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Chemoreception of a Two-Dimensional Cell with Multilayer Diffusion

Steffi Schijf

Department of Astronomy and Theoretical Physics, Lund University

Bachelor thesis supervised by Tobias Ambjörnsson

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Abstract

Previously, Berg and Purcell found an expression for the diffusion current of particles into a set of receptors in their paper Physics of Chemoreception. These receptors were assumed to be uniformly distributed on a spherical cell's surface and the receptors where idealized as circular patches. For their model, the particles' diffusion constant was the same for all points outside of the cell. In this thesis, a model was made that mimics the scenario when there is a higher density of crowding material close to the cell's surface which would obstruct the particles from moving around. This makes the diffusion constant closer to the cell smaller than the diffusion constant further away. For computational reasons, two-dimensional geometry was considered. The model contained a two dimensional circular cell with diffusion constant D_2 within a distance d from the cell's surface and a diffusion constant D_1 further away from the cell. For a fully absorbing cell, the diffusion current was obtained both analytically and numerically. Furthermore, for a cell with equidistantly distributed receptors on its surface, where the remaining parts of the surface were perfectly reflecting, the diffusion current was obtained by numerically solving the diffusion equation. It was shown that the placement of receptors affected the diffusion current. Moreover, the ratio between D_1 and D_2 influenced the number of receptors needed to reach half of the maximum diffusion current.

Popular Abstract

Lets consider a single cell. On the cell's surface, there are receptors which can absorb a specific type of particles. If one of these particles touches a receptor, it is captured and absorbed by the cell. The number of particles that enter the cell for a unit of time is the diffusion current. Previously, Berg and Purcell showed in their paper Physics of Chemoreception that only a small part of the cell needs to be covered by receptors in order to reach half of the maximum diffusion current into a cell. More specifically, depending on the size of the cell and the receptors, it is possible to reach half of the maximum diffusion current when only 1/1000 of the cell's surface is covered by receptors. The diffusion current is at its maximum when the cell's surface is fully absorbing.

However, it can be that there is organic material attached to the surface of the cell. This can be imagined as some sort of gooey layer covering the cell's surface. If a particle is inside this goo, it will move slower than when it is outside the gooey layer.

In this thesis, I made a model that mimics this scenario with a gooey layer around the cell. The cell's surface was represented by a circle and the particle capturing receptors as patches on the cell's surface. This model was used to investigate how such a gooey layer affects the intake of particles into the cell. Furthermore, the receptors were placed in different positions to see how this, combined with the gooey layer, affects the intake of particles through the receptors on the cell's surface. It was found that when this gooey layer slows down the particles, more receptors are needed in order to reach half the maximum diffusion current. Furthermore, the diffusion current was higher when the receptors where spread out uniformly over the cell than when the receptors were clustered together.

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1 Introduction

In this thesis we look at the diffusion current into a cell through receptors. The first step of a cell signaling process is the binding of chemoattracting particles to receptors on cell surfaces. For a diffusion capturing process, the particles attached to the receptors are absorbed by the cell [1]. The chemoattractive particles outside the cell are in the extracellular matrix. The extracellular matrix is composed of molecules which form a structure between cells [2]. For the case where the extracellular matrix is more dense close to the cell's surface, chemoattracting particles would diffuse slower here in this denser region. The aim of this thesis is to to see how this change in diffusion influences the diffusion current.

In the paper Physics of Chemoreception, written by Howard C. Berg and Edward M. Purcell[3], they looked at diffusion into a spherical cell with receptors on its surface. Diffusion into the cell was only possible by binding to receptors, which where evenly distributed over the cell. The maximum diffusion current into the cell is the diffusion current for a cell with a surface that is absorbing everywhere. The expression for the maximum diffusion current into a sphere is

$$I_{\max} = 4\pi D R_{\text{cell}} C_\infty \tag{1.1}$$

where D is the diffusion constant, R_{cell} is the radius of the sphere and C_∞ is the concentration far away from the cell [3]. They found that the diffusion current I for an N number of receptors of radius s over the maximum diffusion current is [3]

$$I/I_{\max} = Ns/(4R_{\text{cell}} + Ns). \tag{1.2}$$

From this it can be found that only a small percentage of the cell's surface needs to be covered for the diffusion current to be $I_{\max}/2$ [3].

The model made by Berg and Purcell considered the diffusion constant to have the same value everywhere. During my thesis project I made a two dimensional model of a cell where D is not the same everywhere. If the consistency of the extracellular matrix within a distance d from the surface of the cell is more dense than outside the region, particles would be obstructed in their movement within this region. This decrease in movement would cause the diffusion constant to change. In this case there would be a diffusion constant D_2 within a distance d from the cell and an other diffusion constant D_1 everywhere else. In the model I made, there is a constant bulk concentration C_0 at a distance R_0 away from the center of the cell. From this bulk concentration, particles diffuse until they reach an receptor on the cell's surface. Like in the Berg and Purcell paper, the receptors are considered to be perfect sinks. Therefore, the absorbing surfaces have a concentration of zero.[3]

Figure 1 shows a schematic representation of the two dimensional model described above. At a distance d away from the cell, there is a diffusion boundary layer, represented by a black dashed line in Figure 1. In Figure 1, the cell's surface is represented by the red line and green dotted line. Here, the red lines are reflecting and the green dotted line

are absorbing receptors. The size and the number of receptors can be changed. The circle with the blue line is the location where the concentration remains constant.

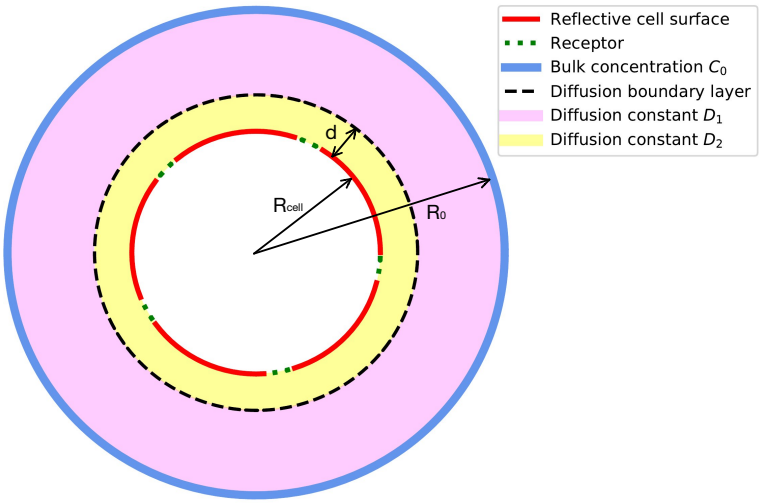


Figure 1: Schematic model of the cell. The cell's surface is reflective at the red line and absorbent at the receptors represented by the green dotted line. The model allows for two diffusion constant, D_2 in the yellow region and D_1 in the pink region. At the blue line, there is a bulk concentration C_0. The radius of the cell is R_{cell}, the radius to the start of the bulk concentration is R_0 and the distance between the cell's surface and the diffusion boundary layer is d.

In this thesis, I investigated how the ratio D_2/D_1 and the thickness d of the layer around the cell where $D = D_2$ affects the diffusion current. This was done by solving the diffusion equation [3, 4] both numerically and analytically. For the models in which the cell's surface is absorbing everywhere, the diffusion current was obtained both numerically and analytically. For a cell with a not fully absorbing surface, the diffusion current is only obtained numerically. The analytically obtained diffusion current for the two dimensional system with two diffusion constants and a cell that is fully absorbing, is

$$I_{\max} = \frac{2\pi C_0 D_1}{(D_1/D_2)\ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right) + \ln\left(\frac{R_0}{R_{\text{cell}}+d}\right)}.$$

In my results, I first compared the numerically and analytically obtained diffusion current $I_{\max}$. Furthermore, I used the numerical model to find $I/I_{\max}$ for different values for D_1 and D_2. Here I is the diffusion current for a cell which is not fully absorbing. This diffusion current I was obtained for a cell where an increasing number of receptors are evenly distributed over the cell's surface. This was done for a cell where the receptors are distributed over the whole surface, a cell where the receptors are only on half of the cell's surface and a cell where the receptors are only on one quarter of the cell's surface.

