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Simple PD Control Scheme for Robotic Manipulation of Biological Cell

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

Abstract—In most manipulation techniques for optical tweezers, open-loop controllers are developed to move the laser source without consideration of the dynamic interaction between the cell and the manipulator of laser source. This paper presents a simple PD control scheme for manipulation of cell using optical tweezers. We formulate a closed-loop setpoint control problem for optical tweezers and show that simple control law is effective for closed-loop manipulation, taking into consideration of the dynamic interaction between the laser beam and the cell. The use of closed-loop feedback control helps to enhance the trapping and also reduces the possibility of photodamage. The setpoint controller is also extended to a region reaching controller, where the desired objective is generalised to a region. Though the overall dynamics that involves the interaction between the cell and the manipulator is a fourth-order system, the proposed controllers do not require the use of acceleration and its derivative or the construction of any observer. Experimental results are presented to illustrate the performance of the proposed controllers.

Index Terms—Biological systems, robotics, optical tweezers, regulation.

I. INTRODUCTION

Optical tweezer [1] has become a common and useful micromanipulation tool in biological and biomedical engineering, because of its ability of manipulating biological cells without physical contact. The capability of rapid and accurate positioning of optical tweezers is very useful for cell fusion [2], where the trapped cell is manipulated to interact with another cell. The application of optical tweezers can also be found in separation of cells [3], where the trapped cell is transported to a specific recipient for further operations such as isolation [4], drug discovery [5], or microencapsulation [6]. Moreover, the positioning technique with optical tweezers is significant for studying mechanical and structural properties of DNA [7], where the DNA is stretched out to a given position by manipulating the optically trapped microbead that is attached to the end of DNA.

Rapid progress in sensor techniques and the integration of automation and biomedical technologies have led to the emergence of a variety of automatic optical tweezers systems [8]–[13]. An automatic micromanipulation system with dual-beam optical trap was established for cell separation [8], with image-processing algorithms for identification of single cell. An automatic system was proposed to flock micro-scale particles with multiple optical traps [9], based on computer-generated holographic optical-tweezers arrays [10]. In [11], an automated optical trapping technique with multiple-force optical clamps was developed. In [12], [13], indirect manipulation systems have been developed to avoid photodamage of cell. Instead of trapping the cell directly by using laser beam, microbeads are trapped and used to manipulate the cell indirectly. To improve the efficiency of optical manipulation, automatic control methods and techniques have also been introduced for optical tweezers recently [14]–[21]. A comparison between several classic control methods was given in [14], [15], to evaluate the performance of those controllers for optical manipulation. In [16], the optical trap was modelled as a flat system and a trajectory tracking controller was proposed. In [17], a stochastic path planning method was introduced for optical tweezers, and the process of optical manipulation was modelled as

an infinite-horizon partially observable Markov decision process. To deal with the regulation problem, a simple controller was proposed for the positioning of single cell in [18]. In [19], [20], PID controllers were developed to manipulate single cell to track a desired position. A nonlinear PID controller was proposed in [21] to control the laser beam and also minimize the effect of uncertainties and external forces in the environment. Along with the development of multiple-beam techniques, control schemes have been developed to coordinate and manipulate multiple cells with optical tweezers [20], [22], [23].

The aforementioned optical manipulation techniques treat the control input as the position of the laser beam, and open-loop controllers are formulated to move the laser source without consideration of the dynamic interaction between the cell and the manipulator of 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. Investigating the interaction between the robotic manipulator and the cell will yield insight into the cell manipulation problem, and the formulation based on the dynamic interaction is also necessary for the development of closed-loop robotic manipulation techniques in optical tweezers system. The first study investigating the dynamic interaction between the robotic manipulator and the cell is proposed in [24]. Based on a backstepping method, a dynamic trapping and manipulation control method was proposed for optical tweezers, which allows the laser beam to automatically trap the cell when it is not within the optical trap. However, the overall dynamics of the manipulator interacting with the cell is a fourth-order system which thus leads to a controller that requires high-order derivatives of state variables. Observer based control strategies [25] were proposed for manipulation of biological cells without measurement of the velocity of the cell and camera calibration.

