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A novel force sensing platform using passive magnetic springs for mechanical characterisation of human oocytes

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ABSTRACT

This article presents a novel low cost force sensing platform for the mechanical characterisation of human oocytes. This platform is compatible with the specific context of Assisted Reproductive Technology (ART). The oocyte is placed inside a standard Petri dish filled with a culture medium. It is immobilized using a holding pipette. The disposable parts used to mechanically test each oocyte are made of glass. This configuration is very similar to the one used in IntraCytoplasmic Sperm Injection protocol excepted that the injection pipette is replaced by a glass indenter. This platform uses two passive and linear magnetic springs to measure the nanoforce applied to the oocyte. The stabilisation of the unstable magnetic springs is passively achieved using the reaction force generated by the compressed oocyte. Some preliminary results obtained with an experimental platform are presented. The global magnetic stiffness of the indenter, evaluated by simulation and experimentally identified, is about 0.0013 N m^{-1}.

1. Introduction

Assisted Reproductive Technology (ART) concerns methods and techniques which help overcoming some difficulties to conceive without necessarily treating the infertility causes. Among them, *in vitro* Fertilization (IVF) and IntraCytoplasmic Sperm Injection (ICSI) are the most used techniques. IVF consists in putting together the oocyte-cumulus complex-OCC extracted from the women ovaries and the sperm inside a Petri dish and letting the fertilization happen autonomously [1]. On the contrary, ICSI forces the fertilization by directly injecting a spermatozoa inside the oocyte by means of an injection pipette [2]. The most important factor for a successful IVF or ICSI, besides the spermatozoa quality, is the oocyte quality and maturity. Indeed the oocyte selection influences the embryo development and therefore has an impact on the ART accomplishment [3].

Usually, the oocyte candidate for fertilization is determined by means of visual estimation. The clinician bases his selection on morphological characteristics such as the shape, the size, the surface of the oocyte and the integrity of the first polar body [4]. However, the results obtained with this subjective and inaccurate approach [5] are quite minor compared to the arduousness of the hormonal treatment proposed to women and to the cost of the intervention. To overcome this problem, different researches were conducted in order either to improve the above mentioned morphological approach or to develop new characterization methods. Among the methods aiming at improving the morphological approach, one can mention the automatic determination of the oocyte quality using image processing [6,7] and polarized light (PolScope) [8]. Among the new approaches which are not based on the morphological characterization, optical spectroscopy seems promising to assess the oocyte quality: transmission spectra of oocytes are used as a criterion to qualify their maturation stage [9,10]. Another promising approach concerns mechanical characterizations. These methods establish a connection between the stiffness of a living cell and its biological properties. A recent study has demonstrated that the mouse embryo's mechanical stiffness is a decisive criterion for zygote quality determination [11]. Yenez and al. proved that there is a difference between the viscoelastic properties of viable and non-viable zygotes. In the same context, several studies adopted the mechanical approach in order to prove that the stiffness should reveal some oocyte physical properties and could then be used as a possible parameter for the oocyte selection. Because oocytes exhibit very low stiffness, experimental implementation

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requires efficient tools like nanoforce sensors to achieve very low measurement range. Many devices were developed for this purpose. For example, Wacogne et al. and Liu et al. proposed a system consisting in compressing the oocyte against one or several flexible beams using a holding pipette [12,13]. Other researchers proposed the study of the mechanical deformation using the injection pipette used in ICSI [14,15]. Systems based on magnetic force sensors were also developed. One can mention the robochip system [16] which consists in compressing the oocyte against a magnetic force sensor using a probe, or the micro and nanoforce sensing platform based on passive magnetic springs [17,18] which compresses the oocyte against the border of a well located at the center of a specifically designed Petri dish. These studies have demonstrated that the mechanical behavior of an oocyte evolves and depends on its maturity stage [12,13,17,19]. However, and at least in France, using these devices with human oocytes requires the approval of the "Agence de Biomédecine" (public organization under the supervision of the French Minister of Health) which may be difficult. Indeed, the French law N° 2011-814 concerning bioethics imposes strict and conservative regulations on the use of new tools in the context of ART. All components in contact with the human oocyte must imperatively be disposable and non-gametotoxic in order to avoid contamination. The oocytes must be individually manipulated in a sterile environment and the temperature of the culture medium must be controlled. In practice, only disposable Petri dishes approved for IVF procedure and glass-made tools are generally authorized. Finally, on a financial point of view, the cost of both the characterization device and the disposable parts is also an important issue. Only low cost disposable parts will be accepted by ART laboratories. As an example, the price of a disposable holding pipette is 20€. This price gives an idea of what should be the final cost of the disposable parts in a characterization device based on nanoforce measurement. To satisfy these challenging requirements, the development of a new low cost device is needed.

