. As a result we get a specific chemical concentration field due to the localised source.

Simulating Brownian motion in an unbounded domain



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

Use Euler scheme applied to Brownian motion SDE to get particle position X at time t

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

with $\zeta \sim \mathcal{N}_d(0, \mathbb{I})$ for $\Omega = \mathbb{R}^d$. Simulate until target is hit and particle gets removed.

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Issues with this naive approach:

- Particles can make large excursions before absorption. If $\Omega = \mathbb{R}^d$ with $d \geq 3$ it can wander around forever without absorption.

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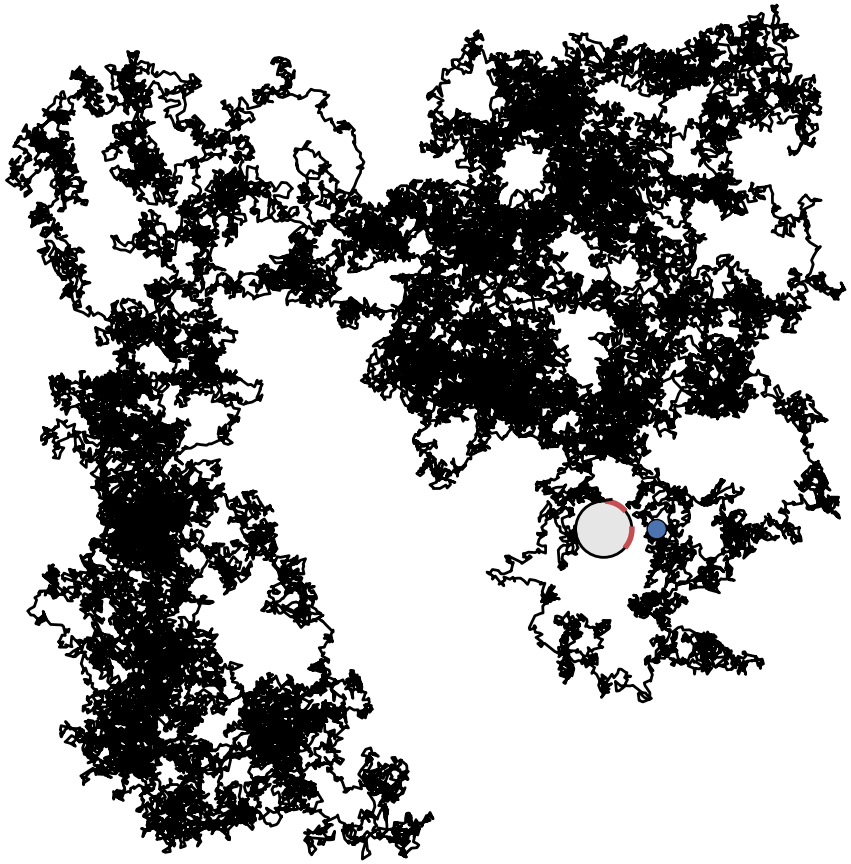

Figure : Large detour of a Brownian particle starting close to the cell.

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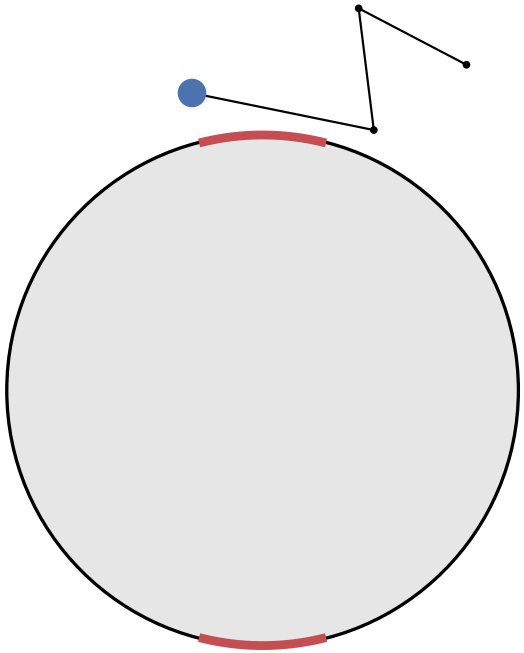
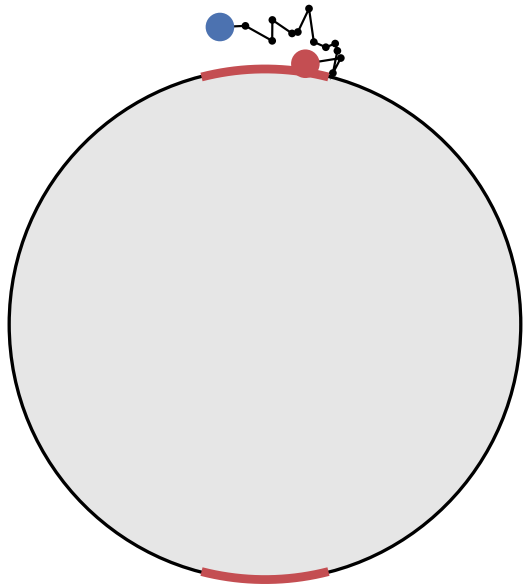


