Design and Control of a New Micro End-effector for Biological Cell Manipulation

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Abstract: Recently, biological technology industry shows great development. Instruments and systems related biological technology have been developed actively. In this paper, we developed a new micro end-effector for biological cell manipulation. The existing micro end-effector for biological cell manipulation has not any force sensing mechanism. Usually, excessive contact force occurring when the end-effector and a cell collide might make a damage on the cell. However, unfortunately, user can not notice the condition in case of using the existing end-effector. In order to overcome we proposed the improved micro end-effector having a force sensing mechanism. This paper presents the design concepts of the new micro end-effector. We carried out calibration of the force sensor and tested the performance of the proposed micro end-effector. Through a series of experiments the new micro end-effector shows the possibility of application for precision biological cell manipulation such as DNA operation

Keywords: micro end-effector, pipette, biological cell, manipulation, force sensor, diaphragm, strain gauge

1. INTRODUCTION

When we manipulate the bio cell such as embryo, microbe and DNA, we should use the fine and precision tools because the bio cells' tissue is very fragile. In this reason, it demanded to develop the micro motion actuators and the sensors measuring the detailed physical quantities[1-3].

Usually, existing micro end-effector has so simple structures and no force sensing mechanism. It can only estimate the positional motions or manipulations of the micro end-effector. Also, when the micro end-effector contacts the cell, it can't understand the physical characteristics. Because of these reasons, there are lots of problems such as slippery and destruction of the cell membrane and damage of the pipette tip etc.

To overcome the above stated problem, in this research, we have developed a new micro end-effector that can measure the contact force. This force information can offer the physical characteristics in the micro world where the pipette tip contact the cell.

This paper is composed of six chapters. In chapter 2, we stated the problems by the existing micro end-effector. And we described the design concepts of a new micro end-effector for biological cell manipulation. In chapter 3, in order to obtain the best design data, we analyzed the structures of the micro end-effector using the finite element analysis software, 'ANSYS'. In chapter 4, we manufactured the micro end-effector using the obtained design data in chapter 2 and 3. And we calibrated the force senso. In chapter 5, we composed the biological cell manipulation system and tested the performance of the micro end-effector.

Through this experiment, we find out that proposed new micro end-effector can sufficiently sense the contact force in the biological cell manipulation. And we can predict that this micro end-effector can solve problems of the existing one.

2. DESIGN CONCEPT OF END-EFFECTOR FOR SENSING CONTACT FORCE

2.1 Characteristics and structures of existing micro end-effector for biological cell manipulation

Figure 1 shows the structure of two existing micro end-effector.

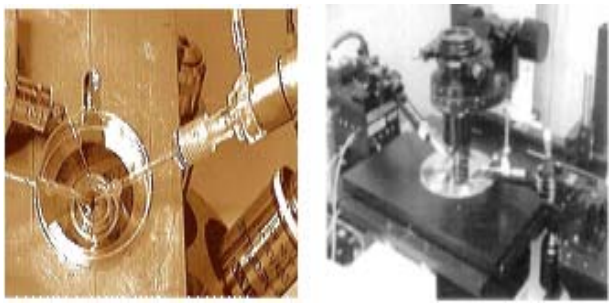


Figure 1. Existing micro end-effector for bio cell manipulation

Existing micro end-effectors for biological cell manipulation used the pipette tip, as shown in Figure 1. But it hasn't a force sensor. Therefore, existing micro end-effector was simple structures to estimate only the positional motions for bio cell manipulation under the optical microscope. Also, the existing micro end-effectors carried out biological cell manipulation by using visual information only. Because of these conditions, it never knows the physical characteristics when the micro end-effector contacted with the biological cell. So it has many problems such as slippery and destruction on the cell membrane and damage of the pipette tip etc. We introduce a new micro end-effector that can solve these problems at next chapter 2.2.

2.2 Design of a new micro end-effector

Figure 2 shows the proposed micro end-effector capable of sensing the contact force.

