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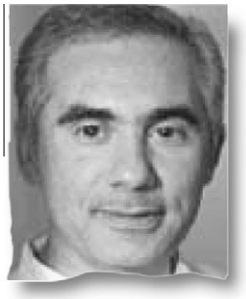
ARTICLE

Artificial intelligence techniques for embryo and oocyte classification

Claudio Manna [a,b], Loris Nanni [c], Alessandra Lumini [d,*], Sebastiana Pappalardo [a]

[a] *Centro Studi GENESIS (Junior Srl), Via Velletri 7, 00198 Rome, Italy;* [b] *Dipartimento di Biomedicina e Prevenzione, Università degli Studi di Roma 'Tor Vergata', Via Montpellier, 1, 00133-Roma, Italy;* [c] *Department of Information Engineering — University of Padua, Via Gradenigo, 6/B-35131 Padova, Italy;* [d] *Department of Electronic, Informatics and Systems (DEIS), Università di Bologna, Via Venezia 52, 47023 Cesena, Italy*
[*] Corresponding author. *E-mail address:* alessandra.lumini@unibo.it (A Lumini).



Claudio Manna obtained his MD degree in 1980 and specialized in obstetrics and gynaecology in 1985. He is a university researcher at the University of Rome Tor Vergata and lectures on the assisted reproduction techniques within the gynaecological specialization course. He is responsible for two centres of assisted reproduction in Rome (Genesis and Biofertility). He has produced several multimedia tools for doctors and people. He is Secretary of the Italian branch of the Mediterranean Society for Human Reproductive Medicine and lecturer for the Ministry of Health programme at the school of fertility. His particular interest is the development of informatics in reproductive medicine.

Abstract One of the most relevant aspects in assisted reproduction technology is the possibility of characterizing and identifying the most viable oocytes or embryos. In most cases, embryologists select them by visual examination and their evaluation is totally subjective. Recently, due to the rapid growth in the capacity to extract texture descriptors from a given image, a growing interest has been shown in the use of artificial intelligence methods for embryo or oocyte scoring/selection in IVF programmes. This work concentrates the efforts on the possible prediction of the quality of embryos and oocytes in order to improve the performance of assisted reproduction technology, starting from their images. The artificial intelligence system proposed in this work is based on a set of Levenberg-Marquardt neural networks trained using textural descriptors (the local binary patterns). The proposed system was tested on two data sets of 269 oocytes and 269 corresponding embryos from 104 women and compared with other machine learning methods already proposed in the past for similar classification problems. Although the results are only preliminary, they show an interesting classification performance. This technique may be of particular interest in those countries where legislation restricts embryo selection.

KEYWORDS: assisted reproduction technology, embryo selection, machine learning techniques, neural networks, oocyte selection, texture analysis

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Introduction

The method routinely used for selecting the highest quality embryos to transfer is still based on morphological analysis. Many morphological embryo scoring systems have been proposed and reviewed for selecting embryos to transfer (Puissant et al., 1987; Giorgetti et al., 1995). The choice of the most suitable embryo to transfer can be achieved by extended culture of human embryos to the blastocyst stage (Gardner et al., 1998). However, approaches involving embryo selection cannot be implemented in countries with restrictive IVF legislation, for example Switzerland, Germany and Italy (Germond and Senn, 1999; van der Ven et al., 2002; Benagiano and Gianaroli, 2004) since these techniques involve the loss of embryos cultured *in vitro* unless oocyte selection is implemented. Several pronuclear morphology scoring systems have been proposed to predict derived embryo quality and implantation or pregnancy success (Scott and Smith, 1998); also used has been a combination of pronuclei and embryo scores (De Placido et al., 2002). Morphological oocyte assessment is still controversial, although oocyte scoring systems have been proposed to help choose the best oocytes to be fertilized (Rienzi et al., 2008).