Ω



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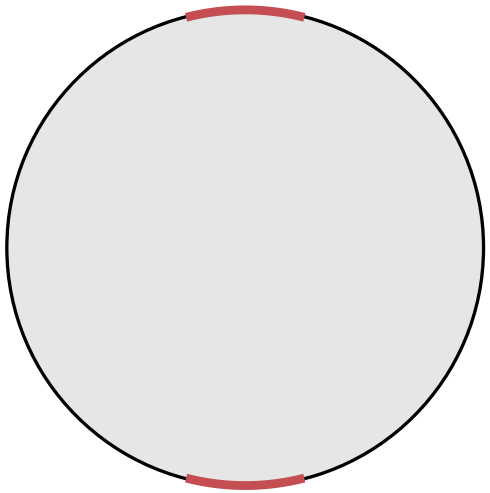
Naive simulations with small holes are therefore (too) expensive.
We are however not interested in the time it takes for chemical to arrive at cell as we consider the steady state problem.

First-passage focussed effort

Instead of spending time simulating particles far away from the objective use first-passage properties of Brownian motion to focus computational effort close to the cell.



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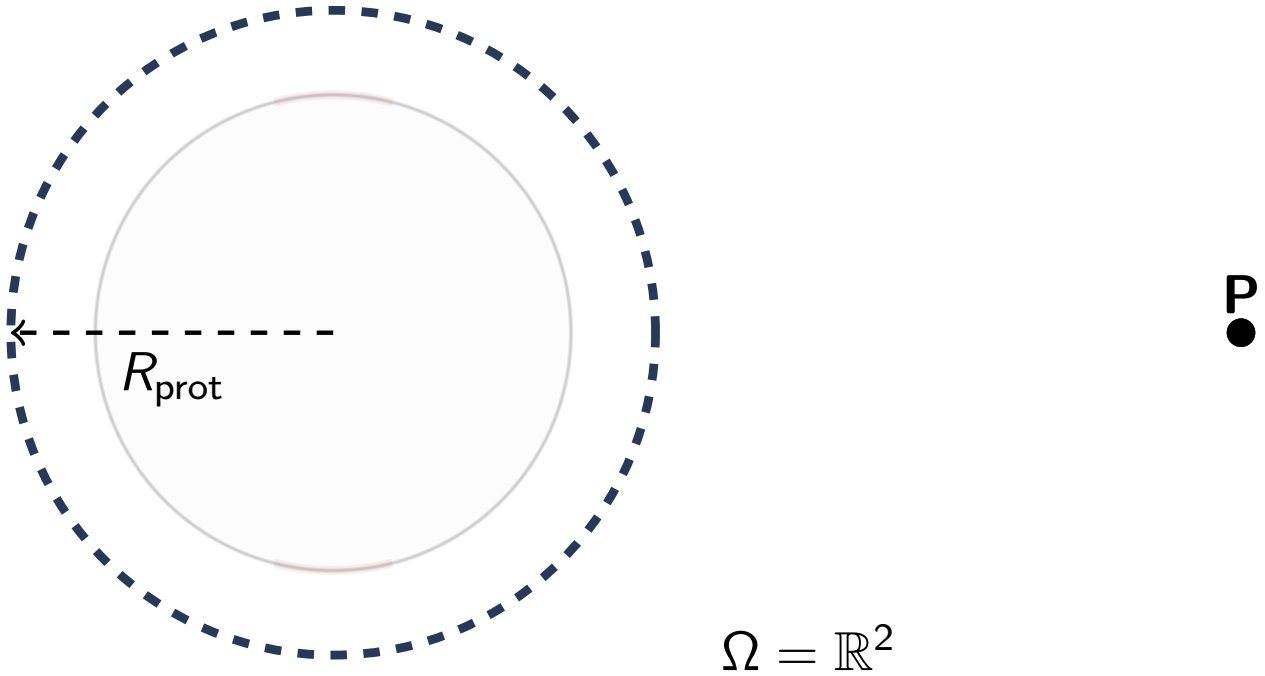

