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# A Simple Setpoint Controller for Dynamic Manipulation of Biological Cells using Optical Tweezers

C. C. Cheah, X. Li, X. Yan, D. Sun, and H. C. Liaw

**Abstract**—Optical tweezers are one of the most common and useful tools in non-contact cell manipulation. While several control methods have been developed for cell manipulation using optical tweezers, the control input is commonly treated as the position of the laser beam and open-loop controllers are designed to move the laser source. Investigating the interaction between the robotic manipulator of laser source and biological cells can help us gain understanding into the dynamic manipulation problem using optical tweezers. However, the interaction between the cell dynamics and the manipulator dynamics leads to a fourth-order overall dynamics, and the use of high-order derivatives of the state variables is usually required in the overall control input. In this paper, a simple setpoint control method is proposed for optical manipulation of biological cells. The proposed method is able to manipulate the trapped cell to a desired position without using the high-order derivatives of the state variables such as acceleration and jerk. The stability of closed-loop system is analyzed by using LaSalle’s invariance principle, with the consideration of the dynamics of both the cell and the robotic manipulator. The proposed control method is simple and easy to implement. Both simulation and experimental results are presented to illustrate the performance of the proposed control method.

## I. INTRODUCTION

The research and development of robotics and automation technology in past few decades has completely revolutionized the modern manufacturing industries, and much progress has been achieved in robot manipulator control [1]–[6]. In parallel, the emerging applications and new initiatives in biological engineering and cell manipulation open up new challenges in the integration of robotics and biomedical technologies at micro and nano scales.

Among the diverse micromanipulators, optical tweezers [7] are one of the most common and useful tools in non-contact cell manipulation because of the capability of manipulating tiny particles precisely without causing damage to the particles. Several automatic optical tweezers systems and control methods have been developed to improve the efficiency of micromanipulation. In [8], the optical micromanipulation was modeled as an infinite-horizon partially observable Markov decision process, and a stochastic programming

method was introduced for the real-time path planning of cell motion. An automatic cell sorting system based on dual-beam trap was introduced in [9], and an image-processing system using thresholding, background subtraction and edge-enhancement algorithms was developed for identification of single cells. In [10], a PID closed-loop feedback controller and a synchronization control technology were proposed for cell transportation, based on a simplified dynamic model of the trapped cell. With the multiple trapping technology based on the computer-generated holographic optical-tweezers arrays [11], Arai et al. [12] developed an automatic system to flock micro-scale particles. In [13], a simple feedback controller was proposed for the positioning of a microscopic particle. In [14], the performance of proportional control, LQG control and nonlinear control in particle positioning was compared, and the dynamics of trapped particle was modeled as a first-order system by ignoring the particle mass. In [15], an automated optical trapping technique was developed based on computer vision and multiple-force optical clamps.

In current robotic manipulation techniques using optical tweezers [8]–[15], the control input is usually treated as the position of the laser beam, and open-loop controllers are designed to move the laser source. The open-loop control does not include the feedback information for the position of laser, and the cell may escape from the optical trap which results in the failure of manipulation task. While dynamic formulations of robotic manipulation have been extensively studied in the literature of robot manipulator control, the optical manipulation problems of cells or nanoparticles with the consideration of the effects of the manipulator dynamics are less well understood. The first study investigating the dynamic interaction between the robotic manipulator and the trapped cell is proposed in [16], [17]. By introducing the dynamics of robotic manipulator, a dynamic formulation is proposed for optical tweezers systems so that the position of the laser source is controlled by closed-loop techniques. However, the overall dynamics of the manipulator interacting with the cell is a fourth-order dynamics which thus leads to a controller that requires high-order derivatives of state variables.

