

# A Dynamic model of Pulmonary Vein Electrophysiology



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# Background to the Project

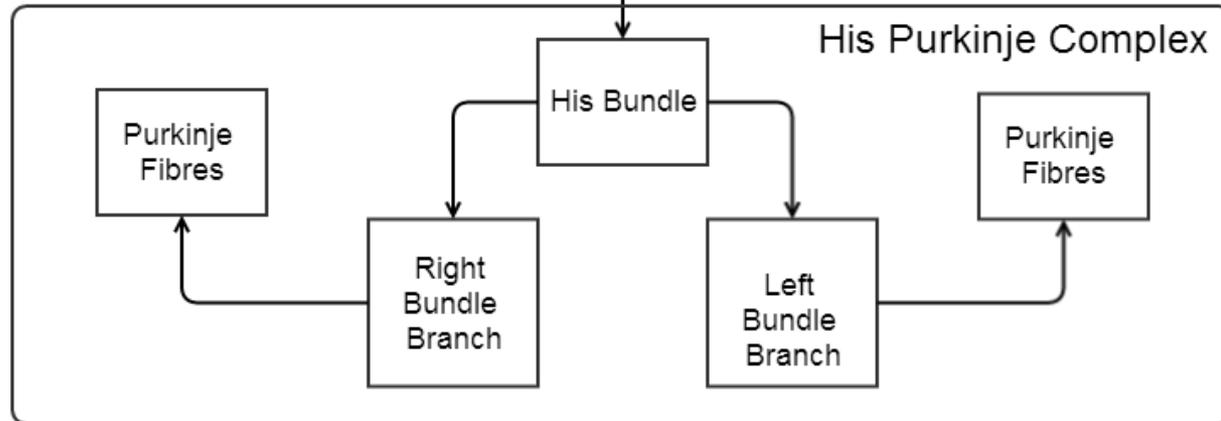
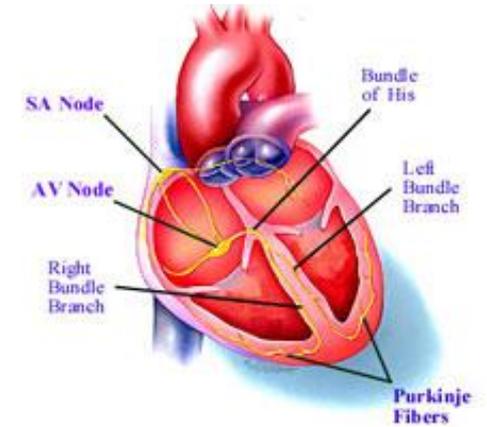
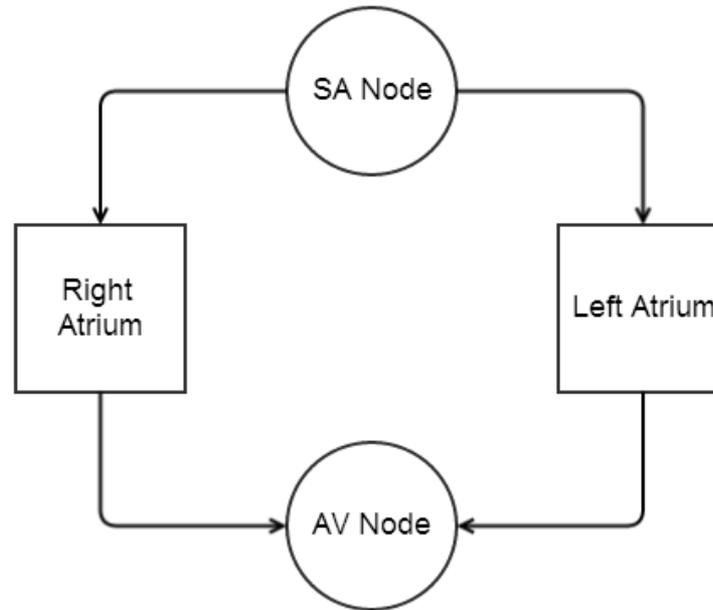
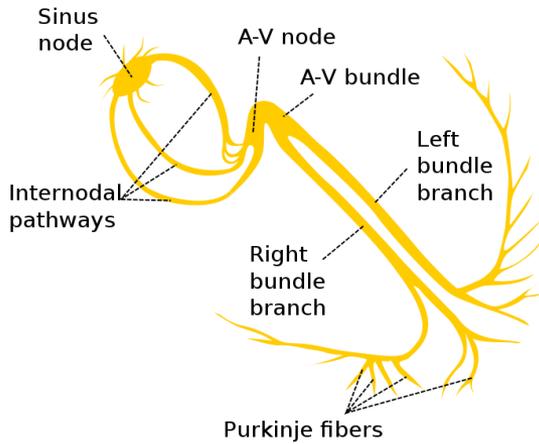


- Cardiac disease is the leading cause of death in most developed countries
- Atrial fibrillation (AF) is the most common type of cardiac arrhythmia, and can lead to stroke, heart failure, and other medical concerns
- The goal of the project is to improve the efficiency of AF treatment using mathematical models

# How the Heart Works

- The heart beats due to an electrical signal propagating through the cardiac muscle
- Starting in the sinoatrial (pacemaker) node, the action potential travels across the atria, then through the atrioventricular node, down the His Purkinje complex, and across the ventricles
- In a healthy heart, the wavefronts form regular shapes and propagate in a regular pattern

# Conduction System of the Heart

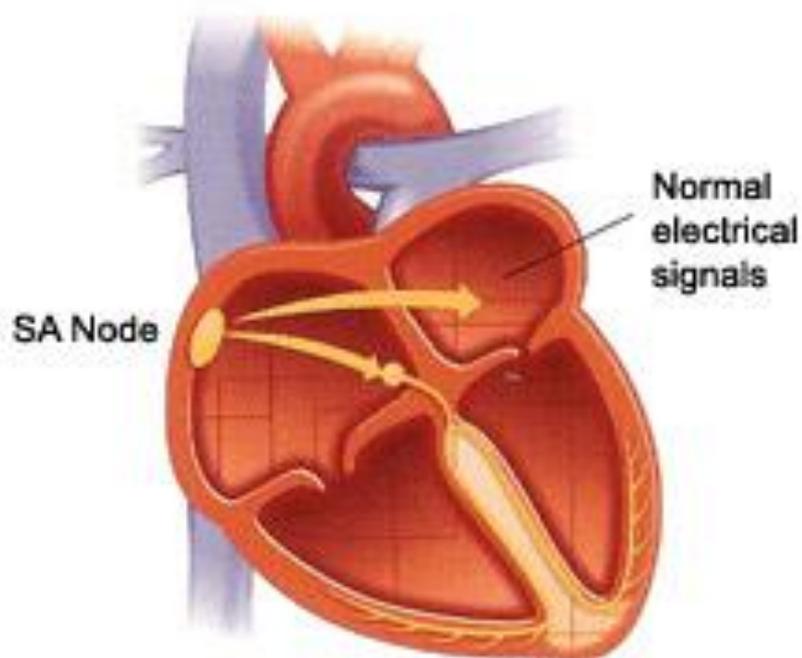


# Atrial Fibrillation

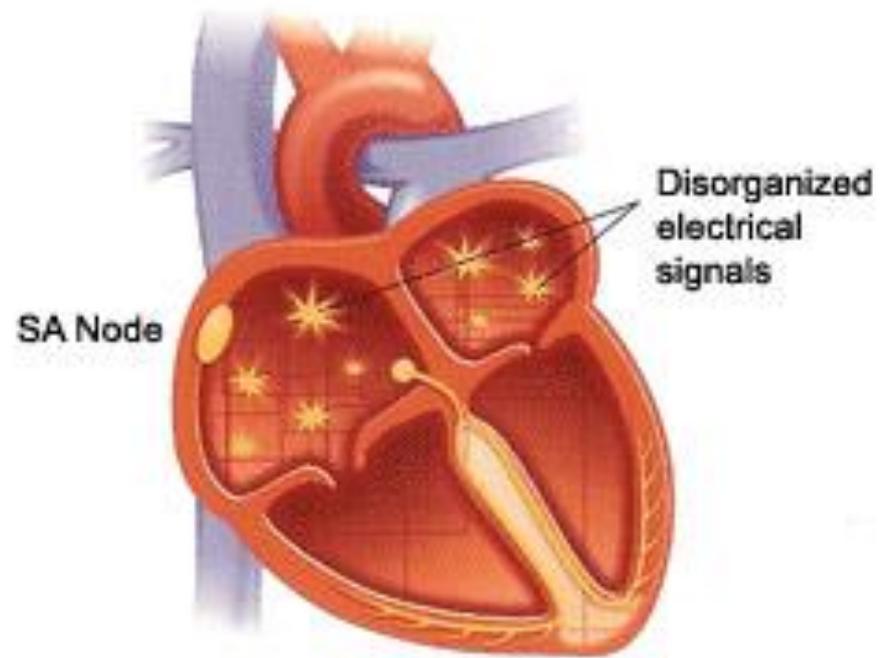
- During atrial fibrillation, the electrical propagation in the atrium is irregular
- Most frequently, this occurs in the left atrium when myocardial sleeves around the base of the pulmonary veins send out ectopic beats that compete with the sinoatrial node
- The ectopic beats are typically faster and dominate the sinoatrial node, sending the atrium into a state of disorder
- This increases the strain on the AV node

