Embryo Development Stage Onset Detection by Time Lapse Monitoring Based on Deep Learning

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Keywords: IVF, Pronuclei Detection, Embryo Selection, Computer Vision, Classification, Deep Learning, Sequential Models.

Abstract: In Vitro Fertilisation (IVF) is a procedure used to overcome a range of fertility issues, giving many couples the chance of having a baby. Accurate selection of embryos with the highest implantation potentials is a necessary step toward enhancing the effectiveness of IVF. The detection and determination of pronuclei number during the early stages of embryo development in IVF treatments help embryologists with decision-making regarding valuable embryo selection for implantation. Current manual visual assessment is prone to observer subjectivity and is a long and difficult process. In this study, we build a CNN-LSTM deep learning model to automatically detect pronuclear-stage in IVF embryos, based on Time-Lapse Images (TLI) of their early development stages. The experimental results proved possible the automation of pronuclei determination as the proposed deep learning based method achieved a high accuracy of 85% in the detection of pronuclear-stage embryo.

1 INTRODUCTION

Statistically, almost 10% to 15% of couples suffer from infertility in the world. Multiple infertility treatments have been developed over the years, collectively referred to as Assisted Reproductive Technology (ART). In Vitro Fertilization (IVF) has prevailed as the most effective and commonly used type of ART.

To undergo an IVF cycle, patients should have an ovarian stimulation in order to collect multiple oocytes which will be incubated with selected motile sperm from a semen collection. The intra cytoplasmic sperm injection is a more advanced technique where every spermatozoa is injected in a mature oocyte. The resulting embryos are kept in an incubator for three to five days where their development is observed continuously by embryologists, on an x400 microscopic scale, to extract their morphokinetic parameters. Morphokinetics comprise the timing and morphological changes of embryo as it grows and passes through a series of sequential developmental stages defined in academic guidelines (Ciray et al., 2014). Based on these observations, embryologists decide whether to transfer the developed embryo for implantation, freeze it for later use, or discard it if it doesn't show a good implantation potential.

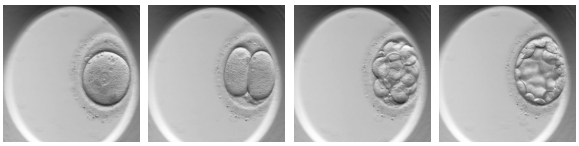
In recent years, new advanced IVF incubators entered the market with Time Lapse Imaging (TLI) technology (Dolinko et al., 2017). These TLI incubators make it possible to monitor embryonic development continuously. They take photographs of each embryo at regular intervals and compile them in a time-lapse video, giving dynamic insight into embryonic development in vitro without disturbing the stable culture conditions. These incubators, often accompanied by a dedicated annotation software, have provided both biologists and clinicians with a new set of data regarding embryonic behaviour during preimplantation development and its association with embryo quality.

As detailed in academic guidelines (Ciray et al., 2014), the human embryo undergoes different development stages, from a fertilized egg (zygote) to a transferable blastocyst. The main developmental events are polar body appearance (pPB2), pronuclei appearance and fading (pPNa and pPNf), cleavage or cell divisions (p2 to p9+), compaction or Morula (phase pM), and Blastocyst formation and expansion (pB and pEB). Figure. 1 illutrates some of these embryo development phases.

Typically, the pronuclear stage occurs within about 16-18 hours, after the sperm is combined with

Miled, W., Chtourou, S., Chakroun, N. and Berjeb, K.
Embryo Development Stage Onset Detection by Time Lapse Monitoring Based on Deep Learning.
DOI: 10.5220/0012390600003636

In *Proceedings of the 16th International Conference on Agents and Artificial Intelligence (ICAART 2024) - Volume 2*, pages 368-375
ISBN: 978-989-758-680-4; ISSN: 2184-433X



(a) (b) (c) (d)

Figure 1: Embryonic development stages. (a) Pronuclear (b) First cleavage (c) Morula (d) Blastocyst.

