2013 IEEE/RSJ International Conference on
Intelligent Robots and Systems (IROS)
November 3-7, 2013. Tokyo, Japan

High throughput Mechanical Characterization of Oocyte Using Robot Integrated Microfluidic Chip

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Abstract— **This paper presents a novel measurement system of cellular mechanical properties based on a robot integrated microfluidic chip. In order to achieve the high throughput measurement of cellular mechacal properties, we proposed the robot integrated microfluidic chip (robochip), taking advantages of both of micromechanical manipulator and Lab-on-a-Chip devices. The robochip contained a pair of a magnetically driven on-chip robotic probe and a force sensor. The characterization system based on the robochip performed by the visual feedback control, and the continuous cell measurement was demonstrated. The throughput of our system was 15 to 20 seconds per one oocyte. Moreover, the measurement of the viscoelastic properties were demonstrated as a quality evaluation of oocyte. Experimental results shows that the oocyte has the viscoelastic properties among the same culture condition, and it is important to analyze the mechanical properties of oocyte for the evaluation of the quality. From these results, we concluded that the high through put cellular mechanical characterization was achieved, and our robochip approach was a promising technique for a cellular characterization because the chip part was disposable.**

I. INTRODUCTION

In the bioengineering field, a mechanical characterization of a single cell is highly demanded for the purpose of evaluations of drug efficiency, cell behavior analyses and quality evaluations of cell itself [1-3]. Particularly, the measurement of oocyte mechanical characteristics is expected to predicts pre-implantation rate, bioviability, quality of cryogenically-preserved oocytes [4, 5].

In general, a deformation of a single cell is required for measuring its mechanical properties such as the spring and dumping coefficient. Moreover, it is necessary to manipulate a single cell, and to analyze the large number of measured cells as a group because there is variability even among the cells in a same condition. Therefore the high throughput sensing technique is required which is possible to measure a lot of the cells individually. Therefore, several measurement methods which can apply the mechanical stimulus to the cell have been proposed and commonly used for cell manipulation, such as kinds of robotic probe [6-8], and on-chip microrobots [9-15]. These manipulation approach are classified into contact manipulations and noncontact manipulations.

Micromechanical manipulators, as a one of contact approach, are widely used for analyzing mechanical and electrical properties of a cell because of their capability for precise operation and high output force. These contact approach, therefore, can precisely measure the shape of a cell and its mechanical parameters by robotic probes attached micromechanical manipulator [6] or atomic force microscopy (AFM) [7, 8]. However, the manipulators are placed outside of the cell culture environment, where they are exposed to air. This leads to there are several problems such as the contamination, fluidic oscillation which restricts the application to the adhered cells. Moreover, technical difficulties, which is caused because mechanical manipulators can be controlled with multi-degrees of freedom (DOF), induce low success rate and low throughput.

On the other hand, Lab-on-a-Chip devices based on a microfluidic chip has closed environment and also help to prevent cell contamination as well as restrict the position of cells in 2 dimension in a plane [11, 12]. Moreover, the cost of microfluidic chips are generally low and disposable because they are fabricated by using MEMS processes that can be mass produced. The microfluidics has a lot of advantages for manipulation of small objects. However, the cell manipulations with microfluidics are generally passive way of fluidic force and therefore the noncontact actuation of microrobot in a microfluidic chip is required to active analysis such as mechanical properties measurement [9, 10].

Taking advantages of both of micromechanical manipulator and Lab-on-a-Chip devices, we have proposed the on-chip cell mechanical characterization using a robot integrated microfluidic chip (robochip) which contained a robotic probe and a force sensor. Figure 1 shows the conceptual view of cell mechanical characterization using robochip. The several microactuators that can be applied in the confined space of microchannels are proposed such as bubble actuators driven by thermocapillary flow [13], optical tweezers [14, 15], and magnetic microactuators [9, 10]. Among the many different microactuation mechanisms, magnetic actuation has certain advantages over other methods due to their suitable force source for deformation of oocyte [16]. Therefore, our robochip has a magnetically driven robotic probe. The target oocyte is transported to the manipulation point in a robochip (fig. 1a), the robotic probe deforms the oocyte and cellular reaction force is measured by deformation of opposite force sensor.