2 Theory

In this section, we introduce the diffusion equation for the multi-layered geometry as depicted in Figure 1. The diffusion equation is used to obtain the diffusion current. To solve this problem, first an expression for the concentration C is obtained. This concentration is then used to find the flux. From the flux, the diffusion current is derived.

The main observable of interest in this thesis is the diffusion current, I, into the cell. The diffusion current is the flux, $J(\mathbf{x}, t)$, integrated over the surface of the cell

$$I = -\int J(\mathbf{x}, t) \cdot \hat{n} \mathrm{d}S \tag{2.1}$$

where $\mathbf{x} = (x, y)$ denotes the spatial coordinates for two dimensions, $\hat{n}$ is the unit vector in the normal direction to the surface of the cell and $\mathrm{d}S$ is $r\mathrm{d}\theta$ in polar coordinates [3]. So to find the diffusion current, first the flux needs to be obtained. The flux can be calculated using Fick's first equation [4],

$$J = -D\nabla C. \tag{2.2}$$

Here, $C = C(\mathbf{x}, t)$ is the concentration where t denotes time.

To obtain the flux, first an expression for C needs to be found. Conservation of mass gives the following relation [1]:

$$\frac{\mathrm{d}C}{\mathrm{d}t} = -\nabla J \tag{2.3}$$

By inserting equation (2.2) into equation (2.3), Fick's second equation also called the diffusion equation, can be derived. This equation is for when the diffusion constant D has the same value for all spatial points.

$$\frac{\mathrm{d}C}{\mathrm{d}t} = D\nabla^2 C \tag{2.4}$$

For a system with multilayer diffusion, the diffusion equation becomes

$$\frac{\mathrm{d}C_i}{\mathrm{d}t} = \nabla \left(D_i \nabla C_i \right). \tag{2.5}$$

for layer i [5]. Here, D_i is the diffusion constant for layer i and C_i is the concentration in layer i. The matching conditions between layer i and $i + 1$ are

$$C_i(\mathbf{x}, t) = C_{i+1}(\mathbf{x}, t) \tag{2.6}$$

and

$$\hat{n}_i \cdot (D_i \nabla C_i(\mathbf{x}, t)) = \hat{n}_i \cdot (D_{i+1} \nabla C_{i+1}(\mathbf{x}, t)). \tag{2.7}$$

where $\mathbf{x}$ is a position between layer i and $i+1$ and $\hat{n}_i$ is the normal vector to the diffusion boundary layer separating region i and $i+1$ [5]. The concentration $C_i = C_i(\mathbf{x}, t)$ is obtained by solving equation (2.5) and using the matching conditions.

The model contains both reflective and absorbing boundary conditions. In Figure 1, the blue line is an absorbing boundary with a constant bulk concentration of C_0 and the green dotted line is an absorbing boundary that serves as a perfect sink and therefore has a concentration of 0 [3]. The red line in Figure 1 is a reflective boundary where the flux into the surface is zero. In the numerical method, the reflective boundaries are represented by Neumann boundaries and absorbing boundaries are represented by Dirichlet boundaries.

3 Method

3.1 Analytical Solutions

In this section, an analytically obtained diffusion current, $I_{\max}$, is provided for the case when the cell's surface is fully absorbing. The model of the cell for which the diffusion current is obtained is as shown in Figure 1. The diffusion current is obtained for a steady state for the cases when the diffusion constant $D = D_1 = D_2$ and when $D_1 \neq D_2$. Here, D_1 is the diffusion constant in the pink region in Figure 1 and D_2 is the diffusion constant in the yellow region. To obtain the diffusion constant, first an expression for the concentration $C(r)$ is found by solving equation (2.4) in polar coordinates for a steady state where r is the distance from the center of the cell. From the expressions for the concentrations, the flux $J(r)$ is derived using Fick's first equation (2.2). The diffusion currents is than obtain using equation (2.1).

Lets first consider the case where $D = D_1 = D_2$. For steady state the diffusion equation (2.4) becomes $\nabla^2 C(r) = 0$. The boundary conditions are $C(R_{\text{cell}}) = 0$ at the cells surface and $C(R_0) = C_0$ at $r = R_0$ where C_0 is a constant bulk concentration. The cell's surface and the boundary at $r = R_0$ can be seen in Figure 1. The general solution for C at steady state in polar coordinates is $C(r) = \ln(r)A_1 + A_2$ where A_1 and A_2 are two unknown constants. Now, using the boundary conditions and the general solution for C, the diffusion equation can be solved for steady state. From this it is found that the concentration can be expressed as

$$C(r) = \begin{cases} \frac{C_0 \ln\left(\frac{r}{R_{\text{cell}}}\right)}{\ln\left(\frac{R_0}{R_{\text{cell}}}\right)}, & \text{if } R_{\text{cell}} < r < R_0 \\ C_0, & \text{if } r = R_0 \\ 0, & \text{if } r = R_{\text{cell}}. \end{cases} \tag{3.1}$$

Notice that $C(r)$ depends linearly on the bulk concentration C_0.

When $D_1 \neq D_2$ the expressions for $C(r)$ in equation (3.1) do not hold. The boundary conditions for this set up are $C(R_{\text{cell}}) = 0$ at the cells surface, $C(R_{\text{cell}} + d) = C_1$ at a distance d from the cells surface and $C(R_0) = C_0$ at the outer Dirichlet boundary. These

boundary conditions, together with the general solution for $C(r)$, leads to the following expressions for the concentration.

$$C(r) = \begin{cases} \frac{C_1 \ln\left(\frac{r}{R_{\text{cell}}}\right)}{\ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right)}, & \text{if } R_{\text{cell}} < r \leq R_{\text{cell}} + d \\ C_0 + \frac{(C_1 - C_0)\ln\left(\frac{r}{R_0}\right)}{\ln\left(\frac{R_{\text{cell}}+d}{R_{C_0}}\right)}, & \text{if } R_{\text{cell}} + d \leq r < R_0 \\ C_0, & \text{if } r = R_0 \\ 0, & \text{if } r = R_{\text{cell}}, \end{cases} \tag{3.2}$$

where

$$C_1 = \frac{C_0 D_1 \ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right)}{D_1 \ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right) + D_2 \ln\left(\frac{R_0}{R_{\text{cell}}+d}\right)}. \tag{3.3}$$

The details of the derivation of $C(r)$ and C_1 are found in Appendix A.

Now, using the obtained expressions for $C(r)$, the diffusion current is found. First, the flux is derived from the obtained expressions for $C(r)$ and Fick's first equation (2.2). Then, the diffusion current is obtained using equation (2.1) and the expression for the flux. When $D = D_1 = D_2$, the diffusion current into the cell is

$$I_{\max} = \frac{2\pi C_0 D}{\ln\left(\frac{R_0}{R_{\text{cell}}}\right)}, \tag{3.4}$$

whereas when $D_1 \neq D_2$, the diffusion current into the cell is

$$I_{\max} = \frac{2\pi C_0 D_1}{(D_1/D_2)\ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right) + \ln\left(\frac{R_0}{R_{\text{cell}}+d}\right)}. \tag{3.5}$$

The derivation of the expression for the diffusion current can be found in appendix A.

