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Segmentation of the blastocyst structures using Image Processing and Machine Learning tools

M. Villota[1,2], J. Ayensa-Jiménez[1,2], M. Doblaré[1,2] and J. Heras[3]

[1] Aragón Health Research Institute (IIS Aragón) , Aragón, Spain
[2]Aragón Institute of Engineering Research (I3A)
University of Zaragoza, Aragón, Spain
[3] Department of Mathematics and Computer Science
University of La Rioja, La Rioja, Spain

Abstract

Embryo selection is a fundamental and indispensable step to ensure the success of in vitro fertilization. There are two techniques to perform embryo selection: preimplantation genetic screening and embryo morphological grading. However, even with these techniques, the embryo implantation probability is barely 65% making extremely difficult to evaluate the implantation potential. This is mainly due to the lack of markers, and the subjectivity associated with experience, judgement, and training of the embryologists. In contrast, a segmentation of the embryo structures offers detailed, quantitative, and objective assessments; and with that, information to predict the pregnancy outcome of embryos. In this work, two independent methods for embryos' component segmentation are proposed. One is based on the combination of image processing techniques with genetic algorithms, and the other on a Deep Learning segmentation approach. Both methods allow us to approach state of the art results for embryos' component segmentation.

Keywords: in vitro fertilization (IVF), preimplantation genetic screening, blastocyst grading, embryo quality assessment, image processing techniques, semantic segmentation.

1 Introduction

In Vitro fertilization (IVF) is an effective solution to the problem of infertility, and also for single mothers or same-sex couples who want to become parents [1]. In the IVF process, woman's ovaries are hyper-stimulated in order to retrieve multiple eggs which are then fertilized outside the body. The fertilized eggs are cultured under controlled environmental conditions until they reach the blastocyst stage (5^{th} – 6^{th} day after fertilization). The blastocyst (Figure 1) is the first morphologically differentiated state of the human pre-implantation embryo, in which cellular structures are arranged in four regions: the Trophectoderm (TE), which surrounds the Blastocoel (BC) and the Inner Cell Mass (ICM) and the Zona Pellucida (ZP) [2].

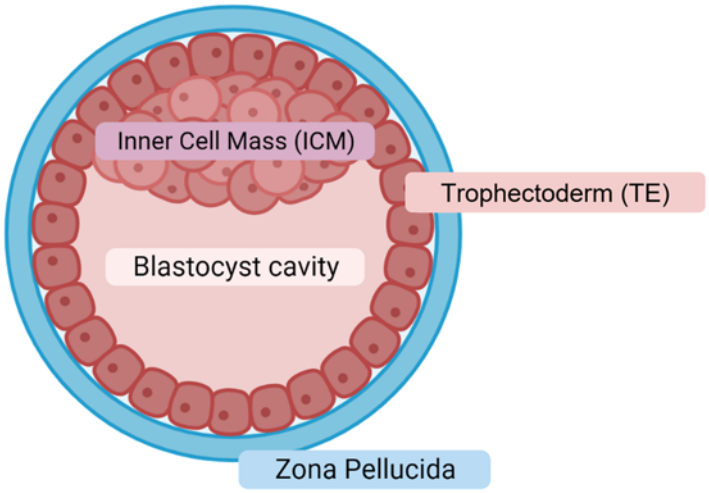


Figure 1: Scheme of a blastocyst, with the different relevant structures annotated.

Multiple embryos are generated to compensate the fact that not all of them develop with an implantation potential [3]. Namely, blastocysts are evaluated and only those with top quality are transferred to the uterus. The current best method of assessment of embryo quality is Preimplantation Genetic Screening (PGS), which is excellent predicting non-implanting embryos but has a modest positive predictive value [4]. However, the utilization of this technology remains low due to the incremental cost with embryo biopsy and genetic testing [5]. Moreover, this technique is very invasive since cells are taken from the embryo at a very early stage and it is possible that cells with important genetic material are being collected: when using this technique, it is extremely important to avoid cells from the ICM because they will be the cells of the embryo's body [6]. Due to these reasons, embryo morphological grading remains the current standard for embryo selection. This technique is based on visual inspection of morphological characteristics and development rate [5]. It is important to highlight that the probability of pregnancy of an embryo with the best characteristics is 65% [7]. This low correlation between embryo classification and pregnancy is due, among other things, to the great subjectivity related to judgement, training, and expertise of the embryologist; in addition to the lack of knowledge of the markers that determine the implantability of the embryo [8].

Therefore, being able to quantify why certain blastocysts have more implantation potential will help embryologists and researchers to increase success rates while minimizing the chances of multiple births due to transferring multiple embryos to increase the success rate.