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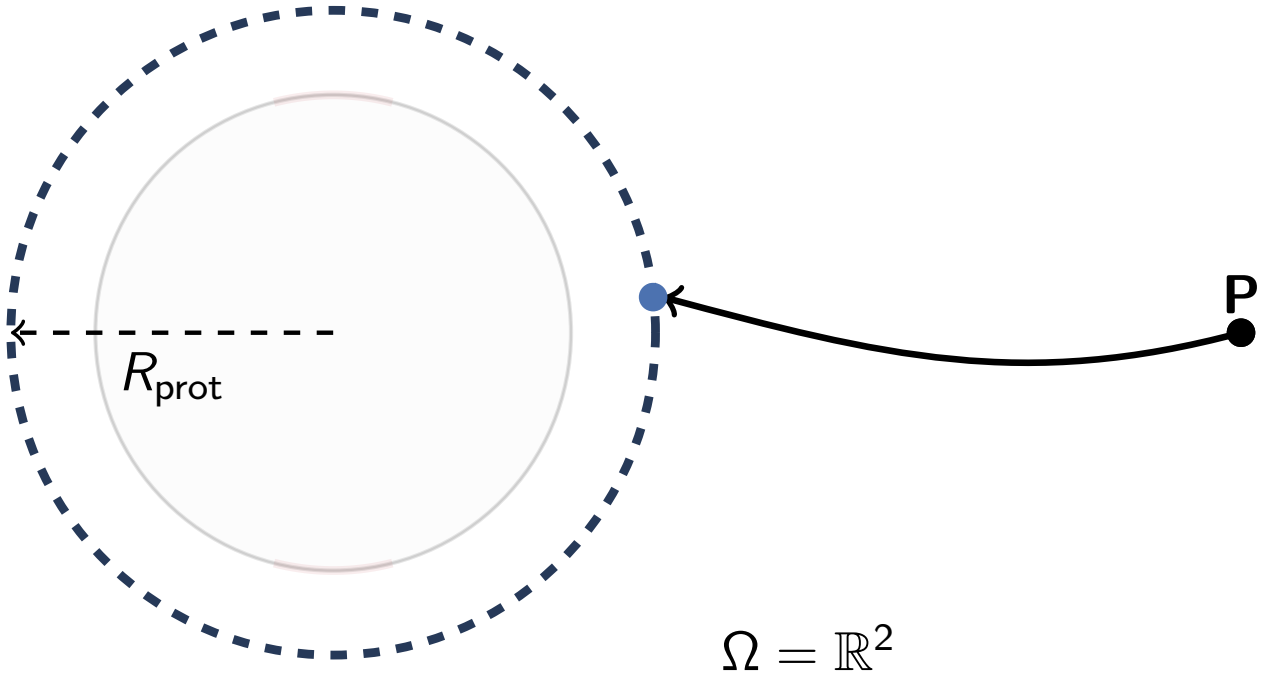

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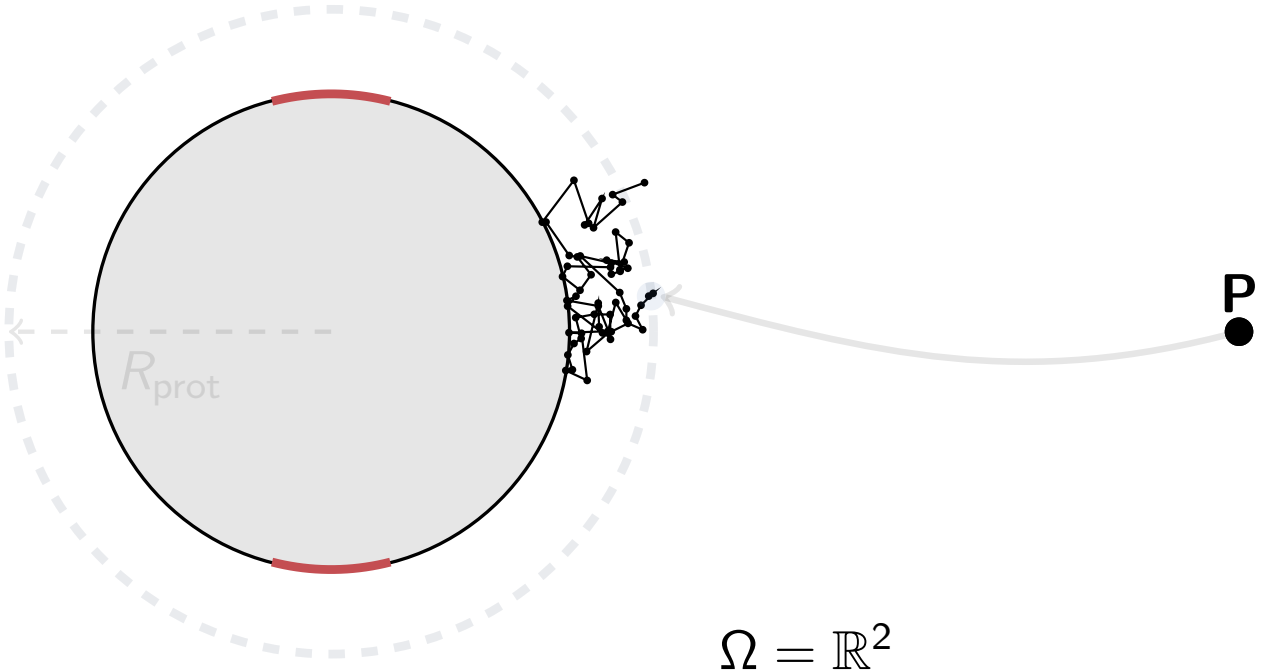

