COMPUTATIONAL MODELS OF THE MICRO ARCHITECTURE OF THE CARDIAC ENDOMYSIAL COLLAGEN

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Abstract: In the last years, cardiomyocytes and collagen matrix have been found responsible of the high passive stiffness of cardiac muscle when compared to the skeletal one. However, the architectural and mechanical aspects of the cardiomyocytes and of the collagen matrix are not completely known.
In particular, the endomysial collagen contribution to the passive mechanics of cardiac muscle as well as its micro anatomical arrangement is still a matter of debate.
In this work we consider two *alternative* computational models of some specific aspects of the cardiac muscle, in order to investigate the mechanical and structural properties of the endomysial collagen.
These two models represent different views of endomysial collagen morphological structure.
This is done by means of a computational technique inspired to pre-structured recurrent neural networks, representing the endomysial collagen matrix as a net of springs.
We found out that in one model a given *stress/strain ratio* (of the net of springs) is obtained with a much smaller (w.r.t the other model) elasticity springs constants mean value.
This seems to indicate that, by a more appropriate structure, a given *stiffness* of the myocardial tissue can be obtained with endomysial collagen fibers of much smaller size.

Introduction

High passive stiffness is one of the mechanical features that characterize the *cardiac muscle* when compared to the *skeletal* one [7]. There are several studies concerning the components and the architectural aspects of the cardiac muscle responsible for this particular feature [8, 7], in particular *cardiomyocytes* and *collagen matrix* have been proposed as candidates.

Cardiomyocyte architecture is now reasonably known and well described in the literature [9, 10]; however, many researchers are investigating how the cardiomyocyte architecture is involved in regulating the electrical and mechanical behavior of the cardiac muscle [10, 11].

On the other hand, the collagen matrix is composed by (1) *endomysial collagen* that connects *myocytes* and surrounds, in a mesh-like structure, the myocytes themselves and (2) *perimysial collagen* that groups myocytes together, running in parallel with *myofibrils* and linking itself to endomysial collagen [12, 13, 14].

In [14] a mathematical model of the perimysial collagen is defined, in order to describe its role in the myocardial mechanics during ventricular filling (*diastolic phase*) and to identify the physical parameters characterizing perimysial collagen.

Much more difficult is the assessment of endomysial collagen contribution to the passive mechanics of the cardiac muscle; in particular, it is still a matter of debate its micro arrangement and how different micro arrangements could influence this mechanic.

As a contribution to this discussion, we propose some computational models to investigate the mechanical and structural properties of the endomysial collagen. In order to do this, we need simplified computational models of some aspects of the cardiac muscle itself. Our aim is to experiment different models based on different morphological structure of endomysial collagen.

We set up two models: one mainly based on the morphological structure described in [15], and the other one based on traditional micro anatomical view of the endomysial collagen.

We model the myocardial tissue as a net of springs representing the cardiomyocytes together with the endomysial collagen distribution. We treat the springs as elementary units, and we connect them in order to imitate the interconnections between collagen fibers forming the collagen distribution. Then, we *stress* the net of springs by applying some external forces of suitable magnitude and direction. In this way, we obtain a *strain* of the net itself, which depends on the elasticity constants of the springs of the net.

Our computational techinique is inspired to the

ISSN: 1727-1983

work proposed in [16, 17], where they use pre-structured recurrent neural network to simulate the dynamic of a viscous-elastic object represented as a spring model as described before. This allows us: *(1)* to avoid to write down the entire differential equations system, *(2)* to learn the main physical parameters determining the spring model and, finally, *(3)* to model quite different-sized systems, ranging from a micro- to a macro-view of the system (i.e., our approach is scalable).

We want to demonstrate that if the net of springs is structured according to the point of view of [15, 18], then to obtain a desired *stress/strain* value we need much smaller elasticity springs constants than the ones obtained structuring the net according to the traditional point of view [19].

In order to do this, we organize our computational model in such a way that it *learns* which have to be the spring constants corresponding to a specified *stress/strain* value.

Our experimental results seem to indicate that, by a more appropriate structure, a given *stiffness* of the myocardial tissue can be obtained with endomysial collagen fibers of much smaller size. This is consistent with the experimental results of [15]. Moreover our numerical results are compatible with the ones in [9] which are obtained via an analytical method on a simple model of the perimysial collagen.