Due to the aforementioned reasons, it is necessary to search for a quantitative and objective evaluation procedure in order to increase the probability of implantation success. Therefore, the objective of this work is to automatically identify the different structures of an embryo at the blastocyst stage. This could improve the workflow in both technologies (PSG and morphological grading) and could aid increasing the objectivity providing more detailed assessments and quantitative information to the embryologist to support and improve the decision-making process during an IVF treatment.

The rest of this paper is organized as follows. In the next section, we provide a description of the two developed methods for blastocyst region segmentation. Subsequently, we perform a comparison of our methods with state-of-the-art techniques. Finally, the paper ends with some conclusions.

All the code developed in this project is available on the following GitHub page: https://github.com/mavillot/Blastocyst-Seg

2 Methods

To achieve the objective of this work, an automatic segmentation of the ZP, TE and ICM regions will be performed. In particular, two independent lines of work have been developed for this purpose:

- An unsupervised pathway, based on the use of image processing techniques (which are optimized using genetic algorithms).
- A supervised pathway in which a convolutional neural network will be trained.

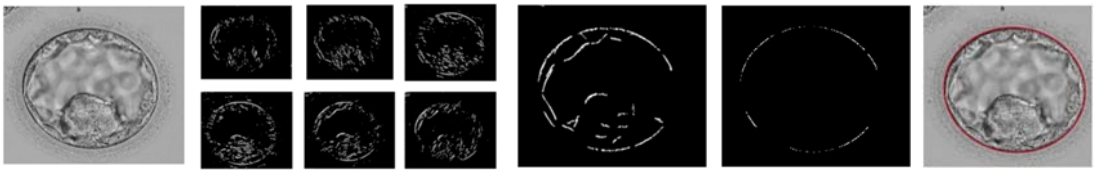
We used the publicly available blastocyst dataset [9]. It has 249 blastocyst images and the ZP, TE and ICM regions of the blastocysts' images were manually annotated by experts at Pacific Centre for Reproductive Medicine (PCRM) in Canada. This database also contains a file showing the classification of each embryo according to the grade of expansion, the grade of Trophectoderm and Inner Cell Mass; and the result of implantation (implanted, not implanted, and unknown).

2.1 UNSUPERVISED PATHWAY

The unsupervised pathway is based on the work of Saeedi [5,9] which consists of applying different image processing techniques to a blastocyst image to extract the contours of the edges of the ZP, TE and MCI regions.

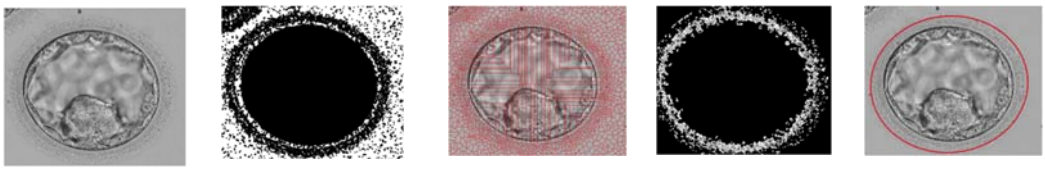
2.2 ZP

This structure is delimited by two ellipses: an inner ellipse and an outer ellipse. The proposed method consists of fitting by least squares the points of the inner and outer contour to an ellipse (one for each contour). These points are obtained by performing different operations on the image including phase congruency in 6 orientations, convex hull, Canny edges and Watershed segmentation. Figure 2 shows the different steps followed to obtain the ellipse that models the inner edge of ZP. Figure 3 shows the procedure followed to detect the outer edge of ZP. Once both ellipses have been calculated, the ZP region is perfectly delimited, see Figure 4.



a. Original image | b. Phase congruency (pc) in 6 orientations | c. Union of thresholded pc | d. Filtering with convex hull | e. Least squares

Figure 2: Detection of the inner ZP boundary



a. Original image | b. Canny and dilating | c. Watershed | d. Filtering | e. Least squares

Figure 3: Detection of the outer ZP boundary

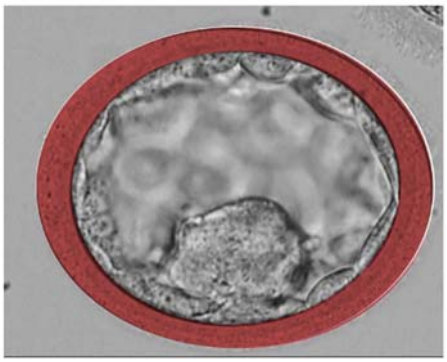


Figure 4: Segmentation of ZP

2.3 TE and ICM

The workflow for the detection of the TE and ICM structures is common. The image is divided into small regions using the Watershed algorithm and with the calculation of different textures each region is classified into two classes: textured or smooth. Biologically, TE always appears at the edge of the blastocyst and ICM in a more central position. With this information, the textured regions attached to the inner edge of ZP (calculated in the previous process) are associated with TE and the textured regions in the center are associated with ICM. These regions form the seeds of TE and ICM. All regions that are connected to the TE seed and have low intensities are added. The edges of this mask are extracted using the edge linking algorithm developed by Kovesi [10], as illustrated in Figure 5. Different regions are iteratively added to the ICM seed if they verify a similarity condition based on textures and a 8-connectivity condition. Finally, the Distance Regularized Level Set Evolution algorithm [11] is applied.