# Atrial Fibrillation

Normal conduction



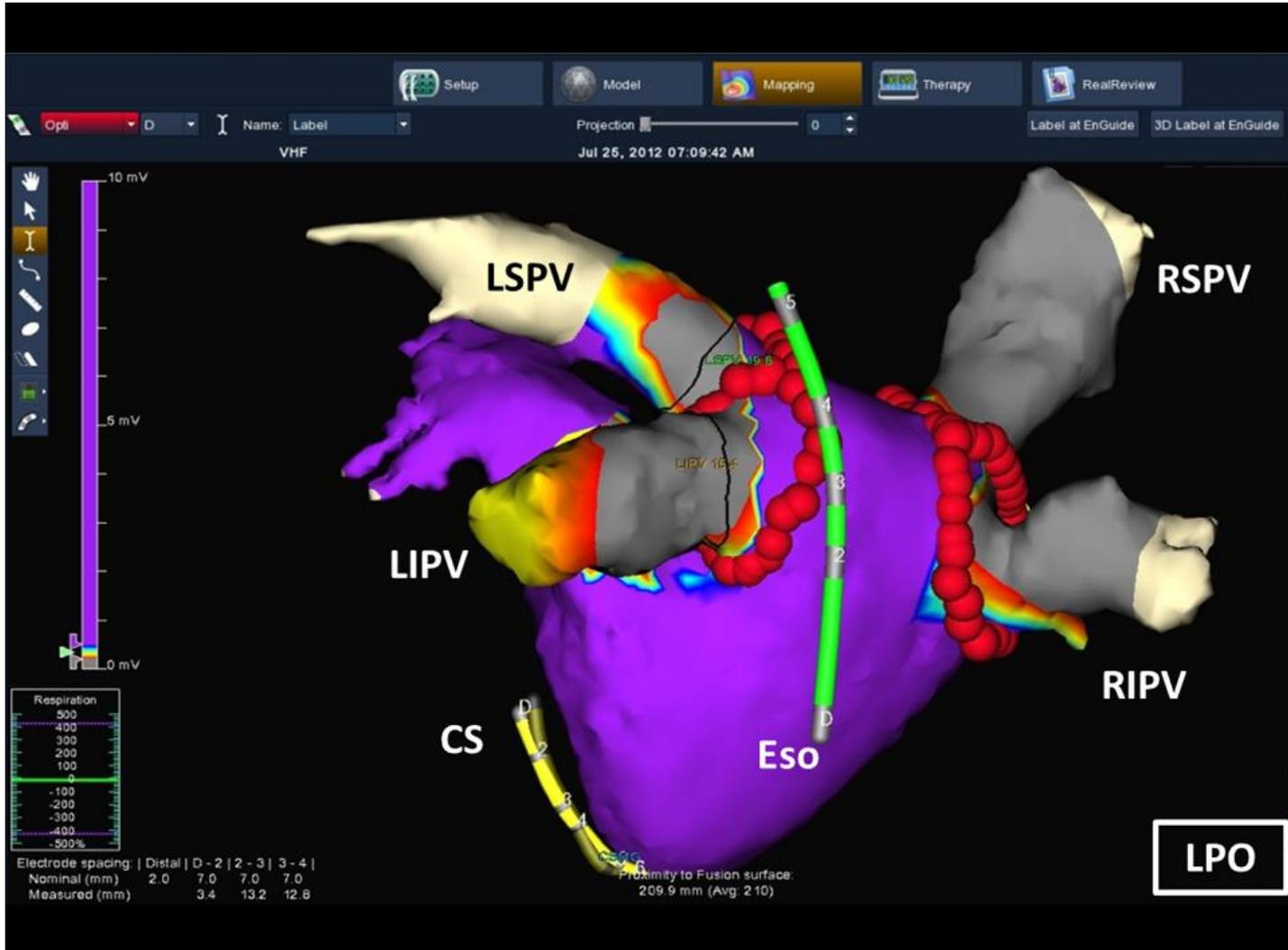
Atrial fibrillation



# Radiofrequency Ablation

- AF can be treated by directing radiofrequency energy to burn small areas of heart tissue on the pulmonary vein
- This electrically isolates the target area, and the action potential cannot pass through it
- Electrical isolation of the pulmonary veins prevents them from disrupting the rest of the atria

# Radiofrequency Ablation



# The Surgical Problem

- Radiofrequency ablation requires a catheter to be literally dragged across the surface of the heart and is rarely a clean procedure
- There are often conduction gaps remaining in the tissue, where the action potential can pass into the atrium, and the ablated tissue can become *pro-arrhythmic*
- Ensuring full electrical isolation requires the detection and ablation of these conduction gaps

# Models of Excitable Media



- Mathematical formulations of excitable media (such as the tissue in the PVs and atria) are of important interest in applied mathematics
- Cardiac models of excitable media range from phenomenological (a spike that moves) to biophysical (a biologically detailed model built on ionic currents)

# Relation to Surgery

- While there has been a lot of research done on cardiac excitable media models, very few people relate models to surgical treatment
- In this project we aim to address that gap by focusing on keeping the work relevant to the clinical procedure through our collaboration with the Bristol Heart Institute and L'Institut de RYthmologie et Modélisation Cardiaque ( LIRYMC Bordeaux)
- We hope to develop models for the signals that heart surgeons actually use and, eventually, to be able to predict the effect of radiofrequency ablation therapy

# Fitzhugh-Nagumo

- Fitzhugh-Nagumo is the simplest example of an excitable media model, given by

$$\begin{aligned}\dot{v} &= a \left( v - \frac{v^3}{3} - w \right) + I_{\text{ext}} \\ \dot{w} &= \mu(v + \beta - \gamma w).\end{aligned}$$

- Application of an external stimulus  $I_{\text{ext}}$  creates an excursion in phase space that returns back to the equilibrium
- Coupling these together allows a travelling wave solution

# Choosing the Right Model

- The complexity of existing models range from simple 2 variable phenomenological models of FitzHugh Nagumo complexity to very large systems of biophysical equations
- More coupled ODEs lead to higher computation time, and for some of the more complex models, '6 hours per cardiac cycle' was considered efficient
- As we aim to produce something that is of use in real time, in the operating theatre, during heart surgery, we use phenomenological models

# Biophysical Models

- Biophysical models are attractive because they are rich in biological detail and mathematical properties
- Typically, a high dimensional ODE representing a cell (or cluster of cells) is coupled on a grid (or mesh) representing the heart
- The action potential takes the form of a spike which travels across the domain
- <http://ajpheart.physiology.org/content/ajpheart/275/1/H301.full.pdf>

# Complexity

- Biophysical models are often extremely complex, with a large amount of parameters, functional parameters and dimensions
- The most detailed models reach hundreds of parameters and 40 – 60 dynamic variables
- For this reason, they resist analytical approaches, and there is little that can be done beyond simulation
- It is also very difficult to adapt the model as it is difficult to understand the effect a parameter change may have

# Bueno-Orovio Cherry Fenton

- The Bueno-Orovio Cherry Fenton (BOCF) model relies on four main quantities, the voltage,  $u$ , and 3 other non-physical variables
- The model has been shown to accurately reproduce the spike and dome action potential morphology of the ventricles, as well as the correct restitution curve
- When spatially extended, the BOCF model can produce reentrant (spiral) waves of the kind seen in fibrillation and tachycardia

# Bueno-Orovio Cherry Fenton

$$\partial_t u = \nabla(\tilde{D}\nabla u) - (J_{fi} + J_{so} + J_{si})$$

$$\partial_t v = (1 - H(u - \theta_v))(v_\infty - v)/\tau_v^+ - H(u - \theta_v)v/\tau_v^+$$

$$\partial_t w = (1 - H(u - \theta_w))(w_\infty - w)/\tau_w^+ - H(u - \theta_w)w/\tau_w^+$$