Setpoint control or regulation problem is a fundamental problem that is of both theoretical and practical importance. Though much progress has been made in robot control [26]–[29], simple controllers such as PD control and PID control [29]–[33] are still widely used in industrial robots because of the advantages of simplicity and ease of implementation.

In this paper, we consider the regulation problem of optical tweezers and present a simple PD control scheme for robotic manipulation of biological cells using optical tweezers. The proposed cell manipulation method is based on closed-loop setpoint control of laser source instead of open-loop control as assumed in the literature. We formulate a closed-loop stability problem that shows the dynamic interaction between the laser beam and the biological cell. This is the first result that shows that a simple PD control law is effective for closed-loop manipulation of biological cell using optical tweezers, taking into consideration of the dynamic interaction between the laser beam and the cell. The use of closed-loop feedback control helps to enhance the trapping and also reduce the possibility of photodamage. The proposed setpoint controller is also extended to a region reaching controller, where the desired objective can be generalised to a region. Though the overall dynamics is a fourth-order system, the proposed controllers do not require the use of acceleration and its derivative or the construction of any observer. Compared with the tracking controllers [24], [25], the setpoint controller is of simpler structure and less computational cost. The stability of the system is analyzed directly by using LaSalle's invariance theorem, without the use of backstepping method. Experimental results are presented to illustrate the performance of the controllers.

II. OPTICAL TWEEZERS SYSTEM

The basic principle of optical trap is based on the transfer of momentum from photons to microscopic objects, when a focused

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beam of light passes through the object that is immersed in a medium. The refraction of the photons at the boundary between the object and the medium, results in a stable trap of the object [1]. Optical tweezers are the scientific instruments based on the optical trap, which can manipulate the microscopic objects without physical contact. A typical optical manipulation system is shown in Fig. 1. The setup consists of a large numerical aperture oil-immersion objective, a standard phase contrast microscope illumination, a CCD camera, a laser system, and a motorized stage. The laser beam is directed into the epifluorescence port of the microscope and then introduced to the microscope's optical path using a dichroic mirror located in the cube turret.

Fig. 1. A typical optical tweezers system. The setup consists of a large numerical aperture oil-immersion objective, a microscope illumination, a CCD camera, a laser system, and a motorized stage.

In this paper, the optical tweezers are employed to manipulate biological cells, and the dynamic model of the cell is described by the following equation [18], [24]:

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

where $M \in \mathbb{R}^{2 \times 2}$ denotes the mass matrix, $B \in \mathbb{R}^{2 \times 2}$ denotes the damping matrix, k_1 and k_2 are the parameters of the laser beam, $x = [x_1, x_2]^T \in \mathbb{R}^2$ 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 positive definite, k_1 and k_2 are positive constants, and x and q are specified with respect to the motorized stage.

The behavior of cell is regulated by the Gaussian potential energy denoted as $P = \frac{k_1}{2k_2}(1 - e^{-k_2\|x - q\|^2})$. Hence, the potential field is represented as: $\frac{\partial P}{\partial(x - q)} = k_1(x - q)e^{-k_2\|x - q\|^2}$ in equation (1). Due to the Gaussian potential energy, the problem of optical manipulation usually consists of two phases: (i) *Trapping phase*: When the cell is far away from the laser, $e^{-k_2\|x - q\|^2} \rightarrow 0$, there is no interaction between the cell and the laser, and the control objective is to drive the laser to move towards the cell; (ii) *Manipulation phase*: When the cell is very near to the laser, $e^{-k_2\|x - q\|^2} \rightarrow 1$, the cell is trapped by the laser, and the control objective is to manipulate the cell to a desired position. The two phases are illustrated in Fig. 2. In this paper, we assume that the cell is initially trapped by the laser.

In the optical tweezers system, the relative distance between the cell and the laser beam is varied by moving the motorized stage which

thus acts as the manipulator of the laser source, and the manipulator dynamics is described [26]:

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

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

Fig. 2. The behavior of the cell is regulated by the Gaussian potential energy. The trapping works only when the cell is very near the laser beam. After the cell is trapped, it is manipulated to the desired position.

