Using Artificial Intelligence to Improve the Evaluation of Human Blastocyst Morphology

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Abstract: The morphology of the human embryo produced by *in vitro* fertilized (IVF) is historically used as a predictive marker of gestational success. Although there are several different proposed methods to improve determination of embryo morphology, currently, all methods rely on a manual, optical and subjective evaluation done by an embryologist. Given that tiredness, mood and distinct experience could influence the accuracy of the evaluation, the results found are very different from embryologist to embryologist and from clinic to clinic. We propose the use of an objective evaluation, with repeatability and automatization, of the human blastocyst by image processing and the use of Artificial Neural Network (*i.e.*, Artificial Intelligence).

1 INTRODUCTION

Since the establishment of assisted reproduction techniques (ART) in humans the quality of the embryos in the blastocyst stage has been shown to be able to predict the efficacy of the implantation and the probability of the embryo to generate pregnancy (della Ragione et al., 2007; Ahlstrm et al., 2011). The predominant technique currently used to determine embryo quality is the morphological analysis by means of optical microscopy; this method, despite being able to establish predictive relations with the pregnancy rate, is still subjective and, in many cases, with limited reproducibility. The main problem of this method lies in the subjectivity in the interpretation of the results by the embryologists, resulting in low interobserver agreement and intraobserver reproducibility (Arce et al., 2006; Sundvall et al., 2013; Richardson et al., 2015)

According to Gardner and Schoolcraft (1999) the embryo classification is made according to three parameters: *i*) stage of expansion and hatching (EE), classified from 1 to 6, being 1 the embryo without any inner cavity (blastocoel) meaning that it not reached the blastocyst stage yet and 6 the blastocyst fully hatched; *ii*) quality of the inner cell mass (ICM) classified from A to C, being A the ICM with the highest quality and C the worst and; *iii*) quality of the trophectoderm (TE), also classified as A to C and in the same way as ICM. Examples of blastocysts classified by the Gardner & Schoolcraft system are shown in Figure 1.

For Gardner and Schoolcraft classification (1999), the technique used is the morphological assessment by stereomicroscopy that is non-invasive, however there are several other methods to classify blastocysts such as metabolism measurement (Tejera et al., 2016) and time-lapse (Tejera, Aparicio-Ruiz and Meseguer, 2017) which are also non-invasive methods. In addition, there are techniques such as blastocyst transcriptome analysis (Kakourou et al., 2013) and chromosomal screening by array comparative genomic hybridization (aCGH) (Yang et al., 2012) that are invasive. Invasive techniques are not appropriate to classify human embryos as they may jeopardize the integrity of the embryo and, consequently, decrease the probability of his implantation.

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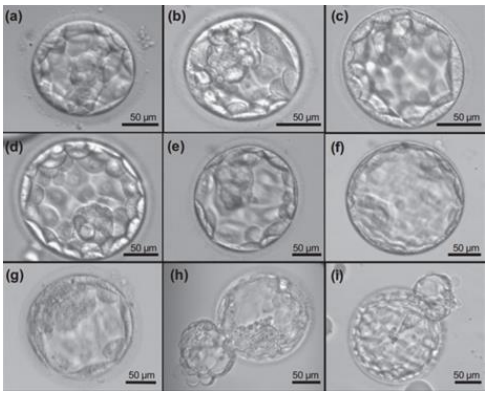

Figure 1: Illustrative images of human blastocysts classification. The first number is referred to the presence and size of the blastocoel as well as the degree of embryo expansion. The first letter is referred to the quality of the inner cell mass and (second letter) of the trophectoderm. (a) 3AA; (b) 3AB; (c) 3BA; (d) 4AA; (e) 4AB; (f) 4BA; (g) 4CC; (h) 5AA; (i) 5CA. From Van den Abbeel, p.357, 2013.

One of the ways to reduce the subjectivity involved in that process and to make a more objective classification is the use of digital image processing and artificial intelligence (AI) techniques such as artificial neural networks (ANNs) and genetic algorithms (GAs). With these methods, it is possible to obtain a high reproducibility independent of experience, attention to detail and systematic approach of the examiner, factors which are confounding with visual morphological assessment of human embryos. Such techniques have already been used to classify mammalian embryos, obtaining promising results (Matos, Rocha and Nogueira, 2014; Rocha et al., 2016).

The technique of digital image processing consists of extracting information of size, colour scale and saturation using mathematical methods (Gonzalez and Woods, 2007). This technique allows the extraction of several variables such as circularity, radius, uniformity, texture, luminosity, and colour scale from the photos of the blastocysts (Rocha et al., 2016), which are important for the use in ANN technique.

