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Caging and Transportation of Biological Cells using Optical Tweezers

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Abstract— **This paper proposes a novel micro-manipulation technique for caging and transportation of cells using optical tweezers. A cage is first formed by several optically trapped micro-particles around a target cell, and robotic stage control is then utilized to move the caged cell to a region. This paper thus offers an optical manipulation technique for cell manipulation, in which the cells are manipulated without being trapped directly by using laser beams. Also, in contrast to other grasping-based control approaches, the cage formed by optically trapped micro-particles only bounds the mobility of the cell without strictly immobilizing it. Therefore, it requires less stringent condition than that of maintaining the stability of the grasps during manipulation. The robotic stage's dynamics is considered, and the stability of the control system is investigated. An experiment on caging and transportation of a yeast cell is then performed to show the feasibility of the control technique.**

I. INTRODUCTION

In recent years, robotic micro-manipulation has received significant attention due to its extensive applications in micro-system technologies and biological sciences. Several systems and approaches have been developed for robotic manipulation in the micro-world. Due to a broad range of applications in biophysical characterization and cell transportation, optical manipulation [1] is of increasing interest among the micro-manipulation techniques. In optical manipulation, an optical field generated by a focused laser beam results in scattering and gradient forces acting on a micro-object which is very closed to the beam's center. The resultant trapping force can be then employed for tweezing and manipulation of dielectric micro-particles, atoms, bacteria, viruses, and biological cells, etc.

While manual optical manipulation is inefficient and inaccurate, various automated approaches have been developed for precise and productive optical tweezing [2], [3]. In these proposed approaches, however, only a single object or cell is manipulated, and therefore, limiting the feasible applications of optical tweezing. Various techniques have been then developed for multiple-cell manipulation [4] or human-guided cell manipulation [5]. In [2]- [5], nevertheless, the manipulated objects or cells are directly tweezed and manipulated by using laser tweezers, and thus leading to the dependence of the proposed approaches on the physical nature of the objects. On the other words, these approaches are only applicable for manipulation of trappable objects or cells.

Limitation of the direct trapping and manipulation techniques has led to the necessity of indirect cell manipulation. Manipulation approaches using micro-tools for adhering and transportation of cells were proposed in [6], [7]. However, it is required that either the micro-tools are fabricated [7] or the gel must be generated by mixing with the medium culture [6] prior to the manipulation processes. In addition, these approaches [6], [7] also depends on temperature control so as to release or adhere the manipulated cells from the tools. An indirect pushing approach for transportation of cell based on a path planning algorithm was developed in [8]. However, it is generally difficult to bound the cell's mobility or prevent it from escaping arbitrary far in the pushing processes. A motion planning approach using a gripper formation of trapped beads for transportation of single manipulated cells was then proposed in [9]. In addition, control approaches using trapped particles have also been developed for grasping and transportation of single objects [10], [11], or multiple objects or cells [12]. In these approaches [9]- [12], the manipulated cells or objects are immobilized by grippers or grasping formations, and thus stringent condition is required for maintaining stable grasps of manipulated objects during manipulation.

This paper proposes a novel micro-manipulation approach for caging and transportation of cells using optical tweezers. A cage is first formed by several optically trapped micro-particles around a target cell so as to bound the cell's mobility. The cell is then transported to a region by stage control while being caged by the optically trapped micro-particles. This paper offers a micro-manipulation approach for caging and transportation of cells, which can also be utilized for transportation of various micro-objects. Comparing to other pushing-based approaches, the usage of the cage formed by optically trapped micro-particles thus allows a certain degree of cell mobility, while preventing the cell from escaping arbitrary far. Besides, as a relatively low degree of accuracy in relative orientations and positions is required, the proposed caging-based technique for cell manipulation are possibly more robust than grasping-based approaches. The robotic stage's dynamics is considered, and the stability of the control system is investigated. An experiment on caging and transportation of cell is then conducted to show the feasibility of the technique.