Remark 1: It is reported in the literature that open-loop control is employed to move the laser source, where the cell dynamics is simplified as the first or the second order system and the position of laser q is assumed to be an input as [14]–[23]:

$$M\ddot{x} + B\dot{x} + k_c x = k_c q, \quad (3)$$

where k_c is a constant trapping stiffness. In this paper, the dynamic interaction between the cell and the manipulator of the laser source is taken into consideration, and the overall dynamics includes the cell dynamics (1) and the manipulator dynamics (2). The purpose of introducing the manipulator dynamics is to formulate a closed-loop manipulation problem such that the control input is specified as the input u exerted on the manipulator rather the position of the laser q . Therefore, the information $x - q$ is now available as a feedback variable, which can be used to keep the cell inside the trapping region of the laser beam. In optical manipulation problem, the cell is trapped by the laser and thus they have similar speed during manipulation. Otherwise, it means that the cell has escaped from the trap. Thus, the manipulator dynamics of the laser source cannot be ignored. $\triangle\triangle\triangle$

III. SETPOINT CONTROL FOR OPTICAL MANIPULATION

Considering the interaction between biological cells and robotic manipulator of laser beam, a setpoint control scheme is proposed for optical manipulation as:

$$u = -k_{p_d}(q - x_d) - K_v\dot{q} - k_{p_x}(q - x)e^{-k_2\|x - q\|^2}, \quad (4)$$

where $x_d \in \mathbb{R}^2$ is the desired constant position of the cell, and $K_v \in \mathbb{R}^{2 \times 2}$ is a positive definite matrix, and k_{p_d} and k_{p_x} are positive constants. The position of the cell x is measured by using the camera, while the position of the laser q can be measured by using the camera or encoders, and the velocity of the laser $\dot{q}$ is obtained by numerical differentiation of the position of the laser. The control term $k_{p_d}(q - x_d)$ is used to drive the cell towards the desired position. The control term $k_{p_x}(q - x)e^{-k_2\|x - q\|^2}$ is used to keep the cell inside the trapping region of the laser beam. It is known that a high-intensity laser beam produces the strong trapping force which can keep the cell inside the trapping region, but it may inflict the photodamage [12]. By using the feedback $x - q$ to keep the cell inside the trapping region, the trapping can now be enhanced by increasing k_{p_x} instead of the intensity of laser, which thus reduces the possibility of photodamage.

The closed-loop equation is obtained by substituting the controller in equation (4) into equation (2) to yield:

$$\begin{aligned} M_q \ddot{q} + B_q \dot{q} + k_{p_x} (q - x) e^{-k_2 \|x - q\|^2} \\ + k_{p_d} (q - x_d) + K_v \dot{q} = 0. \end{aligned} \quad (5)$$

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

$$\begin{aligned} V = \frac{k_{p_x}}{2k_1} \dot{x}^T M \dot{x} + \frac{1}{2} \dot{q}^T M_q \dot{q} + \frac{k_{p_x}}{2k_2} (1 - e^{-k_2 \|x - q\|^2}) \\ + \frac{k_{p_d}}{2} (q - x_d)^T (q - x_d), \end{aligned} \quad (6)$$

where the term $\frac{k_{p_x}}{2k_2} (1 - e^{-k_2 \|x - q\|^2})$ represents the Gaussian potential energy which regulates the behavior of the cell. Differentiating equation (6) with respect to time, we have:

$$\begin{aligned} \dot{V} = \frac{k_{p_x}}{k_1} \dot{x}^T M \ddot{x} + \dot{q}^T M_q \ddot{q} + k_{p_x} (\dot{x} - \dot{q})^T (x - q) e^{-k_2 \|x - q\|^2} \\ + k_{p_d} \dot{q}^T (q - x_d). \end{aligned} \quad (7)$$

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

$$\frac{k_{p_x}}{k_1} \dot{x}^T M \ddot{x} + \frac{k_{p_x}}{k_1} \dot{x}^T B \dot{x} + k_{p_x} \dot{x}^T (x - q) e^{-k_2 \|x - q\|^2} = 0. \quad (8)$$