This work is partially supported by Scientific Research from Ministry of Education, Culture, Sports, Science and Technology (23106002) and also the Japan Society for the Promotion of Science.

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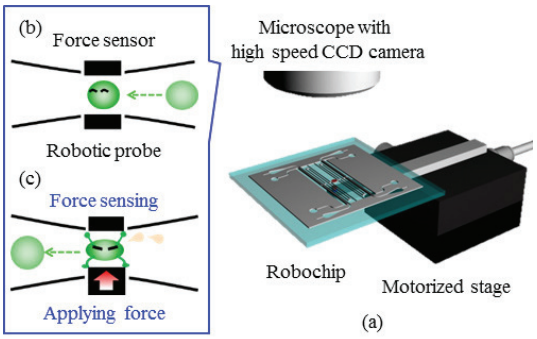

Fig. 1. Concept of on-chip cellular mechanical characterization

In this paper, we present the mechanical characterization of oocyte. Continuous cellular force measurement and cellular characterization was demonstrated. The characterization system performed based on the visual feedback control. Oocytes were positioned by the pump control and the robotic probe was actuated by the external magnetic force produced by the permanent magnet on the motorized stage (figs. 1b, c). Robochip approach has potential to achieve a single cell mechanical characterization with high throughput because our approach based on the microfluidic chip for biomedical application. In section II, the fabrication process of robochip and measurement system configuration are described. Section III outlines the basic experiments. In addition, we evaluate the effectiveness of the proposed approach for measuring the cellular mechanical properties. Finally, the conclusions and our future plans are presented in section IV.

II. CELL MECHANICAL CHARACTERIZATION

A. Fabrication of robochip

In order to reduce the friction force between the on-chip robotic probe and force sensor and the substrate surface, it is required to fabricate the chip with realizing the gap between them. Therefore, a layer fabrication process was employed to realize the required gap. The fabrication process of robochip was based on a two-step procedure. First the substrate layer, the device layer, and the cover layer were fabricated identically. The layers were then packaged, and a multi-layer structure with the narrow gap was easily achieved. Figure 2a-g shows the process flow for the fabrication of the probe.

Substrate layer: Substrate layer has a small step for realizing the gap between the on-chip probe and force sensor and substrate layer. The small step (thickness: 2 μm) was easily fabricated using wet etching technique.

(a) SU-8 (Nippon Kayaku Co., Ltd.), which is negative photoresist, was patterned on the glass substrate.

(b) Glass substrate was etched by hydrofluoric acid, and then SU-8 was removed by O_2 plasma ashing.

Device layer: Device layer composed of the on-chip probe, the force sensor and the microchannel.

(c) An SU-8 layer was patterned on the surface of the Si substrate as a etching mask of deep reactive etching (DRIE).

