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Telerobotic System for Cell Manipulation

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***Abstract* - In this paper, telerobotic system for cell injection applications is proposed. Fidelity and stability are contradicting factors in teleoperation. Most of cells manipulations nowadays are performed manually by the human operators. These highly precise operations require high-skilled professional operators. However, the success and survival rate of the cells is very low due to the great sensitivity of cells. Moreover, while manipulating, operator cannot feel any interaction with the cells because of their negligible mass, therefore all the operations are based on the visual information provided by the high-precision microscope. In addition, during every operation the human's hand has a certain vibration that can affect the quality of teleoperation, especially in telesurgery, nanomanipuation and other precise tasks. All of the reasons listed above show that the cells manipulation is an exclusively complex task for a human operator to perform. Therefore, applying telerobotic system for the cells manipulation may provide us with many advantages and could help us to overcome the problems listed above.**

Index Terms* – *Cell manipulation, telerobotic system, micromanipulation, haptics, signal filtering.

I. INTRODUCTION

"Teleoperation" technology supports a form of control in which the human directly guides master robot and causes each increment of motion of the slave robot. Typically the slave robot follows the human motion exactly (within its physical capabilities) although in more advanced, computer mediated, systems there may be coordinate transformations (other than the distance or scale separation of master and slave) imposed between the two sides. A teleoperation system typically sends one of the conjugate variables (either force or velocity) from the operator's hand (via a transducer) to the slave robot [1].

The first modern master-slave teleoperators were developed by Raymond Goertz around 1945 at Argonne National Laboratory. These were mechanisms by which radioactive materials could be manipulated by an operator outside the cell. Electrical servomechanisms soon replaced the direct mechanical tape and cable linkages (Goertz and Thompson, 1954). Closed-circuit television was introduced, so that now the operator could be an arbitrary distance away. From the early 1960s, telemanipulators and video cameras were being attached to submarines by the US, USSR, and French navies and used experimentally. Also, from that time the race to the moon began. By 1970 the Western interest in teleoperation had turned to undersea applications, for there economic demand for offshore oil. The French developed their ERIC vehicle, the Americans the Hydroproducts RCV150 [2]. In 1976 robot arms were used on the Viking I and II space probes and landed on Mars. In 1993, the experimental robot, ROTEX, of the German Aerospace Agency (DLR) was flown aboard the space shuttle Columbia and performed a variety of tasks under both teleoperated and sensor-based offline programmed modes. In 2001, the first telesurgery has been performed when surgeons in New York performed a laparoscopic gall bladder removal on a woman in Strasbourg, France. In 2005, ROKVISS (Robotic Component Verification on board the International Space Station), the experimental teleoperated arm built by the German Aerospace Center (DLR), underwent its first tests in space [3].

Grasping and manipulating parts with size ranging between a few micrometers and about 1 are required for an increasing number of applications: the assembly of micro systems and micro machines; the operation in tiny and unpredictable environments, such as for inspection and interventions in pipes and for microsurgery [4]. Telerobotic system for cell micromanipulation field is introduced in this paper.

The creation of fully automated cells manipulation process is extremely hard task because of the unpredictable and uncertain microenvironment, lack of derivable information (commonly, no force censors are suitable, only visual information obtained using microscope), and the complexity of required micromanipulation operations. The presence of the human operator is necessary during the cell manipulation. However, the human manual capabilities have severe restrictions for being applied in the tasks where high precision is required, so the direct operator's control of the cell manipulation is not an optimal solution. One of the feasible ways to solve the micro-manipulation problem is to create a telerobotic system which will allow the operator to perform a micro- or even nano-scale manipulations with a required precision.

Using the telerobotic system for the cells manipulation may provide us with several advantages, which are:

- the increased fidelity and speed of the cell manipulation;
- canceling out or reducing the inevitable problems caused by human's body parameters (e.g. human hand trembling, operator's fatigue, etc.);
- the possibility of the providing force feedback to the human operator.