Next, multiplying both sides of equation (5) with $\dot{q}^T$, we have:

$$\begin{aligned} \dot{q}^T M_q \ddot{q} + \dot{q}^T B_q \dot{q} + k_{p_x} \dot{q}^T (q - x) e^{-k_2 \|x - q\|^2} \\ + k_{p_d} \dot{q}^T (q - x_d) + \dot{q}^T K_v \dot{q} = 0. \end{aligned} \quad (9)$$

Then substituting equations (8) and (9) into equation (7):

$$\begin{aligned} \dot{V} = -\frac{k_{p_x}}{k_1} \dot{x}^T B \dot{x} - k_{p_x} \dot{x}^T (x - q) e^{-k_2 \|x - q\|^2} \\ - \dot{q}^T (B_q + K_v) \dot{q} - k_{p_d} \dot{q}^T (q - x_d) e^{-k_2 \|x - q\|^2} \\ + k_{p_x} (\dot{x} - \dot{q})^T (x - q) e^{-k_2 \|x - q\|^2} \\ = -\frac{k_{p_x}}{k_1} \dot{x}^T B \dot{x} - \dot{q}^T (B_q + K_v) \dot{q} \leq 0. \end{aligned} \quad (10)$$

We are now ready to state the following theorem:

Theorem 1: When the cell is initially trapped by the laser, the PD control scheme (4) for the optical tweezers system described by equations (1) and (2) gives rise to the asymptotical stability of the closed-loop system in a local sense.

Proof: Since, $\dot{V} = 0$ implies that $\dot{q} = 0$ and $\dot{x} = 0$ as $t \rightarrow \infty$, the maximum invariant set [27] of equations (1) and (5) is: $k_1(x - q)e^{-k_2 \|x - q\|^2} = 0$, and $k_{p_x}(q - x)e^{-k_2 \|x - q\|^2} + k_{p_d}(q - x_d) = 0$. Therefore, we have $x - q \rightarrow 0$ and $q - x_d \rightarrow 0$, which implies that $x - x_d \rightarrow 0$ as $t \rightarrow \infty$. $\triangle\triangle\triangle$

Remark 2: If the optical manipulation starts from the *trapping phase* where the cell is initially located at a position x_0 which is outside the trapping region (see Fig. 2), the desired position is specified as the position of the cell before it is trapped such that:

$$u = -k_{p_d}(q - x_0) - K_v \dot{q}, \quad (11)$$

which drives the laser to move towards the cell to trap it. After the cell is trapped, the control term $k_{p_x}(q - x)e^{-k_2 \|x - q\|^2}$ is activated to keep the cell inside the trapping region, and the optical manipulation transits from the *trapping phase* to the *manipulation phase*, which manipulates the cell to the desired position x_d . $\triangle\triangle\triangle$

Remark 3: From equation (6), when the cell is initially trapped by the laser and starts from a stationary position, the potential energy of the system at $t = 0$ can be represented as: $V(0) = \frac{k_{p_d}}{2} (q(0) - x_d)^T (q(0) - x_d)$. Since $\dot{V} \leq 0$, we have $V(t) \leq V(0)$ for all t . Next, note that the artificial potential energy that corresponds to the feedback control term $k_{p_x}(q - x)e^{-k_2 \|x - q\|^2}$ is $P_a = \frac{k_{p_x}}{2k_2} (1 - e^{-k_2 \|x - q\|^2})$. Therefore, if the feedback gain k_{p_x} can be set larger such that the energy barrier for the cell to escape is higher than $V(0)$, then the cell can be kept around the neighborhood of the laser beam by the feedback term. In addition, saturation function [26] can also be used

to bound the position error in actual implementation such that the laser beam moves at a slower velocity. $\triangle\triangle\triangle$

The controller in equation (4) is proposed for the optical manipulation tasks with a high Reynolds number, where the mass of the cell cannot be ignored in the dynamic model. When the optical tweezers manipulate very tiny biological cells with a low Reynolds number [34], [35], viscous drag dominates inertia due to the scaling effect, and the mass of the trapping object can be ignored. In addition, the damping for 2-D optical manipulation is usually identical in each axis. Therefore, the dynamic model of cell is simplified as:

$$b\dot{x} + k_1(x - q)e^{-k_2 \|x - q\|^2} = 0, \quad (12)$$

where b is a positive constant.

