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2013

Cheah, C. C., Li, X., Yan, X., & Sun, D. (2013). Optical manipulation of biological cell without measurement of cell velocity. 2013 13th IEEE Conference on Nanotechnology (IEEE-NANO), 813 - 816.

<https://hdl.handle.net/10356/101652>

<https://doi.org/10.1109/NANO.2013.6720886>

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Optical Manipulation of Biological Cell without Measurement of Cell Velocity

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

Abstract—Optical tweezer is a useful tool for non-contact micromanipulation tasks because it can manipulate biological cells precisely without causing damage to the cells. In many optical manipulation techniques, the measurement of the velocity of the cell is necessary. Since it is difficult to measure the velocity of the cell, the velocity information is usually obtained by differentiating the position of the cell in image space, which may result in degraded performance of the control system due to estimation error and the noises induced in differentiation. In this paper, an adaptive observer technique is proposed for optical manipulation of cell with a low Reynolds' number, without measurement of the velocity of the cell. By using the proposed observer technique, a desired position input of the laser beam without measurement of the velocity of the cell is also developed. The stability of closed-loop system is analyzed by using Lyapunov-like method. Experimental results are presented to illustrate the performance of the proposed control method.

I. INTRODUCTION

Optical tweezers are very useful tools for non-contact micromanipulation which are able to trap objects as diverse as atoms, molecules, bacteria, viruses and live cells [1]. Various automatic optical tweezers systems and control methods have been developed over the past few years. A modified A-star path planning algorithm was proposed to transport cell in [2], and the force applied on the trapped cell was also analyzed. An automatic cell sorting system based on dual-beam trap was introduced in [3], and an image-processing system using thresholding, background subtraction and edge-enhancement algorithms was developed for identification of single cell. In [4], a PID feedback controller and a synchronization control technology were proposed for cell transportation, based on a simplified dynamics model of the trapped cell. In [5], a simple feedback controller was proposed for the positioning of a microscopic particle. In [6], 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 [7], a region reaching control method was used to flock multiple micro particles towards a

static region. In [8], an automated optical trapping technique was developed based on computer vision and multiple-force optical clamps.

However, the measurement of velocity of cell is usually required in current manipulation techniques using optical tweezers. In actual implementations of the controllers, the measurement of velocity is not available and hence the velocity information is usually obtained by differentiating the position of the cell in image space. However, differentiation induces noise and estimation error, and hence may result in degraded performance of the control systems.

In most micromanipulation tasks, the viscous drag dominates inertia due to the scaling effect. Therefore, the effect of the inertia force can be ignored and a simplified dynamic model for biological cells can be established [2], [4]–[6]. The simplified dynamic model is applicable for the optical tweezers system especially when it is used to manipulate biological cells with a low Reynolds' number [9]–[12]. By using the simplified dynamic model, we propose a new observer based control method for optical tweezers in this paper. An adaptive observer is developed to estimate the position and velocity of the cell. The proposed controller enables the laser beam to manipulate the cell to follow a time-varying desired trajectory without using the velocity of the cell. The stability of closed-loop system is analyzed by using Lyapunov-like method. Experimental results are presented to illustrate the performance of the proposed control scheme.

II. OPTICAL TWEEZERS SYSTEM

It is known that the optical trapping works only when the cell is located in a small neighborhood of the centroid of the focused laser beam. When the cell is very near the laser beam, and the trapping force is approximately linear to the distance between the center of laser beam and the position of the cell, which is usually modeled as a Hookeian spring, as illustrated in Fig. 1.

Optical tweezers are the scientific instruments based on the optical trap, which can manipulate the microscopic objects without physical contact. A typical optical manipulation system is shown in Fig. 2. The laser beam is expanded using a beam expander, reflected on a Dichroic mirror, and introduced into the inverted microscope.

The dynamic model of the cell in the optical tweezers system is described as [5], [13]:

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

where $M \in \mathbb{R}^{2 \times 2}$ denotes the inertia matrix, $B \in \mathbb{R}^{2 \times 2}$ represents the damping matrix, k denotes the stiffness which

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is a positive constant, $\mathbf{x} = [x_1, x_2]^T \in \mathbb{R}^2$ is the position of the cell, and $\mathbf{q} = [q_1, q_2]^T \in \mathbb{R}^2$ is the position of the laser beam. Both $\mathbf{M}$ and $\mathbf{B}$ are positive definite.

Fig. 1. The trapping force acts as a Hookeian spring when the cell is very near the center of laser beam.