$$\partial_t s = ((1 + \tanh(k_s(u - u_s)))/2 - s)/\tau_s,$$

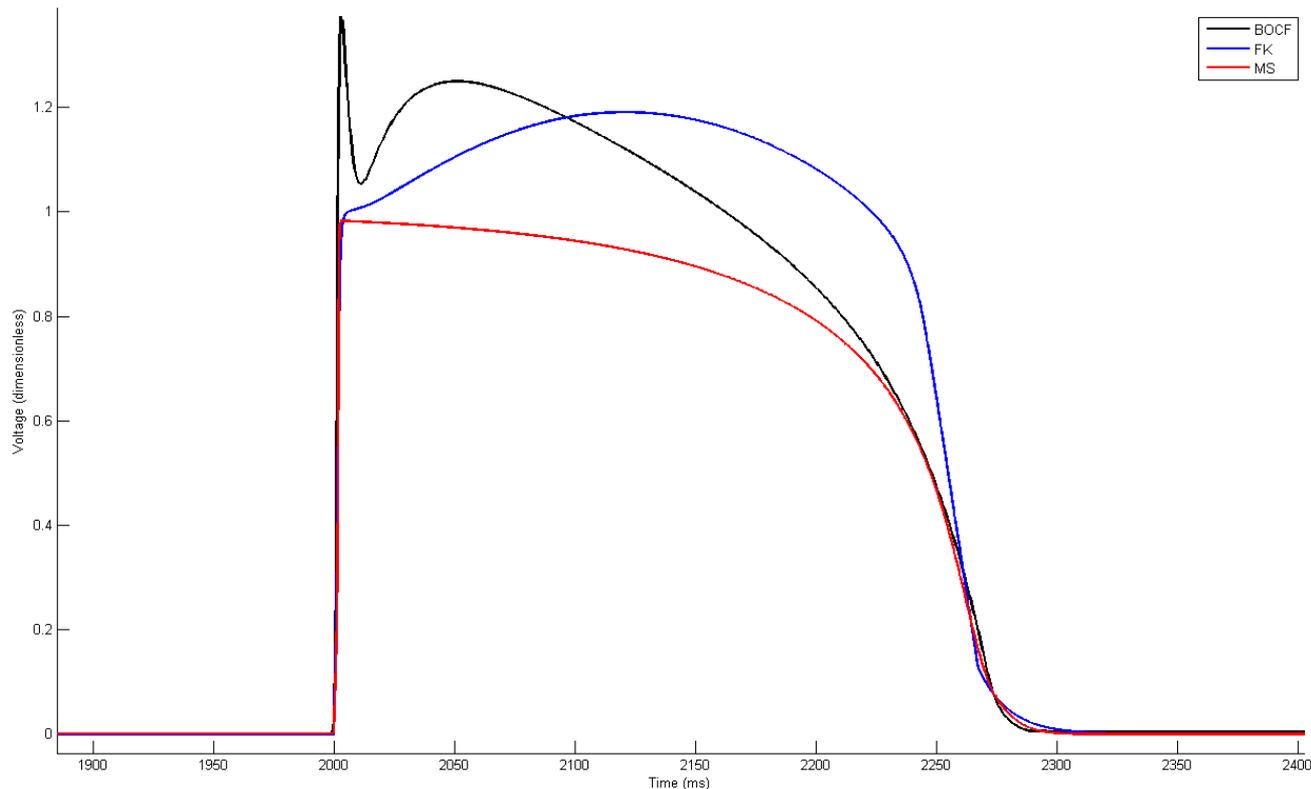
$$J_{fi} = -vH(u - \theta_v)(u - \theta_v)(u_u - u)/\tau_{fi}$$

$$J_{so} = (u - u_o)(1 - H(u - \theta_w))\tau_o + H(u - \theta_w)/\tau_{so}$$

$$J_{si} = -H(u - \theta_w)ws/\tau_{si}.$$

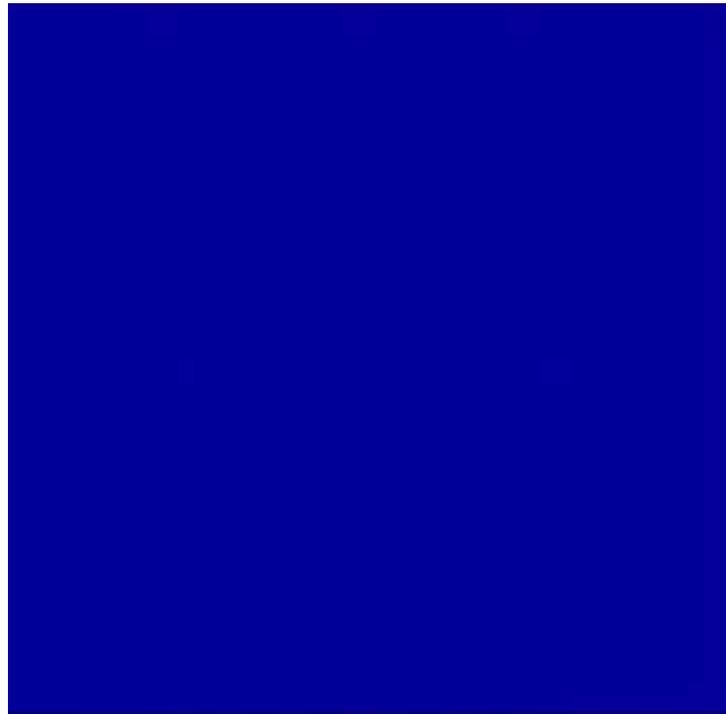
# Action Potential Dynamics

- These single cell action potentials are from the default parameters of three phenomenological cardiac models



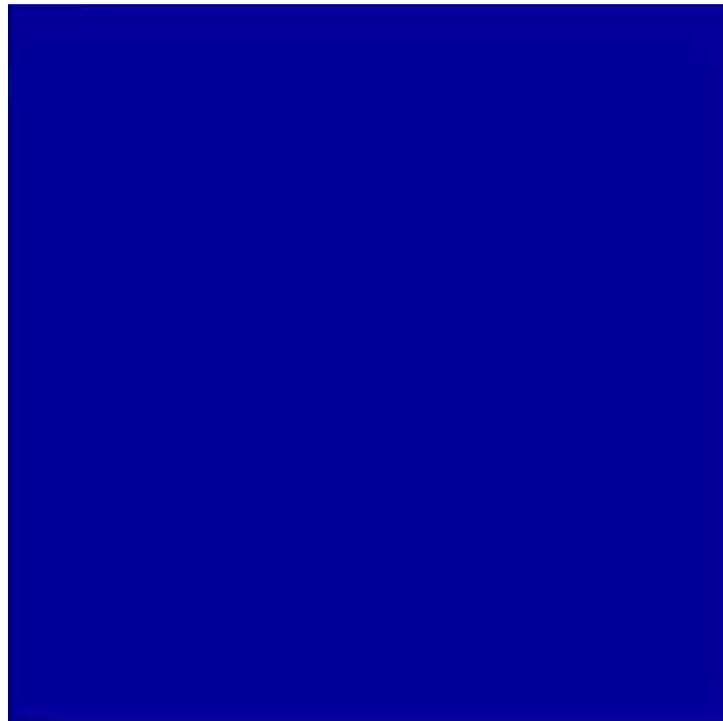
# Diffusive Coupling

- To model the spread of an action potential, a diffusive coupling scheme is used to spatially extend the ODE



# Spiral Waves and Breakup

- We can initiate a wavebreak to send the region of heart tissue into tachycardia (spiral waves) and fibrillation (disorder). The below simulation is from the BOCF model



# Modelling the Pulmonary Vein



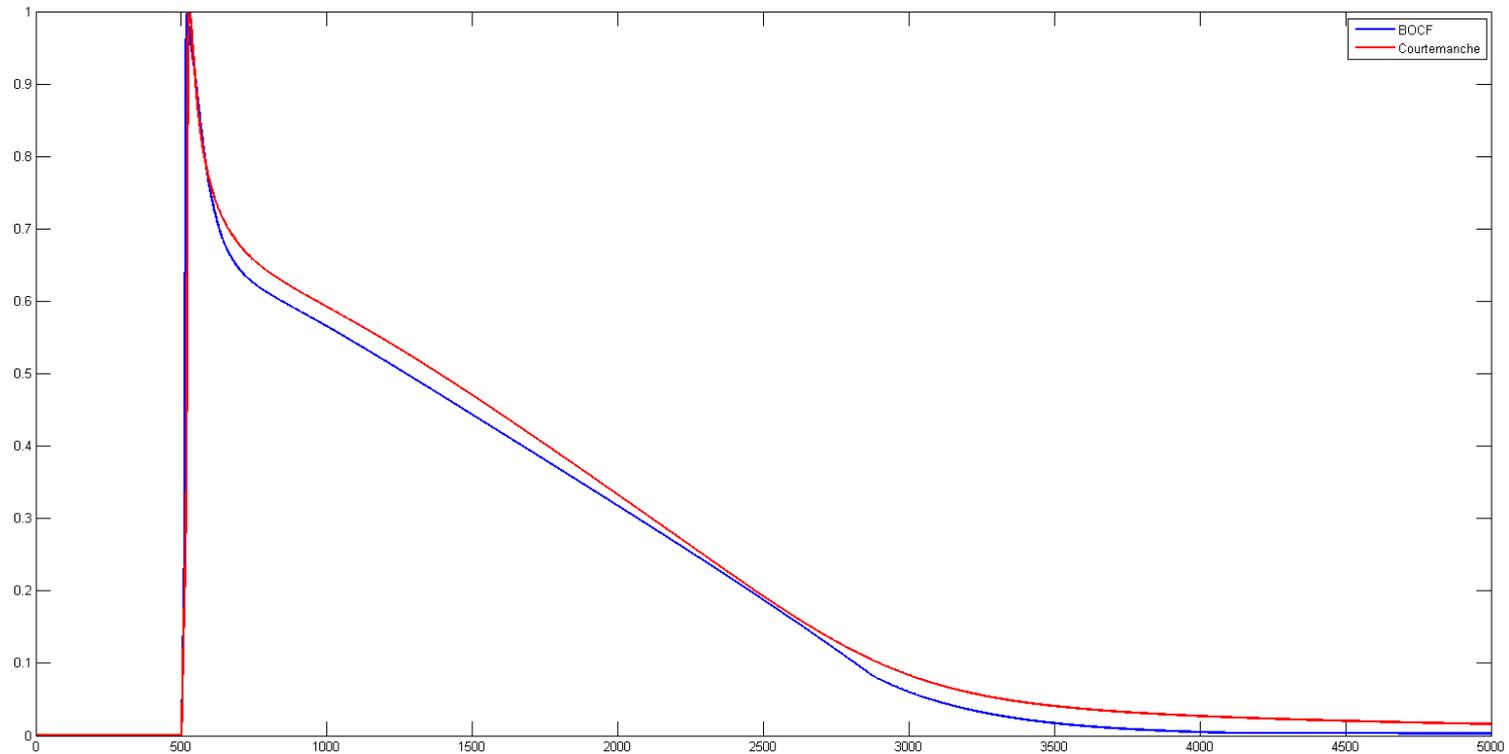
- We model the roughly cylindrical section of excitable tissue where the atrial tissue extends over the base of the pulmonary vein
- Our approach is to use the BOCF model with periodic boundary conditions