A PD controller for the optical manipulation with a low Reynolds number is proposed as:

$$u = -k_{p_d}(q - x_d) - k_{v_x}\dot{x} - K_v\dot{q}, \quad (13)$$

where k_{v_x} is a positive constant. Similarly, the velocity of the cell $\dot{x}$ is obtained by numerical differentiation of x . The closed-loop equation is obtained by substituting equation (13) into the dynamic equation (2) to yield:

$$M_q \ddot{q} + B_q \dot{q} + k_{p_d}(q - x_d) + k_{v_x}\dot{x} + K_v\dot{q} = 0. \quad (14)$$

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

$$\begin{aligned} V_s = \frac{1}{2} \dot{q}^T M_q \dot{q} + \frac{k_1 k_{v_x}}{2k_2 b} (1 - e^{-k_2 \|x - q\|^2}) \\ + \frac{k_{p_d}}{2} (q - x_d)^T (q - x_d). \end{aligned} \quad (15)$$

Differentiating equation (15) with respect to time and substituting equation (14) into it, we have:

$$\begin{aligned} \dot{V}_s = \dot{q}^T M_q \ddot{q} + k_{p_d} \dot{q}^T (q - x_d) \\ + \frac{k_1 k_{v_x}}{b} (\dot{x} - \dot{q})^T (x - q) e^{-k_2 \|x - q\|^2} \\ = -\dot{q}^T (B_q + K_v) \dot{q} - k_{v_x} \dot{q}^T \dot{x} \\ + \frac{k_1 k_{v_x}}{b} (\dot{x} - \dot{q})^T (x - q) e^{-k_2 \|x - q\|^2}. \end{aligned} \quad (16)$$

From equation (12), since $k_1(x - q)e^{-k_2 \|x - q\|^2} = -b\dot{x}$, we have:

$$\dot{V}_s = -k_{v_x} \dot{x}^T \dot{x} - \dot{q}^T (B_q + K_v) \dot{q} \leq 0. \quad (17)$$

Since $\dot{V}_s = 0$ implies that $\dot{q} = 0$ and $\dot{x} = 0$ as $t \rightarrow \infty$, the maximum invariant set of equations (12) and (14) is: $k_1(x - q)e^{-k_2 \|x - q\|^2} = 0$, and $k_{p_d}(q - x_d) = 0$, which implies that $x - q \rightarrow 0$ and $q - x_d \rightarrow 0$ as $t \rightarrow \infty$. Therefore, the closed-loop system is asymptotically stable in a local sense, when the cell is initially trapped by the laser.

IV. REGION CONTROL OF OPTICAL MANIPULATION

In this section, we consider a more general cell manipulation problem where the desired objective is specified as a region. The concept of region control was first introduced in [28] for robotic manipulator, and it is also useful for cell separation, cell fusion, interaction study between different types of cell, and the studies of mechanical characterization and cell affinity [23]. In this paper, we present a region reaching control for optical tweezers based on the fourth-order dynamics. The region function is described by an inequality as follows:

$$f(q - x_d) \leq 0. \quad (18)$$

When the cell is inside the region, $f(q - x_d) \leq 0$, and vice versa. The function $f(q - x_d)$ is a scalar function with continuous partial derivatives, and the partial derivative of the region function $\left(\frac{\partial f(q - x_d)}{\partial (q - x_d)}\right)^T$ represents the vector towards the desired region. Using the region

function in equation (18), a corresponding potential energy function is introduced as follows:

$$P_r(\mathbf{q}-\mathbf{x}_d) = \frac{k_{p_d}}{N} [\max(0, f(\mathbf{q}-\mathbf{x}_d))]^N. \quad (19)$$

where $N \geq 2$ is the order of the potential energy function. The potential energy $P_r(\mathbf{q}-\mathbf{x}_d)$ is smooth and low bounded by zero, and it naturally reduces to zero after the cell enters the desired region where $f(\mathbf{q}-\mathbf{x}_d) \leq 0$. As the size of the region decreases, the bottom of the potential energy also reduces to a point.