In most cases, embryologists select the oocytes/embryos by a non-invasive examination based on simple observation focused on morphology and dynamics of their development (third day of culture or blastocyst stage). The examination is usually performed visually and the evaluation is subjective considering the existence of many scoring systems especially for pronuclei or embryos. Therefore, the experience and expertise of the embryologist is of particular importance for the final success rate. In fact a consensus conference (Balaban et al., 2011; Alpha-ESHRE consensus grading scheme) allowed a standardized reporting of the minimum data set required for an accurate description of embryo development. This grading system established common criteria and terminology for grading oocytes, zygotes and embryos for routine use in IVF laboratories. It could be implemented with other tools that technology might introduce in the future.

Alternative methods, including polar body diagnosis (Verlinsky et al., 1990; Gianaroli et al., 2003), metabolomics (Patrizio et al., 2007) and polarization light microscopy (Oldenbourg, 1996; Montag et al., 2007) are at a preliminary stage or are often time consuming in routine IVF. Many studies have investigated the relationship between the timing of embryonic division and embryo quality (Hesters et al., 2008). In order to decrease the subjectivity of these observations, new promising methods, such as time-lapse monitoring systems of embryo development, are rapidly entering into laboratory practice (Cruz et al., 2011). Meseguer et al. (2011) reported a wide and successful trial for the use of morphokinetics as a predictor of embryo implantation. Lemmen et al. (2008) found a correlation between live birth and embryo development analysis with a time-lapse technique.

As for other medical applications, the use of artificial intelligence techniques may offer a possible solution to help embryologists in their work. Other examples of applying artificial intelligence methods to improve success rates of IVF programmes based on embryo or oocyte scoring/selection have been described. A pattern recognition algorithm has been presented to select embryos from images, which classifies the objects into a number of classes (Patrizi et al., 2004). Preliminary studies (Manna et al., 2004) correlating embryo quality with embryo imaging before transfer showed an improvement of manual selection. Morales et al. (2008a,b) presented a novel intelligent decision support system for IVF treatment based on a detailed analysis of human embryo morphology and clinical data of patients.

The present paper proposes the application of an advanced machine learning system based on a combination of classifiers for oocyte/embryo quality scoring and a state-of-the-art method for texture representation of images, the local binary pattern (LBP) descriptors (Ojala et al., 2002). As far as is known for the first time, an objective methodology is used in assisted reproduction technology to identify images of viable oocytes and embryos.

The proposed decision support system is evaluated on a data set of oocytes and their derived embryos. The aim at the moment is not to demonstrate that the system is able to select the perfect oocyte and embryo that will implant or to predict with great accuracy the chance of pregnancy in a routine clinical setting. The aim is to explore the possibility of using this new system in larger and more structured studies such as those with single-embryo transfer, including a prospective randomized trial for reaching full clinical relevance.

Materials and methods

Study design

The experiments were carried out on two data sets: one includes of 269 photographs of oocytes and the other 269 photographs of the corresponding embryos usually at the 4-cell stage taken 40—50 h after intracytoplasmic sperm injection (ICSI) and immediately before transfer (day 2). The photographs were taken with an inverted microscope (Diaphot-300; Nikon) equipped with Hoffmann interference optics, stain-free objectives and a video camera (Digital SIGHT DS-F (i1); Nikon). The digital photographs were made at 20× magnificataion by one experienced embryologist who chose the plane of the oocyte or embryo that seemed more representative for the judgment of its quality. Each photograph was a JPEG image with a resolution of 2560×1920 pixels.

The research was carried out in one fertility centre and involved 104 couples (mean age 36.2 years), where the main infertility factor was mild andrological infertility (sperm concentration less than 5 million/ml) and other causes of infertility were tubal or unexplained. Of the total couples, 71 underwent ICSI for the first time and 33 had one previous implantation failure. A total number of 104 transfer cycles after ICSI was studied. The result of the transfer cycle (single birth/multiple births or no birth) were used to label the embryos transferred in that cycle (and the related oocyte) as positive (certain birth), negative (no birth) or uncertain (when not all the transferred embryos gave rise to corresponding babies born). The summary of the data set is shown in **Table 1**.