II. SYSTEM DESIGN

An example of common cell manipulation system (in this case, for DNA injection) is given below [5]:

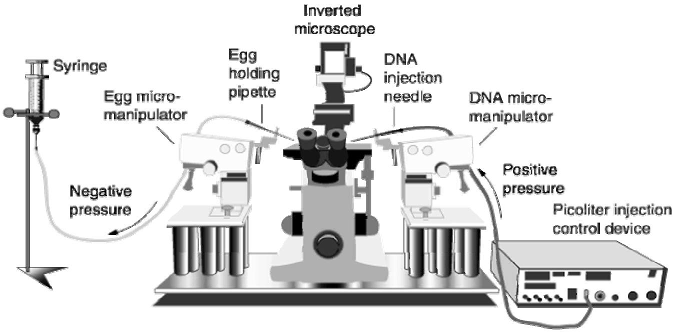

Fig. 1 Common structure of the cell manipulation system.

Generally, every cell micromanipulation system consists of following structural parts:

- Injection unit;
- Imaging unit;
- Vacuum unit;
- Microfabricated device;
- Software unit.

3-DOF X-Y-Z micromanipulators are usually used in the capacity of holding and injecting devices. There is a great number of existing micromanipulators, e.g. MP-285 (applied in [6]), MPC-325 or MPC-385, all by Sutter Instrument, or Ultraprecise Motorized Micromanipulators by Harvard Apparatus. Generally, the driving mechanisms are integral miniature stepper motors with anti-backlash gearheads or precision worm gear capstan drives. However, the prices of these micromanipulators are comparatively high which often makes them not affordable for small laboratories and educational institutions. Moreover, since the average size of the cell lies within the limits of 50 μm and 500 μm, the micromanipulator must at least have a resolution of 1 μm to perform desired injection operations; though, for example, Sutter MPC-385 micromanipulator can provide us with a resolution of 0.04 μm, which turns out to be much smaller than minimum requirements. Therefore, we tried to design our own micromanipulator, not so precise but with more attractive price.

The kinematical structure given on Fig. 2 has been chosen.

The end-effector of the robot (needle or holding pipette) is attached at the point *C* of manipulator, while the motors are attached at points *A* and *E*, respectively.

Let's assume that the points marked on the figure have following coordinates:

Table 1.

Point	Coordinates	Point	Coordinates
A	X_A, Y_A	*D*	X_D, Y_D
B	X_B, Y_B	*E*	X_E, Y_E
C	X_C, Y_C	*O*	X_O, Y_O

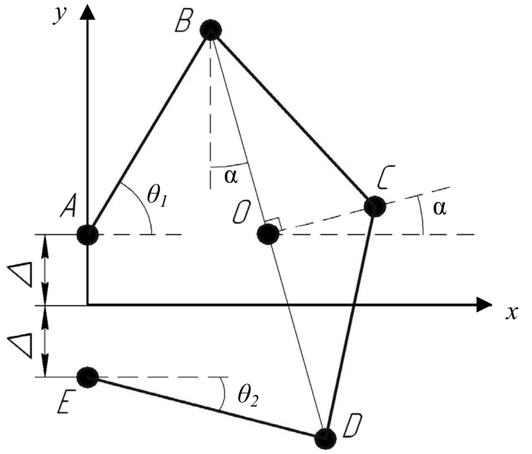

Fig. 2 Kinematical structure of the manipulator.

Knowing that the length of all links *AB* = *BC* = *CD* = *DE* =*l* and angles θ_1 and θ_2, let us evaluate the coordinates of all points of manipulator.

$$\begin{aligned}
&A: X_A = 0, Y_A = \Delta;\\
&E: X_E = 0, Y_E = -\Delta;\\
&B: X_B = X_A + l\cdot\cos(\theta_1); Y_B = Y_A + l\cdot\sin(\theta_1);\\
&D: X_D = X_E + l\cdot\cos(\theta_2); Y_D = Y_E + l\cdot\sin(\theta_2).
\end{aligned}\qquad (1)$$

, where θ_1 and θ_2 are the angles of initial links (*AB* and *ED*) of the manipulator and θ_2 is taken negative.

