

Research Proposal: Media and Motion

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1 Introduction

In 2009 it was recorded by the British Heart foundation that one in three deaths in the United Kingdom occurred because of cardiovascular disease. This is one of many statistics that has motivated the mathematical modelling of the heart, in order to develop our understanding of the heart, which can lead to better treatments and cures. Later in this introduction we will outline some of the causes of heart failure that can be modelled mathematically, namely arrhythmia.

In this proposal, our aim is to add some new understanding to this growing field. First we will outline the setting in which we will pose our questions. There are many properties of the heart that could be discussed, however we will pick out the key features that relate to the modelling we will focus on in this proposal.

1.1 Overview of the anatomy and electric activity in the heart

The electrical process that causes the heart to contract can be summarised as follows. An electrical stimulus comes from the Sino-atrial node situated in the right atrium (see Figure 1) and causes a wave to propagate across the thin walls of the atria. Due to the thin nature of these walls, the propagation of this wave can be qualitatively thought of as a 2 dimensional propagation. Simultaneously, the action potential travels to the Atrio-ventricular node situated centrally at the junction of the atria and the ventricles, where it is delayed in order to allow the ventricles to fill with blood from the atria before they contract. It then travels through the bundle of His and the Purkinje fibres, causing it to spread quickly across the inner lining of the ventricular myocardium before it propagates out through the thicker walls of the ventricles, causing them to contract [9]P15. Due to the thickness of these walls, the propagation of the waves show some three dimensional structure in that they propagate across the thin inner part of the wall of the ventricle first, before moving through the walls to the outside.

This process summarises qualitatively how electrical activity affects and stimulates the mechanical working of the heart. However, it is also crucial to realise that the mechanics of the heart in turn have an effect on its electrical activity. We will outline this coupling in more detail later, and show how it can be represented mathematically in the form of a coupled system of PDE's.

When a wave of excitation is stimulated in a small region of the heart wall (for example at the SA or AV nodes), initially it will travel something like a ripple

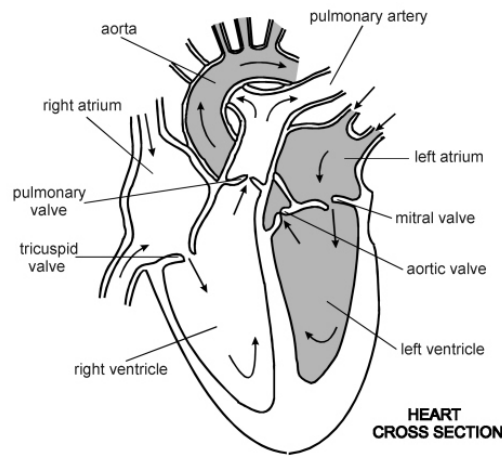


Figure 1: Cross section of the heart, showing the chambers and main blood vessels http://www.patient.co.uk/images/I19_L.JPG

in a pond. However, if it hits an inhomogeneity in the heart wall (for example a region of low conductivity) the wave can break and turn into a spiral wave. It is the behaviour of such spiral waves in the walls of the heart chambers that we will model. It has been known for a long time that the geometry of the chambers affects the propagation of a spiral wave through them. By investigating simple geometries it is possible to glean some understanding of the affect that geometry has on the dynamics of a spiral wave in general [7]Section I.

If there is irregularity in this electrical activity in the heart it is known as arrhythmia. One form of arrhythmia is when there is abnormality in the propagation of electric waves through the walls of the ventricles, causing them to fibrillate instead of contracting. This is know as ventricular fibrillation (VF) and can be fatal. For scientists to understand the behaviour of spiral waves in the heart wall is crucial, as their formation and break up are known to be leading causes of many dangerous cardiac arrhythmias, including VF.

The heart wall itself is composed of various different types of tissue, namely atrial and ventricular muscle, excitatory tissue and muscular fibres [9]P11. The muscle tissue consists of cells called myocytes, which can be thought of as long and thin cylinders that cause the tissue to have a fibrous nature. A wave of excitation travels faster along these muscle fibres than across them, contributing to the fact that the wall of the heart is anisotropic [2]P3-6.