# Parameter Fitting

- We first need better BOCF parameters, as the BOCF model was built for the ventricular action potential
- After AF, the electrophysiological properties of the tissue is changed in a process known as electrical remodeling
- There exists a biophysical model for the atrial action potential that has been fit to the action potentials of remodeled cells (Courtemanche 1999).
- We use this model as a proxy for real data, and fit the BOCF model to it using a standard minimisation algorithm

# Parameter Fitting

- The action potential morphology, upstroke velocity and duration all fit quite well to the Courtemanche model

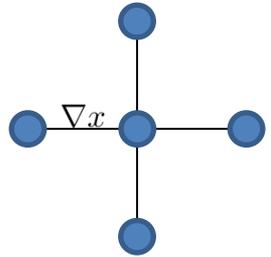


# Spatial Discretisation

- The sleeves that we are concerned with are roughly 12.5 mm in diameter, and 14.8 mm in length
- Solving this equation numerically requires a discretisation of this cylinder. We take a spatial resolution ( $\nabla x$ ) of 0.2 mm, giving us a 196 x 74 grid (approximated to 200 x 75)
- To allow for a non homogenous conduction velocity, we define a 200x75 matrix  $D_{i,j}$ , giving us control of the coupling strength between grid points
- To model ablated points, we create electrical isolation by setting  $D_{i,j} = 0$

# Spatial Discretisation

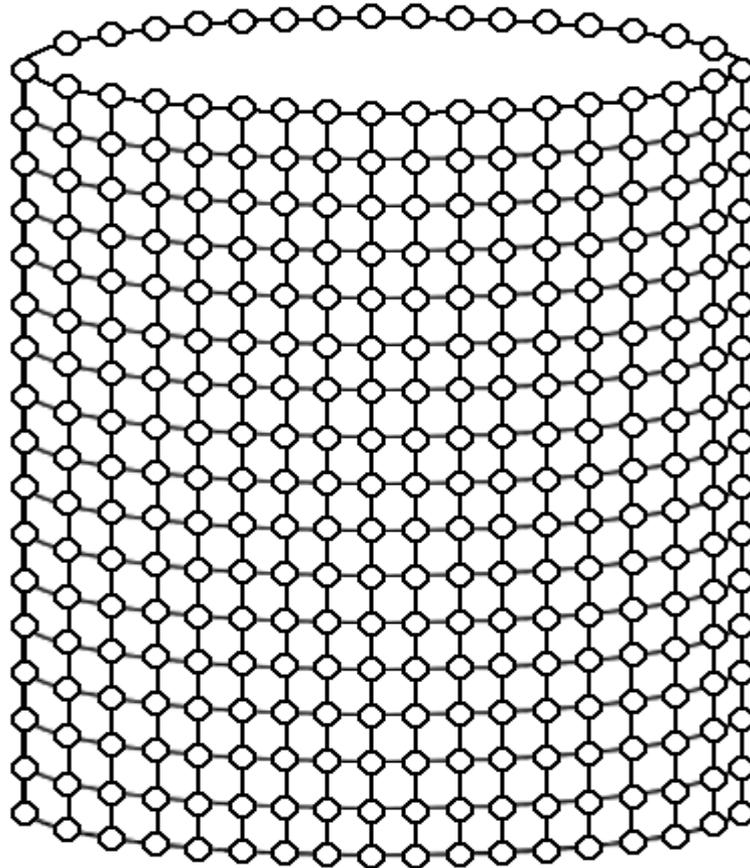
- Presently, we are using a 5 point stencil to compute the diffusion term, so the  $\partial_t u$  equation of the BOCF model becomes

$$\partial_t u_{i,j} = -(J_{fi} + J_{so} + J_{si}) + \dots$$

$$\frac{D_{i,j}}{(\nabla x)^2} (u_{i-1,j} + u_{i+1,j} + u_{i,j-1} + u_{i,j+1} - 4u_{i,j})$$

- This may be changed to a 9 point stencil if anisotropic diffusion becomes an important factor

# Periodic Boundary Conditions

- Using a periodic boundary condition we can roll our domain back into a cylinder



# Extracellular Voltage

- The voltage  $u$  so far has been the voltage in each cell, the intracellular voltage. In the operating theatre, it is only possible to measure the voltage on the surface extracellular voltage
- There are many transformations from intracellular to extracellular voltage, we pick the simplest, an integral across the whole domain that depends on the spatial gradient of  $u$

# Extracellular Voltage

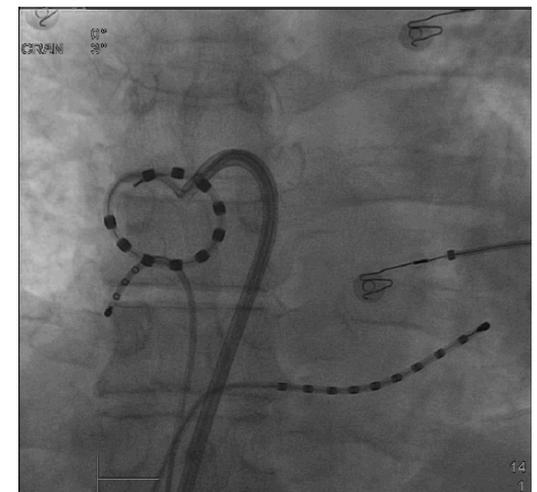
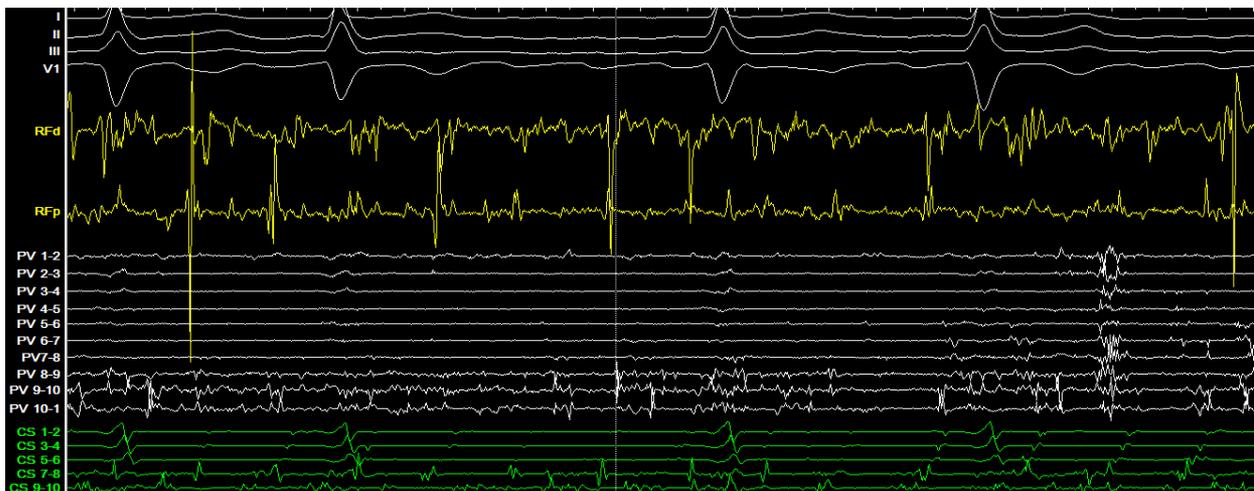
- Extracellular voltage at  $(x', y')$  is given by

