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Research Article

TRANSFORMATION OF A TRADITIONAL MICROMANIPULATOR TO A SEMI-AUTOMATIC CELL SURGERY ROBOTIC SYSTEM FOR IN-VITRO FERTILIZATION

K. Thamrongaphichartkul[1]
S. Vongbunyong[1,*]
L. Nuntakarn[2]
[1] Innovation and Advanced Manufacturing Research Group, Institute of Field Robotics, King Mongkut's University of Technology Thonburi. 126 Pracha Uthit Rd, Bang Mot, Thung Khru, Bangkok, Thailand 10140
[2] Scishine Co., Ltd. 82 Watcharaphon Rd. Tha Raeng, Bang Khen, Bangkok, Thailand, 10220

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ABSTRACT:
Micromanipulators are mechanical devices used for manipulating miniature objects in the order of microns. They are widely used in In-Vitro Fertilization (IVF) process, in which sperms will be held on a micro-needle and penetrate to an oocyte for fertilization. Skilful embryologists need to control the movement of the micro-needle accurately under the microscope by using the micromanipulator. For the proper setup, the micromanipulator should be placed in the hypoxia chamber in order to control the environment of IVF. However, this setup is impractical in actual processes due to the limited accessibility of the devices. This research focuses on addressing this inaccessibility issue by using a master-slave system that allows the embryologist to control the micromanipulator remotely from outside the hypoxic chamber. An added-on slave module is mounted on a joystick of the manual micromanipulator. As a result, the traditional micromanipulator will be transformed to a semi-automatic cell surgery robotics system for IVF.

Keywords: *In-Vitro Fertilization, Micromanipulator, Tele-operation, Robotics*

1. INTRODUCTION

Currently, around 186 million people around the world have encountered an infertility problem [1]. Assistance Reproductive Technology (ART) [2] is technology that is developed in order to help couples suffering with this problem. In-Vitro Fertilization (IVF) is one of the most effective treatments ART that is able to handle infertility and genetic abnormality.

IVF is a conventional method that put sperms and oocytes on a petri dish for the chance to fertilize. Due to a number of uncontrollable factors, conventional IVF results in a low success rate of fertilization. Therefore, Intra-Cytoplasmic Sperm Injection (ICSI) which is one of the IVF methods is more preferable as it is more effective and leads to a higher fertilization rate [3, 4]. ICSI is a procedure in which a selected sperm is injected into an oocyte in order to be fertilized. ICSI process is performed by using a manual micromanipulator where a micro-needle and a holding pipette are equipped and controlled. ICSI consists of 3 steps: (1) selecting a single sperm by using micro needle; (2) holding the oocyte by using holding pipet, and (3) controlling the position micro needle to penetrate into the oocyte and injection sperm into oocyte [5].

* Corresponding author: S. Vongbunyong
E-mail address: supachai.von@kmutt.ac.th

In general, embryologists with ICSI expertise are capable of manually using a micromanipulator to accurately manipulate sperms and oocytes. The movement need to be scaled down due to the miniature size of the subjects which are in the order of microns. The success rate of the current and manual ICSI process are between 50-80% [6]. General setup of IVF process is shown in Fig. 1(a).

Ideally, IVF process must be taken place in a closed environment, i.e. in an IVF chamber (see Fig. 1(b)), since a number of external factors have negative effects on oocyte and sperm in regard to fertilization conditions [7]. These negative effects potentially lead to chronic diseases in the offspring in the future. However, the proper equipment setup with closed environment is impractical in term of operation as the biologist will have limited access to the equipment in the chamber. The operation will be ergonomically difficult to carry out. As a result, this setup is ignored in most IVF activities.