The paper is organized as follows: in Section **Models and Methods** we introduce the micro anatomical architectures we want to compare and the computational tecnique used to this aim; in Section **Experimental Results** we present some experimental results. Section **Conclusion and Future Work** ends the paper with conclusions and future work.

Models and Methods

In this Section we first describe the micro anatomical models of the distribution of myocardial endomysial collagen we want to compare: the old model as described in [19] and the new model as it can be found in [15]. Then, we illustrate our methodology to: *(1)* computationally model different micro anatomical arrangements and *(2)* show that the arrangement proposed in [15] is indeed more suitable w.r.t the experimental results in [15].

Micro Anatomical Models of the Distribution of Myocardial Endomysial Collagen

Generally speaking (see [9]), heart myocytes and capillaries are enmeshed in a net of connective tissue organized in different levels:

epimysium which is the layer of connective tissue surrounding myocardium;
perimysium which is associated with groups of myocytes;
endomysium which surrounds and connects each individual muscular cell.

Thus collagen is an essential component of myocardial connective stroma. Collagen arrangement probably has the significance of preserving heart micro-architecture and chamber geometry, maintaining the correct myocyte alignment and possibly contributing to the control of myocardial contraction [15].

Figure 1 shows the old view of the endomysial collagen arrangement. It has been described as a weave network surrounding each individual myocyte and connecting adjacent myocytes and capillaries.

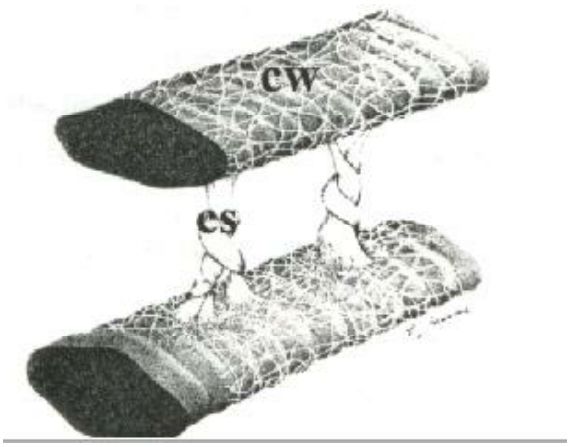

Figure 1: Known model of myocardial endomysial collagen distribution. From [15] with permission

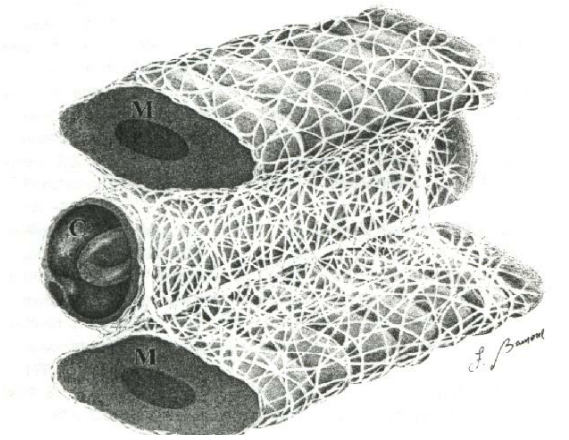

Figure 2: Revisited model of myocardial endomysial collagen distribution. From [15] with permission

Figure 2 shows the new model proposed in [15] of myocardial endomysial collagen distribution, in contrast with the old one. The endomysial collagen fibers are organized in a layer enveloping myocytes and capillaries. The endomysial sheath spreads from one myocyte (*M* in Figure 2) to neighboring one like a lamina, and extends along the fully myocyte length. This

lamina also completely wraps neighboring blood vessels (*C* in Figure 2). For more details see [15, 18].

In modern specialist text-books of cardiology the anatomical site and arrangement of the components of the model of cardiac muscle contraction as originally proposed by Hill ([20]) are still considered uncertain. In this work we try to ascribe some of the properties of cardiac muscle contraction to morphological and physical properties of the connective tissue. To this end, we model various micro anatomical arrangements of the endomysial collagen and then computationally analyze their behavior. We now illustrate our methodology, by first describing the Physical Models of myocardial connective tissue we propose for the collagen arrangements. Then, we illustrate the methodology we used to make our computational experiments.

