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Dynamic Trapping and Manipulation of Biological Cells with Optical Tweezers[★]

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Abstract

Current control techniques for optical tweezers work only when the cell is located in a small neighbourhood around the centroid of the focused light beam. Therefore, the optical trapping fails when the cell is initially located far away from the laser beam or escapes from the optical trap during manipulation. In addition, the position of the laser beam is treated as the control input in existing optical tweezers systems and an open-loop controller is designed to move the laser source. In this paper, we propose a new robotic manipulation technique for optical tweezers that integrates automatic trapping and manipulation of biological cells into a single method. Instead of using open-loop control of the position of laser source as assumed in the literature, a closed-loop dynamic control method is formulated and solved in this paper. We provide a theoretical framework that bridges the gap between traditional robotic manipulation techniques and optical manipulation techniques of cells. The proposed controller allows the transition from trapping to manipulation without any hard switching from one controller to another. Simulation and experimental results are presented to illustrate the performance of the proposed controller.

Key words: Biomedical Systems; Optical Tweezers; Robotic Manipulators; Automatic Control Systems.

1 Introduction

The research and development of robotics and automation technology in past few decades has completely revolutionized the modern manufacturing industries. Rapid advances in biological sciences and nanotechnology have led to the requirement of robotics and automation at micro and nano scales, and thus open up new challenges to understanding robotic manipulation of cells or nanoparticles. Many research groups have developed micromanipulation techniques and systems for various tasks such as micropositioning [Ralis *et al.*, 2000], microinjection [Sun and Nelson, 2002; Xie *et al.*, 2010], and microgripping [Rakotondrabe and Ivan, 2011].

Among the diverse micromanipulators, optical tweezers [Ashkin *et al.*, 1986] 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. By using a highly focused laser beam, the optical tweezers are able to trap particles as diverse as atoms, molecules, bacteria, viruses and live cells [Ashkin, 2000], and hence the optical tweezers have been successfully applied in biological sciences and nanotechnology for realization of various manipulation tasks, such as the cell separation [Murata *et al.*, 2009], evaluation of nonsticky substrate coatings by moving live dissociated neurons [Pine and Chow, 2009], study of mechanical and structural properties of DNA [Chu, 1991; Rusu *et al.*, 2001], etc.

Due to the laborious work of cell manipulation, the manual operation with optical tweezers tends to induce the operator fatigue and thus the reduction of success rate. In addition, it also requires lengthy training and lacks reproducibility. Several automatic optical tweezers systems and control methods have developed to improve the efficiency. An automatic cell sorting system based on dual-beam trap was introduced in [Grover *et al.*, 2001], and an image-processing system using thresholding, background subtraction and edge-enhancement algorithms was developed for identification of single cells.

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With the multiple trapping technology based on the computer-generated holographic optical-tweezers arrays [Dufresne *et al.*, 2001], Arai *et al.* [Arai *et al.*, 2009] developed an automatic system to flock micro-scale particles. In [Ranaweera and Bamieh, 2005], 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 [Tanaka *et al.*, 2008], an automated optical trapping technique was developed based on computer vision and multiple-force optical clamps. In [Banerjee *et al.*, 2010], 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. In [Aguilar-Ibanez *et al.*, 2010], a simple feedback controller was proposed for the positioning of a microscopic particle. In [Hu and Sun, 2011], a PID controller and a synchronization control technology were proposed for cell transportation, based on a simplified dynamic model of the trapped cell.

One common assumption for the existing optical tweezers control systems is that the optical trapping is maintained throughout the entire manipulation process. Therefore, current control techniques for optical tweezers are only valid locally when the cell is in a small neighbourhood of the laser beam. The trapping fails when the laser beam starts from an initial position far away from the cell, or when the laser moves too fast to maintain the trapping. In principle, the hybrid control method can be employed to switch from one controller to another, but the hard-switching mechanism results in chattering and vibration.

In addition, in aforementioned optical tweezers systems, the cell dynamics is either simplified [Ranaweera and Bamieh, 2005; Aguilar-Ibanez *et al.*, 2010; Hu and Sun, 2011] or ignored [Grover *et al.*, 2001; Dufresne *et al.*, 2001; Tanaka *et al.*, 2008; Arai *et al.*, 2009; Banerjee *et al.*, 2010], and open-loop controllers are employed for laser source without the consideration of manipulator dynamics. Investigating the interaction between the robotic manipulator and the cell can help us gain understanding into the dynamic manipulation problem using optical tweezers.

In this paper, we propose a new robotic manipulation technique for optical tweezers that integrates automatic trapping and manipulation of biological cells into a single method. The contributions of the paper are listed as follows. First, unlike the existing methods that assume open-loop control of the position of laser source, the dynamics of robotic manipulator is introduced into optical tweezers system so that a closed-loop manipulator control problem can be formulated and solved. Second, this is the first result that allows the laser beam to start from an initial position that is far away from the cell and au-

tomatically trap then manipulate the cell, and it also works when the cell escapes from the optical trap during the course of manipulation. Third, we provide a theoretical framework that bridges the gap between traditional robotic manipulation techniques and optical manipulation techniques of cells. The stability of the closed-loop system is analyzed by using Lyapunov-like analysis, with the consideration of the dynamics of both the cell and the manipulator of the laser source. Both simulation and experimental results are presented to illustrate the performance of the proposed control methods.

The remainder of the paper is organized as follows. Section 2 presents the dynamics of cell and robotic manipulator. Section 3 is devoted to a dynamic trapping and manipulation control method. Section 4 develops adaptive observers for the optical tweezers system. Section 5 and Section 6 state the simulation and experiments to illustrate the performance of the proposed control method. Section 7 concludes the paper.

2 Dynamics of Cell and Robotic Manipulator

The basic principle of optical trap is based on the transfer of momentum from photons to microscopic objects, when a focused light travels 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 [Ashkin *et al.*, 1986]. 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.

Fig. 1. A typical optical tweezers system.

In this paper, the optical tweezers are employed to manipulate the biological cells. Both the position of the cell and the position of the laser beam are specified in the coordinate of camera frame Σ_C , and the offset between the laser beam and the cell 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.

The dynamic model of the biological cell is described by the following equation:

$$\mathbf{M}\ddot{\mathbf{x}} + \mathbf{B}\dot{\mathbf{x}} + k(\mathbf{x}, \mathbf{q})(\mathbf{x} - \mathbf{q}) = \mathbf{0}, \quad (1)$$

where $\mathbf{M} \in \mathbb{R}^{2 \times 2}$ denotes the inertia matrix, and $\mathbf{B} \in \mathbb{R}^{2 \times 2}$ represents the damping matrix, and $k(\mathbf{x}, \mathbf{q})$ denotes the stiffness, and $\mathbf{x} = [x_1, x_2]^T \in \mathbb{R}^2$ is the position of the cell, and $\mathbf{q} = [q_1, q_2]^T \in \mathbb{R}^2$ is the position of the laser. Both $\mathbf{M}$ and $\mathbf{B}$ are diagonal and positive definite, and the terms $\mathbf{M}\ddot{\mathbf{x}} + \mathbf{B}\dot{\mathbf{x}}$ in equation (1) is linear in a set of physical parameters $\boldsymbol{\theta}_d = [\theta_{d1}, \dots, \theta_{dn_d}]^T \in \mathbb{R}^{n_d}$ as:

$$\mathbf{M}\ddot{\mathbf{x}} + \mathbf{B}\dot{\mathbf{x}} = \mathbf{Y}_d(\dot{\mathbf{x}}, \ddot{\mathbf{x}})\boldsymbol{\theta}_d, \quad (2)$$

where $\mathbf{Y}_d(\dot{\mathbf{x}}, \ddot{\mathbf{x}}) \in \mathbb{R}^{2 \times n_d}$ is a dynamic regressor matrix, and n_d represents the dimension of the unknown physical parameters.

Fig. 2. (a) The trapping stiffness $k(\mathbf{x}, \mathbf{q})$; (b) The trapping force $\mathbf{F}_t$; (c) The optical trap.

In this paper, $k(\mathbf{x}, \mathbf{q})$ in equation (1) is specified as a function of offset between the position of cell and the center of laser beam, which can be described as:

$$k(\mathbf{x}, \mathbf{q}) = \begin{cases} k_c, & \|\mathbf{x} - \mathbf{q}\| \leq R, \\ k_c e^{-(\|\mathbf{x} - \mathbf{q}\| - R)^2}, & \|\mathbf{x} - \mathbf{q}\| > R, \end{cases} \quad (3)$$

where k_c are positive constants, and R denotes the trapping radius. The time-varying stiffness $k(\mathbf{x}, \mathbf{q})$ is illustrated in Fig. 2(a). From equation (3) and Fig. 2(a), note that if the cell is far away from the laser beam, then $k(\mathbf{x}, \mathbf{q}) \rightarrow 0$, thus there is no interaction between the cell and the laser beam. When the cell is very near the laser beam, $\mathbf{x} - \mathbf{q} \rightarrow \mathbf{0}$, $k(\mathbf{x}, \mathbf{q}) = k_c$, thus the cell can be trapped by the laser beam.

Based on the stiffness $k(\mathbf{x}, \mathbf{q})$ in equation (3), the trapping force is specified as:

$$\mathbf{F}_t = -k(\mathbf{x}, \mathbf{q})(\mathbf{x} - \mathbf{q}), \quad (4)$$

which is illustrated in Fig. 2(b). As seen from Fig. 2(b), the trapping force $\mathbf{F}_t$ is linear to the offset $\mathbf{x} - \mathbf{q}$ when the trapped cell is very near the center of the laser beam, and it reduces to zero when the cell is far away from the laser beam.

Therefore, the optical manipulation is consisted of two phases as illustrated in Fig. 3: (i) *trapping phase* - the laser beam moves towards the cell so as to trap it; (ii) *manipulation phase* - the trapped cell is manipulated to follow the desired trajectory. The control scheme for the optical tweezers should be able to smoothly transit between the *trapping phase* and the *manipulation phase* to avoid any chattering and vibration which are not desirable for micromanipulation.

Fig. 3. (i) The laser beam moves towards the cell to trap it; (ii) The trapped cell is manipulated to follow the desired trajectory.

The position of the laser beam $\mathbf{q}$ is treated as the control input in existing manipulation techniques and open-loop controllers are designed to move the laser source. In this paper, the variable $\mathbf{q}$ is set as the position of the laser beam with respect to the motorized stage, and it is varied by moving the motorized stage which thus acts as a robotic manipulator. Therefore, the position of laser beam $\mathbf{q}$ is controlled by closed-loop robotic manipulation techniques, and the dynamic model of the manipulator of the laser source is described as:

$$\mathbf{M}_q \ddot{\mathbf{q}} + \mathbf{B}_q \dot{\mathbf{q}} = \mathbf{u}, \quad (5)$$

where $\mathbf{M}_q \in \mathbb{R}^{2 \times 2}$ denotes the inertial matrix and $\mathbf{B}_q \in \mathbb{R}^{2 \times 2}$ represents the damping matrix, and $\mathbf{u} \in \mathbb{R}^2$ represents the control input for the manipulator. Both $\mathbf{M}_q$ and $\mathbf{B}_q$ are positive definite, and equation (5) is also linear in a set of physical parameters as:

$$\mathbf{M}_q \ddot{\mathbf{q}} + \mathbf{B}_q \dot{\mathbf{q}} = \mathbf{Y}_q(\dot{\mathbf{q}}, \ddot{\mathbf{q}})\boldsymbol{\theta}_q, \quad (6)$$

where $\mathbf{Y}_q(\dot{\mathbf{q}}, \ddot{\mathbf{q}}) \in \mathbb{R}^{2 \times n_q}$ is a dynamic regressor matrix, and $\boldsymbol{\theta}_q = [\theta_{q1}, \dots, \theta_{qn_q}]^T \in \mathbb{R}^{n_q}$ are a set of physical parameters, and n_q represents the dimension of the unknown physical parameters.

Remark 1: In current manipulation techniques using optical tweezers, the trapping force is modeled as a simple spring force with a constant stiffness so that equation (1) is simplified as:

$$M\ddot{\mathbf{x}} + B\dot{\mathbf{x}} + k_c(\mathbf{x} - \mathbf{q}) = \mathbf{0}. \quad (7)$$

The position of the laser beam $\mathbf{q}$ is then treated as the control input and traditional robot control techniques [Arimoto, 1996; Kelly, 1999; Cheah *et al.*, 2006; Cheah *et al.*, 2007; Dixon, 2007; Cheah *et al.*, 2010] can be used to design an open-loop controller (without the feedback of $\mathbf{q}$). Therefore, it is implicitly assumed in the literature that the cell is always located in a small neighbourhood around the center of the laser beam and hence the optical manipulation techniques fail when the cell is initially located far away from the laser beam or escapes from the optical trap during the course of manipulation.