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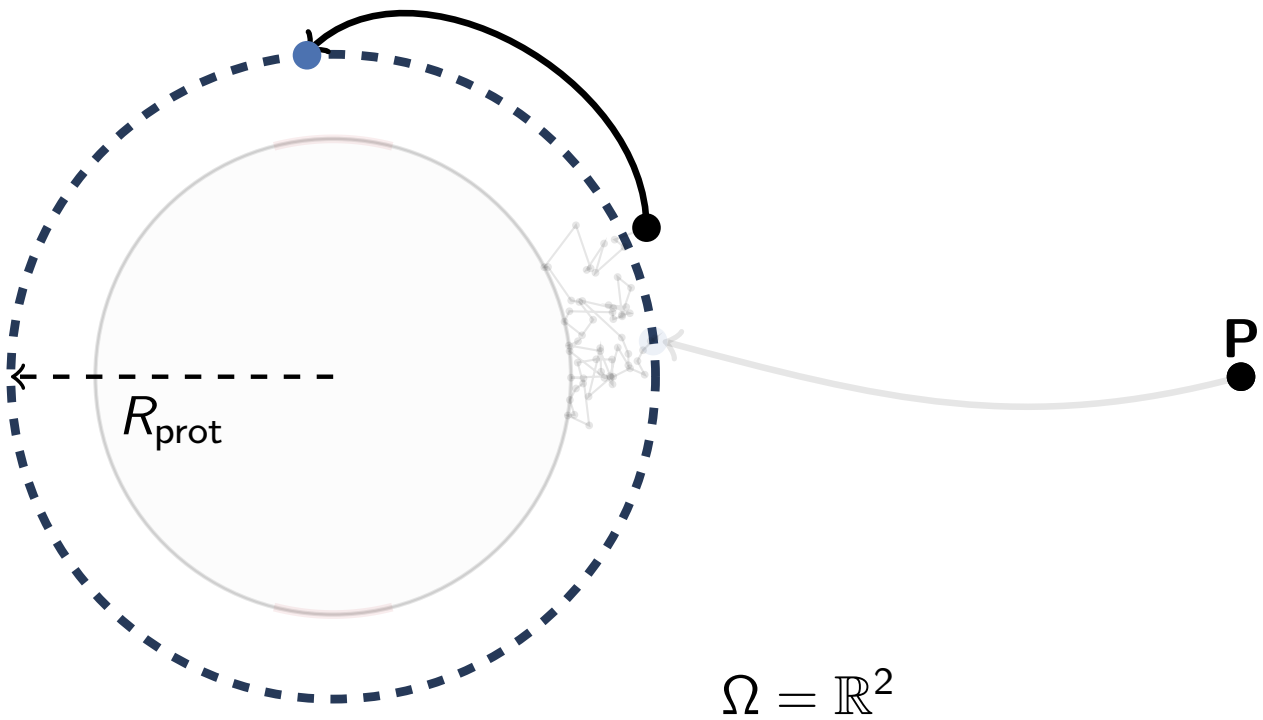