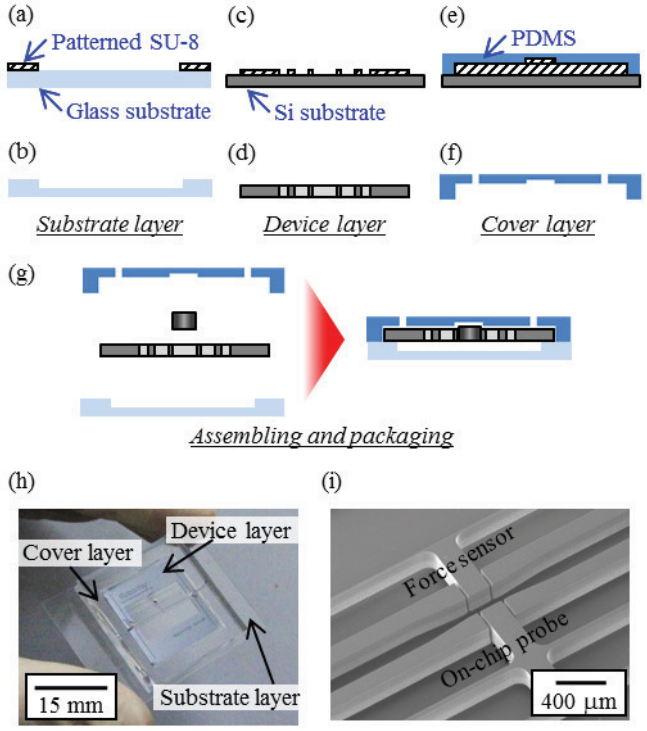

Fig. 2. Fabrication process of robochip and images of fabricated chip

(d) Si substrate was etched using DRIE, and then SU-8 was removed by O_2 plasma ashing.

Cover layer: Poly(dimethylsiloxane) (PDMS) molding technique was adopt to fabricate the cover layer . The cover layer has a pair of inlet and outlet, and a tube which was utilized for installation cell to the chip was connect to the chip.

(e) An SU-8 layer was patterned on the surface of the Si substrate as a mold of PDMS cover. Then, the cover pattern was transcribe to the PDMS.

(f) PDMS cover was removal from the mold, and a pair of inlet and outlet was formed by punching.

Assembling and packaging: The fabricated layers were packaged after a permanent magnet was assembled to the device layer.

(g) A permanent magnet (diameter: 1 mm, height: 0.5 mm, density of magnetic flux: 140 mT) was assembled to the actuation point of device layer. Then, the substrate layer and the device layer were bonded by the anodic bonding. Finally, the bonded layer was packaged using O_2 plasma bonding of the PDMS cover layer.

A photograph of the fabricated robochip and a scanning electron microscope (SEM) image of the manipulation point of the chip are shown in Fig. 2h, i.

B. System configuration

System diagram is shown in Fig.3. Mechanical characterization system lets cells flow through microchannel of robochip, and positions them at the manipulation point

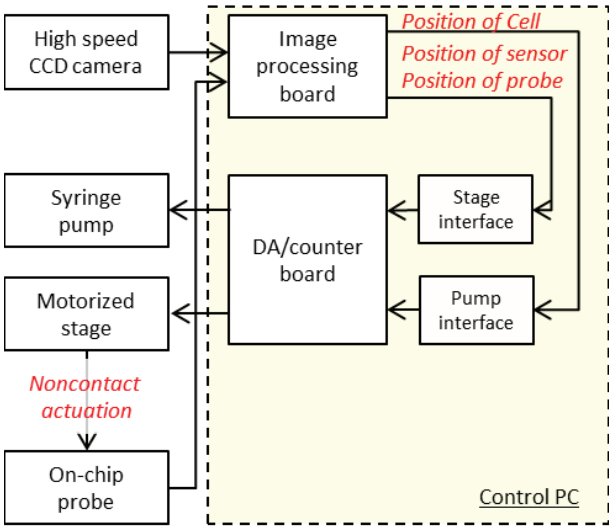

Fig. 3. System diagram for cellular mechanical characterization

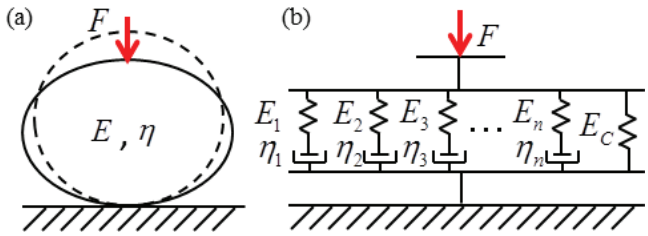

Fig. 4. Modeling of cellular deformation. (a) basic image of deformation and (b) analytical model of deformation (generalized Maxwell model)

one by one. Cells at manipulation point are deformed to some extend by moving robotic probe (whose repetitive positioning was about 200 nm [14]) while measuring the force applied. The system utilizes a desktop computer which interfaces a syringe pump and motorized linear stage. Visual feedback is available through a high speed camera which is attached to a microscope. Position of target cell, force sensor and robotic probe are measured by simple and fast image processing algorithms for a fast response. Deformation of cell is measured by measuring the distance between force sensor and tunable wall, comparing with original size of the cell. Deformation information is then used in PID control of motorized stage. With the image processing being the bottleneck (about 300 Hz), PID control works in 500 Hz enabling accurate positioning and sensing.