Due to the time-varying stiffness of the trapping force described by equation (3) and the dynamic interaction between the robotic manipulator and trapped cell, the overall dynamics changes from a second order system to a fourth order system during the transition from trapping phase to manipulation phase and vice versa. Therefore, the optical trapping and manipulation problem of cell is a challenging control problem that cannot be tackled directly by the traditional robot control techniques.

△△△

3 Dynamic Cell Trapping and Manipulation

3.1 Trapping Region

It is known that the laser beam should be kept near the cell to maintain a stable trapping. To monitor the distance between the laser and the cell, a trapping region is introduced near the position of the cell as:

$$f(\mathbf{x}, \mathbf{q}) = \|\mathbf{x} - \mathbf{q}\|^n - b^n \leq 0, \quad (8)$$

where n is the order of the region function, which is an even integer, and b is a positive constant which is set so that $b < R$. If the position of the cell is outside the trapping region, $f(\mathbf{x}, \mathbf{q}) > 0$, and the laser should be moved towards the cell for trapping. If the cell is inside the trapping region, $f(\mathbf{x}, \mathbf{q}) \leq 0$, the cell is trapped by the laser, and the trapped cell can be transported along the desired trajectory. Therefore, the position of the laser is controlled to ensure that $f(\mathbf{x}, \mathbf{q}) \leq 0$ to maintain trapping.

Next, a reference region smaller than $f(\mathbf{x}, \mathbf{q})$ is introduced as:

$$f_r(\mathbf{x}, \mathbf{q}) = \|\mathbf{x} - \mathbf{q}\|^n - (\kappa b)^n \leq 0, \quad (9)$$

where $\kappa < 1$ is a positive constant. By using $f(\mathbf{x}, \mathbf{q})$ and $f_r(\mathbf{x}, \mathbf{q})$, an auxiliary factor $a(\mathbf{x}, \mathbf{q})$ is introduced as:

$$a(\mathbf{x}, \mathbf{q}) = \begin{cases} 1, & f_r(\mathbf{x}, \mathbf{q}) \leq 0, \\ 1 - \frac{\{[f(\mathbf{x}, \mathbf{q})]^N - [(\kappa b)^n - b^n]^N\}^N}{[(\kappa b)^n - b^n]^N}, & f(\mathbf{x}, \mathbf{q}) < 0, f_r(\mathbf{x}, \mathbf{q}) > 0, \\ 0, & f(\mathbf{x}, \mathbf{q}) \geq 0, \end{cases} \quad (10)$$

where $N \geq 6$ is an even integer, so that $a(\mathbf{x}, \mathbf{q}) \in C^3$. An illustration of $a(\mathbf{x}, \mathbf{q})$ is show in Fig. 4. From equation (10) and Fig. 4, the auxiliary factor $a(\mathbf{x}, \mathbf{q})$ smoothly increases from 0 to 1 when the cell transits from outside to inside the trapping region, and vice versa.

Fig. 4. An illustration of auxiliary factor $a(\mathbf{x}, \mathbf{q})$ with $\mathbf{q} = [0, 0]^T$, $b = 3 \mu m$, $n = 2$, $\kappa = 0.7$, and $N = 6$.

Remark 2: The gradient of the auxiliary factor $a(\mathbf{x}, \mathbf{q})$ can be varied by adjusting the parameter κ . △△△

3.2 Desired Position Input of Laser Beam

Using the trapping region and the auxiliary factor, a new dynamic control method for automatic trapping and manipulation is proposed. Firstly, based on the cell dynamics in equation (1), a desired position input of laser beam $\mathbf{q}_d$ is developed to ensure the convergence of the tracking error. Then based on the manipulator dynamics in equation (5), a backstepping procedure is used to derive a control input $\mathbf{u}$ for the robotic manipulator of the laser source to guarantee that the actual position input $\mathbf{q}$ tracks the desired position input $\mathbf{q}_d$.

Since the desired position is only required after the cell is trapped, the desired trajectory is specified as:

$$\mathbf{x}_d(t) = \mathbf{x}_c + a(\mathbf{x}, \mathbf{q})\mathbf{x}_v(t), \quad (11)$$

where $\mathbf{x}_c$ is the constant part, and $\mathbf{x}_v(t)$ is the time-varying part of the desired trajectory. When the cell is outside the trapping region, $a(\mathbf{x}, \mathbf{q}) = 0$ and $\dot{\mathbf{x}}_d = \mathbf{0}$. After the cell is trapped by the laser, $a(\mathbf{x}, \mathbf{q})$ smoothly increases to 1, and hence $\mathbf{x}_d(t) = \mathbf{x}_c + \mathbf{x}_v(t)$ which is the actual trajectory.

First, a sliding vector is introduced as:

$$\begin{aligned} \mathbf{s}_x &= \dot{\mathbf{x}} - \dot{\mathbf{x}}_r = (\dot{\mathbf{x}} - \dot{\mathbf{x}}_d) + \alpha_x \frac{a(\mathbf{x}, \mathbf{q})}{a^2(\mathbf{x}, \mathbf{q}) + \delta} (\mathbf{x} - \mathbf{x}_d) \\ &= \Delta \dot{\mathbf{x}} + \alpha_x \frac{a(\mathbf{x}, \mathbf{q})}{a^2(\mathbf{x}, \mathbf{q}) + \delta} \Delta \mathbf{x}, \end{aligned} \quad (12)$$

where $\Delta \mathbf{x} = \mathbf{x} - \mathbf{x}_d$, $\Delta \dot{\mathbf{x}} = \dot{\mathbf{x}} - \dot{\mathbf{x}}_d$, $\dot{\mathbf{x}}_r$ is a reference vector defined as $\dot{\mathbf{x}}_r = \dot{\mathbf{x}}_d - \alpha_x \frac{a(\mathbf{x}, \mathbf{q})}{a^2(\mathbf{x}, \mathbf{q}) + \delta} \Delta \mathbf{x}$, α_x is a positive constant, and δ is a very small positive constant. The role of δ is to ensure that the term $\frac{a(\mathbf{x}, \mathbf{q})}{a^2(\mathbf{x}, \mathbf{q}) + \delta}$ is not ill-defined when $a(\mathbf{x}, \mathbf{q}) = 0$.

By using the sliding vector $\mathbf{s}_x$, the cell dynamics described by equation (1) can be represented as:

$$\mathbf{M}\dot{\mathbf{s}}_x + \mathbf{B}\mathbf{s}_x + \mathbf{Y}_d(\dot{\mathbf{x}}_r, \ddot{\mathbf{x}}_r)\boldsymbol{\theta}_d + k(\mathbf{x}, \mathbf{q})(\mathbf{x} - \mathbf{q}) = \mathbf{0}. \quad (13)$$

Supposing the desired position input for the trapped cell is denoted as $\mathbf{q}_d$, then equation (13) can be written as:

$$\begin{aligned} \mathbf{M}\dot{\mathbf{s}}_x + \mathbf{B}\mathbf{s}_x + \mathbf{Y}_d(\dot{\mathbf{x}}_r, \ddot{\mathbf{x}}_r)\boldsymbol{\theta}_d + k(\mathbf{x}, \mathbf{q})\mathbf{x} \\ = k(\mathbf{x}, \mathbf{q})\Delta \mathbf{q} + k(\mathbf{x}, \mathbf{q})\mathbf{q}_d, \end{aligned} \quad (14)$$

where $\Delta \mathbf{q} = \mathbf{q} - \mathbf{q}_d$ represents an input perturbation to the cell dynamics. The system in equation (14) can be viewed as being controlled by the input $k(\mathbf{x}, \mathbf{q})\mathbf{q}_d$ with the perturbation $k(\mathbf{x}, \mathbf{q})\Delta \mathbf{q}$.

The desired position input is proposed as:

$$\begin{aligned} \mathbf{q}_d = \mathbf{x} - k^{-1}(\mathbf{x}, \mathbf{q})a(\mathbf{x}, \mathbf{q})\mathbf{K}_p\Delta \mathbf{x} \\ - k^{-1}(\mathbf{x}, \mathbf{q})a(\mathbf{x}, \mathbf{q})\mathbf{K}_d\mathbf{s}_x + k^{-1}(\mathbf{x}, \mathbf{q})\mathbf{Y}_d(\dot{\mathbf{x}}_r, \ddot{\mathbf{x}}_r)\hat{\boldsymbol{\theta}}_d, \end{aligned} \quad (15)$$

where $\mathbf{K}_p$ and $\mathbf{K}_d$ are diagonal and positive definite, and $\hat{\boldsymbol{\theta}}_d$ is the vector of uncertain dynamic parameters of cell, which is updated as follows:

$$\dot{\hat{\boldsymbol{\theta}}}_d = -\mathbf{L}_d\mathbf{Y}_d^T(\dot{\mathbf{x}}_r, \ddot{\mathbf{x}}_r)\mathbf{s}_x, \quad (16)$$

where $\mathbf{L}_d \in \mathbb{R}^{n_d \times n_d}$ is a positive definite matrix.

From the definition of trapping region $f(\mathbf{x}, \mathbf{q})$ described by equation (8) and the definition of auxiliary factor $a(\mathbf{x}, \mathbf{q})$ described by equation (10), it is clear that if the cell is outside the trapping region, $f(\mathbf{x}, \mathbf{q}) \geq 0$, $a(\mathbf{x}, \mathbf{q}) = 0$, and hence $\dot{\mathbf{x}}_d = \mathbf{0}$ from equation (11). In addition, $\dot{\mathbf{x}}_r$ and $\ddot{\mathbf{x}}_r$ are also equal to zero since $\dot{\mathbf{x}}_r = \dot{\mathbf{x}}_d - \alpha_x \frac{a(\mathbf{x}, \mathbf{q})}{a^2(\mathbf{x}, \mathbf{q}) + \delta} \Delta \mathbf{x}$. Therefore, the regressor matrix $\mathbf{Y}_d(\dot{\mathbf{x}}_r, \ddot{\mathbf{x}}_r)$ reduces to zero. From equation (15), the desired position input is specified as:

$$\mathbf{q}_d = \mathbf{x}. \quad (17)$$

That is, the desired position input is the position of the cell, and the laser beam is moved towards the cell. The desired position input described by equation (17) is called in *trapping phase*.

After the cell enters the trapping region, $a(\mathbf{x}, \mathbf{q}) = 1$, and the desired position input in equation (15) becomes:

$$\mathbf{q}_d = \mathbf{x} - k_c^{-1}\mathbf{K}_p\Delta \mathbf{x} - k_c^{-1}\mathbf{K}_d\mathbf{s}_x + k_c^{-1}\mathbf{Y}_d(\dot{\mathbf{x}}_r, \ddot{\mathbf{x}}_r)\hat{\boldsymbol{\theta}}_d, \quad (18)$$

and it drives the trapped cell towards the desired trajectory. The desired position input (18) is called in *manipulation phase*. In the case that the cell escapes from the trapping region, the auxiliary factor reduces to zero and the *trapping phase* is activated again. Therefore, the auxiliary factor $a(\mathbf{x}, \mathbf{q})$ varies with regard to the relative position between the laser source and the cell, and the desired position input in equation (15) can smoothly transit between the *trapping phase* and the *manipulation phase*. The proposed trapping and manipulation mechanism is illustrated in Fig. 5.

Fig. 5. Two phases of proposed controller.

Substituting the desired position input for the trapped cell (15) into equation (14), we have:

$$\begin{aligned} \mathbf{M}\dot{\mathbf{s}}_x + \mathbf{B}\mathbf{s}_x + a(\mathbf{x}, \mathbf{q})\mathbf{K}_p\Delta \mathbf{x} + a(\mathbf{x}, \mathbf{q})\mathbf{K}_d\mathbf{s}_x \\ + \mathbf{Y}_d(\dot{\mathbf{x}}_r, \ddot{\mathbf{x}}_r)\Delta \boldsymbol{\theta}_d = k(\mathbf{x}, \mathbf{q})\Delta \mathbf{q}, \end{aligned} \quad (19)$$

where $\Delta \boldsymbol{\theta}_d = \boldsymbol{\theta}_d - \hat{\boldsymbol{\theta}}_d$.

