# Homogenisation Theory with Coupled Cellular Reaction Diffusion Equations

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**Abstract**

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## Todo list

# 1 INTRODUCTION

Recent experiments have shown [8] that arterial walls, made from three main circumferential layers, can carry (both upstream and downstream) important information concerning the local environment. The intima constructed of mostly the single layered endothelium and the circumferentially directed smooth muscle cell seems to be the conduit through which information can pass. Both endothelial (EC) and smooth muscle (SMC) cells have gap junction connectivity which can either be homotypic (connections between cells of the same type) or heterotypic (connections between cells of different type). The work of Segal's group especially has shown that the length scales along which electrical signals can propagate are of the order of hundreds and sometimes thousands of cells [1] (ref : Behringer and Segal Circ Res. 2012;110:1311-1321). In addition Socha et al [8] from the same group have investigated $Ca^{2+}$ responses to GPCR (G protein-coupled receptor) activation where responses consisted of Ca2+ waves (oscillations of $Ca^{2+}$ out of phase), although it should be noted that these experiments utilised endothelial tubes rather than the full connectivity of endothelial and smooth muscle cell. The GPCR has an important role to play since it has a significant distribution on the luminal side of the EC and can be activated by a number of agonists including fluid shear induced ATP release from red blood cells .

ref here ?

Using massively parallelised numerical simulations modelling millions of coupled cells it has been shown that there exists a complex structure to the activation of coupled EC and SMC over large length scales [7]. This has been done using a discrete method whereby a unit consisting of a number of coupled EC and SMCs has been mapped to a single node onto the

Blue Gene architecture with each node communicating with each neighbour thus simulating the coupling of $IP_3$, membrane voltage and $Ca^{2+}$. More than ?? nodes comprising up to 7 million cells have been used to investigate the calcium concentration ($Ca^{2+}$) over both time and space. The numerical solution shows that with each EC/SMC coupled entity, modelled using complex cellular chemical pathways, waves of $Ca^{2+}$ propagate upstream. These waves grow in complexity as time progresses with what seems to be spontaneous oscillations of EC/SMC units far from the propagating wavefront. Both experiments and numerical simulations seem to indicate that the phenomena exhibits multiple scales. These scales may be defined with the length of a cell (microscale) and the characteristic length of the artery (macroscale). Homogenisation theory [5] can be used to investigate the effect of cellular (microscale) phenomena at the macroscale. This theory allows a contraction of the microscale in a formalised way; furthermore it is interesting to note that by allowing the cell length $\delta$ to contract to zero a form of the time-dependent reaction diffusion equations evolve.

# 2 Homogenisation theory in the Calculation of Cell Diffusion Coefficients

Keener and Sneyd **??** (page 238) provided a simple method for evaluating effective macroscale diffusion coefficients. Firstly a characteristic macroscale length, L is chosen and this must be substantially larger than a single cell. An arterial endothelial cell is approximately $100\mu m$ long so by choosing a length equivalent to 100 cells then $L = 1cm$. Using the analysis of

Keener and Sneyd $D_e$ is the effective diffusion coefficient (in the macroscale) using D as the coefficient (in the microscale) of an ion diffusing through the cells cytosol estimated as the order of 200 $\mu m^2 s^{-1}$ [6], their analysis provides the relationship as

$$\frac{1}{D_e} = \frac{1}{D} + \frac{1}{LF} \tag{2.1}$$

with a conservative estimate of the permeability coefficient F to be $\simeq 10^{-6} m s^{-1}$. Using these figures we have that $D_e$= 182 $\mu m^2 s^{-1}$. Using a timescale appropriate to the frequency of oscillation of the cell, $\tau_n = 1$ the non-dimensional effective diffusion coefficient is $\frac{D_e}{\tau_n L^2} = 6.8X10^{-6}$ which is very small in the non-dimensional sense. However the above analysis gives an important first estimate of the characteristic size of the effective (or homogenised) diffusion coefficient.

## 2.1 basic homogenisation theory

To introduce the theory into the physiological domain the 1D equation of the form

$$\frac{\partial c}{\partial t} = \frac{\partial}{\partial x}\left(D(x,y)\frac{\partial c}{\partial x}\right) + F(c,t) \tag{2.2}$$

Here $F(\phi, t)$ represents the production and decay of specii c within the cell, whilst the diffusive component models the flux of the specii c through the cell's gap junctions. Assuming that the characteristic length of the cell is of the order $\epsilon$ an ansazt asymptotic expansion is used for both $c$ and $F(c(x,t))$ and assuming that functions $c_i$ and $F_i$ are 1-periodic in the

cell scale length variable y then

$$c = c_0 + \epsilon c_1 + \epsilon^2 c_2 + ... \tag{2.3}$$

$$F = F_0 + \epsilon F_1 + \epsilon^2 F_2 + ... \tag{2.4}$$

A fast variable $y = \frac{x}{\epsilon}$ is defined with the associated derivative mapping so that

$$\Rightarrow \frac{\partial}{\partial x} \rightarrow \frac{\partial}{\partial x} + \epsilon^{-1}\frac{\partial}{\partial y} \tag{2.5}$$

Using the asymptotic expansion and the operator (2.5) on (2.2) we have that

$$\begin{aligned} \frac{\partial}{\partial t}[c_0 + \epsilon c_1 + \epsilon^2 c_2 + ...] &= \epsilon^{-2}\frac{\partial}{\partial y}(D\frac{\partial c_0}{\partial y}) + \epsilon^{-1}[\frac{\partial}{\partial x}(D\frac{\partial c_0}{\partial y}) + \frac{\partial}{\partial y}(D\frac{\partial c_0}{\partial x} + D\frac{\partial c_1}{\partial y})] \\ &\quad + \frac{\partial}{\partial x}(D\frac{\partial c_0}{\partial x} + D\frac{\partial c_1}{\partial y}) + \frac{\partial}{\partial y}(D\frac{\partial c_1}{\partial x}) + \frac{\partial}{\partial y}(D\frac{\partial c_2}{\partial y}) \\ &\quad + O(\epsilon) + F_0 + \epsilon F_1 + \epsilon^2 F_2 + ... \end{aligned} \tag{2.6}$$

For convenience the abbreviated D is taken to mean $D = D(x, y)$. Equating powers of $\epsilon$ in equation (2.6) gives,

$$\epsilon^{-2} \quad : \quad \frac{\partial}{\partial y}(D\frac{\partial c_0}{\partial y}) = 0 \tag{2.7}$$

$$\epsilon^{-1} \quad : \quad [\frac{\partial}{\partial x}(D\frac{\partial c_0}{\partial y}) + \frac{\partial}{\partial y}(D\frac{\partial c_0}{\partial x} + D\frac{\partial c_1}{\partial y})] = 0 \tag{2.8}$$

$$\epsilon^{0} \quad : \quad \frac{\partial c_0}{\partial t} = \frac{\partial}{\partial x}(D\frac{\partial c_0}{\partial x} + D\frac{\partial c_1}{\partial y}) + \frac{\partial}{\partial y}(D\frac{\partial c_1}{\partial x} + D\frac{\partial c_2}{\partial y}) + F_0 \tag{2.9}$$

integrating the $\epsilon^{-2}$ equation we have,

$$\begin{aligned} \int_{\Omega_y} \frac{\partial}{\partial y}(D\frac{\partial c_0}{\partial y})dy &= 0 \\ Dc_0\frac{\partial c_0}{\partial y} - \int_{\Omega_y} D(\frac{\partial c_0}{\partial y})^2 &= 0 \end{aligned} \tag{2.10}$$