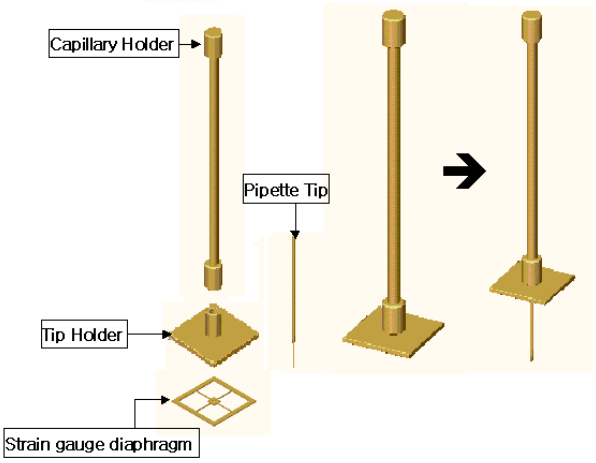


Figure 2. Proposed micro end-effector for bio cell manipulation

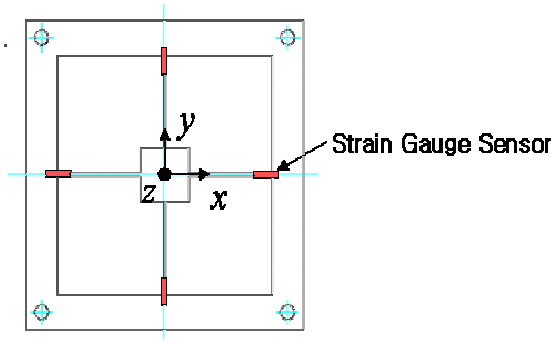


Figure 3. Diaphragm attached strain gauges

The micro end-effector is composed of pipette tip, tip holder, capillary holder and strain gauges as shown in Figure 2. In Figure 3, the diaphragm had strain gauges that measure the compressive force which is transmitted via the pipette tip. It is attached under the tip holder. The pipette tip is mounted the center hole of the strain gauge diaphragm. The four strain gauges can be attached to the diaphragm as shown in Figure 3. It can measure three kinds of forces such as F_z, M_x, M_y. F_z means two generated force information occurring when the pipette tip contact(contact force) and penetrate the cell membrane(penetration force). Because the cell membrane is so slippery, the pipette tip can slip when it contact to the cell. M_x and M_y mean moment information for slipping. This moment information offer the wrong operation of the pipette tip. For example, when the pipette tip is injected into the cell correctly, the perpendicular repulsion force is only measured. So the magnitude of F_z value is bigger than that of M_x and M_y. On the other hand, when the pipette tip is injected into the cell incorrectly, it gets bent on the cell membrane. The magnitude of F_z is smaller than M_x and M_y.

By using these information, we can improve the biological cell manipulation.

3. DESIGN AND ANALYSIS OF THE PROPOSED MICRO END-EFFECTOR

We obtained two dimensional displacement and stress of the diaphragm by using the finite element method. It generated stress concentration on the frame that encountered thin nodes. In this paper, we used the ANSYS that is famous commercial finite element method software.

The materials of diaphragm is stainless steel(SUS304). We set the Young's modulus: 198GPa, Poisson's rate: 0.3. We analyzed the plane elasticity that changed thickness. When put the force at the perpendicular direction Z, displacement is generated at direction X, Y. Using these data, the whole stresses of the diaphragm is computed.

We perform the analysis by the finite element method as follows;

(a) We set the static force 0.1mN in the middle of the diaphragm by changing the thickness of the node T; 1.5mm, 2.5mm, and 3.5mm. And, we observed principle stress.

(b) We set the static force 0.1mN in the middle of the diaphragm to change the thickness of the diaphragm; 0.1mm and 0.12mm. And, we observed principle stress.

Figure 5 and 6 show the result of the stress analysis. We know that the hinge is the part of stress concentration.