To analyze the stability of the closed-loop system of the cell, a Lyapunov-like candidate V_x is proposed as:

$$V_x = \frac{1}{2}\mathbf{s}_x^T\mathbf{M}\mathbf{s}_x + \frac{a(\mathbf{x}, \mathbf{q})}{2}\Delta \mathbf{x}^T\mathbf{K}_p\Delta \mathbf{x} + \frac{1}{2}\Delta \boldsymbol{\theta}_d^T\mathbf{L}_d^{-1}\Delta \boldsymbol{\theta}_d. \quad (20)$$

Differentiating V_x with respect to time, we have:

$$\begin{aligned} \dot{V}_x = \mathbf{s}_x^T\mathbf{M}\dot{\mathbf{s}}_x - \dot{\boldsymbol{\theta}}_d^T\mathbf{L}_d^{-1}\Delta \boldsymbol{\theta}_d + \frac{\dot{a}(\mathbf{x}, \mathbf{q})}{2}\Delta \mathbf{x}^T\mathbf{K}_p\Delta \mathbf{x} \\ + a(\mathbf{x}, \mathbf{q})(\dot{\mathbf{x}} - \dot{\mathbf{x}}_d)^T\mathbf{K}_p\Delta \mathbf{x}, \end{aligned} \quad (21)$$

and substituting equations (12), (16), and (19) into equation (21), we have:

$$\begin{aligned} \dot{V}_x = -\mathbf{s}_x^T[(\mathbf{B} + a(\mathbf{x}, \mathbf{q})\mathbf{K}_d)\mathbf{s}_x + a(\mathbf{x}, \mathbf{q})\mathbf{K}_p\Delta \mathbf{x} \\ - k(\mathbf{x}, \mathbf{q})\Delta \mathbf{q}] + \frac{\dot{a}(\mathbf{x}, \mathbf{q})}{2}\Delta \mathbf{x}^T\mathbf{K}_p\Delta \mathbf{x} \\ + a(\mathbf{x}, \mathbf{q})(\dot{\mathbf{x}} - \dot{\mathbf{x}}_d)^T\mathbf{K}_p\Delta \mathbf{x} \\ = -\mathbf{s}_x^T(\mathbf{B} + a(\mathbf{x}, \mathbf{q})\mathbf{K}_d)\mathbf{s}_x + \frac{\dot{a}(\mathbf{x}, \mathbf{q})}{2}\Delta \mathbf{x}^T\mathbf{K}_p\Delta \mathbf{x} \\ + k(\mathbf{x}, \mathbf{q})\mathbf{s}_x^T\Delta \mathbf{q} + a(\mathbf{x}, \mathbf{q})(\dot{\mathbf{x}} - \dot{\mathbf{x}}_d)^T\mathbf{K}_p\Delta \mathbf{x} \\ - a(\mathbf{x}, \mathbf{q})(\dot{\mathbf{x}} - \dot{\mathbf{x}}_d + \alpha_x \frac{a(\mathbf{x}, \mathbf{q})}{a^2(\mathbf{x}, \mathbf{q}) + \delta} \Delta \mathbf{x})^T\mathbf{K}_p\Delta \mathbf{x} \\ = -\mathbf{s}_x^T(\mathbf{B} + a(\mathbf{x}, \mathbf{q})\mathbf{K}_d)\mathbf{s}_x + k(\mathbf{x}, \mathbf{q})\mathbf{s}_x^T\Delta \mathbf{q} \\ - \Delta \mathbf{x}^T(\alpha_x \frac{a^2(\mathbf{x}, \mathbf{q})}{a^2(\mathbf{x}, \mathbf{q}) + \delta} \mathbf{K}_p - \frac{\dot{a}(\mathbf{x}, \mathbf{q})}{2} \mathbf{K}_p)\Delta \mathbf{x}. \end{aligned} \quad (22)$$

Since δ is very small, the bound of $\frac{\delta}{a^2(\mathbf{x}, \mathbf{q})}$ exists when $a(\mathbf{x}, \mathbf{q}) \neq 0$. In addition, since the derivative $\dot{a}(\mathbf{x}, \mathbf{q})$ is continuous and $\dot{a}(\mathbf{x}, \mathbf{q})=0$ where $f(\mathbf{x}, \mathbf{q}) \geq 0$ or $f_r(\mathbf{x}, \mathbf{q}) \leq 0$, $\dot{a}(\mathbf{x}, \mathbf{q})$ is bounded.

From equation (12), note that α_x is only employed when $a(\mathbf{x}, \mathbf{q}) \neq 0$. Therefore, the control parameter α_x can be chosen large enough so that

$$\alpha_x > \mathbf{b}_{max} \left[\frac{\dot{a}(\mathbf{x}, \mathbf{q})}{2} \left(1 + \frac{\delta}{a^2(\mathbf{x}, \mathbf{q})} \right) \right], \quad (23)$$

where $\mathbf{b}_{max} \left[\frac{\dot{a}(\mathbf{x}, \mathbf{q})}{2} \left(1 + \frac{\delta}{a^2(\mathbf{x}, \mathbf{q})} \right) \right]$ denotes the upper bound of $\frac{\dot{a}(\mathbf{x}, \mathbf{q})}{2} \left(1 + \frac{\delta}{a^2(\mathbf{x}, \mathbf{q})} \right)$. If the condition (23) is satisfied, $\alpha_x \frac{a^2(\mathbf{x}, \mathbf{q})}{a^2(\mathbf{x}, \mathbf{q}) + \delta} - \frac{\dot{a}(\mathbf{x}, \mathbf{q})}{2}$ in equation (22) is positive.

In the following lemma, we first consider the case when $\Delta \mathbf{q} = \mathbf{0}$ to show the convergence of the tracking errors, and we will propose a control input to ensure the convergence of $\Delta \mathbf{q} \rightarrow \mathbf{0}$ in the next section.

Lemma 1: *The desired position input of the laser beam in equation (15) and the update law in equation (16) for the closed-loop equation (19) guarantee the convergence of $\mathbf{x} \rightarrow \mathbf{x}_d$ and $\dot{\mathbf{x}} \rightarrow \dot{\mathbf{x}}_d$ as $t \rightarrow \infty$ if $\Delta \mathbf{q} = \mathbf{0}$, and the control parameter α_x is chosen to satisfy equation (23).*

Proof: Since $\Delta \mathbf{q} = \mathbf{0}$, we have $V_x > 0$ and $\dot{V}_x \leq 0$. Therefore, V_x is bounded, and $\mathbf{s}_x$, $\Delta \theta_d$ and $\Delta \mathbf{x}$ are bounded. The boundedness of $\mathbf{s}_x$ and $\Delta \mathbf{x}$ ensures the boundedness of $\Delta \dot{\mathbf{x}}$ from equation (12). Therefore, $\Delta \mathbf{x}$ is uniformly continuous. Since $\Delta \mathbf{x}$ is bounded, the reference vector $\dot{\mathbf{x}}_r$ is bounded. Since $\Delta \dot{\mathbf{x}}$ is bounded, $\ddot{\mathbf{x}}_r$ is bounded. From equation (19), since $\Delta \mathbf{q} = \mathbf{0}$, $\Delta \mathbf{x}$, $\mathbf{s}_x$, $\dot{\mathbf{x}}_r$, $\ddot{\mathbf{x}}_r$ and $\Delta \theta_d$ are all bounded, it is concluded that $\dot{\mathbf{s}}_x$ is bounded. Therefore, $\mathbf{s}_x$ is uniformly continuous. Moreover, from equation (22), it is easy to verify that $\Delta \mathbf{x}$, $\mathbf{s}_x \in L_2(0, +\infty)$. Then it follows [Spong and Vidyasagar, 1989, Arimoto, 1996] that $\Delta \mathbf{x} \rightarrow \mathbf{0}$ and $\mathbf{s}_x \rightarrow \mathbf{0}$.

If the cell is outside the trapping region, $f(\mathbf{x}, \mathbf{q}) > 0$, thus $a(\mathbf{x}, \mathbf{q}) = 0$, $\mathbf{q}_d = \mathbf{x}$, and the laser is moved towards the cell. When the cell enters the trapping region, $f(\mathbf{x}, \mathbf{q}) \leq 0$, and the trapping force drives the cell towards the centroid of the laser beam, and $a(\mathbf{x}, \mathbf{q})$ increases from 0 to 1. Therefore, the cell can be successfully trapped by the laser beam in the end, and $\Delta \mathbf{x} \rightarrow \mathbf{0}$ indicates that the trapped cell converges to the desired trajectory. That is, $\mathbf{x} \rightarrow \mathbf{x}_d$. From equation (12), $\mathbf{x} \rightarrow \mathbf{x}_d$, and $\mathbf{s}_x \rightarrow \mathbf{0}$ indicate that $\dot{\mathbf{x}} \rightarrow \dot{\mathbf{x}}_d$. $\triangle\triangle\triangle$

3.3 Control Input of Manipulator of Laser Beam

In the previous section, the desired position input for the trapped cell $\mathbf{q}_d$ is proposed, we can now proceed to

formulate a control input for the manipulator of the laser beam $\mathbf{u}$ which ensures the convergence of $\Delta \mathbf{q} \rightarrow \mathbf{0}$.

First, another sliding vector by using the desired position input is proposed as:

$$\mathbf{s}_q = \dot{\mathbf{q}} - \dot{\mathbf{q}}_r = \dot{\mathbf{q}} - \dot{\mathbf{q}}_d + \alpha_q \Delta \mathbf{q}, \quad (24)$$

where α_q is a positive constant, and $\dot{\mathbf{q}}_r$ is a reference vector defined as $\dot{\mathbf{q}}_r = \dot{\mathbf{q}}_d - \alpha_q \Delta \mathbf{q}$.

Next, the control input for the robotic manipulator of laser beam is proposed as:

$$\mathbf{u} = -\mathbf{K}_s \mathbf{s}_q - \mathbf{K}_q \Delta \mathbf{q} + \mathbf{Y}_q(\dot{\mathbf{q}}_r, \ddot{\mathbf{q}}_r) \hat{\boldsymbol{\theta}}_q, \quad (25)$$

where $\mathbf{K}_s$ and $\mathbf{K}_q$ are diagonal and positive definite matrices, and the estimated parameters $\hat{\boldsymbol{\theta}}_q$ are updated as:

$$\dot{\hat{\boldsymbol{\theta}}}_q = -\mathbf{L}_q \mathbf{Y}_q^T(\dot{\mathbf{q}}_r, \ddot{\mathbf{q}}_r) \mathbf{s}_q, \quad (26)$$

where $\mathbf{L}_q \in \mathbb{R}^{n_q \times n_q}$ is a positive definite matrix. Note that the desired position input $\mathbf{q}_d$ in equation (15) is continuous, and hence the control input $\mathbf{u}$ in equation (25) is also continuous without hard switching.

By using the sliding vector $\mathbf{s}_q$, the manipulator dynamics in equation (5) can be rewritten as:

$$\mathbf{M}_q \dot{\mathbf{s}}_q + \mathbf{B}_q \mathbf{s}_q + \mathbf{Y}_q(\dot{\mathbf{q}}_r, \ddot{\mathbf{q}}_r) \boldsymbol{\theta}_q = \mathbf{u}. \quad (27)$$

Substituting the control input (25) into equation (27), the closed-loop equation is given as:

$$\mathbf{M}_q \dot{\mathbf{s}}_q + (\mathbf{B}_q + \mathbf{K}_s) \mathbf{s}_q + \mathbf{K}_q \Delta \mathbf{q} + \mathbf{Y}_q(\dot{\mathbf{q}}_r, \ddot{\mathbf{q}}_r) \Delta \boldsymbol{\theta}_q = \mathbf{0}. \quad (28)$$

To prove the stability of the overall system, a Lyapunov-like candidate is proposed as:

$$\begin{aligned} V &= V_x + V_q \\ &= V_x + \frac{1}{2} \mathbf{s}_q^T \mathbf{M}_q \mathbf{s}_q + \frac{1}{2} \Delta \mathbf{q}^T \mathbf{K}_q \Delta \mathbf{q} + \frac{1}{2} \Delta \boldsymbol{\theta}_q^T \mathbf{L}_q^{-1} \Delta \boldsymbol{\theta}_q, \end{aligned} \quad (29)$$

where V_x is defined in equation (20).