C. Modeling of cellular deformation

Our system based on the visual feedback control, therefore, it is possible to measure the cellular force and the magnitude of deformation as a function of the time. This section describe that the evaluation of the cellular mechanical properties. To analyze the mechanical properties of oocyte, a deformation model written as shown in Fig. 4a was applied.In order to characterize the oocyte mechanical proparties, the unique viscoelastic properties should be considered[4]. Therefore, in our model, a oocyte is assumed as a microparticle which has viscoelastic properties, and the microparticle is pushed against the rigid plane. At first, a oocyte is regarded as a homogeneous isotropic elastic microparticle, and Hertz's theory is applied to the contact model between the microparticle and the plane. The applied force F can be described as a function of the displacement of microparticle δ as follows: (the deformation of the plane can be ignored).

$$F = \frac{4}{3}\frac{R_0^{\frac{1}{2}}}{1-\nu^2}E'\delta^{\frac{3}{2}} \tag{1}$$

where R_0 is the radius of microparticle; ν is the Poisson's ratio of the microparticle E' is the Young's module of microparticle. Then, considering the viscoelastic properties of oocyte, we assumed that the E' is expressed by the generalized Maxwell model as shown in Fig. 4b. In the case of , the relaxation modulus $E(t)$ can be expressed as follows;

$$E(t) = E_c + \sum_{i=1}^{n} E_i e^{-\frac{t}{T}} \tag{2}$$

where E_c is the long term modulus once the material is totally relaxed E_i is the constant value of the time dependence parameter, τ_i is the relaxation time defined as the time required until the initial value turn to the value of $1/e$. By substituting the equation (2) into the equation (1) ignoring the effect of the acceleration due to mass of the microparticle, unstably force can be expressed as follows,

$$F(t) = \frac{4}{3}\frac{R_0^{\frac{1}{2}}}{1-\nu^2}\left(E_c + \sum_{i=1}^{n} E_i e^{-\frac{t}{T}}\right)\delta^{\frac{3}{2}} \tag{3}$$

Now, in order to simplify the calculation, we consider that oocyte has a single dependence term in the our model ($i = 1$). In order to obtain the value of E_c and E_1, we measure the cellular force and the deformation of oocyte as a function of the time by the images taken with the CCD camera. Therfore, we can obtain the total number of n equations for two unknown parameters as shown in equation (4).

$$\begin{cases} F(t_1) = \frac{4}{3}\frac{R_0^{1/2}}{1-\nu^2}\left(E_c + E_1 e^{-\frac{t_1}{T}}\right)\delta^{\frac{3}{2}} \\ F(t_2) = \frac{4}{3}\frac{R_0^{1/2}}{1-\nu^2}\left(E_c + E_1 e^{-\frac{t_2}{T}}\right)\delta^{\frac{3}{2}} \\ \vdots \\ F(t_n) = \frac{4}{3}\frac{R_0^{1/2}}{1-\nu^2}\left(E_c + E_1 e^{-\frac{t_n}{T}}\right)\delta^{\frac{3}{2}} \end{cases} \tag{4}$$

Here, defined matrices A and B is defined as the following equation,

$$A = \begin{bmatrix} 1 & e^{-t_1/T} \\ 1 & e^{-t_2/T} \\ \vdots & \vdots \\ 1 & e^{-t_n/T} \end{bmatrix}, \quad B = \begin{bmatrix} F(t_1)/\delta(t_1)^{3/2} \\ F(t_2)/\delta(t_2)^{3/2} \\ \vdots \\ F(t_n)/\delta(t_n)^{3/2} \end{bmatrix}, \tag{5}$$

the unknown parameters is obtained using equation (6).