Fig. 2. A typical optical tweezers system.

The optical tweezers are able to manipulate various biological cells. As the dimension of cell decreases, the Reynolds' number decreases as illustrated in Fig. 3. When the optical tweezers manipulate very tiny cells with a low Reynolds' number [9]–[12], viscous drag dominates inertia due to the scaling effect. That is, the mass of the cell can be ignored, and the dynamic equation can be simplified as:

$$\mathbf{B}\dot{\mathbf{x}} + k(\mathbf{x} - \mathbf{q}) = \mathbf{0}, \quad (2)$$

where the term $\mathbf{B}\dot{\mathbf{x}}$ in equation (2) can also be written as:

$$\mathbf{B}\dot{\mathbf{x}} = \mathbf{Y}_b(\dot{\mathbf{x}})\boldsymbol{\theta}_b, \quad (3)$$

where $\mathbf{Y}_b(\dot{\mathbf{x}}) \in \mathbb{R}^{2 \times n_b}$ is a dynamic regressor matrix, and $\boldsymbol{\theta}_b = [\theta_{b1}, \dots, \theta_{bn_b}]^T \in \mathbb{R}^{n_b}$ is a set of physical parameters.

III. OBSERVER BASED TRACKING CONTROLLER

When the optical tweezers manipulate a cell with a low Reynolds' number, the dynamic model can be simplified as equation (2). Based on equation (2), an observer based tracking control strategy is proposed in this section.

Fig. 3. The Reynolds' number decreases as the dimension of object decreases.

Suppose the desired position input of the laser beam is denoted as $\mathbf{q}_d$, then equation (2) can be written as:

$$\mathbf{B}\dot{\mathbf{x}} + k\mathbf{x} = k\Delta\mathbf{q} + k\mathbf{q}_d, \quad (4)$$

where $\Delta\mathbf{q} = \mathbf{q} - \mathbf{q}_d$ represents an input perturbation to the dynamics of the cell. The system in equation (4) can be viewed as being controlled by the input $k\mathbf{q}_d$ with the perturbation $k\Delta\mathbf{q}$.

Let $\Delta\mathbf{x} = \mathbf{x} - \mathbf{x}_d$ denote the position errors of the cell, then:

$$\dot{\mathbf{x}} = \dot{\mathbf{x}}_d + \Delta\dot{\mathbf{x}}. \quad (5)$$

Substituting equation (5) into equation (4), we have:

$$\mathbf{B}\dot{\mathbf{x}}_d + \mathbf{B}\Delta\dot{\mathbf{x}} + k\mathbf{x} = k\Delta\mathbf{q} + k\mathbf{q}_d. \quad (6)$$

Note that $\mathbf{B}\dot{\mathbf{x}}_d = \mathbf{Y}_b(\dot{\mathbf{x}}_d)\boldsymbol{\theta}_b$, we have

$$\mathbf{B}\Delta\dot{\mathbf{x}} + k\mathbf{x} + \mathbf{Y}_b(\dot{\mathbf{x}}_d)\boldsymbol{\theta}_b = k\Delta\mathbf{q} + k\mathbf{q}_d. \quad (7)$$

Next, an adaptive observer is developed to estimate the velocity of the cell as:

$$\dot{\hat{\mathbf{x}}} = \hat{\mathbf{B}}^{-1}[-k(\mathbf{x} - \mathbf{q}) + \mathbf{K}_x \mathbf{e}_x], \quad (8)$$

where $\hat{\mathbf{x}}$ is the observed velocity of the trapped cell, $\mathbf{e}_x = \mathbf{x} - \hat{\mathbf{x}}$ is the observation error, $\mathbf{K}_x$ is a positive definite matrix, and $\hat{\mathbf{B}}$ is the estimated model for $\mathbf{B}$ which is updated through the following update law:

$$\dot{\hat{\boldsymbol{\theta}}}_o = -\mathbf{L}_o \mathbf{Y}_b(\dot{\hat{\mathbf{x}}}) \mathbf{e}_x, \quad (9)$$

where $\hat{\boldsymbol{\theta}}_o$ is the vector of estimated parameters, and $\mathbf{L}_o$ is a positive definite matrix.

