

A COMPUTATIONAL STUDY OF THE INJECTION THERAPY FOR MYOCARDIAL INFARCTION DURING THE NECROTIC STAGE

Sebastian Skatulla†‡, Dieter Legner†‡, Ritesh Rao Rama†‡, James Mbewu‡, Carlo Sansour *, Neil Davies¶ and Thomas Franz¶‡♦

† Department of Civil Engineering, University of Cape Town, South Africa, sebastian.skatulla@uct.ac.za
‡ Centre for Research in Computational and Applied Mechanics, University of Cape Town, South Africa
§ Department of Mathematics and Applied Mathematics, University of Cape Town, South Africa
* Division of Materials, Mechanics, and Structures, The University of Nottingham, United Kingdom
¶ Cardiovascular Research Unit, University of Cape Town, South Africa
♦ PERC, Research Office, University of Cape Town, South Africa
♫ Centre for High Performance Computing, Rosebank, South Africa

ABSTRACT
Myocardial infarction is an increasing health problem worldwide. Due to an under-supply of blood, the cardiomyocytes in the affected region permanently lose their ability to contract. This in turn gradually weakens the overall heart function. A new therapeutic approach based on the injection of gel into the infarcted area aims to support the healing and to inhibit adverse remodelling that can lead to heart failure. An accurate computational model is the basis for obtaining a better understanding of the heart mechanics, in particular, how myocardial infarction and gel injections affect its pumping performance. We are using the in-house code SESKA which is based on the meshfree moving least square approximation scheme as a computational framework. To model the passive mechanical behaviour we employ a nonlinear transversly isotropic material law. The main focus of this contribution is to show how gel injections influence the mechanics of the left ventricle during diastolic filling and systolic isovolumetric contraction in the necrotic phase.

KEY WORDS
Heart modelling, Myocardial infarction, Injection therapy, Meshfree methods.

1 Introduction
Myocardial infarction and the cardiac dysfunction linked to it constitutes a severe health problem. The reason for a myocardial infarction is the blockade of a heart coronary. Due to an associated oxygen under-supply myocytes in the region nearby die what in turn reduces the amount of contractile tissue and gradually weakens the overall heart function. A new therapeutic approach is based on the injection of a gel into the infarcted heart. Computational methods can be used for obtaining a better understanding of how myocardial infarction affects the heart’s pumping performance and in turn can help to design suitable therapeutic treatment.

Studying computationally the influence of biomaterial injections into an infarcted heart began only a few years ago, see KORTSMIT et al. [8], WALL et al. [16], WENK et al. [18], WENK et al. [17]. The usual method of choice to solve this kind of cardiac mechanics problem is the finite element method. These studies are restricted to the left ventricle of the heart. To reduce the complexity of the computational model the left ventricle is idealized by an ellipsoidal geometry, see WALL et al. [16]. Compared to the healthy remote tissue the infarcted tissue is described with modified material properties. The latter change throughout the healing process, see e.g. GUPTA et al. [5], HOLMES et al. [7]. Research aiming at developing and optimizing injectable gels suitable to improve cardiac function has been initiated only recently, see e.g. NELSON et al. [11] giving a good overview. A great variety of gels have been investigated ranging from biological to synthetic.

In this work, preference is given to a moving least square (MLS)-based meshfree method as a computational framework. As MLS is very well documented in literature, we refer the reader for further details to e.g. [1, 9, 10]. It is shown that it can be effectively applied to cardiac mechanics to study a new therapeutic method of myocardial infarction. More specifically, an infarcted left ventricle of a rat during the diastolic filling and systolic isovolumetric (isochoric) contraction is considered. Its geometry is represented by a truncated ellipsoidal model. The impact of gel injections into the infarcted area concentrates on the necrotic healing stage. The structure of this paper is as follows: In section 2 the used constitutive models for cardiac mechanics are discussed. Section 3 contains a numerical study of an infarcted and injected rat left ventricle. Section 3 briefly sums up the innovational aspects and the findings of this article.
2 Constitutive model of the left ventricle

2.1 Passive stress model

To describe the passive stress within the left ventricle’s wall the strain energy function

\[ W = C \frac{(Q - 1)}{2} + C_{\text{compr}}(J \cdot \ln J - J + 1) \]  (1)

with

\[ Q = b_{11} E_{11}^2 + b_{22} E_{22}^2 + b_{33} E_{33}^2 + b_{12}(E_{12}^2 + E_{21}^2) + b_{13}(E_{13}^2 + E_{31}^2) + b_{23}(E_{23}^2 + E_{32}^2) \]  (2)