$$\begin{bmatrix} E_c \\ E_1 \end{bmatrix} = \frac{4}{3}\frac{R_0^{1/2}}{1-\nu^2}\left(A^{\mathrm{T}}A\right)^{-1}A^{\mathrm{T}}B \tag{6}$$

Equation (6) indicates that the mechanical parameters of oocyte is determined by the value of cellular force and the deformation displacement of oocyte

D. Oocyte preparation

Bovine oocytes with cumulus cells were obtained from Livestock Improvement Association of Japan Inc. (Tokyo, Japan) and transported to the laboratory within 24h in cryogenic vials with culture medium. The oocytes with cumulus cells were then transferred to a culture dish containing 1% hyaluronidase (Sigma) in Medium 199 (Gibco), and the surrounding cumulus cells were removed enzymatically by pipetting. Each oocyte was picked to immerse in the prepared Medium 199 in a 35mm culture dish.

III. RESULTS AND DISCUSSIONS

A. Experimental setup

Figure 5 shows the overall view of the experimental setup. Robochip was placed under a microscope with CCD camera and a tube with syringe pump was connected to the chip for the controlling the cell position. A permanent magnet (diameter: 1 mm, height: 1 mm, density of the magnetic flux: 176 mT) was placed on the motorized stage to actuate the on-chip probe, and the density of magnetic flux on the glass substrate was 32 mT. Figure 6 shows the frequency response characteristics of the on-chip probe in a robochip. The magnitude graph shows the on-chip probe amplitude compared to the stage amplitude, and the phase graph shows the on-chip probe phase lag from the stage movement. The results show that the on-chip probe can follow the stage up to 40 Hz.

B. Continuous cell measurement

Continuous cell measurement was demonstrated using cellular mechanical characterization system. Figure 7 shows the typical results of continuous measurement. Oocyte was transported through microchannel of robochip, and positions them at the manipulation point one by one. The position of oocyte was controlled by the syringe pump, and oocyte at manipulation point are deformed by robotic probe. Position of target cell, force sensor and robotic probe are measured by the image processing. The measurement time was about 10 seconds per one oocyte, and time interval was about form 5 to 10 seconds. Eventually, total measurement time was about from 15 to 20 seconds per one oocyte. We concluded that the high through put cellular mechanical characterization was achieved, and our robochip approach was suitable for biomedical application because the chip part was disposable.

C. On-chip mechanical characterization of oocyte

Figure 8 shows the concept of the cellular mechanical characterization using a robochip. First, a oocyte is transported to the manipulation point of robochip (Fig. 8a). Then, the oocyte is deformed by the on-chip probe (Fig. 8b, c). Finally, we evaluated the displacement and the cellular force as a function of the time by the images taken by the CCD