Ovarian stimulation was carried out by administering recombinant FSH (Gonal F; Serono International, Geneva, Switzerland) at a dosage of 150–400 IU according to the individual response after suppression with a gonadotrophin-releasing hormone analogue in a 0.3 ml daily preparation (Suprefact; Hoechst Marion Roussel Deutschland, Bad Soden, Germany) from day 21 of the previous menstrual cycle for an average of 13 consecutive days. Oocyte retrieval was carried out with ultrasound-guided transvaginal follicular aspiration around 36 h after the administration of human chorionic gonadotrophin (Ovitrelle; Serono Europe, UK) and when at least two follicles $\geq$17 mm were observed. Gametes and embryos were cultured under oil in drops of a culture medium (IVF Scandinavia; Vitrolife Sweden, Kungsbacka, Sweden) with an atmosphere of 5% CO_2 in air. ICSI was performed according to current methodology (Van Steirteghem et al., 1993). Sperm preparation was performed with the swim-up technique using gamete medium (IVF Scandinavia). Insemination/ICSI was performed in IVF-50 and the oocytes were individually placed in 25 μl IVF-50. Oocytes were checked 18–20 h after insemination/ICSI. Each embryo was cultured individually in 25 μl IVF-50.

Artificial intelligence techniques

The artificial intelligence techniques commonly used for a classification system of biomedical images are based on the followings steps: (i) segmentation (the selection of the correct region of interest in an image) and preprocessing for reducing the presence of artefacts due to noise, blur or varying illumination conditions; (ii) feature extraction, which relies on the extraction of (usually numerical) descriptors which represent in a compact way the starting image, such as LBP (Ojala et al., 2002); and (iii) definition of a classification system, in which the classifier is trained using the data stored in the knowledge base (training set). The result of the classification is a score between a test image and each of the different classes.

A combination of different feature extractors and classification methodologies permits a higher accuracy and reliability. This work proposes a multiclassifier system which combines good texture descriptors with high performance general purpose classifiers. The architecture of the system is schematized in **Figure 1**. Complete descriptions of the preprocessing, feature extraction and classification steps are given in the following sections.

Segmentation and preprocessing

The first step of the preprocessing procedure is the segmentation of the region of interest from the background which is performed manually. After the segmentation, the images are rescaled to fixed dimensions (75 × 75 pixels) and preprocessed by applying a contrast enhancement method (**Figure 2**), in order to deal with the inherent non-uniform illumination problems.

Table 1 A summary of the labels of the data sets.

Data set	*Certain*		*Uncertain*	*Total*
	Birth	*No birth*		
Oocytes/embryos	12	150	107	269
Women	5	57	42	104

Feature extraction

Good texture descriptors are invariant to image rotation and scaling and possibly robust in terms of variations in illumination. This study used the LBP (Ojala et al., 2002), a local texture operator with powerful discrimination, low computational complexity and low sensitivity to changes in illumination which has already been successfully applied to bioimaging problems (Nanni et al., 2010).

Classification

This work uses an ensemble of neural network to perform the classification task. An artificial neural network (Duda et al., 2001) is a set of simple processing elements connected together to form a network of nodes that uses a mathematical model for information processing. Different neural network classifiers can be obtained by varying the network architecture and the choice of the algorithm designed to infer the strength (weights) of the connections in the network to produce a desired signal flow. A particular class of networks – Levenberg–Marquardt neural networks – is used (Hagan and Menhaj, 1994). A stand-alone classifier is not a good choice in this classification problem, thus this work uses a random subspace ensemble of classifiers (Nanni and Lumini, 2008), drawing a subset of all available features to train the classifiers within an ensemble. This system makes it possible to partially solve the problem of low number of samples in the training set. The final score of the ensemble is obtained by summing the scores of all classifiers ('sum rule').

Statistical analysis

The accuracy of the proposed decision support system depends on how well it separates the group of images being tested (oocytes/embryos) into the two classes in question (resulting/not resulting in a pregnancy). Accuracy is measured by the area under the receiver operating characteristic (ROC) curve (AUC) (Fawcett, 2004). An area of 1 represents a perfect system; an area of 0.5 represents a worthless system (the same result can be obtained by randomly selecting the output class). A rough guide for evaluating the accuracy of a system is the traditional academic point system: 0.9–1 = excellent (A); 0.8–0.9 = good (B); 0.7–0.8 = fair (C); 0.6–0.7 = poor (D); 0.5–0.6 = fail (F).