The expressions for $I_{\max}$ in equations (3.4) and (3.5) share some similarities. Both scale linearly with the bulk concentration C_0. Also, it can be seen that when $D = D_1 = D_2$, equation (3.5) is equal to equation (3.4). Furthermore, if $d = 0$ or $d = R_0 - R_{\text{cell}}$, equation (3.5) becomes equation (3.4) where D is either D_1 or D_2, respectively.

3.2 Numerical Solution of the Diffusion Equation where $D_1 = D_2$

Lets now turn to the problem where the surface is not absorbing everywhere, but instead has absorbing patches, as can be seen in Figure 1. To solve this problem, equations (2.2) and (2.4) are solved numerically in cartesian coordinates by using a finite difference approximation. A cartesian coordinate was used for. The numerical solution was obtained using the programming language Python version 3.7. For the finite difference approximation, a spatial and time discretization procedure is used.

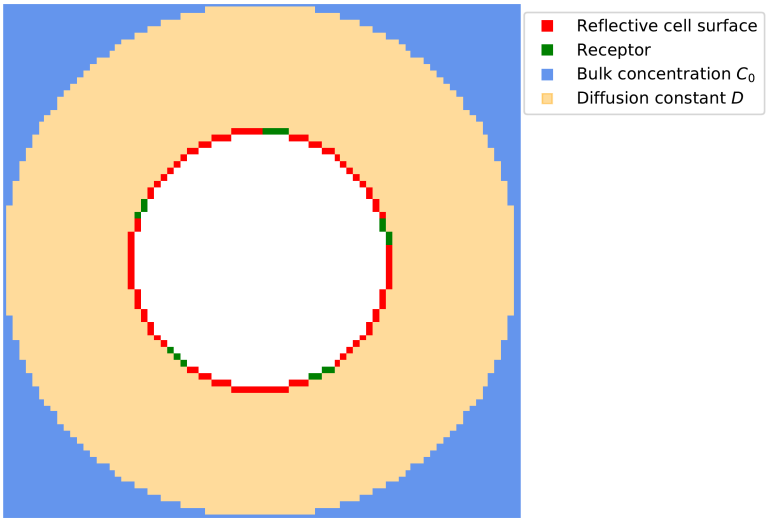


Figure 2: Spatial discretization of a two dimensional cell. The red domain is a reflective area on the cell's surface and the green domain is absorbing. The concentration is kept constant in the blue domain while the concentration for each spatial point is updated in the orange domain.

The spatial discretization of the schematic model of the cell in Figure 1 can be seen in Figure 2. For the discretization of this two dimensional model, the coordinates x and y are discretized as $x = aj$ and $y = ak$ where $a = 1$ is the lattice spacing. The spatial discretization as seen in Figure 2 is compiled from four binary matrices. These matrices are masks where a matrix element equals 1 if it is part of the domain stored by the matrix and 0 otherwise. The masks are of size $(2R_0{+}1) \times (2R_0{+}1)$. The domains of the cell's reflective surfaces are marked red in Figure 2 and are stored in a mask called **R**. These reflective surfaces are Neumann boundaries which have a zero flux. The green domains in Figure 2 are the receptors and are stored in a mask called **G**. The receptors are perfect sinks [3] and are therefore Dirichlet boundaries with a concentration of 0. The large blue domain is the area where the concentration maintains at a constant value C_0 and is stored in a mask called **B**. This blue domain contains Dirichlet boundaries with a concentration of C_0. The spatial points for which the concentration is updated, using the diffusion equation (2.4), are part of the orange domain in Figure 2 and are stored in mask **O**.

To find the domains shown in Figure 2, first all the points of the cell's surface need to be identified. These surface points are found as follows:

- First, all the cell's interior points where found including the points on the cell's surface. A point (j, k) was defined as being an interior point if $\sqrt{(j - R_0)^2 + (k - R_0)^2} \leq R_{\text{cell}} + 0.5$. These interior points form a circular like shape in the middle of the $(2R_0{+}1) \times (2R_0{+}1)$ sized masks.

- Secondly, a point was defined to be part of the surface of the cell, if it is an interior point with at least one neighbouring exterior point.

Now using the cell's surface points, the domains of the receptors and the reflective cell surfaces is found as follows:

- A function $\theta(x, y)$ is defined that gives the radian angle between the line from the center of the cell (j_0, k_0) to a point (j, k) and the line from (j_0, k_0) to a point with x-coordinate j_0 and a y-coordinate which is larges than k_0.

- If $\theta(x, y)$ is between certain values at a point on the cells surface, that point part of the receptor domain stored in mask **G**.

- The domains of the reflective cell surfaces stored in mask **R**, are all the points that are part of the cell's surface but not part of the domains of the receptors in mask **G**.

The domain in mask **B**, which contains all the points where the concentration stays stable at C_0, was found in a similar way as the domain of the interior points of the cell.

- A point (j, k) in mask **B** is 1 if $\sqrt{(j - R_0)^2 + (k - R_0)^2} \geq R_0$ and 0 otherwise.

Lastly, the orange domain is obtained;

- All spatial points that are not part of the blue, red and green domain in Figure 1 and not part of the interior of the cell, are stored as 1 on mask **O**. All other elements in mask **O** are 0.

The diffusion equation (2.4) is used to update points that are not Dirichlet boundary, Neumann boundary or interior points of the cell. For this a matrix **u** is used. For matrix **u**, the concentrations at the Dirichlet boundaries are kept constant. The Dirichlet boundary points in the domains of the receptors, green in Figure 2, have a concentration of zero and the Dirichlet boundary points in the domain of the bulk constant, blue in Figure 2, have a concentration of C_0. The diffusion equation (2.4) can be expressed numerically by using the forward difference derivative[6]. The left hand side of the diffusion equation (2.4) can be approximated as

$$\left.\frac{\mathrm{d}C(x_j, y_k, t)}{\mathrm{d}t}\right|_{t=t_n} \approx \frac{C_{j,k}^{(n+1)} - C_{j,k}^{(n)}}{h}. \tag{3.6}$$

Here, $C_{j,k}^{(n)} = C(x_j, y_k, t_n)$ is the concentration at spatial point in **u**, h is the step size and n the number of time steps.

Using a finite difference approximation for the second order derivative [6], the right hand side of the diffusion equation can be rewritten as

$$D\nabla^2 C_{j,k}^{(n)} = D\left(\frac{\mathrm{d}^2 C_{j,k}^{(n)}}{\mathrm{d}x^2} + \frac{\mathrm{d}^2 C_{j,k}^{(n)}}{\mathrm{d}y^2}\right) \tag{3.7}$$

$$\approx \frac{D}{a^2}\left[C_{j+1,k}^{(n)} + C_{j-1,k}^{(n)} + C_{j,k+1}^{(n)} + C_{j,k-1}^{(n)} - (4 - NB_{j,k})C_{j,k}^{(n)}\right]. \tag{3.8}$$

Here, $NB_{j,k}$ is the number of neighbouring Neumann boundaries of site (j,k). Combining equations (3.6) and (3.8) leads to the following expression for $C_{j,k}^{(n+1)}$.

$$C_{j,k}^{(n+1)} = C_{j,k}^{(n)} + \frac{hD}{a^2}\Big[\underbrace{C_{j+1,k}^{(n)} + C_{j-1,k}^{(n)} + C_{j,k+1}^{(n)} + C_{j,k-1}^{(n)}}_{\text{Concentration flowing in}} - \underbrace{(4 - NB_{j,k})C_{j,k}^{(n)}}_{\text{Concentration flowing out}}\Big] \tag{3.9}$$

This equation updates the spatial points in matrix **u** which are part of the domain stored in mask **O**. Updating these points is done while keeping the concentrations of the Neumann and Dirichlet boundary points, which are stored in masks **R**, **G** and **B**, fixed. The concentration $C_{j,k}^{(n+1)}$ is the updated concentration of the previous time step $C_{j,k}^{(n)}$. The first four terms between the bracket are proportional to the concentration flowing into site (j,k) from neighbouring sites and the remaining terms between the brackets are proportional to the concentration flowing from site (j,k) to its neighbouring sites. If one or more of the neighbouring sites of site (j,k) are Neumann boundaries, $NB_{j,k}$ will be larger than 0 and less concentration will flow out. Also, the Neumann boundary sites in matrix **u** are zero, meaning that no concentration is flowing into site (j,k) from the Neumann boundary either.

