# The Effects of Non-ischemic Fibrosis Texture and Density on Mechanisms of Reentry

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## Abstract

*Patients who present with non-ischemic dilated cardiomyopathy and enhancement on late gadolinium magnetic resonance imaging (LGE-CMR), are at high risk of sudden cardiac death. Further risk stratification of these patients based on LGE-CMR may be improved through better understanding of fibrosis micro-structure. Our aim is to examine variations in fibrosis micro-structure based on LGE imaging, and quantify the effect on reentry inducibility.*

*2D Computational models were created from a single short axis LGE-CMR image, with variations in fibrosis type (interstitial, replacement) and density. For each fibrosis-type density combination 10 different models were created, each representing a separate random realization. In total 200 models were tested. Reentry inducibility showed a dependence on fibrosis type and density as well as on the specific random realization of the type-density combination.*

## 1. Introduction

Non-ischemic dilated cardiomyopathy (NIDCM) is characterized by enlarged ventricular cavity size, and impaired ventricular systolic function, which is not as a consequence of myocardial ischaemia. Patients who present with NIDCM are known to be at high risk of sudden cardiac death (SCD), with an estimated 20% mortality rate over 5 years [1]. Late gadolinium enhanced cardiac magnetic resonance imaging (LGE-CMR) studies of NIDCM have highlighted that approximately one third of NIDCM patients have significant mid-wall fibrosis, corresponding to areas of late gadolinium enhancement (LGE), which are associated with an approximate 4-5-fold increased risk of sudden cardiac death (SCD) [1]. Despite this clear association, the specific physiological processes by which the structural remodelling associated with NIDCM underlies such increased arrhythmic burden remains poorly understood.

Further risk stratification in NIDCM based on LGE-CMR is therefore vital, yet is challenged by the lack of knowledge of both the underlying fibrosis micro-structure, as well as its implications for the generation of reentrant arrhythmia. Based on a single LGE-CMR image, we explored possible variations in fibrosis micro-structure, and determined the consequences for reentry inducibility.

## 2. Methods

### 2.1. Image Acquisition and Processing

An anonymized LGE-CMR image set of a patient presenting with NIDCM and LGE was acquired from the Royal Brompton Hospital, using a previously described protocol [1]. A single short axis (SA) image (Figure 1), with the largest LGE area (semi-automatic segmentation, 3 std $>$ reference mean), was selected. A triangular mesh (max 250 $\mu$m edge length) of the myocardium was made (CGAL), from smoothed epi, endo and LGE contours, with local myofibre orientations assigned by a Laplace-Dirichlet rule based method [2].

### 2.2. Fibrosis Microstructures

Interstitial and replacement fibrosis were modelled by modifying mesh edges and triangles respectively, with a single density parameter $\alpha$ controlling the density of fibrosis in LGE. The probability of fibrosis was related to the

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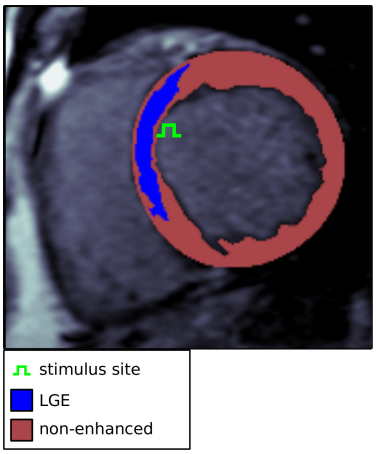


Figure 1. Source late gadolinium enhanced MRI with location of stimulus site and enhanced and non-enhanced areas.

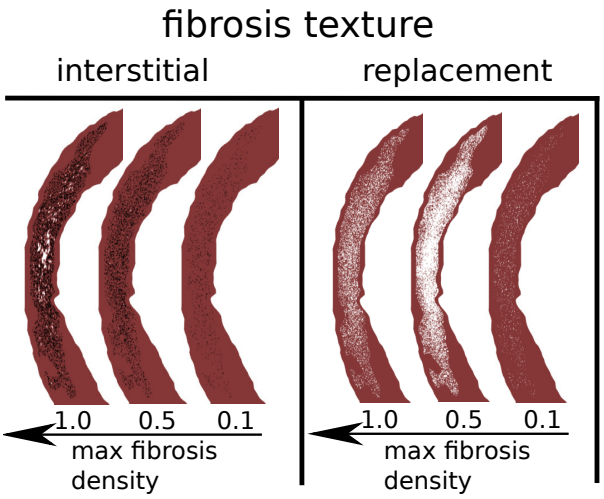


Figure 2. Zoomed-in views of model intersitial and replacement fibrosis patterns with varying maximum fibrosis density.

normalized image intensity

$$I^* = \frac{I - I_{ref}}{I_{max} - I_{ref}}, \tag{1}$$

with $I$, $I_{max}$, $I_{ref}$ denoting the local, maximum, and mean non-LGE reference image intensities respectively, so that higher intensity areas were more likely to contain fibrosis. For replacement fibrosis, the probability of a mesh triangle being fibrotic was

$$p_{replacement} = \alpha I^*, \tag{2}$$

where $\alpha$ is the global fibrosis density. Fibrotic triangles were removed from the mesh, making them electrically inert and non-conducting.

