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2014

Li, X., & Cheah, C. C. (2014). Robotic cell manipulation using optical tweezers with unknown trapping stiffness and limited FOV. IEEE/ASME transactions on mechatronics, 99, 1-9.

<https://hdl.handle.net/10356/102294>

<https://doi.org/10.1109/TMECH.2014.2364620>

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Robotic Cell Manipulation Using Optical Tweezers with Unknown Trapping Stiffness and Limited FOV

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Abstract—In existing control methods for optical tweezers, the trapping stiffness is usually assumed to be constant and known exactly. However, the stiffness varies according to the size of the trapped particle and is also dependant on the distance between the center of the laser beam and the particle. It is therefore difficult to identify the exact model of the trapping stiffness. In addition, it is also assumed that the entire workspace is visible within the field of view (FOV) of microscope. During trapping and manipulation, certain image features such as the desired position may leave the FOV and therefore visual feedback is not available. In this paper, a robotic setpoint control technique is proposed for optical manipulation with unknown trapping stiffness and limited FOV of microscope. The proposed method allows the system to operate beyond the FOV and perform trapping and manipulation tasks without any knowledge of the trapping stiffness. The stability of the overall system is analyzed by using Lyapunov-like method, with consideration of the dynamics of both the cell and the manipulator of laser source. Experimental results are presented to illustrate the performance of the proposed method.

Index Terms—Cell manipulation, robot tweezers, limited FOV, unknown trapping stiffness.

I. INTRODUCTION

INCREASING demands of cell manipulation in biological and biomedical engineering reflect the need for robotics and automation at micro and nano scales. This leads to the emergence of various robotic cell manipulation systems with high reproducibility and precision, such as optical tweezers [1], micro insertion system [2], nanoprobe [3], micro-gripper [4], injection system [5]. Because of the capability of manipulating micro or nano particles without physical contact, optical tweezers has gained increasing interest and has been utilized in a diversity of cell manipulation tasks. The application of optical tweezers can be found in separation of cells [6] or cell sorting [7], where the trapped cell is transported to designated recipient. The capability of rapid and accurate positioning of optical tweezers is also very useful for cell fusion [8], where the target cell is trapped and manipulated to interact with another cell. Moreover, the positioning technique with optical tweezers plays an important role in studies of the elastic behavior of DNA [9], and studies of the properties of molecular motors [10], where microbeads are attached to microsystems and then manipulated by laser such that the microsystems are stretched out to given positions.

Over the past years, considerable works have been done in automated cell manipulation using optical tweezers [11]–

[19]. Setpoint control schemes [11], [12] and tracking control methods [12], [13] have been developed for manipulation of single cell, to suit different applications in optical manipulation. A comparison was carried out in [14] to evaluate the performance of various control methods for optical manipulation. To minimize the Brownian motion in an optical trap, a minimum variance control method was presented in [15]. In [16], an adaptive disturbance observer was developed for on-line estimation of probe-sample interaction force in an optical trap. To eliminate the requirement of measurement of the velocity of cell, observer-based controllers were introduced in [17] to estimate the velocity of cell. Besides various control schemes for optical manipulation, path-planning techniques have also been developed for transportation of biological cell by using optical tweezers, such as the stochastic path planning [18], and the modified A-star path planning [19]. With the development of multiple-beam techniques [20], [21], several control schemes and automation techniques have been proposed for the multi-cellular manipulation using optical tweezers [22]–[25].

The aforementioned control methods for optical tweezers [11]–[15], [17], [24], [25] assume that the trapping stiffness in an optical trap is constant and exactly known. The assumption of constant trapping stiffness implies that the cell is always kept in a small neighborhood around the centroid of the laser beam such that the optical trapping is maintained. However, due to Gaussian distribution of the intensity of laser beam around the centroid of the laser beam, the trapping stiffness reduces when the distance between the cell and the centroid of the laser beam increases. Most existing controllers thus fail when the laser beam starts from an initial position which is far away from the cell or when the cell escapes from the optical trap during manipulation. The overall effect that describes the dynamic interaction between the manipulator of laser beam and the cell was first considered in [26], where a spatial varying trapping stiffness was used for the dynamic trapping and manipulation of biological cell. By assuming that the exact model of the trapping stiffness is known, a robotic manipulation technique was developed in [26], which allows the laser beam to automatically trap and manipulate the cell to a desired trajectory, even when the cell is not inside the optical trap. However, it is difficult to identify the exact model of the trapping stiffness which is dependent on the distance between the cell and the center of the laser beam. In addition, the stiffness may vary according to the size of the particles.

In existing control methods for optical tweezers, it is also assumed that the entire workspace is always visible throughout the course of manipulation. While a high resolution micro-

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scope provides a large spectrum of visual details and improves the accuracy of optical manipulation, the FOV is very limited. As a result, certain image features such as the desired position may leave the FOV during manipulation. While some results have been obtained for robot visual servoing [27] with limited FOV [28], [29], the optical manipulation problem with limited FOV has not been solved. Therefore, most existing controllers also fail when there is a transitory loss of visual feedback during manipulation.

In this paper, a robotic setpoint control scheme is proposed for cell manipulation using optical tweezers, which ensures the convergence of the optical manipulation within the workspace. The proposed controller allows the laser beam to automatically trap and manipulate the cell even when the cell is not inside the optical trap, and the assumption of having exact knowledge of the trapping stiffness is eliminated. In addition, the proposed controller works even when the image feedback error is lost due to limited FOV. Therefore, the problems of unknown stiffness and limited FOV are solved. The stability of the overall system is shown by using Lyapunov-like method, with consideration of the dynamic interaction between the manipulator of laser source and the biological cell. Experimental results are presented to illustrate the performance of the proposed cell manipulation method with unknown trapping stiffness and limited FOV.

