A FRAMEWORK FOR MULTI-SCALE MODELLING OF THE MYOCARDIUM

H. Schmid*, M.P. Nash*, C. Walker**, G.B. Sands*, A. Pope***,
I.J. LeGrice*, A.A. Young*, P. Nielsen* and P.J. Hunter*

* Bioengineering Institute, University of Auckland, Auckland, New Zealand
** Department of Engineering Science, University of Auckland, Auckland, New Zealand
*** School of Medicine, University of South Carolina, Columbia, South Carolina, USA

h.schmid@auckland.ac.nz

Abstract: The last decades have shown tremendous improvement in modelling the electromechanical behaviour of the myocardium. Early attempts at modelling the gross structure of the heart assumed an ellipsoidal shape of the left ventricle and transversely isotropic material behaviour. Recent studies have generalized these models to fully orthotropic finite element models, capturing the anatomy of both ventricles and the transmural changes of fiber, sheet and normal directions. However, material properties are described in terms of theories which are based on continuum electromechanics, therefore being restricted to a certain scale; usually the macro scale. Microstructural data of the myocyte arrangement and its enclosing collagen is now available and can be utilized for a model that encapsulates both the micro- and the macro-structural scales. In particular, this data informs an algorithm that is capable of generating an anatomically realistic finite element model of the myocyte topology that also provides a scaffold for the various collagen types (mechanical behaviour) as well as gap junctions (electrical features). The macro parameters can then be explained by means of the micro parameters. This paper presents a framework for the parameter identification in the context of system identification theory based on the setup of the microstructural topology.

Introduction

Knowledge of the mechanical behaviour of myocardium is central to understanding mechanisms of impaired function in regions of the heart, caused by abnormalities such as ischaemia, hypertrophy or remodelling of the collagen microstructure.

Recent advances have improved the models of the mechanical behaviour from a transversely isotropic behaviour [1], by incorporating the findings of a laminar like structure [2] to build full 3D finite element models which capture the orthotropic nature of the myocardium [3,4]. Furthermore it was possible to determine the material law that most appropriately describes the orthotropic behaviour [5].

Ideally, spatially varying material properties should be taken into account, as for example occurs with transmural changes in the collagen content [2]. Measuring the spatially varying material properties is not feasible. However, it is possible to observe structure on various length scales and therefore a relationship between the mechanical behavour and structure can be established.

Sands et. al. [6], were able to image extended volumes of myocardial microstructure which enabled them to utilize an anatomically accurate representation of the cleavage planes to simulate wave propagation throughout a myocardial block [7,8].

These advances in imaging make it possible to firstly take spatial variation of mechanical properties into account and secondly attribute physiological meaning to the macro scale parameters. A common approach is to consider compartments on the micro scale and use homogenization techniques to relate the micro parameters to those on the macro scale. This, however, requires a certain repeatability in this compartment and is therefore not a feasible approach for the myocardium which exhibits marked heterogeneities on several scales (see Fig.1,2).

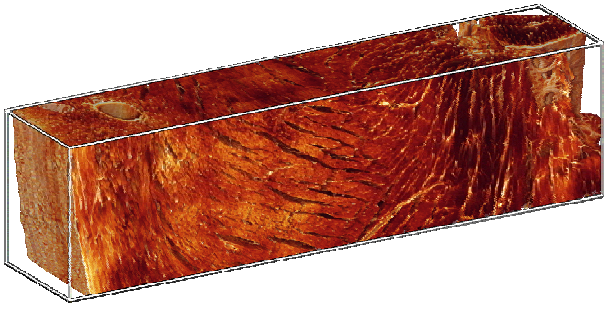

Figure 1: A block (4x1x1mm) of rat myocardium showing the heterogeneous transmural arrangement of the myocytes.

We therefore propose a multi-scale model which enables us to identify the macro-scale parameters in terms of the micro-scale ones via a system identification technique. It will be presented in the next section in the context of the mechanical behaviour but can equally well be applied to the electrical properties [9,10].