In this paper, we propose a simple control method for dynamic optical manipulation of biological cells. The proposed method is able to manipulate the trapped cell to the desired position without the use of high-order state derivatives which are sensitive to measurement noises. A complete model that describes the dynamic interaction between the cell and the manipulator is introduced, and the behavior of cell is

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naturally regulated by the Gaussian potential field around the centre of laser beam. The stability of closed-loop system is analyzed by using LaSalle's invariance principle, with the consideration of the dynamics of both the cell and the robotic manipulator. The main contributions are the formulation and solution of a simple setpoint control method that has the advantages of simplicity and ease of implementation. We believe that such dynamic formulation of optical manipulation will yield insight into the cell manipulation problems and bridge the gap between traditional robot manipulation techniques and optical manipulation techniques of cells. Simulation and experimental results are presented to illustrate the performance of the proposed control method.

## II. DYNAMICS OF BIOLOGICAL CELLS AND ROBOTIC MANIPULATORS

A typical optical manipulation system is shown in Fig. 1. The laser beam is expanded using a beam expander, reflected on a Dichroic mirror, and introduced into the inverted microscope. The offset between the laser beam and the object can be varied by directly adjusting the position of the laser beam with beam steering techniques or acousto-optic deflectors (AOD). It can also be varied by moving the stage with motor control while fixing the laser beam.

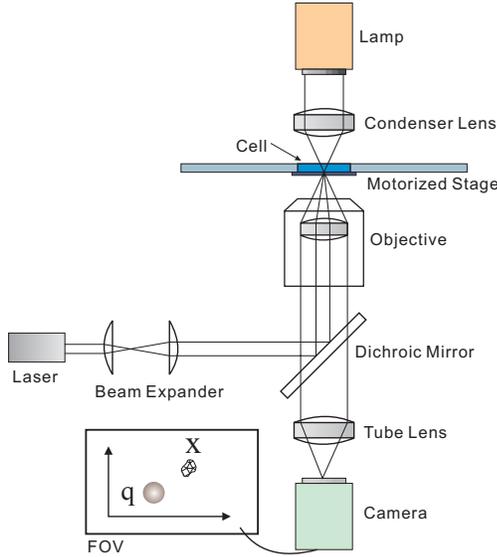


Fig. 1. A typical optical tweezers system.

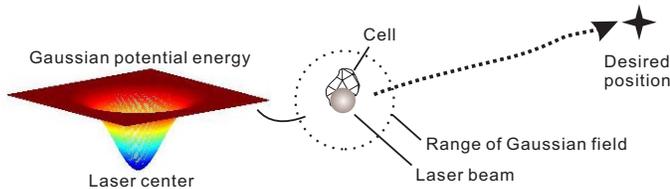


Fig. 2. The cell behavior is regulated by the Gaussian field. The trapping works only when the cell is very near the center of laser beam. The trapped cell is then transported to the desired position.

In this paper, the optical tweezers are employed to manipulate the biological cells, and the cell dynamics is described by the following equation [13], [16]:

$$M\ddot{x} + B\dot{x} + k_1(x - q)e^{-k_2\|x - q\|^2} = 0, \quad (1)$$

where  $M \in \mathbb{R}^{2 \times 2}$  denotes the inertia matrix, and  $B \in \mathbb{R}^{2 \times 2}$  denotes the damping matrix, and  $k_1$  and  $k_2$  represent the parameters of laser beam, and  $x = [x_1, x_2]^T \in \mathbb{R}^2$  is the position of the cell, and  $q = [q_1, q_2]^T \in \mathbb{R}^2$  is the position of the laser. Both  $M$  and  $B$  are diagonal and positive definite, and  $k_1$  and  $k_2$  represent the laser parameters which are positive constants.

From equation (1), the behavior of the cell is regulated by the Gaussian potential field (see Fig. 2), which is described by the term  $k_1(x - q)e^{-k_2\|x - q\|^2}$  in equation (1). If the cell is far away from the laser beam,  $e^{-k_2\|x - q\|^2} \rightarrow 0$ , thus there is no interaction between the cell and the laser beam. When the cell is very near the laser beam,  $x - q \rightarrow 0$ ,  $e^{-k_2\|x - q\|^2} \rightarrow 1$ .