The diffusion coefficient D is 1-periodic and hence the boundary conditions give

$$\int_{\Omega_y} D(\frac{\partial c_0}{\partial y})^2 = 0 \tag{2.11}$$

and by ellipticity $\int_{\Omega_y} > 0$ then

$$\frac{\partial c_0}{\partial y} = 0$$

$$c_0 = c_0(x,t) \tag{2.12}$$

Using the $\epsilon^{-1}$ equation and the fact that $c$ is independent of y then

$$\begin{aligned} \frac{\partial}{\partial y}(D\frac{\partial c_0}{\partial x} + D\frac{\partial c_1}{\partial y}) &= 0 \\ -\frac{\partial}{\partial y}(D\frac{\partial c_1}{\partial y}) &= \frac{\partial D}{\partial y}\frac{\partial c_0}{\partial x} \end{aligned} \tag{2.13}$$

We can now define a "unit-cell" variable $\chi$ such that

$$\frac{\partial D}{\partial y} = -\frac{\partial}{\partial y}(D\frac{\partial \chi}{\partial y}) \tag{2.14}$$

Equations (2.13) and (2.14) and integrating over y gives

$$c_1(x,y,t) = \chi(y)\frac{\partial c_0}{\partial x} \tag{2.15}$$

now by substituting into 2.6 and using periodic boundary conditions and integrating over the whole cell length it is found that to leading order

$$\begin{aligned} \frac{\partial c_0}{\partial t} = \frac{1}{V}\int_{\Omega y}\frac{\partial}{\partial x}[D(\frac{\partial c_0}{\partial x} + \frac{\partial \chi}{\partial y'}\frac{\partial c_0}{\partial x})]dy' + F_0 \\ = \frac{\partial}{\partial x}[\widehat{D}\frac{\partial c}{\partial x}] + F_0 \end{aligned} \tag{2.16}$$

with the definition of the effective diffusion coefficient $\widehat{D}$ as

$$\widehat{D} = \frac{1}{V}\int_{\Omega_y} D(1 + \frac{\partial \chi}{\partial y'})dy' \tag{2.17}$$

where using equation (2.14) $\chi$ is the solution to

$$\frac{\partial}{\partial y}(D(x,y)[1+\frac{\partial \chi}{\partial y}]) = 0 \tag{2.18}$$

## 2.2 Multiple ionic species with electro diffusion

The extension to multiple ionic species and the inclusion of electro diffusion now provides a more rich environment to investigate the interaction of multiple species and their time and spatial variation. At the cellular or sub-cellular model, the accepted model is the Planck-Nernst-Poisson (PNP) equation. Under physiological conditions, the PNP model normally leads to electroneutrality except in the region near the cell boundary (membrane) within a thin (nanometer scale) Derby layer. Since interest is centred on the scale that is much larger than that of individual cells, in this paper we will ignore the effect of the Derby layer and impose electroneutrality in the entire domain. The effect of the Derby layer will be the subject of a future paper. Suppose that in the model there exist N species $c_i \quad i = 1, ...N$ with valence $z_i$ respectively. Electroneutrality states that

$$\sum_{i=1,N} (z_i c_i) = 0 \tag{2.19}$$

We show below how the above homogenised theory can be extended to electrodiffusion . We start with the formal 1D conservation equation for species i stated at the macro scale (that corresponding to a characteristic length much larger than that of the cell) since this will provide a comparison with the equation derived by Keener and Sneyd equation (2.1). The time-dependent variation in cell species concentration consists of both the reaction terms $F_i(v, c_1, c_2, ...)$ internal to the cell and the flux through the gap junctions. This gap junction

flux is composed of two parts, that of the Fickian concentration gradient and electrodiffusional "drift" due to the product of concentration and the gradient of membrane potential. This can be written as

$$J_{drift} = -\mu z c_i \frac{\partial v}{\partial x} \tag{2.20}$$

with $\mu$ the mobility of the ion i. A diffusion coeffcient can be written using Einstein's equation as

$$D = \frac{kT}{q}\mu = \frac{RT}{F}\mu \tag{2.21}$$

with k, Boltzmann's constant, T temperature and q, coulombic charge. The total flux due to electrodiffusive and Fickian processes is

$$\begin{aligned} J_{drift} + J_{diff} &= -\mu z c_i \frac{\partial v}{\partial x} - D\frac{\partial c}{\partial x} \\ &= -\mu z c_i \frac{\partial v}{\partial x} - \frac{RT}{F}\mu\frac{\partial c}{\partial x} \end{aligned} \tag{2.22}$$

so that the current $I$ flowing through the gap junction between cells is written as

$$I = -RTz\mu\left[\frac{\partial c}{\partial x} + \frac{zc_iF}{RT}\frac{\partial v}{\partial x}\right] \tag{2.23}$$

We can write the conservation of specii i as

$$\frac{\partial c_i}{\partial t} = \frac{\partial}{\partial x}[D_i(\frac{\partial c_i}{\partial x} + \gamma z_i c_i \frac{\partial v}{\partial x})] + F_i(v, c_1, c_2, ...) \tag{2.24}$$

As before a regular asymptotic expansion is assumed for $c_i$, $F_i$ and v so that

$$c_i = c_{i0} + \epsilon c_{i1} + \epsilon^2 c_{i2} + ... \tag{2.25}$$

$$v = v_0 + \epsilon v_1 + \epsilon^2 v_2 + ... \tag{2.26}$$

$$F_i = F_{i0} + \epsilon F_{i1} + \epsilon^2 F_{i2} + ... \tag{2.27}$$

and as before introduce the "fast" variable $y = \frac{x}{\epsilon}$ with the additional derivative mapping

$$\frac{\partial}{\partial x} \rightarrow \frac{\partial}{\partial x} + \epsilon^{-1}\frac{\partial}{\partial y}$$

using this mapping and comparing coefficients for orders of $\epsilon$ then

$$\epsilon^{-2} : \frac{\partial}{\partial y}(D_i(\frac{\partial c_{i0}}{\partial y} + \gamma c_{i0} z_i \frac{\partial v_0}{\partial y}) = 0 \tag{2.28}$$

$$\epsilon^{-1} : \frac{\partial}{\partial x}[D_i(\frac{\partial c_{i0}}{\partial y} + \gamma z_i c_{i0}\frac{\partial v_0}{\partial y}) + \frac{\partial}{\partial y}[D_i(\frac{\partial c_{i1}}{\partial y} + \gamma z_i c_{i0}\frac{\partial v_1}{\partial y} + \gamma z_i c_{i1}\frac{\partial v_0}{\partial y})]+$$
$$\frac{\partial}{\partial y}[D_i(\frac{\partial c_{i0}}{\partial x} + \gamma z_i c_{i0}\frac{\partial v_0}{\partial x})] = 0 \tag{2.29}$$