3.3 Numerical Solution of the Diffusion Equation where $D_1 \neq D_2$

In the previous section the diffusion equation was solved numerically for the case when $D = D_1 = D_2$. Now that model is expended to allow for the case when $D_1 \neq D_2$. For this case, three additional domains are required. The domain where $D = D_1$ (pink in Figure 3) and the domain where $D = D_2$ (yellow in Figure 3) are stored in masks. Furthermore, a mask containing the points between to two diffusion domains is needed which is marked black in Figure 3. Besides the updating equation (3.9), an additional updating equation is needed for spatial point that are part of the diffusion boundary layer between the two diffusion constant domains.

Figure 3: Spatial discretization of a two dimensional cell with multilayer diffusion. The red area is where the cell's surface is reflective and the green area is absorbing. The concentration is kept constant in the blue area. The black area is the diffusion boundary layer. The yellow area on the inside of the diffusion boundary layer has a diffusion constant D_2. The pink area outside the diffusion boundary layer has a diffusion constant D_1.

When the diffusion constant is not the same everywhere, the spatial descretization has three additional domains which can be seen in Figure 3. The black domain in Figure 3 is the diffusion boundary layer and its location is stored in a mask called $\mathbf{L}$. The domain where $D = D_1$ is pink and the domain where $D = D_2$ is yellow in Figure 3. These two domains are stored in the masks $\mathbf{P}$ and $\mathbf{Y}$ respectively.

The addition domains mentioned above are obtained as followed:

- First, a circle is made that includes all points (j, k) for which the following condition holds $\sqrt{(j - R_0)^2 + (k - R_0)^2} \leq R_{\text{cell}} + d + 0.5$. Here d is the distance between the cell's surface and the diffusion boundary layer.

- If a point inside the circle with one or more neighbouring points outside the circle is part of the diffusion boundary layer and is stored as a 1 in mask $\mathbf{L}$.

- The remaining points inside the circle, that are not part of the cell's surface or the interior of the cell, are part of the yellow domain where $D = D_2$. This domain is stored in mask $\mathbf{Y}$.

- A point outside the circle that is not part of the blue domain in Figure 3, is part of the pink domain where $D = D_1$. This domain is stored in mask $\mathbf{P}$.

When (j, k) is not a point in the domain of the diffusion boundary layer, the equation that updates the concentration of points in matrix $\mathbf{u}$ is (3.9). This is the same equation as for the case without a diffusion boundary layer. However, for the model that includes

diffusion boundary layers, the D in equation (3.9) is D_1 for a point (j,k) in the pink domain or D_2 if (j,k) is a point in the yellow domain as can be seen in Figure 3.

If (j,k) is a point on the diffusion boundary layer a few more conditions apply [5]. The diffusion flow between a diffusion boundary point (j,k) and a point where $D = D_1$, has diffusion constant D_1. If that point has $D = D_2$, the diffusion constant is D_2 [5]. This condition can be seen in equation (2.5). The flow between two points on the diffusion boundary layer has a diffusion constant of $D = D_{\text{av}} = (D_1 + D_2)/2$. Figure 4 shows an enlarged part of the diffusion boundary layer from Figure 3. This enlarged image shows which diffusion constant is used where at the diffusion boundary layer.

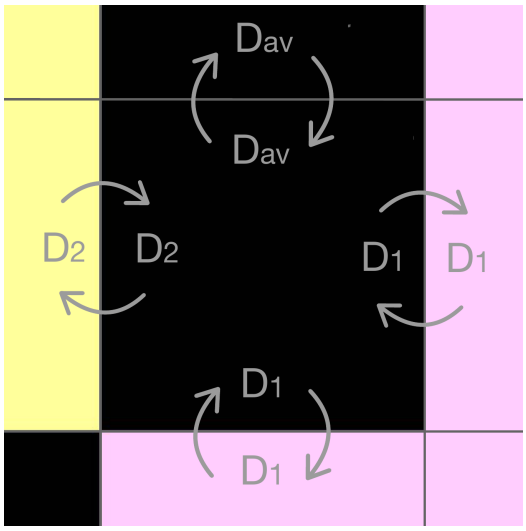


Figure 4: Diffusion boundary layer point showing the diffusion constants of the diffusion flow between neighbouring points. The black domain is part of the diffusion boundary layer, the yellow domain has that $D = D_2$ and the pink domain has that $D = D_1$.

To fill these conditions, a matrix $\mathbf{D}$ is compiled using mask $\mathbf{L}$ which contains the diffusion boundary layer, masks $\mathbf{P}$ which contains the domain where $D = D_1$, mask $\mathbf{Y}$ which contains the domain where $D = D_2$, mask $\mathbf{G}$ which contains the receptors and mask $\mathbf{B}$ which contains the domain of the bulk concentration. An element in matrix $\mathbf{D}$ has a value of D_1 if it is part domain stored in mask $\mathbf{P}$ or mask $\mathbf{B}$, D_2 if it is part of the domain stored in mask $\mathbf{Y}$ or mask $\mathbf{G}$ and $D = D_{\text{av}} = (D_1 + D_2)/2$ if it is of the domain stored in mask $\mathbf{L}$. All other elements in matrix Using the diffusion equation (2.5) for multiple layers for different D, the expression for $C_{j,k}^{(n+1)}$ for points at the diffusion boundary layer becomes

$$C_{j,k}^{(n+1)} = C_{j,k}^{(n)} + \frac{h}{a^2}\Big[\overbrace{D_{\text{j+1,k}}C_{j+1,k}^{(n)} + D_{\text{j-1,k}}C_{j-1,k}^{(n)} + D_{\text{j,k+1}}C_{j,k+1}^{(n)} + D_{\text{j,k-1}}C_{j,k-1}^{(n)}}^{\text{Concentration flowing in}} - \underbrace{(D_{\text{j+1,k}} + D_{\text{j-1,k}} + D_{\text{j,k+1}} + D_{\text{j,k-1}})C_{j,k}^{(n)}}_{\text{Concentration flowing out}}\Big] \quad (3.10)$$

where $D_{j,k}$ is an element of matrix $\mathbf{D}$. For all other spatial points in $\mathbf{u}$ that are not part of the diffusion boundary layer, the concentration is updated using equation (3.9) where $D = D_1$ if they part of the domain stored in mask $\mathbf{P}$ and $D = D_2$ if they are part of the domain stored in mask $\mathbf{Y}$. In equation (3.10), no $NB_{j,k}$ term is needed. Instead, if a neighbouring site is a Neumann boundary, that point will be zero in matrix $\mathbf{D}$. Therefore, no concentration will flow in or out of the Neumann boundary point.