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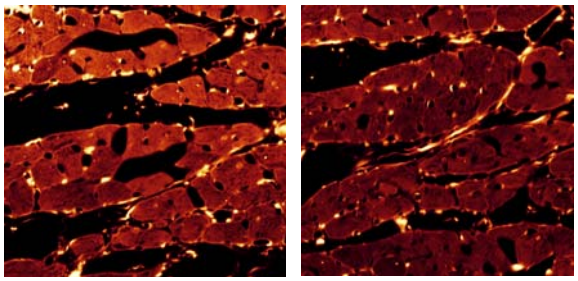

Figure 2: Two sample images of the myocardial microstructure showing the cross-sectional area perpendicular to the myocyte direction. (200x200µm).

Methods

The mechanical behaviour of the myocardium on the continuum mechanical level is described in terms of a material law of the following form:

$$\sigma = f(E, \xi), \qquad (1)$$

Where σ, f, E, ξ denote the Cauchy stress tensor, the constitutive relation, the Green strain tensor and the material parameters, respectively [11].

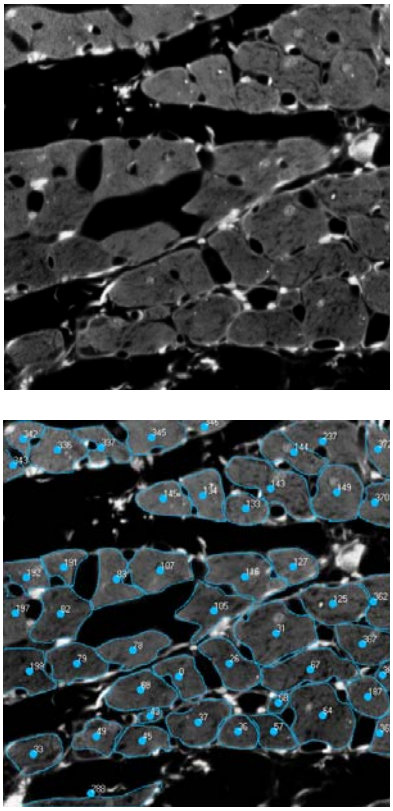

Figure 3: Top, the original image; bottom, the digitized image.

The task was now to determine a relation between the macro parameters ξ and parameters on the micro scale. We therefore utilized the imaga data available and digitized for the splitting and merging pattern of a block (200x200x197µm) with a resolution of 0.4 µm/voxel (see Fig 3).

A split or merging was defined when the endomysial collagen changed from one contour into two contours from one picture to the subsequent one, or vice versa. We denote the straight line between two centroids of these contours as a fibre segment.

The whole block yielded a total number of 287 fibre segments which gave a solid basis for a statistical analysis of *directional* data [12], e.g. of direction, length and connectivity between the myocytes (see Fig 4). Furtherore we could extract the mean laminae orientation and its distribution.

This data serves as the basis for an algorithm to build up both the sheet orientation, shape and connectivity as well as the myocyte section arrangement within the sheets. This algorithm will be designed to synthesize finite element models resembling myocardial blocks up to a size which can be utilized for inverse finite element studies as for example presented by Schmid et. al. [5], now extended to the finite element environment.

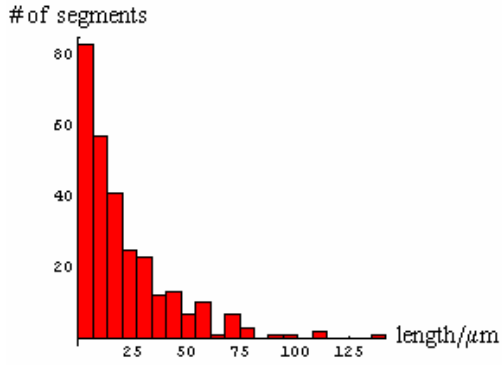

Figure 4: This histogram shows the distribution of the total length of the fibre segments versus number of occurences. The mean length of segments is 21.43 µm.

Note that this algorithm only captures the myocardial scaffold on top of which the collagen is wrapped and described by a separate algorithm. It is therefore helpful to distinguish two parameter sets on the micro level.

Firstly, parameters which are associated with the myocardial topology which we will denote as a vector τ. They partly consist of parameters which are known, like the statistical distribution parameters for length, direction, connectivity, etc. and partly of parameters which are necessary to enable the algorithm to stay within certain boundaries.