When considering a wave propagating on a 2 dimensional domain, this is one of the two main factors affecting its behaviour, thus it is a crucial consideration when modelling. The other factor that affects the behaviour of the wave is the curvature of the wave front. This is the front edge of the wave of excitation as it travels through the tissue. A concave wave front travels faster than a convex one [2]P3-6. Therefore curvature of the 2 dimensional domain is potentially also an important consideration.

Apart from the shape of the chambers, the surface of each chamber is also pierced by several holes where blood vessels and valves facilitate the flow of blood through the heart [9]P8. Therefore another aspect of geometry that we can

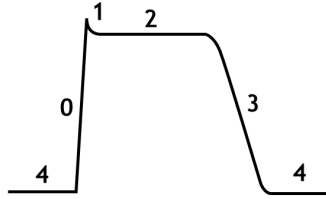


Figure 2: The cardiac action potential: At (0) the potential difference jumps from the resting state (4) into the excited state (1,2) after some time the recovery period (3) begins. www.wikidoc.org/images/f/fd/Action_potential.png

consider is simple connectedness of the domain on which the wave propagates.

Now we will briefly explain some of the biology/physics that underpins the model we have chosen to focus on .

1.2 Mathematical model of cardiac tissue

To pump blood through the body the muscular walls of the heart contract and expand. This movement could be described as a coordinated contraction of many heart muscle cells. Each one of these cells can change its length by up to 20 %.

The action potential at a cell

The contraction of the muscle cell is initiated by the arrival of an “action potential”. Experimentally one can detect the arrival of the action potential by measuring the potential difference between the interior and the exterior of the cell membrane.

This potential difference is caused by a difference in concentration of ions, such as Na^+ and K^+ , inside and outside of the membrane at certain regions in the membrane. But this potential does not remain constant in any one region on the membrane at any one time. It is dynamic, as the membrane locally allows ions to flow in or out of the cell. This exchange process is governed by a law which makes sure that the initial concentration difference travels along the cell membrane.

Typically the dynamic of the action potential at a specific point on the cell membrane looks like figure 1.2. A initial difference of the current inside and outside of the cell membrane leads to an exchange process which increases the potential difference across the membrane. Once it has reached a certain level, the difference decays again.

The behaviour of the cell membrane is similar to a wild range of different things like, a fire moving through a forest or some chemical systems. These objects or systems are called **excitable**. A system is excitable if,

1. it could be found in following two states: resting state, excited state.

2. there is a threshold value for a variable in the system, and after this variable exceeds this threshold value, the system changes its state from resting state to excited state.
3. there is a recovery period after the system has been in an excited state.

(see [15] chapter 1.10)

The FitzHugh–Nagumo model is one of the simplest models that describes the behaviour of such a system:

$$\dot{V} = V(1 - V)(V - e) - g \quad (1)$$

$$\dot{g} = \epsilon(ke - g) \quad (2)$$

where V is the observed variable and g is a helping variable (see [15]).

The tissue

The action potential can now not only travel along one cell membrane but also from one cell to the other.

Instead of modelling the muscle tissue by taking into account all properties of a single cell and the mechanism of how the single cells are coupled, the model used here takes a macroscopic view.

This ansatz is analog to the idea behind continuum mechanics, where one ignores the fact that any material consist of atoms.

It is assumed that each infinitesimal point of the tissue consists of a part which is inside a cell and another part which is outside a cell. So that at each point of the tissue a potential difference V can be observed.

The following equation is used as a generic model of the movement of an action potential through the muscle tissue:

$$\nabla \cdot (D\nabla V) = C_m \frac{\partial V}{\partial t} + I_m \quad (3)$$

In chapter 12.3.3 of [6] the author has explained how the equation is derived from the so called Bidomain model, through some simplification.

The variable I_m represents the trans-membrane current. The term $\nabla \cdot (D\nabla V)$ models the coupling of the muscle cells. A more specific explanation of these two terms is given in the next subsections.

So the model with $D = 0$ should capture most of the behaviour which could be observed for a isolated cell. Or in other words the I_m term must reproduce the action potential. There are models which choose I_m in order that it reflects the changes of concentration of all relevant ions along an membrane. But as written earlier, a carefully chosen FitzHugh–Nagumo-type model can reproduce the action potential with acceptable accuracy, even though it does not take into account the behaviour of different types of ions. A example of such a model is the one which was developed in [1]:

$$\frac{\partial V}{\partial t} = \nabla \cdot (D\nabla u) - kV(V - a)(V - 1) - rV + I_s \quad (4)$$

$$\frac{\partial r}{\partial t} = \left(\varepsilon + \frac{\mu_1 r}{\mu_2 + V} \right) (-r - kV(V - b - 1)) \quad (5)$$

The parameters a , ε , μ_1 and μ_2 are chosen so that the equations reproduce the action potential. The main ideas of the model are summarised in [10].