Physical Models

We propose two physical models, both intended to capture some aspects and characteristics of the myocardial tissue during the diastolic phase.

To illustrate the most important features of the proposed physical models, consider Figure 3. The main characteristic consists in the fact that we represent the connective tissue (which is supposed to be made up primarily of collagen [20, 15, 18, 19]) with a set of connected springs (continuous lines in Figure 3). The geometrical arrangements of these springs are intended to reflect the different micro anatomical views of the collagen distribution we want to experiment. Some other springs (those included in the dashed lines in Figure 3) represent myocytes, which are considered essential elements in developing passive tension [8, 21, 7]. A value for the elasticity constants of the springs representing myocytes was extrapolated from the Young module of myocytes [7].

Furthermore, the myocytes dimension and disposition [22] gives us the initial disposition of the mass points. As an example, the initial distance between points P_i (the second node in the first row starting from the left) and P_j (the second node in the last row starting from the left) represents the resting length of the myocyte [8, 21, 22], whereas the distance between points P_i and P_k (the third node in the first row starting from the left) corresponds to an estimate of the distance between two myocytes [15, 18]. Finally, we suppose that the whole system is stressed by some external forces (the arrows in Figure 3), which are applied to each mass point.

As for the forces directions, we have that the forces simulate the stress induced by blood pressure on a microscopic piece of myocardial tissue. Thus, we suppose that the stress acts in all directions and so the vectors representing the forces are initialized in such a way to reflect this assumption (Figure 3). The magnitude of this vector was approximated starting from the mean value of diastolic pressure and it was comparable with values in the literature [22], regarding the passive strength on sarcomeres during diastole.

In order to investigate the differences between the model inspired to old micro arrangement view as opposed to the model inspired to the new view proposed in [15], we will use the physical models shown in Figures 3 and 4, respectively.

The physical model in Figure 3 is based on the old micro arrangement showed in Figure 1: in fact, there are few connections and only between adjacent myocytes. On the contrary in Figure 4, which is based on Figure 2, we have that each mass point is connected in a more complex way to the other mass points. The connections are such that all the mass points which are sufficiently close are connected.

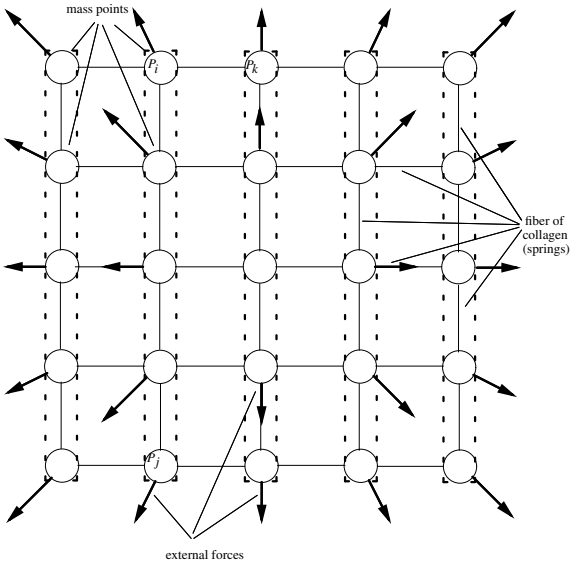

Figure 3: The physical model inspired to the traditional view of the distribution of endomysial collagen

System Dynamics

The dynamic of the entire system could be separated in two distinct phases:

Diastolic phase The system is *stressed* by external forces (see vector forces in Figure 3); the springs representing the connective tissue react to these external inputs and the entire net is *strained*. If we consider our system immersed in a viscous fluid, the system will stop in a position of equilibrium, where the internal forces of the system (due to the springs reaction to the external forces) balance the external forces. In this work, we will deal only with this phase.