IRB approval was deemed not necessary for this type of work.

Results

The aim of this section is to validate the proposed approach with the available data set, according to two different testing protocols. The first testing protocol is the 'leave-one-out-woman', which uses only the embryos/oocyte where the label is certain: the testing set is composed of all the oocytes/embryos of a given woman (considering only those with a label that is certain). There-

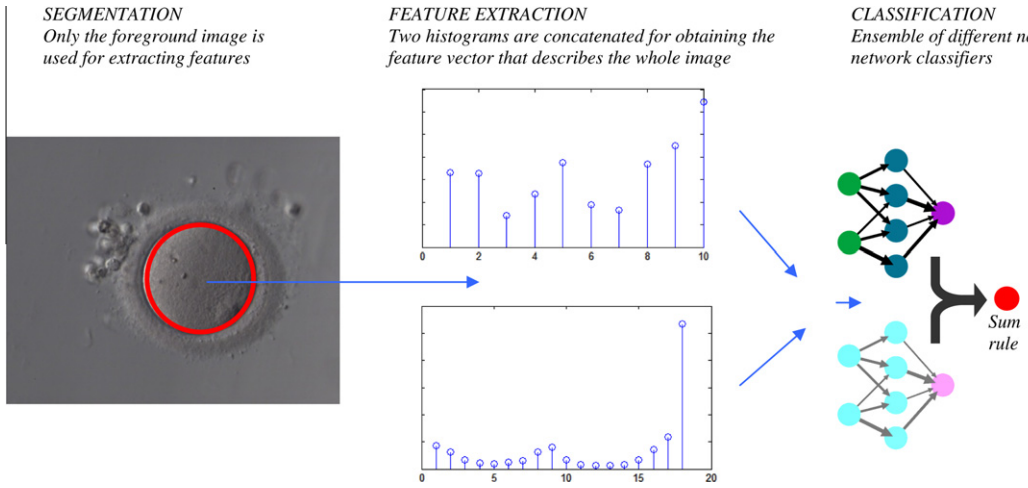

Figure 1 Proposed system for embryo and oocyte image classification.

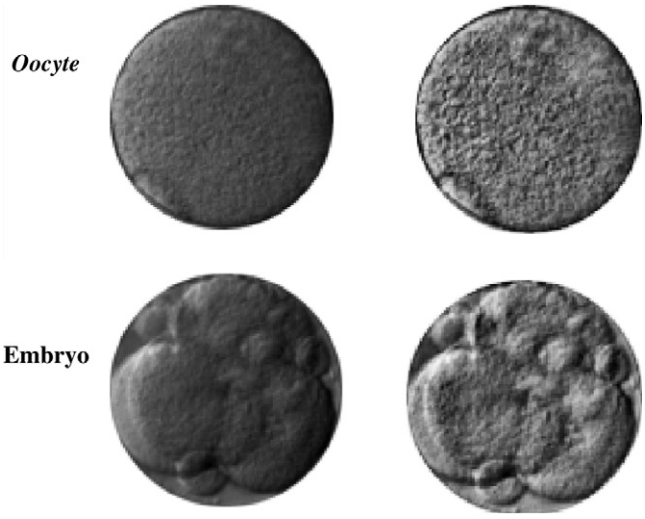

Figure 2 Segmented images (left) and their enhanced versions (right) of an oocyte and an embryo.

fore the results are obtained by considering the performance of 62 experiments (**Table 1**). The second testing protocol is the 'leave-one-out-woman' using all the women of the data set. Therefore the results are obtained by considering the performance of 104 experiments (**Table 1**).

The delivery rate in this study was 26.5%. It was not affected by causes of infertility or repeated implantation failure.

Using the first test protocol, the AUC is calculated according to the score of each embryo/oocyte of the test set, since their label can be obtained without uncertainty. Using the second test protocol, the classes of the images in the test set can be assigned with certainty only when all the n transferred embryos gave rise to no births or to n births (in 57 out of 104 experiments); therefore the AUC is calculated according to the scores and the labels of each woman, which are determined in the following way: for each woman the maximum score among her embryos/oocytes is selected and her label is 'birth' only if the woman had at least one birth.