If one chooses D to be the identity operator then $\nabla \cdot (D\nabla V)$ is the Laplace operator. If one additionally sets I_m to zero the equation becomes the well known heat equation, which describes the propagation of heat through a body. For a body which is initially heated at one point the maximal temperature of the whole body decays until the heat is equally distributed. But with the I_m term in the FitzHugh–Nagumo-type model a fundamentally different behaviour is observed. This is because, after the cell membrane is excited the action potential at this place will go to its maximum autonomously.

One can choose D so that the diffusion has a preferred direction. For the heart it is suitable to choose D in a way which incorporates the direction of the muscle fibres.

Stress in the Heart

As said earlier, the arrival of the action potential causes the muscle cell to contract. The contraction of muscle cells leads to a deformation of the heart tissue, so the heart tissue is under stress. The action potential travels through areas of contracted muscle tissue differently than it does in relaxed tissue. A detailed justification why to include a coupling between the action potential and the contraction, and how the biology behind this coupling works, can be found in the first paragraph of [11].

Mathematical setting: Stress appears in a deformed material. To model this stress mathematically, a reference state of the material is defined. This is a set \mathcal{S} of points in \mathbb{R}^3 . The shape of the material at time t is given by the map $T(t, \mathcal{S})$. One possible measure for stress at a material point is the **right Cauchy-Green deformation tensor** \mathbf{C} which can be defined as,

$$C := F^T F \tag{6}$$

where F is the scale factor from the reference coordinates dX to the deformed material coordinates dx ie.

$$dx = FdX. \tag{7}$$

. To illustrate this equation think of a long thin body which could be modelled by an line. In this case dX is a small part part of the line at point X . During the deformation of body, the length of the infinitesimal element is changed from dX to dx . So F and C measures this local stretching.

Generic Equation: For the modelling of the propagation of the action potential through the heart, the following equation can be used as a generic equation.

$$\nabla \cdot (D(C)\nabla V) = C_m(C) \frac{\partial V}{\partial t} + I_m(C) \tag{8}$$

The equation is basically the same as 3. The difference is the dependence of the parameters on C , where C could be any measure for stress, for example the right Cauchy-Green deformation tensor.

Possible application of the generic equation: With this generic equation the following question could be formulated: Assume the movement of the heart is given by the map T , how does the action potential move? There are generally two ways to change the generic equation in order to answer this:

The first way, is to specify a map $T(t, \mathcal{S})$ and adapt the equation 8 on all the successive states of the deformed body according to this map. Consequently, the domain of the equations then changes over time.

The second way, is to map the time dependent domains back to the reference domain and then define the equations on this fixed reference domain. The equations must now be rewritten in terms of this backwards mapping. This approach was taken in [10] in the setting of a full mechano-electric and electro-mechanic coupling.

If one adds an equation which models the effect the action potential has on the deformation of the heart tissue, the model gets more complex, since a coupling of the mechanics and electronics of the heart is needed. The following equations were derived in [10].

$$\frac{\partial V}{\partial t} = \frac{1}{\sqrt{C}} \frac{\partial}{\partial X^M} \left(\sqrt{C} D_N^M C^{NL} \frac{\partial V}{\partial X^L} \right) - kV(V-a)(V-1) - rV + I_s \quad (9)$$

$$\frac{\partial r}{\partial t} = \left(\epsilon + \frac{\mu_1 r}{\mu_2 + V} \right) (-r - kV(V-b-1)) \quad (10)$$

$$\frac{\partial T_a}{\partial t} = \epsilon(V) (k_{T_a} V - T_a) \quad (11)$$

The quantities C , C^{NL} and T_a are dependent on one and another, qualitatively they model all the stress of the material at a specific point.

$$\epsilon(V) = \begin{cases} \epsilon_0 & \text{for } V < 0.05 \\ 10\epsilon_0 & \text{for } V \geq 0.05 \end{cases} \quad (12)$$

For the details of how these new equations were derived see [10]P6. To understand the derivation a good background in continuum mechanics is required. Generally it could be said such a model can be very difficult to simulate. Since, as we run the model, both the contraction of the domain and the motion of the action potential affect one another.