This paper presents a new platform for human oocyte mechanical characterization using a nanoforce sensor based on passive magnetic springs. A passive sensor was chosen in order to reduce the complexity of the device, while magnetic springs were chosen because of their insignificant cost, high linearity and low stiffness. All passive magnetic springs exhibit one unstable direction which is always passively stabilized using an additive repulsion force field which is necessarily based on a non-magnetic principle (in order to respect the Earnshaw's theorem). Several principles were used in the past to generate this repulsion force field like the diamagnetism (generated by diamagnetic plates [20]) or the up-thrust buoyancy (generated by a liquid [18]). To simultaneously simplify the design and respect the bioethics requirement, the originality of the design proposed in this article is that no repulsion force field is required to stabilize the sensor when no measurement is performed. Furthermore, the unstable direction of the springs is chosen collinear to the measurement direction. In measurement conditions, the unstable direction is passively stabilized by the oocyte reaction force. Indeed, this is the characterized object itself which stabilizes the sensor. Such approach to stabilize passive magnetic springs is new for nanoforce sensors based on this technology.

The experimental platform as well as the oocyte mechanical characterization process is described in Section 2. In Section 3, the magnetic modelling of the nanoforce sensor is developed. Some results concerning the simulation of the magnetic behavior of the indenter (the sensor's transducer) are presented. Preliminary experimental results of mechanical characterizations done with a human oocyte are presented in Section 4. Finally, a calibration approach of the nano-force sensor is detailed in Section 5.

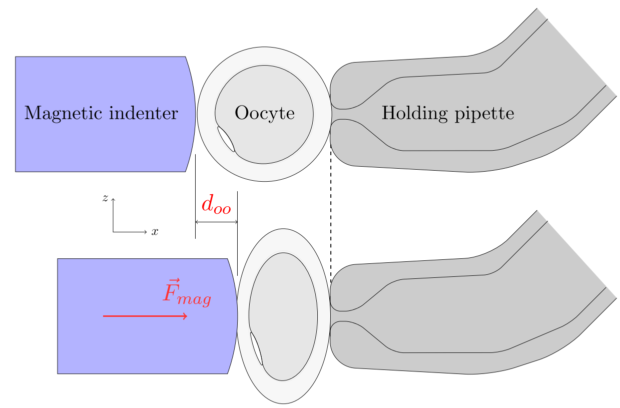

Fig. 1. Principle of the mechanical characterisation of the oocyte.

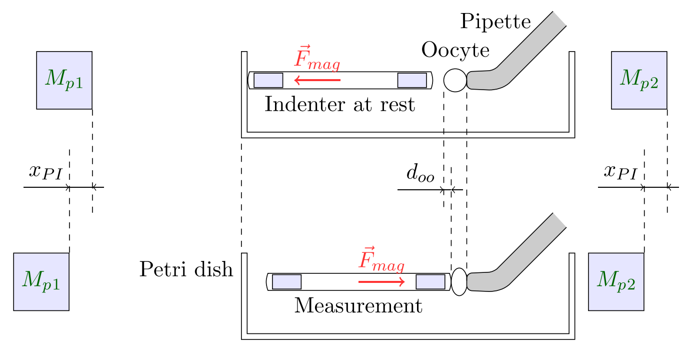

Fig. 2. Operating principle of the loading device.

2. Description of the platform

2.1. Mechanical characterisation of oocytes

The mechanical characterization consists in determining the oocyte mechanical response during a compression cycle by using a magnetic indenter which applies a controlled compression force F_{mag} on it. Fig. 1 shows the configuration of the oocyte inside the platform. This configuration is very similar to the one used in ICSI procedure, except that the injection pipette is replaced by a glass indenter.

The oocyte to be characterized is placed inside a culture dish filled with a culture medium[1] for providing isolation from the environment. The oocyte is immobilized using a holding pipette to prevent spurious movements during the measurement. It is compressed by a magnetic indenter placed at the opposite side of the holding pipette (see Fig. 1). The magnetic force $\vec{F}_{mag}$ applied on the oocyte is controlled by two mobile magnets M_{p1} and M_{p2} placed on Physik Instrumente (PI) micro translation stages (see Fig. 2). These two magnets are placed near but outside the culture dish.[2] The measurement of the magnetic force $\vec{F}_{mag}$ generated by the loading device and the measurement of the compression length d_{oo} defined in Fig. 1 provide the oocyte mechanical response during the compression cycle.

2.2. Operating principle of the force device

The loading device uses a 6−DOF magnetic indenter which comes under the influence of the magnetic field generated by the two mobile magnets M_{p1} and M_{p2} (see Fig. 2). This magnetic

[1] Vitrolife: medium for in vitro fertilization, culture and transfer of embryos.
[2] BD Falcon Petri Dish 50 × 9 – ref 351006.