The first test is aimed to compare different descriptors and classifiers for the classification of both oocytes and embryos. In particular, in **Tables 2–5** two texture descriptors are considered, i.e. the grey-level moments as previously proposed (Manna et al., 2004) and the LBP as proposed in this work. Three general-purpose classifiers are tested: the TRACE algorithm (Manna et al., 2004), a stand-alone neural network (NN) and a random subspace ensemble of neural networks (RSNN). The approach proposed in Materials and methods corresponds to the intersection between LBP and RSNN. The results reported in **Tables 2 and 3** represent the AUC obtained on the oocyte and embryo data sets, respectively, according to the first testing protocol and the results reported in **Tables 4 and 5** represent the AUC obtained on the oocyte and embryo data sets, respectively, according to the second testing protocol.

From the results reported in **Tables 2–5**, it is clear that the best descriptor is LBP, that the best classifier is RSNN and that both oocytes and embryos are useful. These results prove that LBP descriptor performs better than the grey-level moments described (Patrizi et al., 2004; Manna et al., 2004; Morales et al., 2008a,b) even if the results are not directly comparable since they used a different testing protocol and data set.

The second test was aimed to evaluate the proposed approach using a semi-supervised learning method. For this second test, only the final method proposed in this paper (LBP + RSNN) was used. The results reported in **Table 6** are obtained using an 'imperfect teacher' to label the uncertain training patterns (Manna et al., 2004). In brief, certain instances of the training set are used to classify the other training patterns, i.e. if, in a group of n oocytes/embryos transferred to the same uterus, d births were obtained, then the d embryos with highest similarities to the class 'birth' are assigned to that class and the remaining $n - d$ are assigned to the class 'no-birth'. This procedure allows uncertain labels to be eliminated.

Finally in **Table 7**, the proposed method is evaluated using a different semi-supervised learning system, consisting of performing 150 times a 10-fold cross validation on the training set. The 10-fold cross validation consists in randomly dividing the data set into 10 equally sized subsets D_i:

Table 2 AUC obtained on the oocyte data set according to the first testing protocol.

Descriptor	*Classifier*		
	TRACE	*NN*	*RSNN*
Moments	0.45	0.51	0.49
LBP	0.62	0.79	0.79

LBP = local binary patterns; NN = stand-alone neural network; RSNN = random subspace ensemble of neural networks; TRACE = the TRACE algorithm (Manna et al., 2004).

Table 3 AUC obtained on the embryo data set according to the first testing protocol.

Descriptor	*Classifier*		
	TRACE	*NN*	*RSNN*
Moments	0.60	0.60	0.71
LBP	0.71	0.75	0.83

LBP = local binary patterns; NN = stand-alone neural network; RSNN = random subspace ensemble of neural networks; TRACE = the TRACE algorithm (Manna et al., 2004).

Table 4 AUC obtained on the oocyte data set according to the second testing protocol.

Descriptor	*Classifier*		
	TRACE	*NN*	*RSNN*
Moments	0.49	0.50	0.51
LBP	0.70	0.75	0.72

LBP = local binary patterns; NN = stand-alone neural network; RSNN = random subspace ensemble of neural networks; TRACE = the TRACE algorithm (Manna et al., 2004).

nine of these subsets are used for training and one as test set. Each time, the training patterns with an uncertain label are assigned to a given class and the final labels are obtained considering the major vote rule among the 150 times. In any case if a group of n embryos transferred to the same uterus gave rise to d births, only the d embryos with highest similarities to the class 'birth' are assigned to that class.

A ROC curve for the semi-supervised learning system is depicted in **Figure 3**. The AUC of this system is around 0.8 using the first testing protocol and can be considered good. It is interesting to note that only the supervised classification is useful to improve the classification performance, probably because in this problem there are only a very few patterns that have a certain label 'birth'. Another interesting result of the experiment is that the best performance is obtained using oocytes: this is due to the fact that the oocytes are more similar in texture, therefore they probably fit better to textural information analysis.

