AUTOMATIC MYOCARDIAL INFARCTION SIZE EXTRACTION IN AN EXPERIMENTAL MURINE MODEL USING AN ANATOMICAL MODEL

Tiago Esteves[1,2] *M. Valente*[2] *D. S. Nascimento*[2] *P. Pinto-do-Ó*[2] *P. Quelhas*[1,2]

[1] Departamento de Engenharia Electrotécnica e de Computadores
Faculdade de Engenharia, Universidade do Porto
Rua Dr. Roberto Frias, 4200-465 Porto, Portugal
[2] INEB - Instituto de Engenharia Biomédica
Rua do Campo Alegre, 823, 4150-180 Porto, Portugal

ABSTRACT

Experimental rodent models of induced ischemic injury have been extensively used in biomedical research to study molecular, cellular and histological alterations following myocardial infarction.

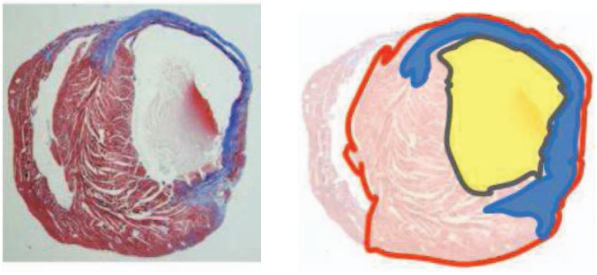
These models are increasingly employed to assess the potential of newly developed therapies for functional restoration of the damaged heart. Such studies are based on myocardial infarction induction followed by different therapeutic interventions and subsequent analysis of the infarct size. This analysis is used to evaluate the extent to which such interventions meet recovery of the lost myocardial tissue. Infarct size is defined as the percentage of the left ventricle affected by coronary artery occlusion.

The infarct size is traditionally estimated manually delineating the infarcted and normal tissue areas in the left ventricle of the excised heart. However, this is a time-consuming, arduous and prone to bias process. Herein, we developed an anatomic model, adapted through expectation maximization, which allows for fully automatic analysis of the data. Experimental validation is performed comparing the proposed approach with manual annotation. The results obtained through anatomical model adaptation were coherent with those manually obtained and the differences where never higher than 10%.

Index Terms— Myocardial infarction size, anatomical model, expectation maximization.

1. INTRODUCTION

Acute myocardial infarction (MI) is one of the major causes of premature morbidity and mortality worldwide. It results from the occlusion of coronary arteries and the establishment of tissue ischemia which can lead to heart failure. To study the lesions subjacent to this health condition and test the efficiency of potential therapeutic interventions, assays are conducted in animal models by inducing MI, e.g. by permanent ligation of a main branch of the left coronary artery [1, 2]. The latter procedure models several of the pathological features observed in the human diseased heart. In these assays myocardial infarction size, which is defined as the percentage of the left ventricle (LV) affected by the coronary occlusion, is one parameter measured obtained by the analysis of the dissected heart stained with Masson's Trichrome, that enables the identification of collagen deposition, a hallmark of established infarction [1, 3].



(a) (b)

Fig. 1. Example of a heart cross section image: a) Original image; b) Delineation of the heart tissue. The affected tissue is marked by blue color, the LV is bounded in red and the LV lumen is shown in yellow.

Myocardial infarction size in animal model systems is estimated by identifying the percentage of infarcted tissue in the LV of the heart (figure 1). In this evaluation task researchers must delineate the contour of the infarcted area and that of the LV. The right ventricle (RV) region is ignored in this analysis since it is not affected by the MI induction [3, 4].

Currently the infarct size analysis is a fully manual task performed by biologists; it is time-consuming, arduous and prone to subjective bias.

To automatically perform such analysis it is necessary to select both healthy and infarcted tissue regions. The task of automatic tissue classification was already considered by using automatic digital image segmentation approaches [4, 5]. Semi-automatic and automatic segmentation techniques were applied to this problem. However, those techniques still re-

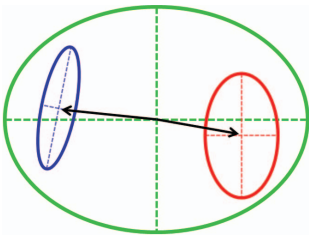


Fig. 2. Anatomical model assumed for the heart tissue.

quire manual user interaction to perform the delineation of the RV, which is not considered in the analysis. Additional manual correction of tissue anomalies (tear) and retained-blood areas manual removal are also required [5]. This motivates development of fully automatic approaches for such analysis. Our approach is based on a simple anatomical model for the segmentation of the heart cross sections. This model is adapted through Expectation Maximization (EM) which allows for fully automatic analysis of the data.