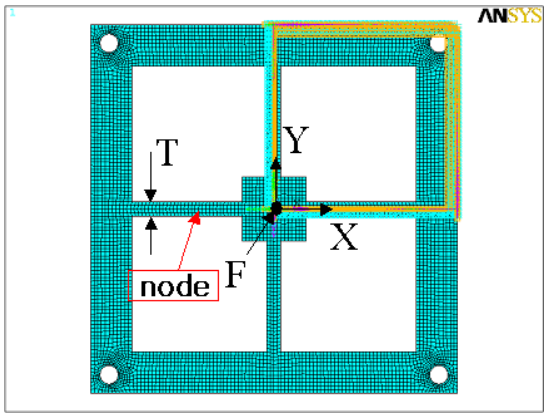
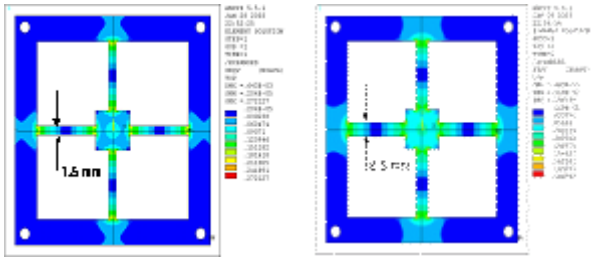
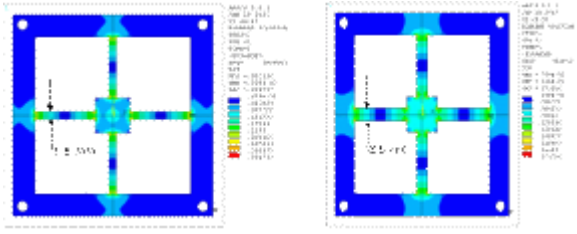


Figure 4. Initial finite element mesh in analysis



(a) (b)

Figure 5. Stress in case of applying the 0.1mN force on 0.12t diaphragm normally



(a) (b)

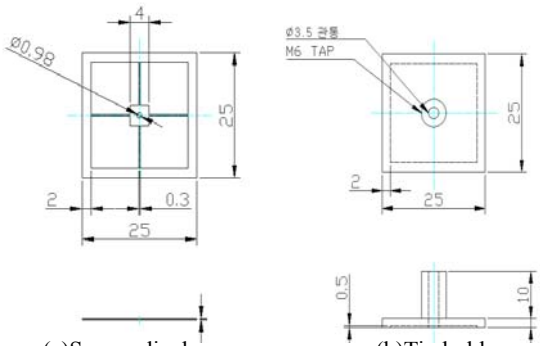
Figure 6. Stress in case of applying the 0.1mN force on 0.1t diaphragm normally

The maximum stress of Figure 5(a) is 0.272N/mm and that of Figure 5(b) is 0.186N/mm. The maximum stress of Figure 6(a) is 0.394N/mm and that of Figure 6(b) is 0.271N/mm. From the result of the analysis, we find out that thinner the thickness of the node and the diaphragm are, the bigger the stress is. And we know that the stress is concentrated at the hinge which thin rim and base meet. Therefore, to increase the sensitivity of the strain gauge sensor, the sensor must be attached to the hinge. And we decided the thickness of the node, T, as 0.3mm, because the semiconductor strain gauge's width is 0.3mm.

4. ASSEMBLY AND CALIBRATION OF THE PROPOSED END-EFFECTOR

4.1 Structure of the proposed end-effector

Concerned with the result of the stress analysis which mentioned at chapter 3 and the system integration, we designed and manufactured the micro end-effector that can sense the force for biological cell manipulation as shown in Figure 7.