3.4 Obtaining the diffusion current numerically

The diffusion current is obtained by summing up the flux in the normal direction of the cell's surface, for each absorbing element on the cell's surface. Due to the spatial discretization, the normal direction of the cell's surface is either $\hat{n} = \hat{x}$ or $\hat{n} = \hat{y}$ as can be seen in Figure 2. To find expressions for the flux, equation (2.2) was approximated using forward and backward difference derivatives. The components of the flux in the normal direction that were summed up are;

$$j_x^{(n)}(j,k) = -\frac{D}{a^2}\left(C_{j+1,k}^{(n)} - C_{j,k}^{(n)}\right) \text{ if } (j+1,k) \text{ is an absorbing site,} \quad (3.11)$$

$$j_x^{(n)}(j,k) = -\frac{D}{a^2}\left(C_{j,k}^{(n)} - C_{j-1,k}^{(n)}\right) \text{ if } (j-1,k) \text{ is an absorbing site,} \quad (3.12)$$

$$j_y^{(n)}(j,k) = -\frac{D}{a^2}\left(C_{j,k+1}^{(n)} - C_{j,k}^{(n)}\right) \text{ if } (j,k+1) \text{ is an absorbing site,} \quad (3.13)$$

$$j_y^{(n)}(j,k) = -\frac{D}{a^2}\left(C_{j,k}^{(n)} - C_{j,k-1}^{(n)}\right) \text{ if } (j,k-1) \text{ is an absorbing site.} \quad (3.14)$$

Here, the diffusion constant is $D = D_2$ if $D_1 \neq D_2$, else $D = D_1 = D_2$.

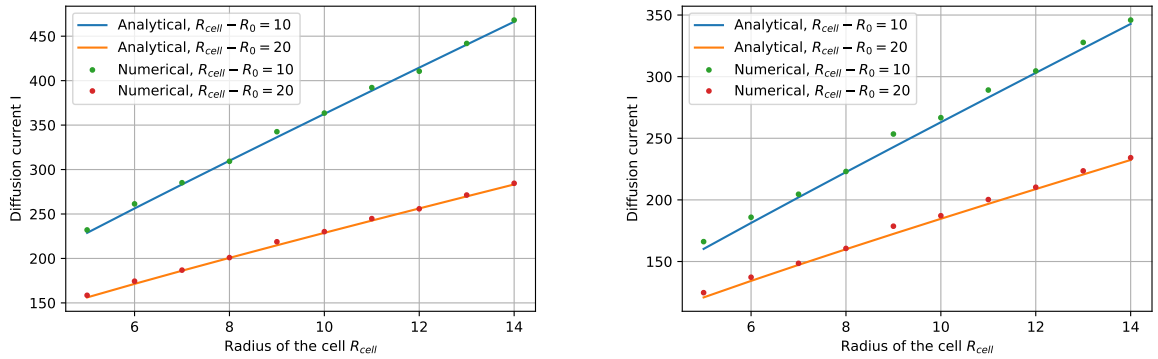
The sum of the flux over all the cell's absorbing boundary points gives the numerical value for the diffusion current I. For this thesis, the aim was to find the stationary flux. It takes some steps for a concentration to reach the cells surface and even more time for the flux to reach a stable value. The number of times steps needed to reach a stationary flux depends on the variables R_{cell}, R_0, d, D or D_1 and D_2 and the distribution of receptors. I considered the total flux stationary if during the last 10% of time steps n the flux would change with less than 10^{-4}. More on how long it takes to reach a steady state can be seen in Appendix B.

4 Results and Discussion

The aim of this thesis was to obtain the flux into a two dimensional cell. For the case when the cell's surface is fully absorbing, the flux is determined both numerically and analytically. This section will start with the results for a fully absorbing cell both for the case where $D = D_1 = D_2$ and $D_1 \neq D_2$. Secondly, it will show the results for the flux of a cell that has receptors on it surface through which diffusion takes place.

For the units, the concentration is in particles/length^2, the diffusion constant is in length^2/time and the diffusion current is in particles/time. The values for the diffusion constants were chosen so that the system would remain stable which was for $hD \leq 0.25$ with a set to 1. The value for the bulk concentration was decided to be 20.

The numerically and analytically obtained diffusion current for a fully absorbing cell for different radii is plotted in Figure 5. The difference between R_{cell} and R_0 remained the same while R_{cell} was increasing. In Figure 5(a), the diffusion constant is $D = D_1 = D_2 = 2.0$ and in Figure 5(b) $D_2 < D_1$ where $D_1 = 2.0$ and $D_2 = 1.0$. In Figure 5, it can be seen that the diffusion current depends linearly with the radius of the cell R_{cell}. This was expected since the equations (3.4) and (3.5) for the diffusion current has a linear dependency on R_{cell}. Additionally, it can be seen that the diffusion current is less for the case $D_2 < D_1$ than when $D = D_1 = D_2$.



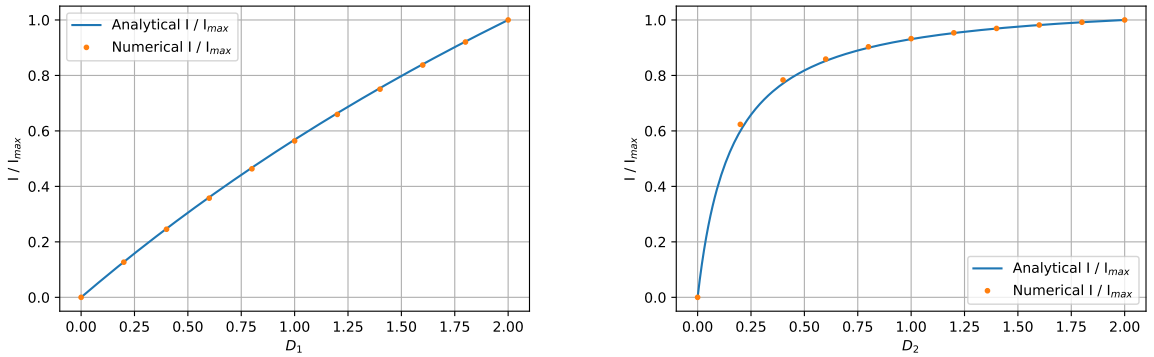
(a) $D = 2.0$. **(b)** $D_2 = 1.0$, $D_1 = 2.0$.

Figure 5: The numerically and analytically obtained diffusion current for models with different distances between the cells surface and the outer Dirichlet boundary. The step size is $h = 0.1$ and the concentration at R_0 is $C_0 = 20$. The cell's surface is absorbing everywhere. The intensity is plotted versus the radius of the cell, R_{cell}. (a) has the same diffusion constant $D = 2.0$ everywhere and (b) has diffusion constant $D_2 = 1.0$ within a distance $d = 3$ of the cells surface and a diffusion constant of $D_1 = 2.0$ elsewhere.

The plots in Figure 6 show the numerical and analytical I/I_{max} for a model where either D_1 or D_2 is increasing while either D_2 or D_1 remain constant respectively. Here, I is the diffusion current for an increasing D_1 in Figure 6(a) and for an increasing D_2 in Figure

6(b) and $I_{\max}$ is the maximum diffusion current obtained for I. Notice that $I_{\max}$ in Figure 6(a) is not the same as the $I_{\max}$ in Figure 6(b).

In Figure 6 it can be seen that if one of the diffusion constants is 0, the diffusion current is 0. Additionally, for a changing D_2, $I/I_{\max}$ reaches a value of 1/2 for a much lower value for D_2 than that D_1 needs to be to reach $I/I_{\max} = 1/2$ for the case when D_1 is changing. This is because with $d = 1$, the domain where $D = D_2$ is smaller than the the domain where $D = D_1$. When d approaches a value of $R_0 - R_{\text{cell}}$ this effect is reversed.

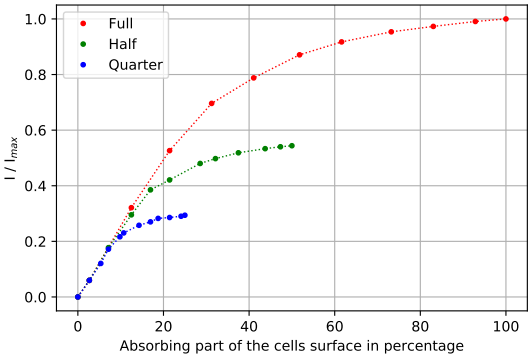


(a) $D_2 = 1$ and D_1 increases from 0 to 2. **(b)** $D_1 = 1$ and D_2 increases from 0 to 2.