$$\epsilon^0 : \frac{\partial c_i}{\partial t} = \frac{\partial}{\partial x}[D_i(\frac{\partial c_{i0}}{\partial x} + \gamma c_{i0}\frac{\partial v_0}{\partial x}) + D_i(\frac{\partial c_{i1}}{\partial y} + \gamma z_i c_{i0}\frac{\partial v_1}{\partial y})] + \frac{\partial}{\partial y}[D_i(\frac{\partial c_{i1}}{\partial x} + \gamma c_{i1}\frac{\partial v_0}{\partial x}$$
$$+ \gamma c_{i0}\frac{\partial v_1}{\partial x} + \frac{\partial c_{i2}}{\partial y} + \gamma c_{i2}\frac{\partial v_0}{\partial y} + \gamma c_{i0}\frac{\partial v_2}{\partial y})] + F_{i0} \tag{2.30}$$

taking the $\epsilon^{-2}$ coefficient and integrating w.r.t. y we can write

$$\frac{\partial c_{i0}}{\partial y} + \gamma c_{i0} z_i \frac{\partial v_0}{\partial y} = \frac{G_i(x)}{D_i} \tag{2.31}$$

now using the integrating factor $e^{\gamma z_i v_0}$ then

$$\frac{\partial}{\partial y}(e^{\gamma z_i v_0} c_{i0}(x,y)) = \frac{G_i(x)}{D_i} e^{\gamma z_i v_0} \tag{2.32}$$

$$(e^{\gamma z_i v_0} c_{i0}) = G_i(x)\int_0^y \frac{(e^{\gamma z_i v_0} c_{i0})}{D_i} + f_i(x) \tag{2.33}$$

imposing periodic boundary conditions gives

$$(e^{\gamma z_i v_0} c_{i0}(x,0)) = f_i(x) \tag{2.34}$$

$$(e^{\gamma z_i v_0} c_{i0}(x,1)) = f_i(x) = G_i(x)\int_0^1 \frac{(e^{\gamma z_i v_0} c_{i0})}{D_i} + f_i(x) \tag{2.35}$$

$$\Rightarrow G_i = 0, ...\forall i \text{ since } \frac{e^{\gamma z_i v_0}}{D_i} > 0 \tag{2.36}$$

using the above then

$$e^{\gamma z_i v_0} c_{i0} = f_i(x) \tag{2.37}$$

$$\sum_i z_i c_{i0} = \sum_i z_i e^{-\gamma z_i v_0} f_i(x) = 0 \tag{2.38}$$

by electroneutrality so,

$$\frac{\partial}{\partial y}[\sum_i z_i c_{i0}] = \frac{\partial}{\partial y} \sum_i [z_i e^{-\gamma z_i v_0} f_i(x)] = 0 \tag{2.39}$$

$$= \sum_i z_i^2 e^{-\gamma z_i v_0} f_i(x) \frac{\partial v_0}{\partial y} = 0 \tag{2.40}$$

but

$$\sum_i z_i^2 e^{-\gamma z_i v_0} f_i(x) > 0 \tag{2.41}$$

$$\Rightarrow \frac{\partial v_0}{\partial y} = 0 \Rightarrow v_0 = v_0(x,t) \tag{2.42}$$

then since $e^{\gamma z_i v_0} c_{i0}(x,y,t) = f_i(x) \Rightarrow c_{i0} = c_{i0}(x,t)$.

We have now shown that the leading order terms for concentration and field potential are independent of y (the "fast" variable). We turn our attention to the $\epsilon^{-1}$ terms looking at the ith species and noting that both $c_{i0}$ and $v_0$ are functions of x and t only then

$$\frac{\partial D_i}{\partial y}[\frac{\partial c_{i0}}{\partial x} + \gamma z_i c_{i0} \frac{\partial v_0}{\partial x}] + \frac{\partial}{\partial y}[D_i(\frac{\partial c_{i0}}{\partial y} + \gamma z_i c_{i0} \frac{\partial v_1}{\partial y})] = 0 \tag{2.43}$$

where the function $H_i(x)$ is defined to be

$$H_i(x) = \frac{\partial c_{i0}}{\partial x} + \gamma z_i c_{i0} \frac{\partial v_0}{\partial x} \tag{2.44}$$

and integrating once w.r.t. y we have

$$D_i H_i(x) + D_i[\frac{\partial c_{i1}}{\partial y} + \gamma z_i c_{i0} \frac{\partial v_1}{\partial y}] = B(x) \tag{2.45}$$

and integrating again with periodic boundary conditions then

$$c_{i1} + \gamma z_i c_{i0} \frac{\partial v_1}{\partial y} = B(x) \int_0^y \frac{dy}{D_i} - H_i(x)y + c(x) \Rightarrow B(x) = \frac{H_i(x)}{\int_0^1 \frac{dy}{D_i(y)}} \tag{2.46}$$

the $\epsilon^0$ terms are used to eliminate the $c_{i1}$ and $v_1$ variables from the equation to leading order. Firstly integrating w.r.t. y and noting that the $\frac{\partial}{\partial y}$ terms are zero by the periodicity condition whilst secondly substituting equation (2.46) we obtain finally that

$$\frac{\partial c_i}{\partial t} = \frac{\partial}{\partial x}[\widehat{D_i}(\frac{\partial c_{i0}}{\partial x} + \gamma c_{i0} \frac{\partial v_0}{\partial x})] + F_{i0} \tag{2.47}$$

with

$$\widehat{D_i} = \frac{1}{\int_0^1 \frac{dy}{D_i(y)}} \tag{2.48}$$

We compare equation (2.48) with the coefficient derived by Keener and Sneyd equation (2.1).

### 2.2.1 Multiple Species with electro-diffusion in 2D

We note that the potential used in the electro-diffusion equation is the membrane potential even though it should correctly be the field potential hence an assumption that the extra-cellular space potential does not vary. Otherwise this would require the determination of the ECS potential and use the difference between the ECS potential and the membrane potential to evaluate the field potential. We also assume that the difference in the ion flux out of the cell for different species of ion accumulates in the small boundary layer next to the membrane (the size of this layer is effectively determined by the Debye length). This accumulation is assumed to be held in the capacitance of the membrane. The "diffusive" flux

due to concentration gradient and field potential can be written as in multiple dimensions as

$$J_{D,i} = D_{c_i}[\nabla_{\underline{x}} c_i + \gamma c_i \nabla_{\underline{x}} V] \tag{2.49}$$

where $D_{c_i}$ is some homogenised diffusion coefficient for species i

The analysis and solution given below follows closely the work of Holmes [5]

We start with a description of the geometry. We assume that the cells are rectangular in shape, of the same size, are contiguous and each cell fills a specified 2D space $\Omega_0$ defined with macro co-ordinates $(x_1, x_2) = \underline{x}$ and have cell co-ordinates $(\frac{x_1}{\epsilon}, \frac{x_2}{\epsilon}) = (y_1, y_2) = \underline{y}$. A sketch is shown in Figure (1). For simplicity the steady state equation is considered since