1.3 Spiral and scroll waves and ventricular arrhythmias.

Spiral and scroll waves are one of the most common patterns closely studied in excitable media. They are governed by many factors, like the excitability of the media, spatial inhomogeneity (heterogeneity) and the geometry. One motivation to study such waves is to understand the role that they play in ventricular fibrillation (VF) mentioned in the introduction. Ventricular tachycardia (VT), an abnormal rapid heart beat is organised by a rotating spiral wave and the break up of this spiral wave are considered the most likely mechanism leading to VT. Therefore, one major question is what are the factors that determine the deterioration of VT into VF, or in other words, under what conditions the spiral breakup occurs (see Figure 1.3). In theoretical and modelling research a number of hypotheses have been formulated regarding the mechanism through

which spiral wave break up occurs see [14]. However, the role of the tissue inhomogeneity in the stability of cardiac spiral waves is still being investigated.

Geometry is also very important role in spiral and scroll wave propagation . In the heart, an abnormally large chambers are more susceptible to serious cardiac arrhythmias (VT and VF). Therefore, studying how geometry effect the dynamics of these waves is important.

In general scroll and spiral waves dynamics are specified by the way they drift. Spiral waves rotates around a point in 2D and scroll wave drift in 3D while rotating around filaments. These filament are curves that move in space and time and change in shape. The phase of rotation may vary along the filament causing the scroll wave to twist. The twist of scroll waves and the curvature of its filament are factors of its dynamics in three-dimension. Turbulence in scroll waves, happens when the filaments are bent, increase in length, break up and multiply this is known as scroll wave turbulence (SWT), and this related to spiral wave breakup in 2 dimension. However, (SWT) is a 3D phenomenon that can be observed in systems which show no 2D turbulence behavior (see Figure 1.3).

Its worth mentioning that the evolution of spiral and scroll waves in excitable media with spherical geometry was studied in extensively (see [4], [7]) but these studies did not consider the deformation of the spherical domain.

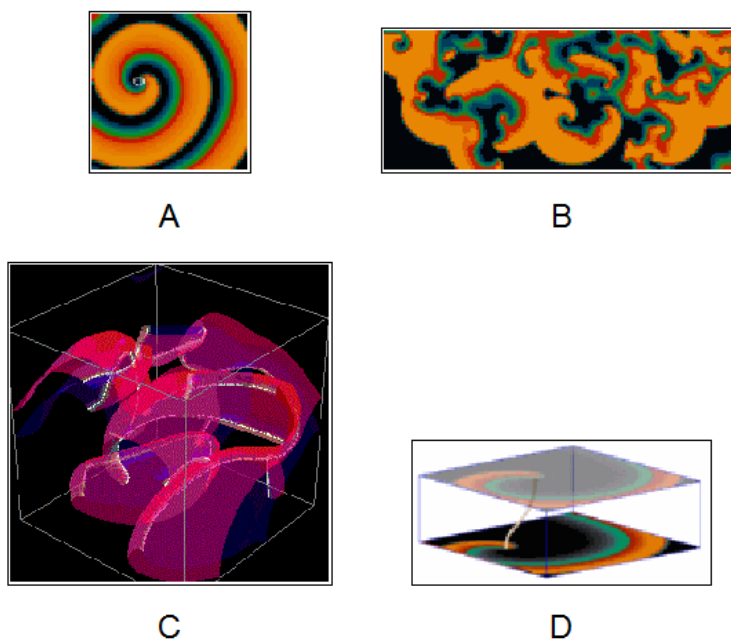


Figure 3: A: Free rotating spiral wave; B: Continuous breaks lead to the formation of multiple spirall; C: Scroll wave turbulence; D Scroll wave.
http://www.scholarpedia.org/article/Cardiac_arrhythmia (A B D),
http://www.scholarpedia.org/article/Scroll_wave_turbulence (C)

2 Research proposal.

This proposal will be presented in four main research aims:

- Research aim one: Model excitable media on moving surfaces.
- Research aim two: Investigate the effect of a moving surface in the propagation of waves.
- Research aim three: Investigate the effect of deforming shells on the dynamics of the waves with and without homogeneities.
- Research aim four: Investigate the effect of holes in the domain on the propagation of spiral waves.
- Research aim four : A coupled model of mechanic and electronic effects.