the egg. At this stage, a male and female pronuclei (2PN) appear containing the genetic material from the sperm and the egg, respectively. The two pronuclei of a normal fertilization are generally equal in size and centrally located. Indeed, several studies have shown that the morphology of the embryo at the pronuclear stage is a valuable parameter in the process of evaluating embryo quality and developmental potential. Currently, embryologists do the assessment visually, in a manual process, leaning on their visual experience. This poses several challenges including: the selection is prone to human perception error, which can lead to the loss of promising embryos, or to failed pregnancies; the process is highly subjective as it is difficult to agree on quality assessment between embryologists (Adolfsson and Andershed, 2018). Manual assessment is also a difficult and time-consuming process. Apart from having to take out the embryo from the incubators thus disturbing its culture conditions. These challenges suggest that an automated evaluation solution leveraging computer vision and artificial intelligence would provide a more reliable and accurate solution that helps embryologists and supports their decision-making with embryo selection.

Artificial intelligence (AI) is a field whose goal is to create machines capable of learning and improving themselves in an autonomous way. This technology is proving to be useful in all intellectual tasks. The concept of (IA) has been extended to encompass several subfields, including image classification, which has made considerable progress in recent years (Yadav and Sawale, 2023). This progress is due to numerous works in this field and to the availability of public datasets that have allowed researchers to report the execution of their approaches. This direction of research has resulted in the emergence and evolution of Deep Learning (DL), with the advent of Convolutional Neural Networks (CNN), a particular type of neural network whose architecture of connections is inspired by that of the visual cortex. In the same trend, the use of artificial intelligence (AI) techniques is being intensively researched in the field of IVF. Many automated systems based on artificial intelligence have been proposed to improve IVF success rates by assisting embryologists with their decision and ensuring more consistent results. Recent AI and DL advancements in the embryology laboratory are summarized in the review of Dimitratis *et al.* (I. Dimitriadis and Bormann, 2022).

In this work, we are concerned with the problem of automatic detection of pronuclei in the early stages of IVF embryos development. We aim to develop a proof of concept (PoC) computer vision solution to automatically grade the quality of pronuclei in fertilized embryos, based on time-lapse images of their early development stages.
The main contributions of this work are as follows:

- We build a supervised data collected from TLI IVF incubators making a dataset of 250 annotated time-lapse sequences of unique embryos framed each into 20 annotated images. The annotations refer to critical embryo development instants, namely tPB2, tPNa, tPNf, and t2. We infer from these annotations the tPN assessment, which confirms successful fertilization.
- We create a deep learning model based on a CNN-LSTM network with a pre-trained VGG16 backbone.
- Hyperparameter selection and comparative experiments are conducted to optimize and evaluate the proposed CNN-LSTM model
- To our knowledge, this work represents the first attempt at automatic video annotation of human embryos from an ART center in north Africa.

2 RELATED WORK

According to the literature review by Louis *et al.* (Louis et al., 2021), existing research employing computer vision and deep learning techniques for IVF embryo selection focuses on the following main tasks: automatic embryo stage development annotation (Gomez et al., 2022), (V. Raudonis, 2019) cell counting and detection during cleavage (Rad and Havelock, 2019), blastocyst quality grading according to Gardner's grading system (Gardner and Schoolcraft, 1999), (L. Lockhart and Havelock, 2019), (G. Vaidya and Banker, 2021), (M. F. Kragh and Karstoft, 2019) and implantation outcome prediction.

Leahy *et al.* (Leahy et al., 2020) created a pipeline of five CNNs for automated measurements of key morphological features of human embryos for IVF. A Mask R-CNN network with a ResNet50 backbone was proposed for pronucleus object instance segmentation. The model detects pronuclei by outputting an object mask and a confidence score from 0 to 1 for each frame of a TLI embryo sequence, cropped

around the embryo region of interest. Another insightful research that uses deep learning for automating assessment of human embryos in IVF treatment is reported in (Lockhart, 2018). Three tasks were the focus of this work: blastocyst grading, cell detection and counting, and embryo stage classification and onset detection. For the latter task, the proposed model incorporates temporal learning over the TLI sequence and automatically detects three classes, namely cleavage, morula, and blastocyst stage onsets. In order to detect stage transitions, two image sequence batches are fed in parallel, in pairwise learning, through two separate CNNs, which are based on VGG16 architectures pre-trained on the ImageNet dataset with three final convolution layers fine-tuned. Fully connected layers from each classifier are concatenated and used to predict whether the input images fed through each branch were at the same stage. Synergic loss from this binary output is backpropagated through both classifier branches. Stage transitions predictions are then refined using temporal context in an LSTM layer separately for each synergic branch.