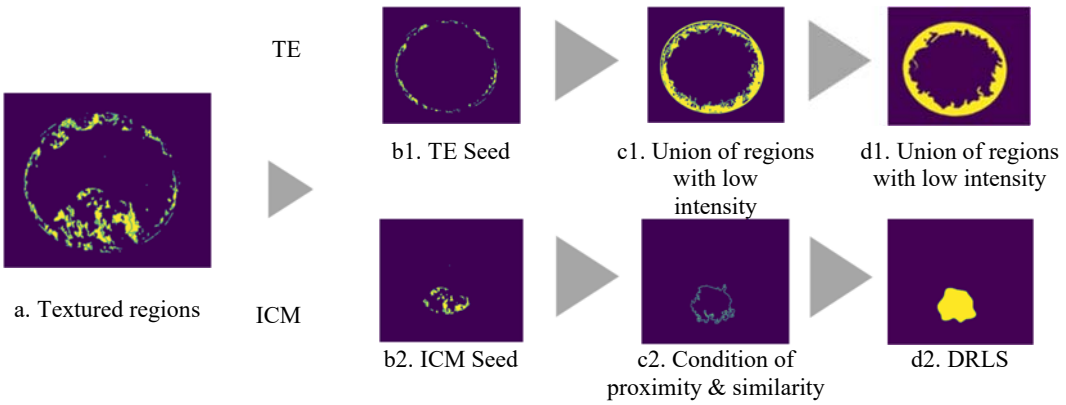


Figure 5: Segmentation of TE and ICM

Most image processing techniques involved in ZP, TE and ICM segmentation workflows have parameters that can be adjusted to improve their performance (thresholds, filter size, degree of connection...). In order to find the parameters that best adjust the segmentation of the different structures, we have used genetic algorithms [12]. These algorithms are based on Darwin's theory of evolution and are used to obtain suitable solutions to complex optimization problems. Towards that aim, the function to be optimized is established, in our case an error function (the difference between the predicted region and the gold standard) to be minimized is defined; and an also an initial population, which are different sets of parameters for which the error is calculated. The parameter sets that minimize the error the most are selected; they are crossed two by two (the values of some parameters are exchanged) according to an established crossing probability and they are mutated (adding or subtracting a random value to some parameter of the set) according to the established mutation

probability. This new set of parameters forms a new population called a generation. Genetic algorithms are iterative algorithms, so for each generation, selection, crossover, and mutation are performed. After a set number of generations, a solution is reached. The higher the number of generations, the closer the solution obtained is to the real solution. For the implementation of these genetic algorithms, we have followed the methodology proposed in [12].

2.4 SUPERVISED PATHWAY

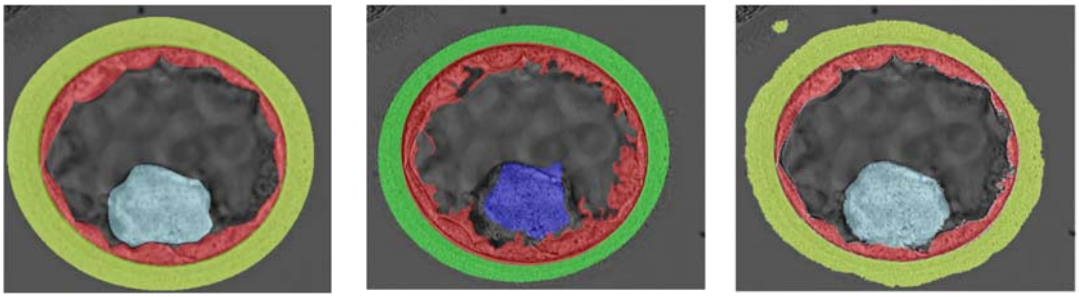
In the supervised path, masks are used to train a segmentation model. To complete the segmentation objective, a convolutional neural network will be trained, more specifically a U-Net architecture [13].

For training this network, the database has been divided into a training set (85%) and a test set (15%). For the TE and ICM segmentation, the same architecture proposed in [14] has been used and for the ZP segmentation, the basic U-Net architecture [13] was used. Both networks have been trained for 30 epochs using the Keras library and with a GPU NVIDIA GeForce RTX 3060. To evaluate the performance of the network, the masks of the test set images are obtained, and the different metrics are calculated.