(a)Sensor diaphragm (b)Tip holder

Figure 7. A drawing of micro end-effector for bio cell manipulation

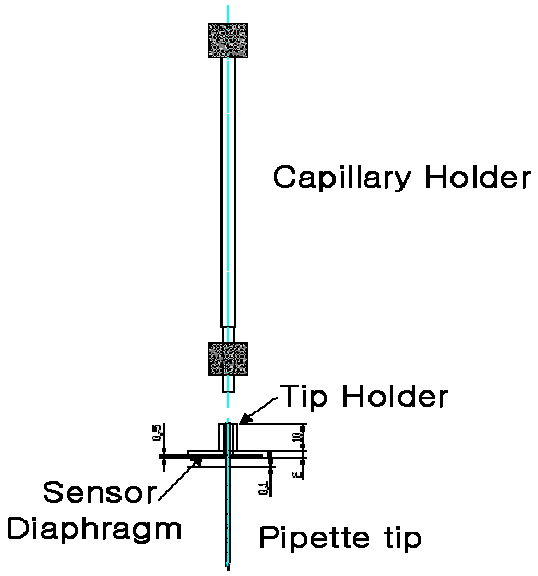


Figure 8. A drawing of assembly of the micro end-effector for bio cell manipulation

As shown in Figure 8, after the part of pipette which is composed of pipette tip, strain gauge, diaphragm and tip holder set up, it is designed that the part of pipette is assembled compactly with the capillary holder.

The strain gauge diaphragm is designed using the design data obtained from chapter 2 and 3 as shown in Figure 7. Its material is stainless steel(SUS 304), and made by using the laser cutting method.

Tip holder is designed compactly by considering the interference with other objects when it is integrated. It is made of aluminum. We have made the pipette tip using the alcohol lamp by ourselves.

There are many methods for sensing micro force, such as strain gauges, piezo electric transducer and piezo resistive etc. Among them we used the strain gauge type sensor. The strain gauge is semiconductor type (KSN-2-120-E5-11, KYOWA Co., Ltd. Japan). Size of the sensor is $2\times0.3mm^2$. This sensor is attached on the diaphragm. And the diaphragm is assembled with the tip holder. The wires of the strain gauge are soldered the terminal on the tip holder. The pipette tip is mounted on the center of the strain gauge diaphragm. Finally, the assembled tip holder is connected with the capillary holder.

4.2 Force sensor calibration

For the calibration of the proposed micro end-effector, we used the highly precise load cell(GSO-10 transducer, Techniques Co., Ltd. Maximum measuring ranges : 100mN, Resolutions : 10uN).

We set the perpendicular static linear force, and compared the signal of load cell with the signal of strain gauge sensor. Figure 9 shows the configuration of the calibration instruments. Output signal was obtained through the strain gauge amplifier and the low pass filer.

Figure 10 shows the result of the calibration for various thickness of the node of the diaphragm. It represents nonlinear sensitivity of the sensor. We think the characteristics are derived from the following reasons; Firstly, the strain gauge amplifier is too sensitive, Secondly, very small vibration around the instruments effect the nonlinearity. And the last, electronic noise of the strain gauge is yet effective. We will further study to solve these problems in the near future.