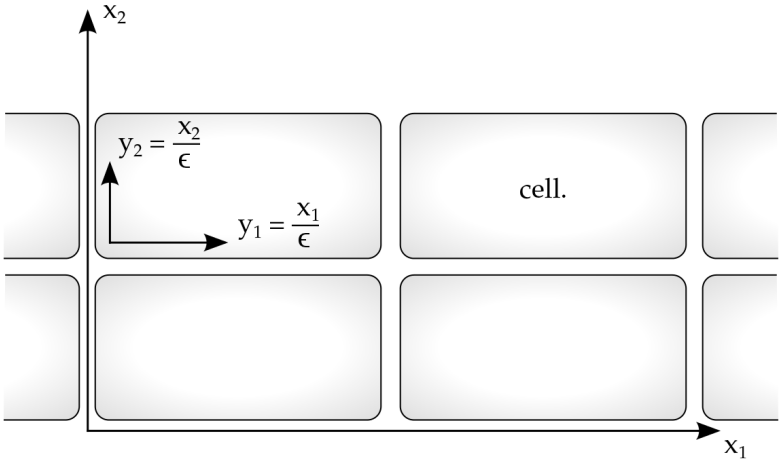



Figure 1: sketch of cells arrangement

time dependency is a trivial addition to the solution. The full equation is then

$$\nabla_{\underline{x}} . J_{D,i} = \nabla_{\underline{x}} . \left[ D_{c_i} [\nabla_{\underline{x}} c_i + \gamma c_i \nabla_{\underline{x}} V] \right] = F(\underline{x}) \tag{2.50}$$

Finally we assume that our functions are at least $C^1$ so as to enable periodicity arguments to carry through. As in the case of 1D the derivative transform is used and let

$$\nabla_{\underline{x}} \to \nabla_{\underline{x}} + \epsilon^{-1}\nabla_{\underline{y}} \tag{2.51}$$

To avoid confusion we allow the underline to drop and simply use $\nabla_x$. Then (2.50) becomes

$$(\nabla_x + \epsilon^{-1}\nabla_y).[D(\nabla_x c + \epsilon^{-1}\nabla_y c + \gamma c(\nabla_x V + \epsilon^{-1}\nabla_y V))] = F(\underline{x}) \tag{2.52}$$

We now introduce a regular expansion of the variables $c$ and V such that

$$\begin{aligned} c(x,y) &= c_0(x,y) + \epsilon c_1(x,y) + \epsilon^2 c_2(x,y) + O(\epsilon^3) \\ V(x,y) &= V_0(x,y) + \epsilon V_1(x,y) + \epsilon^2 V_2(x,y) + O(\epsilon^3) \end{aligned} \tag{2.53}$$

importantly all functions $c_i$ and $V_i$ are treated as being periodic in $\underline{y}$. Individual equations for the coefficients of $\epsilon$ can be written and after a little algebra it is found that

$$\begin{aligned} &\epsilon^{-2} : \nabla_y.D(\nabla_y c_0 + \gamma c_0 \nabla_y V_0) = 0 \\ &\epsilon^{-1} : \nabla_x.[D\nabla_y c_0 + D\gamma c_0 \nabla_y V_0] + \nabla_y.[D\nabla_x c_0 + D\gamma c_0 \nabla_x V_0] + \nabla_y.[D\nabla_y c_1 + D\gamma c_0 \nabla_y V_1 + D\gamma c_1 \nabla_y V_0] = 0 \\ &\epsilon^{0} : \nabla_x.[D\nabla_x c_0 + D\gamma c_0 \nabla_x V_0] + \nabla_y.[D\nabla_x c_0 + D\gamma c_0 \nabla_x V_0] + \nabla_y.[D\nabla_y c_1 + D\gamma c_0 \nabla_y V_1] + \\ &\qquad \nabla_y.[D\nabla_y c_2 + D\gamma c_0 V_2] + \nabla_y.[D\gamma c_1 \nabla_y V_1] = F_0(x) \end{aligned} \tag{2.54}$$

in the equations for $\epsilon^{-1}$ and $\epsilon$ we have utilised the $\epsilon^{-2}$ equation and periodicity to show that $c_0 = c_0(x)$ and that $V_0 = V_0(x)$. We now look at the order $\epsilon^{-1}$ equations.

$$\nabla_y.[D\nabla_y c_0 + D\gamma c_0 \nabla_y V_1] = -\nabla_y.[D\nabla_x c_0 + D\gamma c_0 \nabla_x V_0] \tag{2.55}$$

let

$$\nabla_y.D = \nabla_y.(D\nabla_y \underline{a}) \tag{2.56}$$

then (2.55) becomes

$$\nabla_y.[D\nabla_y c_0 + D\gamma c_0 \nabla_y V_1] = -\nabla_y.(D\nabla_y \underline{a}).[\nabla_x c_0 + \gamma c_0 \nabla_x V_0] \tag{2.57}$$

integrating twice and noticing that $c_0 = c_0(x)$ then

$$c_1 + \gamma c_0 V_1 = -\underline{a}.[\nabla_x c_0 + \gamma c_0 \nabla_x V_0] \tag{2.58}$$

by substituting for $c_1 + \gamma c_0 V_1$ it can be shown that the components of the vector $\underline{a} = \{a_{ij}\}$ are the solution to

$$\nabla_y.(D\nabla_y a_i) = -\partial_{y_i} D \in \Omega_0 \tag{2.59}$$

hence

$$\nabla_y c_1 + \gamma c_0 \nabla_y V_1 = -\nabla_y \underline{a}.[\nabla_x c_0 + \gamma c_0 \nabla_x V_0] \tag{2.60}$$

Introducing an averaging operator over the cell

$$< \zeta >_{cell} = \frac{1}{|\Omega_0|} \int_{\Omega_0} \zeta(\underline{x}, \underline{y}) dV_{cell} \tag{2.61}$$

we apply this to order $\epsilon^0$ equation of (2.54) , using the divergence theorem and periodicity such that with $\partial\Omega_0$ the cell boundary

$$< \nabla_y.[D\nabla_x c_1 + D\gamma c_0 \nabla_x V_1] >_{cell} = \frac{1}{|\Omega_0|} \int_{\partial\Omega_0} D\underline{n}.(\nabla_x c_1 + \gamma c_0 \nabla_x V_1) dS_{cell} = 0 \tag{2.62}$$

by periodicity. This is true for all other $\nabla_y(...)$ terms. The order $\epsilon^0$ equation is now left with only two terms. Using (2.56) we can combine these to form

$$\nabla_x.[D(\nabla_y \underline{a} + \mathbf{I}).(\nabla_x c_0 + \gamma c_0 \nabla_x V_0)] = F(\underline{x}) \tag{2.63}$$

with $\mathbf{I}$ the identity matrix. Averaging over the cell as before gives

$$\nabla_x.[< D(\nabla_y \underline{a} + \mathbf{I}) >_{cell} .(\nabla_x c_0 + \gamma c_0 \nabla_x V_0)] =< f(\underline{x}) >_{cell} = F(\underline{x})$$

$$\Rightarrow < D(\nabla_y \underline{a} + \mathbf{I}) >_{cell} = \overline{D} \tag{2.64}$$

Equation (2.64) should be compared with both (2.1) and (2.48). To complete the picture coefficients of $\underline{a}$ are evaluated and this is done using equation (2.59).