II. DYNAMIC MODEL OF OPTICAL TWEEZERS

An optical trap is obtained by focusing a laser beam with an objective lens of high numerical aperture, and dielectric particles (polystyrene beads, yeast, and bacteria) near the focus will experience a force due to the transfer of momentum from the photons [1]. A typical optical manipulation system is shown in Fig. 1.

For micromanipulation problems, the Reynolds number is usually low [30]–[33]. That is, viscous drag dominates inertia, and the cell dynamics in an optical trap is described as:

$$B\dot{\mathbf{x}} + k(\mathbf{x}, \mathbf{p})(\mathbf{x} - \mathbf{p}) = \mathbf{F}, \quad (1)$$

where $B \in \mathbb{R}^{2 \times 2}$ represents the damping matrix which is diagonal and positive definite, $k(\mathbf{x}, \mathbf{p})$ is the trapping stiffness, $\mathbf{x} = [x_1, x_2]^T \in \mathbb{R}^2$ and $\mathbf{p} = [p_1, p_2]^T \in \mathbb{R}^2$ represent the positions of cell and the center of laser in image space respectively, and $\mathbf{F} \in \mathbb{R}^2$ is the disturbance force due to Brownian motion, which is random and bounded.

The trapping stiffness in equation (1) is modelled as [26]:

$$k(\mathbf{x}, \mathbf{p}) = \begin{cases} k_c, & \|\mathbf{x} - \mathbf{p}\| \leq R, \\ k_c e^{-(\|\mathbf{x} - \mathbf{p}\| - R)^2}, & \|\mathbf{x} - \mathbf{p}\| > R, \end{cases} \quad (2)$$

where k_c is a positive constant, and R represents the trapping radius which is a positive constant. This implies $k(\mathbf{x}, \mathbf{p})$ is constant when the cell is near the center of the laser beam and is reduced when the cell leaves the neighborhood of the center of the laser beam. That is, the trapping stiffness is dependent on the distance between $\mathbf{x}$ and $\mathbf{p}$. Moreover, k_c is usually unknown since it varies for different sizes of particles. Both the position of cell $\mathbf{x}$ and that of laser $\mathbf{p}$ are specified with respect to the stage as illustrated in Fig. 2.

Fig. 1. A typical optical tweezers system. The setup consists of a large numerical aperture oil-immersion objective, a standard phase contrast microscope illumination, a motorized stage, a laser system, and a CCD camera. The offset between the cell and the laser can be varied by the motorized stage which acts as a robotic manipulator.

Fig. 2. Both the camera frame O_c and the laser beam are fixed with respect to the world frame O_w , while the stage frame O_s is moving such that the relative distance between the cell and the center of laser is varied. Both the position of cell $\mathbf{x}$ and that of laser $\mathbf{p}$ are specified with respect to the stage.

In this paper, the relative distance is varied by moving the motorized stage while fixing the laser beam, and the motorized stage is thus treated as the manipulator of the laser source. The manipulator dynamics is specified as:

$$M_q \ddot{\mathbf{q}} + B_q \dot{\mathbf{q}} = \mathbf{u}, \quad (3)$$

where $\mathbf{q} = [q_1, q_2]^T \in \mathbb{R}^2$ is the position of laser beam in Cartesian space which is measured by encoders mounted on the motorized stage, $M_q \in \mathbb{R}^{2 \times 2}$ is the mass matrix which is diagonal and positive definite, $B_q \in \mathbb{R}^{2 \times 2}$ represents the friction matrix which is also diagonal and positive definite, and $\mathbf{u} \in \mathbb{R}^2$ denotes the control input which is the force exerted on the manipulator. In addition, the dynamic model described by equation (3) can be parameterized as: $M_q \ddot{\mathbf{q}} + B_q \dot{\mathbf{q}} = \mathbf{Y}_q(\dot{\mathbf{q}}, \ddot{\mathbf{q}})\boldsymbol{\theta}_q$, where $\mathbf{Y}_q(\dot{\mathbf{q}}, \ddot{\mathbf{q}}) \in \mathbb{R}^{2 \times n_q}$ represents a known regressor matrix, and $\boldsymbol{\theta}_q = [\theta_{q1}, \dots, \theta_{qn_q}]^T \in \mathbb{R}^{n_q}$ is a set of unknown constant parameters. By introducing the manipulator dynamics (3), the laser source is now controlled by closed-loop robotic manipulation techniques, where the position of laser is available as a feedback variable.

The position of laser in image space $\mathbf{p}$ is obtained by

image processing techniques within the FOV. The relationship between the Cartesian space of the motorized stage and the image space of the microscope is defined by the pinhole camera model [27], [34]. Based on the pinhole camera model, the velocity of laser in image space is related to that in Cartesian space by using the image Jacobian matrix [35], [36]:

$$\dot{\mathbf{p}} = \mathbf{J}_I(\mathbf{q})\dot{\mathbf{q}}, \quad (4)$$

where $\mathbf{J}_I(\mathbf{q}) \in \mathbb{R}^{2 \times 2}$ is the image Jacobian matrix, $\dot{\mathbf{p}}$ is the image-space velocity of laser beam, and $\dot{\mathbf{q}}$ is the velocity of laser beam in Cartesian space. If the laser beam evolves in the 2-D plane of the stage while the camera is perpendicular to the evolving plane of the laser beam, the image Jacobian matrix is constant. If the cell is submerged in a 3D space, the depth information is not constant.