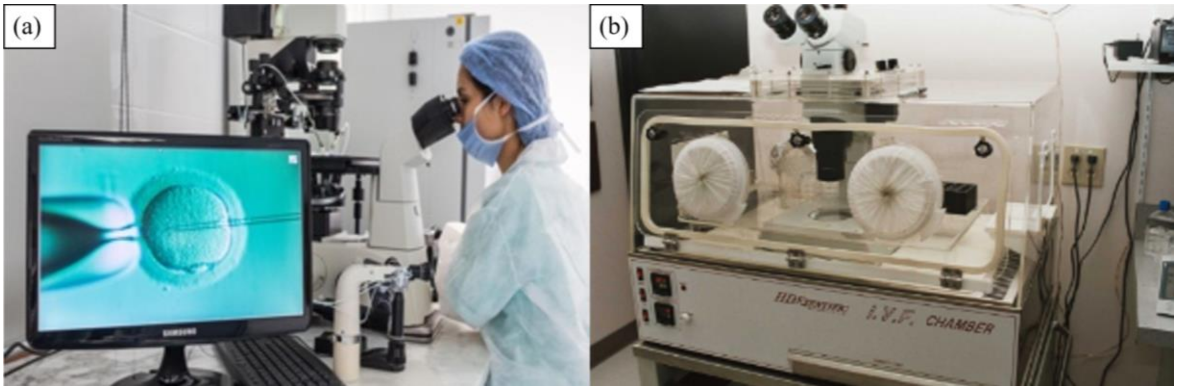

Fig. 1. IVF environment: (a) Open environment. (b) IVF chamber.

In the past two decades, a number of researchers have worked in the areas of robotics in biomedical fields. Zhe Lu *et al.* (2011) designed a robotic system for ICSI process to track and immobilize sperms [6]. Le Mattos *et al.* (2006) developed a semi-automated blastocyst microinjection system that the speed and precision of manipulation was improved [8]. Mehdi Ammi *et al.* (2006) improved the manipulation skill of embryologists by using human machine interface in training [9].

From the point of view of IVF practitioners, commercially micromanipulators with manual control types (e.g. [10, 11]) are preferred due to the fast response in manipulation of subjects. The user can control them more intuitively and accurately due to this fast response. In Thailand, 80% of ART clinics use manual manipulators. According to the high investment cost on the manual micromanipulator, the added-on module proposed in this research will enhance the capability of the existing devices with low cost investment.

In this research, a manual micromanipulator is enhanced by equipping an added-on system that allow to semi-automatic control of the existing manual manipulator. After the modification, embryologist will be able to perform IVF process in closed environment. In addition, repeatability and precision of the operation can be improved. The data during the operation can also be recorded and used for studying the factors relating to fertilization in the next phase of this research.

2. SYSTEM DESIGN

2.1 System Overview

The system overview is illustrated as a connection diagram on Fig. 2. The system consists of a PC platform, master arm, slave arm, a micromanipulator, a semi-automatic air syringe, and controlled environment chamber. The slave arm mounted on the joystick of the micromanipulator is controlled by the software running on the PC platform. The human user controls the movement of the micromanipulator from outside of the controlled environment chamber. The master arm is a haptic device connecting between the user and micromanipulator [12, 13]. A semi-automatic air syringe is a device controlling the pressure in the micro-needle in order to suck a sperm or hold an oocyte. In this research, the part of slave arm is focused (the red circle in Fig. 2). The user can control the system via the graphical user interface (GUI) console on the PC platform.