# 3 Application to a set of coupled cells

We now turn our attention to the application of the above theory to that of a set of coupled cells. In particular the cells model coupled smooth muscle cells that make up part of the arterial wall. At present it is assumed that the artery has been cut along an axially aligned line and therefore the cells form a flat 2D plane. Appropriate boundary conditions are zero flux at the x-scale boundaries. The model consists of the conservation of ionic species within the cell and the implementation of cable-like equation to the membrane potential defined as the difference between the field potential outside and that inside the cell.

$$C_m \frac{\partial V_0}{\partial t} = \sum_i [AFz_i J_{i,coupling}] + \sum_k I_{k,channel} \tag{3.1}$$

$$\frac{\partial c_{0,i}}{\partial t} = \nabla_x \cdot [\overline{D}_i(\nabla_x c_{0,i} + \gamma_i c_{0,i} \nabla_x V_0)] + F_{0,i}(\underline{x}) \tag{3.2}$$

here $J_{i,coupling}$ represents the ion flux through the coupling gap junction of species i, $I_{k,channel}$ the ion current through the membrane ion channel for species i and $F_i(\underline{x})$ the reaction terms for species i. These reaction terms include the ionic fluxes $J_i$ across the membrane and the surface of the sarcoplasmic reticulum due to the opening of the associated receptors, ion channels and the internal reactions existing in the cytosol of the cell. $C_m$ is the capacitance of the membrane, A is the surface area adjoining each coupled cell, F , Faraday's constant and $z_i$ the valence of specie i. We first look at the RHS of the membrane equation since it contains the diffusive element described above in section 2.2.1.

$$\begin{aligned}\sum_i [AFz_iJ_i] =& AF\sum_i (z_i\nabla_x.[\overline{D}_i.(\nabla_x c_{0,i} + \gamma c_{0,i}\nabla_x V_0)]) \\ =& AF\left[\nabla_x.\sum_i(\overline{D}_i z_i \nabla_x c_{0,i})\right] + \frac{AF^2}{RT}\nabla_x.\left[\sum_i(\overline{D}_i z_i^2 c_{0,i})\nabla_x V_0\right] \end{aligned} \tag{3.3}$$

If $\overline{D}_i$ is independent of species and constant over the macroscale then the membrane equation becomes

$$\frac{dV_0}{dt} = \frac{\overline{D}AF}{C_m}\left[\nabla_x^2\sum_i z_i c_{0,i}\right] + \frac{\overline{D}AF^2}{C_m RT}\left[\sum_i\left(z_i^2\nabla_x c_{0,i}.\nabla_x V_0 + z_i^2 c_{0.i}\nabla_x^2 V_0\right)\right] + \frac{1}{C_m}\sum_k I_{k,channel} \tag{3.4}$$

We should note that if $i > 1$ then the first term on the RHS of equation (3.4) becomes zero since by electroneutrality $\sum_i(z_i c_{0,i}) = 0$. For a single species then the equation for membrane potential becomes

$$\frac{dV_0}{dt} = \frac{z\overline{D}AF}{C_m}\left[\nabla_x^2 c_0 + \frac{zF}{RT}\left(\nabla_x c_0.\nabla_x V_0 + c_0\nabla_x^2 V_0\right)\right] + \frac{1}{C_m}\sum_k I_{k,channel} \tag{3.5}$$

for this case it seems that the concentration diffusive term in (3.5) could be neglected in

comparison with the second term (since $\frac{F}{RT} \sim 40$). However this is not the case for the concentration conservation equation (3.2).

## 3.1 Evaluation of the homogenised Diffusion Coefficient

We are required to solve equation (2.59) which is restated here for clarity

$$\nabla_y.(D\nabla_y a_i) = -\partial_{y_i} D \in \Omega_0 \tag{3.6}$$

For the case of modelling transport of information along and through the arterial wall we principally concern ourselves with the coupled smooth muscle cells. All cells have the same function and geometric make up. In terms of the diffusion of species through the cell and importantly through the membrane axial diffusion may be somewhat different from that in the circumferential direction. However a simplification that does not alter the physiological outcome is that the anisotropic diffusion is independent of each direction. We assume therefore that the diffusion coefficient function $D(\underline{x}, \underline{y})$ is written as a separable function in terms of the micro scale co-ordinates thus,

$$D(\underline{x}, \underline{y}) = D_0(\underline{x})h(y_1)m(y_2) \tag{3.7}$$

In a similar manner the analysis follows closely that of [5]. We may write the diffusion coefficient as

$$\begin{aligned} \nabla_y(hm\nabla_y a_i) &= \frac{\partial}{\partial y_i}(hm) \\ h, m &\neq 0, \forall y_1, y_2 \end{aligned} \tag{3.8}$$

WLOG the system can be simplified by noting that by a suitable choice of co-ordinates at the cell level and thus arbitrarily allow $y_1 \in [0, Y_1]$; in addition $y_2 \in [0, Y_2]$

We may also suppose that $a_i = a_i(y_i)$ so that for i = 1 the p.d.e. becomes

$$\begin{aligned} \partial y_1(hm\frac{\partial a_1}{\partial y_1}) + \partial y_2(hm\frac{\partial a_1}{\partial y_2}) &= -m\frac{\partial h}{\partial y_1} \\ \Rightarrow m\frac{\partial}{\partial y_1}(h\frac{\partial a_1}{\partial y_1}) &= -m\frac{\partial h}{\partial y_1} \end{aligned} \tag{3.9}$$

dividing by m and integrating w.r.t. $y_1$ twice gives

$$a_1 = -y_1 + \kappa_1 \int_0^{y_1} \frac{1}{h(s)} ds \tag{3.10}$$

in a similar manner the solution for $a_2$ can be written as

$$a_2 = -y_2 + \kappa_2 \int_0^{y_2} \frac{1}{m(s)} ds \tag{3.11}$$

We require periodicity in both $a_1$ and $a_2$ such that $a_1(0) = a_1(Y_1)$ and $a_2(0) = a_2(Y_2)$. This gives

$$\kappa_1 = \left( \frac{1}{Y_1} \int_0^{Y_1} \frac{1}{h(s)} ds \right)^{-1} \tag{3.12}$$

$$\kappa_2 = \left( \frac{1}{Y_2} \int_0^{Y_2} \frac{1}{m(s)} ds \right)^{-1} \tag{3.13}$$

Now that a solution is found for the $a_i's$ we can solve completely equation (2.59). Since $a_i = a_i(y_i)$ so that $\partial y_i a_j = 0$ then

$$< D\partial y_1 a_1 >_{cell} = \frac{1}{A}\int_0^{Y_1}\int_0^{Y_2} D_0\, h\, m\left(-1 + \frac{\kappa_1}{h(y_1)}\right) dy_1\, dy_2 \tag{3.14}$$

$$= \frac{1}{A}\left[-\int_0^{Y_1}\int_0^{Y_2} D_0\, h\, m\, dy_1 dy_2 + \kappa_1 \int_0^{Y_1}\int_0^{Y_2} D_0\, m\, dy_1 dy_2\right] \tag{3.15}$$

$$= \frac{1}{A}\left[-A < D >_{cell} + Y_1 \kappa_1 D_0 \int_0^{Y_2} m\, dy_2\right] \tag{3.16}$$

$$= - < D >_{cell} + D_0 \left(\int_0^{Y_1} \frac{1}{h(s)} ds\right)^{-1} \frac{1}{Y_2}\int_0^{Y_2} m(s) ds \tag{3.17}$$

Similarly we have that

$$< D\partial y_2 a_2 >_{cell} =$$

$$- < D >_{cell} + D_0 \left(\int_0^{Y_2} \frac{1}{m(s)} ds\right)^{-1} \frac{1}{Y_1}\int_0^{Y_1} h(s)\, ds \tag{3.18}$$

By the previous definition of $D_{ij}$

$$D_{11} = D_0 \left(\int_0^{Y_1} \frac{1}{h(s)} ds\right)^{-1} \frac{1}{Y_2}\int_0^{Y_2} m(s) ds \tag{3.19}$$

$$D_{22} = D_0 \left(\int_0^{Y_2} \frac{1}{m(s)} ds\right)^{-1} \frac{1}{Y_1}\int_0^{Y_1} h(s)\, ds \tag{3.20}$$

We now need to choose particular functions for h(s) and m(s).