Due to the nature of these aims, it was more convenient to mention related work and task through literature as we go. Some of the tasks are seen in literature, but were included in the task plan to initiate the flow of achieving the aims above.

The over all purpose of this proposal is meant to be flexible. Since there are many models to consider and new models are constantly being developed. Since we intend for the proposal frame work to be flexible enough to incorporate any model, from here on we will refer to the cardiac excitation model in a more abstract form:

$$\begin{aligned}\frac{\partial u}{\partial t} &= \nabla \cdot (D\nabla u) + R_u(u, r) \\ \frac{\partial r}{\partial t} &= R_r(u, r)\end{aligned}\tag{13}$$

where $u : \Gamma \times [0, T] \rightarrow \mathbb{R}$ is the time dependent cardiac action potential and $r : \Gamma \times [0, T] \rightarrow \mathbb{R}$ is the recovery variable. For this equation a suitable initial condition and boundary condition (depending on Γ) needs to be chosen.

2.1 Research aim one: Modelling excitable media on moving surfaces.

The motivation behind this research aim comes from one of the general assumption of mathematical modelling. When studying the heart system one can separate certain functionality or divide the system into subsystems and study them individually. The main heart function is its contractibility. It is what characterises the cardiac muscle as a pump. However, this contractibility is very complex and this proposal aim is to study it in a generic way.

Task 1 a: Modelling excitable media on a fixed surface.

The objective of this task is to make a start on modelling excitable media on moving surfaces. Considering model (13) in the case that Γ is a fixed compact, smooth connected hyper surface $\Gamma_0 \subset \mathbb{R}^3$. There are several ways to model a reaction-diffusion (RD) equation on Γ_0 (this applies to the two component

excitation model in (13)). One approach is to realise the RD equations on curved surface see [7].

The model (13) will now have this new abstract form,

$$\begin{aligned}\frac{\partial u}{\partial t} &= \nabla_{\Gamma} \cdot (D\nabla_{\Gamma} u) + R_u(u, r) \\ \frac{\partial r}{\partial t} &= R_r(u, r)\end{aligned}\tag{14}$$

Task 1 b: Modelling excitable media on a moving surface.

During the normal cardiac activation and recovery processes, the cardiac geometry undergoes significant deformation. The objective of this section is to model (13) on an arbitrary moving surface. One approach is to utilise the method of evolving surfaces (see [3]). Let $\Gamma(t)$ be a compact connected hyper surface that is moving in time. Then (13), when introducing the surface $\Gamma(t)$, will be in the following abstract form:

$$\begin{aligned}\dot{\partial} u &= \nabla_{\Gamma} \cdot (D\nabla_{\Gamma} u) + R_u(u, r) \\ \dot{\partial} r &= R_v(u, r)\end{aligned}\tag{15}$$

where $\dot{\partial}$ denotes the dot material derivative of the scalar function. A frame work on how to formulate the model is given in [3].

2.2 Research aim two: Investigating the effect of a moving surface on the propagation of waves.

Task 2 a: Simulations on a fixed surface.

Computational simulations can yield a great deal of useful frame work for the theoretical explanation of the heart behaviour. At this stage other simple surfaces can be simulated such as a sphere, ellipsoid (etc.) or any other similar simple surfaces with different curvatures. For example, a simulation can be perfomed when specifying $\Gamma_0 = B_R(0)$ to be sphere of radius R , while changing the surface to an ellipsoid is just a matter of changing its curvature. The choice of the coordinate system is important at this stage. Refer to [4] to see how spherical coordinates were used and the implications and advantages of these coordinates. Cartesian coordinates are of course the other choice. We suggest to discretize the coupled spatiotemporal excitation equation (13) with finite difference scheme in time and a finite element scheme in space [8]. Then study how does the spiral wave propagate through the surface of the sphere. Similar simulations can be seen in [4], [7] where regular and random distribution of the spiral wave was initiated on the sphere surface, it was also been noticed that the radius of the sphere plays an important role in the spiral density.