Existing manipulation techniques treat the position of the laser beam  $q$  as the control input and open-loop controllers are designed to move the laser source. In this paper, the variable  $q$  is controlled by closed-loop robotic manipulation techniques. The control input is set as the torque or voltage of the manipulator of the laser source, and hence the information of  $x - q$  is available as a state feedback variable for the control input.

The variable  $q$  can be set as the position of the laser beam with respect to the stage, and it is varied by moving a linear motorized stage which thus acts as a robotic manipulator. Therefore, the dynamics of the manipulator of the laser source is described as:

$$M_q\ddot{q} + B_q\dot{q} = u, \quad (2)$$

where  $M_q \in \mathbb{R}^{2 \times 2}$  denotes the inertial matrix and  $B_q \in \mathbb{R}^{2 \times 2}$  represents the damping matrix, and  $u \in \mathbb{R}^2$  is the control input for the manipulator. Both  $M_q$  and  $B_q$  are diagonal and positive definite.

## III. SETPOINT CONTROL FOR OPTICAL MANIPULATION

Regulation or setpoint control problem is an important problem in control theory and applications as most controllers in industrial applications are setpoint controllers because of their simplicity and effectiveness. In this section, by investigating the interaction between biological cells and robotic manipulators, a setpoint control scheme is proposed for optical manipulation as:

$$u = -K_p(q - x_d) - K_v\dot{q} + k_{px}(x - q)e^{-k_2\|x - q\|^2}, \quad (3)$$

where  $x_d$  is the desired constant position of the cell, and  $K_p$  and  $K_v$  are positive definite matrices, and  $k_{px}$  is a positive constant.

Note that the information of offset between the cell and the center of laser beam  $x - q$  is included in the control input in equation (3). The position control term  $k_{px}(x - q)e^{-k_2\|x - q\|^2}$  is used to monitor the offset and maintain the trapping between the cell and the laser. The other position

control term  $\mathbf{K}_p(\mathbf{q} - \mathbf{x}_d)$  is used to drive the trapped cell towards the desired position.

The closed-loop equation is obtained by substituting the controller in equation (3) into the dynamics of the manipulator in equation (2) to yield:

$$\mathbf{M}_q \ddot{\mathbf{q}} + \mathbf{B}_q \dot{\mathbf{q}} - k_{px}(\mathbf{x} - \mathbf{q})e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} + \mathbf{K}_p(\mathbf{q} - \mathbf{x}_d) + \mathbf{K}_v \dot{\mathbf{q}} = \mathbf{0}. \quad (4)$$

To prove the stability, a Lyapunov-like function is proposed as:

$$V = \frac{k_{px}}{2k_1} \dot{\mathbf{x}}^T \mathbf{M} \dot{\mathbf{x}} + \frac{1}{2} \dot{\mathbf{q}}^T \mathbf{M}_q \dot{\mathbf{q}} + \frac{k_{px}}{2k_2} (1 - e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2}) + \frac{1}{2} (\mathbf{q} - \mathbf{x}_d)^T \mathbf{K}_p (\mathbf{q} - \mathbf{x}_d), \quad (5)$$

where  $P(\mathbf{x} - \mathbf{q}) = \frac{k_{px}}{2k_2} (1 - e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2})$  is the Gaussian potential energy function, which is illustrated in Fig. 2.