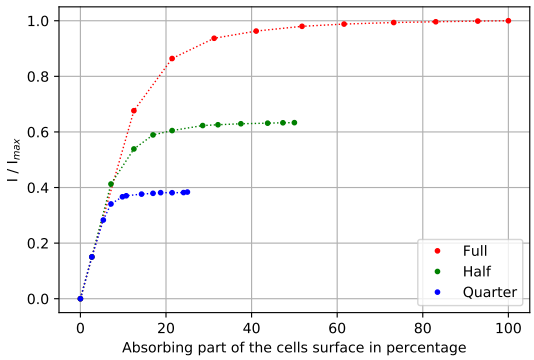
Figure 6: Numerically and analytically obtained diffusion current where either D_1 or D_2 is held constant while the other diffusion constant is increasing. The radius of the cell is $R_{\text{cell}} = 10$, the radius of the outer Dirichlet boundary is $R_0 = 20$, step size is $h = 0.1$ and the distance between the cells surface and the diffusion boundary layer is $d = 1$. In **(a)** $D_2 = 1$ and D_1 is increasing from 0 to 2.0 and in **(b)** $D_1 = 1$ and D_2 is increasing from 0 to 2.0.

For both Figures 5 and 6, the analytical and numerical results do not give the same values, although they are close. The difference between the numerically and analytically obtained diffusion current was up to 2.0% for $D = D_1 = D_2$ and up to 5.5% for $D_1 \neq D_2$ for the results shown in Figures 5 and 6. This is to large to be caused by only truncation and round off errors. Therefore, the main source of error comes from the spatial discretization of the model.

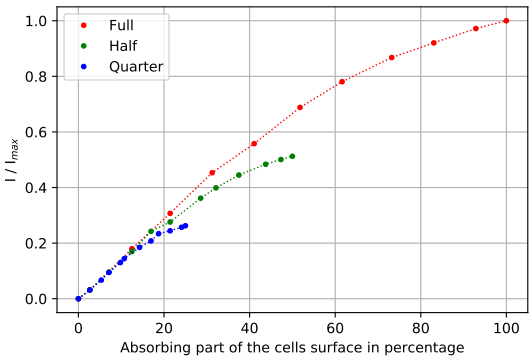
The plots in Figure 7 show $I/I_{\max}$ for different number of receptors. Here, $I_{\max}$ is the diffusion current of a fully absorbing cell and I is the diffusion current of a cell where and increasing number of receptors are either evenly spread out over the entire surface, evenly spread out over half of the surface or evenly spread out over a quarter of the surface. This was done to see how the diffusion current is affected by the positioning of the receptors. More specifically, we were interested in the difference between the diffusion current that occurs when receptors are spread out over the whole surface and the diffusion current that occurs when receptors are clustered together. The diffusion currents for these three receptor patterns were obtained for the cases where $D_1 = D_2$, $D_1 < D_2$ and $D_1 > D_2$.



(a) $D_1 = D_2 = 2$



(b) $D_1 = 0.2$, $D_2 = 2$



(c) $D_1 = 2$, $D_2 = 0.2$

Figure 7: Numerically obtained diffusion current for a cell with an increasing number of receptors in it surface. The receptors are either spread out evenly over the entire surface, half of the surface or a quarter of the surface. The size of the receptors was 1/40 part of the circumference of the circle, the radius of the cell was $R_{\text{cell}} = 20$, the radius of the outer Dirichlet boundary is $R_0 = 30$, the distance between the cell's surface and the diffusion boundary layer is $d = 2$, the bulk concentration at the outer Dirichlet boundary is $C_0 = 20$ and the step size was $h = 0.1$. In **(a)** $D_1 = D_2 = 2$, in plot **(b)** $D_1 = 0.2$ and $D_2 = 2$ and for **(c)** $D_1 = 2$ and $D_2 = 2.0$.

In Figure 7, it can be seen that for all cases the diffusion current is less when the receptors are clustered together. Furthermore, when the diffusion constant within the diffusion boundary layer is smaller than the diffusion constant outside the diffusion boundary layer, $D_1 > D_2$, more receptors are needed for the diffusion current to reach half of $I_{\max}$. When $D_1 < D_2$, the least number or receptors are needed to reach a diffusion current of $I_{\max}/2$. Hence, when $D_2 < D_1$ receptors can take in particles less efficiently than when $D_2 \leq D_1$.

5 Summary and Outlook

During this thesis, the diffusion current into a cell was obtained numerically and analytically. The main objective was to find how multilayer diffusion affects the diffusion current. For the case when the cell is fully absorbing, the diffusion current was obtained both numerically and analytically. When the cell is not fully absorbing and instead has receptors on its surface through which absorption takes place, the diffusion current was only obtained numerically. It was found that for the fully absorbing case, the numerical and analytical method agreed with one an other. Additionally, for the case where diffusion takes place through receptors, it was shown that the placement of receptors affected the diffusion current. Also, the ratio between D_1 and D_2 influenced the number of receptors needed to reach $I_{\max}/2$. More specifically, when $D_2 < D_1$ receptors can take in particles less efficiently than when $D_2 \leq D_1$.

To expand on what was done in this thesis, one could try and find the analytical solution for the diffusion current for a two dimensional cell with receptors on its surface, both for the case where $D = D_1 = D_2$ and $D_1 \neq D_2$. In the paper Physics of Chemoreception by Berg and Purcell, to obtain the diffusion current of a three dimensional cell with equidistant distributed receptors on its surface, first expressions of the diffusion current of a fully absorbing cell and the diffusion current through a circular receptor on a flat surface were obtain separately [3]. This model did not include multilayer diffusion. They then solved for the diffusion current by using an analogous problem in electrostatics [3]. To solve the two dimensional model in a similar way, one would need to find an expression for a diffusion current through a gap in a straight line. This expression can then be combined with the equation for a fully absorbing two dimensional diffusion current, $I_{\max}$. This maximum diffusion current for the cases with and without multilayer diffusion, can be seen in equations (3.5) and (3.4) respectively.

Another thing that could be done is expanding the model from two dimensions to three dimensions. A three dimensional model would more closely resemble real live situations. Obtaining the diffusion current numerically for a three dimensional model would require more computational effort and would take longer to run than the two dimensional method. To avoid this problem, one could find the diffusion current of a three dimensional cell with multilayer diffusion analytically. An expression for such a model without multilayer diffusion is already obtained by Berg and Purcell [3].

In this thesis, the topic of how geometric arrangements of receptors affect the diffusion current was briefly touched upon. For the three dimensional case, this has been investigated previously, but the effect of multilayer diffusion was not taken into account [7, 8]. A three dimensional model would significantly increase the time it takes to compute the diffusion current numerically using the diffusion equation.

An other way of finding the diffusion current numerically is by using random walkers simulations instead of solving the diffusion equation. Depending on the number of random walkers used, this method could be faster than solving the diffusion equation numerically as was done in this thesis project.

Hopefully this thesis project will inspire further work on how multilayer diffusion and

geometric arrangements of receptors affect cellular uptake and activation.

Acknowledgments

I would like to thank my supervisor Tobias Ambjörnsson for his support and guidance during this project. Additionally, I would like to thank my friends and family for their feedback and mental support.

A Derivations

In this section, the diffusion current is derived analytically both for a system with and without multilayer diffusion. First, an expression for the concentration is found. From the concentration, the flux is obtained. Than the flux is used to find an expression for the diffusion current.