Gomez *et al.* (Gomez et al., 2022) worked on the automatic annotation of the 16 embryo development phases. In addition to providing a fully annotated dataset composed of 704 time-lapse videos, authors applied ResNet, ResNet-LSTM and ResNet3D models to automatically annotate the stage development phases. The evaluation results showning the superiority of ResNet-LSTM and ResNet-3D over ResNet, prove the importance of using the temporal information in the automatic annotation process. However, predicting the 16 classes of embryonic development is prone to numerous challenges, primarily due to the extensive computational requirements necessary for training DL models on more than 300k images, which demand high-performance GPUs. Fukunaga *et al.* (Fukunaga et al., 2020) proposed an automated pronuclei determination system based on few amount of supervised data. In their paper, authors proposed a framework of four stages. First, images are preprocessed to detect and focus on the embryo area using a circular Hough mask. Then, images are passed for main processing to two CNNs, both composed of two convolution layers and two fully connected layers. The first model detects the outline around pronuclei and passes these outline images to the second CNN, which gives a probability distribution of the number of pronuclei (0PN, 1PN, 2PN). Finally, predictions are postprocessed through a Hidden Markov model, while setting conditions for the change in the number of pronuclei over time. Thus, the change of the number of pronuclei, if occurred (the state can remain unchanged), is only valid from 0PN to either 1PN or 2PN and from 1PN to 2PN. This integration of time-series information resulted in improvement of performance in sensitivity, however the accuracy remains relatively low. To the best of our knowledge, this workb (Fukunaga et al., 2020) is the only existing reference that deals with detecting and determining pronuclei number in IVF embryos.

In this work, we aim to automate the annotation process of the early stages of embryonic development, from Polar Body appearance (tPB2) to just before the first cell division (t2). We create a deep learning model that analyzes the TLI incubator's sequences of embryonic development and annotates tPN, defined as the time at which fertilization status is confirmed, immediately before the time fading of pronuclei (tPNf) (Ciray et al., 2014).

3 METHODOLOGY

3.1 Dataset

The dataset used in this work is a collection of 352 videos of unique embryos exported from a private TLI IVF Incubator manufactured by Esco Medical®. The frames of each video are time-lapse embryo images taken every five minutes, starting shortly after fertilization. Each video contains between 600 and 1400 frames in gray scale with a resolution of 1280×720 pixels.

An experienced biologist notes the start and end time of each phase of the embryo's development. Each image of each video has therefore a class, which corresponds to the phase seen in the image. The annotations follow the same convention used by Gomez *et al.* (Gomez et al., 2022) and academic guidelines (Ciray et al., 2014). There are, in general, 16 annotations corresponding to 16 different instants of embryo evolution. Here, as we are only interested in detecting two key instants, namely tPB2 and tPN, we only consider the following phases:

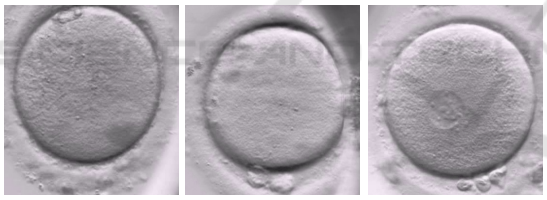
- tPB2: time of appearance of second polar body
- tPNa: time of pronuclei appearance
- tPNf: time of pronuclei fading
- t2: time of first cell division marks the end of pronuclear phase

The stage tPN, which is defined as the time at which fertilization status is confirmed, is calculated from tPNa and tPNf (Ciray et al., 2014). We received the annotation in Excel sheets generated by the software of the TLI incubator, which we had to parse to extract useful information.