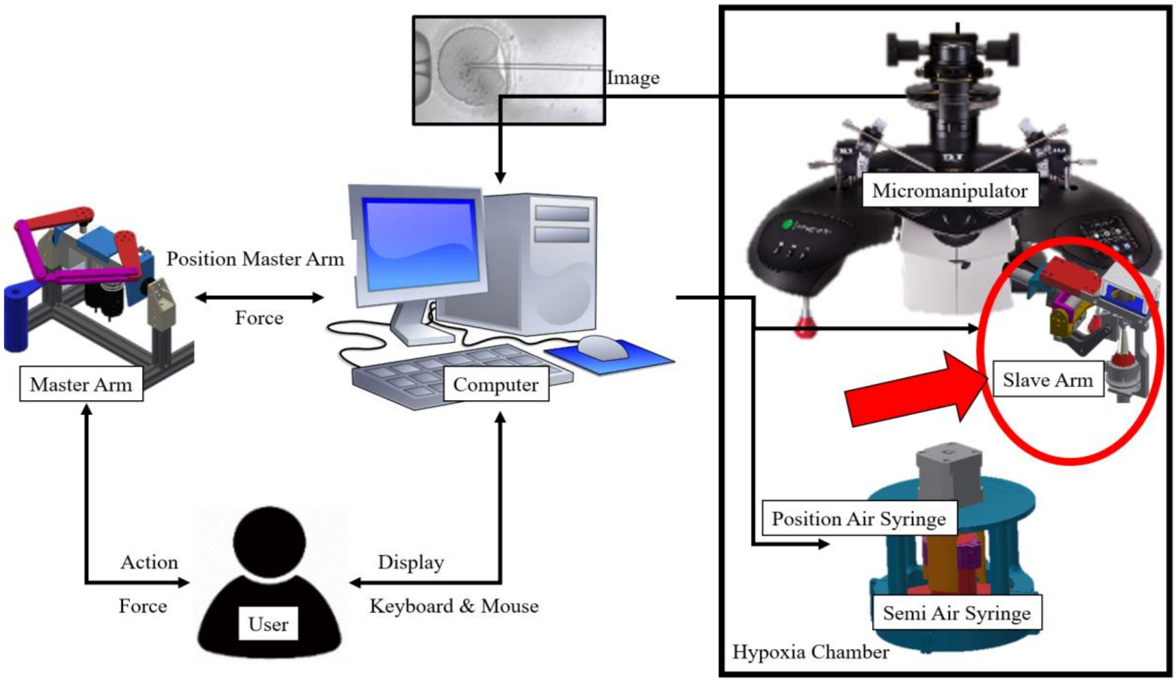

Fig. 2. System overview in this research

2.2 Mechanical of Micromanipulator

The micromanipulator is a mechanical device (see Fig. 3) used to manipulate miniature objects under a microscope, where the manipulation cannot be achieved by human solely according to the natural visual and manipulation limitation. The mechanism of a micromanipulator scales down the magnitude of the movement from the order of millimeter at the input side to the order of micron at the output side.

In this research, a micromanipulator RI Integra-3 is modified to a semi-automatic micromanipulator. The position *(x,y,z)* of the micro-needle is a function of the joystick as show in Fig. 3. The micro-needle moves according to the conversion ratio between the joystick and the micro-needle. The reference frame of the micro needle at point B is rotates around z-axis with respect to the reference frame of micromanipulator at point A show in Eq. (1).

$$\begin{bmatrix} x \\ y \\ z \end{bmatrix} = \begin{bmatrix} K_m \cos\theta_m & -K_m \sin\theta_m & 0 \\ K_m \sin\theta_m & K_m \cos\theta_m & 0 \\ 0 & 0 & K_z \end{bmatrix} \begin{bmatrix} \theta_1 \\ \theta_2 \\ \theta_3 \end{bmatrix} \quad (1)$$

Where

K_m : Ratio between micro-needle and joystick (*micron/degree*);
K_z : Ratio in z axis;
x, y, z : Position of micro needle (*micron*);
$\theta_1, \theta_2, \theta_3$: Position of slave arm (*degree*); and,
θ_m : Angle between of micro-needle and micromanipulator (*degree*).

The parameter K_m, K_z and θ_m can be estimated by measuring the angle of the joystick and position of the micro-needle in microscope show in Fig. 4.

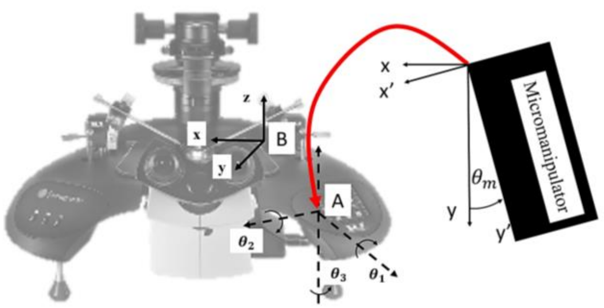

Fig. 3 . Position reference frame of micro needle and joystick.

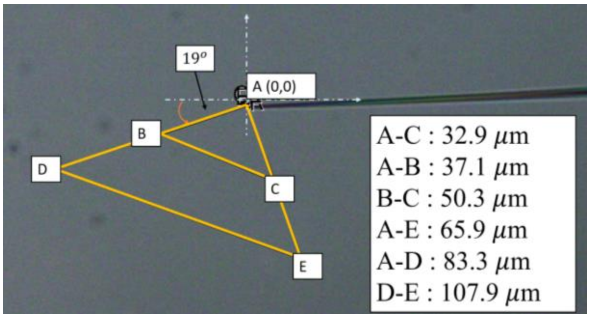

Fig. 4 . Find the parameter in micromanipulator.