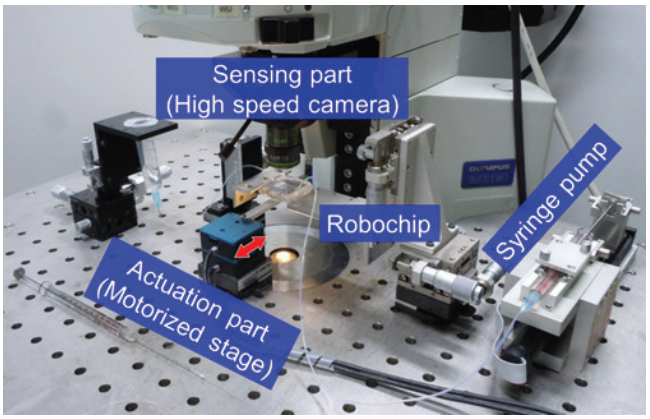

Fig. 5. Experimental system setup

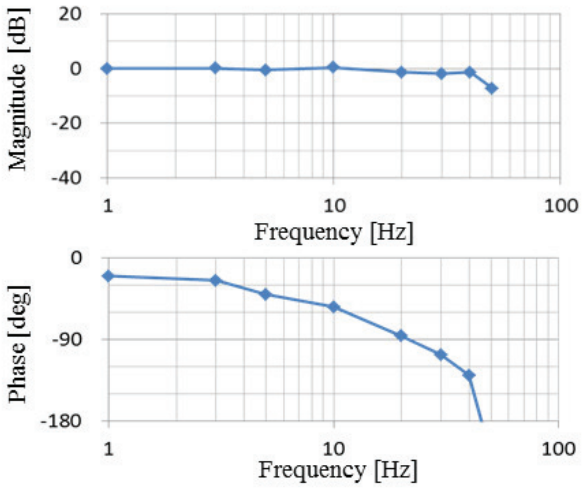

Fig. 6. Frequency response characteristic of the on-chip probe

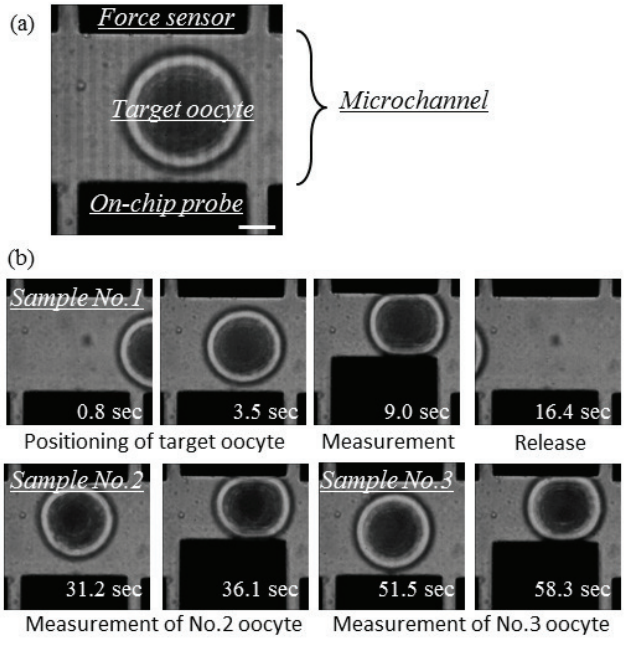

Fig. 7. Demonstration of continuous measurement. (a) details of manipulation point, scale bar is 30 μm and sequential photographs of demonstration

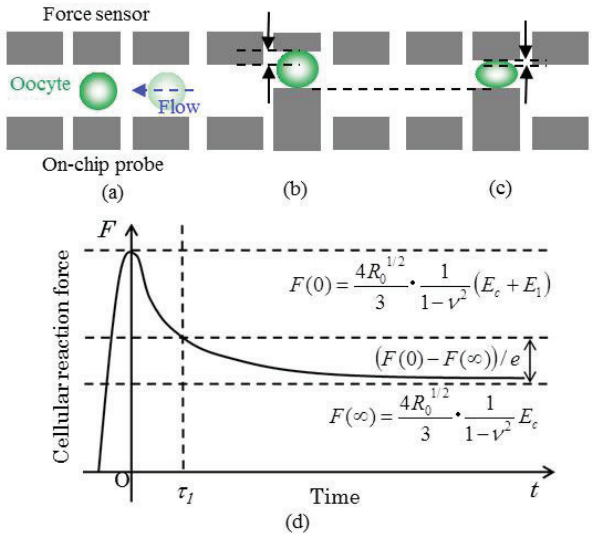

Fig. 8. Concept of mechanical characteristics of oocyte. (a) positioning of oocyte, (b), (c) measurement characteristics using relaxing phenomenon of deformation, and (d) measurement stress relaxation of deformation as a function of time.