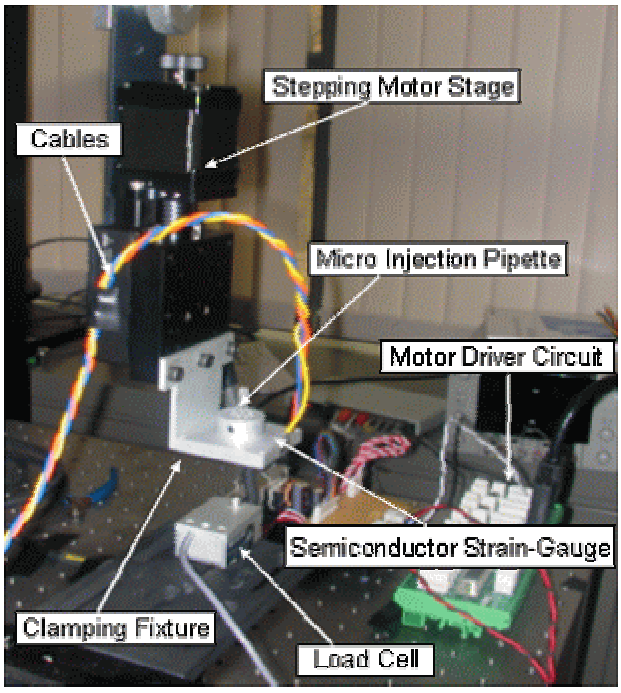
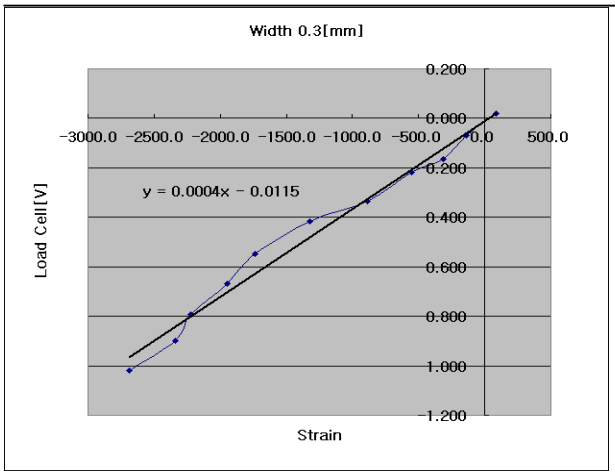
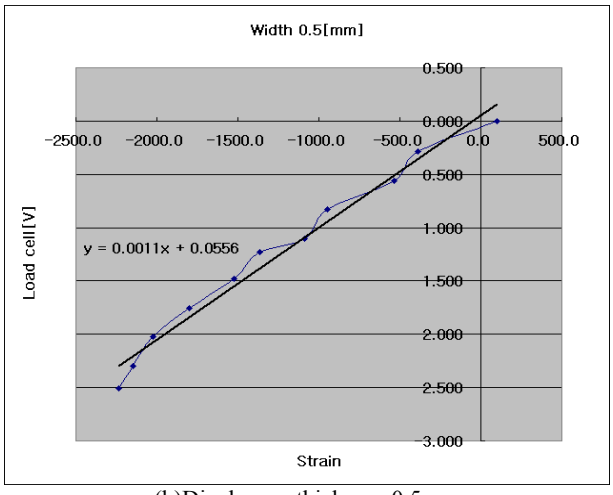


Figure 9. Experimental devices for force sensor calibration



(a)Diaphragm thickness 0.3mm



(b)Diaphragm thickness 0.5mm

Figure 10. Calibration data for Force sensor calibration

5. EXPERIMENTS AND DISCUSSION FOR BIOLOGICAL CELL MANIPULATION

5.1 System configuration

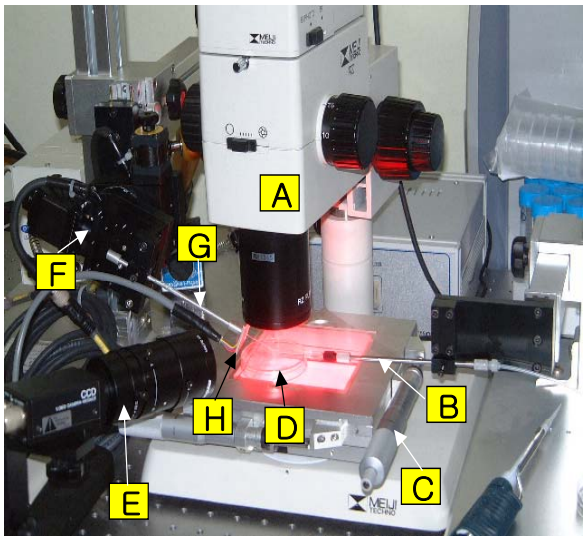
Two personal computers are used; the one is for motor control and the other is for vision processing.