Differentiating V with respect to time, we have:

$$\begin{aligned} \dot{V} &= \dot{V}_x + \dot{V}_q \\ &= \dot{V}_x + \mathbf{s}_q^T \mathbf{M}_q \dot{\mathbf{s}}_q + \Delta \mathbf{q}^T \mathbf{K}_q \Delta \dot{\mathbf{q}} - \dot{\hat{\boldsymbol{\theta}}}_q^T \mathbf{L}_q^{-1} \Delta \boldsymbol{\theta}_q. \end{aligned} \quad (30)$$

Substituting equations (22), (24), (26), and (28) into

equation (30), we have:

$$\begin{aligned}
\dot{V} &= \dot{V}_x + \Delta \mathbf{q}^T \mathbf{K}_q \Delta \dot{\mathbf{q}} - \dot{\hat{\boldsymbol{\theta}}}_q^T \mathbf{L}_q^{-1} \Delta \boldsymbol{\theta}_q \\
&- \mathbf{s}_q^T [(\mathbf{B}_q + \mathbf{K}_s) \mathbf{s}_q + \mathbf{K}_q \Delta \mathbf{q} + \mathbf{Y}_q(\dot{\mathbf{q}}_r, \ddot{\mathbf{q}}_r) \Delta \boldsymbol{\theta}_q] \\
&= \dot{V}_x + \Delta \mathbf{q}^T \mathbf{K}_q \Delta \dot{\mathbf{q}} - \mathbf{s}_q^T (\mathbf{B}_q + \mathbf{K}_s) \mathbf{s}_q - \mathbf{s}_q^T \mathbf{K}_q \Delta \mathbf{q} \\
&= -\Delta \mathbf{x}^T (\alpha_x \frac{a^2(\mathbf{x}, \mathbf{q})}{a^2(\mathbf{x}, \mathbf{q}) + \delta} \mathbf{K}_p - \frac{\dot{a}(\mathbf{x}, \mathbf{q})}{2} \mathbf{K}_p) \Delta \mathbf{x} \\
&\quad - \alpha_q \Delta \mathbf{q}^T \mathbf{K}_q \Delta \mathbf{q} + k(\mathbf{x}, \mathbf{q}) \mathbf{s}_x^T \Delta \mathbf{q} \\
&\quad - \mathbf{s}_q^T (\mathbf{B}_q + \mathbf{K}_s) \mathbf{s}_q - \mathbf{s}_x^T (\mathbf{B} + a(\mathbf{x}, \mathbf{q}) \mathbf{K}_d) \mathbf{s}_x \\
&= -\Delta \mathbf{x}^T (\alpha_x \frac{a^2(\mathbf{x}, \mathbf{q})}{a^2(\mathbf{x}, \mathbf{q}) + \delta} \mathbf{K}_p - \frac{\dot{a}(\mathbf{x}, \mathbf{q})}{2} \mathbf{K}_p) \Delta \mathbf{x} \\
&\quad - \mathbf{s}_q^T (\mathbf{B}_q + \mathbf{K}_s) \mathbf{s}_q - \left[\mathbf{s}_x^T \Delta \mathbf{q}^T \right] \mathbf{Q} \left[\mathbf{s}_x^T \Delta \mathbf{q}^T \right]^T, \quad (31)
\end{aligned}$$

where $\mathbf{Q} = \begin{bmatrix} \mathbf{B} + a(\mathbf{x}, \mathbf{q}) \mathbf{K}_d - \frac{k(\mathbf{x}, \mathbf{q})}{2} \mathbf{I}_2 \\ -\frac{k(\mathbf{x}, \mathbf{q})}{2} \mathbf{I}_2 & \alpha_q \mathbf{K}_q \end{bmatrix}$, and $\mathbf{I}_2 \in \mathbb{R}^{2 \times 2}$

is an identity matrix. Note that $k(\mathbf{x}, \mathbf{q}) \leq k_c$. Therefore, if we choose the controller parameters α_q and $\mathbf{K}_q$ sufficiently large so that

$$\alpha_q \lambda_{\min}[\mathbf{K}_q \mathbf{B}] > \frac{k_c^2}{4}, \quad (32)$$

then the matrix $\mathbf{Q}$ is positive definite. The notation $\lambda_{\min}[\cdot]$ denotes the minimum eigenvalue of the matrix.

We can now state the following theorem:

Theorem 1: *If the manipulator control input $\mathbf{u}$ given by equations (25), (26), (15) and (16) is applied to the robot-assisted optical tweezers system described by (1), (5), then the closed-loop system gives rise to the convergence of $\mathbf{x} \rightarrow \mathbf{x}_d$, $\dot{\mathbf{x}} \rightarrow \dot{\mathbf{x}}_d$ and $\mathbf{q} \rightarrow \mathbf{q}_d$ as $t \rightarrow \infty$ when the control parameters α_x , α_q and $\mathbf{K}_q$ are chosen to satisfy conditions (23) and (32).*

Proof: If equations (23) and (32) are satisfied, we have $V > 0$ and $\dot{V} \leq 0$. Therefore, V is bounded, and $\mathbf{s}_x$, $\Delta \boldsymbol{\theta}_d$, $\Delta \mathbf{x}$, $\mathbf{s}_q$, $\Delta \mathbf{q}$ and $\Delta \boldsymbol{\theta}_q$ are all bounded. The boundedness of $\mathbf{s}_q$ and $\Delta \mathbf{q}$ ensures the boundedness of $\Delta \dot{\mathbf{q}}$ from equation (24). Therefore, $\Delta \mathbf{q}$ is uniformly continuous. From equation (31), it is easy to verify that $\Delta \mathbf{q} \in L_2(0, +\infty)$. Then it follows [Spong and Vidyasagar, 1989, Arimoto, 1996] that $\Delta \mathbf{q} \rightarrow \mathbf{0}$ and thus $\mathbf{x} \rightarrow \mathbf{x}_d$ and $\dot{\mathbf{x}} \rightarrow \dot{\mathbf{x}}_d$. $\triangle \triangle \triangle$

Remark 3: The manipulator of the laser source can also be extended to a general manipulator. In this case, let $\mathbf{q} \in \mathbb{R}^m$ denote a vector of joint angles of the manipulator, and the dynamic model of the manipulator is specified as follows [Arimoto, 1996]:

$$\mathbf{M}_q(\mathbf{q}) \ddot{\mathbf{q}} + \mathbf{C}_q(\mathbf{q}, \dot{\mathbf{q}}) \dot{\mathbf{q}} + \mathbf{g}(\mathbf{q}) = \mathbf{u}, \quad (33)$$

where $\mathbf{M}_q(\mathbf{q})$ is the inertial matrix, $\mathbf{C}_q(\mathbf{q}, \dot{\mathbf{q}}) \dot{\mathbf{q}}$ includes centripetal and Coriolis forces, and $\mathbf{g}(\mathbf{q})$ represents the gravitational force. The matrix $\mathbf{M}_q(\mathbf{q})$ is positive definite, the matrix $\frac{1}{2} \dot{\mathbf{M}}_q(\mathbf{q}) - \mathbf{C}_q(\mathbf{q}, \dot{\mathbf{q}})$ is skew symmetric, and equation (33) can be parameterized as: $\mathbf{M}_q(\mathbf{q}) \ddot{\mathbf{q}} + \mathbf{C}_q(\mathbf{q}, \dot{\mathbf{q}}) \dot{\mathbf{q}} + \mathbf{g}(\mathbf{q}) = \mathbf{Y}_c(\mathbf{q}, \dot{\mathbf{q}}, \ddot{\mathbf{q}}) \boldsymbol{\theta}_c$ where $\mathbf{Y}_c(\mathbf{q}, \dot{\mathbf{q}}, \ddot{\mathbf{q}})$ is a known regressor matrix, and $\boldsymbol{\theta}_c$ represents a set of dynamic parameters. The velocity of the robot end effector in image space is related to the joint velocity as follows [Cheah *et al.*, 2006, Cheah *et al.*, 2010]:

$$\dot{\mathbf{p}} = \mathbf{J}(\mathbf{q}) \dot{\mathbf{q}}, \quad (34)$$

where $\mathbf{p} = [p_1, p_2]^T \in \mathbb{R}^2$ denotes the position of end effector in image space, and $\mathbf{J}(\mathbf{q}) \in \mathbb{R}^{2 \times m}$ is the Jacobian matrix. The end effector is controlled to manipulate the laser source.

Next, the dynamic model of the cell is stated as:

$$\begin{aligned}
\mathbf{M} \ddot{\mathbf{x}} + \mathbf{B} \dot{\mathbf{x}} + k(\mathbf{x}, \mathbf{p}) \mathbf{x} &= k(\mathbf{x}, \mathbf{p}) \mathbf{p} \\
&= k(\mathbf{x}, \mathbf{p}) \Delta \mathbf{p} + k(\mathbf{x}, \mathbf{p}) \mathbf{p}_d, \quad (35)
\end{aligned}$$

where $k(\mathbf{x}, \mathbf{p})$ denotes the stiffness, $\Delta \mathbf{p} = \mathbf{p} - \mathbf{p}_d$, and $\mathbf{p}_d$ is the desired position input of the laser beam.

In this case, the desired position input is proposed as:

$$\begin{aligned}
\mathbf{p}_d &= \mathbf{x} - k^{-1}(\mathbf{x}, \mathbf{p}) a(\mathbf{x}, \mathbf{p}) \mathbf{K}_p \Delta \mathbf{x} - k^{-1}(\mathbf{x}, \mathbf{p}) \\
&\quad \times a(\mathbf{x}, \mathbf{p}) \mathbf{K}_d \mathbf{s}_x + k^{-1}(\mathbf{x}, \mathbf{p}) \mathbf{Y}_d(\dot{\mathbf{x}}_r, \ddot{\mathbf{x}}_r) \hat{\boldsymbol{\theta}}_d, \quad (36)
\end{aligned}$$

where $a(\mathbf{x}, \mathbf{p})$ denotes the auxiliary factor. The closed-loop equation for the cell is obtained as: $\mathbf{M} \dot{\mathbf{s}}_x + \mathbf{B} \mathbf{s}_x + a(\mathbf{x}, \mathbf{p}) \mathbf{K}_p \Delta \mathbf{x} + a(\mathbf{x}, \mathbf{p}) \mathbf{K}_d \mathbf{s}_x + \mathbf{Y}_d(\dot{\mathbf{x}}_r, \ddot{\mathbf{x}}_r) \Delta \boldsymbol{\theta}_d = k(\mathbf{x}, \mathbf{p}) \Delta \mathbf{p}$.

Next, the control input for the manipulator of the laser beam is proposed as:

$$\mathbf{u} = -\mathbf{K}_s \mathbf{s}_c - \mathbf{J}^T(\mathbf{q}) \mathbf{K}_q \Delta \mathbf{p} + \mathbf{Y}_c(\mathbf{q}, \dot{\mathbf{q}}, \ddot{\mathbf{q}}_{cr}) \hat{\boldsymbol{\theta}}_c, \quad (37)$$

and $\mathbf{s}_c = \dot{\mathbf{q}} - \dot{\mathbf{q}}_{cr} = \dot{\mathbf{q}} - \mathbf{J}^+(\mathbf{q}) \dot{\mathbf{p}}_d + \alpha_q \mathbf{J}^+(\mathbf{q}) \Delta \mathbf{p}$ where $\mathbf{J}^+(\mathbf{q})$ is the pseudo-inverse of $\mathbf{J}(\mathbf{q})$, and $\hat{\boldsymbol{\theta}}_c$ are updated by $\dot{\hat{\boldsymbol{\theta}}}_c = -\mathbf{L}_q \mathbf{Y}_c^T(\mathbf{q}, \dot{\mathbf{q}}, \ddot{\mathbf{q}}_{cr}) \mathbf{s}_c$. Substituting the control input into the robot dynamic equation, the closed-loop equation is obtained as: $\mathbf{M}_q(\mathbf{q}) \dot{\mathbf{s}}_c + (\mathbf{C}_q(\mathbf{q}, \dot{\mathbf{q}}) + \mathbf{K}_s) \mathbf{s}_c + \mathbf{J}^T(\mathbf{q}) \mathbf{K}_q \Delta \mathbf{p} + \mathbf{Y}_c(\mathbf{q}, \dot{\mathbf{q}}, \ddot{\mathbf{q}}_{cr}) \Delta \boldsymbol{\theta}_c = \mathbf{0}$.