By applying several theorems and relations essential for triangles (particularly, isosceles triangle), we can write down following formulations:

$$\begin{aligned}
&O: X_O = \frac{X_D - X_B}{2}; Y_O = \frac{Y_D - Y_B}{2};\\
&BO = \sqrt{\left(X_O - X_B\right)^2 + \left(Y_O - Y_B\right)^2};\\
&OC = \sqrt{BC^2 - BO^2};\\
&\alpha = \arcsin\left(\frac{X_D - X_B}{\sqrt{\left(X_D - X_B\right)^2 + \left(Y_D - Y_B\right)^2}}\right);\\
&X_C = X_O + OC\cdot\cos\alpha;\\
&Y_C = Y_O + OC\cdot\sin\alpha.
\end{aligned}\qquad (2)$$

In the particular case when point *C* (the end-effector of the robot, e.g., the needle) is moving along the horizontal axis *X* (Y_C remains zero), we can significantly reduce the number of performed calculations. From the triangle *BCO*, we find that

$$\begin{aligned}
OC &= \sqrt{BC^2 - OB^2} = \sqrt{l^2 - (\Delta + l\sin\theta_1)^2} = \sqrt{l^2 - l^2\sin^2\theta_1 - \Delta^2 - 2\Delta\cdot l\sin\theta_1}\\
&= \sqrt{l^2\cos^2\theta_1 - 2\Delta\cdot l\sin\theta_1 - \Delta^2}
\end{aligned}\qquad (3)$$

Returning to the overall structure, we get

$$X_C = X_O + OC = l\cos\theta_1 + \sqrt{l^2\cos^2\theta_1 - 2\Delta\cdot l\sin\theta_1 - \Delta^2} \qquad (4)$$

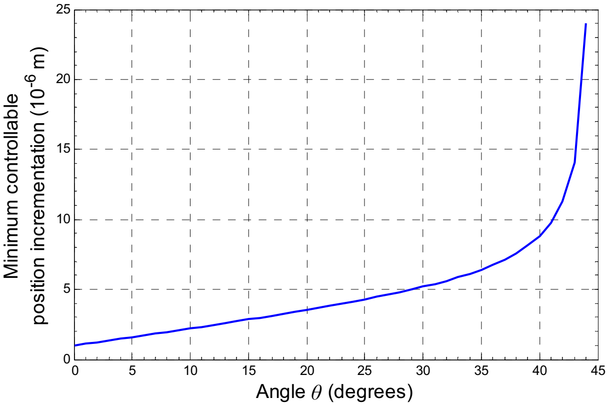

Fig. 3 Minimum controllable end-effector position incrementation subject to angle θ.

Abovementioned case (when end-effecter moves along the horizontal axis) can be achieved when both of motors are synchronized ($\theta_1 = -\theta_2$) during rotation. Therefore, we may speak about a general angle θ since these two remain equal in absolute value and keep opposite direction, and we may also substitute θ_1 with just θ in (4). All of the formulas derived above do not include third DOF of our system, θ_3, which is intended to adjust the slope of the links. However, the only thing we have to do to switch from 2-DOF (planar) formulation to 3-DOF one is to multiply the result by term ($\cos\theta_3$), where θ_3 equals zero when the overall structure keep horizontal position.

As we can see from (4) and Fig. 3, *DC* changes non-linearly subject to angle θ: a small incrementation of θ around 0° degrees will cause a smaller incrementation of *DC* than, for example, around $\theta = 30°$. Therefore, we can smoothly achieve desired position, lying at $\theta = 0°$, without reducing angular velocity $\dot{\theta}$ due to the robot's geometry.

As we can see, around $\theta = 0°$ we can achieve an accuracy of 1 μm (without considering quadrupling effect provided by 2-channel encoders which will actually allow us to have an accuracy of 0.25 μm).

Minimum controllable position incrementation (MCPI) is increasing subject to increasing θ; thus, MCPI equals 5 μm and 23 μm when $\theta = 29°$ and 44°, respectively.

Having this kind of parallel structure, we do not need to include any additional angular-to-translational motion transducers into the system – the rotational motion of the motors will provide us with translational motion of point C on X-Y plane. Having one more motor placed orthogonally with respect to previous two motors, we can change the slope of the links with respect to horizontal plane.

Following hardware have been used to create suggested telerobotic system (not including pico-injecting pumps, needles, etc.):

- Maxon RE 25 motors, 3 pieces;
- Maxon MR encoders, 1000 CPT, 3 pcs;
- LLC CSF-5-2XH harmonic drives, rat. 1:100, 3 pcs;
- Maxon 4-Q-DC servoamplifier motor driver, 3 pcs;
- MOTIC AE31 microscope.

Having such a configuration, we can control each 360°/1000/100 = 0.0036° incrementation of the harmonic drive's shaft angle. As we could see from Fig. 3, this angular accuracy is enough to provide us with precise enough translational motion of the end-effector.

All links, joints and other supplementary parts were designed by us independently.