2. METHODOLOGY

To automatically obtain the infarct size it is necessary to determine the extension of the regions of healthy and infarcted tissue. This is performed based on histological cross sections collected from the heart, stained with an histological staining that enables the identification of the infarcted tissue in blue.

We propose a model based methodology for the segmentation of the heart tissue. We define an anatomical model similar to the structure of the heart which iteratively evolves until achieving the best fit to the heart tissue in the image. The model parameters are estimated through EM.

2.1. Unsupervised tissue segmentation through model adaptation

In order to perform heart tissue segmentation by using an anatomical model we must define a model and a way to adapt such a model to existing image data. As we observe in images from the heart sections (figure 1, 4, 5), the heart tissue has an oval shape with two holes inside its overall region (lumens).

Based on this standard structure the anatomical model chosen for this task was an ellipsoid heart shape with two smaller ellipsoids inside. The model governs the size and position of each ellipsoid as well as the spatial relationships between them (figure 2). The spatial relationships imposed are: all lumen ellipsoids must be inside the heart ellipsoid, and left and right lumen ellipsoids must be on separate side of the minor axis of the heart ellipsoid.

Considering as hidden variable the real location and scale of the heart tissue regions Z and the input image data as X we can assume a model for our anatomical model parameterized by θ for which the likelihood functional is:

$$L(\theta; X, Z) = P(X, Z|\theta). \quad (1)$$

Given that we have three different regions to adapt the model parameters θ can be divided into those responsible for the modeling of each part:

$$\theta = \{\theta_{ht}, \theta_{rl}, \theta_{ll}\}, \quad (2)$$

where θ_{ht} are the parameters for the heart ellipsoid and θ_{rl} and θ_{ll} are the parameters for the right and left lumen ellipsoids respectively.

As the parameters govern the position and shape properties of ellipsoids we have that:

$$\theta_{ht} = \{c_{ht}, e_{ht}, \sigma_{ht}, o_{ht}\}, \quad (3)$$

where c_{ht}, e_{ht}, σ_{ht} and o_{ht} are the position, eccentricity, scale and orientation of the ellipsoid of the total heart tissue respectively. Similar parametrization is performed for the lumen ellipsoids' parameters (θ_{rl}, θ_{ll}).

In a similar way the heart regions hidden variable can be specified for each different parts of the model:

$$P(X, Z|\theta) = P(X, Z_{ht}, Z_{ll}, Z_{rl}|\theta), \quad (4)$$

where Z_{ht}, Z_{ll} and Z_{rl} correspond to the real heart tissue, left lumen and right lumen regions, respectively.

By using Bayes rule and exploring inherent conditional independence between the different regions given the parameters we obtain:

$$P(X, Z_{ht}, Z_{ll}, Z_{rl}|\theta) = P(X, Z_{rl}|\theta)P(X, Z_{ll}|\theta)P(X, Z_{ht}|\theta), \quad (5)$$

where we assume that each tissue regions' probability distribution is independent of all other given the parameters of the model. This provides an adequate framework where we can sequentially estimate the heart, LV and RV tissue regions and the corresponding parameters through the EM algorithm.

The model adaptation process using EM is initiated with the placement of the anatomical model in the center of the image with a scale adequate to the image dimensions (figure 3a). Given the initial model parameters the adaptation of the anatomical model is performed iteratively, starting with the heart tissue ellipsoid followed by the left and right ventricles' lumens.

In Figure 3 we can observe the sequential steps of the anatomical model's adaptation. At each step, from the current parameters (figure 3 a, c, e), a mask of the current model position is built (figure 3 b, d, f). All the masks have the region of interest represented as white, the background represented as black and regions not considered in the process as gray. From the image information inside the regions of the current mask and background we obtain a threshold value used to segment the original image and obtain an estimate of the true region under adaptation (figure 3 c, e, g). This estimated region, together with the current parameter values, allows the maximization of the related parameters (solid lines in figure 3 c, e, g). It is at this point that the restriction on each ellipsoid size and position are enforced by limiting the estimated parameters to only possible values (position and size limitations).