Differentiating equation (5) with respect to time, we have:

$$\dot{V} = \frac{k_{px}}{k_1} \dot{\mathbf{x}}^T \mathbf{M} \ddot{\mathbf{x}} + \dot{\mathbf{q}}^T \mathbf{M}_q \ddot{\mathbf{q}} + k_{px}(\dot{\mathbf{x}} - \dot{\mathbf{q}})^T (\mathbf{x} - \mathbf{q})e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} + \dot{\mathbf{q}}^T \mathbf{K}_p (\mathbf{q} - \mathbf{x}_d). \quad (6)$$

Multiplying both sides of equation (1) with  $\frac{k_{px}}{k_1} \dot{\mathbf{x}}^T$ , we have:

$$\frac{k_{px}}{k_1} \dot{\mathbf{x}}^T \mathbf{M} \ddot{\mathbf{x}} + \frac{k_{px}}{k_1} \dot{\mathbf{x}}^T \mathbf{B} \dot{\mathbf{x}} + k_{px} \dot{\mathbf{x}}^T (\mathbf{x} - \mathbf{q})e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} = 0. \quad (7)$$

Next, multiplying both sides of equation (4) with  $\dot{\mathbf{q}}^T$ , we have:

$$\dot{\mathbf{q}}^T \mathbf{M}_q \ddot{\mathbf{q}} + \dot{\mathbf{q}}^T \mathbf{B}_q \dot{\mathbf{q}} - k_{px} \dot{\mathbf{q}}^T (\mathbf{x} - \mathbf{q})e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} + \dot{\mathbf{q}}^T \mathbf{K}_p (\mathbf{q} - \mathbf{x}_d) + \dot{\mathbf{q}}^T \mathbf{K}_v \dot{\mathbf{q}} = 0. \quad (8)$$

Then substituting equations (7) and (8) into equation (6), we have:

$$\begin{aligned} \dot{V} &= -\frac{k_{px}}{k_1} \dot{\mathbf{x}}^T \mathbf{B} \dot{\mathbf{x}} - k_{px} \dot{\mathbf{x}}^T (\mathbf{x} - \mathbf{q})e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} \\ &\quad - \dot{\mathbf{q}}^T (\mathbf{B}_q + \mathbf{K}_v) \dot{\mathbf{q}} + k_{px} \dot{\mathbf{q}}^T (\mathbf{x} - \mathbf{q})e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} \\ &\quad + k_{px}(\dot{\mathbf{x}} - \dot{\mathbf{q}})^T (\mathbf{x} - \mathbf{q})e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} \\ &= -\frac{k_{px}}{k_1} \dot{\mathbf{x}}^T \mathbf{B} \dot{\mathbf{x}} - \dot{\mathbf{q}}^T (\mathbf{B}_q + \mathbf{K}_v) \dot{\mathbf{q}} \leq 0. \end{aligned} \quad (9)$$

We are now ready to state the following theorem:

**Theorem:** *If the control input of the manipulator of laser beam in equation (3) is applied to the optical tweezers system in equations (1) and (4), the closed-loop system is globally asymptotically stable such that  $\mathbf{x} \rightarrow \mathbf{x}_d$ ,  $\mathbf{q} \rightarrow \mathbf{x}_d$ ,  $\dot{\mathbf{x}} \rightarrow \mathbf{0}$ , and  $\dot{\mathbf{q}} \rightarrow \mathbf{0}$  as  $t \rightarrow \infty$ .*

**Proof:** Since  $\dot{V} \rightarrow 0$  indicates that  $\dot{\mathbf{q}} \rightarrow \mathbf{0}$  and  $\dot{\mathbf{x}} \rightarrow \mathbf{0}$  as  $t \rightarrow \infty$ , the maximum invariant set [18] of equations (1) and (4) is:

$$k_1(\mathbf{x} - \mathbf{q})e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} = \mathbf{0}, \quad (10)$$

$$-k_{px}(\mathbf{x} - \mathbf{q})e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} + \mathbf{K}_p(\mathbf{q} - \mathbf{x}_d) = \mathbf{0}. \quad (11)$$

From equation (10), we have  $\mathbf{x} \rightarrow \mathbf{q}$ . Then from equation (11), we can conclude that  $\mathbf{q} \rightarrow \mathbf{x}_d$ , which also indicate that  $\mathbf{x} \rightarrow \mathbf{x}_d$  as  $t \rightarrow \infty$ . Therefore, the closed-loop system is globally asymptotically stable.  $\triangle\triangle\triangle$

## IV. SIMULATION

Simulations were carried out to verify the performance of the proposed control methods. The optical tweezers system as illustrated in Fig. 3 is employed to manipulate biological cells. In Fig. 3, the cell is placed on a motorized stage and the laser beam is fixed downwards, and the relative distance between the laser beam and the stage is dependent on the variation of the stage position. The motorized stage thus act as a robotic manipulator, and we can control the relative distance between the laser beam and the cell. In the simulations, the variable  $\mathbf{q}$  is set as the position of the laser beam with respect to the motorized stage.