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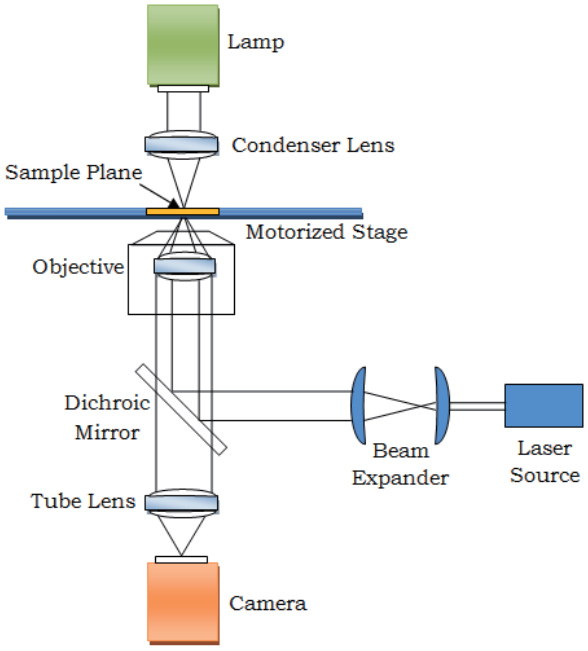

Fig. 1. An optical tweezers system.

The following sections are organized as follows. Section II states the control problem. A micro-manipulation technique for caging and transportation of cells together with controller design and stability analysis is then presented in Section III, followed by experimental result in Section IV. Conclusions are given in Section V.

II. PROBLEM FORMULATION

Optical manipulation has recently attracted a considerable attention among the micro-manipulation techniques due to its ability to perform precise cell manipulate. Fig. 1 shows an optical manipulation system.

This paper proposes a novel micro-manipulation technique for caging and transportation of biological cells. Several trappable micro-particles are first trapped by the lasers. The optically trapped micro-particles are then employed to form a cage around a target cell so as to bound the cell's mobility. By using stage control while fixing the cage of optically trapped micro-particles, the relative position of the cell with the robotic stage is thus varied. An illustration of the proposed control technique is shown in Fig. 2. In this paper, the objective of the control problem is to transport the caged cell to a desire region. In contrast to other grasping-based control approaches for cell manipulation, the cage formed by several optically trapped micro-particles only bounds the mobility of cells without immobilizing it. Therefore, it requires less stringent condition than that of maintaining the stability of the grasps during manipulation.

To formulate the control problem, a coordinated frame $\sum_S$ is specified with respect to the stage and move with the stage, as shown in Fig. 3. A vector $\boldsymbol{s}$ is defined as the position of the center of the cage, and $\boldsymbol{x}$ is the cell's position, both are specified with the coordinate frame $\sum_S$.

The dynamics of the robotic stage is then given as [12]:

$$\boldsymbol{M}\ddot{\boldsymbol{s}} + \boldsymbol{B}\dot{\boldsymbol{s}} = \boldsymbol{u}, \tag{1}$$

with an inertia matrix $\boldsymbol{M} \in \Re^{2\times 2}$, a damping matrix $\boldsymbol{B} \in \Re^{2\times 2}$, and a control input $\boldsymbol{u}$ applied to the robotic stage.

III. CAGING AND TRANSPORTATION OF CELLS

In this section, a micro-manipulation technique is presented for caging and transportation of a target cell using optically trapped micro-particles and robotic stage control. The target cell is first caged by using several optically trapped micro-particles. Robotic stage control is then utilized for transportation of the caged cell to a desired region.

A. Caging of a Biological Cell using Optically Trapped Micro-particles

In this control technique, several optically trapped micro-particles are first employed to form a cage around a target cell, as illustrated in Fig. 4. With d_o being the smallest dimension of the target cell, and d_{ij} being the distance between two neighboring optically trapped micro-particles, we thus have an inequality for caging of cell given as:

$$d_{ij-max} < d_o, \tag{2}$$

where d_{ij-max} is the largest distance between any two neighboring micro-particles in the cage. The requirement (2) is to ensure that the cell is bounded inside the cage without escaping arbitrary far from it.

In addition, to avoid jamming between the optically trapped micro-particles, it is also required that:

$$d_{ij-min} \geq r, \tag{3}$$

with a positive constant r defining the minimum-allowed distance between two neighboring optically trapped micro-particles. The requirement (3) is thus equivalent to maintaining a minimum predefined distance between two neighboring optically trapped micro-particles.

It is worth noting that the cage formed by the optically trapped micro-particles can also be squeezed so as to form a grasping formation of the target cell. The contacts between the optically trapped micro-particles and the target cell in the grasping formation, however, needs to be adjusted carefully to ensure the stability of the grasping formation, especially during the manipulation processes.