3.2 Data Preprocessing

Before feeding the sequence of images to the proposed deep learning based model, we made some preprocessing treatments. First, as we reviewed the dataset, we observed that some videos suffered from excessive lighting changes and motion blur. Other images were taken from a bad angle where the embryo was not entirely visible. Some other videos did not cover some critical stages of the embryo's development. After discarding these unusable videos, we obtained 250 annotated videos of unique embryos. Then, as the embryo cell presents only a small part of the image, we cropped them, reducing the frame size to 360×360 and gaining in memory efficiency. To achieve this, we applied the Hough transform to detect circular shapes in the images, then we cropped the detected circles with a fixed size of 360×360 pixels.

After choosing the frames and preprocessing them, each frame has been labeled based on the expert's annotations. We repeated the same process for every video in the dataset. For each video, we ended up with 20 images, sampled over the first 18 hours of embryo development. The retained frames are annotated as 0 (neither tPB2 nor tPN occured), 1 (tPB2 occured), 2 (tPN occured). We can see examples of the three classes in Figure. 2.



class 0 (no event) class 1 (tPB2) class 2 (tPN)

Figure 2: Examples of labelled images from the dataset.

3.3 Proposed Model

In this work, we are concerned with a sequence classification problem, which implies that the model's input is not a series of independent images to be classified as categorical targets, but rather a time-dependent sequence of images to be predicted according to a certain order. Sequence classification is a challenging problem because the sequences can vary in length, contain a very large vocabulary of input symbols, and may require the model to learn the long-term context or dependencies between symbols in the input sequence. The solution to this sequentially-classified problem is to use a combination of the two approaches: the LSTM architecture, and the CNN architecture.

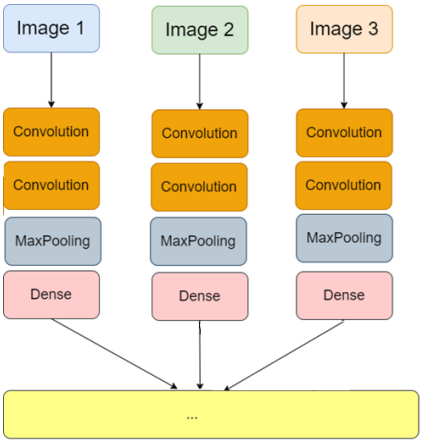


Figure 3: Proposed input convolution flows.

It should be noted that a sequence of images must not be fed to a single convolution. If we take a common sequential network, each entry is connected to all the neurons in the first layer. With multiple images as batch entries to the CNN network, all the pixels of all images are merged and sent to the first layer. Consequently, their distinctive features and the temporal information will be lost. To overcome this problem, as illustrated in Figure 3, we need to share the network layers across the video frames to reduce the number of tensors, thus having filters for each image input, not for the whole stack of frames.

With this adopted architecture, each image has got its own convolution flows. If we separately train each convolution flow, we will have several unwanted behaviors:

- We will need long training time because several convolution flows need to be trained (one per input image).
- Some convolution flows will not detect what other flows could detect.
- Each convolution flow, for one sequence, can have several different weights, and so we get different detection features that are not linked.

In order to make sure that all the convolution flows can extract the same features, we propose to add a time distributed layer which applies the same convolution layer to several inputs. This allows to apply the layer operation on each timestamp. Otherwise, when we flatten the data all the image instances will be combined and the time dimension will be lost.

As shown in Figure 4, the proposed model has two main parts: a CNN and an LSTM network, linked by a time distributed layer. Each layer that is *time distributed* will share the same weights, saving calculation and computation time.