III. OPTICAL MANIPULATION WITH UNKNOWN TRAPPING STIFFNESS

The dynamic interaction between the cell and the laser leads to an overall third-order system, as seen in equations (1) and (3). With the consideration of the dynamic interaction, a control scheme with unknown varying trapping stiffness is proposed for optical manipulation. The development of the proposed control scheme follows a backstepping approach.

The backstepping approach [37] provides a recursive method for stabilizing the system described by equations (1) and (3): First, based on the cell dynamics (1), a desired fictitious position input $\mathbf{p}_d$ without the knowledge of trapping stiffness $k(\mathbf{x}, \mathbf{p})$ is developed in image space, to drive the laser beam to automatically trap and manipulate the cell to the desired position. Next, based on the manipulator dynamics (3), a control input for the manipulator of laser beam $\mathbf{u}$ is derived to realize the fictitious signal, such that the actual position of laser beam $\mathbf{p}$ tracks the desired position input $\mathbf{p}_d$.

By adding and subtracting the term $k(\mathbf{x}, \mathbf{p})\mathbf{p}_d$ from equation (1), we have:

$$\mathbf{B}\dot{\mathbf{x}} + k(\mathbf{x}, \mathbf{p})\mathbf{x} = k(\mathbf{x}, \mathbf{p})\mathbf{p}_d + k(\mathbf{x}, \mathbf{p})\Delta\mathbf{p} + \mathbf{F}. \quad (5)$$

where $\Delta\mathbf{p} = \mathbf{p} - \mathbf{p}_d$ denotes an input perturbation. The system in equation (5) can be viewed as being controlled by the fictitious input $k(\mathbf{x}, \mathbf{p})\mathbf{p}_d$ with the perturbation $k(\mathbf{x}, \mathbf{p})\Delta\mathbf{p}$. Note that $k(\mathbf{x}, \mathbf{p})$ in equation (5) is part of the system model and is used only in the analysis but not in the controller which will be detailed later.

It is known that the trapping works only when the cell is located in a small neighborhood of the centroid of the focused laser beam, which implies that the optical manipulation consists of two phases: *Trapping phase*: When the cell is far away from the laser, $k(\mathbf{x}, \mathbf{p}) \rightarrow 0$, there is no interaction between the cell and the laser beam, and the control objective is to drive the laser beam to move towards the cell; *Manipulation phase*: When the cell is very near to the laser, $k(\mathbf{x}, \mathbf{p}) \rightarrow k_c$, the cell is trapped by the laser, and the control objective is to manipulate the cell to a desired position.

To guarantee the smooth transition between the *trapping phase* and the *manipulation phase*, a weight factor $a(\mathbf{x}, \mathbf{p})$ is introduced as:

$$a(\mathbf{x}, \mathbf{p}) = 1 - \frac{\{\min[0, \min(0, f(\mathbf{x}, \mathbf{p}))]^4 - [(\kappa b)^2 - b^2]^4\}}{[(\kappa b)^2 - b^2]^{16}}, \quad (6)$$

where $0 < \kappa < 1$ is a positive constant, $f(\mathbf{x}, \mathbf{p}) = \|\mathbf{x} - \mathbf{p}\|^2 - b^2 \leq 0$ is the trapping region, b is a positive constant which is set smaller than the trapping radius R . When the cell enters the trapping region such that $f(\mathbf{x}, \mathbf{p}) \leq 0$, the trapping force has already been activated, and thus the cell can be trapped by the laser. Note that $a(\mathbf{x}, \mathbf{p})$ smoothly increases from 0 to 1 when the cell moves from outside to inside the trapping region.

By using the weight factor $a(\mathbf{x}, \mathbf{p})$, the desired position input for the laser beam $\mathbf{p}_d$ is proposed as:

$$\mathbf{p}_d = \mathbf{x} - a(\mathbf{x}, \mathbf{p})\mathbf{K}_p\Delta\mathbf{x}, \quad (7)$$

where $\mathbf{K}_p \in \mathbb{R}^{2 \times 2}$ is a positive definite matrix, $\Delta\mathbf{x} = \mathbf{x} - \mathbf{x}_d$ is the position error, $\mathbf{x}_d$ is the desired position for the cell where $\mathbf{x}_d \in L_\infty$ and $\dot{\mathbf{x}}_d = \mathbf{0}$. Note that the variable $\mathbf{p}$ is used as a feedback variable to construct the weight factor $a(\mathbf{x}, \mathbf{p})$.

The two phases of optical manipulation are integrated into the desired position input $\mathbf{p}_d$ so that: when the cell is far away from the laser, $f(\mathbf{x}, \mathbf{p}) > 0$, and $a(\mathbf{x}, \mathbf{p}) = 0$. From equation (7), the desired position input becomes $\mathbf{p}_d = \mathbf{x}$ (*trapping phase*), i.e., the laser is controlled to move towards the cell to trap it. After the relative distance between the cell and the center of laser is decreased such that the cell is inside the trapping region, $f(\mathbf{x}, \mathbf{p}) \leq 0$, and $a(\mathbf{x}, \mathbf{p})$ increases from 0 to 1. From equation (7), the desired position input is specified as $\mathbf{p}_d = \mathbf{x} - \mathbf{K}_p\Delta\mathbf{x}$ (*manipulation phase*), which drives the trapped cell to the desired position.