Interstitial fibrosis was represented by a network of random fibrotic clefts, implemented by doubling mesh vertices across fibrotic edges [3]. Each doubled vertex was assigned to a different neighbouring mesh element along the edge, thereby creating a local no-flux boundary condition aligned with the mesh edge. The probability of an edge being fibrotic was

$$p_{interstitial} = \alpha \cos^4(\theta) I^*, \tag{3}$$

where $\theta$ is the angle between the triangle edge and the local myocardial fibre direction. Model tissues within circuits of interstitial fibrosis were removed, since they were electrically isolated. Example models with both interstitial and replacement fibrosis at various densities are shown in Figure 2.

## 2.3. Conductivities and Conduction Velocities

Conductivity values in non-enhanced areas were tuned to match conduction velocity (CV) from NIDCM [4], 84 and 23 cm/s in the fibre and transverse directions respectively. Model LGE areas were assigned one of four reduced CVs based on image intensity. Regions in the intensity range 0-25% and 25-50% above threshold had transverse conductivity (CVT) reduced by 25% and 50% respectively, with normal fibre direction conductivity (CVF). Finally, regions in the intensity ranges 50-75% and 75-100% above threshold had CVF reduced by 25% and 50% respectively, and CVT reduced by 50%. These four reduced sets of CV values are consistent with [4], which reported a correlation between fibrosis level and CV slowing, as well as a tendency for preserved longitudinal CV with milder levels of fibrosis.

## 2.4. Electrophysiology Simulation

Electrical activity was simulated by the standard monodomain formulation, with ionic currents represented by the Ten-Tusscher 2006 model of the human ventricular action potential [5], integrated with step size 20 $\mu$s. Both monodomain solver and cell model are implemented in the Cardiac Arrhythmia Research Package (CARP) [6].

All models were paced from the same site on the LV septal endocardium, approximately halfway down the extent of the LGE (see Figure 1). Stimuli had a square shape with 500 $\mu$m edge length, strength 500 $\mu$A/cm2, and duration 2 ms.

## 2.5. Stimulation Protocols

Reentry inducibility was tested with a dynamic algorithm, with up to six stimuli with variable coupling interval (CI). Each CI was determined by adjusting the timings

of the next stimulus, and examining whether the stimulus generated a new wave of activation lasting at least 20ms. The minimum CI which generated a new wave was selected, up to a a lower limit of 200 ms.

Reentry was detected if any activations were present after 170ms in a circle with radius 3 mm, centered at the stimulus site, and excluding LGE.

## 3. Results

Figure 3 shows the number of reentries per fibrosis type-density combination. In total 133 reentries were induced, 71 were with interstitial fibrosis, and 62 with replacement fibrosis. For both fibrosis types there was a minimum level of fibrosis density necessary for reentry. These were 0.2, 0.4 for the interstitial and replacement types respectively.

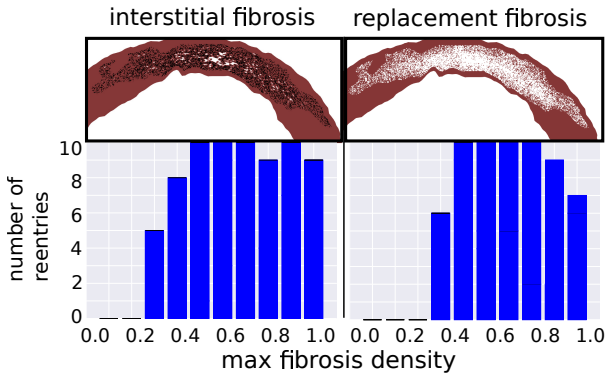


Figure 3. Number of reentries observed out of 10 realizations for each fibrosis density-type combination.

## 4. Discussion

Both fibrosis density and type played a role in the possibility of generating a reentry in our model NIDCM geometry. This is significant because detailed quantification of the absolute type and level of fibrosis in LGE images in NIDCM patients is currently not possible, due to the lack of comparison between core scar and remote tissue, as is commonly used in assessing infarct fibrotic density in patients with ischemic cardiomyopathy [7].

Future developments should address the in-vivo estimation of key fibrosis characteristics, such as density and fibrosis type, as these would greatly improve the predictive capability of computational modelling. This information, when combined with our modelling methodology, has the potential to predict SCD in a manner similar to that which has recently been demonstrated for ischemic disease [8], and thereby pave the way for personalized in-silico prediction of arrhythmic risk in NIDCM.

### 4.1. Limitations

All models were based on a single image and used a single pacing site. Consequentially our results do not account for geometric variability, such as wall thickness, scar transmurality, scar extent as well as pacing location. These factors may affect simulated reentry inducibility.

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