The new micro end-effector consists of 2DOF actuators. The 2DOF actuators have two motions. The one is rotation, and the other is straight motion. It composed of two stepping motors. Rotation actuator adjusts the angle of injection and the straight motion actuator is used to force the pipette penetrate biological cells. The 2DOF actuators are controlled by MEI motion control board in PC. The Strain gauge sensor is connected to the bridge-circuit box and the bridge-circuit box is connected with the strain gauge amplifier. The analog output signal in the strain gauge amplifier is connected to the MEI board which performs A/D conversion. This converted A/D data is used to control the 2DOF actuators. In this way, the micro end-effector is controlled by the force sensor.

A holding tip is attached to the capillary holder's gripper. The holding tip is used to hold the biological cell by using the vacuum force. Capillary holder is connected the holding device that is called CellTram Oil(Effendorf Co., Ltd.).

A CCD camera is mounted on the top of the optical microscope. This camera is connected the vision processing board, Meteor(Matrox Co., Ltd.), in the PC for vision processing. Another CCD camera with zoom lens is connected with the Meteor board in the same PC. In the vision processing PC, it processes the images through the two CCD cameras. The processing result data is transmitted the motor control PC by RS 232 serial communication. This data is used to contact the cell safely.

We developed dual illumination system that is composed of the back-light(white highly-brightness LED) and the upper-light(halogen) illumination system for observing various biological cells. The XY stage on a microscope's support adjusts the position of the observing cell. The optical microscope(MEIJI TECHNO, Japan) has lens with magnification ratio 300. The left side of the microscope is the micro end-effector and the right side is the capillary holder.



A: Optical Microscope B: Holding Pipette
C: XY Stage D: Petridish
E: Zoom CCD F: 2 D.O.F. Micromanipulator
G: Injecting Pipette H: Force Sensor

Figure 13. The proposed biological cell manipulation system

5.2 Experiment and discussion

To show the performance of the proposed micro end-effector, we applied to the manipulation of the fish egg cell. Since the fish egg cell is very transparency, it can easily separate the growth procedure. Fish egg cell is composed of membrane and york. Its diameter is 700um ~ 1000um approximately.

Figure 12 shows procedures of the injection for fish egg cell. No.1 of the Figure 12 shows the pipette tip contact to the membrane of the cell. No.2 and No.3 of the Figure 12 show that the pipette tip penetrate the membrane. No.4 of the Figure 12 shows the pipette tip contact with the york. No.5 and No.6 of the Figure 12 show that the pipette tip penetrate the york. No.7 and No.8 show the destruction of the cell due to excessive injection force of the pipette.

Figure 13 shows the information of force reflection occurring when the pipette tip is injected into the cell. The High level of the force signal represents the condition that the pipette tip pushed the cell. On the other hand, low level of the force signal shows that the pipette tip is pulled out of the cell. When the pipette tip penetrates the cell in various velocity, the force reflection is also varied. As a result of the injection according to various velocities, we can find out that about the several mN force is required for pipette to penetrate the

biological cell such as fish egg.