The θ_m and K_m can measure is microscope is 19 degree and 14.58 micron/degree while K_z cannot be estimated directly with microscope

2.3 Conceptual Design

The general concept of this research is to control a manual micromanipulator by using a robotic arm which is called "a slave arm". This can also enable tele-operation capability. The slave arm is an added-on module attached to the joystick of micromanipulator that is normally used by the user to control a micro needle. The requirement and conceptual design of the added-on module is as follows:

- The added-on module for controlling the micromanipulator's joysticks as shown in Fig. 5 (a, b, c);
- Non-invasive installation on the existing micro-manipulator;
- A prototype slave arm with 3-DOF drive with high precision geared servo motor; and,
- To assume that the mechanism of micromanipulator is linearity.

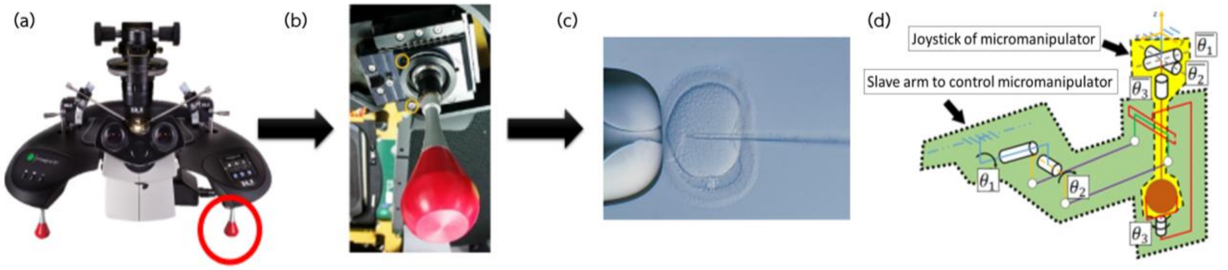

Fig. 5. Concept to control micromanipulator (a) Micromanipulator (b) Joystick to control (c) Picture in microscope (d) The 4-bar linkage simple mechanism of slave arm.

The mechanism of the joystick is a ball joint with 3 degrees of freedoms (DOFs). The slave arm is designed based on Four-bar linkage mechanism which can make the device compact. The kinematic diagram of the mechanism is presented in Fig. 5 (d).

2.4 Mechanical Design

Four bar linkage mechanism are simple and can be designed the system to have low moving inertia by placing the actuators close to the base [14]. In summary, the mechanism of the slave-arm consists of Four-bar linkage is used for axis-1 and axis-2, while axis-3 is direct driven by a motor. The base of the slave arm is clamped on the micro-manipulator. *Axis-1* and *Axis-2* is designed using a parallel mechanism as shown in Fig. 6 (a, b). *Axis-3* of joystick are revolute joint, so that it is directly driven by the motor. The coupling method is shown in Fig. 6(c).

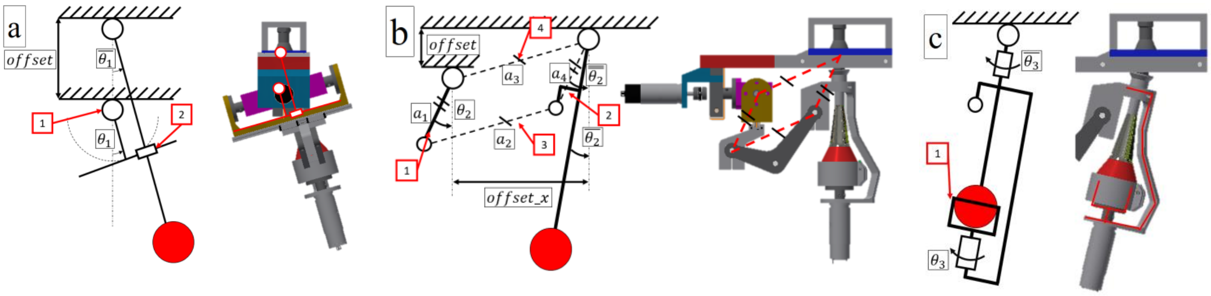

Fig. 6. Mechanic of slave arm: (a) Axis-1 (b) Axis-2 (c) Axis-3

3. SLAVE ARM CONTROL (PI-PI CONTROL)

Proportional-Integral-Derivative (*PID*) Controller is widely used in motion control of machines. This controller has a simple structure and robust. The control signal is dependent summation of 3 terms which are proportional (*P*), integral (*I*), and derivative (*D*) is as follows (Eq. 2).

$$u(t) = K_p e(t) + K_i \int_0^t e(t)dt \int + K_d \frac{de(t)}{dt}] \quad (2)$$

Where

- $u(t)$: Control input signal;
- $e(t)$: Error between input signal and output signal;
- K_p : Proportional gain;
- K_i : Integral gain; and,
- K_d : Derivative gain.