Substituting the desired position input for the laser beam (7) into the dynamic equation (5), we have:

$$\mathbf{B}\dot{\mathbf{x}} + k(\mathbf{x}, \mathbf{p})a(\mathbf{x}, \mathbf{p})\mathbf{K}_p\Delta\mathbf{x} = k(\mathbf{x}, \mathbf{p})\Delta\mathbf{p} + \mathbf{F}. \quad (8)$$

Equation (8) describes a nonlinear system, since the trapping stiffness $k(\mathbf{x}, \mathbf{p})$ is nonlinear. Lyapunov method has been extensively used in stability analysis of nonlinear systems and robot control. The proposed method in this paper also aims to bridge the gap between traditional robotic manipulation techniques and optical manipulation techniques. Therefore, the stability for the dynamic equation of cell is analyzed by using Lyapunov method. In Lyapunov method, the Lyapunov function is positive definite in state variables, while its time derivative is negative definite, which implies the origin of the stage space is asymptotically stable [38].

A Lyapunov-like candidate V_x is proposed as:

$$V_x = \frac{1}{2}\Delta\mathbf{x}^T\mathbf{B}\Delta\mathbf{x}. \quad (9)$$

Differentiating equation (9) with respect time and substituting equation (8) into it, it is obtained that:

$$\frac{d}{dt}V_x + W_x = \Delta\mathbf{x}^T(k(\mathbf{x}, \mathbf{p})\Delta\mathbf{p} + \mathbf{F}), \quad (10)$$

where

$$W_x = k(\mathbf{x}, \mathbf{p})a(\mathbf{x}, \mathbf{p})\Delta\mathbf{x}^T\mathbf{K}_p\Delta\mathbf{x}. \quad (11)$$

Then, if $\Delta\mathbf{p} = \mathbf{0}$ and $\mathbf{F}$ is negligible, we have $\dot{V}_x = -W_x < 0$, and it can be shown that $\mathbf{x} \rightarrow \mathbf{x}_d$ and $\dot{\mathbf{x}} \rightarrow \mathbf{0}$ as $t \rightarrow \infty$. When $\mathbf{F}$ is not negligible, the position error $\Delta\mathbf{x}$ is bounded, which will be detailed later.

Remark 1: The desired position $\mathbf{x}_d$ for the trapped cell is specified in image space, and the relative image error $\Delta\mathbf{x}$ is

obtained for feedback control. In cell fusion [8], $\mathbf{x}_d$ is specified as the position of the cell that is to be fused, which can only be specified in image space. During manipulation, the particle or cell may also escape and stop at a unknown position which can be obtained by the camera system. $\triangle\triangle\triangle$

IV. OPTICAL MANIPULATION WITH LIMITED FOV

Note that $\mathbf{p}_d$ in equation (7) is related to the desired position $\mathbf{x}_d$, which may not be always visible during manipulation due to limited FOV. An illustration of the problem of limited FOV of optical tweezers is shown in Fig. 3. In Fig. 3(a), the cell and the desired position are initially within the FOV, and the laser is controlled to move towards the cell to trap it. In Fig. 3(b), the cell has been trapped by the laser beam, but the desired position leaves the FOV and thus visual feedback error is lost, that is, $\Delta\mathbf{x}$ is not available and hence $\mathbf{p}_d$ is not available either.

Fig. 3. An illustration of limited FOV: (a) In *trapping phase*, the laser moves towards the cell to trap it; (b) In *manipulation phase*, the cell has been trapped by the laser, but now the desired position is outside the FOV.

The problem of limited FOV is addressed by designing a control input $\mathbf{u}$ for the laser beam in equation (3), which also guarantees that $\mathbf{p}$ tracks $\mathbf{p}_d$, such that $\Delta\mathbf{p} \rightarrow 0$.

A. Cartesian-Space Region

To deal with the problem of limited FOV, a Cartesian-space region is specified to enclose the desired position. In the presence of temporary loss of image feedback error during the course of manipulation, the laser is outside the Cartesian-space region, and the Cartesian-space feedback is employed to drive the laser to move towards the Cartesian-space region. After the laser beam enters the Cartesian-space region, the desired position $\mathbf{x}_d$ is inside the FOV again, and the visual feedback error $\Delta\mathbf{x}$ is available.

The Cartesian-space region is specified as:

$$f_c(\mathbf{q}) = \frac{(q_1 - q_{c1})^{n_h}}{(q_{b1} - q_{c1})^{n_h}} + \frac{(q_2 - q_{c2})^{n_h}}{(q_{b2} - q_{c2})^{n_h}} - 1 \leq 0, \quad (12)$$

where $\mathbf{q}_c = [q_{c1}, q_{c2}]^T \in \mathbb{R}^2$ represents the center of the Cartesian-space region, $\mathbf{q}_b = [q_{b1}, q_{b2}]^T \in \mathbb{R}^2$ denotes the bound of the region, and n_h is the order of the region function which is also a positive even integer. In general, $n_h \geq 10$, such that $f_c(\mathbf{q})$ is specified as a rectangle with rounded corners.

To activate or deactivate the Cartesian-space feedback, a weight factor $w(\mathbf{q})$ is defined based on the Cartesian-space region as:

$$w(\mathbf{q}) = 1 - \frac{\{\min[0, \min(0, f_c(\mathbf{q}))]^4 - [\kappa_w^{n_h} - 1]^4\}}{[\kappa_w^{n_h} - 1]^{16}}, \quad (13)$$

where $0 < \kappa_w < 1$ is a positive constant. Note that $w(\mathbf{q})$ is continuous and smooth. It equals to zero when the laser beam is outside the Cartesian-space region where $f_c(\mathbf{q}) > 0$, and it smoothly increases to 1 after the laser beam enters the Cartesian-space region where $f_c(\mathbf{q}) \leq 0$, as shown in Fig. 4.

Fig. 4. An illustration of $w(\mathbf{q})$. The weight factor smoothly increases from 0 to 1 after the laser beam enters the Cartesian-space region where $f_c(\mathbf{q}) \leq 0$.