The partial differentiation of the energy function in equation (19) with respect to $\mathbf{q}-\mathbf{x}_d$ can be written as:

$$\left(\frac{\partial P_r(\mathbf{q}-\mathbf{x}_d)}{\partial (\mathbf{q}-\mathbf{x}_d)} \right)^T = k_{p_d} [\max(0, f(\mathbf{q}-\mathbf{x}_d))]^{N-1} \left(\frac{\partial f(\mathbf{q}-\mathbf{x}_d)}{\partial (\mathbf{q}-\mathbf{x}_d)} \right)^T, \quad (20)$$

where $\left(\frac{\partial P_r(\mathbf{q}-\mathbf{x}_d)}{\partial (\mathbf{q}-\mathbf{x}_d)} \right)^T$ is the gradient of the potential energy. When the cell is inside the desired region, $f(\mathbf{q}-\mathbf{x}_d) \leq 0$, the gradient of the potential energy reduces to zero.

Next, a region controller is proposed as:

$$\begin{aligned} \mathbf{u} = & -k_{p_x}(\mathbf{q}-\mathbf{x})e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} - \mathbf{K}_v\dot{\mathbf{q}} \\ & - k_{p_d}[\max(0, f(\mathbf{q}-\mathbf{x}_d))]^{N-1} \left(\frac{\partial f(\mathbf{q}-\mathbf{x}_d)}{\partial (\mathbf{q}-\mathbf{x}_d)} \right)^T. \end{aligned} \quad (21)$$

Note that the control term $k_{p_d}[\max(0, f(\mathbf{q}-\mathbf{x}_d))]^{N-1} \left(\frac{\partial f(\mathbf{q}-\mathbf{x}_d)}{\partial (\mathbf{q}-\mathbf{x}_d)} \right)^T$ is employed instead of the position error $\mathbf{q}-\mathbf{x}_d$, such that the cell is manipulated to a region instead of a point.

The closed-loop equation is obtained by substituting the region controller in equation (21) into the dynamic equation (2) to yield:

$$\begin{aligned} \mathbf{M}_q\ddot{\mathbf{q}} + \mathbf{B}_q\dot{\mathbf{q}} + k_{p_x}(\mathbf{q}-\mathbf{x})e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} + \mathbf{K}_v\dot{\mathbf{q}} \\ + k_{p_d}[\max(0, f(\mathbf{q}-\mathbf{x}_d))]^{N-1} \left(\frac{\partial f(\mathbf{q}-\mathbf{x}_d)}{\partial (\mathbf{q}-\mathbf{x}_d)} \right)^T = \mathbf{0}. \end{aligned} \quad (22)$$

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

$$\begin{aligned} V_r = & \frac{k_{p_x}}{2k_1} \dot{\mathbf{x}}^T \mathbf{M} \dot{\mathbf{x}} + \frac{1}{2} \dot{\mathbf{q}}^T \mathbf{M}_q \dot{\mathbf{q}} + P_r(\mathbf{q}-\mathbf{x}_d) \\ & + \frac{k_{p_x}}{2k_2} (1 - e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2}). \end{aligned} \quad (23)$$

Differentiating V_r with respect to time and substituting equations (1) and (22) into it, we have:

$$\begin{aligned} \dot{V}_r = & \frac{k_{p_x}}{k_1} \dot{\mathbf{x}}^T \mathbf{M} \ddot{\mathbf{x}} + \dot{\mathbf{q}}^T \mathbf{M}_q \ddot{\mathbf{q}} + k_{p_x}(\dot{\mathbf{x}}-\dot{\mathbf{q}})^T (\mathbf{x}-\mathbf{q})e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} \\ & + k_{p_d}\dot{\mathbf{q}}^T [\max(0, f(\mathbf{q}-\mathbf{x}_d))]^{N-1} \left(\frac{\partial f(\mathbf{q}-\mathbf{x}_d)}{\partial (\mathbf{q}-\mathbf{x}_d)} \right)^T \\ = & -\frac{k_{p_x}}{k_1} \dot{\mathbf{x}}^T \mathbf{B} \dot{\mathbf{x}} - \dot{\mathbf{q}}^T (\mathbf{B}_q + \mathbf{K}_v) \dot{\mathbf{q}} \leq 0. \end{aligned} \quad (24)$$

We are now ready to state the following theorem:

Theorem 2: When the cell is initially trapped by the laser, the region control scheme (21) for the optical tweezers system described by equations (1) and (2) guarantees the position of the cell converges to the desired region in a local sense.