The controller of the slave arm is designed based on a PID controller with 2 loops (Fig. 7.). The outer loop is a position control loop using *PI* (Proportional – Integral) controller. The input of the controller is a position reference and output of the controller is velocity data from the inner loop. An inner loop is a velocity control loop using *PI* controller. The input of the controller is velocity reference and output of the controller is controlling input signal.

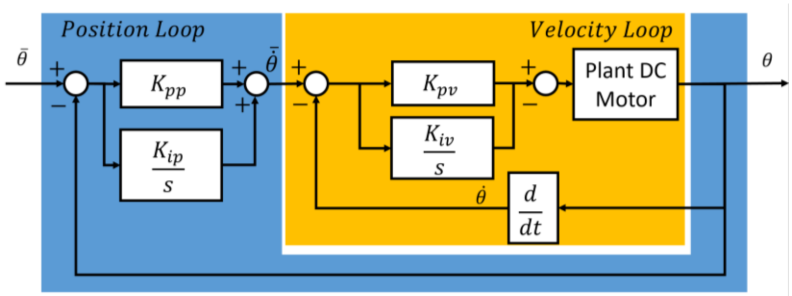

Fig. 7. PI-PI controller structure.

4. EXPERIMENT

The experiment is designed to assess the performance of the semi-automatic micromanipulator that is controlled by the slave arm. The performance of the system is assessed in regard to these factors: resolution, precision, accuracy, linearity, and backlash. The vision system is used to locate the micro needle in the experiment. The experiment consists of 2 parts:

4.1 Experiment to find relation between slave arm and micromanipulator

The experiment aims for observing the kinematic relation between the micromanipulator and the slave arm. The unit step command as in Fig. 8 were given as the input signal for each axis. The position in XY-coordinate of micro-needle measured by vision system were the output. The microneedle moved from point A (home position) to point B according to the input signal.

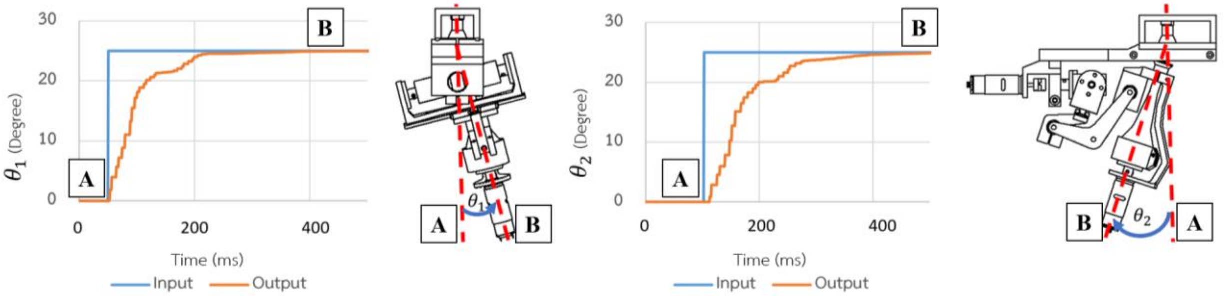

Fig. 8. The slave arm moves in each axis.

As the results shown in Fig. 9, the slave arm was able to operate with the control resolution of 1 micron. It should be noted that this value is limitation of the measurement due to the highest resolution (0.4 micron/pixel) that the image sensor of the microscope can obtain. Non-linearity was occurred in Axis-1 and linearity in Axis-2. The backlash of 15 micron and 5 microns were observed in Axis-1 and Axis-2, respectively.