The parameters of the cell dynamics in equation (1) were set as:  $\mathbf{M} = \text{diag}\{10^{-10}, 10^{-10}\}$ kg,  $\mathbf{B} = \text{diag}\{1.8 \times 10^{-9}, 1.8 \times 10^{-9}\}$ kg/s,  $k_1 = 2 \times 10^{-5}$ ,  $k_2 = 9.5 \times 10^9$ . From the value of  $k_1$  and  $k_2$ , it can be obtained that the Gaussian field is in effect when the cell is less than 18  $\mu\text{m}$  from the laser. The parameters of the manipulator dynamics in equation (2) were set as:  $\mathbf{M}_q = \text{diag}\{0.02218, 0.011386\}$ kg,  $\mathbf{B}_q = \text{diag}\{0.04749, 0.04023\}$ kg/s.

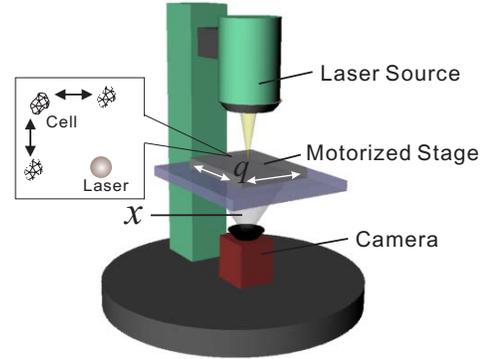
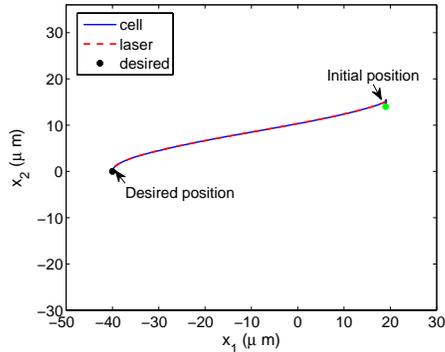


Fig. 3. The optical tweezers system. The laser beam is fixed downwards, and the relative distance between the cell and the laser is adjusted by the robotic stage.

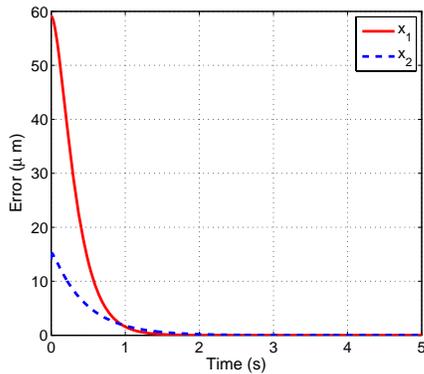
The control parameters in equation (3) were proposed as:  $\mathbf{K}_p = \text{diag}\{0.7, 0.7\}$ ,  $k_{px} = 1$ , and  $\mathbf{K}_v = \text{diag}\{0.3, 0.3\}$ . The initial position of the cell was located at  $(19, 14)\mu\text{m}$ , and the cell was trapped by the laser beam and transported to the desired position at  $(-40, -0)\mu\text{m}$ . The path of the trapped cell and the laser beam is shown in Fig. 4(a) and the position error is shown in Fig. 4(b). The position errors converged to zero in less than 1.5 seconds.