Proof: Since $\dot{V}_r = 0$ implies that $\dot{\mathbf{q}} = \mathbf{0}$ and $\dot{\mathbf{x}} = \mathbf{0}$ as $t \rightarrow \infty$, the maximum invariant set satisfies:

$$k_1(\mathbf{x}-\mathbf{q})e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} = \mathbf{0}, \quad (25)$$

$$\begin{aligned} & k_{p_x}(\mathbf{q}-\mathbf{x})e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} + \\ & k_{p_d}[\max(0, f(\mathbf{q}-\mathbf{x}_d))]^{N-1} \left(\frac{\partial f(\mathbf{q}-\mathbf{x}_d)}{\partial (\mathbf{q}-\mathbf{x}_d)} \right)^T = \mathbf{0}. \end{aligned} \quad (26)$$

From equation (25), we have $\mathbf{x}-\mathbf{q} \rightarrow \mathbf{0}$. Then, from equation (26), we can conclude that $[\max(0, f(\mathbf{q}-\mathbf{x}_d))]^{N-1} \left(\frac{\partial f(\mathbf{q}-\mathbf{x}_d)}{\partial (\mathbf{q}-\mathbf{x}_d)} \right)^T \rightarrow \mathbf{0}$ which is satisfied when $\mathbf{q}-\mathbf{x}_d \rightarrow \mathbf{0}$ or $f(\mathbf{q}-\mathbf{x}_d) \leq 0$. In either case, the cell is inside the desired region. $\triangle\triangle\triangle$

Remark 4: In the presence of obstacles in the workspace, repulsive regions can be used to keep the laser beam away from the

obstacles. The region around the i^{th} obstacle is formulated as: $f_{oi}(\mathbf{q}) = (q_1 - x_{oi1})^2 + (q_2 - x_{oi2})^2 - R_{oi}^2 \leq 0$, where R_{oi} are positive constants, and $\mathbf{x}_{oi} = [x_{oi1}, x_{oi2}]^T$ is the position of the i^{th} obstacle. The potential energy for the repulsive region is proposed as: $P_{oi}(\mathbf{q}) = \frac{k_{oi}}{N} [\min(0, f_{oi}(\mathbf{q}))]^N$, where k_{oi} are positive constants. Partial differentiating $P_{oi}(\mathbf{q})$ with respect to $\mathbf{q}$, the gradient of the potential energy is obtained as: $\left(\frac{\partial P_{oi}(\mathbf{q})}{\partial \mathbf{q}} \right)^T = k_{oi} [\min(0, f_{oi}(\mathbf{q}))]^{N-1} \left(\frac{\partial f_{oi}(\mathbf{q})}{\partial \mathbf{q}} \right)^T$. That is, $\left(\frac{\partial P_{oi}(\mathbf{q})}{\partial \mathbf{q}} \right)^T$ is nonzero when the laser beam is inside the repulsive region where $f_{oi}(\mathbf{q}) < 0$, which thus pushes the laser beam away from the obstacle, and the gradient naturally reduces to zero after the laser leaves the repulsive region where $f_{oi}(\mathbf{q}) \geq 0$. Therefore, the controller (4) can be modified as:

$$\begin{aligned} \mathbf{u} = & -k_{p_d}(\mathbf{q}-\mathbf{x}_d) - \mathbf{K}_v\dot{\mathbf{q}} - k_{p_x}(\mathbf{q}-\mathbf{x})e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} \\ & - \sum_{i=1}^{N_o} k_{oi} [\min(0, f_{oi}(\mathbf{q}))]^{N-1} \left(\frac{\partial f_{oi}(\mathbf{q})}{\partial \mathbf{q}} \right)^T, \end{aligned} \quad (27)$$

where N_o is the number of obstacles. The stability of the system can be proved similarly. $\triangle\triangle\triangle$