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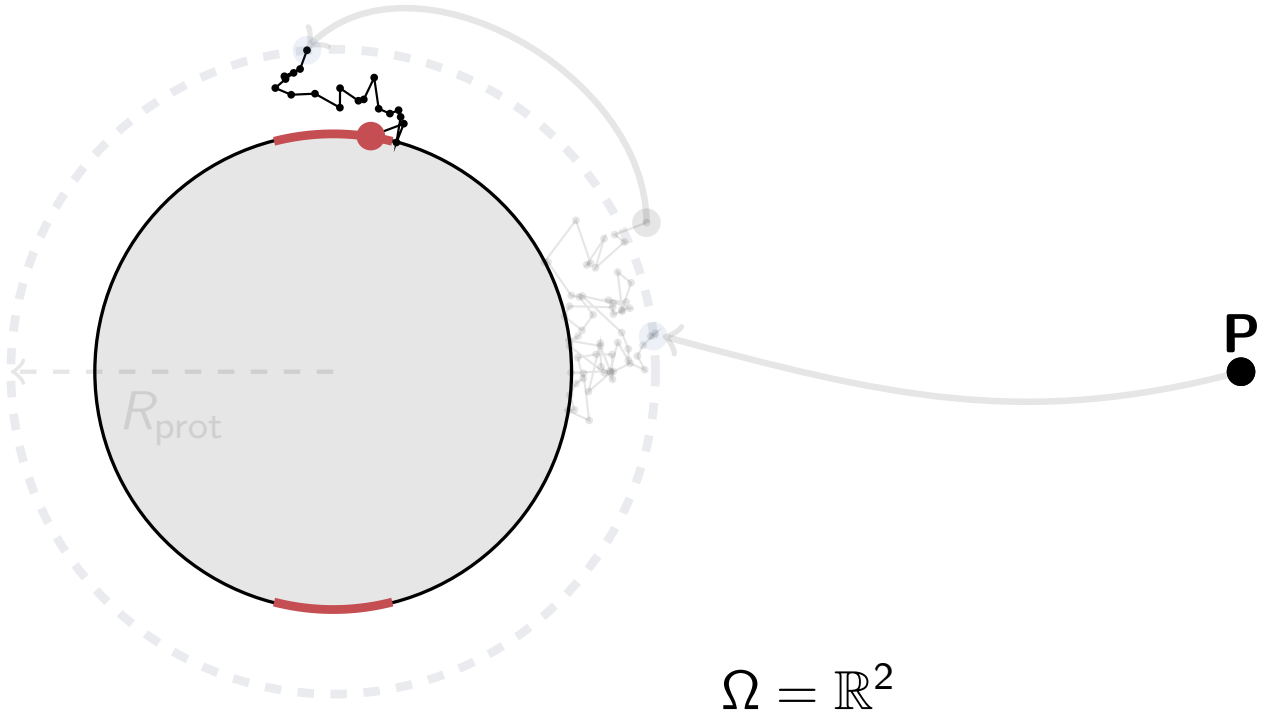

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Cells' task: inverse problem

Up until now we have focused on the forward problem, *given a source location* $\mathbf{P}$ *what is the signal at the receptors.*

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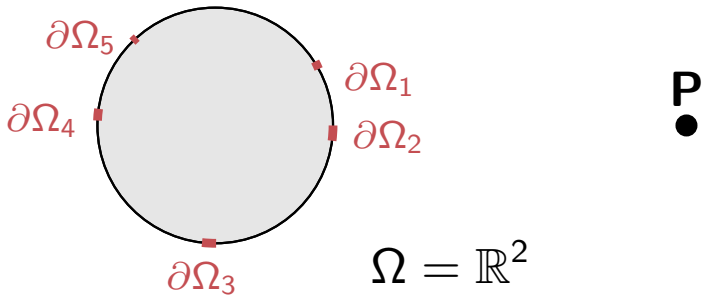
More interesting from the cells' perspective is the inverse problem, *given an influx signal at the receptors, what was the location of the source* **P**.

Narrow escape theory

We turn to asymptotics to derive inverse relations between the fluxes at the receptors and the source location **P**. Use the fact that the receptor area is supposed to be small compared to the cell surface area introducing natural small parameters $\varepsilon_i = |\partial\Omega_i|/|\partial\Omega|$.



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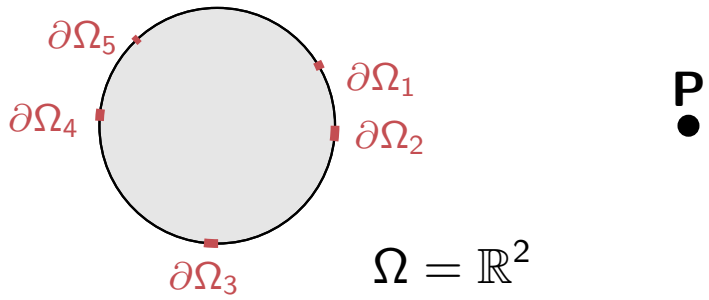


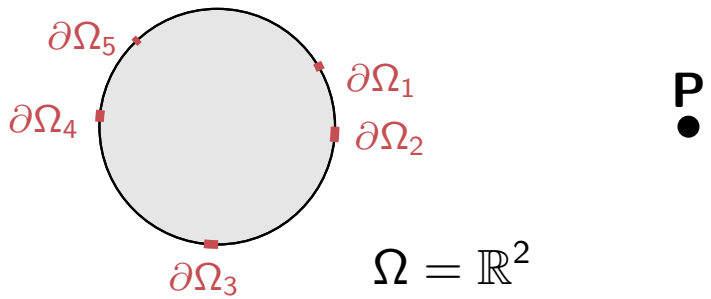
Framework of narrow escape problems[4] very suitable, now however we consider a narrow entry problem as we approach the absorbing windows from outside.