## 3.2 Cell Diffusion Coefficients

Cells have a small lipid bi-layer which encloses the nucleus and cytosol along with other units within the cell. The cytosol makes up the majority of the cell volume and is essentially

a single phase liquid. In this case we can assume that the diffusion coefficient inside the cell is a constant value. Transport through the lipid bi-layer depends on the permeability of the connexin hemi-channel and in normal circumstances the effective diffusion coefficient would be much smaller than that for the cytosol. In choosing these functions it is recognised that the original constraint meant that the functions are required to be at least $\mathcal{C}^2$. For the presented case the only constraint is that they are integrable. We assume the following functions for $h(s)$ and $m(s)$.

$$h(s) = \begin{cases} D_{min} & 0 \leq s < \delta \\ D_{max} = \alpha D_{min} & \delta \leq s < Y_1 - \delta \\ D_{min} & Y_1 - \delta \leq s \leq Y_1 \end{cases} \tag{3.21}$$

$$m(s) = \begin{cases} D_{min} & 0 \leq s < \delta \\ D_{max} = \alpha D_{min} & \delta \leq s < Y_2 - \delta \\ D_{min} & Y_2 - \delta \leq s \leq Y_2 \end{cases} \tag{3.22}$$

then

$$\frac{1}{Y_1} \int_0^{Y_1} \frac{1}{f(s)}\, ds = \frac{1}{Y_1 D_{min}} \left( 2\delta + \frac{Y_1 - 2\delta}{\alpha} \right) \tag{3.23}$$

$$\left( \frac{1}{Y_1} \int_0^{Y_1} \frac{1}{f(s)}\, ds \right)^{-1} = \frac{Y_1 D_{min}}{\left( 2\delta + \frac{Y_1 - 2\delta}{\alpha} \right)} \tag{3.24}$$

in a similar fashion we have that

$$\frac{1}{Y_2} \int_0^{Y_2} g(s)\, ds = \frac{D_{min}}{Y_2} \left( \alpha \left( Y_2 - 2\delta \right) + 2\delta \right) \tag{3.25}$$

so that the non-zero components of the diffusion matrix are given by

$$D_{11} = \frac{Y_1}{Y_2} D_0 D_{min}^2 \left[ \frac{\alpha\left(Y_2 - 2\delta\right) + 2\delta}{\frac{(Y_1 - 2\delta)}{\alpha} + 2\delta} \right] \tag{3.26}$$

$$D_{22} = \frac{Y_2}{Y_1} D_0 D_{min}^2 \left[ \frac{\alpha\left(Y_1 - 2\delta\right) + 2\delta}{\frac{(Y_2 - 2\delta)}{\alpha} + 2\delta} \right] \tag{3.27}$$

### 3.2.1 Influence of the membrane

The thickness of a cell lipid bi-layer is much smaller than the characteristic cell size. For example the size of an endothelial cell (in the axial co-ordinate) is approximately 60 $\mu m$, whereas the bi-layer is the order of nanometers. Hence $\delta \to 0$ and compare the diffusion coefficients in both directions.

$$\begin{aligned} \lim_{\delta \to 0} \left(D_{11}\right) &= D_0 \alpha^2 D_{min}^2 \\ &= D_0 D_{max}^2 \\ &= \lim_{\delta \to 0} \left(D_{22}\right) \end{aligned} \tag{3.28}$$

Hence by allowing the cell layer to become negligible the anisotropic nature of the diffusion coefficient is lost. In constructing a function that represents the variation of diffusion across the cell which takes into account the difference in the transport of ions through the cytosol and through the membrane it is assumed that close to the membrane the diffusion will be considerably smaller and through the majority of the cytosol the diffusion coefficient will essentially be constant. We thus formulate a function $f(s)$ representing the diffusion of ions across the cell as being of the form

$$f(s) = F_{left}(s) + H_{centre}(s) + F_{right}(s) \tag{3.29}$$

For a "standard" cell the thickness of the membrane is very small compared to the total length (width) of the cell. Hence for this case $\delta \ll \epsilon$. In addition if the left-hand part of the cell is taken to be represented by the origin of the micro-scale axes then the function $F_{left}(s)$ will be such that for

$$y_i \in [0, \delta] \quad F_{left}(s) > 0 \qquad \frac{dF_{left}}{dy_i} \geq 0 \quad i = 1, 2 \tag{3.30}$$

We show that for any continuous function $F_{left}(s)$ with the above constraints then

$$\lim_{\delta \to 0} \int_0^{\delta} \frac{1}{F_{left}(s)}\, ds = 0 \tag{3.31}$$

**Proof**

Since $F_{left}(s)$ is monotonic increasing and bounded then

$$\begin{aligned} &\exists \quad \eta \text{ such that } F_{left}(0) = \eta \text{ and } M = \frac{1}{F_{left}(\eta)} \\ &\Rightarrow \int_0^{\delta} \frac{1}{F_{left}(s)}\, ds < M\delta \\ &\lim_{\delta \to 0} \int_0^{\delta} \frac{1}{F_{left}(s)}\, ds < \lim_{\delta \to 0} (M\delta) = 0 \end{aligned} \tag{3.32}$$

A similar proof can be constructed for the right-hand end of the cell. So what does this mean for the investigation of diffusion through large numbers of coupled cells? Given that $\delta \ll \epsilon$ then it is a reasonable assumption to take $\delta \to 0$. On the macroscale the diffusion coefficient is simply that obtained in the cyotsol and the membrane plays no part in the conduction of ions from cell to cell.

# 4 A Physiological Example

Chemical constituents of cells in the human arterial tree can oscillate due to a number of cellular pathways associated with the spatially varying parameters which are known to occur in the human. In arterial cells parameters exist which are functions of space, such as the agonist ATP or the action of wall shear stress on the endothelium. These agonists or mechanical forces acting on cells are spatially varying due in the most part to the flowing blood in the arterial vessels. Importantly in a significant number of cases the frequency of oscillation is also a function of one or more parameters and hence adjacent cells may very well oscillate with different frequencies when acted upon by the spatially varying parameter. Cells do not oscillate for all physiological values of the parameter. In cases of either endothelial or smooth muscle cells in the arterial wall then as a particular parameter varies there may exist domains of oscillation bounded by bifurcation points. Given that both Fickian and ion drift diffusion are driven by spatial gradients one would expect wave phenomena over large spatial scales to occur if there exists variation in concentrations across the adjacent cell membranes. If there exists little or no initiation such as a sudden increase in either say $Ca^{2+}$ or $IP_3$ for example then one would expect a steady state to occur with the consequential lack of any wave propagation. However this would only be the case if the cell concentrations were either not oscillating or that any parameter which induced cell oscillations had no spatial dependence. This very rarely occurs in vivo.