The concentration of a system will reach a steady state system such that $\mathrm{d}C(r)/\mathrm{d}t = 0$ where $C(r)$ is the concentration at a distance r from the center. Considering equation (2.4) this means that

$$\nabla^2 C(r) = 0. \tag{A.1}$$

Using polar coordinates, the above equation gives the following.[9]

$$\frac{1}{r}\frac{\mathrm{d}}{\mathrm{d}r} r \frac{\mathrm{d}C(r)}{\mathrm{d}r} = 0 \tag{A.2}$$

This can be rewritten as

$$\frac{1}{r}\left(r\frac{\mathrm{d}^2 C(r)}{\mathrm{d}r^2} + \frac{\mathrm{d}C(r)}{\mathrm{d}r} \right) = 0. \tag{A.3}$$

Now a change of variable was made;

$$\frac{\mathrm{d}C(r)}{\mathrm{d}r} = v(r) \implies \frac{\mathrm{d}^2 C(r)}{\mathrm{d}r^2} = \frac{\mathrm{d}v(r)}{\mathrm{d}r}. \tag{A.4}$$

When plugging this into equation (A.3) the following is obtained.

$$\frac{1}{r}\left(r\frac{\mathrm{d}v(r)}{\mathrm{d}r} + v(r) \right) = 0 \implies \frac{\mathrm{d}v(r)}{\mathrm{d}r} = -\frac{v(r)}{r} \implies \frac{\frac{\mathrm{d}v(r)}{\mathrm{d}r}}{v(r)} = -\frac{1}{r}. \tag{A.5}$$

Now, both sides are integrated. This results in the following expression.

$$\int \frac{\frac{\mathrm{d}v(r)}{\mathrm{d}r}}{v(r)} \mathrm{d}r = -\int \frac{1}{r}\mathrm{d}r \implies \ln(v(r)) = -\ln(r) + A_1 \implies \ln(v(r)r) = A_1 \tag{A.6}$$

Here, A_1 is an unknown constant. From this, an expression for $v(r)$ is obtained,

$$v(r) = \frac{A_2}{r} \tag{A.7}$$

where A_2 is an unknown constant. From the previous change of variable, this expression for $v(r)$ gives

$$\frac{\mathrm{d}C(r)}{\mathrm{d}r} = v(r) = \frac{A_2}{r}. \tag{A.8}$$

Integrating both sides gives an expression for C where A_3 is an unknown constant;

$$\int \frac{\mathrm{d}C(r)}{\mathrm{d}r}\mathrm{d}r = \int \frac{A_2}{r}\mathrm{d}r \implies C(r) = \ln(r)A_2 + A_3. \tag{A.9}$$

Now, using boundary conditions, this general expression can be used to find an expression for the concentration. The radius of the cell is R_{cell} and the radius of the Dirichlet boundary is R_{C_0}. The boundary conditions are $r = R_{\text{cell}} \rightarrow C(R_{\text{cell}}) = 0$ and $r = R_0 \rightarrow C(R_0) = C_0$ where C_0 is a constant concentration at the Dirichlet boundary. When $r = R_{\text{cell}}$ the general expression for $C(r)$ becomes

$$C(R_{\text{cell}}) = A_2 \ln(R_{\text{cell}}) + A_3 = 0 \implies -A_2 \ln(R_{\text{cell}}) = A_3 \tag{A.10}$$

and at $r = R_0$ it gives

$$C(R_0) = A_2 \ln(R_0) + A_3 = C_0 \implies -A_2 \ln(R_0) + C_0 = A_3. \tag{A.11}$$

Combining the two equation above leads to the following expressions for A_2 and A_3.

$$A_2 = \frac{C_0}{\ln(\frac{R_0}{R_{\text{cell}}})}$$

$$A_3 = -\frac{C_0 \ln(R_{\text{cell}})}{\ln(\frac{R_0}{R_{\text{cell}}})}$$

Putting this into the expression for $C(r)$ of equation (A.9), the expression for $C(r)$ becomes

$$C(r) = \frac{C_0}{\ln(\frac{R_0}{R_{\text{cell}}})}(\ln(r) - \ln(R_{\text{cell}})). \tag{A.12}$$

To get the flux, this expression for $C(r)$ is put into equation (2.2).

$$J = -D\nabla C(r) = -D\frac{\mathrm{d}C(r)}{\mathrm{d}r}\hat{r} \tag{A.13}$$

Here, $\hat{r}$ is the unit vector in the direction pointing away from the center of the cell. The flux of the system for $R_{\text{cell}} < r < R_0$ is

$$J(r) = -\frac{DC_0}{\ln\left(\frac{R_0}{R_{\text{cell}}}\right)}\frac{\mathrm{d}}{\mathrm{d}r}\ln(r)\hat{r} = -\frac{DC_0}{r\ln\left(\frac{R_0}{R_{\text{cell}}}\right)}\hat{r}. \tag{A.14}$$

Using equation (2.1), the diffusion current through the cells surface for a system with a constant D is found to be

$$I = \frac{2\pi D C_0}{\ln\left(\frac{R_0}{R_{\text{cell}}}\right)}. \tag{A.15}$$

Now the same way for a system with containing two diffusion constants. For this system there is an unknown concentration C_1 at $r = R_{\text{cell}} + d$ where d is the distance between the cell's surface and the diffusion boundary layer. As with the case for the constant D the concentrations at the Dirichlet boundaries are $C(R_{\text{cell}}) = 0$ and $C(R_0) = C_0$. When $R_{\text{cell}} + d \leq r < R_0$, $D = D_1$ and when $R_{\text{cell}} < r \leq R_{\text{cell}} + d$, $D = D_2$. Now equation (A.9) is used for the above boundary condition at $r = R_{\text{cell}} + d$.

$$C(R_{\text{cell}} + d) = \ln(R_{\text{cell}} + d)A_2 + A_3 = C_1 \tag{A.16}$$

For the case where $R_{\text{cell}} + d \leq r < R$, combining the equation for $C(R_{\text{cell}} + d)$ and equation (A.11) for $C(R_0)$, expressions for A_2 and A_3 can be obtained.

$$A_3 = C_0 - \ln(R_{C_0})A_2 = C_1 - \ln(R_{\text{cell}} + d)A_2 \tag{A.17}$$

$$\implies A_2 = \frac{C_1 - C_0}{\ln\left(\frac{R_{\text{cell}}+d}{R_0}\right)} \implies A_3 = C_0 - \ln(R_0)\frac{C_1 - C_0}{\ln\left(\frac{R_{\text{cell}}+d}{R_0}\right)} \tag{A.18}$$

Plugging these two values into equation (A.9), the expression for the concentration in the region $R_{\text{cell}} + d \leq r < R_0$ is obtained.

$$C(r) = C_0 + \frac{(C_1 - C_0)\ln\left(\frac{r}{R_0}\right)}{\ln\left(\frac{R_{\text{cell}}+d}{R_0}\right)} \text{ if } R_{\text{cell}} + d \leq r < R_0 \tag{A.19}$$

Now, equation (A.13) is used to find the flux.

$$J(r) = -\frac{D_1(C_1 - C_0)}{\ln\left(\frac{R_{\text{cell}}+d}{R_0}\right)}\frac{\mathrm{d}\ln(r)}{\mathrm{d}r}\hat{r} = -\frac{D_1(C_1 - C_0)}{r\ln\left(\frac{R_{\text{cell}}+d}{R_0}\right)}\hat{r} \text{ if } R_{\text{cell}} + d \leq r < R_0 \tag{A.20}$$

For the case $R_{\text{cell}} < r \leq R_{\text{cell}} + d$ equations (A.10) and (A.16) are used to obtain A_2 and A_3.