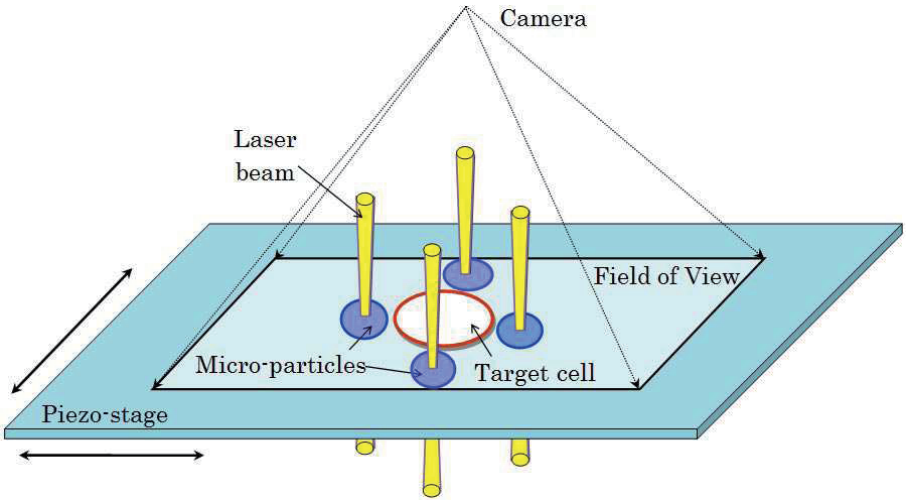

Fig. 2. The control system for caging and transportation of cell using optical tweezers. Four micro-particles are first trapped by four laser beams, and thus forming a fixed cage around the target cell. While being caged in the fluid medium, the cell is transported by controlling the robotic stage.

B. Transportation of the Caged Cell using Robotic Stage Control

In the previous subsection, a cage generated from several optically trapped micro-particles is utilized to bound the mobility of a target cell in a fluid medium. This subsection aims to develop a controller for the robotic stage so as to transport the caged cell. In this control technique, the caged cell is transported to a desired region, which is specified as:

$$f(\Delta \boldsymbol{x}) = \begin{bmatrix} f_1(\Delta \boldsymbol{x}) \\ f_2(\Delta \boldsymbol{x}) \\ \vdots \\ f_m(\Delta \boldsymbol{x}) \end{bmatrix} \leq 0, \tag{4}$$

where $\Delta \boldsymbol{x} = \boldsymbol{x} - \boldsymbol{x}_o$ with $\boldsymbol{x} = [x_1, x_2]^T \in \Re^2$ being the position of the cell, and $\boldsymbol{x}_o = [x_{o1}, x_{o2}]^T \in \Re^2$ being the center of the region, both are specified with respect to $\sum_S$. The desired region in (4) is thus the overlap of all the sub-regions specified by $f_i(\Delta \boldsymbol{x})$ with $i = 1, ..., m$ where $f_i(\Delta \boldsymbol{x})$ with $i = 1, ..., m$ are scalar functions with continuous partial derivatives. Therefore, a desired region with arbitrary shape can be generated with a combination of appropriate scalar functions $f_i(\Delta \boldsymbol{x})$. A desired rectangular region centered at $\boldsymbol{x}_o$, for instance, can be generated by a set of scalar functions as:

$$\begin{cases} f_1(\Delta \boldsymbol{x}) = (x_1 - x_{o1})^2 - a^2 \leq 0, \\ f_2(\Delta \boldsymbol{x}) = (x_2 - x_{o2})^2 - b^2 \leq 0, \end{cases} \tag{5}$$

with a and b being positive constants. In addition, a desired elliptical region centered at $\boldsymbol{x}_o$ can be generated by a scalar function:

$$f(\Delta \boldsymbol{x}) = \frac{(x_1 - x_{o1})^2}{r_1^2} + \frac{(x_2 - x_{o2})^2}{r_2^2} - 1 \leq 0, \tag{6}$$

with r_1 and r_2 being positive constants. And by choosing $r_1 = r_2$, the elliptical region specified in (6) then becomes a circular region.