## V. EXPERIMENT

The proposed control method was also implemented in a robot-tweezer manipulation system in the City University of Hong Kong, as shown in Fig. 5. The system is constituted of three modules for sensing, control and execution [10]. The sensing module consists of a microscope and a CCD camera, and the cell positions can be obtained through image processing. The control module consists of a phase modulator and a stepping motor controller. The execution module consists of the holographic optical trapping and the motorized stage,



(a) Path of cell and laser



(b) Position error

Fig. 4. Simulation: the cell was manipulated from  $(19, 14)\mu\text{m}$  to  $(-40, -0)\mu\text{m}$ .

and the offset between the laser beam and the cell can be varied by directly adjusting the position of the laser beam or by moving the stage with motor control while fixing the cell with an optical trap. All of the mechanical components are supported by an anti-vibration table in a clean room. The optical tweezers were controlled to manipulate the yeast cell. Due to the limited access to the software interface, the acceleration of the laser source is set as the control input.

The control parameters in equation (3) were set as:  $\mathbf{K}_p = \text{diag}\{5, 5\}$ ,  $k_{px} = 1$ ,  $\mathbf{K}_v = \text{diag}\{1, 1\}$ , and the parameter of the laser was set as  $k_2 = 7.2 \times 10^{11}$  [19]. In the first experiment, both the laser beam and the cell started from the initial position at  $(522.1, 380.7)\mu\text{m}$ , and the cell was trapped by the laser beam from the beginning. The trapped cell was then transported to the desired position at  $(100, 100)\mu\text{m}$ . The path is shown in Fig. 6(a), and the position errors are given in Fig. 6(b). The position errors converge to zero in less than 3 seconds.

In this second experiment, both the laser beam and the trapped cell started from the initial position at  $(58.3, 384.9)\mu\text{m}$ , and the cell was transported to the desired position at  $(500, 240)\mu\text{m}$ . The control parameters remained the same. The path is shown in Fig. 7(a), and the position errors are given in Fig. 7(b). The position errors converge to zero in less than 4 seconds.

The snapshots of cell and laser beam at different time

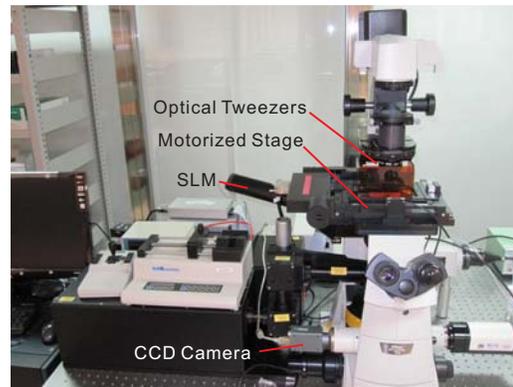


Fig. 5. A robot-tweezer manipulation system.

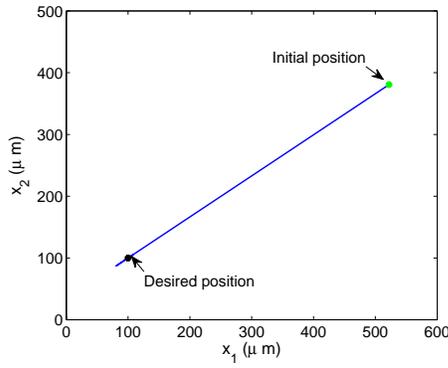
instants are shown in Fig. 8 and Fig. 9, where the bright points represent the position of laser beam. As seen from Fig. 8 and Fig. 9, the trapped cell was successfully transported from the initial position to the desired position.