The diffusion coefficients for both $Ca^{2+}$ and $IP_3$ in cytosol are quite small, of the order of $2X10^{-10} \quad m^2s^{-1}$ for $IP_3$ and $6X10^{-12} \quad m^2s^{-1}$ for $Ca^{2+}$ [6]. Wave velocities in the cytosol

of the cell are also relatively small ($10\mu ms^{-1}$). On the basis of simple diffusion through the cell one would expect wave propagation over large length scales to be extremely slow or non-existent.

We are now in a position to investigate with the example given below the possibility of large scale wave phenomena derived from spatially varying cell oscillation induced by parametric spatial variation rather than simple diffusion. In addition investigations can be made into wave propagation in domains of space where oscillation would not normally be found. We use the case of calcium induced calcium release (CICR) originally derived by Endo et al. [3], Endo [2] and analysed by Goldbeter et al [4] since this provides oscillatory domains (with corresponding variations in frequency) for a range of a single parameter and is relatively simple to solve numerically. CICR is initially induced by a rise in $IP_3$ triggered by an external stimulus allowing $Ca^{2+}$ to be released from a section of the sarcoplasmic reticulum (SR). Increased cytosolic $Ca^{2+}$ mediates even further release of $Ca^{2+}$ from a second store which is insensitive to $IP_3$. This feedback mechanism produces oscillations in the cytosolic $Ca^{2+}$ and in contrast to the model of Meyer and Stryer [6] does not require $IP_3$ oscillations. To avoid confusion we use the same notation as that of Goldbeter. Here $Z = [Ca^{2+}]_{cyt}$, the calcium concentration in the cytosol and $Y = [Ca^{2+}]_{SR}$, the calcium concentration in the sarcoplasmic reticulum. The conservation equations for both Z and Y are given as

$$\frac{\partial Z}{\partial t} = D_Z \frac{\partial^2 Z}{\partial x^2} + \nu_0 + \nu_1 \beta - \frac{V_{m2} Z^n}{K_2^n + Z^n} + \frac{V_{m3} Y^m}{K_R^m + Y^m} \frac{Z^p}{K_a^p + Z^p} + k_f Y - kZ \tag{4.1}$$

$$\frac{\partial Y}{\partial t} = \frac{V_{m2} Z^n}{K_2^n + Z^n} - \frac{V_{m3} Y^m}{K_R^m + Y^m} \frac{Z^p}{K_a^p + Z^p} - k_f Y \tag{4.2}$$

Note that Y is not diffused since this is the concentration in the SR and cannot diffuse from cell to cell. The parameter $\nu_0$ denotes the assumed constant influx of $Ca^{2+}$ whilst $kZ$ the linear outflux. $\nu_1\beta$ models the efflux of $Ca^{2+}$ out of the SR due to the presence of $IP_3$, $\beta$ is recognised as a spatially varying parameter since it models the influx of $IP_3$ by agonists flowing in the blood. The fourth term in (4.1) denotes the ATPase pumping of $Ca^{2+}$ back into the SR whilst the fifth term models the cooperative efflux of $Ca^{2+}$ from the SR by $Ca^{2+}$ itself. $k_f Y$ is a simple leak from the SR. Diffusion is included in the equation set and simulations involve allowing $\beta = \beta(x)$. For this particular case $m = n = 2; \quad p = 4;$. The equation for Y is treated as the balance of $Ca^{2+}$ into the sarcoplasmic reticulum. For full details of this particular cell model the reader is directed to [4].

We non-dimensionalise the equation set by choosing the characteristic time scale $\tau$ to be such that $\tau = \frac{1}{k_f}$ and the characteristic concentration to be $K_r$. Table 4 shows the dimensioned and non-dimensional parameters.

| Constant | Dimensional Value | Non-dimensional name | Non-dimensional value |
|---|---|---|---|
| $\nu_0$ | $1\mu M s^{-1}$ | $\alpha_0 = \frac{\nu_0}{k_f K_r}$ | 0.5 |
| $\nu_1$ | $7.3\mu M s^{-1}$ | $\alpha_1 = \frac{\nu_1}{k_f K_r}$ | 3.65 |
| $V_{m2}$ | $65\mu M s^{-1}$ | $\alpha_2 = \frac{V_{m2}}{k_f K_r}$ | 32.5 |
| $V_{m3}$ | $500\mu M s^{-1}$ | $\alpha_4 = \frac{V_{m3}}{k_f K_r}$ | 250 |
| k | $10 s^{-1}$ | $\alpha_6 = \frac{k}{k_f}$ | 10 |
| $k_f$ | $1 s^{-1}$ | 1 | 1 |
| $K_2$ | $1\mu M$ | $\alpha_3 = \frac{K_2}{K_r}$ | 0.5 |
| $K_r$ | $2\mu M$ | 1 | 1 |
| $K_a$ | $0.9\mu M$ | $\alpha_5 = \frac{K_a}{K_r}$ | 0.45 |

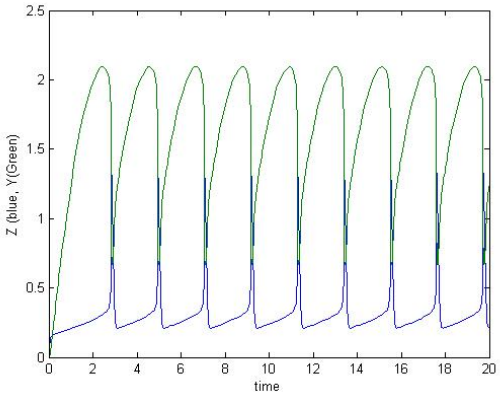
Equations (4.3) and (4.4) represent the non-dimensionalised set where Z and Y are denoted as the non-dimensional concentrations and $\overline{D_Z}$ as the non-dimensionalised diffusion coefficient.

$$\frac{\partial Z}{\partial \tau} = \overline{D_Z}\frac{\partial^2 Z}{\partial x^2} + \alpha_0 + \alpha_1\beta - \frac{\alpha_2 Z^n}{\alpha_3^n + Z^n} + \frac{\alpha_4 Y^m}{1+Y^m}\frac{Z^p}{\alpha_5^p + Z^p} + Y - \alpha_6 Z \tag{4.3}$$

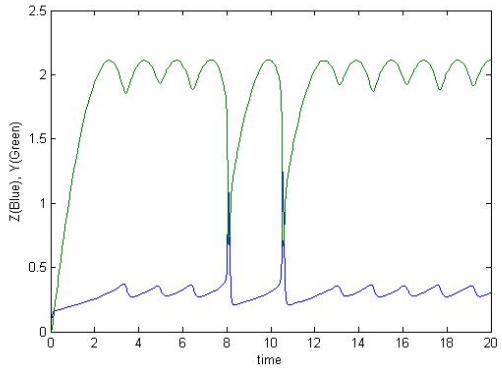
$$\frac{\partial Y}{\partial \tau} = \frac{\alpha_2 Z^n}{\alpha_3^n + Z^n} - \frac{\alpha_4 Y^m}{1+Y^m}\frac{Z^p}{\alpha_5^p + Z^p} - Y \tag{4.4}$$

We first show that for some non-zero value of $\beta$ the system oscillates. Figure (2a) shows Z and Y plotted as a function of time where $\beta = 0.3$.