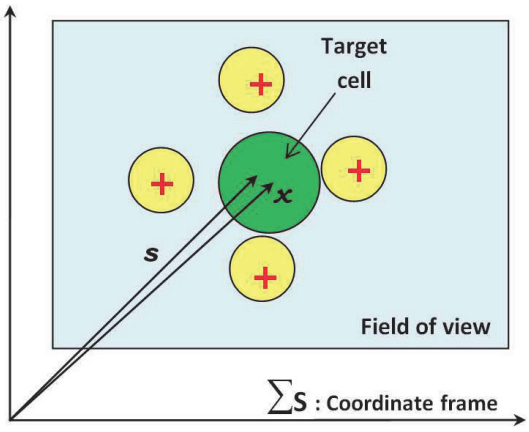

Fig. 3. A coordinated system for the control problem. The '+' signs denote the laser beams' position.

It is worth noting that the manipulation task to transport the caged cell to a desired region $f(\Delta \boldsymbol{x})$ specified in (4) is directly analogous to the task that transports the center of the cage to the following reference region:

$$f(\Delta \boldsymbol{s}) = \begin{bmatrix} f_1(\Delta \boldsymbol{s}) \\ f_2(\Delta \boldsymbol{s}) \\ \vdots \\ f_m(\Delta \boldsymbol{s}) \end{bmatrix} \leq 0, \tag{7}$$

where $\Delta \boldsymbol{s} = \boldsymbol{s} - \boldsymbol{s}_o(t)$ in which $\boldsymbol{s}_o(t)$ is the center of the reference region being specified as:

$$\boldsymbol{s}_o(t) = \boldsymbol{x}_o + \Delta \boldsymbol{\omega}(t), \tag{8}$$

with $\Delta \boldsymbol{\omega}(t) = \boldsymbol{s} - \boldsymbol{x}$ being the displacement of the cell from the center of the cage.

Therefore, our control objective is to transport the center of the cage to a reference region $f(\Delta \boldsymbol{s})$ centered at $\boldsymbol{s}_o$. An

energy function associated with the reference region is then specified as:

$$E = \sum_{i=1}^{m} \frac{\alpha}{\beta} \left[max(0, f_i(\Delta \boldsymbol{s})) \right]^{\beta}, \tag{9}$$

where α and β are positive constants, and $\beta > 2$ so that E is at least twice differentiable.

The control force that attracts the center of the cage toward the reference region is then given as:

$$\begin{aligned} \Delta \boldsymbol{\xi} &= \frac{\partial E}{\partial \Delta \boldsymbol{s}} \\ &= \sum_{i=1}^{m} \alpha [max(0, f_i(\Delta \boldsymbol{s}))]^{\beta - 1} \left(\frac{\partial f_i(\Delta \boldsymbol{s})}{\partial \Delta \boldsymbol{s}} \right)^T . \end{aligned} \tag{10}$$

The control force $\Delta \boldsymbol{\xi}$ in (10) is activated when the cage's center is outside of the reference region, that is $\Delta \boldsymbol{\xi} > \boldsymbol{0}$ so as to transport the cage's center to the reference region. As $f_i(\Delta \boldsymbol{s})$ with $i = 1, ..., m$ are all less than or equal to 0 when the cage's center is inside of the reference region, the control force $\Delta \boldsymbol{\xi} = \boldsymbol{0}$, and the cage's center thus stays inside the reference region.

C. Controller Design

This subsection aims to develop a controller for the robotic stage so as to achieve the control objective. A reference vector is first given as:

$$\dot{\boldsymbol{s}}_r = \dot{\boldsymbol{s}}_o - \Delta \boldsymbol{\xi}, \tag{11}$$

with $\Delta \boldsymbol{\xi}$ being defined in (10). A sliding vector is then specified as:

$$\boldsymbol{z} = \dot{\boldsymbol{s}} - \dot{\boldsymbol{s}}_r = \Delta \dot{\boldsymbol{s}} + \Delta \boldsymbol{\xi}. \tag{12}$$

Eq. (1) can be now rewritten as:

$$\boldsymbol{M} \dot{\boldsymbol{z}} + \boldsymbol{B} \boldsymbol{z} + \boldsymbol{M} \ddot{\boldsymbol{s}}_r + \boldsymbol{B} \dot{\boldsymbol{s}}_r = \boldsymbol{u}, \tag{13}$$