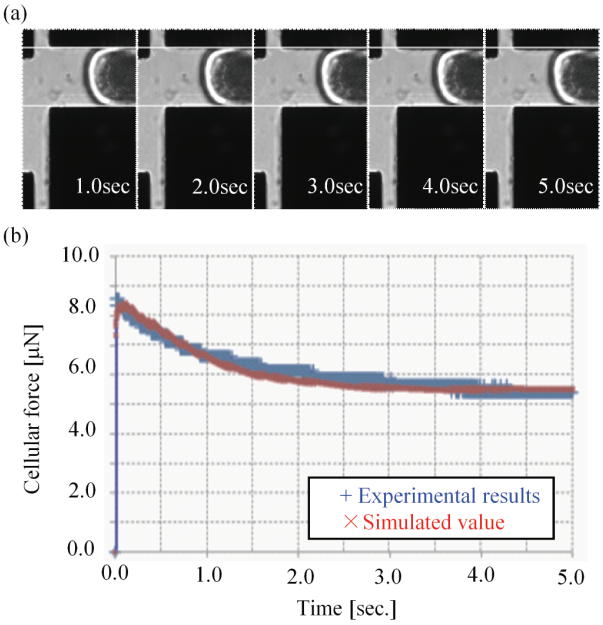

Fig. 9. Demonstration of cellular mechanical characterization. (a) sequential photographs of demonstration and (b) measurement result of cellular force of oocyte as a function of time

camera(Fig. 8d). Figure 9a shows sequential photographs of the typical experimental results. The on-chip probe was actuated and the oocyte was deformed at the tip of the force sensor. The reaction force of oocyte was decrease with passing the time. In order to evaluate the validity of the deformation model, analytical values were simulated using equation (3) with the measured cellular parameters. Then, the E_c and E_1 were calculated using equation (6). Figure 9b shows the cellular force of oocyte as a function of time. The blue plots indicate the experimental values, while the red plots indicate the calculated values. The experimental values were measured by the images (200 frame per second). In this case, the value of E_c and E_1, were calculated as 4.83 kPa and 4.86 kPa. Experimental values and simulated values are good agreement and the results shows that it is possible to adopt the deformation model to analyze the mechanical properties of oocyte. Finally, mechanical properties of oocytes, which were cultured for 2 (group A), 14 (group B), 18 (group C) days after harvest, were measured as a quality evaluation of oocyte. Each group has 10 samples. The experimental results were shown in Tab. 1 and the average of measured characters were shown in figure 10. Especially, in the group A, the value of E_1 for the sample number 6 and 9 has a big difference, respectively although the value of E_c was close. The results indicated that the oocyte has the viscoelastic properties and it is important to analyze the mechanical properties of oocyte for the evaluation of the quality. Moreover, the average of E_c decreased as a function of the culture days and the average of E_1 increased. Eventually, a quality evaluation of cell will be possible by mechanical characterization. Therefore, the evaluation of the relationship between E_c and E_1 will be a promising technology to evaluate the quality of cell itself.

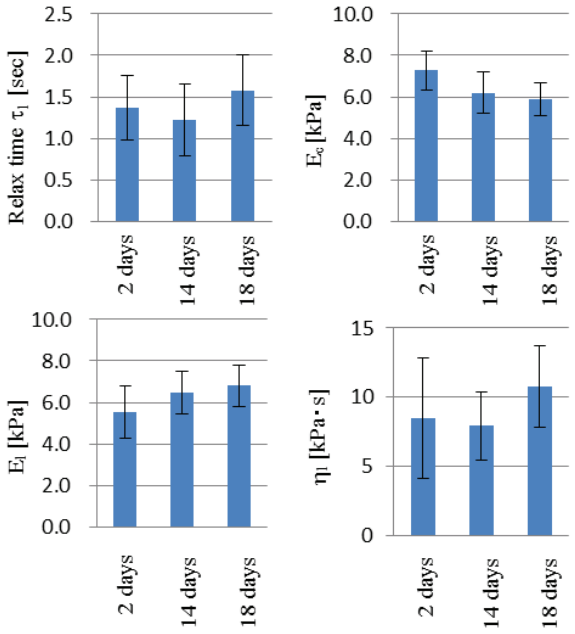

Fig. 10. Measured cellular mechanical characters of oocytes

IV. CONCLUSIONS

In this paper, we demonstrated the on-chip mechanical characterization of oocyte. We have proposed the robot integrated microfluidic chip (robochip) for high throughput characterization, taking advantages of both of micromechanical manipulator and Lab-on-a-Chip devices. The robochip contained a pair of a magnetically driven on-chip robotic