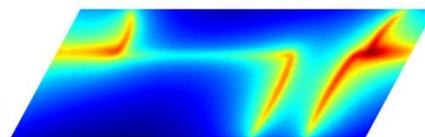
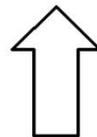
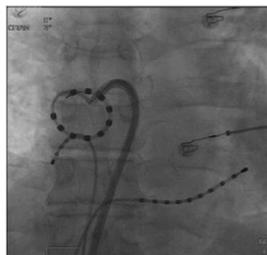
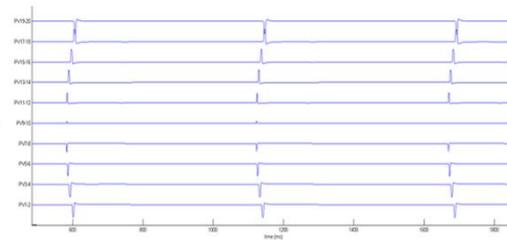
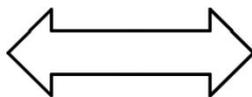
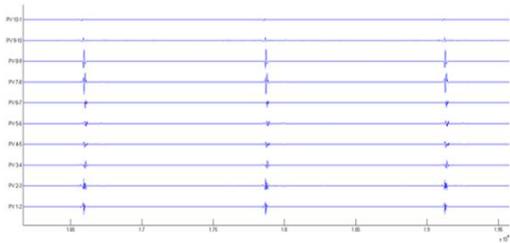
$$\Phi(x', y') = aD(x', y') \int (-\nabla u(x, y)) \left( \frac{1}{r} \right) dx$$

- Where  $r = \sqrt{(x - x')^2 + (y - y')^2}$  and  $a$  is a constant depending on physical characteristics

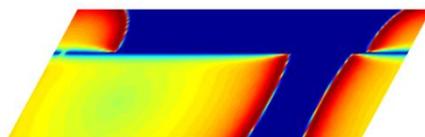
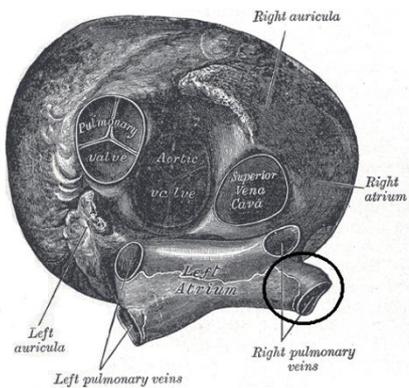
# Pulmonary Vein Recordings

- The main signal used clinically are taken by a lasso catheter situated inside the pulmonary vein
- The potential difference between electrodes is used to identify the earliest spiking time, which is the site closest to the conduction gap

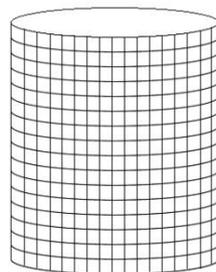
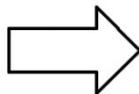




$$\Phi = a \int D(-\nabla u) \frac{1}{r} dx$$



$$\partial_t u = \nabla(\tilde{D}\nabla u) - (J_{fi} + J_{so} + J_{si})$$



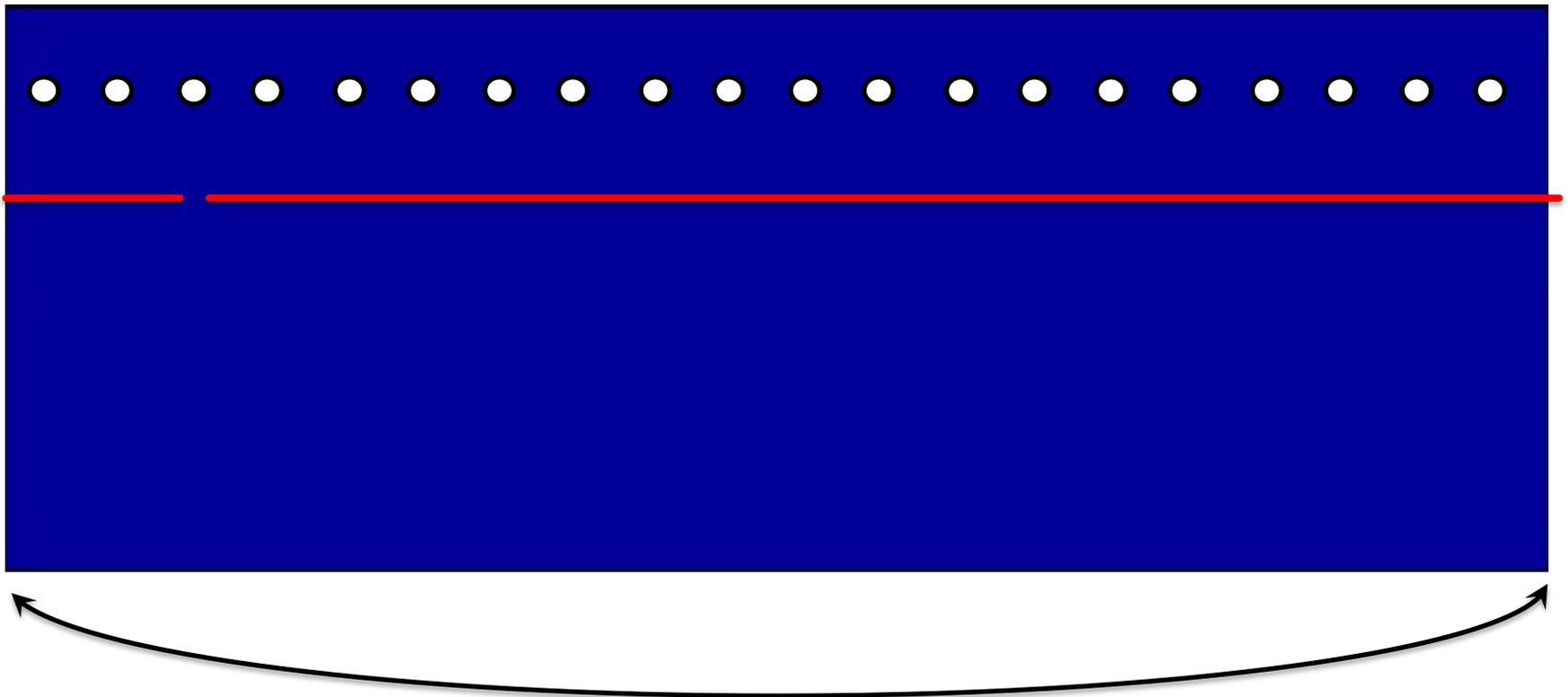
# Results



- The results we have are still preliminary as data has only recently been collected and the model is undergoing changes
- We have integrated our model over the cylindrical domain and produced realistic synthetic PV signals

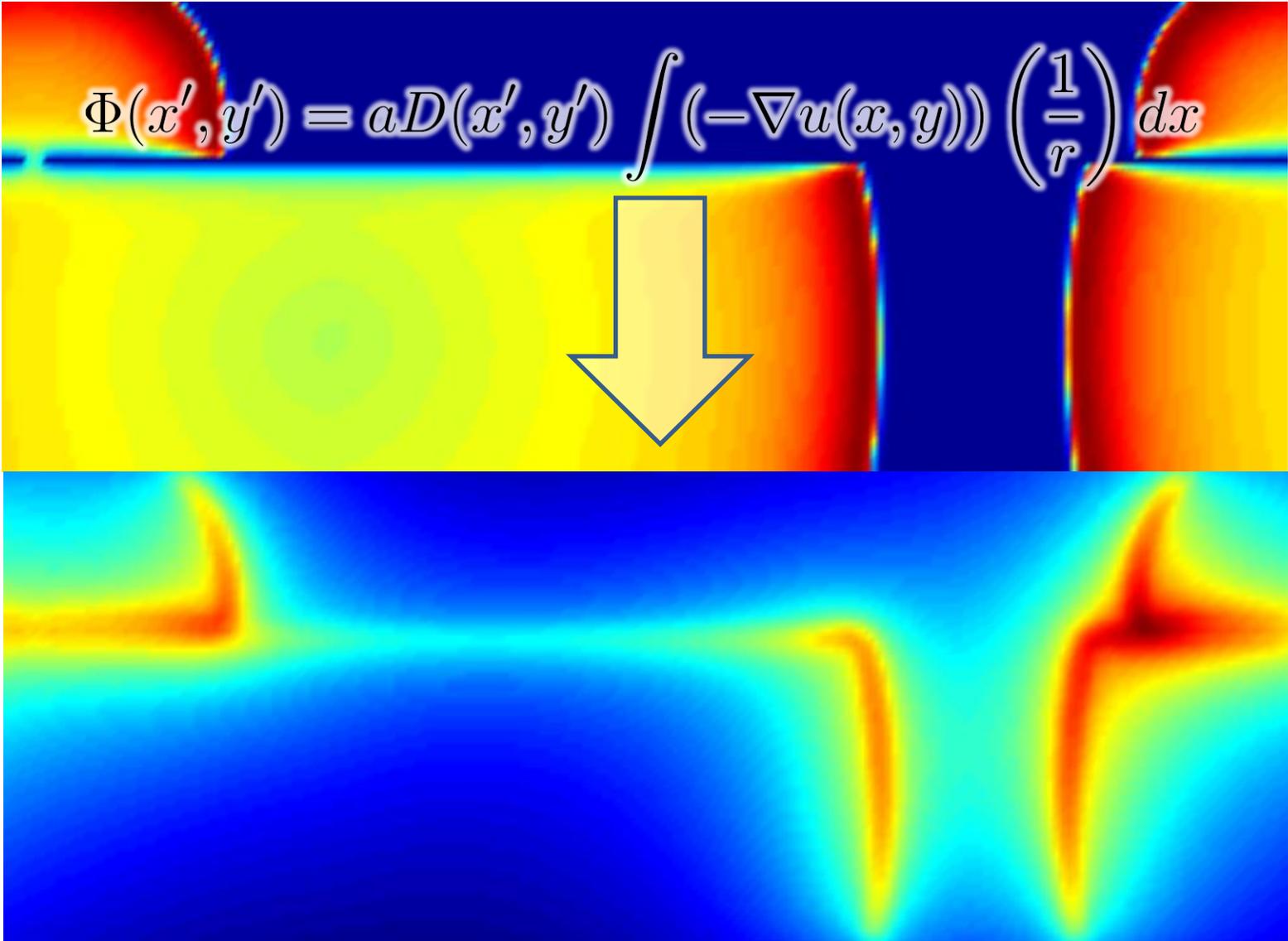
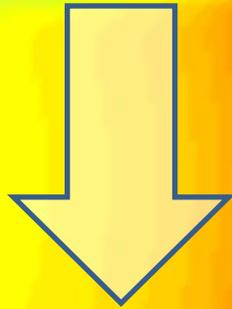
# Intracellular Potential Propagation