Secondly, parameters that are associated with the collagen are denoted κ, and include descriptions of collagen type, density strength and orientation and

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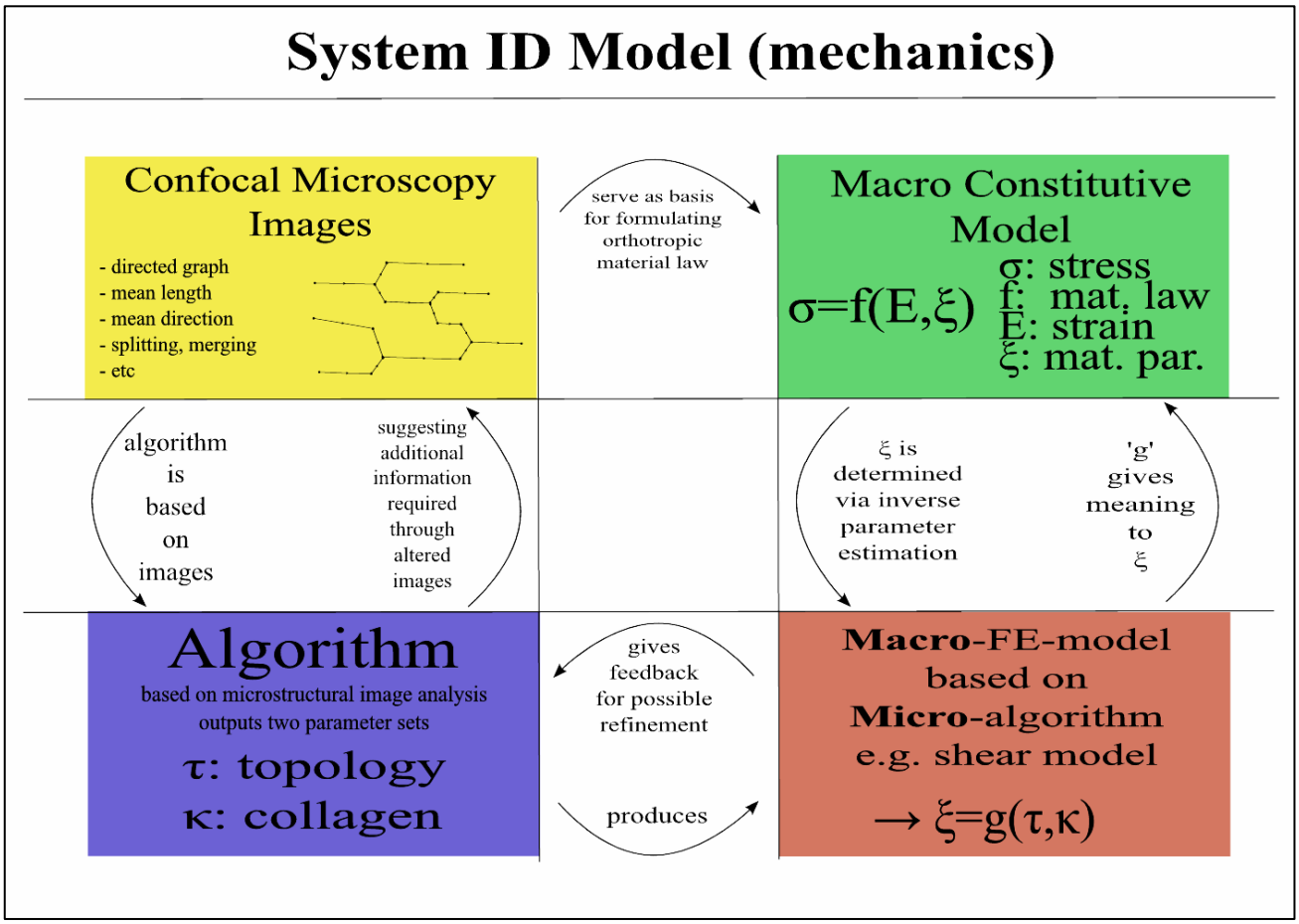

Figure 6: A diagram visualizing the four major features involved in the system identification process.

perhaps other, that need to be addressed. Some data for this kind of algorithm is also available (see Fig 5) [6].