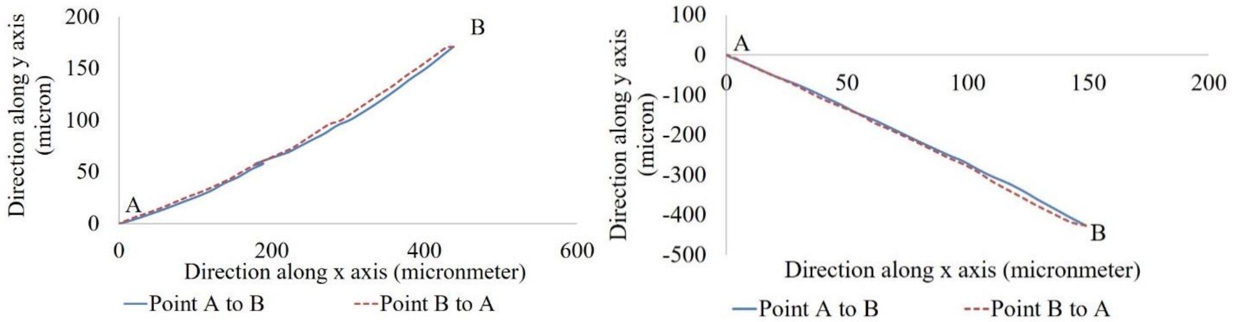

Fig. 9. Position of micro needle between point A to B of axis 1(left) and axis 2(right).

4.2 Command Tracking

This experiment aims for finding the traceability of the slave arm by using PI-PI controller. Sinusoidal input signal with various frequency to the system. As a result, the output is shown in the graph in Fig. 10 and data is shown in Table 1. The recommended frequency range for both axes is at least 10 rad/s.

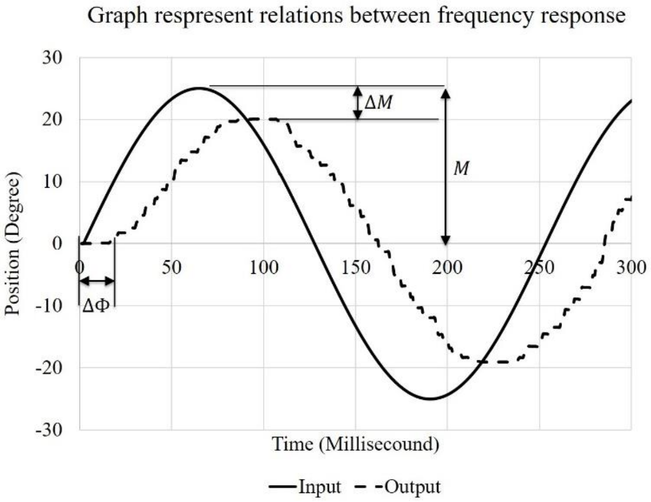

Fig. 10. Command tracking response of slave arm.

Where

$\Delta\Phi$: Phase lag in position (degree)

ΔM : Different magnitude of input and output

4.3 Repeatability

To assess the repeatability, the slave arm was used to control the microneedle to move between 3 points in a set of destination points shown in Fig. 11. The experiment was repeated for 10 times per each set shown in Table 2 and Table 3.

From the experimental result. The slave arm has the repeatability of slave arm is within 1 micron in both axis with low error accumulation.

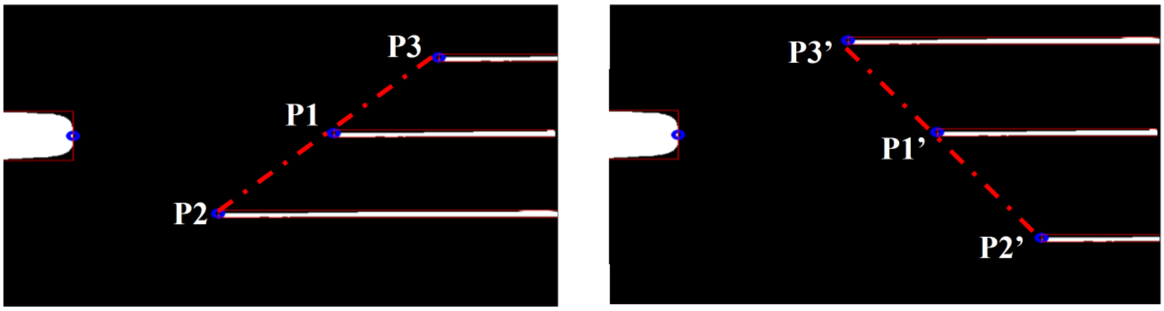

Fig. 11. (a) P1 P2 and P3 is destination point of microneedle. (b) P1' P2' and P3' is destination point of microneedle.