- This video shows the intracellular potential propagating through a conduction gap in ablated pulmonary vein tissue



# Extracellular Potential Transformation

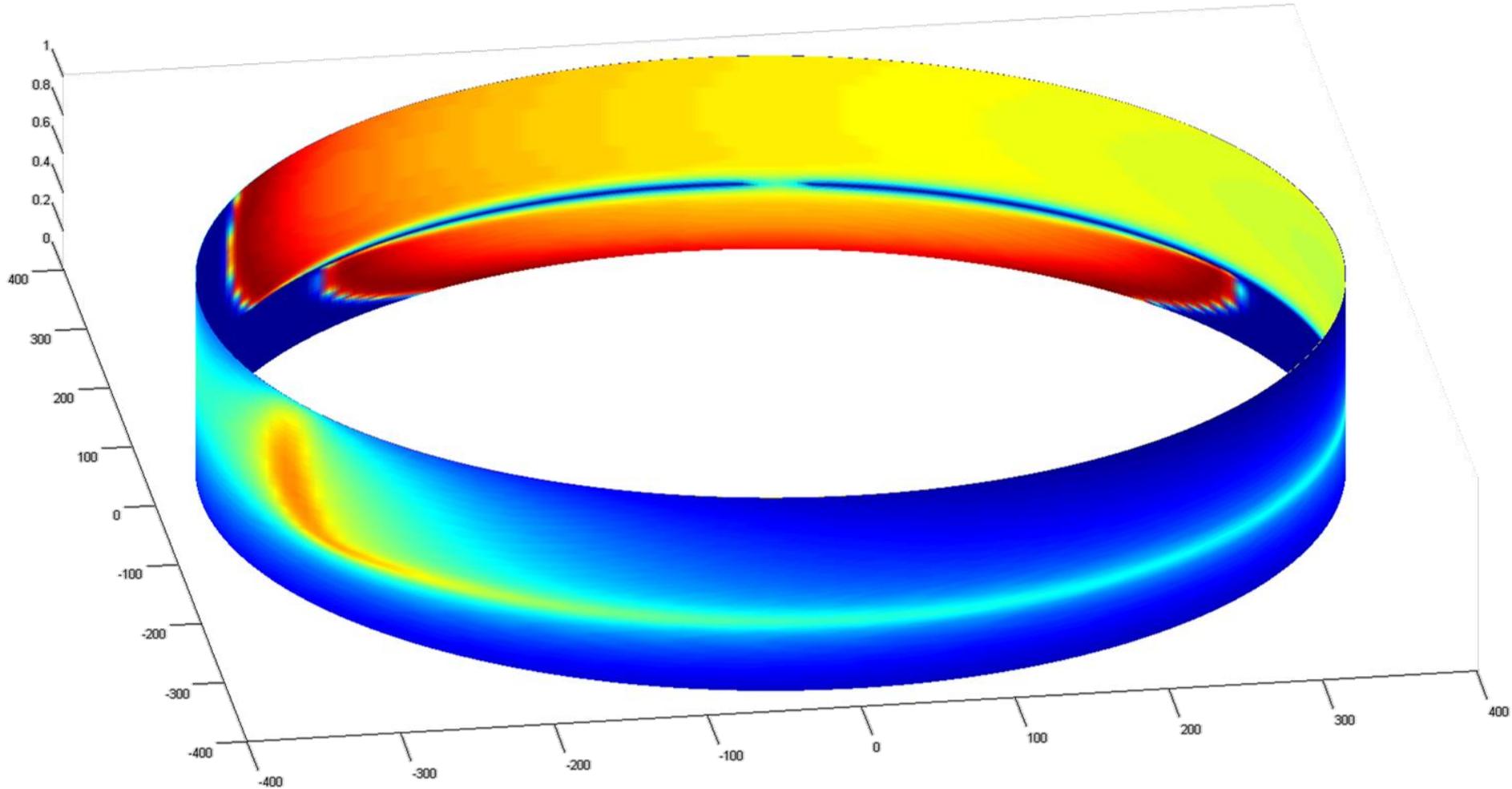
- $$\Phi(x', y') = aD(x', y') \int (-\nabla u(x, y)) \left( \frac{1}{r} \right) dx$$



# Extracellular Potential Propagation

- Ongoing task, not presently working as planned

# Cylindrical Representation

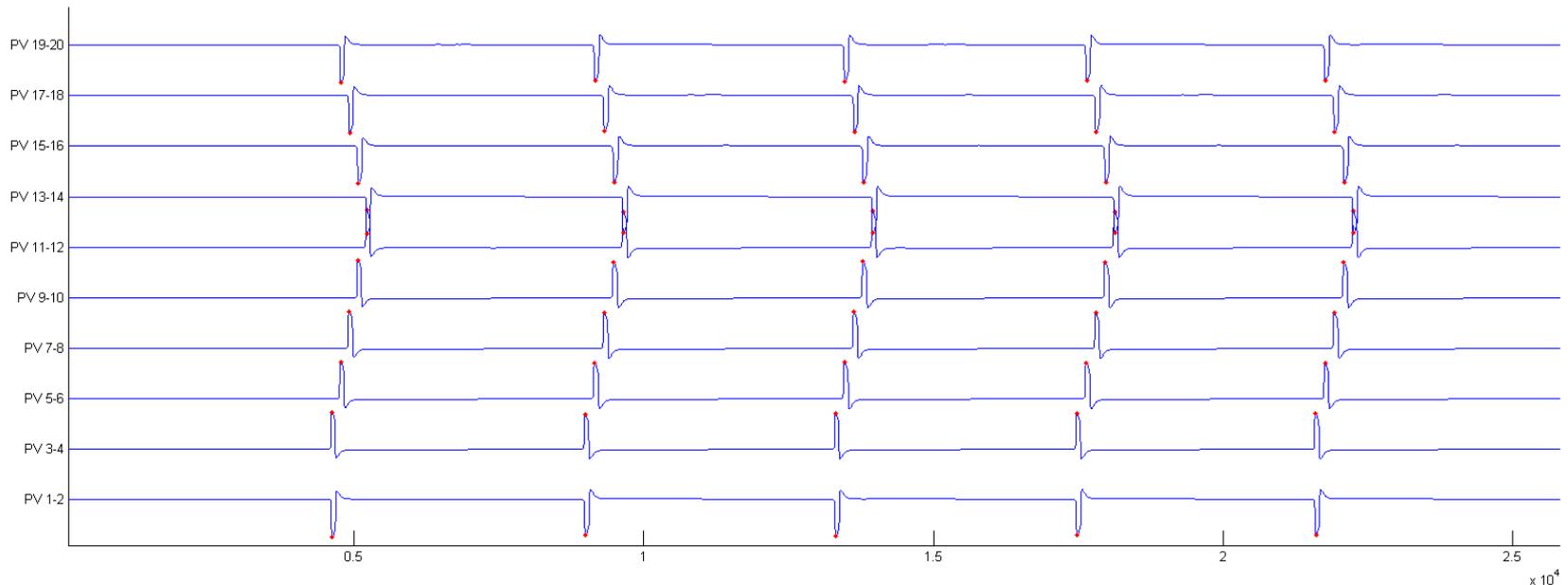


# Synthetic Pulmonary Vein Signal

- We can simulate a pulmonary vein recording catheter by simply taking points equally spaced around the cylinder and monitoring the difference between them
- Ideally, this would be done using the extracellular voltage, but that is currently in progress. Results shown use the intracellular voltage