## VI. CONCLUSION

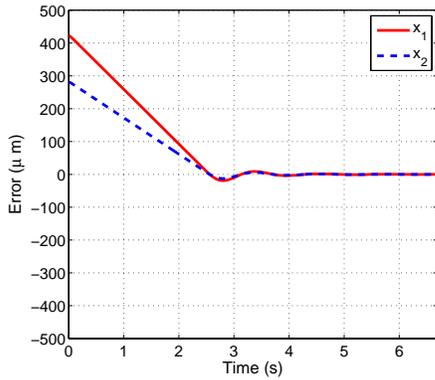
In this paper, a simple control method for optical dynamic manipulation of biological cells has been proposed. The proposed method is able to manipulate the trapped cell to the desired position without the use of high-order state derivatives. A complete model that describes the dynamic interaction between the cell and manipulator is introduced, and the cell behavior is naturally regulated by the Gaussian potential field around the centre of laser source. The stability of closed-loop system is analyzed by using LaSalle's invariance principle, with the consideration of the dynamics of both the cell and the robotic manipulator. Simulation and experimental results are presented to illustrate the performance of the proposed control method.

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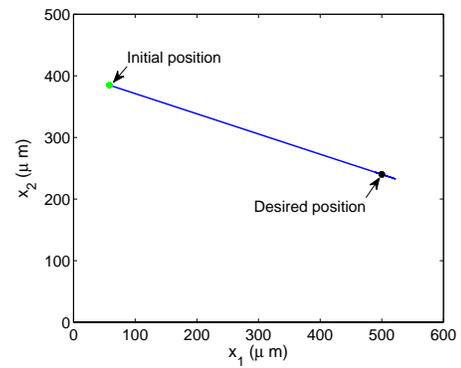


(a) Path of cell and laser

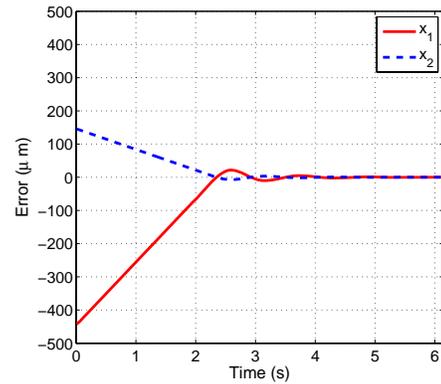


(b) Position error

Fig. 6. Experiment 1: the cell was manipulated from  $(522.1, 380.7)\mu\text{m}$  to  $(100, 100)\mu\text{m}$ .



(a) Path of cell and laser

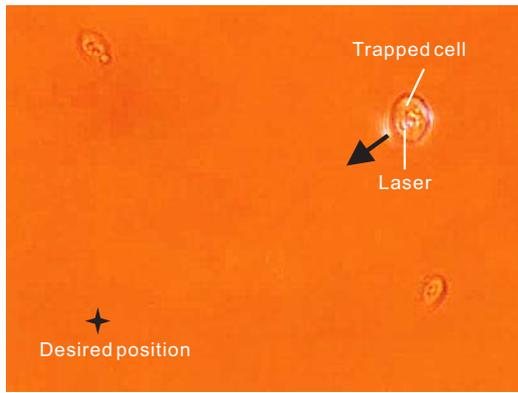


(b) Position error

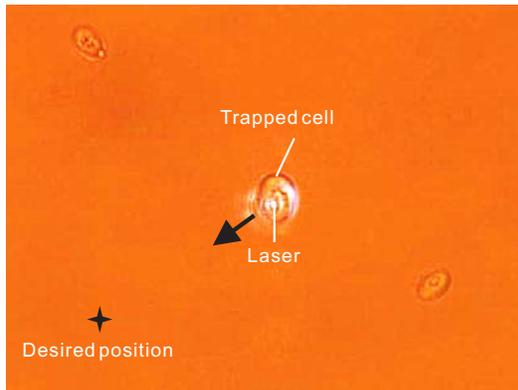
Fig. 7. Experiment 2: the cell was manipulated from  $(58.3, 384.9)\mu\text{m}$  to  $(500, 240)\mu\text{m}$ .