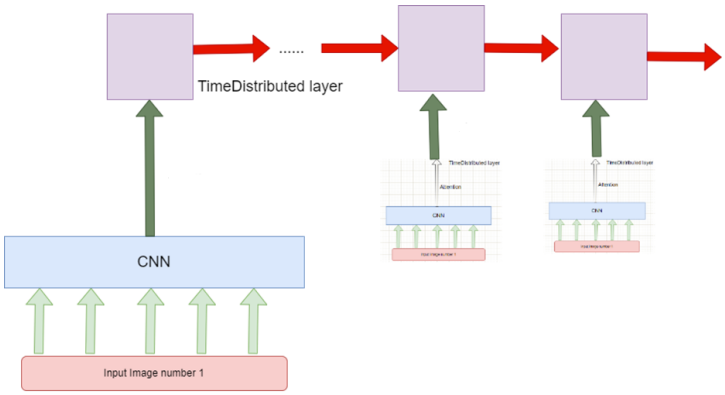


Figure 4: The proposed architecture integrating a time distributed layer.

For the CNN backbone, in the field of medical image analysis, it is common to use a deep learning model pre-trained on a large and challenging image classification task, such as the ImageNet classification competition. The research organizations that develop models for these competitions often release their final models under a permissive license for reuse. These models can take days or weeks to train on modern hardware. But, we can directly use them pre-trained employing transfer learning technique for a target specific task. In this work, we opted for a VGG16 model pre-trained on the ImageNet competition dataset.

4 EXPERIMENTAL RESULTS

4.1 Dataset

In this section, the performance of the proposed deep learning model for the task of early stage human embryo detection is discussed. Our dataset contains 250 annotated videos of unique embryos augmented five times (Horizontal flip, vertical flip, transpose, and transpose horizontal flip). We further resized the images from 360×360 to 180×180 resolution. Since the number of frames can be very large, it is impractical to feed all of them to the model, as this would slow the training and reduce the performance. Our strategy was to choose 20 frames between the start of the video and the instant tPNf (which denotes the fading of the pronuclei) and feed them to the model, since this range covers all the phases we are interested in. We chose our frames in a way where the number of frames between two consecutive chosen frames is constant. Every sequence is therefore framed into 20 ($180 \times 180 \times 3$) images. As the VGG model requires 3-channels input images, we converted our grayscale images into RGB. Furthermore, as each pixel value can vary from 0 to 255, representing the color intensity, feeding an image directly to the neural network will result in complex computations and a slow training process. To address this problem, we normalize the high numeric values to range from 0 to 1 by dividing all pixel values by 255. Then, we labeled the dataset marking images in the tPB2 phase as class 1, those attaining the stage tPN as class 2, and the remaining images where no event occurs into class 0. Finally, we split the dataset, conventionally, into 80% training data and 20% test data.

4.2 Models Implementation

Since the backbone pre-trained CNN model wasn't designed to annotate pronuclei stage development phases in embryo image datasets, we have to make it more specific to our needs, taking advantage of the transfer learning technique and using the ImageNet pre-tuned weights. We chose to train only the last four layers and reduce the number of outputs using the last pooling layer with a maximum operation applied to the convolutional values. First, we specify the top layers by the VGG implementation, taking our custom input $180 \times 180 \times 3$ images. We then link the time distributed layer with the VGG16 output layer via a sequential mode, which will fully connects each neuron from both sides. The next layers are the LSTM layers, followed by five dense layers, separated with 50% dropout layers to prevent over-fitting. We use the ReLu activation function and Softmax as a final activation function, which will output the corresponding class probabilities. As an optimization algorithm, we opted for Adam (Adaptive Moment Estimation), as it is straightforward to implement, is computationally efficient, has little memory requirements and is well suited for problems with large data and/or parameters (Kingma and Ba, 2014). We fix the learning rate at a value of 0.01, to converge the learning in a

faster, more efficient way, and to avoid the problem of vanishing gradients. We choose the categorical cross-entropy as the loss function since we are dealing with a multi-class dataset.

After experimenting with the transfer learning technique, we decided to build a custom CNN model using six convolutional layers. We also introduced a batch normalization to reduce the inter-variance of the layer inputs. This technique stabilizes the learning process and dramatically reduces the number of epochs required for training. The batch normalization momentum uses the moving average of the sample mean and variance in a mini-batch for training. By adjusting a dynamic momentum parameter, the noise level in the estimated mean and variance can be well controlled. We fixed the momentum value to 0.9. We kept the Adam optimizer and categorical cross-entropy loss function. We set the learning rate to 0.001, which is considerably lower than the one used with the VGG16 architecture. The model is built from scratch, so the gradients are initially randomized, and to reach a similar accuracy, the weights need to be adjusted carefully.