By using the weight factor, the desired position input is now proposed as:

$$\mathbf{p}_d = \mathbf{x} - a(\mathbf{x}, \mathbf{p})w(\mathbf{q})\mathbf{K}_p\Delta\mathbf{x}. \quad (14)$$

In the *trapping phase*, $a(\mathbf{x}, \mathbf{p}) = 0$, $\mathbf{p}_d = \mathbf{x}$, and the laser moves towards the cell to trap it. After the cell is trapped by the laser, $a(\mathbf{x}, \mathbf{p}) = 1$, but $w(\mathbf{q})$ remains zero if the laser beam is outside the Cartesian-space region, which also implies that the problem of limited FOV occurs such that the desired position $\mathbf{x}_d$ is not available. The Cartesian-space feedback will be designed later, to drive the laser together with the trapped cell towards the Cartesian-space region. After the laser enters the Cartesian-space region, $w(\mathbf{q}) = 1$, $\mathbf{p}_d = \mathbf{x} - \mathbf{K}_p\Delta\mathbf{x}$, that is, the desired position input transits to the *manipulation phase*.

Substituting the desired position input for the laser beam (14) into the dynamic equation (5), we have:

$$\mathbf{B}\dot{\mathbf{x}} + k(\mathbf{x}, \mathbf{p})a(\mathbf{x}, \mathbf{p})w(\mathbf{q})\mathbf{K}_p\Delta\mathbf{x} = k(\mathbf{x}, \mathbf{p})\Delta\mathbf{p} + \mathbf{F}. \quad (15)$$

Then, it can be shown by using Lyapunov stability analysis that $\mathbf{x} \rightarrow \mathbf{x}_d$ and $\dot{\mathbf{x}} \rightarrow 0$ as $t \rightarrow \infty$, if $\Delta\mathbf{p} = 0$, and $\mathbf{F}$ is negligible.

B. Control Scheme for Manipulator of Laser Source

We can now develop the control input $\mathbf{u}$ for the manipulator of laser source, to ensure that the actual position of laser tracks the desired position input such that $\Delta\mathbf{p} = \mathbf{p} - \mathbf{p}_d \rightarrow 0$. First, a sliding vector is introduced as:

$$\mathbf{s}_q = \dot{\mathbf{q}} - \dot{\mathbf{q}}_r = \dot{\mathbf{q}} - \mathbf{J}_I^{-1}(\mathbf{q})\dot{\mathbf{p}}_d + \alpha_x \mathbf{J}_I^{-1}(\mathbf{q})\Delta\mathbf{p} + \alpha_r a(\mathbf{x}, \mathbf{p})(1 - w(\mathbf{q}))\Delta\mathbf{q}, \quad (16)$$

where α_x and α_r are positive constants, $\mathbf{J}_I^{-1}(\mathbf{q})$ is the inverse of $\mathbf{J}_I(\mathbf{q})$, $\dot{\mathbf{p}}_d$ is the time-derivative of $\mathbf{p}_d$, $\Delta\mathbf{q} = \mathbf{q} - \mathbf{q}_c$, and $\dot{\mathbf{q}}_r$ is a reference vector which is defined as: $\dot{\mathbf{q}}_r = \mathbf{J}_I^{-1}(\mathbf{q})\dot{\mathbf{p}}_d - \alpha_x \mathbf{J}_I^{-1}(\mathbf{q})\Delta\mathbf{p} - \alpha_r a(\mathbf{x}, \mathbf{p})(1 - w(\mathbf{q}))\Delta\mathbf{q}$.

In equation (16), $\alpha_r a(\mathbf{x}, \mathbf{p})(1 - w(\mathbf{q}))\Delta\mathbf{q}$ corresponds to the Cartesian-space feedback control term, which is activated outside the Cartesian-space region where $w(\mathbf{q}) = 0$, to drive the laser beam to move towards the Cartesian-space region. After the laser enters the Cartesian-space region, $w(\mathbf{q}) = 1$, and $(1 - w(\mathbf{q}))\Delta\mathbf{q}$ naturally reduces to zero. Moreover, the Cartesian-space feedback control term is only activated after the cell is trapped by the laser such that $a(\mathbf{x}, \mathbf{p}) = 1$.

TABLE I
VARIATIONS OF THE CONTROL TERMS

	$a(\mathbf{x}, \mathbf{p})$	$w(\mathbf{q})$	$\mathbf{p}_d$	$\mathbf{s}_q$	Remark
Trapping phase	0	not applicable	$\mathbf{x}$	$\dot{\mathbf{q}} - \mathbf{J}_I^{-1}(\mathbf{q})\dot{\mathbf{x}} + \alpha_x \mathbf{J}_I^{-1}(\mathbf{q})\Delta\mathbf{p}$	Laser moves to $\mathbf{x}$, and $a(\mathbf{x}, \mathbf{p})$ increases to 1 when cell is trapped.
Manipulation phase (visual feedback is lost.)	1	0	$\mathbf{x}$	$\dot{\mathbf{q}} - \mathbf{J}_I^{-1}(\mathbf{q})\dot{\mathbf{x}} + \alpha_x \mathbf{J}_I^{-1}(\mathbf{q})\Delta\mathbf{p} + \alpha_r \Delta\mathbf{q}$	Laser moves to $f_c(\mathbf{q}) \leq 0$, and $w(\mathbf{q})$ increases to 1 when vision is restored.
Manipulation phase (visual feedback is valid.)	1	1	$\mathbf{x} - \mathbf{K}_p \Delta\mathbf{x}$	$\dot{\mathbf{q}} - \mathbf{J}_I^{-1}(\mathbf{q})\dot{\mathbf{p}}_d + \alpha_x \mathbf{J}_I^{-1}(\mathbf{q})\Delta\mathbf{p}$	Laser and cell move to $\mathbf{x}_d$.