Remark 5: The proposed controllers in equations (4) and (21) require only the information about the parameter k_2 , while the proposed controller in equation (13) does not require it. The parameter k_2 is obtained by parameter identification such as the method in [36]. The term $e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2}$ in equations (4) and (21) can be expressed by using Taylor series as: $e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} = 1 - k_2\|\mathbf{x}-\mathbf{q}\|^2 + \frac{k_2^2}{2}\|\mathbf{x}-\mathbf{q}\|^4 + \dots$. In actual implementations, the cell is kept around the neighborhood of the laser beam, and hence $\|\mathbf{x}-\mathbf{q}\|$ is very small. In addition, the parameter k_2 is also very small, and hence $e^{-k_2\|\mathbf{x}-\mathbf{q}\|^2} \approx 1$. Therefore, the stability of the closed-loop system is not very sensitive to the variation of k_2 . $\triangle\triangle\triangle$

V. EXPERIMENT

The proposed control methods were implemented in a robot-tweezer manipulation system in the City University of Hong Kong. The system is constituted of three modules for sensing, control and execution [20]. The sensing module consists of a microscope and a CCD camera, and the position of the cell 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. All of the mechanical components are supported by an anti-vibration table in a clean room, and the optical tweezers were controlled to manipulate the yeast cell. To reduce the possibility of photodamage, the power of the laser beam was set as 1 mW.

In the first experiment, the desired position of the cell is specified as a point, and the setpoint controller in equation (4) was implemented to manipulate the cell to the desired position. The control parameters in equation (4) were set as: $k_{p_d} = 10$, $k_{p_x} = 1$, $\mathbf{K}_v = \text{diag}\{1, 1\}$, the laser parameter was set as $k_2 = 7.2 \times 10^{11}$, and the trapping radius was estimated as $2.5 \mu\text{m}$ [36].

The cell was initially trapped by the laser and manipulated from different initial positions ((92, 120), (84, 387), (42, 230) pixel), to the desired position at (500, 240) pixel. The position errors are given in Fig. 3. It can be seen that all the position errors converge to zero in less than 4 seconds. The snapshots of the cell manipulation starting from the initial position at (92, 120) pixel are shown in Fig. 4, and the cell was successfully manipulated to the desired position.

In the second experiment, the desired position of the cell is specified as a region, and the proposed region controller in equation (21) was implemented. The control parameters in equation (21) were set as: $k_{p_d} = 5$, $k_{p_x} = 1$, and $\mathbf{K}_v = \text{diag}\{1, 1\}$.

The desired region was specified as a circle where the centre was set as $\mathbf{x}_d = [x_{d1}, x_{d2}]^T = [500, 240]^T$ pixel, and the radius

was set as $R = 20$ pixel. The cell was initially trapped by the laser and manipulated from different initial positions ((71, 351), (68, 130), (170, 119) pixel) to the desired region. The position errors for different initial positions are given in Fig. 5. It can be seen that all the position errors are bounded by the desired region at steady state. The snapshots of the cell starting from the initial position at (68, 130) pixel are shown in Fig. 6, and the cell was successfully manipulated to the desired region.

VI. CONCLUSION

In this paper, a simple PD controller has been proposed for optical manipulation of biological cell. The proposed methods are based on the comprehensive framework where the laser source is controlled by closed-loop robotic manipulation techniques with consideration of the dynamic interaction between the manipulator of the laser beam and the cell. Due to the dynamic interaction, the overall dynamic model of the optical tweezers system is a fourth-order nonlinear system, which is significantly different from the control problems of optical tweezers in the literature. This is the first result that shows that a simple PD control law is effective for closed-loop cell manipulation using optical tweezers, with consideration of the overall fourth-order dynamics. The use of closed-loop feedback control helps to enhance the trapping and also reduce the possibility of photodamage. The setpoint controller has also been extended to a region reaching controller, and both the setpoint controller and the region reaching controller do not require the use of acceleration and its derivative or the construction of any observer. Experimental results have been presented to illustrate the performance of the proposed control methods.

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Fig. 3. Position errors when the cell was manipulated towards the desired position at (500, 240) pixel.

Fig. 4. The cell was manipulated from (92, 120) pixel to (500, 240) pixel.

Fig. 5. Position errors when the cell was manipulated towards a circular region with the radius of 20 pixel.

Fig. 6. The cell was manipulated from (68, 130) pixel to a circular region with the radius of 20 pixel.