5. DISCUSSION

From the experiment, the results present the control characteristics of the slave arm when mounting and controlling the micromanipulator. Five issues of the movement characteristics are discussed as follows:

(1) *Response*: the maximum time constant of slave arm is 63 milliseconds due to the limitation in hardware (motors, encoder, and control board) and control software (PI-PI controller). The time constant can be shortened by improving those issues. However, in practice, the slow response time issue can be overcome automatically by user perception. The users will automatically compensate for the error by controlling the position of the micro-needle to the correct destination according to the visual perception and motor skill.

(2) *Command Tracking*: the slave arm was able to track the given reference command in the frequency range of 10 rad/s. It did not affect the control of the micromanipulator because the user is input command is generally slower that 1 rad/s. Command tracking can be improved as the response was improved.

(3) *Backlash*: the backlash in axis-1 is larger than Axis-2. However, the human user can overcome the effect of backlash by automatically compensate the effect with human visual perception and motor skill.

(4) *Linearity*: as Axis-1 is not linearity and Axis-2 is linearity. The exact kinematic model of the mechanism and fine calibration are needed to improve the precision and accuracy of the system.

(5) *Repeatability*: repeatability of the slave arm is 1 micron. This is affected by the backlash that is discussed earlier. In addition, this can be a limitation due to the structure type of the robot arm (revolute joints). Redesigning the mechanism based on a Cartesian robot structure will help to improve the repeatability of the system.

6. CONCLUSION

This paper presents a semi-automatic cell surgery robotic system for IVF that was transformed from the traditional and manual micromanipulator. The added-on module concept can apply to a micromanipulator and the new system has a slave arm to control micromanipulators to improve controllability in the physical control of micromanipulators.

In summary, the maximum backlash is 15 microns. However, the repeatability of the system observed at the end-effector, the micro-needle, is 1 micron, the slave arm can use be to control the micromanipulator with some acceptable time delay. In conclusion, as a result of the transformation, the embryologists will have an opportunity to perform IVF in a closed environment. The repeatability and precision were improved.

For future work, the slave arm concept will be applied to biological study and experiment. In addition, the performance and capability in regard to engineering issues will be improved and aimed for fully automatic operation in the future.

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REFERENCES

[1] Marcia, P.P. and Inhorn C. Infertility around the globe: new thinking on gender, reproductive technologies and global movements in the 21st century, Human Reproduction Update, Vol. 21(4), 2015, pp. 411-426.

[2] Matsota, P., Kaminioti E. and Kostopanagiotou G. Anesthesia related toxic effects on in vitro fertilization outcome: Burden of proof, BioMed Research International, Vol. 2015, 2015, pp. 1-9.

[3] Poehl, M., Holagschwandtner, M., Bichler, K., Krischker, U., Jurgen, S. and Feichtinger, W. IVF-patients with nonmale factor "To ICSI" or "Not to ICSI" that is the question?, Journal of Assisted Reproduction and Genetics, Vol. 18(4), 2001, pp. 205-208.

[4] Palermo, G., Joris, H., Devroey P. and Van Steirteghem, A.C. Pregnancies after intracytoplasmic injection of single spermatozoon into an oocyte, The Lancet, Vol. 340(8810), 1992, pp. 17-18.

[5] Perry, N.Y.A.C. Piezo-actuated mouse intracytoplasmic sperm injection (ICSI), Nature Protocols, Vol. 2(2), 2007, pp. 296-304.

[6] Lu, Z., Xuping, Z., Leung, C., Esfandiari, N., Casper, R.F. and Sun, Y. Automated cell manipulation: Robotic ICSI, paper presented in IEEE International Conference on Robotics and Automation 2011, Shanghai, China.

[7] Oozoa Biomedical Inc. Technical report: Benefits of using the IVF chamber in human IVF, 2002, Oozoa Biomedical, Vancouver.

[8] Mattos, L., Grant, E. and Thresher, R. Semi-automated blastocyst microinjection, paper presented in IEEE International Conference on Robotics and Automation 2006, Orlando, USA.