Table 5 AUC obtained on the embryo data set according to the second testing protocol.

Descriptor	*Classifier*		
	TRACE	*NN*	*RSNN*
Moments	0.51	0.53	0.52
LBP	0.58	0.65	0.65

LBP = local binary patterns; NN = stand-alone neural network; RSNN = random subspace ensemble of neural networks; TRACE = the TRACE algorithm (Manna et al., 2004).

Discussion

This paper focuses on a new method for embryo and oocyte image classification based on a textural descriptor (local binary pattern) and on a random subspace ensemble of Levenberg–Marquardt neural networks. The results clearly outperform the existing approaches (Patrizi et al., 2004; Manna et al., 2004) and are encouraging, in particular considering that they have been obtained using a 'small' training set with very few positive samples (~0.8 AUC considering the leave-one-out-woman testing protocol). For pronucleated oocytes and embryos, it is probable that other type of descriptors not specifically designed for prevalent textural images might be used. In fact, the alignment and the number of nucleoli or the number and size of blastomeres are not textural features.

Experience shows that embryo quality is not clearly related to oocyte appearance. Similar clinical pregnancy and implantation rates have been published after the transfer of embryos from 'abnormal' or 'normal' appearing oocytes (Balaban et al., 1998; Balaban and Urman, 2006). However a score based on the morphological appearance of the oocyte has been proposed to indicate some developmental potential of the subsequent embryo (Rienzi et al., 2008).

Features incorporated in the texture of images are not usually perceived by the human eye and their analysis by artificial intelligence methodology might be used in a new tool for the recognition of viable embryos or oocytes. At the same time, the human perception of other features (i.e. evenness and number of blastomeres with their nuclei, frag-

Table 6 AUC obtained using local binary patterns + random subspace ensemble of neural networks and one iteration of the semi-supervised system.

Data set	*Testing protocol*	
	First	*Second*
Oocytes	0.73	0.68
Embryos	0.81	0.72

Table 7 AUC obtained using local binary pattern features and 150 iterations of the semi-supervised system.

Data set	*Testing protocol*	
	First	*Second*
Oocytes	0.80	0.75
Embryos	0.83	0.69

mentation, number and disposition of nucleoli) is subjective and clearly limited also because they change with time. A possible future investigation might include pattern recognition modalities with new tools such as time-lapse monitoring systems (Meseguer et al., 2011) for a comprehensive prediction of oocyte or embryo implantation rate. With time-lapse techniques, a very great number of images could be offered to pattern recognition processing and artificial intelligence methodology in a very controlled condition. In the present work, the time of observations is that used in the traditional score given by an experienced embryologist. It should be noted that the analysis was performed on bidimensional images, whereas in the IVF laboratory a three-dimensional score is applied to each element (oocyte, pronuclei, embryo). However, pattern recognition analysis might also be performed in several planes with automated devices (Javidi and Tajahuerce, 2001) although even with two dimensions the current results were reliable.

Aiduk and Zernicka-Goetz (2012) reported morphodynamic patterns of cytoplasmic movements in human oocytes and embryos imaged by time lapse. They could be processed with pattern recognition and artificial intelligence methodologies. Certainly time lapse is a significant advantage over a static assessment scheme but it does not necessarily rule out the possibility of adding valuable information coming from large databases of stored images especially when used with new technologies such as pattern recognition and artificial intelligence techniques. The two possibilities (dynamic and static observation) might be used together and integrated in a more thorough analysis for practical aims in a normal IVF clinical setting.

An important application for the selection of viable oocytes might be the optimization of the cryopreservation strategy and the avoidance of embryo selection in countries where it is not permitted. In this perspective, this system