To prove the stability, a Lyapunov-like candidate is proposed as: $V_c = V_x + \frac{1}{2} \mathbf{s}_c^T \mathbf{M}_q(\mathbf{q}) \mathbf{s}_c + \frac{1}{2} \Delta \mathbf{p}^T \mathbf{K}_q \Delta \mathbf{p} + \frac{1}{2} \Delta \boldsymbol{\theta}_c^T \mathbf{L}_q^{-1} \Delta \boldsymbol{\theta}_c$, where V_x is defined in equation (20). Differentiating V_c with respect to time and substituting the closed-loop equation and the update law into it, we have: $\dot{V}_c = -\Delta \mathbf{x}^T (\alpha_x \frac{a^2(\mathbf{x}, \mathbf{p})}{a^2(\mathbf{x}, \mathbf{p}) + \delta} \mathbf{K}_p - \frac{\dot{a}(\mathbf{x}, \mathbf{p})}{2} \mathbf{K}_p) \Delta \mathbf{x} - \mathbf{s}_c^T \mathbf{K}_s \mathbf{s}_c - \left[\mathbf{s}_x^T \Delta \mathbf{p}^T \right] \mathbf{Q} \left[\mathbf{s}_x^T \Delta \mathbf{p}^T \right]^T$. Therefore, if the

controller parameters α_x , α_q and $\mathbf{K}_q$ are chosen sufficiently large to satisfy equations (23) and (32), $\dot{V}_c \leq 0$. Since $V_c > 0$ and $\dot{V}_c \leq 0$, it can be proved similarly that the closed-loop system gives rise to the convergence of the tracking errors. $\triangle\triangle\triangle$

Remark 4: When the viscous friction force and the disturbance is taken into consideration, the robot dynamic model is specified as:

$$\mathbf{M}_q(\mathbf{q})\ddot{\mathbf{q}} + \mathbf{C}_q(\mathbf{q}, \dot{\mathbf{q}})\dot{\mathbf{q}} + \mathbf{B}_q\dot{\mathbf{q}} + \mathbf{g}(\mathbf{q}) = \mathbf{u} + \mathbf{d}, \quad (38)$$

where $\mathbf{B}_q\dot{\mathbf{q}}$ represents the viscous friction force, and $\mathbf{d}$ represents the disturbance force. The dynamic model in equation (38) can also be parameterized as: $\mathbf{M}_q(\mathbf{q})\ddot{\mathbf{q}} + \mathbf{C}_q(\mathbf{q}, \dot{\mathbf{q}})\dot{\mathbf{q}} + \mathbf{B}_q\dot{\mathbf{q}} + \mathbf{g}(\mathbf{q}) = \mathbf{Y}_f(\mathbf{q}, \dot{\mathbf{q}}, \ddot{\mathbf{q}})\boldsymbol{\theta}_f$, where $\mathbf{Y}_f(\mathbf{q}, \dot{\mathbf{q}}, \ddot{\mathbf{q}})$ is a known regressor matrix, and $\boldsymbol{\theta}_f$ represents a set of dynamic parameters.

In this case, the control input for the manipulator of the laser beam is proposed as:

$$\mathbf{u} = -\mathbf{K}_s \mathbf{s}_c - \mathbf{J}^T(\mathbf{q})\mathbf{K}_q \Delta \mathbf{p} + \mathbf{Y}_f(\mathbf{q}, \dot{\mathbf{q}}, \ddot{\mathbf{q}}_{cr})\hat{\boldsymbol{\theta}}_f, \quad (39)$$

where $\hat{\boldsymbol{\theta}}_f$ are updated by $\dot{\hat{\boldsymbol{\theta}}}_f = -\mathbf{L}_q \mathbf{Y}_f^T(\mathbf{q}, \dot{\mathbf{q}}, \ddot{\mathbf{q}}_{cr})\mathbf{s}_c$. Substituting $\mathbf{u}$ into equation (38), the closed-loop equation is obtained as: $\mathbf{M}_q(\mathbf{q})\dot{\mathbf{s}}_c + (\mathbf{C}_q(\mathbf{q}, \dot{\mathbf{q}}) + \mathbf{K}_s)\mathbf{s}_c + \mathbf{J}^T(\mathbf{q})\mathbf{K}_q \Delta \mathbf{p} + \mathbf{Y}_f(\mathbf{q}, \dot{\mathbf{q}}, \ddot{\mathbf{q}}_{cr})\Delta \boldsymbol{\theta}_f = \mathbf{d}$.

The disturbance force $\mathbf{d}$ in the closed-loop equation can be attenuated with the H_∞ tuning [Cheah *et al.*, 2001]. If $\mathbf{K}_s$ is chosen sufficiently large so that $2\lambda_{min}[\mathbf{K}_s] - 1 > 0$, the following H_∞ tuning can be established for disturbance attenuation as:

$$\int_0^t \|\mathbf{s}_c(\varsigma)\|^2 d\varsigma \leq \gamma^2 \int_0^t \|\mathbf{d}(\varsigma)\|^2 d\varsigma + \gamma^2 \mu, \quad (40)$$

where μ is a positive constant depending on initial conditions of the state variables, and $\frac{1}{\gamma^2} \triangleq 2\lambda_{min}[\mathbf{K}_s] - 1$.

Thus viscous frictions can be compensated by expressing the dynamic model in the form of regressor, and bounded disturbances or uncompensated bounded frictions can be attenuated. It has been shown in [Arimoto, 1996] that Coulomb's frictions can also be compensated by expressing them in the form of regressor (see section 7.7), but the proof is more sophisticated. $\triangle\triangle\triangle$

4 Adaptive Observers for Optical Tweezers

In the previous section, the concept of the dynamic trapping and manipulation is demonstrated. However, since the overall dynamics of the manipulator interacting with the cell described by equations (1) and (5) is a fourth-order dynamics, the acceleration information and its

derivatives are required in the proposed control method in equations (15) and (25). In this section, a set of adaptive observers are introduced to avoid the use of the acceleration and its derivatives due to the fourth-order dynamics.

4.1 Desired Position Input of Laser Beam

To eliminate the requirement of the acceleration and its derivatives in the desired position input, observed signals $\hat{\mathbf{x}}$ and $\hat{\mathbf{q}}$ instead of the actual position information $\mathbf{x}$ and $\mathbf{q}$ are employed to construct the auxiliary factor. First, the observer dynamics for $\hat{\mathbf{x}}$ is given as:

$$\begin{cases} \dot{\hat{\mathbf{x}}} = \boldsymbol{\eta}_x + \beta_x \mathbf{e}_x \\ \dot{\boldsymbol{\eta}}_x = \hat{\mathbf{M}}_o^{-1}[-k(\mathbf{x}, \mathbf{q})(\mathbf{x} - \mathbf{q}) - \hat{\mathbf{B}}_o \boldsymbol{\eta}_x + \mathbf{K}_x \mathbf{e}_x], \end{cases} \quad (41)$$

where $\mathbf{e}_x = \mathbf{x} - \hat{\mathbf{x}}$ is the observation error, and $\boldsymbol{\eta}_x$ is an auxiliary variable, and β_x is a positive constant and $\mathbf{K}_x$ is a positive definite matrix. The matrices $\hat{\mathbf{M}}_o$ and $\hat{\mathbf{B}}_o$ are the approximate models for $\mathbf{M}$ and $\mathbf{B}$ respectively, which are updated through the update laws:

$$\begin{aligned} \dot{\hat{\boldsymbol{\theta}}}_{M_o} &= -\mathbf{L}_{M_o} \mathbf{N}_{M_o}(\dot{\boldsymbol{\eta}}_x) \mathbf{z}_x, \\ \dot{\hat{\boldsymbol{\theta}}}_{B_o} &= -\mathbf{L}_{B_o} \mathbf{N}_{B_o}(\boldsymbol{\eta}_x) \mathbf{z}_x, \end{aligned} \quad (42)$$

where $\mathbf{z}_x = \dot{\mathbf{x}} - \boldsymbol{\eta}_x$, and $\hat{\boldsymbol{\theta}}_{M_o}$ and $\hat{\boldsymbol{\theta}}_{B_o}$ are the vectors of estimated parameters, and $\mathbf{L}_{M_o}$ and $\mathbf{L}_{B_o}$ are positive definite matrices, and $\mathbf{N}_{M_o}(\dot{\boldsymbol{\eta}}_x) = \text{diag}\{\dot{\eta}_{x1}, \dot{\eta}_{x2}\}$ and $\mathbf{N}_{B_o}(\boldsymbol{\eta}_x) = \text{diag}\{\eta_{x1}, \eta_{x2}\}$.

Similarly, the observer dynamics for $\hat{\mathbf{q}}$ is given as:

$$\begin{cases} \dot{\hat{\mathbf{q}}} = \boldsymbol{\eta}_q + \beta_q \mathbf{e}_q \\ \dot{\boldsymbol{\eta}}_q = \hat{\mathbf{M}}_{qo}^{-1}(\mathbf{u} - \hat{\mathbf{B}}_{qo} \boldsymbol{\eta}_q + \mathbf{K}_z \mathbf{e}_q), \end{cases} \quad (43)$$

where $\mathbf{e}_q = \mathbf{q} - \hat{\mathbf{q}}$ is the observation error, and $\boldsymbol{\eta}_q$ is an auxiliary variable, and β_q is a positive constant, and $\mathbf{K}_z$ is a positive definite matrix. The matrices $\hat{\mathbf{M}}_{qo}$ and $\hat{\mathbf{B}}_{qo}$ are the approximate models for $\mathbf{M}_q$ and $\mathbf{B}_q$ respectively, which are updated as follows:

$$\begin{aligned} \dot{\hat{\boldsymbol{\theta}}}_{M_{qo}} &= -\mathbf{L}_{M_{qo}} \mathbf{N}_{M_{qo}}(\dot{\boldsymbol{\eta}}_q) \mathbf{z}_q, \\ \dot{\hat{\boldsymbol{\theta}}}_{B_{qo}} &= -\mathbf{L}_{B_{qo}} \mathbf{N}_{B_{qo}}(\boldsymbol{\eta}_q) \mathbf{z}_q, \end{aligned} \quad (44)$$

where $\mathbf{z}_q = \dot{\mathbf{q}} - \boldsymbol{\eta}_q$, and $\hat{\boldsymbol{\theta}}_{M_{qo}}$ and $\hat{\boldsymbol{\theta}}_{B_{qo}}$ are the vectors of estimated parameters, and $\mathbf{L}_{M_{qo}}$ and $\mathbf{L}_{B_{qo}}$ are positive definite matrices, and the matrices $\mathbf{N}_{M_{qo}}(\dot{\boldsymbol{\eta}}_q) = \text{diag}\{\dot{\eta}_{q1}, \dot{\eta}_{q2}\}$ and $\mathbf{N}_{B_{qo}}(\boldsymbol{\eta}_q) = \text{diag}\{\eta_{q1}, \eta_{q2}\}$.

Using the observed signals $\hat{\mathbf{x}}$ and $\hat{\mathbf{q}}$, a new desired trajectory is defined as:

$$\hat{\mathbf{x}}_d(t) = \mathbf{x}_c + \hat{\mathbf{a}}(\hat{\mathbf{x}}, \hat{\mathbf{q}}) \mathbf{x}_v(t), \quad (45)$$

where $\hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}})$ is the approximate auxiliary factor of $a(\mathbf{x}, \mathbf{q})$. The difference is that the estimated cell position $\hat{\mathbf{x}}$ and the estimated laser position $\hat{\mathbf{q}}$ is employed in $\hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}})$ instead of the actual positions $\mathbf{x}$ and $\mathbf{q}$.

Next, a new sliding vector $\hat{\mathbf{s}}_x$ is defined as:

$$\hat{\mathbf{s}}_x = \dot{\mathbf{x}} - \dot{\hat{\mathbf{x}}}_r = \dot{\mathbf{x}} - (\dot{\hat{\mathbf{x}}}_d - \alpha_x \frac{\hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}})}{\hat{a}^2(\hat{\mathbf{x}}, \hat{\mathbf{q}}) + \delta} \Delta \hat{\mathbf{x}}), \quad (46)$$

where $\Delta \hat{\mathbf{x}} = \mathbf{x} - \hat{\mathbf{x}}_d$, and $\dot{\hat{\mathbf{x}}}_r = \dot{\hat{\mathbf{x}}}_d - \alpha_x \frac{\hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}})}{\hat{a}^2(\hat{\mathbf{x}}, \hat{\mathbf{q}}) + \delta} \Delta \hat{\mathbf{x}}$ is a reference vector.