[4] D. Holcman and Z. Schuss. "The Narrow Escape Problem". en. In: *SIAM Review* 56.2 (2014), pp. 213–257.

Matched asymptotic expansions

In effect we are looking for the solution to the mixed boundary value problem describing the chemical concentration c

$$\begin{aligned} \Delta c &= -\delta(\mathbf{x}-\mathbf{P}), && \mathbf{x}\in\Omega, \\ c &= 0, && \mathbf{x}\in\cup_i\partial\Omega_i, \\ \frac{\partial c}{\partial n} &= 0, && \mathbf{x}\in\partial\Omega/\left(\cup_i\partial\Omega_i\right). \end{aligned}$$



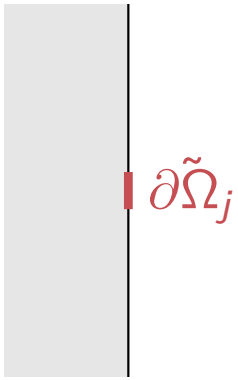
Quantities of interest, fluxes at the receptors $J_i = -\int_{\partial\Omega_i} \frac{\partial c}{\partial n}\,\mathrm{d}S$.

Matched asymptotic expansions

Following the approach by Pillay et. al[5].

Inner problem $\partial\Omega_j$

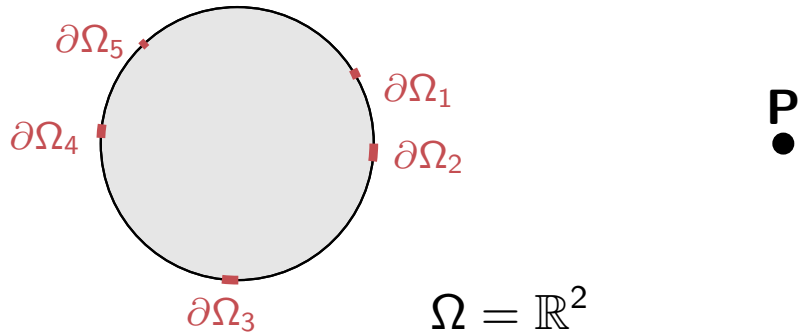
$$\begin{aligned} \Delta c_{\text{inner,j}} &= 0, && \mathbf{x} \in \tilde{\Omega}, \\ c_{\text{inner,j}} &= 0, && \mathbf{x} \in \partial\tilde{\Omega}_j, \\ \frac{\partial c_{\text{inner,j}}}{\partial n} &= 0, && \mathbf{x} \in \partial\tilde{\Omega}/\partial\tilde{\Omega}_j. \end{aligned}$$



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

Outer problem

$$\begin{aligned} \Delta c_{\text{outer}} &= -\delta(\mathbf{x} - \mathbf{P}), && \mathbf{x} \in \Omega, \\ c_{\text{outer}} &\to c_{\text{inner,j}}, && \mathbf{x} \to \mathbf{x}_j, \\ \frac{\partial c_{\text{outer}}}{\partial n} &= 0, && \mathbf{x} \in \partial\Omega/\left\{\mathbf{x}_j\right\}_{j=1}^{N}. \end{aligned}$$



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[5] S. Pillay et al. "An Asymptotic Analysis of the Mean First Passage Time for Narrow Escape Problems: Part I: Two-Dimensional Domains". In: *SIAM Multiscale Modelling & Simulation* 8.3 (2010), pp. 803–835.

Matched asymptotic expansions

The matching of the inner and outer solutions leads to a linear system of equations of the form

$$M\mathcal{J} = \mathcal{G} + \chi,$$

where

- $\mathcal{J} = (J_1, .., J_N)^T$ are the fluxes,
- M is a matrix only depending on the geometry of the cell and the receptors,
- $\mathcal{G}_i = G(\mathbf{x}_i, \mathbf{P})$, the Neumann-Green's function (only depends on $|\mathbf{x}_i - \mathbf{P}|$),
- χ is a constant which remains to be determined.

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- χ is a constant which remains to be determined.

However as χ is not measurable by the cell in terms of the fluxes we need to find an extra equation to get $N + 1$ equations for the unknown $\mathcal{J}$ and χ.

Reconstructing the source location

For the inverse problem we assume that the cell measures $\mathcal{J}$. Can we determine $\mathbf{P}$?