Therefore, all conditions (27)-(29) can be met for all phases by setting $\mathbf{K}_p$, α_x , and $\mathbf{K}_s$ sufficiently large, and $\mathbf{K}_q$ small. At micro-scale, the Brownian force is negligible as compared to the drag force [39] (see Chapter 3). If the Brownian force is negligible such that $\mathbf{F} \approx \mathbf{0}$, the convergence of the position error for the cell is concluded by the following Theorem.

Theorem: The control scheme (18) and the update law (19) for the closed-loop equation (20) guarantee the convergence of the manipulation task, when conditions (27)-(29) are satisfied and the Brownian force is negligible. That is, $\mathbf{x} \rightarrow \mathbf{x}_d$, $\dot{\mathbf{x}} \rightarrow \mathbf{0}$, and $\mathbf{p} \rightarrow \mathbf{p}_d$ as $t \rightarrow \infty$.

Proof: When conditions (27)-(29) are satisfied and $\mathbf{F} \approx \mathbf{0}$, we have from (22) that $\frac{d}{dt}V = -W \leq 0$. That is, V is bounded. From equation (21), $\mathbf{s}_q$, $\Delta\theta_q$, $\Delta\mathbf{x}$, $\Delta\mathbf{p}$ are bounded. Since $\Delta\mathbf{x}$ is bounded, $\mathbf{x}$ is bounded if $\mathbf{x}_d$ is bounded. The boundedness of $\mathbf{x}$ and $\Delta\mathbf{x}$ ensures the boundedness of $\mathbf{p}_d$, as seen from equation (14). Since $\mathbf{p}_d$ and $\Delta\mathbf{p}$ are bounded, $\mathbf{p}$ is also bounded and hence $\mathbf{q}$ is bounded. The boundedness of $\mathbf{q}$ ensures the boundedness of $\Delta\mathbf{q}$. In addition, the boundedness of $\Delta\mathbf{x}$ and $\Delta\mathbf{p}$ ensures the boundedness of $\dot{\mathbf{x}}$, as seen from equation (15). Differentiating equation (14) with respect to time, it can be seen that $\dot{\mathbf{p}}_d$ is bounded. Since $\dot{\mathbf{p}}_d$, $\Delta\mathbf{p}$, and $\Delta\mathbf{q}$ are all bounded, $\dot{\mathbf{q}}_r$ is bounded. From equation (16), $\dot{\mathbf{q}}$ is bounded since $\mathbf{s}_q$ and $\dot{\mathbf{q}}_r$ are bounded. The boundedness of $\dot{\mathbf{q}}$ guarantees the boundedness of $\dot{\mathbf{p}}$ since $\mathbf{J}_I(\mathbf{q})$ are trigonometric functions of $\mathbf{q}$ or constant. Therefore, $\Delta\dot{\mathbf{p}}$ is also bounded. Since W is positive semi-definite, **Barbalat's lemma** will be used to prove the convergence of the position error. Since $\dot{\mathbf{x}}$ and $\Delta\dot{\mathbf{p}}$ are bounded, $\Delta\mathbf{x}$ and $\Delta\mathbf{p}$ are uniformly continuous. From equation (26), it is also concluded that $\Delta\mathbf{x}, \Delta\mathbf{p} \in L_2(0, +\infty)$. Then it follows from **Barbalat's lemma** [38], [40], [41] that: $\Delta\mathbf{x}, \Delta\mathbf{p} \rightarrow \mathbf{0}$. From equation (15), $\Delta\mathbf{x} \rightarrow \mathbf{0}$ and $\Delta\mathbf{p} \rightarrow \mathbf{0}$ implies that $\mathbf{x} \rightarrow \mathbf{x}_d$, $\dot{\mathbf{x}} \rightarrow \mathbf{0}$ as $t \rightarrow \infty$. $\triangle\triangle\triangle$

If the Brownian force is not negligible such that $\mathbf{F} \neq \mathbf{0}$, $\Delta\mathbf{x}$ is bounded as described by the following Corollary.

Corollary: If the Brownian force is not negligible, the control scheme (18) and the update law (19) for the closed-loop equation (20) guarantee the boundedness of the position error for the cell, when conditions (27)-(29) are satisfied and $\mathbf{K}_p$ is chosen sufficiently large such that:

$$2k(\mathbf{x}, \mathbf{p})a^2(\mathbf{x}, \mathbf{p})w^2(\mathbf{q})\lambda_{\min}[\mathbf{K}_p] \geq (\dot{a}(\mathbf{x}, \mathbf{p})w(\mathbf{q}) + a(\mathbf{x}, \mathbf{p})\dot{w}(\mathbf{q}))\lambda_{\max}[\mathbf{B}] + (k(\mathbf{x}, \mathbf{p}) + 1)a(\mathbf{x}, \mathbf{p})w(\mathbf{q}). \quad (30)$$

Proof: Integrating both sides of equation (22) with respect to

time yields:

$$\int_0^t a(\mathbf{x}(\varsigma), \mathbf{p}(\varsigma))w(\mathbf{q}(\varsigma))\Delta\mathbf{x}^T(\varsigma)\mathbf{F}(\varsigma)d\varsigma = V(t) - V(0) + \int_0^t W(\varsigma)d\varsigma. \quad (31)$$

where $V(0)$ denotes the initial value of V at $t=0$. Since V is positive definite, we have:

$$-V(0) + \int_0^t W(\varsigma)d\varsigma \leq \frac{1}{2} \int_0^t a(\mathbf{x}(\varsigma), \mathbf{p}(\varsigma))w(\mathbf{q}(\varsigma))\|\Delta\mathbf{x}(\varsigma)\|^2 d\varsigma + \frac{1}{2} \int_0^t a(\mathbf{x}(\varsigma), \mathbf{p}(\varsigma))w(\mathbf{q}(\varsigma))\|\mathbf{F}(\varsigma)\|^2 d\varsigma. \quad (32)$$