A new estimated desired position input for the laser beam by using $\hat{\mathbf{x}}$ and $\hat{\mathbf{q}}$ is proposed as:

$$\begin{aligned} \bar{\mathbf{q}}_d &= \mathbf{x} - k^{-1}(\mathbf{x}, \mathbf{q}) \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}}) \mathbf{K}_p \Delta \hat{\mathbf{x}} \\ &- k^{-1}(\mathbf{x}, \mathbf{q}) \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}}) \mathbf{K}_d \hat{\mathbf{s}}_x + k^{-1}(\mathbf{x}, \mathbf{q}) \mathbf{Y}_d(\dot{\hat{\mathbf{x}}}_r, \ddot{\hat{\mathbf{x}}}_r) \hat{\boldsymbol{\theta}}_d, \end{aligned} \quad (47)$$

where the uncertain parameters $\hat{\boldsymbol{\theta}}_d$ are updated as:

$$\dot{\hat{\boldsymbol{\theta}}}_d = -\mathbf{L}_d \mathbf{Y}_d^T(\dot{\hat{\mathbf{x}}}_r, \ddot{\hat{\mathbf{x}}}_r) \hat{\mathbf{s}}_x. \quad (48)$$

Substituting equation (47) into equation (1) and using the sliding vector $\hat{\mathbf{s}}_x$, we have:

$$\begin{aligned} \mathbf{M} \dot{\hat{\mathbf{s}}}_x + \mathbf{B} \hat{\mathbf{s}}_x + \mathbf{Y}_d(\dot{\hat{\mathbf{x}}}_r, \ddot{\hat{\mathbf{x}}}_r) \Delta \boldsymbol{\theta}_d + \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}}) \mathbf{K}_p \Delta \hat{\mathbf{x}} \\ + \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}}) \mathbf{K}_d \hat{\mathbf{s}}_x = k(\mathbf{x}, \mathbf{q}) \Delta \bar{\mathbf{q}}, \end{aligned} \quad (49)$$

where $\Delta \bar{\mathbf{q}} = \mathbf{q} - \bar{\mathbf{q}}_d$.

Next, the closed-loop observer dynamics is to be developed. Multiplying both sides of equation (41) with $\hat{\mathbf{M}}_o$ and using equation (1), we can get the closed-loop observer dynamics for $\hat{\mathbf{x}}$ as:

$$\begin{aligned} \mathbf{M} \dot{\hat{\mathbf{z}}}_x + \mathbf{B} \hat{\mathbf{z}}_x + \mathbf{K}_x \mathbf{e}_x &= (\hat{\mathbf{M}}_o - \mathbf{M}) \dot{\hat{\mathbf{\eta}}}_x + (\hat{\mathbf{B}}_o - \mathbf{B}) \hat{\boldsymbol{\eta}}_x \\ &= -\mathbf{N}_{M_o}(\dot{\hat{\mathbf{\eta}}}_x) \Delta \boldsymbol{\theta}_{M_o} - \mathbf{N}_{B_o}(\hat{\boldsymbol{\eta}}_x) \Delta \boldsymbol{\theta}_{B_o}, \end{aligned} \quad (50)$$

where $\Delta \boldsymbol{\theta}_{M_o} = \boldsymbol{\theta}_{M_o} - \hat{\boldsymbol{\theta}}_{M_o}$ and $\Delta \boldsymbol{\theta}_{B_o} = \boldsymbol{\theta}_{B_o} - \hat{\boldsymbol{\theta}}_{B_o}$. Similarly, multiplying both sides of equation (43) with $\hat{\mathbf{M}}_{qo}$ and using equation (5), we can get the closed-loop observer dynamics for $\hat{\mathbf{q}}$ as:

$$\begin{aligned} \mathbf{M}_q \dot{\hat{\mathbf{z}}}_q + \mathbf{B}_q \hat{\mathbf{z}}_q + \mathbf{K}_z \mathbf{e}_q &= (\hat{\mathbf{M}}_{qo} - \mathbf{M}_q) \dot{\hat{\mathbf{\eta}}}_q + (\hat{\mathbf{B}}_{qo} - \mathbf{B}_q) \hat{\boldsymbol{\eta}}_q \\ &= -\mathbf{N}_{M_{qo}}(\dot{\hat{\mathbf{\eta}}}_q) \Delta \boldsymbol{\theta}_{M_{qo}} - \mathbf{N}_{B_{qo}}(\hat{\boldsymbol{\eta}}_q) \Delta \boldsymbol{\theta}_{B_{qo}}, \end{aligned} \quad (51)$$

where $\Delta \boldsymbol{\theta}_{M_{qo}} = \boldsymbol{\theta}_{M_{qo}} - \hat{\boldsymbol{\theta}}_{M_{qo}}$ and $\Delta \boldsymbol{\theta}_{B_{qo}} = \boldsymbol{\theta}_{B_{qo}} - \hat{\boldsymbol{\theta}}_{B_{qo}}$.

4.2 Control Input of Manipulator of Laser Beam

To avoid the use of the acceleration and its derivatives in the control input for the manipulator of the laser beam,

another observed signal $\hat{\mathbf{q}}_d$ is employed instead of the actual desired position input $\mathbf{q}_d$. Therefore, equation (49) can be rewritten as:

$$\begin{aligned} \mathbf{M} \dot{\hat{\mathbf{s}}}_x + \mathbf{B} \hat{\mathbf{s}}_x + \mathbf{Y}_d(\dot{\hat{\mathbf{x}}}_r, \ddot{\hat{\mathbf{x}}}_r) \Delta \boldsymbol{\theta}_d + \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}}) \mathbf{K}_p \Delta \hat{\mathbf{x}} \\ + \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}}) \mathbf{K}_d \hat{\mathbf{s}}_x \\ = k(\mathbf{x}, \mathbf{q}) [\mathbf{q} - \hat{\mathbf{q}}_d - (\bar{\mathbf{q}}_d - \hat{\mathbf{q}}_d)] = k(\mathbf{x}, \mathbf{q}) (\Delta \hat{\mathbf{q}} - \mathbf{e}). \end{aligned} \quad (52)$$

where $\Delta \hat{\mathbf{q}} = \mathbf{q} - \hat{\mathbf{q}}_d$, and $\mathbf{e} = \bar{\mathbf{q}}_d - \hat{\mathbf{q}}_d$.

The estimated desired position input is updated by the following observer as:

$$\begin{cases} \dot{\hat{\mathbf{q}}}_d = \boldsymbol{\eta} + \beta \mathbf{e} \\ \dot{\hat{\boldsymbol{\eta}}} = \hat{\mathbf{M}}_{do}^{-1} (\mathbf{u} - \hat{\mathbf{B}}_{do} \boldsymbol{\eta} + \mathbf{K}_e \mathbf{e}), \end{cases} \quad (53)$$

where $\boldsymbol{\eta}$ is an auxiliary variable, and β is a positive constant. The matrices $\hat{\mathbf{M}}_{do}$ and $\hat{\mathbf{B}}_{do}$ are the approximate models for $\mathbf{M}_q$ and $\mathbf{B}_q$ respectively, which are updated as follows:

$$\begin{aligned} \dot{\hat{\boldsymbol{\theta}}}_{M_{do}} &= -\mathbf{L}_{M_{do}} \mathbf{N}_{M_{do}}(\dot{\hat{\boldsymbol{\eta}}}) \mathbf{z}, \\ \dot{\hat{\boldsymbol{\theta}}}_{B_{do}} &= -\mathbf{L}_{B_{do}} \mathbf{N}_{B_{do}}(\hat{\boldsymbol{\eta}}) \mathbf{z}, \end{aligned} \quad (54)$$

where $\mathbf{z} = \hat{\mathbf{q}} - \boldsymbol{\eta}$, and $\hat{\boldsymbol{\theta}}_{M_{do}}$ and $\hat{\boldsymbol{\theta}}_{B_{do}}$ are the vectors of estimated parameters, and $\mathbf{L}_{M_{do}}$ and $\mathbf{L}_{B_{do}}$ are positive definite matrices, and $\mathbf{N}_{M_{do}}(\dot{\hat{\boldsymbol{\eta}}}) = \text{diag}\{\dot{\eta}_1, \dot{\eta}_2\}$ and $\mathbf{N}_{B_{do}}(\hat{\boldsymbol{\eta}}) = \text{diag}\{\eta_1, \eta_2\}$.

Next, a new sliding vector is obtained as:

$$\hat{\mathbf{s}}_q = \dot{\hat{\mathbf{q}}} - \dot{\hat{\mathbf{q}}}_r = \dot{\hat{\mathbf{q}}} - \dot{\hat{\mathbf{q}}}_d + \alpha_q (\mathbf{q} - \hat{\mathbf{q}}_d), \quad (55)$$

where $\dot{\hat{\mathbf{q}}}_r = \dot{\hat{\mathbf{q}}}_d - \alpha_q (\mathbf{q} - \hat{\mathbf{q}}_d)$ is a new reference vector.

The control input of robotic manipulator is proposed as:

$$\mathbf{u} = -\mathbf{K}_q \Delta \hat{\mathbf{q}} - \mathbf{K}_s \hat{\mathbf{s}}_q + \mathbf{Y}_q(\dot{\hat{\mathbf{q}}}_r, \ddot{\hat{\mathbf{q}}}_r) \hat{\boldsymbol{\theta}}_q, \quad (56)$$

where the uncertain parameters $\hat{\boldsymbol{\theta}}_q$ are updated as:

$$\dot{\hat{\boldsymbol{\theta}}}_q = -\mathbf{L}_q \mathbf{Y}_q^T(\dot{\hat{\mathbf{q}}}_r, \ddot{\hat{\mathbf{q}}}_r) \hat{\mathbf{s}}_q. \quad (57)$$

Substituting equation (56) into equation (5) and using the sliding vector $\hat{\mathbf{s}}_q$, the closed-loop equation for the control input of the robotic manipulator is obtained as:

$$\mathbf{M}_q \dot{\hat{\mathbf{s}}}_q + \mathbf{B}_q \hat{\mathbf{s}}_q + \mathbf{K}_q \Delta \hat{\mathbf{q}} + \mathbf{K}_s \hat{\mathbf{s}}_q + \mathbf{Y}_q(\dot{\hat{\mathbf{q}}}_r, \ddot{\hat{\mathbf{q}}}_r) \Delta \boldsymbol{\theta}_q = \mathbf{0}. \quad (58)$$

Next, multiplying both sides of equation (53) with $\hat{\mathbf{M}}_{do}$ and using equation (5), we can get the closed-loop observer dynamics for $\hat{\mathbf{q}}_d$ as:

$$\begin{aligned} \mathbf{M}_q \dot{\hat{\mathbf{z}}} + \mathbf{B}_q \hat{\mathbf{z}} + \mathbf{K}_e \mathbf{e} &= (\hat{\mathbf{M}}_{do} - \mathbf{M}_q) \dot{\hat{\boldsymbol{\eta}}} + (\hat{\mathbf{B}}_{do} - \mathbf{B}_q) \hat{\boldsymbol{\eta}} \\ &= -\mathbf{N}_{M_{do}}(\dot{\hat{\boldsymbol{\eta}}}) \Delta \boldsymbol{\theta}_{M_{do}} - \mathbf{N}_{B_{do}}(\hat{\boldsymbol{\eta}}) \Delta \boldsymbol{\theta}_{B_{do}}, \end{aligned} \quad (59)$$

where $\Delta\theta_{M_{do}} = \theta_{M_{do}} - \hat{\theta}_{M_{do}}$ and $\Delta\theta_{B_{do}} = \theta_{B_{do}} - \hat{\theta}_{B_{do}}$.