TABLE I

OOCYTE CHARACTERIZATION RESULTS

	No	Size [μm]	τ_1 [s]	E_1 [kPa]	E_c [kPa]	η_1 [kPa*s]
A	1	143	1.29	8.90	2.95	3.9
	2	142	1.59	7.39	6.56	10.6
	3	141	1.88	6.05	6.88	13.1
	4	149	1.90	8.14	5.31	10.1
	5	151	0.81	8.05	4.97	4.0
	6	145	2.30	6.42	7.28	16.8
	7	150	1.58	7.10	6.10	9.8
	8	149	0.79	6.19	5.84	4.6
	9	146	1.43	6.68	4.73	6.6
	10	147	1.12	7.86	4.75	5.3
B	1	149	1.10	6.66	6.81	7.5
	2	148	0.87	7.30	7.10	6.4
	3	150	0.85	5.90	8.01	7.2
	4	155	1.59	6.91	6.36	10.2
	5	152	0.77	6.08	5.83	4.6
	6	149	1.71	5.87	7.19	12.2
	7	147	1.91	4.83	5.02	9.5
	8	145	0.97	7.91	7.58	7.6
	9	148	0.86	5.00	4.97	4.5
	10	148	1.62	5.41	5.93	9.4
C	1	154	0.99	4.28	7.17	7.2
	2	152	1.68	6.07	6.94	11.7
	3	145	2.17	6.67	6.98	15.4
	4	151	1.44	6.28	7.93	11.1
	5	148	2.25	6.05	5.82	13.3
	6	153	1.51	6.45	7.32	11.0
	7	150	1.67	6.85	7.41	12.6
	8	150	1.77	5.84	5.80	10.4
	9	153	1.24	5.50	7.88	9.5
	10	149	1.05	4.89	4.84	5.3

probe and a force sensor.

In fabrication of robochip, layer fabrication was employed and the small gap (2 μm) was easily achieved for the purpose of reduction the friction force between the on-chip robotic probe and force sensor and the substrate surface.

The continuous characterization was demonstrated. The target oocytes was transported to the manipulation point one by one, and the robotic probe, then, deformed the oocyte. The cellular reaction force was measured by deformation of opposite force sensor. The characterization system performs based on the visual feedback control, and continuous cellular characterization was automated. Oocyte is positioned by the pump control and the robotic probe is actuated by the external magnetic force produced by the permanent magnet on the motorized stage. The throughput of our system was 15 to 20 seconds per one oocyte. We concluded that the high through put cellular mechanical characterization was achieved.

In order to evaluate the quality of oocyte, the mechanical characterization was demonstrated using the defomation relaxing phenomenon. The deformation model was assumed using Hertz's theory and Maxwell model. Experimental values and simulated values are good agreement and the results shows that it is possible to adopt the deformation model to analyze the mechanical properties of oocyte. Mechanical properties of oocytes, which were cultured for 2, 14, 18 days after harvest, were measured as a quality evaluation of oocyte. Experimental results shows that the oocyte has the viscoelastic properties among the same culture condition, and it is important to analyze the mechanical properties of oocyte for the evaluation of the quality. Moreover, the average of E_c decreased as a function of the culture days and the average of E_1 increased. Eventually, a quality evaluation of cell will be possible by mechanical characterization. Therefore, the evaluation of the relationship between E_c and E_1 will be a promising technology to evaluate the quality of cell itself.

Robochip approach has potential to achieve a single cell mechanical characterization with high throughput because our approach based on the microfluidic chip for biomedical application. In the future, the oocyte management system, which consists not only the characterization of oocyte but also the controlling the culture condition depends on the character of oocyte, will be developed.

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