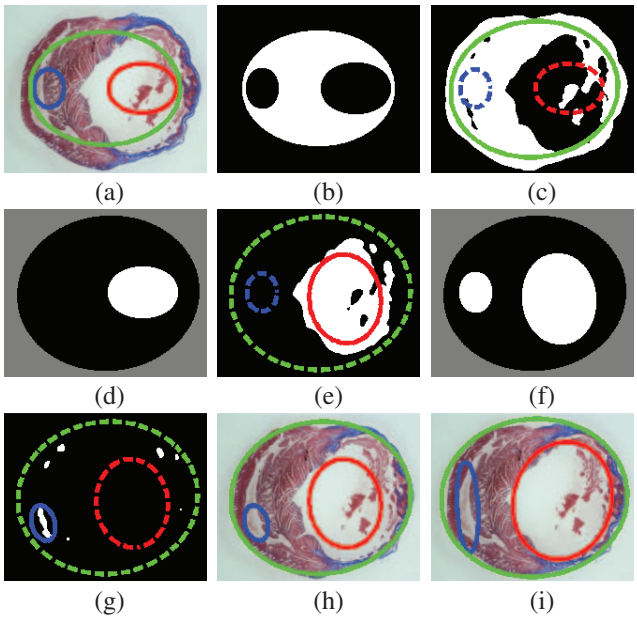


Fig. 3. Sequential adaptation of the anatomical model: a) initial model placement; b) mask obtained from the model used to compute $P(X, Z_{ht}|\theta)$; c) model's shape after the adaptation of θ_{ht} (green continuous line); d) mask obtained from updated model used to compute $P(X, Z_{ll}|\theta)$; e) model's shape after the adaptation of θ_{ll} (red continuous line); f) mask obtained from updated model used to compute $P(X, Z_{rl}|\theta)$; g) model's shape after the adaptation of θ_{rl} (blue continuous line); h) anatomical model after one iteration; i) final adapted anatomical model. The dashed lines represent the ellipses that are not optimized in the specific adaptation step.

The process is continued until no alteration of parameter is performed or a limit number of iterations has been reached.

The robustness of this method allows for usable results even when the heart cross section show a highly deformed anatomical structure, when there is blood in the ventricle and even when the heart tissue is torn (figure 4).

Finally, to evaluate the infarct size it is necessary to identify both normal and infarcted regions within the adapted anatomical model.

2.2. Normal and infarcted tissue identification

To measure the infarct size we use the final adapted anatomical model spatial configuration. First we estimate the region of the LV, where the infarct size evaluation is performed. This is performed by obtaining the distance from the center of the LV lumen to the center of the RV lumen (figure 5a). The circular limit defined by that distance and the center of the LV is where we assume the LV tissue ends. The final LV tissue region estimated is shown in figure 5b. To measure the infarct size it is necessary to define the regions of normal and infarct tissue within the LV. This is performed by splitting the LV into two regions using two radial separations. We then iteratively

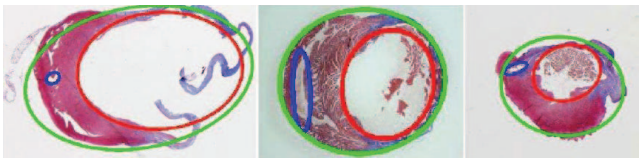


Fig. 4. Model adaptation results for irregular heart cross sections: heart with torn LV wall (left); heart with blood in the LV (middle and right).

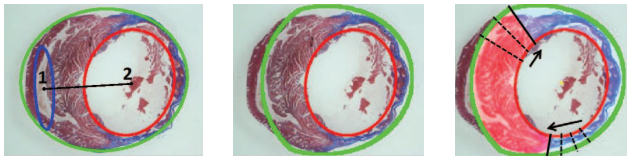


Fig. 5. Different steps in the infarct size estimation process: (a-b) LV tissue estimation; (c) Identification of the normal and infarcted tissue within the LV. The black continuous line shows the final radial separation of each tissue type.

improve the initial position for each section by analyzing the average intensity of the green image channel within each region (figure 5c). The pixels intensity is better distinguished in this channel. We move the separators so that the difference between the average green image channel level intensity value between each of the two regions is increased. The motion of the separators is performed iteratively in 5 degree steps. The process stops when no further improvements are possible by moving the separators' positions. The black continuous line in figure 5c shows the final radial separation of each tissue type.

From the information of the regions of infarcted and healthy heart tissue we are able to estimate the infarct size.

3. RESULTS

We performed the infarct size evaluation on sections of five complete hearts which represents experiments in 57 images. All the images were provided by INEB - Instituto Nacional de Engenharia Biomédica by the NEWTherapies Group.

The infarct size was calculated manually and using the proposed approach by two different methods:

Area measurement - The infarct size is calculated by dividing the LV infarct area by the total area of the LV tissue [4, 6].

Midline length measurement - To perform the midline measurement we need to define the LV midline and within this we have to identify the LV infarcted midline. First, we automatically find the LV midline by tracing lines from the center of the lumen to the exterior of the heart tissue. The midline is given by midpoint between tissue borders. The points of the middle line where there is more infarcted tissue than normal tissue (in the radial direction) are used to define the LV infarct midline. Secondly, we divide the length of the LV infarct midline by the total length of the LV midline [4, 6].

Table 1. Infarct size measurement according to the area and the midline length measurements. Manual results contemplate the average value of the infarct size obtained by four experts and also the minimum and maximum values obtained.