4.3 Evaluation

The metrics we used for the performance evaluation of proposed DL models are accuracy and sensitivity. Accuracy is defined as the ratio of correctly classified instances by the total amount of instances. Sensitivity is defined as the number of correctly classified positive samples divided by the number of all positive samples.

We conduct a first experiment where we trained the CNN-LSTM model based on a pre-trained VGG16 backbone for a total of 90 epochs and a batch size of 16. The accuracy and loss graphs for training and validation are shown in Figure 5. The accuracy curve represents few variations and is up to 0.86%. In addition, the loss curve is almost stable and the validation and training curves are almost similar, showing that the model is well fitted.

In order to make the proposed classification model interpretable, we implemented the Grad-Cam method that exploits the features map from the last convolution layers to calculate the gradients of the features map against the class score to identify the most important filters. Figure 6 shows the generated heatmaps on the tPN stage prediction, where red pixels indicate highest contribution towards stage prediction and no colour represents no contribution, As seen in this figure, for tPN stage prediction, the network mainly relied on the circles in the centre of the embryo, which correspond to the two pronucleus. Thus, the Grad-Cam method makes it possible the visualisation of the areas that contributed the most to the prediction of the specific tPN class.

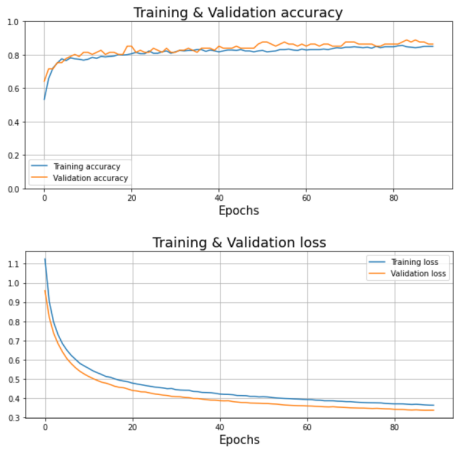


Figure 5: Accuracy and loss graphs of the CNN-LSTM proposed model.

In a second experiment, we trained the custom-built CNN model, along with a LSTM network, for a total of 50 epochs and a batch size of 8. We noticed that this second model has taken more time, and more failed attempts to reach the threshold accuracy. We can visibly conclude this from all the fluctuations in the accuracy per epoch graph in Fig. 7, where the validation accuracy doesn't exceed 60%. This was expected since the pre-trained model has already learned high-level features, is assigned pre-trained weights and only needs fine-tuning to fit the training dataset on the target task, while the custom-built CNN model starts with randomized weights.

4.4 Comparison with State of the Art

For state-of-the-art comparison, as there is no benchmark available in the literature, we reported the results of Fukunaga *et al.* (Fukunaga et al., 2020) and those of Gomez *et al.* (Gomez et al., 2022) given in their corresponding papers and conducted on their own datasets. Comparative results in terms of accuracy and sensitivity metrics are reported in Table 1.

The common aspects between our work and the work of Fukunaga *et al.* (Fukunaga et al., 2020) are the limited amount of supervised data available, and the classification task. However, the main difference is the methodology of the detection systems: we proposed a CNN network linked to an LSTM layer while they developed a 2-CNN architecture, with no deployment of a sequential model that would deal with time dependency with a deep learning technique. Their model's sensitivity reached 82%, but with only a 40% accuracy rate, which makes our method more accurate

Table 1: Comparison with state-of-the-art methods.