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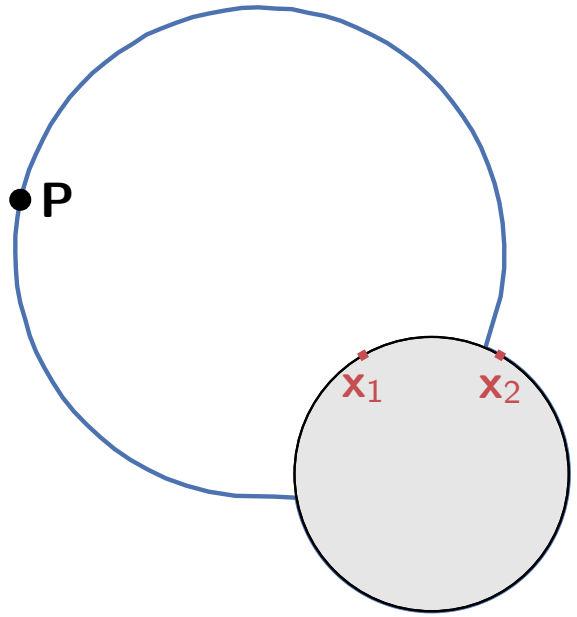
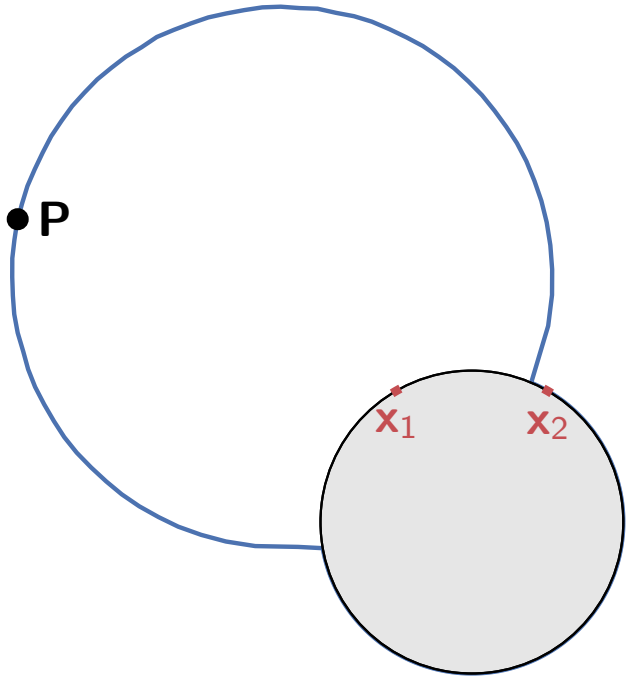
Solution: this gives us the manifolds for which $|\mathbf{x}_i - \mathbf{P}|/|\mathbf{x}_j - \mathbf{P}|$ is constant.



Reconstructing the source location

We can conclude that for $\Omega = \mathbb{R}^2$ two receptors are not enough to determine a chemical source location.



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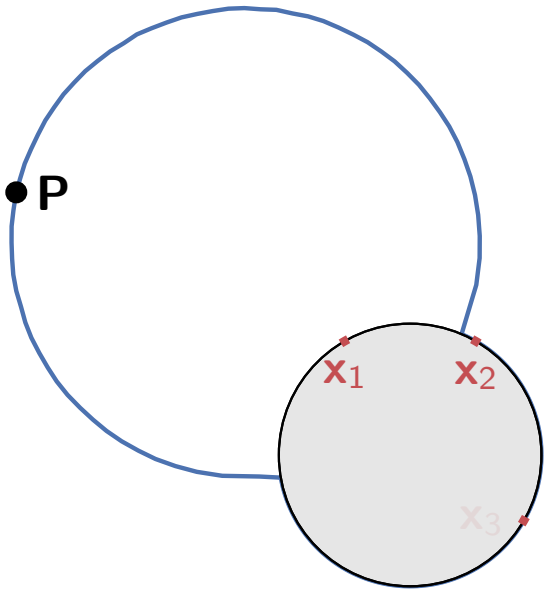
Having 3 or more receptors (in $\mathbb{R}^2$) yields intersecting manifolds so that we can reconstruct the source.