(see USYK et al. [15]) is employed here, treating the left ventricle as nonlinear, orthotropic and nearly incompressible. Herein, the components \( E_{ij} \) of the Green stain \( E \) are associated with a local Cartesian basis \( V_i \) with \( V_1 \) orientated in the direction of the fibre, i.e.

\[ E = E_{11} V_1 \otimes V_1 + E_{22} V_2 \otimes V_2 + \]
\[ E_{33} V_3 \otimes V_3 + E_{12}(V_1 \otimes V_2 + V_2 \otimes V_1) + \]
\[ E_{13}(V_1 \otimes V_3 + V_3 \otimes V_1) + \]
\[ E_{23}(V_2 \otimes V_3 + V_3 \otimes V_2) \]  (3)

The second term in Eq. (1) serves to enforce the assumed nearly incompressible material behaviour where \( J = \sqrt{\det(2E + 1)} \) denotes the Jacobian. The parameters \( b_{ij} \) are constants which determine the contribution of each strain component to the strain energy.

2.2 Active stress model

In the active stress formulation the sum of a passive stress \( S_P \) representing the passive mechanical response of tissue to loads and an active contractile stress \( S_A \) defines the total stress

\[ S = S_P + S_A \]  (4)

The passive stress is obtained from the passive mechanical constitutive law, so that when there is no active stress \( (S_A = 0) \), the myocardium simply behaves passively. The active stress acts in the direction of the fibre \( V_1 \); that is,

\[ S_A = T_A V_1 \otimes V_1 \]  (5)

The variable \( T_A \) represents the active tension developed in the myocyte and is derived from a cellular model of tension development in myocytes. For the purpose of studying the tissue-level mechanics of the heart the model of GUCCHIONE et al. [4] is adopted. This model was derived from biophysical considerations of calcium dynamics and crossbridge formation. The parameters used in the model were calibrated to fit experimental tension test data of a dog, while the magnitude of the active tension was modified to represent that of a rat. The Guccione model predicts the tension according to

\[ T_A = T_{\text{max}} \frac{C a_{\text{max}}^2}{C a_{\text{max}}^2 + E C a_{50}(l)} C_t(l, t) \]  (6)

where \( C_t \) represents the time transient, a function of time and sarcomere length, \( E C a_{50}^2 \) represents the calcium concentration at 50% tension, \( C a_0 \) is the peak intracellular calcium concentration, \( l \) is the sarcomere length, and \( T_{\text{max}} \) is the maximum tension developed. The functions \( C_t \) and \( E C a_{50} \) are given by

\[ C_t = \frac{1}{\pi} (1 - \cos \omega (l, t)) \]  (7)
\[ E C a_{50}(l) = \begin{cases} \frac{C a_{\text{max}}^2}{\sqrt{\exp[B(l-t_0)]-1}} & \text{for } l > l_0, \\ 0 & \text{for } l \leq l_0, \end{cases} \]  (8)

where \( t_0 \) is the time at maximum tension, \( B \) is a constant and \( l_0 \) is the sarcomere length below which there is no active tension developed. The sarcomere length is a function of the stretch with respect to the reference configuration in the fibre direction so that

\[ l = l_R \sqrt{2E_{R} + 1} \]  (9)

where \( l_R \) is the sarcomere rest length in the undeformed reference configuration and \( E_R \) the direct component of Green strain in the fibre direction. The time-dependence of the active tension is described by

\[ \omega (l, t) = \begin{cases} \frac{\pi}{t_0} & \text{for } 0 \leq t < t_0, \\ \pi \left[ \frac{t-t_0}{t_r(t)} + 1 \right] & \text{for } t_0 \leq t < t_0 + t_r, \\ 0 & \text{for } t \geq t_0 + t_r, \end{cases} \]  (10)

which also takes into account the influence of the current sarcomere length on the duration of active contraction, that is, the length-dependence of the calcium sensitivity of proteins that cause tension development. The constant \( t_0 \) is the time to peak tension and \( t_r \) is the duration of the relaxation period described as a function of the sarcomere length

\[ t_r = m \cdot l + b \]  (11)

with constants \( m \) and \( b \). The parameters used in the Guccione model are given by \( T_{\text{max}} = 56.7 \text{kPa} \), \( C a_0 = 4.35 \mu M \), \( C a_{\text{max}}^2 = 4.35 \mu M \), \( B = 4.75 \mu m \), \( t_0 = 1.58 \mu m \), \( t_0 = 250 \mu s \) \( m = 1.0489 \mu m \) and \( b = -1429 \mu s \).