Model	Dataset	LSTM usage	Accuracy.	Sensitivity	Classes
Proposed Model	250 videos	Yes	85%	96%	3
Fukunaga et al. (Fukunaga et al., 2020)	300 videos	No	40%	82%	3
Gomez et al. (Gomez et al., 2022)	873 videos	Yes	73%	96%	16

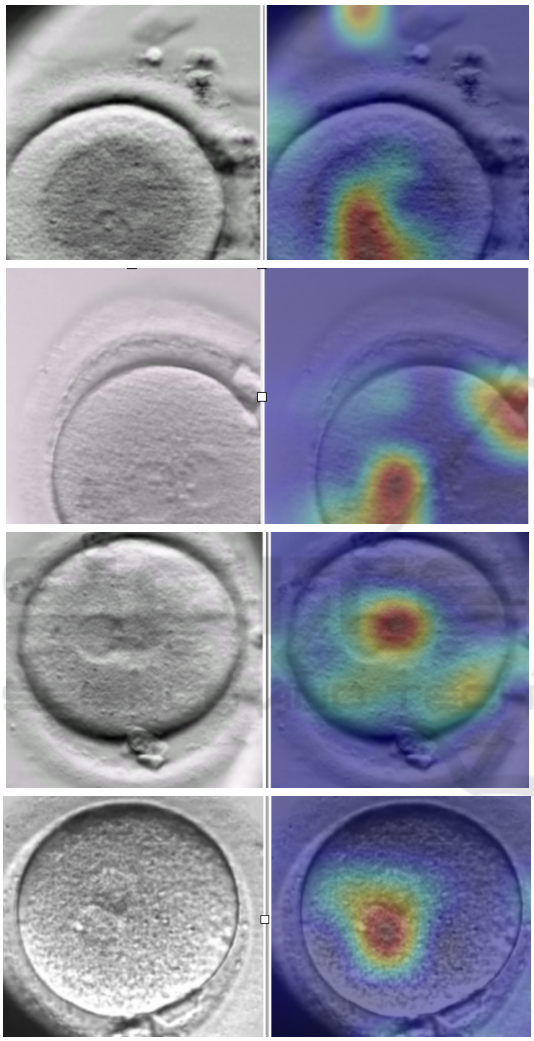


Figure 6: The heatmaps generated by the Grad-CAM method on the tPN stage.

with 85% accuracy score and 96% sensitivity score.

Regarding Gomez *et al.* (Gomez et al., 2022), the used dataset is composed of 337 thousand images from 873 annotated videos. This big ground-truth helped apply three approaches: ResNet, LSTM, and ResNet-3D architectures, and demonstrate that they outperform algorithmic approaches to the automatic annotation of embryo development phases. Furthermore, the compared models are detecting 16 classes of 16 morphokinetic events, compared to 2 events in our case. The three models they benchmarked concluded a 73% accuracy score.

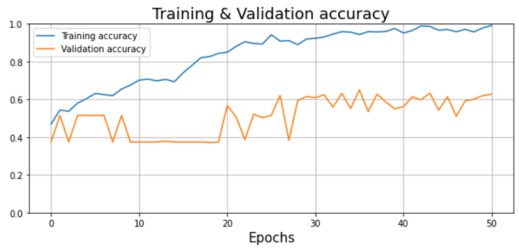


Figure 7: Accuracy graph of the custom CNN proposed model.

5 CONCLUSION

Continuous embryo monitoring with time-lapse imaging enables time based development metrics alongside visual features to assess an embryo's quality before transfer and provides valuable information about its likelihood of leading to a pregnancy. In this work, we developed a deep learning based model to classify a sequence of time-lapse Human embryo images with the aim of helping embryologists with embryo selection for IVF implantations. The classification task aims to detect tPB2 and tPN key instants from an input sequence of images by predicting the class of each image among three classes; denoting the appearance of the second polar body (tPB2), the appearance of the pronuclei (tPN), or none of the two events. The proposed model is a combination of a pre-trained VGG16 backbone, and an LSTM network. It has proven to be powerful enough to fit the data as it achieved a high training accuracy, In future work, our model can be enhanced by being incorporated into a pipeline where the second part detects the number of pronuclei as 0PN, 1PN, 2PN or more. This pipeline can then be part of a whole automatic embryo assessment deep learning framework, integrating the work on blastocyst segmentation and cell counting.

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