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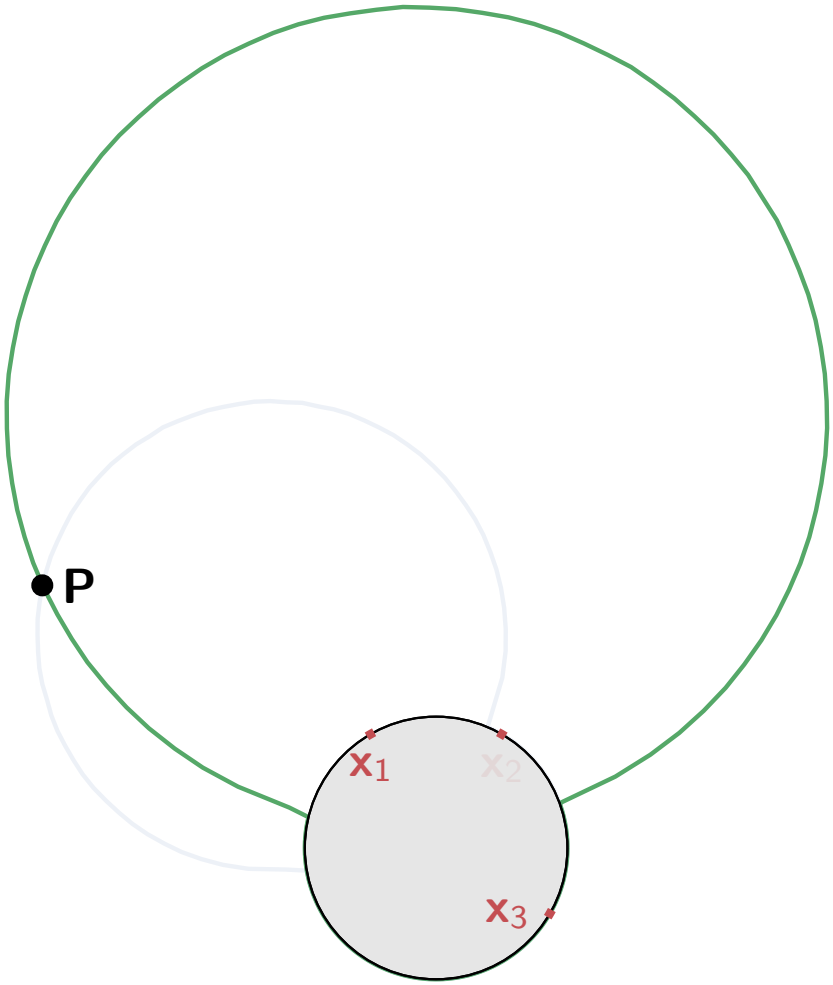

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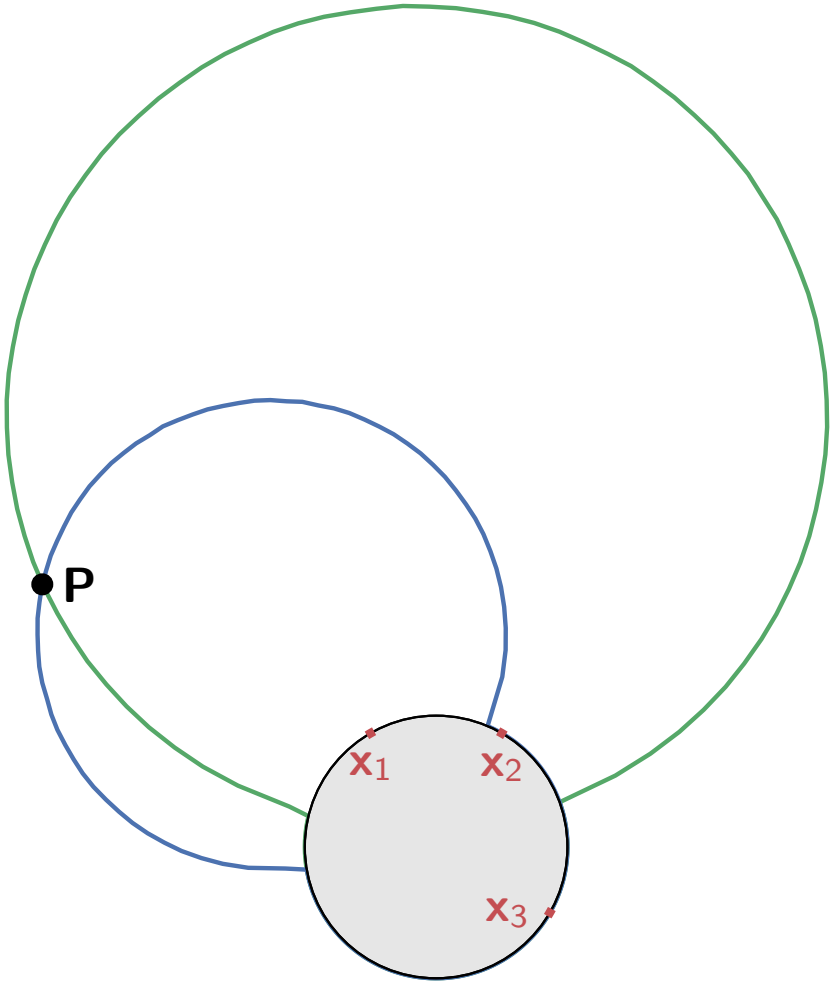

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Future work:

- Robustness of having more than 3 receptors and clustering of receptors.
- Sensitivity of receptors and influence on fluxes.