Task 2 b: Simulations on a deforming surface.

Using the work done in task 1 b, we intend to preform computational simulations on a moving surface for example,

$$\Gamma(t) = B_{R(t)}(0).$$

At this stage one can model the motion of the whole surface, for example $R(t) = R + r_0 \sin(t)$, where R is the radius of the original sphere and the constant r_0 influence the oscillating motion generated by $\sin t$ as time progress. Then observe how does that deformation influence the spiral waves moving through the sphere surface. And testing this in different radius lengths. More complex motions, for example where the deformation moves from the top of the sphere to the bottom, can be considered in order to capture the true deformation of the heart more closely.

2.3 Research aim three: Investigating the effect of deforming shells on the dynamics of the waves with and without homogeneities.

Task 3 a: Simulations on moving shells.

Studying wave dynamics in excitable media on fixed spherical shells can be seen in [4], [7]. These studies described the way scroll waves (3D version of spiral waves) propagated in different sizes of shell thickness. The objective of this section is motivated by the role that scrolls and filaments play in ventricular fibrillation (VF). Computational simulations of fibrillation in an generic setting will yield a great deal of useful data of heart behaviour. The difference between simulations done over shells and surfaces is that surfaces do not require any boundary conditions. In this stage its important to identify two things:

- The effect of the motion on the spherical shell boundaries, i.e. does the inner radius of the shell deform or is it fixed.
- It has to be specified how the waves behave when they reach the two boundaries. This leads to the type of boundary conditions which have to be used.

The filament curve in this case can be observed in different shell thickness and then a comparison of this observation to the results in [4], [7] can be done.

Task 3 b: Simulations on inhomogeneous fixed shells.

The challenging objective of this task, is to study the effect of the inhomogeneous media on the filaments. The thickness of the shell is influences the attachment of the filament on both sides of the boundaries, this was observed in fixed spherical shell [7]. The inhomogeneity of the excitable media may effect the speed with witch a scroll wave propagates and therefore may influence the filament.

2.4 Research aim four: Investigating the effect of inhomogeneities in the propagation of waves.

We have considered how movement and curvature of the domain affects the behaviour of spiral waves. However, there are other important aspects of the geometry of the chambers that could play a significant role, and to understand how spiral waves behave in the walls of the heart chambers, we need to investigate other changes to the domain of the action potential.

Now we want to look at making this domain more realistic. There are several aspects of the geometry of the chambers that we could consider, one of which is the presence of heterogeneities. Thus far we have considered how contraction affects the propagation of spiral waves on simply connected domains. However, the presence of heterogeneities can cause the domain to no longer be simply connected. The wall of the heart can be inhomogeneous for various reasons, some causes are; the presence of scar tissue due to myocardial infarction, genetic disorders, the presence of major blood vessels, connective tissue, cells other than myocytes present in the tissue etc. See [13] for more details and a discussion of simulating these inhomogeneities on a flat domain.

Main research aim: Investigate the effect of inhomogeneities in the heart wall on the propagation of spiral waves.

Inhomogeneities can be roughly divided into two categories; conductive inhomogeneities and ionic inhomogeneities. Conductive inhomogeneities are regions of no conductivity, for example scar tissue or regions where the chambers of the heart are pierced by holes where blood vessels and valves allow blood to pass in and out of them. Ionic inhomogeneities are collections of cells where the conductivity is abnormal due to changes in single cell properties like effectiveness of ion channels, which can be due to chemical or metabolic inconsistencies.

We will again work from the view point of gaining knowledge about certain properties of spiral wave dynamics by simulating them on simplified domains in order to gain insight into the underlying principals that govern the behaviour of the spiral waves. The aim of this being to see whether basic changes in the geometry have a significant effect on the dynamics of a wave.

We suggest that you proceed with the main research aim as follows;

Task 4 a: Investigate the effect of conductive inhomogeneities on the waves.

This has already been studied on a flat 2 dimensional domain by J.I Ramos in [5]. Ramos used the Belousov-Zhabotinski reaction diffusion model and looked at the propagation of a spiral wave in a flat domain, punctured by square holes. He found that when the spiral passed over the region with the hole, it broke into two separate waves. Also, the part of the wave that passed over the hole was slowed down, causing the two wave branches to bend slightly around the hole [5]P5. Another, slightly less relevant to our problem, citation where a hole in the flat domain of the action potential was studied, is the paper by V I Biktashev and others [12]P12 who looked at how the drift of the centre of the spiral wave behaved on a punctured domain.