[9] Ammi, M., Ladjal, H. and Ferreira, A. Evaluation of 3D pseudo-haptic rendering using vision for cell micromanipulation, paper presented in IEEE/RSJ International Conference on Intelligent Robots and Systems 2006, Beijing, China.

[10] CooperSurgical. Integra 3™ Micromanipulator, 2017, Målov, Denmark.

[11] Narishige International USA, MTK-1 Four-axis Hanging Joystick Oil Hydraulic Micromanipulator, New York, USA, URL: https://usa.narishige-group.com/new/index.html, accessed on 2019.

[12] Thamrongaphichartkul, K., Vongbunyong, S. and Nuntakarn L. Development master arm of 2-DOF planar parallel manipulator for In-Vitro Fertilization, IOP Conference Series: Materials Science and Engineering, Vol. 297(1), 2018, pp. 1-10.

[13] Thamrongaphichartkul, K., Vongbunyong, S. and Nuntakarn, L. Design slave arm for in-vitro fertilizations process, paper presented in TRS Conference on Robotics and Industrial Technology 2017, Bangkok, Thailand.

[14] Sclater, N. Mechanisms and mechanical devices sourcebook, 5th Edition, 2011, McGraw-Hill, New York.

APPENDIX

Table 1: The experiment of command tracking.

Frequency Input (rad/s)	**ΔΦ (degree)**		**Δ*M* (degree)**	
	θ_1	θ_2	θ_1	θ_2
0.5	0.74	1.49	0.01	0.037
1	2.46	1.89	0.01	0.16
2	4.01	7.22	0.05	0.39
4	7.56	8.02	0.20	0.48
10	19.4	17.77	1.45	1.56
15	24.9	23.21	2.26	2.82
20	33.24	28.66	3.70	3.48
25	40.12	45.85	4.99	5.66
30	60.19	61.91	5.44	6.28
50	68.78	134.71	8.022	7.45

Table 2: The experiment of repeatability (axis 1).

No.	**P1 (Micron)**		**P2 (Micron)**		**P3 (Micron)**		**P4 (Micron)**	
	x	**y**	**x**	**y**	**x**	**y**	**x**	**y**
1	0.0	0.0	-84.8	26	76.0	-34.4	-0.8	0.0
2	-0.8	0.0	-84.8	26.8	76.0	-34.4	-0.8	0.0
3	-0.8	0.0	-84.8	26.8	76.0	-34.4	-0.8	0.4
4	-0.8	0.4	-84.8	26.8	76.0	-34.4	-0.8	0.4
5	-0.8	0.4	-84.8	26.8	76.0	-34.0	0	0.4
6	0.0	0.4	-84.8	27.2	76.0	-34.0	0	0.4
7	0.0	0.4	-84.8	27.2	76.0	-34.0	0	0.0
8	0.0	0.0	-84.8	26.8	76.0	-34.4	-0.2	0.0
9	-0.4	0.0	-85.2	26.8	76.0	-34.4	-0.2	0.0
10	-0.4	0.0	-85.6	27.2	76.0	-34.4	-0.2	0.0

Table 3: The experiment of repeatability (axis 2).

No.	**P1 (Micron)**		**P2 (Micron)**		**P3 (Micron)**		**P4 (Micron)**	
	x	**Y**	**x**	**y**	**x**	**y**	**x**	**y**
1	0.0	0.0	24.8	74.4	-26.4	-70.4	0	-0.8
2	0.0	-0.8	25.2	76	-25.6	-69.2	-0.4	0.4
3	-0.4	-0.4	25.2	75.6	-25.6	-70	-0.4	-0.4
4	-0.4	-0.4	25.2	75.2	-25.6	-70	-0.4	-0.4
5	-0.4	-0.4	25.2	75.2	-25.6	-70	-0.4	-0.4
6	-0.4	-0.4	25.2	75.6	-26.0	-70	-0.8	-0.4
7	-0.8	-0.4	26.4	74.8	-24.8	-70	0.4	-0.8
8	0.4	-0.8	26.4	75.2	-24.4	-70	0.8	-0.8
9	0.8	-0.8	26.4	75.2	-24.4	-70	0.8	-0.8
10	0.8	-0.8	26.4	75.2	-24.4	-70	0.8	-0.8