To analyze the stability of the closed-loop system, a Lyapunov-like candidate $\hat{V}$ is proposed as:

$$\begin{aligned} \hat{V} = & \frac{1}{2} \hat{s}_x^T M \hat{s}_x + \frac{1}{2} \Delta\theta_d^T L_d^{-1} \Delta\theta_d + \frac{\hat{a}(\hat{x}, \hat{q})}{2} \Delta\hat{x}^T K_p \Delta\hat{x} \\ & + \frac{1}{2} \hat{s}_q^T M_q \hat{s}_q + \frac{1}{2} \Delta\theta_q^T L_q^{-1} \Delta\theta_q + \Delta\hat{q}^T \left(\frac{1}{2} K_q + \alpha_q K_s \right) \Delta\hat{q} \\ & + \frac{1}{2} e_x^T K_x e_x + \frac{1}{2} e_q^T K_z e_q + \frac{1}{2} z_x^T M z_x + \frac{1}{2} z_q^T M_q z_q + \frac{1}{2} z^T M_q z \\ & + \frac{1}{2} \Delta\theta_{M_o}^T L_{M_o}^{-1} \Delta\theta_{M_o} + \frac{1}{2} \Delta\theta_{B_o}^T L_{B_o}^{-1} \Delta\theta_{B_o} + \frac{1}{2} \Delta\theta_{M_{qo}}^T L_{M_{qo}}^{-1} \Delta\theta_{M_{qo}} \\ & + \frac{1}{2} \Delta\theta_{B_{qo}}^T L_{B_{qo}}^{-1} \Delta\theta_{B_{qo}} + \frac{1}{2} \Delta\theta_{M_{do}}^T L_{M_{do}}^{-1} \Delta\theta_{M_{do}} + \frac{1}{2} \Delta\theta_{B_{do}}^T L_{B_{do}}^{-1} \Delta\theta_{B_{do}}. \end{aligned} \quad (60)$$

Differentiating $\hat{V}$ with respect to time, and substituting equations (42), (44), (48), (50), (51), (52), (54), (57), (58), and (59) into it, we have:

$$\begin{aligned} \dot{\hat{V}} = & \hat{s}_x^T M \dot{\hat{s}}_x - \dot{\theta}_d^T L_d^{-1} \Delta\theta_d + \frac{\hat{a}(\hat{x}, \hat{q})}{2} \Delta\hat{x}^T K_p \Delta\hat{x} \\ & + \hat{a}(\hat{x}, \hat{q}) (\dot{\hat{x}} - \dot{\hat{x}}_d)^T K_p \Delta\hat{x} + \hat{s}_q^T M_q \dot{\hat{s}}_q - \dot{\theta}_q^T L_q^{-1} \Delta\theta_q \\ & + \Delta\hat{q}^T (K_q + 2\alpha_q K_s) \Delta\hat{q} + e_x^T K_x \dot{e}_x + e_q^T K_z \dot{e}_q \\ & + z_x^T M \dot{z}_x + z_q^T M_q \dot{z}_q + z^T M_q \dot{z} \\ & - \dot{\theta}_{M_o}^T L_{M_o}^{-1} \Delta\theta_{M_o} - \dot{\theta}_{B_o}^T L_{B_o}^{-1} \Delta\theta_{B_o} - \dot{\theta}_{M_{qo}}^T L_{M_{qo}}^{-1} \Delta\theta_{M_{qo}} \\ & - \dot{\theta}_{B_{qo}}^T L_{B_{qo}}^{-1} \Delta\theta_{B_{qo}} - \dot{\theta}_{M_{do}}^T L_{M_{do}}^{-1} \Delta\theta_{M_{do}} - \dot{\theta}_{B_{do}}^T L_{B_{do}}^{-1} \Delta\theta_{B_{do}} \\ = & -\hat{s}_x^T (B + \hat{a}(\hat{x}, \hat{q}) K_d) \hat{s}_x + k(x, q) \hat{s}_x^T \Delta\hat{q} - k(x, q) \hat{s}_x^T e \\ & - \Delta\hat{x}^T \left(\alpha_x \frac{\hat{a}^2(\hat{x}, \hat{q})}{\hat{a}^2(\hat{x}, \hat{q}) + \delta} K_p - \frac{\hat{a}(\hat{x}, \hat{q})}{2} K_p \right) \Delta\hat{x} \\ & - \hat{s}_q^T B_q \hat{s}_q - \Delta\hat{q}^T K_s \Delta\hat{q} - \Delta\hat{q}^T (\alpha_q K_q + \alpha_q^2 K_s) \Delta\hat{q} \\ & - z_x^T B z_x - z_q^T B_q z_q - z^T B_q z - z^T K_x e_x \\ & - z_q^T K_z e_q - z^T K_e e + e_x^T K_x \dot{e}_x + e_q^T K_z \dot{e}_q. \end{aligned} \quad (61)$$

Note that $z_x = \dot{x} - \eta_x = \dot{e}_x + \beta_x e_x$, $z_q = \dot{q} - \eta_q = \dot{e}_q + \beta_q e_q$ and $z = \dot{q} - \eta = \Delta\dot{q} + \beta e$. Therefore, equation (61) can be rewritten as:

$$\begin{aligned} \dot{\hat{V}} = & -\hat{s}_x^T (B + \hat{a}(\hat{x}, \hat{q}) K_d) \hat{s}_x + k(x, q) \hat{s}_x^T \Delta\hat{q} - k(x, q) \hat{s}_x^T e \\ & - \Delta\hat{x}^T \left(\alpha_x \frac{\hat{a}^2(\hat{x}, \hat{q})}{\hat{a}^2(\hat{x}, \hat{q}) + \delta} K_p - \frac{\hat{a}(\hat{x}, \hat{q})}{2} K_p \right) \Delta\hat{x} - \hat{s}_q^T B_q \hat{s}_q \\ & - \Delta\hat{q}^T K_s \Delta\hat{q} - \Delta\hat{q}^T (\alpha_q K_q + \alpha_q^2 K_s) \Delta\hat{q} - z_x^T B z_x - z_q^T B_q z_q \\ & - z^T B_q z - \beta_x e_x^T K_x e_x - \beta_q e_q^T K_z e_q - \Delta\hat{q}^T K_e e - \beta e^T K_e e \\ = & -\Delta\hat{x}^T \left(\alpha_x \frac{\hat{a}^2(\hat{x}, \hat{q})}{\hat{a}^2(\hat{x}, \hat{q}) + \delta} K_p - \frac{\hat{a}(\hat{x}, \hat{q})}{2} K_p \right) \Delta\hat{x} - \hat{s}_q^T B_q \hat{s}_q \\ & - z_x^T B z_x - z_q^T B_q z_q - z^T B_q z - \beta_x e_x^T K_x e_x - \beta_q e_q^T K_z e_q \\ & - [\hat{s}_x^T \Delta\hat{q}^T \Delta\hat{q}^T e^T] P [\hat{s}_x^T \Delta\hat{q}^T \Delta\hat{q}^T e^T]^T, \end{aligned} \quad (62)$$

where $P \in \mathbb{R}^{8 \times 8}$ is:

$$P = \begin{bmatrix} B + \hat{a}(\hat{x}, \hat{q}) K_d & -\frac{k(x, q)}{2} I_2 & 0 & \frac{k(x, q)}{2} I_2 \\ -\frac{k(x, q)}{2} I_2 & \alpha_q K_q + \alpha_q^2 K_s & 0 & 0 \\ 0 & 0 & K_s & \frac{1}{2} K_e \\ \frac{k(x, q)}{2} I_2 & 0 & \frac{1}{2} K_e & \beta K_e \end{bmatrix} \quad (63)$$

If the controller parameters α_x , α_q , K_q , K_s , β , and K_e are chosen so that

$$\alpha_x > b_{max} \left(\frac{\hat{a}(\hat{x}, \hat{q})}{2} \left(1 + \frac{\delta}{\hat{a}^2(\hat{x}, \hat{q})} \right) \right),$$

$$\alpha_q \lambda_{min}[(K_q + \alpha_q K_s)B] > \frac{k_c^2}{4},$$

$$\beta \lambda_{min}[K_s] > \frac{1}{4} \lambda_{max}[K_e],$$

$$\lambda_{min}[K_e] \{ \beta \lambda_{min}[K_s] - \frac{1}{4} \lambda_{max}[K_e] \} \{ \alpha_q \lambda_{min}[(K_q +$$

$$\alpha_q K_s)B] - \frac{k_c^2}{4} \} > \frac{k_c^2}{4} \alpha_q \lambda_{max}[(K_q + \alpha_q K_s)K_s], \quad (64)$$

then P is positive definite and $\alpha_x \frac{\hat{a}^2(\hat{x}, \hat{q})}{\hat{a}^2(\hat{x}, \hat{q}) + \delta} - \frac{\hat{a}(\hat{x}, \hat{q})}{2} > 0$. The proof that P is positive definite if equation (64) is satisfied is given in the Appendix. Since P is positive definite and $\alpha_x \frac{\hat{a}^2(\hat{x}, \hat{q})}{\hat{a}^2(\hat{x}, \hat{q}) + \delta} - \frac{\hat{a}(\hat{x}, \hat{q})}{2} > 0$, it is obtained that $\dot{\hat{V}} \leq 0$. We are now ready to state the following theorem:

Theorem 2: The input of the robotic manipulator (56), and the update laws (42), (44), (48), (54), and (57) ensure the convergence of the closed-loop system. That is, $x \rightarrow x_d$, $\dot{x} \rightarrow \dot{x}_d$ as $t \rightarrow \infty$ when the control parameters α_x , α_q , K_q , K_s , β , and K_e are chosen to satisfy conditions (64).

Proof: If equation (64) is satisfied, we have $\hat{V} > 0$ and $\dot{\hat{V}} \leq 0$, and hence $\hat{V}$ is bounded. The boundedness of $\hat{V}$ ensures the boundedness of $\hat{s}_x$, $\Delta\theta_d$, $\Delta\hat{x}$, $\hat{s}_q$, $\Delta\theta_q$, $\Delta\hat{q}$, e_x , e_q , z_x , z_q , z , $\Delta\theta_{M_o}$, $\Delta\theta_{B_o}$, $\Delta\theta_{M_{qo}}$, $\Delta\theta_{B_{qo}}$, $\Delta\theta_{M_{do}}$ and $\Delta\theta_{B_{do}}$. The boundedness of $\hat{s}_x$ and $\Delta\hat{x}$ ensures the boundedness of $\Delta\dot{\hat{x}}$ from equation (46). Therefore, $\Delta\hat{x}$ is uniformly continuous. The boundedness of $\Delta\hat{x}$ ensures the boundedness of $\dot{\hat{x}}_r$. Moreover, $\ddot{x}_r$ is bounded since $\Delta\dot{\hat{x}}$ is bounded. In addition, since $\hat{s}_q$ and $\Delta\hat{q}$ are bounded, $\Delta\dot{\hat{q}}$ is bounded. Since $\Delta\dot{\hat{q}}$ and z are bounded, e is bounded. From the closed-loop equation (52), it is obtained that $\dot{\hat{s}}_x$ is bounded. Therefore, $\hat{s}_x$ is also uniformly continuous. In addition, the boundedness of z_x and e_x ensures the boundedness of $\dot{e}_x$. Therefore, e_x is uniformly continuous. The boundedness of z_q and e_q ensures the boundedness of $\dot{e}_q$. Therefore, e_q is also uniformly continuous. From equation (62), it is easy to

verify that $\hat{s}_x, \Delta\hat{x}, e_x, e_q \in L_2(0, +\infty)$. Then it follows [Arimoto, 1996, Spong and Vidyasagar, 1989] that $\hat{s}_x \rightarrow 0, \Delta\hat{x} \rightarrow 0, e_x \rightarrow 0$ and $e_q \rightarrow 0$. The convergence of $e_x \rightarrow 0$ and $e_q \rightarrow 0$ implies that $\hat{x} \rightarrow x$ and $\hat{q} \rightarrow q$, and hence $\hat{a}(\hat{x}, \hat{q}) \rightarrow a(x, q)$, $\hat{x}_d \rightarrow x_d$. Then $\hat{s}_x \rightarrow 0$ and $\Delta\hat{x} \rightarrow 0$ indicates that $x \rightarrow x_d$ and $\dot{x} \rightarrow \dot{x}_d$. $\triangle\triangle\triangle$

5 Simulation

Simulations have been carried out to verify the performance of the proposed control methods. The optical tweezers system is illustrated in Fig. 6. In Fig. 6, the cell is placed on a motorized stage and the laser beam is fixed downwards, and the offset between the laser beam and the biological cell is varied by moving the motorized stage which thus acts as a robotic manipulator. In the simulations, the variable q is set as the position of the laser beam with respect to the motorized stage.

Fig. 6. 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 parameters of the cell dynamics in equation (1) were set as: $M = \text{diag}\{10^{-9}, 10^{-9}\} \text{kg}$, $B = \text{diag}\{2 \times 10^{-9}, 2 \times 10^{-9}\} \text{kg/s}$, $k_c = 2 \times 10^{-5}$, $R = 18 \mu\text{m}$. The parameters of the manipulator dynamics in equation (5) were set as: $M_q = \text{diag}\{0.02218, 0.011386\} \text{kg}$, $B_q = \text{diag}\{0.04749, 0.04023\} \text{kg/s}$. The values of the dynamic parameters of biological cells and the manipulator of the laser beam are selected with reference to [Aguilar-Ibanez *et al.*, 2010; Lee *et al.*, 2003; Huang *et al.*, 2006].