These things can be investigated on both surfaces and shells. We leave the decision of which to use open. In terms of what to do once this decision is made, we outline a possible approach.

First consider using the same methods as in the first question to simulate the 2 dimensional Aliev and Panfilov model 4 on a simply connected domain like S^2 in order to observe the generic behaviour of the waves on a simply connected domain.

Now simulate the wave on the domain $S^2 - U$ where U is a region of no conductivity. Compare the behaviour of the waves on the different domains when changing for example the size of U , the number of such regions and the

position of these regions with respect to the centre of the spiral wave. Does the propagation of the wave on the punctured sphere have any properties that are significantly different to that on the simply connected domain? How does the behaviour compare to that observed in the paper by Ramos [5]?

Task 4 b: Investigate the effect of ionic inhomogeneities in the domain of the action potential on the behaviour of spiral waves.

We suggest proceeding with this investigation using many of the same steps as in task one, but instead of using regions of no conductivity, vary the conductivity of the regions. See [13] for a discussion on ionic inhomogeneities and simulating them. Compare your results to those of the previous task.

Note that this analysis can be carried out on either a surface or a shell or both. The shell has the obvious advantage of being closer to the geometry of the heart, however the surface will be easier to simulate.

2.5 Research aim five : A coupled model of mechanic and electornic effects.

The above research aims consider only how the movement of the domain affects the behaviour of the action potential. The fact that the arrival of a action potential at a cell causes the contraction of the cell, hence the movement of the domain, was not considered.

In the previous research aims it was necessary to fix the movement of the domain on which the equations modelling the movement of the action potential where defined. In the context of the model, this means that there is a mechanism outside of heart which forces the heart to move in a specific way. However, in reality the heart does not move in this way. A more realistic model should include the fact that the propagation of the action potential has an effect on the movement of the domain.

Main research aim: Include this coupling between the action potential and the contraction of the tissue into a model of excitable media.

Abstractly, the contraction of a heart cell is a locally initiated change which effects the whole form of the tissue. Depending on the chosen model for the heart tissue, the way that these local changes are modelled is not always obvious. For example, for the model where cells are assumed to be infinitesimal points, a change of length of the cells makes no sense. Therefore, one needs to find a way to mathematically model these locally initiated changes. After this is done the effect of the changes on the whole shape of the domain has to be specified.

M Nash and A Panfilov [10] describe one way to do this for a specific model of excitable media. By doning this they have choosen constitutive laws to model proberties of the material the heart consist of. They simulated there derived model on a flat reference domain. Changing the equation for the media, the material or the domain where the simulation is performed on, lead to interesting analytical and numerical tasks. Modelling tasks will involve continuum mechanics and knowledge about elastic mediums.

3 Working Schedule

We propose a rough outline of how the proposal could be carried out.

- We advise starting with the modelling tasks outlined in research aim one. These should take no more than a couple of weeks once the context of the problem is understood and the appropriate models chosen. It is necessary to carry out these tasks before moving on to simulation.
- Once the modelling is done, it will then be possible to move onto simulating the models, as outlined in research aims two and three. We advise starting with aim two because the task of simulating on a shell is significantly more complicated than on a surface, and carrying out the simulation on a surface will. This task will take longer than the modelling tasks, however could be completed in one to two months.
- Next we advise using the code written for aim two, to carry out the analysis outlined in research aim four, which should take no more than two weeks.
- Once some experience has been gained, we advise moving on to simulations on shells. This task is more challenging and could take in the region of two months. Once the simulation is done, carrying out the analysis as outlined in aim four will take no more than two weeks.
- One of the most challenging tasks is outlined in research aim five. This modelling task can be carried out parallel to all the others, as it will require at least the three months allocated to this work.

The above suggestions are one possible outline of how the proposal could be carried out. They are not intended to be restrictive. For example, if simulation on a shell is carried out before simulation on a surface (or parallel to it) this would also work. Note also that the last task may be beyond the scope of what can be achieved in three months, and if not completed could be proposed as further work in this field.

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