In order to place some of the results from the full reaction diffusion model in context Figure (2b) shows the time-dependent profile of both Z and Y for $\beta$ "close" to the bifurcation




(a) **Caption required here**




(b) **Caption required here**

Figure 2: caption here

value such that $\beta = 0.3 - \epsilon$ with $\epsilon = 0.0103$. This indicates that large amplitude oscillations of both Z and Y occur on a larger period infrequently and aperiodically for values in the small neighbourhood of $\beta$ =0.3.

Figure 3 presents an x/t (space/time) colour-coded map of cytosolic $Ca^{2+}$ for simple Fickian diffusion where the parameter $\beta = \beta(x) = \frac{1}{2}\left[1 + tanh\left[\frac{(x-x_0)}{x_{scale}}\right]\right]$. The non-dimensional diffusion coefficient is $6.0 \times 10^{-6}$. Horizontal black lines denote the bifurcation points separating the domain of oscillation if diffusion were absent. Figure 4 presents a similar x/t (space/-time) colour-coded map of cytosolic $Ca^{2+}$ for both Fickian and Elctro diffusion combined. Both Figures 3 and 4 show similar profiles. For large values of $\beta$ oscillations are absent as in the case of no diffusion however, for small values of $\beta$ waves of $Ca^{2+}$ propagate into the lower domain.

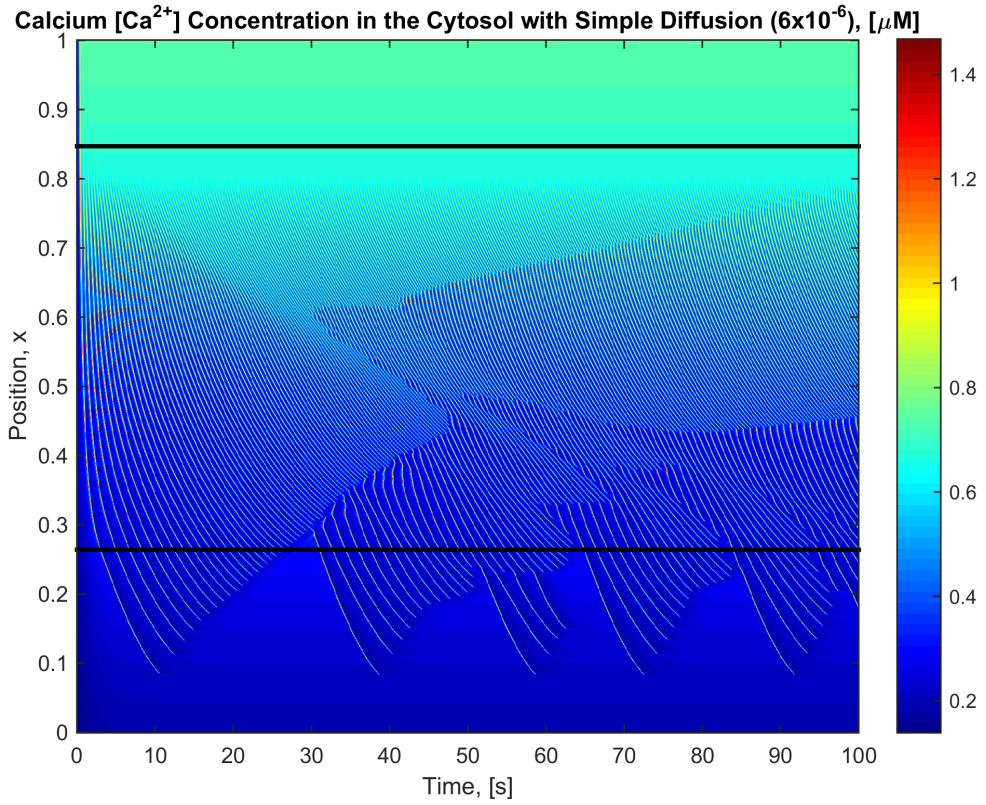



Figure 3: x/t (space/time) colour-coded map of cytosolic $Ca^{2+}$ for simple Fickian diffusion where the parameter $\beta = \beta(x) = \frac{1}{2}\left[1 + tanh\left[\frac{(x-x_0)}{x_{scale}}\right]\right]$. The non-dimensional diffusion coefficient is $6.0 \times 10^{-6}$. Horizontal black lines denote the bifurcation points separating the domain of oscillation if diffusion were absent

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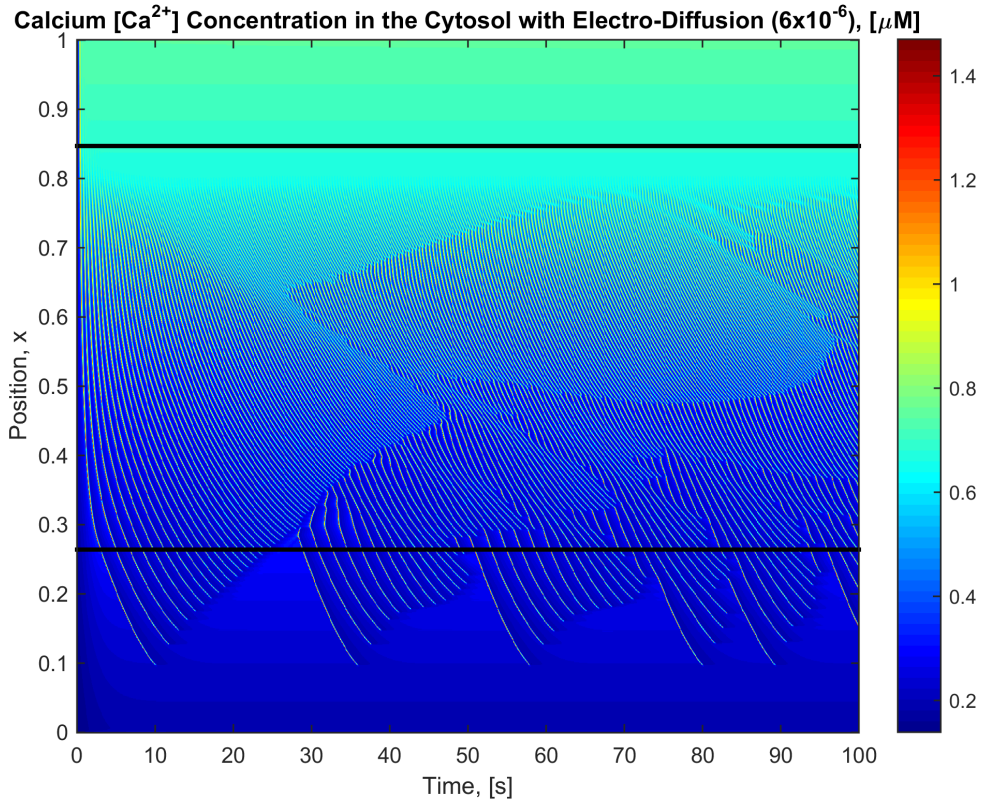


Figure 4: x/t (space/time) colour-coded map of cytosolic $Ca^{2+}$ with electro diffusion where the parameter $\beta = \beta(x) = \frac{1}{2}\left[1 + tanh\left[\frac{(x-x_0)}{x_{scale}}\right]\right]$. The non-dimensional diffusion coefficient is $6.0 \times 10^{-6}$. Horizontal black lines denote the bifurcation points separating the domain of oscillation if diffusion were absent

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