Measurement	*Area (%)*		*Midline (%)*	
Heart	*Manual* (min;max)	*Model*	*Manual* (min;max)	*Model*
#1	25 (21;28)	23	40 (39;41)	34
#2	42 (39;44)	52	68 (66;70)	65
#3	37 (28;42)	32	42 (36;47)	38
#4	28 (27;30)	27	36 (35;37)	35
#5	19 (18;19)	21	33 (31;34)	33

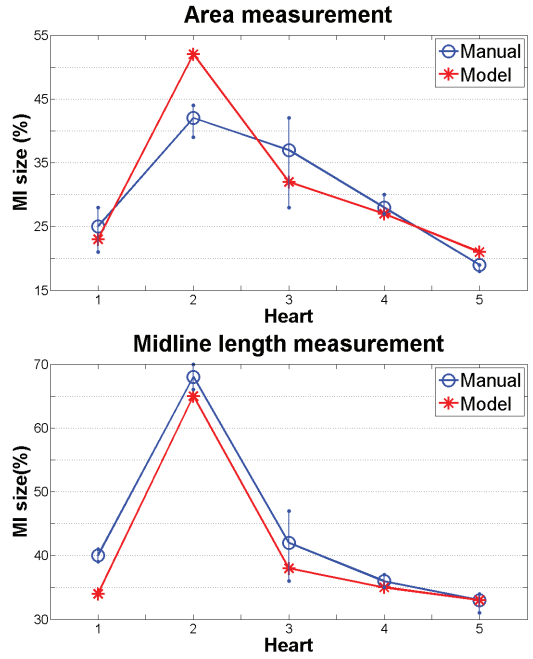


Fig. 6. Graph representation of the manual and model based results of MI size analysis: Top) Area measurement; Bottom) Midline length measurement (error bars for manual results are shown).

To evaluate the performance of the proposed approach, we compared the results with the results obtained by four investigators with extensive training on MI size quantification (experts). Table 1 shows the average value of the infarct size over all cross-sections of each heart. In case of manual evaluation the results are the average value of the infarcted size obtained by the four experts. Tissue segmentation through anatomical model adaptation by EM produced results with differences never greater than 10% (6% for midline length measurement). These results show high consistency and proximity between manual and model based results (figure 6).

In the manual results an average variation inter experts of 3% and 2% was found in the case of area measurement and midline measurement respectively, with a maximum difference of 9% and 6% also respectively. This indicates that model based and manual MI size measurements are coherent and that differences between automatic and manual measurements are close to the range of inter expert evaluation variability.

This approach is completely automatic, representing a considerable advantage in terms of analysis work by the researcher. Otherwise the analysis would be performed manually, a process that takes approximately 30 minutes for each heart.

4. CONCLUSION

The proposed approach enabled the fully automatic measurement of myocardial infarct size in cross sections of the heart, based on images of heart tissue regions requiring no human intervention. Given the segmentation results, the infarct size was automatically estimated. The results of infarct size obtained using the anatomical model were in close agreement with the manual annotation with differences never higher than 10%.

As future work, both the adoption of a more specific anatomical model for the heart and the possibility for a final deformable model adaptation stage for better shape estimation will be researched.

5. REFERENCES

[1] N. Degabriele, U. Griesenbach, and K. Sato, "Critical appraisal of the mouse model of myocardial infarction," *Experimental Physiology*, vol. 89, no. 4, pp. 497–505, 2004.

[2] E. Lutgens, M. Daemen, and E. Muinck, "Chronic myocardial infarction in the mouse: cardiac structural and functional changes," *Cardiovascular Research*, vol. 41, pp. 586–593, 1998.

[3] J. Takagawa, Y. Zhang, and M. Wong, "Myocardial infarct size measurement in the mouse chronic infarction model: comparison of area- and length-based approaches," *Journal of Applied Physiology*, vol. 102, pp. 2104–2111, 2007.

[4] D Nascimento, M. Valente, T. Esteves, M.F. Pina, J.G. Guedes, Freire A., P. Quelhas, and P. Pinto-do Ó, "Miquant - semi-automation of infarct size assessment in models of cardiac ischemic injury," *Plos One*, vol. 6(9), pp. 1–8, 2011.

[5] T. Esteves, M. Valente, D. Nascimento, P. Pinto-do Ó, and P. Quelhas, "Automatic and semi-automatic analysis of the extension of myocardial infarction in an experimental murine model," *Proceedings of IbPRIA, LNCS 6669*, pp. 151–158, 2011.

[6] M. Pfeffer, J. Pfeffer, and M. Fishbein, "Myocardial infarct size and ventricular function in rats," *Circulation Research*, vol. 44, pp. 503–512, 1979.