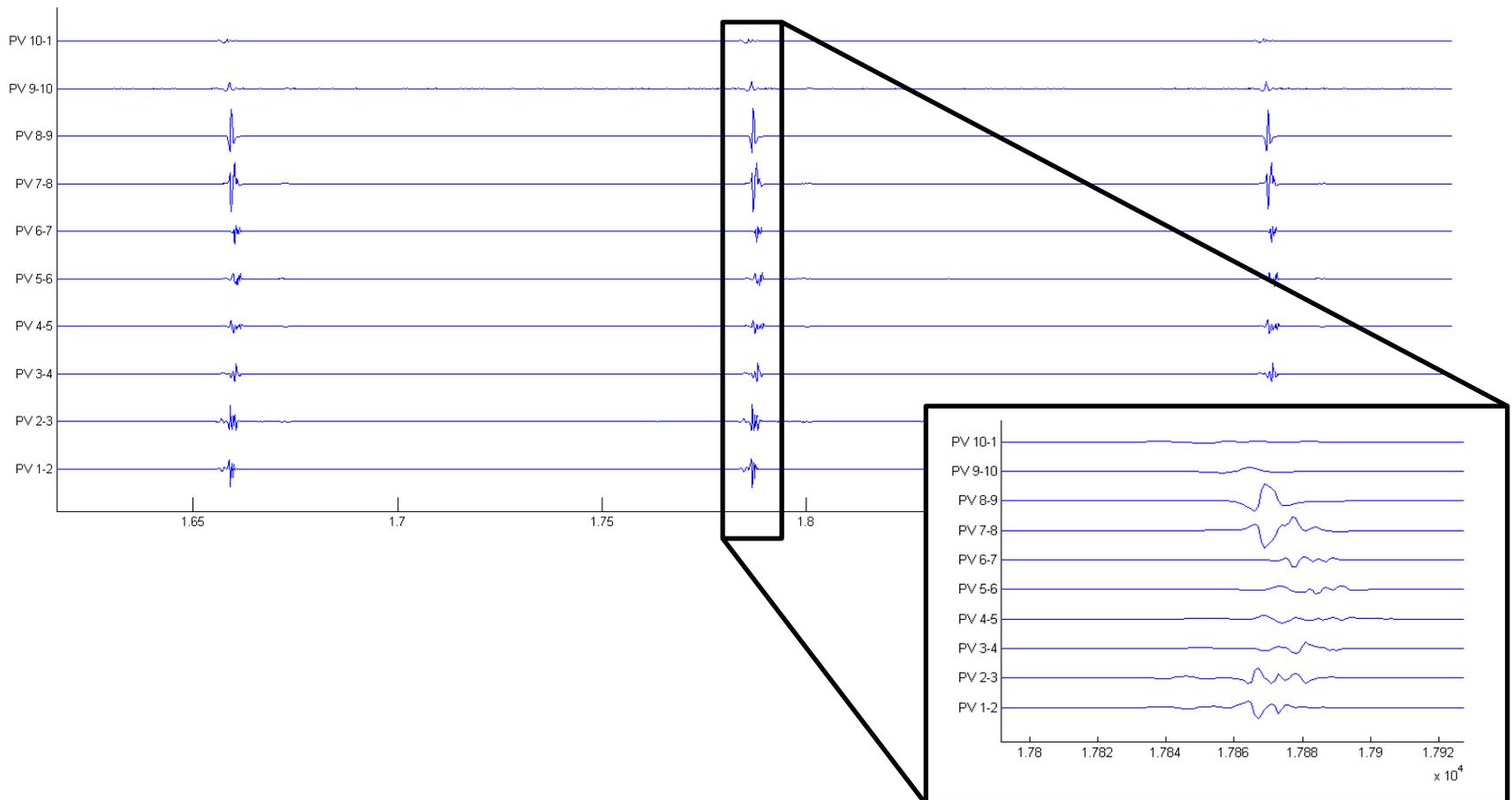
# Synthetic Pulmonary Vein Signal

- This signal was mistaken for a real recording by most doctors at Bristol Heart Institute
- As far as we know, it is the first synthetic creation of this signal

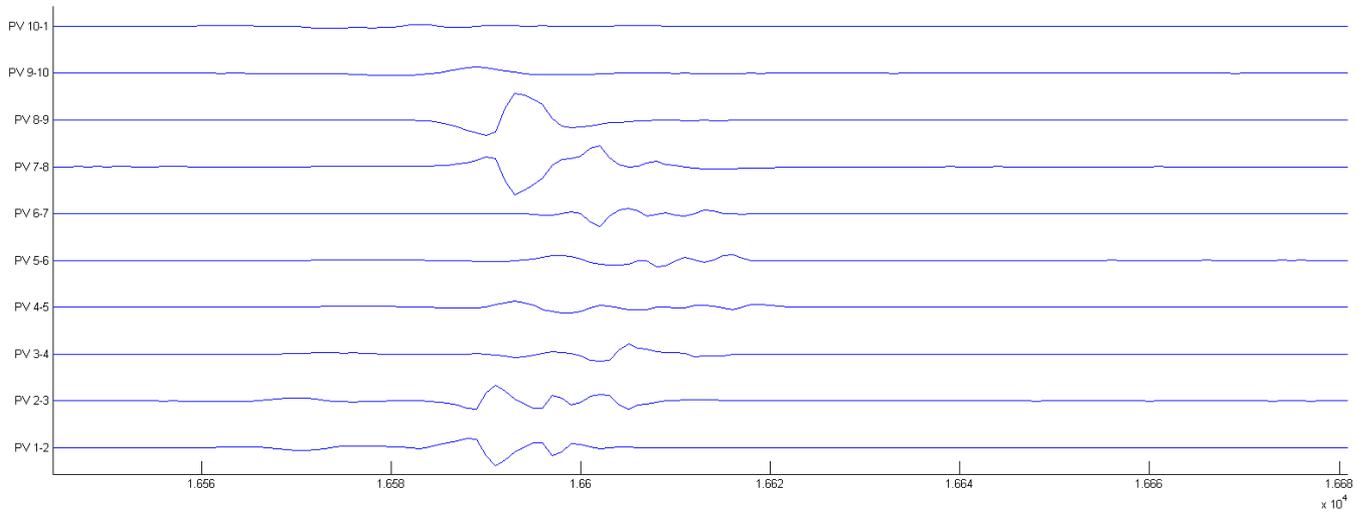
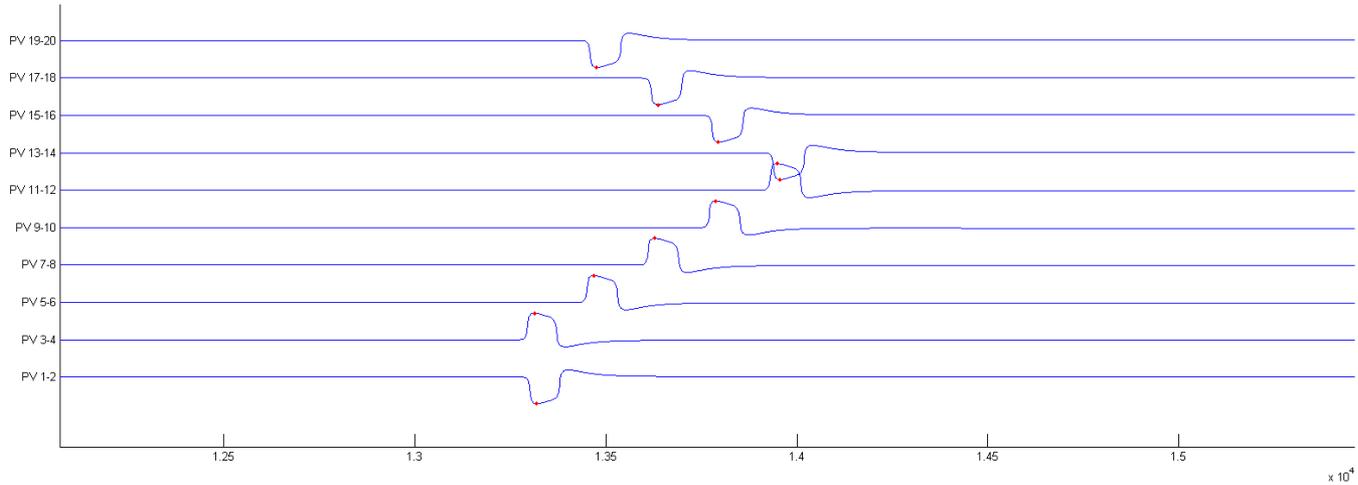