In the first simulation, the laser started from a large initial position at $(1.1, 0.7) \mu\text{m}$ and moved towards a cell located at $(126, -130.8) \mu\text{m}$. Therefore, the trapping was not established initially, which is shown in Fig. 7(a).

The trapping region was set as a circle as:

$$f(x, q) = (x_1 - q_1)^2 + (x_2 - q_2)^2 - 10^2 \leq 0, \quad (65)$$

where $b = 10 \mu\text{m}$ is the radius, and the parameters of the reference region in equation (9) were set as: $\kappa = 0.99$. The cell was trapped by the laser beam after it

entered the trapping region. Then the trapped cell was manipulated to follow the desired trajectory that was specified as a lemniscate of Bernoulli as:

$$\begin{cases} x_{d1} = 200 + \frac{15\cos(0.35t)}{1+\sin^2(0.35t)} a(x, q) \mu\text{m}, \\ x_{d2} = -150 + \frac{15\sin(0.35t)\cos(0.35t)}{1+\sin^2(0.35t)} a(x, q) \mu\text{m}. \end{cases} \quad (66)$$

The parameters of the desired position input of the laser beam in equations (15) and (16) were proposed as: $N = 6$, $\delta = 10^{-30}$, $\alpha_x = 1$, $K_p = 3 \times 10^{-6} I_2$, $K_d = 3.5 \times 10^{-7} I_2$, $L_d = 10^{-10} I_4$ where $I_4 \in \mathbb{R}^{4 \times 4}$ is an identity matrix, and the parameters of the control input for the manipulator of the laser beam in equations (25) and (26) were set as: $\alpha_q = 1$, $K_q = I_2$, $K_s = 1.5 I_2$, $L_q = 10^{-5} I_4$.

The path of the laser beam and the cell is shown in Fig. 7, which is consisted of three stages: (1) the laser starts from a large initial position and moves towards the cell (Fig. 7(a)); (2) the cell enters the trapping region and is trapped by the laser (Fig. 7(b)); (3) the trapped cell is manipulated to follow the desired trajectory (Fig. 7(c)). The tracking errors are shown in Fig. 7(d), and the tracking errors converge to zero in less than 1 s, which indicates the successful realization of the manipulation task.

In the second simulation, the adaptive observers are introduced to eliminate the requirement of acceleration and its derivatives. The initial positions of the cell and the laser beam remained the same, and the cell cannot be trapped by the laser beam in the beginning as well. After the cell was trapped by the laser beam, it was moved to track the desired trajectory. The desired trajectory was the same as that specified in equation (66).

The parameters of the adaptive observer for $\hat{x}$ in equation (41) are set as: $\beta_x = 3 \times 10^{-6}$, $K_x = 10^{-10} I_2$, $L_{M_o} = 10^{-10} I_2$, $L_{B_o} = 10^{-10} I_2$, while the initial estimates of the dynamic parameters of the cell were set as: $\hat{M}_o = 5 \times 10^{-10} I_2 \text{kg}$ and $\hat{B}_o = 1.8 \times 10^{-9} I_2 \text{kg/s}$. The parameters of the adaptive observer for $\hat{q}$ in equation (43) are set as: $\beta_q = 3$, $K_z = 0.01 I_2$, $L_{M_{qo}} = 10^{-10} I_2$, $L_{B_{qo}} = 10^{-10} I_2$, while the initial estimates of the dynamic parameters of the robotic manipulator were set as: $\hat{M}_{qo} = \text{diag}\{0.0222, 0.0114\} \text{kg}$ and $\hat{B}_{qo} = \text{diag}\{0.05, 0.04\} \text{kg/s}$. The parameters of the adaptive observer for $\hat{q}_d$ in equation (53) are set as: $\beta = 9$, $K_e = 0.01 I_2$, $L_{M_{do}} = 10^{-10} I_2$, $L_{B_{do}} = 10^{-10} I_2$, while the initial estimates of the dynamic parameters of the robotic manipulator were set as: $\hat{M}_{do} = \text{diag}\{0.0222, 0.0114\} \text{kg}$ and $\hat{B}_{do} = \text{diag}\{0.05, 0.04\} \text{kg/s}$.

The parameters of the trapping region remained the same, but now the estimated laser position $\hat{q}$ and the estimated cell position $\hat{x}$ instead of the actual positions q and x were used to construct the auxiliary factor $\hat{a}(\hat{x}, \hat{q})$.

Fig. 7. Simulation 1: Dynamic cell trapping and manipulation.

Fig. 8. Simulation 2: Adaptive observers for optical tweezers.

The parameters of the desired position input for the trapped cell in equations (47) and (48) were proposed as: $N = 8$, $\delta = 10^{-30}$, $\kappa = 0.99$, $b = 10 \mu m$, $\alpha_x = 1$, $K_p = 10^{-6} I_2$, $K_d = 2 \times 10^{-7} I_2$, $L_d = 10^{-10} I_4$, and the parameters of the control input in equations (56) and (57) were set as: $\alpha_q = 1$, $K_q = I_2$, $K_s = 1.5 I_2$, $L_q = 10^{-5} I_4$.

The path of the laser beam and the cell is shown in Fig. 8, which is also consisted of three stages: (1) the laser starts from a large initial position and moves towards the cell (Fig. 8(a)); (2) the cell enters the trapping region and is trapped by the laser (Fig. 8(b)); (3) the trapped cell is manipulated to follow the desired trajectory (Fig. 8(c)). The tracking errors are shown in Fig. 8(d), and the tracking errors converge to zero in about 4 s. As seen from Fig. 8, the cell is successfully trapped by the laser and manipulated to follow the desired trajectory.

6 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. 9(a). The system is constituted of three modules for sensing, control and execution [Hu and Sun, 2011]. The sensing module consists of a microscope and a CCD camera, and the positions of biological cells and the laser beam 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. The optical tweezers were controlled to manipulate the yeast cell, but due to the limited access to the software interface, the desired position of the laser source is set as the control input.

In the experiment, the position of the laser beam is fixed, and the desired position input q_d in equation (15) is applied on the motorized stage to vary the relative distance between the laser beam and the cell. The trapping region was set as a circle with the radius $b = 1 \mu m$, and the parameters of the reference region in equation (9) were set as: $\kappa = 0.99$. The trapped cell was initially located at $(0, 31.97) \mu m$, and the laser beam was at $(0, 0.08) \mu m$. Therefore, the initial distance between the laser and the cell was very large, and the cell was not trapped in the beginning. The laser beam is moved towards the cell to trap it first, and then manipulate the cell to follow the desired trajectory which was specified as: $x_{d1} = -15 + 15\cos(0.01t)a(x, q) \mu m$, $x_{d2} = 32 + 15\sin(0.01t)a(x, q) \mu m$. Different desired trajectories for the trapped cell are used in the simulation and the experiment respectively, to illustrate that the proposed method is feasible for various trajectory tracking control problems.

The control parameters were set as: $N = 8$, $K_p = 0.00006 I_2$, $\alpha_x = 1$, $K_d = 0.2 I_2$, $L_d = 10^{-7} I_4$. The tracking errors are shown in Fig. 9(b), and the path of the laser and the cell is shown in Fig. 9(c). The pictures of the trapped cell at different time instants are shown in Fig. 10. As seen from Fig. 10, the laser beam moves to trap the cell initially, and the cell is trapped by the

Fig. 9. Experiment: The cell is trapped and manipulated to follow a circle.

Fig. 10. Experiment: Positions of the cell at various time instants.

laser beam in less than 10 s, and it is manipulated to follow the desired trajectory after that.

7 Conclusions

In this paper, a new control method has been proposed for optical manipulation systems, which can integrate automatic trapping and manipulation of biological cells into a single method. The dynamics of the manipulator of the laser source is introduced in the optical tweezers system. Therefore, a closed-loop control method is formulated and solved. The proposed control method is able to transit between the operation of trapping and manipulation without hard switching. Simulation and experimental results are used to illustrate the performance of the proposed method.

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Appendix

According to Sylvester's Theorem [Horn and Johnson, 1990], the symmetric matrix $\mathbf{P}$ in equation (63) is positive definite if all its leading principal minors $(A_1, \dots, A_8)$ are strictly positive. Since $\mathbf{B} = \text{diag}\{b_1, b_2\}$, $\mathbf{K}_d = \text{diag}\{k_{d1}, k_{d2}\}$, $\mathbf{K}_q = \text{diag}\{k_{q1}, k_{q2}\}$, $\mathbf{K}_s = \text{diag}\{k_{s1}, k_{s2}\}$, and $\mathbf{K}_e = \text{diag}\{k_{e1}, k_{e2}\}$, the leading principal minors of $\mathbf{P}$ are computed as follows:

- (i) $A_1 = b_1 + \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}})k_{d1}$;
- (ii) $A_2 = (b_1 + \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}})k_{d1})(b_2 + \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}})k_{d2})$;
- (iii) $A_3 = (b_2 + \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}})k_{d2})[(b_1 + \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}})k_{d1})(\alpha_q k_{q1} + \alpha_q^2 k_{s1}) - \frac{k^2(\mathbf{x}, \mathbf{q})}{4}]$;
- (iv) $A_4 = [(b_1 + \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}})k_{d1})(\alpha_q k_{q1} + \alpha_q^2 k_{s1}) - \frac{k^2(\mathbf{x}, \mathbf{q})}{4}][(b_2 + \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}})k_{d2})(\alpha_q k_{q2} + \alpha_q^2 k_{s2}) - \frac{k^2(\mathbf{x}, \mathbf{q})}{4}]$;
- (v) $A_5 = k_{s1}A_4$;
- (vi) $A_6 = k_{s2}A_5$;
- (vii) $A_7 = k_{e1}k_{s2}(\beta k_{s1} - \frac{k_{e1}}{4})[(b_1 + \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}})k_{d1})(\alpha_q k_{q1} + \alpha_q^2 k_{s1}) - \frac{k^2(\mathbf{x}, \mathbf{q})}{4}][(b_2 + \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}})k_{d2})(\alpha_q k_{q2} + \alpha_q^2 k_{s2}) - \frac{k^2(\mathbf{x}, \mathbf{q})}{4}]$;
- (viii) $A_8 = \{k_{e1}(\beta k_{s1} - \frac{k_{e1}}{4})[(b_1 + \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}})k_{d1})(\alpha_q k_{q1} + \alpha_q^2 k_{s1}) - \frac{k^2(\mathbf{x}, \mathbf{q})}{4}] - k_{s1}(\alpha_q k_{q1} + \alpha_q^2 k_{s1})\frac{k^2(\mathbf{x}, \mathbf{q})}{4}\}\{k_{e2}(\beta k_{s2} - \frac{k_{e2}}{4})[(b_2 + \hat{a}(\hat{\mathbf{x}}, \hat{\mathbf{q}})k_{d2})(\alpha_q k_{q2} + \alpha_q^2 k_{s2}) - \frac{k^2(\mathbf{x}, \mathbf{q})}{4}] - k_{s2}(\alpha_q k_{q2} + \alpha_q^2 k_{s2})\frac{k^2(\mathbf{x}, \mathbf{q})}{4}\}$.

Next, the conditions in equation (64) is reproduced as:

$$\alpha_q \lambda_{\min}[(\mathbf{K}_q + \alpha_q \mathbf{K}_s)\mathbf{B}] > \frac{k_c^2}{4}, \quad (C.1)$$

$$\beta \lambda_{\min}[\mathbf{K}_s] > \frac{1}{4} \lambda_{\max}[\mathbf{K}_e], \quad (C.2)$$

$$\lambda_{\min}[\mathbf{K}_e]\{\beta \lambda_{\min}[\mathbf{K}_s] - \frac{1}{4} \lambda_{\max}[\mathbf{K}_e]\}\{\alpha_q \lambda_{\min}[(\mathbf{K}_q + \alpha_q \mathbf{K}_s)\mathbf{B}] - \frac{k_c^2}{4}\} > \frac{k_c^2}{4} \alpha_q \lambda_{\max}[(\mathbf{K}_q + \alpha_q \mathbf{K}_s)\mathbf{K}_s]. \quad (C.3)$$

Therefore, we have: A_1 and A_2 are positive; A_3 and A_4 are positive if condition (C.1) is satisfied; A_5 is positive if A_4 is positive; A_6 is positive if A_5 is positive; A_7 is

positive if conditions (C.1) and (C.2) are satisfied. A_8 is positive if condition (C.3) is satisfied.

Therefore, the matrix $\mathbf{P}$ is positive definite if the conditions in equation (64) are satisfied.