Systolic phase Each myocyte [20, 19] contracts in response to the activation of its sarcomeres and it tends to generate a force in the opposite direction of the corresponding external force; the idea is that the system will return in a position of equi-

ISSN: 1727-1983

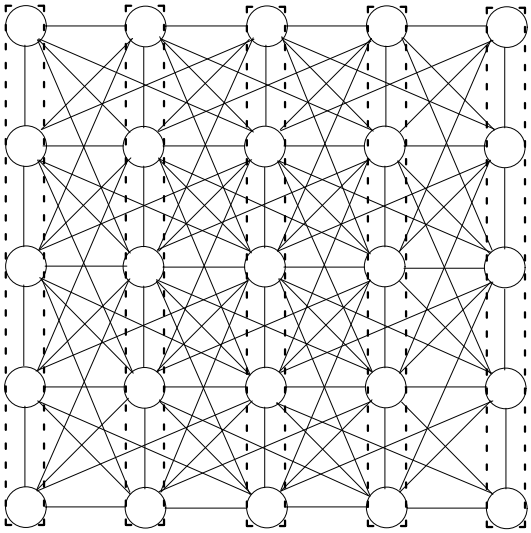

Figure 4: The physical model inspired to the view of the distribution of endomysial collagen proposed in [15]

librium corresponding to the initial position. This phase will be considered in a future work.

The Computational Model

The computational model of myocardial connective tissue proposed in this work is inspired to Nurnberger and Radetzky study on pre-structured neural network [16, 17]. The main idea is to model the system through a set of connected springs, and to compute the dynamic of the whole system via a recurrent neural network that simulates the springs behaviour.
Note that, in a conventional approach, a system of differential equations must be constructed for the physical model, e.g. by linear or non-linear springs models. Depending on the complexity of the system to model, the construction of differential equations could be extremely difficult as well as the identification of the right parameters [16, 17].
More in detail, in [16, 17] two distinct network modules are used, each computing the dynamic of a particular element of the physical model. The first module (*mass point module*) is composed by neurons that compute the dynamic of the mass points, whereas the second module (*spring module*) is composed by neurons that compute the dynamic of the springs. These modules are connected together in according to the physical model. The resulting neural network is recurrent, since there are self-connected neurons (called integrator units, see [16]). More in detail, the mass point module (Figure 5) consists of three distinct neurons as shown in Figure 5. These neurons compute respectively the *acceleration*, the *velocity* and the *position* of each *mass point* (white circle in Figures 3 and 4).
On the other hand, the spring module (Figure 6) computes the instantaneous reaction force engendered by a stressed spring. This force depends on the position and the velocity of the uttermost points of the spring. Note that in Figure 6 the weights of the connections to the neuron computing the instantaneous reaction force (neuron F in Figure 6) represent directly the constants characterizing the spring: the elastic (k in Figure 6) and the viscous one (v in Figure 6); the viscous constant is required to be different from zero in order to obtain an equilibrium distribution at the end of the propagation step.

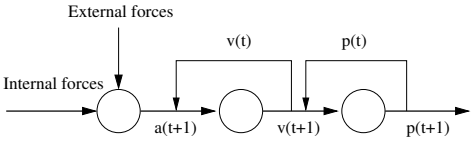

Figure 5: A mass point module

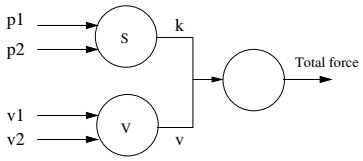

Figure 6: A spring module

The Learning Procedure

We now illustrate the learning procedure used to obtain the desired behavior of the system. Our goal is to learn the right physical parameters (i.e. the elastic constants values) of the springs in a way such that the system will stop in a desired position of equilibrium.

This is achieved in the following way. The system is stressed by the external forces; this input is propagated on the network, and all the mass points positions are recomputed according to it. This *propagation procedure* will stop only when the network reaches equilibrium. If the computed equilibrium is not sufficiently close to the given target position, then the elastic constants of the springs are updated and the propagation procedure is restarted. When the equilibrium is sufficiently close to the target position, the learning process is complete.
The most crucial step of our learning algorithm is the update of the springs elastic constants.To cope with this problem, we adopt a particular updating method different from those suggested in literature [23, 16, 17]. In the following, we illustrate our updating procedure.

We suppose we are given n springs. The global error at the end of the propagation procedure is computed by $E = \max_{0\leq i\leq n} E_i$ being, for all $i = 0,\ldots,n$, $E_i = \frac{a_i - d_i}{d_i}$, where a_i is the actual length and d_i is the desired length of the spring i. If the global error is less or equal to a given tolerance then the learning procedure terminates, otherwise we update the springs elasticity constants in the following way: $k'_e{}_i = k\_e_i + E_i k\_ e_i$. By doing so, we have that we are able to reduce the overall error.