# Real Pulmonary Vein Signal

- This is a real signal taken from an AF patient at Hôpital Xavier Arnozan



# Comparison between Real and Synthetic

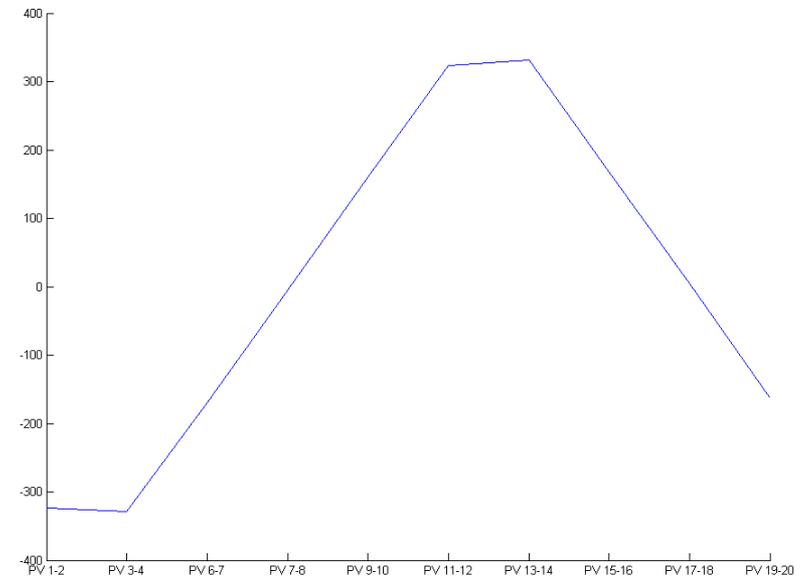
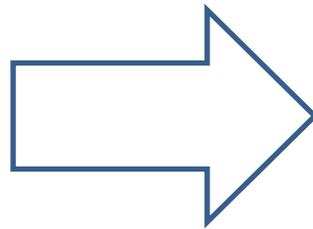
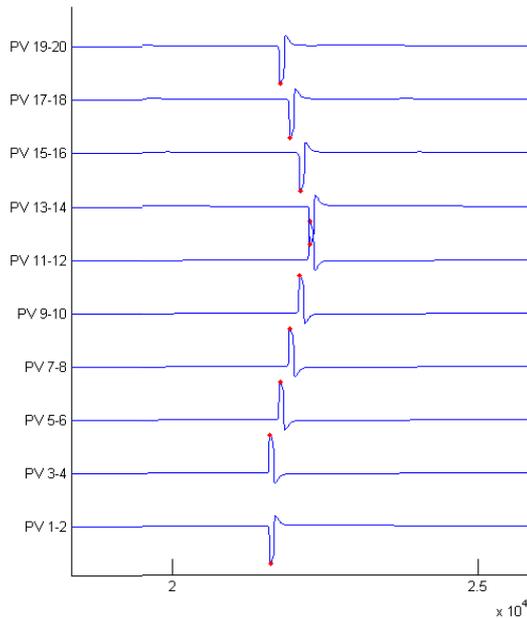


# Signal Properties

- The activation delay is reduced by a higher conduction velocity or catheter placement further from the lesions
- A larger conduction gap (or multiple conduction gaps), and a variable onset location within the PV provides more beat to beat variation
- These properties can be determined by plotting a curve through the spikes to determine the relative activation times of multiple ectopics

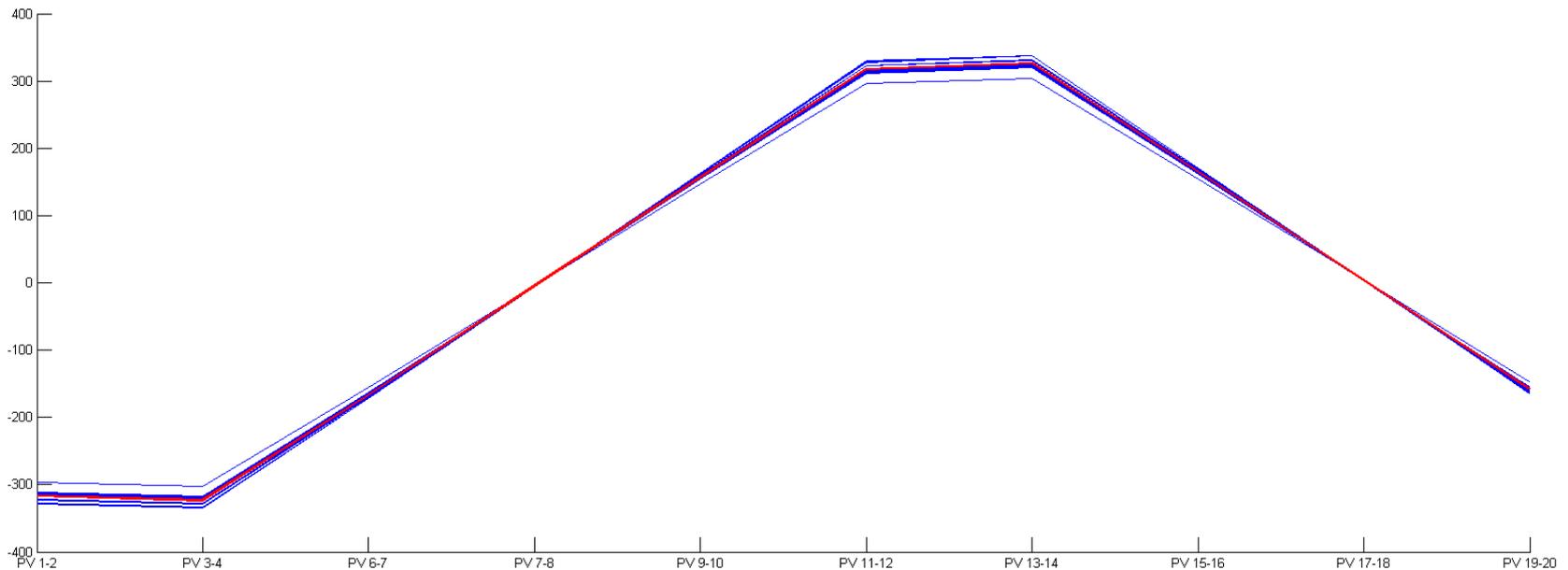
# Relative Activation Time Curve

- We determine the spike peak and form a curve using as many points as we have electrodes on the catheter



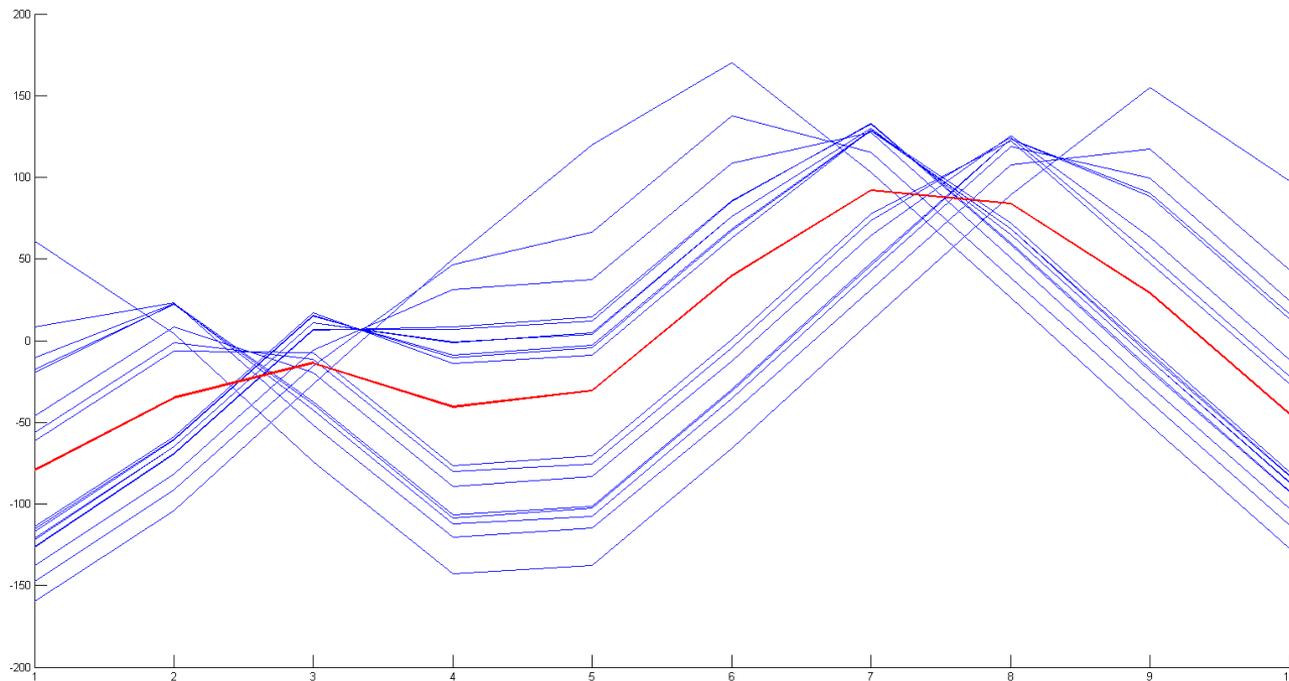
# Average Relative Activation Time

- Averaging over multiple ectopics eliminates beat to beat variation
- Interpolating this curve to locate minima allowed us to find the conduction gap to within 1% of the cylinder circumference

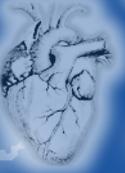


# Relative Activation Time Curve

- Interpolating this curve to locate minima allowed us to find the conduction gap to within 1% of the cylinder circumference



# Future Work



- This is very much a work in progress and there's far more to do to the model in the near future
- Future work is concerned with establishing a more concrete relationship with the underlying biology

# Anisotropic Diffusion

- The diffusion of the cardiac action potential travels along fibres, and can travel up to 5 times faster in one direction than another. This is something we need to consider
- There is a PhD thesis by a student of our collaborators in Bordeaux who has worked in the area
- From them, we can obtain a mesh of the PV with dominant propagation directions

# Predictive Power

- Our data from Bordeaux has no recordings of where the ablation was performed, but our collaborators in Bristol may have recorded this information
- With this, we can test our model's power to make predictions based on ablation times / locations for use in a therapeutic decision support system by warning the surgeon of potential effects of their ablation target

Thank you for listening