3 Results

Once the two paths have been implemented, the models have been evaluated on the test set. Figure 6 shows the final result of segmenting a blastocyst following the unsupervised and supervised pathway compared with the ground truth.

For each class (ZP, TE and MCI) the problem is considered as a binary problem and the following metrics are calculated: accuracy, precision, recall, specificity and the dice coefficient. A detailed description of these metrics can be found in Harun's work [14]. In Tables 1, 2, and 3 we compare the results with state-of-the-art methods based on same dataset.



a. Ground truth b. Unsupervised c. Supervised

Figure 6: Results of the blastocyst segmentation

ZP	Accuracy	Precision	Recall	Specificity	Dice Coefficient
Farias et al. [8]	0.94	0.85	0.69	0.98	0.75
Unsupervised	0.91	0.79	0.62	0.97	0.67
Unsupervised + genetic algorithm	0.91	0.79	0.64	0.97	0.68
Supervised	**0.96**	**0.90**	**0.78**	**0.99**	**0.83**

Table 1: ZP segmentation results. In bold the best results.

Regarding the segmentation of the ZP, we observe that the proposed supervised method outperforms the Farias' model and that the unsupervised methods are not far from the state of the art. When selecting the set of parameters obtained by minimising the above-mentioned error function using genetic algorithms, we manage to slightly improve the recall and Dice coefficient's results.

ICM	Accuracy	Precision	Recall	Specificity	Dice Coefficient	Jaccard index
Saeedi et al. [5]	0.91	0.77	0.84	0.92	0.79	-
Saeedi et al. [5] with DRLS	0.93	0.84	0.78	0.96	0.83	-
Kheradmand et al. [15]	0.93	0.76	0.56	-	0.64	0.48
Kheradmand et al. [16]	0.96	-	-	-	0.87	0.77
Rad et al. [17]	-	0.79	0.87	-	0.83	0.70
Rad et al. [18]	0.98	0.89	0.92	-	0.90	0.82
Harun et al. [14]	**0.99**	**0.95**	**0.94**	-	**0.94**	**0.89**
Farias et al. [8]	0.96	0.87	0.62	**0.99**	0.67	-
Unsupervised	0.93	0.79	0.86	0.95	0.64	-
Supervised	0.98	0.91	0.84	0.99	0.86	0.78

Table 2: ICM segmentation results. In bold the best results.

TE	Accuracy	Precision	Recall	Specificity	Dice Coefficient	Jaccard index
Saeedi et al. [5]	0.86	0.69	0.89	0.86	0.77	-
Singh et al. [19]	0.87	0.71	0.83	-	0.77	0.62
Kheradmand [15]	0.9	0.69	0.8	-	0.74	0.59
Harun et al. [14]	**0.98**	**0.92**	**0.93**	-	**0.92**	0.85
Farias et al. [8]	0.93	0.80	0.59	0.98	0.67	-
Unsupervised	0.91	0.78	0.91	0.91	0.69	
Supervised	0.97	0.89	0.85	**0.99**	0.77	**0.87**

Table 3: TE segmentation results. In bold the best results.

The results for both the supervised and unsupervised pathways regarding TE and ICM are very close to those found in the literature. It is observed that the supervised model obtains better results in all metrics except recall. However, this does not lead us to discard the unsupervised workflow, since when generalising to new images only a parameter adjustment would have to be made, whereas for the U-Net model it would be necessary to retrain the network with similar images. Moreover, recall is the most relevant metric if the aim is to minimise the risk of extracting a biopsy of the ICM (which in the future will be the cells of the embryo's body), something very common for assessing implantability, but which could completely ruin the structure of the future foetus and thus its viability.

4 Conclusions and further work

In Vitro Fertilisation (IVF) is a technique whose use is increasing. Despite great advances in IVF procedures and techniques, the implantability of an embryo remains an unknown. Despite the efforts of clinicians to find the best embryos, the probability of success of an embryo considered to be excellent is only 65%.

An automatic identification of blastocyst structures is not only useful to improve the workflow in evaluation work, but also provides a source of detailed, quantitative and objective information to support embryologists in their decision-making.

Two independent workflows have been proposed for this purpose:

- An unsupervised pathway based on image processing techniques and genetic algorithms.
- A supervised pathway, a U-Net segmentation model.

With both procedures, results close to the state of the art were obtained. Although the supervised pathway has shown better results than the unsupervised pathway, it is possible that information from both procedures can be used to obtain more robust predictions. Among the next steps of this project is to identify the different structures that are formed from fertilisation of the egg to the blastocyst. To obtain quantitative information on this phenomenon so that, together with the measurements made in the blastocyst, this information can be correlated with the implantability of the embryos.

Acknowledgments

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