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Experimental Results

Finally, we present some experimental results we obtained in the learning phase of our recurrent neural networks.

In the following, we call *simple network* the model inspired to the oldest view of micro arrangement of endomysial collagen (Figure 3), while we call *complex network* the model inspired to the newest one (Figure 4).

The experiments we carried out depend on various factors:

Geometrical dimensions Here we deal with the dimension of myocytes and the distance between them. In order to reflect the real myocytes arrangement (as it can be found in the literature [15, 18, 8, 21, 22]), we set the distance between two mass points (see Figures 3 and 4) to $1.6\mu m$, that is the resting sarcomere length for human myocytes. The distance between two parallel myocytes is estimated to $15\mu m$ [15].

Physical parameters Here we deal with physical parameters of the springs and of the environment they are embedded in: *external forces* magnitude and direction, *desired network strain*, *initial elastic constant* and *viscosity coefficient*. As already said, the external forces are applied on each mass point and have a radial direction (see Figure 3). Moreover, their magnitude is calculated from the mean value of end diastolic pressure (about $20mmHg$) and by considering the dimensions of the system.

In order to choose the desired network strain parameter we consider both the vertical and the horizontal strain. For the vertical strain, in our experiments we use values taken from the interval ranging from 20% to 35%. This range is consistent with values which can be found in in the literature (e.g. [15]).

On the other hand, the horizontal strain is chosen in the range between 0% and 2%. In fact, we suppose that in the desired final disposition the sarcomeres will be slightly spaced out.

Finally, the initial elastic constants are chosen (by trials) in a way such that the initial strain is not too far from the desired network strain, while the viscosity coefficient is chosen (by trials) to reduce the number of iterations required to obtain an equilibrium state.

Numerical method parameters Here we deal with tolerances, namely the *propagation tolerance* and the *learning tolerance*. The propagation tolerance regulates the equilibrium state trapping. Indeed, we say that the system is in a equilibrium state when the resulting force on all of the mass points is less than or equal to the propagation tolerance.

The learning tolerance is used in order to decide the termination of learning algorithm. Namely, the error defined in the previous section has to be less or equal to the learning tolerance in order to stop the learning process.

Numerical results We focused on the *mean value of the springs elasticity constants (MVSEC)*.

The values for all the experimental parameters are summarized in Table 1.

Table 1: System parameters

Geometrical and Physical Parameters	
Sarcomere initial length	$1.6\mu m$
Sarcomere final length	$1.92, 2.0, 2.2\mu m$
Myocyte diameter	$15\mu m$
External Force	$3^{-6}N$
Viscosity constant	1.0^{-4}
Initial k_e for *simple network*	3.0
Initial k_e for *complex network*	10.0
Numerical Parameters	
Propagation tolerance	$1e^{-10}$
Learning tolerance	$1e^{-3}$

Our experimental results (obtained by properly varying the vertical and horizontal strains as described above) are in Table 2, where in the *simple network* and *complex network* we show the respective mean values of the elasticity constants computed by our learning procedure.

Table 2: Experimental results of the learning procedure

Strain		**Network MVSEC**	
Vertical	Horizontal	simple	complex
20%	0%	173.25	12.25
25%	0%	172.13	10.29
35%	0%	170.85	7.47
20%	1%	20.87	3.61
25%	1%	19.75	3.21
35%	1%	18.46	2.68
20%	2%	13.63	2.63
25%	2%	12.50	2.30
35%	2%	11.22	1.90

Conclusion and Future Work

Our experimental results seem to indicate that, by an appropriate structure, a given *stiffness* of the myocardial tissue can be obtained with endomysial collagen fibers of much small size. Moreover, as already noticed our results are consistent with the ones in [9]. We also hope that the possibility that larger collagen fibers do not necessarily give a greater stiffness could help to explain some problems exposed in [12].

ISSN: 1727-1983

In a future work we plan to model also the systolic phase and make computational experiments similar to those performed for the diastolic phase. In the systolic phase model will be more complex since we have to take into account also the myocytes contraction. This will allow us to have a rather complete model for the myocardial tissue behavior.

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ISSN: 1727-1983