III. HAPTIC INTERFACE

As we mentioned above, one of the great advantages of telerobotic system can be an opportunity to implement force feedback within it regardless of the parameters of object which slave robot interact with. Providing operator with a force (or haptic) feedback is a critical task in the field of micro- and nano-manipulation due to extremely small size and mass of the manipulated objects.

However, since the mass and stiffness of the cell are very small, the force measurement using classical force and torque sensors is not possible. One of the feasible solutions is to use alternative type of sensors. One of them is shown below:

This is a MEMS-based multi-axis cellular force sensor (patented version) developed in Institute of Robotics and Intelligent Systems (IRIS) of Zurich, Switzerland [7], and has been successfully used, for example, to measure forces exerted by a drosophila in flight.

Although there is a number of suggested MEMS-based miniature force sensors, there are several problems relating their small size (hundreds of micro-meters), problems with mounting, and so on, which prevent this type of sensors to be applied widely. Moreover, in many cases, including cell injection field, it is impossible to mount force sensor at the end-effector directly, and engineers have to make slave robot's structure more complicated to overcome arising problems.

Another solution is to use visual information obtained from the microscope. During the cell manipulation, operator picks up or spoils the cell with the end-effector of the slave robot, e.g. microgripper or needle, which causes the curving of cell capsule.

Making assumption of several mechanical parameters of the cell capsule, such as Young's modulus or stiffness coefficient, we can estimate the emerging force depending on the capsule deformation Δ or the curvature of it. Moreover, we do not need to know the exact values of the capsule mechanical parameters; they may be used in any relative scale to apply required force to the master manipulator.

At first, the auto-focusing is performed using phase detection (alike with a number of existing passive autofocus systems). After we get the clear picture of cell, we apply real-time edge-detection algorithm to mark-out the brightest edges on the picture. However, it doesn't guarantee that we will see cell capsule boundary only; there will remain other objects with sharp edges, e.g. the needle, holding pipette, etc. To filter them out, a variety of circle-detection algorithms (Hough transform, snake algorithm, etc.) can be implemented.

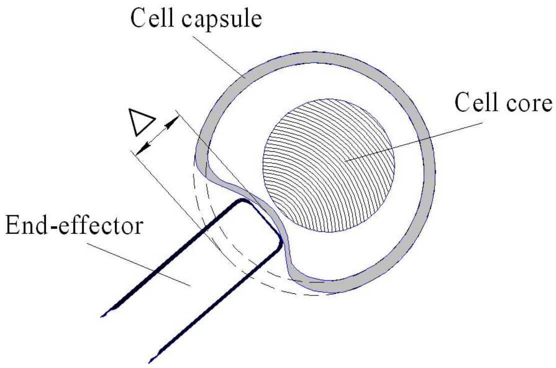

Fig. 4 Cell capsule deformation during the manipulation.

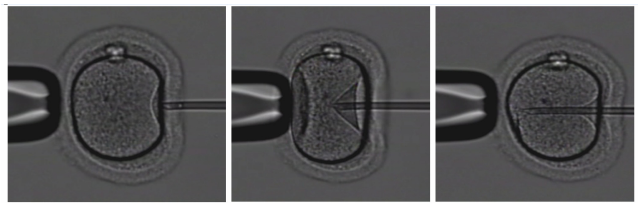

Fig. 5 Deformation of the cell capsule during injection process.

However, many problems arise while dealing with force estimation via image obtained from the microscope. For example, in many cases it is hard to focus on the cell to make a boundary of the cell capsule look sharp and clear. This is especially important when we have to deal with cells that have a vide variety of diameter sizes (e.g., zebrafish cell diameter may vary from 600 µm to 1200 µm, as mentioned in [6]). In addition, the cell itself is a sphere, not a circle, and it is much better to have a 3-D model of a cell instead of 2-D picture obtained from microscope because the injection process may vary for different slopes of injection needle. However, since it is possible to use only one microscope in cell manipulation system, the only way we can get 3-D model of a cell is by rotating 2-D picture with respect to its axis of symmetry assuming that the properties of all parts of the cell are equal (that, in fact, is not true). Moreover, different force response coefficients are required for different types of cells because their properties (stiffness, damping ratio, size, etc.) are different

IV. HAND TREMBLING FILTERING

Human's hand vibration in terms of stability can be represented as some disturbance added to the dynamical equation describing the motion of master manipulator. This vibration has a certain influence on a master's behavior, and the oscillation damping is very critical sometimes, especially in tasks where high precision is required.