$$A_3 = -\ln(R_{\text{cell}})A_2 = C_1 - \ln(R_{\text{cell}} + d)A_2 \tag{A.21}$$

$$\implies A_2 = \frac{C_1}{\ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right)} \implies A_3 = -\frac{\ln(R_{\text{cell}})C_1}{\ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right)} \tag{A.22}$$

These values for A_2 and A_3 give the following expression for the concentration;

$$C(r) = \frac{\ln\left(\frac{r}{R_{\text{cell}}}\right) C_1}{\ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right)} \text{ if } R_{\text{cell}} < r \leq R_{\text{cell}} + d. \tag{A.23}$$

The same way as before, equation (A.13) was used to find the flux.

$$J(r) = -\frac{D_2 C_1}{\ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right)} \frac{\mathrm{d}\ln(r)}{\mathrm{d}r}\hat{r} = -\frac{D_2 C_1}{r\ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right)}\hat{r} \text{ if } R_{\text{cell}} < r \leq R_{\text{cell}} + d. \tag{A.24}$$

Now the matching conditions from equations (2.6) and (2.7) are used to find an expression for C_1. Equation (2.7) gives the following condition for C which only depends on r;

$$D_1 \frac{\mathrm{d}}{\mathrm{d}r} C_{R_{\text{cell}}+d \leq r < R_0}(r)\Big|_{r=R_{\text{cell}}+d} = D_2 \frac{\mathrm{d}}{\mathrm{d}r} C_{R_{\text{cell}} < r \leq R_{\text{cell}}+d}(r)\Big|_{r=R_{\text{cell}}+d} \tag{A.25}$$

$$\implies \frac{D_2 C_1}{(R_{\text{cell}}+d)\ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right)} = \frac{D_1(C_1 - C_0)}{(R_{\text{cell}}+d)\ln\left(\frac{R_{\text{cell}}+d}{R_0}\right)} \tag{A.26}$$

Rewriting the above equation gives the following expression for C_1 for which the condition of equation (2.7) holds.

$$C_1 = \frac{C_0 D_1 \ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right)}{D_1 \ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right) - D_2 \ln\left(\frac{R_{\text{cell}}+d}{R_0}\right)}. \tag{A.27}$$

Equation (2.6) gives the following condition;

$$C_{R_{\text{cell}}+d \leq r < R_0}(R_{\text{cell}}+d) = C_{R_{\text{cell}} < r \leq R_{\text{cell}}+d}(R_{\text{cell}}+d) \tag{A.28}$$

$$\implies C_0 + \frac{(C_1 - C_0)\ln\left(\frac{R_{\text{cell}}+d}{R_0}\right)}{\ln\left(\frac{R_{\text{cell}}+d}{R_0}\right)} = \frac{\ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right) C_1}{\ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right)}. \tag{A.29}$$

To see if the expression for C_1 as shown in equation (A.27) holds for the above condition, the expression for C_1 is put into equation (A.29).

$$C_0 + \frac{C_0 D_1 \ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right)}{D_1 \ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right) - D_2 \ln\left(\frac{R_{\text{cell}}+d}{R_0}\right)} - C_0 = \frac{C_0 D_1 \ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right)}{D_1 \ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right) - D_2 \ln\left(\frac{R_{\text{cell}}+d}{R_0}\right)} \tag{A.30}$$

Since the left and right hand side of the above equation are equal to each other, the condition of equation (2.6) holds for the expression for C_1 in equation (A.27).

Now, equation (2.1) is used to find the diffusion current. This gives the following expressions for the diffusion current I for a model with two different diffusion currents.

$$I(r) = \begin{cases} \frac{2\pi D_2 C_1}{\ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right)}, & \text{if } R_{\text{cell}} < r \leq R_{\text{cell}} + d \\ \frac{2\pi D_1 (C_1 - C_0)}{\ln\left(\frac{R_{\text{cell}}+d}{R_0}\right)}, & \text{if } R_{\text{cell}} + d \leq r < R_0 \\ 0, & \text{otherwise} \end{cases} \tag{A.31}$$

When plugging in the expression for C_1, it can be found that $I_{R_{\text{cell}}<r\leq R_{\text{cell}}+d} = I_{R_{\text{cell}}+d\leq r<R_0}$. This leaves the following expression for the diffusion current for a system with two diffusion currents.

$$I(r) = \frac{2\pi D_1 C_0}{D_1/D_2 \ln\left(\frac{R_{\text{cell}}+d}{R_{\text{cell}}}\right) + \ln\left(\frac{R_0}{R_{\text{cell}}+d}\right)} \tag{A.32}$$

B Run time and time to steady state

As mentioned in section 3.4, diffusion current is the total flux through the cell's surface once the flux has met some criteria for stability. The number of steps n needed to reach a stationary flux depends on the distance between the cell's surface and the outer Dirichlet boundary, the number and the position of receptors, the diffusion constant or constants, step size h and the size of the system. The size of the system also affects the number of n needed but this effect is relatively small.

How different number of receptors that are evenly spread out of the cells surface affect the number of time needed to reach a stationary flux can be seen in Figure 8. Here, $D = D_1 = D_2 = 2$, $R_{\text{cell}} = 20$ and $R_0 = 30$. The $I/I_{\max}$ of this set up can be seen in Figure 7(a). The time it took to run for each number of receptors was between 2-3.5 minutes. The computer used to solve the diffusion equation numerically has an Intel Core i5.

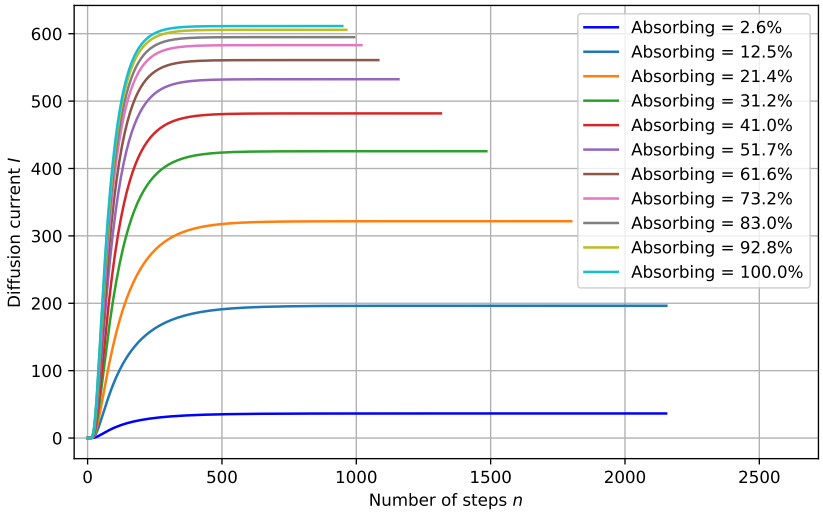


Figure 8: Numerically obtained diffusion current for different number of receptors over time. The coverage is the percentage of the cell that is covered by absorbing patches. The diffusion current is of a cell with an increasing number of receptors on its surface. The cell's radius is $R_{\text{cell}} = 20$, the outer Dirichlet boundary is $R_0 = 30$, the diffusion constant is $D = 2$, step size is $h = 0.1$ and the absorbing patches have a length of 1/40th of the cell's circumference.

As mentioned above, the time it takes to run strongly depends on the diffusion constant. For a set up that is the same as that was used to obtain the results in Figure 8 but with $D_1 = 0.2$, it takes longer to run. The time it takes to run is between 5-16 minutes, depending on the number of receptors. The I/I_{max} that was obtained for this set up can be seen in Figure 7(b).

Additionally, the distance between between the cell and the bulk concentration and the size of the system affect the run time. For the case where the cell is fully absorbing, where the difference between the cell and the bulk concentration is 5 and $D = 2$, from which the result can be seen in Figure 5(a), the run time was between 4 and 14 seconds. Here, the larger the cell's radius, and therefore the larger the system as a whole, the longer it took.

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