By using the observed position $\hat{\mathbf{x}}$, the desired position input for the laser beam is proposed as:

$$\mathbf{q}_d = \hat{\mathbf{x}} - k^{-1} \mathbf{K}_p (\hat{\mathbf{x}} - \mathbf{x}_d) + k^{-1} \mathbf{Y}_b(\dot{\hat{\mathbf{x}}}) \hat{\boldsymbol{\theta}}_b. \quad (10)$$

The uncertain parameters $\hat{\boldsymbol{\theta}}_b$ are updated by:

$$\dot{\hat{\boldsymbol{\theta}}}_b = -\mathbf{L}_b \mathbf{Y}_b^T(\dot{\hat{\mathbf{x}}}) \Delta\mathbf{x}, \quad (11)$$

where $\mathbf{L}_b$ is a positive definite matrix. Note that the velocity information of the cell is not required in the desired position input described by equations (10) and (11), and hence the differentiation of image-space position of the cell is not necessary.

Substituting equation (10) into equation (7), we have:

$$\mathbf{B}\Delta\dot{\mathbf{x}} + \mathbf{Y}_b(\dot{\hat{\mathbf{x}}}) \Delta\boldsymbol{\theta}_b + k(\mathbf{x} - \hat{\mathbf{x}}) + \mathbf{K}_p (\hat{\mathbf{x}} - \mathbf{x}_d) = k\Delta\mathbf{q}. \quad (12)$$

Note that equation (12) can be rewritten as:

$$B\Delta\dot{x} + Y_b(\dot{x}_d)\Delta\theta_b + k(x - \hat{x}) + K_p(x - x_d) - K_p(x - \hat{x}) = k\Delta q. \quad (13)$$

That is,

$$B\Delta\dot{x} + Y_b(\dot{x}_d)\Delta\theta_b + (kI_2 - K_p)e_x + K_p\Delta x = k\Delta q, \quad (14)$$

where $I_2 \in \mathbb{R}^{2 \times 2}$ is an identity matrix.

Next, multiplying both sides of equation (8) with $\hat{B}$ and substituting $-k(x - q)$ in equation (2) into it, the observer dynamics is obtained as:

$$\hat{B}\dot{\hat{x}} = B\dot{x} + K_x e_x. \quad (15)$$

Note that equation (15) can be rewritten as:

$$B(\dot{x} - \dot{\hat{x}}) + (B - \hat{B})\dot{\hat{x}} + K_x e_x = 0. \quad (16)$$

That is,

$$B\dot{e}_x + Y_b(\dot{\hat{x}})\Delta\theta_o + K_x e_x = 0. \quad (17)$$

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

$$V_x = \frac{1}{2}\Delta x^T B \Delta x + \frac{1}{2}e_x^T B e_x + \frac{1}{2}\Delta\theta_b^T L_b^{-1} \Delta\theta_b + \frac{1}{2}\Delta\theta_o^T L_o^{-1} \Delta\theta_o. \quad (18)$$

Differentiating V_x with respect to time, we have:

$$\dot{V}_x = \Delta x^T B \Delta\dot{x} + e_x^T B \dot{e}_x - \dot{\theta}_b^T L_b^{-1} \Delta\theta_b - \dot{\theta}_o^T L_o^{-1} \Delta\theta_o. \quad (19)$$

Substituting equations (9), (11), (14), and (17) into equation (19), we have:

$$\begin{aligned} \dot{V}_x &= \Delta x^T [-Y_b(\dot{x}_d)\Delta\theta_b + (K_p - kI_2)e_x - K_p\Delta x \\ &\quad + k\Delta q] + e_x^T [-Y_b(\dot{\hat{x}})\Delta\theta_o - K_x e_x] \\ &\quad - \dot{\theta}_b^T L_b^{-1} \Delta\theta_b - \dot{\theta}_o^T L_o^{-1} \Delta\theta_o \\ &= k\Delta x^T \Delta q - [\Delta x^T e_x^T] P_x [\Delta x^T e_x^T]^T, \end{aligned} \quad (20)$$

where

$$P_x = \begin{bmatrix} K_p & \frac{k}{2}I_2 - \frac{1}{2}K_p \\ \frac{k}{2}I_2 - \frac{1}{2}K_p & K_x \end{bmatrix}. \quad (21)$$

If the control parameters K_p and K_x are chosen so that

$$\lambda_{\min}[K_x] > \frac{1}{4}\lambda_{\min}[K_p], \quad (22)$$

then P_x is positive definite.