Two algorithms are now able to generate a 3D finite element model based on the microstructural topology and the collagenous network. We therefore have material parameters τ and κ on the micro scale and ξ on the macro scale. τ will be partially known from histological measurements, and otherwise estimated or fixed externally as model parameters. τ, however, is not prone to contribute a lot to the mechanical behaviour itself, because its very nature is not mechanical. κ,on the other hand describes the collagen

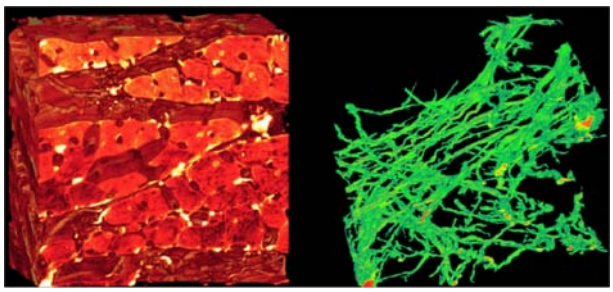

Figure 5: Left, shows a 3D rendered volume image of the block that was digitized; right, one of its corresponding collagenous branching networks (right).

properties and therefore knowledge about the stiffness, curliness and the density will have a major impact on the macro-scale behaviour. This is a well-known phenomenon when the myocardium remodels in diseased states [13].

The task of determining a relationship 'g' between the microstructural parameters τ and κ and the macro parameters ξ,

$$\xi = g(\tau, \kappa), \qquad (2)$$

can be addressed by a "black box" system identification process as outlined in detail by Sjöberg et. al. [14], and Ghoniem et. al. [15].

The nonlinear black box situation, as is the case for us, is very hard to compute as a very rich spectrum of model descriptions must be handled. The area is quite diverse and covers topics from mathematical approximation theory, via estimation theory and regression analysis to algorithms and currently much discussed neural networks, wavelets and fuzzy models. If we apply the principle of parsimony in the sense of simplicity then we are left with starting the identification process by setting up polynomial relationships between the micro and macro parameters determining the parameters via a nonlinear least square

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minimization method. If this approach is either too restricted or requires too many parameters other techniques such as radial basis functions or genetic algorithms remain as other possibilities [16].

Figure 6 shows a diagram that depicts the system identification process and the relationships between the various features of the modelling process.

Results & Discussion

We have presented a computational system identification framework which allows us to associate parameters on the micro- and macro-scale.

The micro scale parameters are currently based on image data by Sands et. al. [6], with a resolution of 0.4 μm/voxel. These images were taken of tissue stained for collagen with picrosirius red and therefore detection of cell and sheet boundaries was performed. Intercalated discs, however, were not detectable which would be a desirable extension of currently available data.

The algorithms allow for a wide range of features that could be taken into account. The question of which features should be included into each algorithm can only be answered in an iterative manner and for the beginning we followed the principle of parsimony, i.e. we digitized the the 3D volume for cell boundaries and created the algorithm on the basis of the statistical data obtained from that digitization procedure. Note the digitized segments were defined with respect to changes in the boundaries of the endomysial collagen and might slightly differ with higher resolution images. The algorithm includes length, direction, and connectivity distributions of the myocytes and could easily be extended to include area distributions, as well as statistics on the laminar structure.

Similar arguments hold for the collagenous network and parameters like density, strength and orientation with respect to the scaffold will suffice to comply with the principle of parsimony.

For the case of modelling the electrical behaviour of the myocardium one would also need to introduce parameters associated with gap junction frequency, conductivity, etc; again on both levels, i.e. the topological level and on the phenomenological level as it is the case for the mechanical modeling.

Conclusions

This paper presents a framework for multi-scale modelling of the myocardium within the context of system identification and is based on anatomically realistic data for both the myocardial topology and the collagenous network.

The system identification process allows us to attribute meaning of the macro-scale parameters in terms of micro-scale parameters. In particular growth and remodeling and their effect on the macro-scale could be addressed in a straight forward manner and therefore be made more accessible for a clinical interpretation.

It is therefore another step towards the integration of multiple scales within the Physiome Project [17].

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