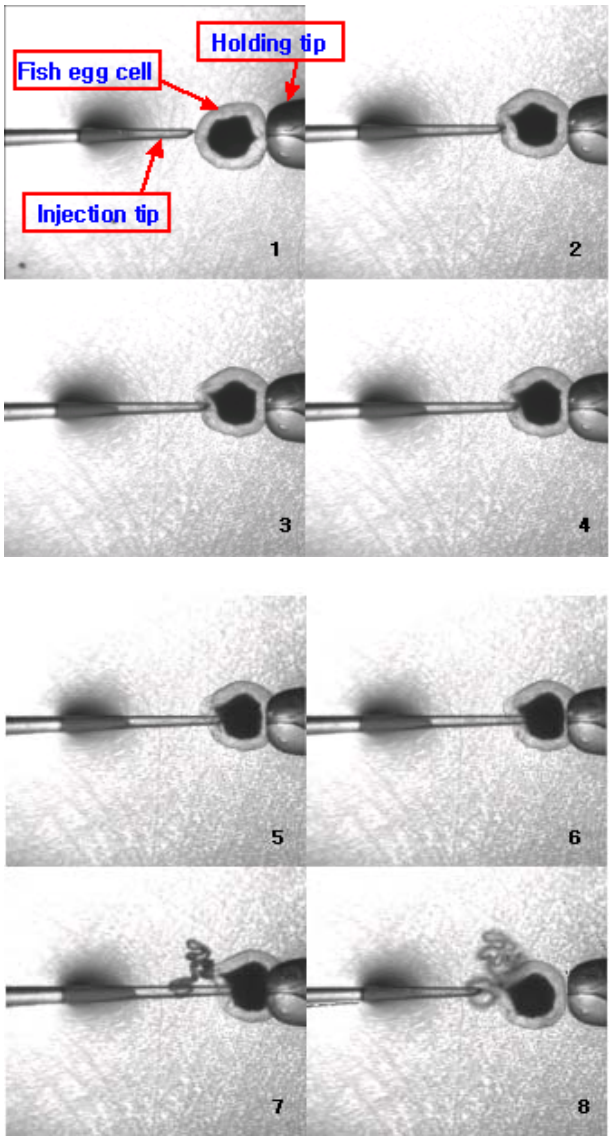


Figure 12. Experiments of fish egg cell injection

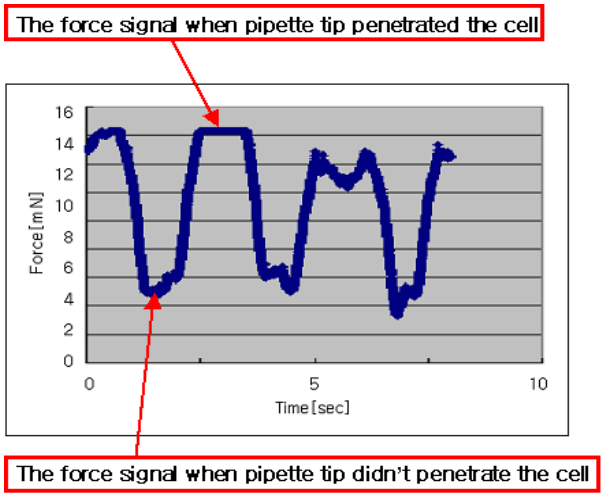


Figure 13. Force reflection occurring in fish egg cell injection

6. CONCLUSION

In this paper, we proposed a new micro end-effctor that is composed of strain gauge sensors, diaphragm, pipette tip, tip holder and capillary holder. The proposed micro end-effector will be used for the biological cell manipulation. Particulary, the end-effector has a sensitive force sensor inside itself. It can sense the several mili Newton force when the pipette tip contact with the membrane of the biological cell. The force sensor is a type of diaphragm. We analyzed the displacement and stress of the diaphragm according to shape and structures by using the finite element method. We designed the proper structure of the sensor diaphragm from the results of the finite element method. In this paper, the sensor diaphragm is made of SUS304. Four semiconductor type strain gauge sensors were attached on the diaphragm. We could obtaine three kinds of force information such as F_z, M_x and M_y.

We constructed a biological cell manipulation system. The system is composed of high-magnification optical microscope, CCD camera with zoom lens, dual illumination, 2DOF micro actuators, injection tip, holding tip and capillary holder etc.

We tested the performance of the developed micro end-effector for fish egg cell. And we find out that when the pipette tip penetrate the membrane of the cell, it required degree of several mN force. Through a series of same experiments, we know that the force sensor of the proposed micro end-effector has good S/N(signal to noise) ratio and repeatability.

To improve the performance of the proposed micro end-effector, we will modify this system in near future. Particularly using the haptic devices, operator will manipulate the biological cell conveniently.

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