2.3 Homogenization approach

The infarcted and injected myocardial tissue is modelled as homogenized, i.e. averaged, material response. For this let us introduce a stored energy function of the following form:

\[ \psi = \sum_{I=1}^{m} n_I \psi_I(E) \]  (12)
where \( m \) denotes the number of superimposed material phases, \( n_l \) the volume fractions associated with the stored energy function \( \psi_I \) representing each constituent’s material behaviour. It holds \( \sum_{I=1}^{m} n_l = 1 \). Consequently, the averaged second Piola-Kirchhoff stress tensor is given by

\[
S = \frac{\partial \psi}{\partial E} = \sum_{I=1}^{m} n_I \frac{\partial \psi_I}{\partial E}
\] (13)

In particular, the healthy myocardium consists of one single active anisotropic phase, the injected infarct region consists of two passive phases, an anisotropic and an isotropic one, the latter for the injected biogel.

### 3 Numerical study

This numerical study aims to investigate the influence of an infarct and an injection of a hydrogel into the infarct area of a rat’s left ventricle (LV). To represent the geometry, a truncated ellipsoid is used which is commonly described in terms of some prolate ellipsoidal coordinates \((\xi, \eta, \theta)\) which are related to the Cartesian ones \((x, y, z)\) by

\[
\begin{align*}
x &= C \sinh \xi \sin \eta \cos \theta \\
y &= C \sinh \xi \sin \eta \sin \theta \\
z &= C \cosh \xi \cos \eta
\end{align*}
\] (14)

In accordance to NIEDERER et al. [12] the endocardial and epicardial radius at the widest point is 2.4\,mm and 5.1\,mm, respectively. The distance from the apex to the base is 11.5\,mm for the endocardium (endo) and 13.2\,mm for the epicardium (epi). This corresponds to \( \xi_{\text{endo}} = 0.31, \xi_{\text{epi}} = 0.60 \) and the focal lengths \( C_{\text{endo}} = 7.61\,mm, C_{\text{epi}} = 8.01\,mm \). For the cavity volume it follows \( V_{\text{cav}} = 156\,\mu l \). The varying fibre directions throughout the wall are adopted from RUCKEN et al. [14]. The cavity pressure is represented by a surface pressure \( p_{\text{cav}} \) applied to the endocardial wall. With respect to geometric boundary conditions the natural deformation of the LV during a heart beat shows that almost the whole LV undergoes vertical, horizontal and transversal movements simultaneously. Only the movement of the base is restricted. Hence, to model that, at the base the endocardial ring is fixed and the base’s surface displacement is restrained in vertical direction.

Using the parameters \( C_{\text{compr}} = 3.0\,kPa \) and \( b_{ij} \) in accordance to NIEDERER et al. [12], the strain energy function Eq. (1) used to model the healthy LV has been calibrated by adapting the weighting factor \( C \) with regards to pressure-volume relations given in literature, see Fig. 1. The coefficients finally used in Eq. (1) are summarized in Tab. 1 yielding a transversal isotropic constitutive tensor.

A fatal rupture of the infarct tissue mostly happens during the necrotic phase caused by increased wall stresses [7]. Due to that we consider an infarct at that healing stage and investigate the influence of a hydrogel injection directly into the infarct zone (green). To represent the fact that the injectate does not have a sharp edge we consider a so called overlap zone (black) into the healthy remote (blue) having a reduced gel volume fraction compared to the gel volume fraction of the infarct area, see Fig. 3. The infarct zone and overlap zone have been incorporated by intersecting the truncated ellipsoid with two spheres of different radii. Finally, we distinguish three cases: (a) healthy LV, (b) infarcted LV, (c) infarcted and injected LV. The volume fractions for those three cases can be found in Tab. 2. According to GUPTA et al. [5], HOLMES et al. [7] for the

![Figure 1. pressure-volume relations for the left ventricle model using the present local Maximum Entropy approximation approach and a MLS approximation approach compared with data from NIEDERER et al. [12], CINGOLANI et al. [3], OMENS et al. [13], HERRMANN et al. [6]](image1)

![Figure 2. pressure-volume relations during diastolic filling of (a) healthy, (b) infarcted (c) injected left ventricle using the present local Maximum Entropy approximation approach](image2)

<table>
<thead>
<tr>
<th>( C )</th>
<th>( b_{ff} )</th>
<th>( b_{ss} )</th>
<th>( b_{nn} )</th>
<th>( b_{fs} )</th>
<th>( b_{fn} )</th>
<th>( b_{ns} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0,kPa</td>
<td>2.8</td>
<td>1.0</td>
<td>1.0</td>
<td>6.4</td>
<td>1.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