If both position and force responses from master and slave manipulators are identical, whatever the object dynamic is, the operator can maneuver the system as he were manipulating the remote object himself [8]. But sometimes the position response and force response are not required to be identical. For example, in nanomanipulation or in telesurgery, it is required to reduce the position response of the slave robot and to increase the force response from slave to master; in some fields, like construction, it is necessary to increase the position response and to decrease the force response.

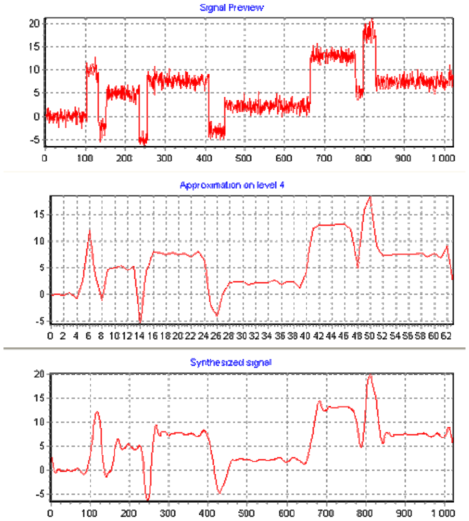

Fig. 6 Initial signal (top), approximation on level 4 (middle) and synthesized signal (bottom) after wavelet filtering.

It may seem that in the telerobotic system for cell manipulation we can cancel out the influence of the vibration because we have to reduce position response significantly. It is true, however, in general case, the motors may not be necessary controlled identically. This can provide us with a different angle of the end-effector (e.g., injection needle or pipette) mounted at point *C*. The control of this angle may be required in several operations (like DNA deposition because DNA must be deposited within core of a cell) and give more freedom to the operator. Therefore, this angle must not be scaled down.

The fact that master and slave manipulators are not rigidly connected to each other provides us with a great opportunity to filter all undesired oscillations of the master manipulator caused by operator's hand and feed a "clean" signal to slave robot controller.

A number of fast and sophisticated filters is well-known nowadays (wavelet filters, Kalman filters, etc.). For our telerobotic system, an original filtering software has been developed. The filtering algorithm is based on wavelet filtering, and different types of wavelets and decomposition order may be chosen by the operator. For example, if we filter the input signal using Daubechies-type wavelets with decomposition order of 4, a graph presented on Fig. 6 can be achieved.

CONCLUSION

As we can see, applying micro-telerobotic system in cell manipulation field will increase the quality and speed of desired micro-manipulations; moreover, telecontrolled manipulator does less damage to the cell. Suggested telerobotic system will take a possibility to manipulate cell in special environment, uncomfortable to a human, such as high or low temperature, radiation, etc. In addition, suggested micro-telerobotic system is universal and may be applied in other fields where highly-precise manipulation is required (stem cells and DNA manipulations, assembly of microelectronics, etc.).

The proposed kinematical structure of the robot have never been applied in microtelerobotic systems for cell manipulation before. This kind of structure allows us to create cheap but robust and precise system suitable for cell injection operations.

Applying force feedback may sufficiently speed-up the training process. In addition, substituting manual cell manipulation process by telerobot-aided process will sufficiently increase the economical efficiency of performed operations. The possibility to control strictly the actuator's translation can help to protect the cells from being damaged after any inaccurate actions of the operator, which will result in decreasing number of the cells required for each experiment. Proposed force estimation algorithm is original and will be discussed in detail in later publications.

Original kinematical structure may reduce the price of the overall system without losing necessary accuracy, which, in turn, provide us with opportunity to create affordable and precise microtelerobotic system. Therefore, the flexibility and universality of the designed telerobotic system will give us an opportunity to create easily an educational system for students and medical staff.

Implementing intelligent filtration algorithm based on wavelet filtering and fuzzy logic may reduce the noise in the initial signal significantly and will provide slave robot controller with a "clean" signal without undesired oscillations. This can may possible for our system to perform highly precise operation not only in cell micromanipulation field, but also in other fields where high precision is required, e.g. telesurgery, microelectronics assembling, etc. As a future work, we are planning to design a filter that will determine decomposition order automatically basing on fuzzy logic. This will ease the work of operator and remove the need to control the filtering process.

ACKNOWLEDGEMENT

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