When conditions (27)-(29) are satisfied, $W \geq 0$. Then, from equation (26), it is obtained that:

$$\int_0^t \nu(\varsigma)\|\Delta\mathbf{x}(\varsigma)\|^2 d\varsigma \leq \int_0^t a(\mathbf{x}(\varsigma), \mathbf{p}(\varsigma))w(\mathbf{q}(\varsigma))\|\mathbf{F}(\varsigma)\|^2 d\varsigma + 2V(0), \quad (33)$$

where $\nu = 2k(\mathbf{x}, \mathbf{p})a^2(\mathbf{x}, \mathbf{p})w^2(\mathbf{q})\lambda_{\min}[\mathbf{K}_p] - (\dot{a}(\mathbf{x}, \mathbf{p})w(\mathbf{q}) + a(\mathbf{x}, \mathbf{p})\dot{w}(\mathbf{q}))\lambda_{\max}[\mathbf{B}] - (k(\mathbf{x}, \mathbf{p}) + 1)a(\mathbf{x}, \mathbf{p})w(\mathbf{q})$. If $\mathbf{K}_p$ is chosen sufficiently large such that condition (30) is satisfied, $\nu \geq 0$, and the boundedness of $\Delta\mathbf{x}$ is obtained from equation (33). Therefore, the increase of the feedback control gain $\mathbf{K}_p$ reduces the effect of the Brownian noise, with the trade-off of reducing the bandwidth of the closed-loop system. $\triangle\triangle\triangle$

Remark 2: In the presence of calibration errors and variations in depth information, the sensory transformation between Cartesian space and image space is uncertain, and an adaptive control law with uncertain image Jacobian matrix can be proposed by following a similar development in [42]. $\triangle\triangle\triangle$

Remark 3: From equations (14) and (18), the control input $\mathbf{u}$ includes the time derivatives $\dot{\mathbf{p}}_d$ and $\ddot{\mathbf{p}}_d$ which requires the high-order derivatives of the positions of cell and laser beam. The high-order derivatives are usually obtained by differentiating the positions, which amplifies noises. To eliminate the requirement of the high-order derivatives, an observer can be developed for the estimated desired position input $\hat{\mathbf{p}}_d$ as in [26]. $\triangle\triangle\triangle$

Remark 4: In the presence of obstacles in the workspace, repulsive regions are used to keep the laser far away from the obstacles. The region is formulated as:

$$f_{oi}(\mathbf{p}) = (p_1 - x_{oi1})^2 + (p_2 - x_{oi2})^2 - R_{oi}^2 \leq 0, \quad (34)$$

where R_{oi} are positive constants, and $\mathbf{x}_{oi} = [x_{oi1}, x_{oi2}]^T \in \mathbb{R}^2$ is the position of the i^{th} obstacle. The potential energy for the region is proposed as: $P_o(\mathbf{p}) = \sum_{i=1}^m \frac{k_{oi}}{2} [\min(0, f_{oi}(\mathbf{p}))]^2$, where k_{oi} are positive constants and m is the number of obstacles within the FOV. The repulsive force is obtained by partially differentiating $P_o(\mathbf{p})$ with respect to $\mathbf{p}$ as:

$$\Delta\boldsymbol{\varepsilon}_o = \sum_{i=1}^m k_{oi} [\min(0, f_{oi}(\mathbf{p}))](\frac{\partial f_{oi}(\mathbf{p})}{\partial \mathbf{p}})^T. \quad (35)$$

That is, $\Delta\epsilon_o$ is nonzero when the laser is inside the repulsive region, which pushes it away from the obstacle, and $\Delta\epsilon_o$ naturally reduces to zero after the laser leaves the repulsive region. Then, the controller (18) can be modified as:

$$\begin{aligned} \mathbf{u}_o = & -\mathbf{K}_s \mathbf{s}_q - \mathbf{J}_f^T(\mathbf{q}) \mathbf{K}_q \Delta \mathbf{p} \\ & - \mathbf{J}_f^T(\mathbf{q}) \mathbf{K}_o \mathbf{R} \Delta \epsilon_o + \mathbf{Y}_q(\dot{\mathbf{q}}_r, \ddot{\mathbf{q}}_r) \hat{\boldsymbol{\theta}}_q, \end{aligned} \quad (36)$$

where $\mathbf{K}_o \in \mathbb{R}^{2 \times 2}$ is a diagonal and positive definite matrix, and $\mathbf{R} \in \mathbb{R}^{2 \times 2}$ is a rotation matrix [43]. The stability of the system can be proved similarly. $\triangle\triangle\triangle$

Remark 5: The adaptive controller is developed to deal with the uncertain dynamic parameters. Parameters drift may occur in adaptive control systems in presence of measurement noise and thus results in divergence. To alleviate this problem, techniques such as "dead-zone" method [38] can be implemented in practical implementation. $\triangle\triangle\triangle$

V. EXPERIMENT

The proposed control method was implemented in the optical tweezers system as shown in Fig. 6. The main setup consists of the inverted microscope (Nikon, Eclipse Ti-U), the motorized stage (Marzhauser Wetzlar, SCAN IM), the optical trap device (Elliot Scientific, E3500), the large numerical aperture objective (100 $\times$), the digital camera (Basler, piA640-210gm), and the laser source (YLM-10-LP-SC). The laser is capable of producing more than 10 watts of optical power at a wavelength of 1070 nm. To avoid the problem of photodamage, the actual power of the laser beam was set as 0.7 watts. The FOV of the camera is specified as 648 pixel $\times$ 488 pixel. The position of laser beam is fixed at the centre of FOV, while the relative distance between the cell and the center of the laser is varied by moving the stage. The stage is operated in a 2-D space, with the range of 120 $\times$ 100 mm and the resolution of 0.01 μm . The relationship between the Cartesian space and the image space is known as 0.074 $\mu\text{m}/\text{pixel}$. The optical tweezers were controlled to manipulate yeast cells, and the cell is not attached to a bead but directly trapped by the laser.