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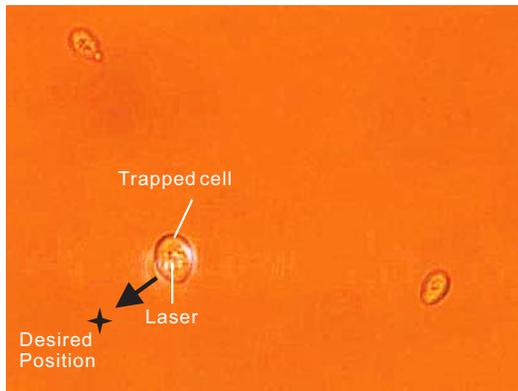
planning for automated cell transportation with optical tweezers," *IEEE/ASME Trans. Mech.*, Vol. 18, No. 2, pp. 706-713, 2013.



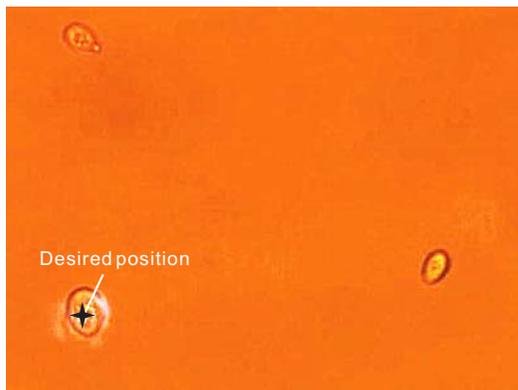
(a) t=0 s



(b) t=2 s

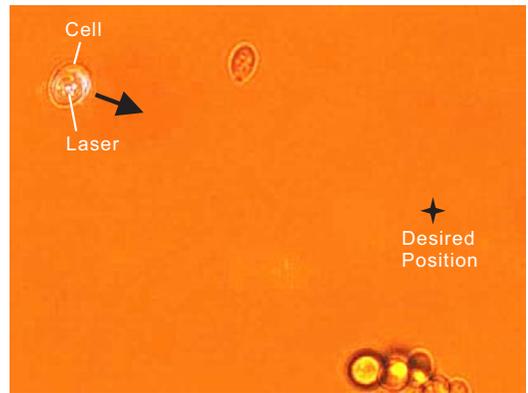


(c) t=4 s

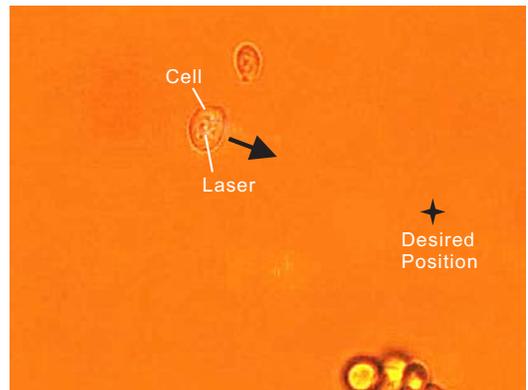


(d) t=6 s

Fig. 8. Experiment 1: the cell started from  $(522.1, 380.7)\mu\text{m}$ , and was transported to  $(100, 100)\mu\text{m}$ .



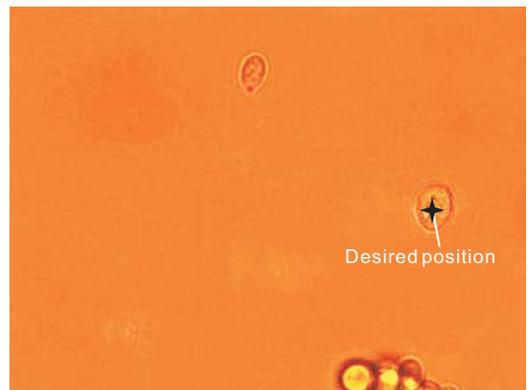
(a) t=0 s



(b) t=2 s



(c) t=4 s



(d) t=6 s

Fig. 9. Experiment 2: the cell started from  $(58.3, 384.9)\mu\text{m}$ , and was transported to  $(500, 240)\mu\text{m}$ .