We are now ready to state the following theorem:

Theorem: *The desired position input of the laser beam in equation (10) and the update laws in equations (9) and (11) for the optical tweezers system guarantees the convergence of $x \rightarrow x_d$ and $\dot{x} \rightarrow \dot{x}_d$ as $t \rightarrow \infty$ if $\Delta q = 0$, and the condition in (22) is satisfied.*

Proof: Since $\Delta q = 0$, we have that $V_x > 0$, and $\dot{V}_x \leq 0$ if condition (22) is satisfied. Therefore, V_x is bounded, which also indicates that Δx , e_x , $\Delta\theta_b$, and $\Delta\theta_o$ are all bounded. From equation (14), it is concluded that $\Delta\dot{x}$ is also bounded. The boundedness of $\Delta\dot{x}$ ensures the boundedness of $\dot{x}$ if $\dot{x}_d$ is bounded. The boundedness of $\dot{x}$ and e_x ensures the boundedness of $\dot{\hat{x}}$ from equation (15). Since both $\dot{x}$ and $\dot{\hat{x}}$ are bounded, $\dot{e}_x = \dot{x} - \dot{\hat{x}}$ is also bounded. Therefore,

$\ddot{V}_x$ is bounded, and $\dot{V}_x$ is uniformly continuous. From the Barbalat's Lemma [14], [15], we have $\dot{V}_x \rightarrow 0$ as $t \rightarrow \infty$. That is, $x \rightarrow x_d$ and $e_x \rightarrow 0$.

In addition, the boundedness of Δx ensures the boundedness of $\dot{\theta}_b$ from equation (11). Differentiating equation (14), it is seen that $\Delta\ddot{x}$ is bounded since $\Delta\dot{x}$, $\dot{\theta}_b$, $\dot{e}_x$ are bounded. Therefore, $\Delta\dot{x}$ is uniformly continuous. Since $\Delta x \rightarrow 0$ and $\Delta\dot{x}$ is uniformly continuous, $\Delta\dot{x} \rightarrow 0$. That is, $\dot{x} \rightarrow \dot{x}_d$. $\triangle\triangle\triangle$

Remark: The convergence that $\Delta q \rightarrow 0$ can be guaranteed by developing a control input for the robotic manipulator of the laser source, and the dynamic model of the manipulator is described as:

$$M_q \ddot{q} + B_q \dot{q} = u, \quad (23)$$

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

By introducing the dynamics of the manipulator of the laser source into the optical tweezers system, a dynamic approach that takes into account the combined effects of manipulator and cell can be formulated for optical manipulation, so that the position of the laser source is controlled by closed-loop techniques [13]. Therefore, the control input is set as the torque or voltage of the manipulator of the laser source, and the offset between the cell and the laser $x - q$ is available as a state feedback variable for the control input, which can be utilized to keep the laser near the cell so as to maintain a stable trapping. $\triangle\triangle\triangle$

IV. EXPERIMENT

The proposed control method was implemented in a robot-tweezer manipulation system in the City University of Hong Kong, as shown in Fig. 4(a). The system is constituted of three modules for sensing, control and execution [4]. 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, and the desired position of the laser source is set as the control input.

For our experimental environment, the Reynolds' number is around 3×10^{-4} . Therefore, the mass of the cell is negligible, and the dynamic model of the yeast cell can be described in equation (2).

In the experiment, the position of the laser beam is fixed, and the positions of both the cell and the laser are specified with respect to the motorized stage. Initially, both the cell and the laser beam were located at $(16.8, 16.8)\mu m$, and the trapped cell was manipulated to track the desired trajectory as: $x_{d1} = 17 + 0.2t \mu m$, and $x_{d2} = 17 + 0.2t \mu m$.

The control parameters were set as: $K_p = I_2$, $K_x = 0.1I_2$, $L_d = 10^{-7}I_2$, and $L_o = 10^{-7}I_2$. The tracking errors

Fig. 4. Line tracking

Fig. 5. Positions of the cell at various time instants.

are shown in Fig. 4(b), and the path of the laser and the cell is shown in Fig. 4(c). As seen from Fig. 4(b) and Fig. 4(c), the trapped cell is manipulated to follow the desired linear trajectory. The pictures of the trapped cell at various time instants are shown in Fig. 5.

V. CONCLUSIONS

In this paper, an adaptive observer technique is developed to eliminate the requirement of measuring the velocity of the cell in optical manipulation. The proposed observer is also useful for other optical manipulation control systems that require the velocity information of the cell. The proposed observer based control strategy enables the laser beam to manipulate the cell to track the desired trajectory. The stability of closed-loop system is analyzed by using Lyapunov-like method.

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