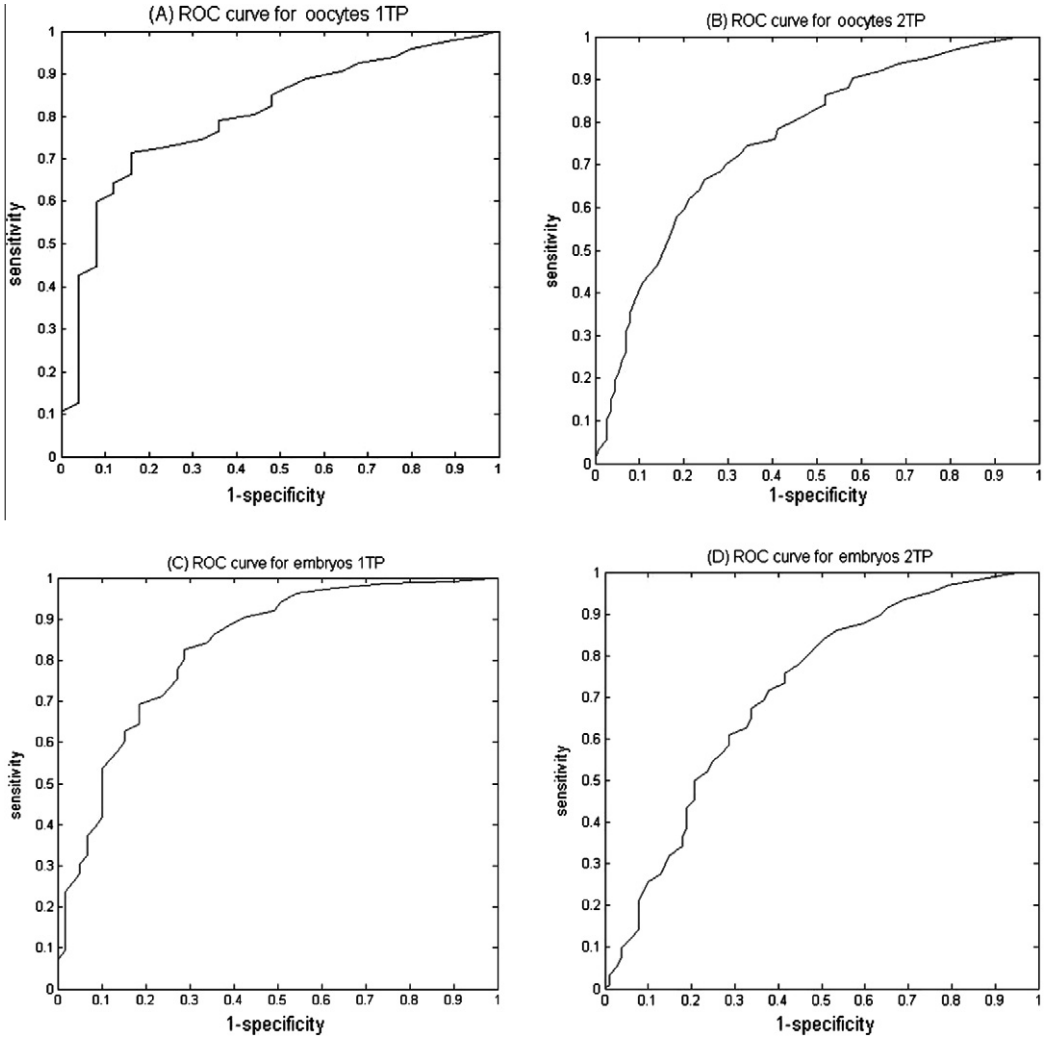

Figure 3 Receiver operating characteristic (ROC) curves: (**A**) oocytes with first testing protocol (1TP), (**B**) oocytes with second testing protocol (2TP), (**C**) embryos with 1TP, (**D**) embryos with 2TP. Areas under the curve are reported in **Table 7**.

gave interesting performances for oocyte quality assessment.

Another advantage of the system described in this work derives from the digital format of the images and its relatively simple possibility of capture, storing, displacement and sharing. A great and growing number of image files might be collected in large databases and shared among IVF laboratories, also to improve pattern recognition methodology.

The most practical and original perspective of this study is the possibility of obtaining a reliable method to help physicians and biologists in selecting embryos or oocytes. This study group is planning to test the proposed method on a larger data set, using an automated segmentation procedure and to combine the information coming from the oocytes, pronuclei and embryos.

The proposed approach might become a tool shared among several IVF laboratories for objective, automatic and non-invasive oocyte or embryo assessment.

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