Genetic algorithms are algorithms of global optimization of functions, based on the theory of natural selection proposed by Charles Darwin. In this theory, individuals whose phenotype is better fitted to the environment are more likely to achieve reproductive success, so they are more likely to propagate their genes to the next generation. In addition to this, processes such as recombination, crossing over and mutation imply in differentiation between the chromosomes of the offspring and the parents promoting genetic variation and thus they evolve increasingly adapting to the environment to which they are inserted (Lacerda and Carvalho, 1999). In this case the individuals are the ANNs and the genes are the various parameters that define the network architecture.

The algorithm works with iterations that are called generations and for each generation, the principles of selection, migration, replication and repopulation are applied to a population of ANN architectures.

ANNs are based on the biological neuron model, which can to learn through experience and error. The main characteristic of a biological neuron is the ability to receive and interpret stimuli, transmitting information to nearby neurons (Kovács, 2002). This learning capacity is achieved through interconnected neurons in layers that upon receiving a stimulus, process this information through a weighted value, called weight, that ends up storing the knowledge of the ANN. The weights indicate the influence of the signal at the output of each neuron (Haykin, 2001). Currently, the greatest difficulty is the determination of the number of neurons and layers to be used, so that these are usually obtained through exhaustive case studies (Jayas, Paliwal and Visen, 2000).

However, with a statistically relevant database and evolutionary algorithms (like the GAs) the architecture that best fits the classification problem can be found more effectively (Schaffer, Whitley and Eshelman, 1992).

Tools such as time-lapse monitoring - present in some equipment as EmbryoScope® - have been used for observation and data retrieval from human embryos, without limiting the number of observations made (*i.e.*, images obtained). By this technology, coupled with an appropriate software, a video is produced and it reports the embryonic development during the *in vitro* culture period. Through this, much information is provided on the whole process of morphological transformations occurring in the embryo, such as kinetics and asymmetry of cleavages (Kovacs, 2014).

The aim of the present work is to use the time-lapse monitoring to extract images of human blastocysts at a specific moment post-insemination and submit these images to the digital processing techniques to obtain mathematical variables representatives of the embryos. After this step and using AI techniques, we intend to obtain, through a computer software, an automatized classification of human blastocysts images as already developed for the bovine species (Rocha et al., 2016, 2017).

The images of human blastocysts used in the digital processing, as well as their classification, that will be used for the AI technique, were provided by the London-based Boston Place Clinic, which is our partner in the development of this work.

2 METHODOLOGY

2.1 Digital Image Processing

Images of human blastocysts, obtained through EmbryoScope® by the Boston Place Clinic, were standardized to have the same resolution and illumination characteristics. The proposed algorithm automatically imports the image into the MatLab® software environment, and standardizes the image by converting the image into grayscale, adjusting the resolution and the aspect ratio. Conversion to grayscale allows for avoidance of the variation due to colour, thus all images are converted to 8-bit gray scale. This process provides a higher speed in the processing of the next steps, as it decreases the spectral dimension of the image. To solve the problem of the different illuminations of the images, a histogram adjustment was made. In the image, 1% of all information was saturated between light and dark pixels, increasing the contrast of the image and, thus, facilitating the next step of segmentation. Figure 2 shows the standardization of a human blastocyst.

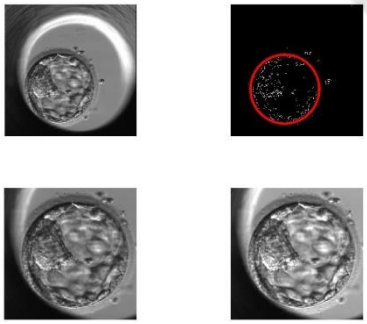

Figure 2: Human blastocyst standardization.

After standardization, the blastocyst was isolated from the rest of the image (*i.e.*, background) before the extraction of the variables. This process consists in altering the image gradient so that the limits of the blastocyst become more evident. For this step, the Hough's Transform function was used (Atherton and Kerbyson, 1999), which delineates the circumference that best characterizes the blastocyst. An example of the isolated blastocyst is shown in Figure 3.

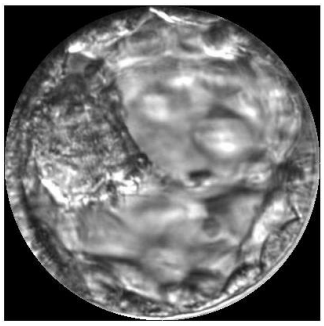

Figure 3: Isolated human blastocyst by Hough's Transform.

The complete image processing is performed using several algorithms that act individually as Gray Level Co-Occurrence Matrix (GLCM) (Haralick, Shanmugam and Dinstein, 1973) for texture analysis, the Watershed Transform, which seeks to segment the image (Beucher, 1992) in addition to the Gabor filter that differentiates the various textures of the image through the characterization of a signal simultaneously in the time domain and in the domain of the spatial frequencies (Marmol, 2011). After the application of these techniques, the TE and the ICM were separately identified, whilst isolating the blastocyst completely. The complete processing of an illustrative image of the human blastocyst is demonstrated in Figure 4.