Table 1. Strain energy function coefficients

![Figure 3.](image3)
infarct region we double the stiffness parameters compared to those which are used for the healthy remote. The hydrogel is described by a Neo-Hookean material model using the material parameters $\mu = 24.6 \text{ Pa}$ and $\lambda = 983.6 \text{ Pa}$ determined from unpublished experiments. To represent the wall thinning effect in case (b) the infarct’s volume contains 90% infarct material and 10% of a dummy material with negligible stiffness emulating the dead material transported away on micro-structural level. The hydrogel-treated infarct region case (c) is made up of a homogenized mixture of infarct and hydrogel material. Basically, the volume of the injectate in that case replaces the dummy material of case (b). The overlap zone consists of 95% healthy tissue and 5% hydrogel.

For the cavity pressure $p_{\text{cav}} = 1 \text{ kPa}$ a at the end of diastolic filling, comparing the healthy with the infarct case in Fig. 2 an overall reduction in cavity volume is observed which indicates that the overall infarct stiffness is increased in the considered necrotic healing stage. This is reasonable and also reported in literature, e.g. [2, 7], as the resulting infarct stiffness takes into account two kinds of effects: (i) A slight reduction in stiffness as a portion of dead myocytes has been transported away leading to a lower material density on micro-structural level and thus, a reduced effective wall thickness. (ii) A significant increase of stiffness of the remaining infarcted myocardium [5]. The homogenized, i.e. averaged, stiffness in the infarct zone is consequently higher than in the healthy remote explaining the reduction in LV compliance. For the injected case, the end-diastolic cavity volume is predicted the smallest which leads to the conclusion that the injectate is fairly stiff and hampers diastolic filling considerably.

In contrast to the diastolic filling phase, the left ventricle during the systolic isovolumetric phase is subjected to active contraction at constant cavity volume, causing a significant increase in cavity pressure. The resulting fibre stresses at the end of the isovolumetric phase are depicted in Fig. 4 for case (a), Fig. 5 for case (b) and Fig. 6 for case (c). On the one hand, the fibre stresses are drastically reduced within the infarcted region for the untreated infarct...
case (b) and the injected infarct cases (c) compared to the healthy case (a). On the other hand it can be observed that at the interface between the healthy and infarcted area in case (b) the maximal fibre stresses are greater than for the healthy case (a). Studying the injected case (c), it can be seen that the injection relieves this highly stressed zone of case (b) even below healthy levels.

4 Conclusion

4.1 The applicability of the model

The objective of the present investigation is not to provide definitive, quantitative results for a realistic LV. Instead, the focus of the contribution has been to study qualitatively the influence of hydrogel injections into an infarcted left ventricle, modelled by a geometry that is simple yet able to capture key features. Of particular interest are representative values for the pressure, volume, deformation, and stress quantities. In this regard, for the sake of simplicity a rotational symmetric geometry is used and an overlap zone representing a more realistic gel distribution is considered. Further, the active contraction is simultaneously initiated throughout the LV. Attention is restricted to the necrotic healing phase by considering a grade 1 infarct, with the assumption that the amount of injectate is equal to the amount of removed tissue for both the infarct and the overlap zone.

4.2 Novel aspects of this contribution

A meshless method is used as the basis for the numerical model and simulations. A strain invariant-based stored energy function is introduced, allowing frame-invariant and more compact expressions for the stress tensors and material tensors. A homogenization approach is introduced to account for representative material behaviour of an arbitrary mix of different materials and volume fractions. The impact of hydrogel injection is investigated and compared with the healthy and infarcted case.

4.3 Findings

This investigation shows that gel injections are able to reduce maximal fibre stresses caused by an infarct. The gel stiffness hampers the diastolic filling which is expected to influence pumping function as a side effect. A reduction of maximal fibre stresses is of importance with respect to the prevention of fatal rupture, which typically occurs during the necrotic phase. This could be more likely in the highly stressed area, which on the basis of the results presented can be found at the interface between the infarct and healthy remote. The presence of stress peaks in that area is explained by the discontinuity of stiffness and contraction behaviour (contracting, non-contracting).

Acknowledgements

The research leading to this work has been supported by the Centre for High Performance Computing of South Africa. The financial support of the Claude Leon Foundation through a postdoctoral fellowship for D.L. is gratefully acknowledged. Furthermore, we want acknowledge the contribution of Professor B. Daya Reddy (Centre for Research in Computational and Applied Mechanics, University of Cape Town, Cape Town, South Africa) in aiding the development of the computational LV model.

References