Fig. 6. Optical tweezers system. The setup consists of the microscope, the motorized stage, the optical trap device, and the cameras.

First, a PID controller [12] was implemented in the optical tweezers system for comparison. As seen in Fig. 7, the optical trapping fails if the cell is not initially trapped by the laser, where the laser moves directly to the desired position rather than trapping the cell first. To solve the problem, the desired position is first specified as the position of the target cell, and PID controller drives the laser beam to trap the cell. However, the

optical trapping still fails when the problem of limited FOV occurs, since the final desired position is unknown after the laser traps the cell, as seen in Fig. 8.

Next, the proposed control scheme described by equations (14) and (18) was implemented in the optical tweezers system. A Cartesian-space region was specified to enclose the desired position, where the bounds of the region function in equation (12) were set as: $q_{b1} = q_{c1} - 0.007$ mm when $q_1 \leq q_{c1}$ else $q_{b1} = q_{c1} + 0.007$ mm; $q_{b2} = q_{c2} - 0.007$ mm when $q_2 \leq q_{c2}$ else $q_{b2} = q_{c2} + 0.007$ mm. The size of the Cartesian-space region is less than one quarter of the corresponding size of FOV in Cartesian-space, and hence the desired position is always inside the FOV when $f_c(\mathbf{q}) \leq 0$. When $f_c(\mathbf{q}) > 0$, the Cartesian-space feedback is employed such that the laser is driven back to the Cartesian-space region.

Fig. 7. PID control: the laser moves directly to the desired position without first trapping the cell.

Fig. 8. PID control: the final desired position is not available when the problem of limited FOV occurs.

In the experiment, both the initial position of the cell (151, 159) pixel and the desired position (347, 475) pixel were inside the FOV. However, after the cell was trapped by the laser, the desired position was outside the limited FOV which was not available. Then, the Cartesian-space feedback was activated to drive the laser back to the Cartesian-space region. After the laser entered the Cartesian-space region, the desired position $\mathbf{x}_d$ also appeared within the FOV, and the visual feedback error was available and employed to ensure that the position of cell converges to the desired position. The parameters of $a(\mathbf{x}, \mathbf{p})$ were set as: $b=47$ pixel, and $\kappa=0.9$. The parameters of $w(\mathbf{q})$ were set as: $\mathbf{q}_c = [2.4603, 0.8813]^T$ mm, and $\kappa_w = 0.7$. The control parameters in equations (14) and (18) were set in Table II.

The path of the laser in Cartesian space was shown in Fig. 9(a), and the path of the cell in image space was shown in Fig. 9(b). It is seen that the laser first traps the cell and then moves from $f_c(\mathbf{q}) > 0$ to $f_c(\mathbf{q}) \leq 0$. After the desired position $\mathbf{x}_d$ is inside the FOV, the visual feedback error $\Delta\mathbf{x}$ is available and employed such that the position of the trapped

Fig. 9. Using the proposed controller, the cell is initially at (151, 159) pixel and manipulated to the desired position at (347, 475) pixel.

(a) $t=0$ s: The laser starts far away from the target cell. (b) $t=1$ s: The desired position is outside FOV. (c) $t=2$ s: The desired position is inside FOV again. (d) $t=3$ s: The cell reaches the desired position.

Fig. 10. Both the cell and the desired position are inside the FOV initially. However, after the cell is trapped by the laser, the desired position is outside the limited FOV. Using the proposed control method, the laser moves towards the Cartesian-space region. After it enters the region, the desired position appears within the FOV, thus the visual feedback error is also available, which ensures the convergence of the position error.

cell converges to the desired position. The position error of the cell is shown in Fig. 9(c), which converges to zero in about 3 s. The snapshots of the cell at different time instants are shown in Fig. 10(a)-10(d).

TABLE II
CONTROL PARAMETERS

K_p	K_s	K_q	α_x	α_r	L_q
$0.2I_2$	$I_2 \text{ kg} \cdot \text{mm/s}$	$0.2I_2 \text{ kg/s}^2$	$10/\text{s}$	$5 \times 10^{-7}/\text{s}$	$10^{-4}I_4$

Both $I_2 \in \mathbb{R}^{2 \times 2}$ and $I_4 \in \mathbb{R}^{4 \times 4}$ are identity matrices.

VI. CONCLUSIONS

In this paper, a robotic setpoint control technique has been proposed for cell manipulation using optical tweezers. The proposed controller allows the laser beam to automatically trap and manipulate the cell to the desired position, without any knowledge of the trapping stiffness. The proposed method works even in the presence of temporary loss of the feedback error in image space due to limited FOV. The proposed control scheme is based on the dynamic formulation where the position of laser beam is controlled by closed-loop techniques, and both the cell dynamics and the dynamics of the manipulator of laser source are taken into consideration for stability analysis. Experimental results have been presented to illustrate the performance of the proposed control scheme with unknown trapping stiffness and limited FOV.

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