Following the process of image segmentation, a numerical vector is derived that will represent the extracted characteristics of the images. This vector will be used as input variable for the ANN, thus making the image-derived information proper for use in computational techniques.

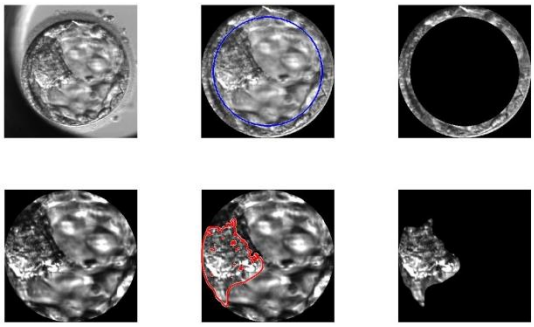

Figure 4: An illustrative sequence of the complete processing of the human blastocyst image. In the upper row (left) it is the original image without processing. In the right column, it is shown the trophectoderm mask (upper) and the inner cell mass (lower) after segmentation.

2.2 Artificial Intelligence

After obtaining the variables, that identify the human embryo and that will be used for the GA technique, a population of individuals will be constructed – which represent several architectures of the ANNs in their chromosomes. The chromosomes will be randomly generated forming an initial population of individuals. Each population will contain from 100 to 200 individuals. Each chromosome, which will represent a specific ANN, will contain in its genes the maximum and minimum number of neurons per layer, the number of layers to be used, the learning rate, the transfer functions to be used (logsig, purelin, tansig, hardlim, tribas, radbas or satlin) and the learning functions (trainrp, trainscg, traincgb, traincgf, traincgp, traingdm or traingd) (Beale, Hagan and Demuth, 2017). The entire process will be developed in the MatLab® environment (MATLAB 2017a, The MathWorks Inc., Natick, MA) that has tools for creating and modelling ANNs.

After the generation of the ANNs (individuals), the entire population will be trained, validated, and tested using the blastocyst images database, which will be divided into training (from 50% to 70% of the data), validation and test (can be 15% to 25% each) sets.

For the following generations, 20% of the selected individuals will be kept as the fittest, 60% will be composed by the recombination and mutation of the individuals of the previous population and the remaining 20% will come from the migration. The number of generations will be a maximum of 1000. The most fitted individuals will be chosen from the smallest error of the test set when applying the ANN technique.

It is intended that at the end of the iterations, previously established, the software will present an optimized ANN architecture that classifies the human embryos in a less subjective way and with greater reproducibility and assertiveness. Of course, the whole processing will be in an automatized way (*i.e.*, without human intervention unless the upload of the original image).

3 DISCUSSION

Currently, we have observed that the human blastocyst images, in terms of digital processing, is quite different from the mouse and bovine blastocysts already studied in previous research (Van Soom et al., 2003; Matos, Rocha and Nogueira, 2014; Rocha *et al.*, 2016, 2017) Differently from murine and bovine blastocysts, which present well defined ICM and blastocoel at the time of implantation, human blastocysts have a huge ICM variation in terms of shape that, consequently, decreases the accuracy of ICM masking by digital processing (Figure 5).

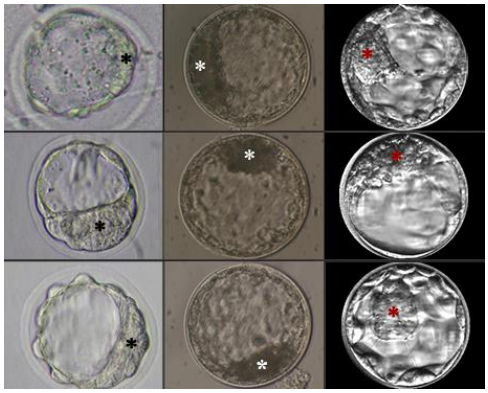

Figure 5: Illustrative images of mouse, bovine and human blastocysts (from left to right) to show the differences found on the inner cell mass shape mainly on the human embryos. Asterisk (*) marks the inner cell mass on each image.

This fact can difficult in the determining the mathematical variables that characterize the human embryo and, consequently, the ANN inputs. Those inputs, if not properly extracted from the image, will not be representative of the blastocyst and thus the ANN will be wrongly trained.

The next step is to enhance the way to obtain the fittest mask of the isolated ICM since the mask of isolated TE already seems fitted. In this way, it is essential to choose carefully what frame coming from the time-lapse record will be used on the image processing, since the same embryo in a short time frame could be registered with different images by the equipment.

4 CONCLUSIONS

Although in its early steps of development, the automatized, reproducible, and objective evaluation of human blastocysts by AI, is a promising tool to improve the way that in the future the embryologist could choose which embryo should be transferred to the patient. Since this proposed method is based on a long previous study with mouse and bovine blastocysts, to adapt the knowledge previously obtained to the human scope would be not a hindrance.

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