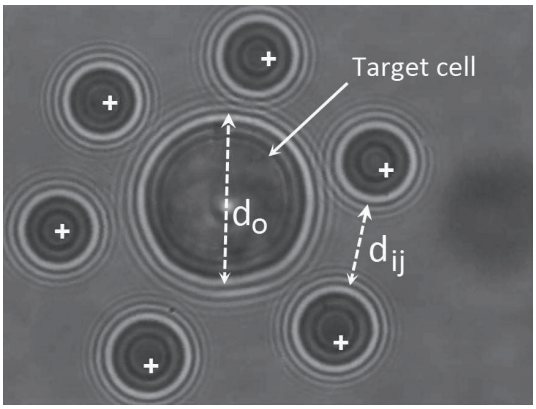

Fig. 4. An illustration for caging of cell. Six optically trapped microparticles are spread around the target cell, and thus bounding the mobility of the cell so as to prevent it from escaping arbitrary far.

in which the third and the forth terms in (13) is linearly parameterized as:

$$\boldsymbol{M} \ddot{\boldsymbol{s}}_r + \boldsymbol{B} \dot{\boldsymbol{s}}_r = \boldsymbol{Y}(\ddot{\boldsymbol{s}}_r, \dot{\boldsymbol{s}}_r) \boldsymbol{\theta}, \tag{14}$$

with a regressor matrix $\boldsymbol{Y}(\ddot{\boldsymbol{s}}_r, \dot{\boldsymbol{s}}_r) \in \Re^{2 \times p}$ and an unknown vector of parameters $\boldsymbol{\theta} \in \Re^p$. Substituting (14) into (13) to obtain:

$$\boldsymbol{M} \dot{\boldsymbol{z}} + \boldsymbol{B} \boldsymbol{z} + \boldsymbol{Y}(\ddot{\boldsymbol{s}}_r, \dot{\boldsymbol{s}}_r) \boldsymbol{\theta} = \boldsymbol{u}. \tag{15}$$

The control input applied to the robotic stage is now proposed as:

$$\boldsymbol{u} = -\boldsymbol{K}_z \boldsymbol{z} + \boldsymbol{Y}(\ddot{\boldsymbol{s}}_r, \dot{\boldsymbol{s}}_r) \hat{\boldsymbol{\theta}} - k_p \Delta \boldsymbol{\xi}, \tag{16}$$

with $\boldsymbol{K}_z \in \Re^{2 \times 2}$ being a gain matrix, k_p being a positive gain, $\boldsymbol{z}$ being defined in (12). In (16), $\hat{\boldsymbol{\theta}}$ is an approximation of $\boldsymbol{\theta}$ whose update law being given as:

$$\dot{\hat{\boldsymbol{\theta}}} = -\boldsymbol{L}_\theta \boldsymbol{Y}^T(\ddot{\boldsymbol{s}}_r, \dot{\boldsymbol{s}}_r) \boldsymbol{z}, \tag{17}$$

where a positive definite matrix $\boldsymbol{L}_\theta \in \Re^{p \times p}$ is symmetric. The closed-loop control system is then achieved by substituting (16) into (15) as:

$$\boldsymbol{M} \dot{\boldsymbol{z}} + (\boldsymbol{B} + \boldsymbol{K}) \boldsymbol{z} + \boldsymbol{Y}(\ddot{\boldsymbol{s}}_r, \dot{\boldsymbol{s}}_r) \Delta \boldsymbol{\theta} + k_p \Delta \boldsymbol{\xi} = \boldsymbol{0}, \tag{18}$$

with $\Delta \boldsymbol{\theta} = \boldsymbol{\theta} - \hat{\boldsymbol{\theta}}$.

A Lyapunov-like candidate function is given as:

$$V = \frac{1}{2} \boldsymbol{z}^T \boldsymbol{M} \boldsymbol{z} + \frac{1}{2} \Delta \boldsymbol{\theta}^T \boldsymbol{L}_\theta^{-1} \Delta \boldsymbol{\theta} + k_p E. \tag{19}$$

Taking time-derivative of V to have:

$$\dot{V} = \boldsymbol{z}^T \boldsymbol{M} \dot{\boldsymbol{z}} - \Delta \boldsymbol{\theta}^T \boldsymbol{L}_\theta^{-1} \dot{\hat{\boldsymbol{\theta}}} + k_p \Delta \dot{\boldsymbol{s}}^T \Delta \boldsymbol{\xi}. \tag{20}$$

Substituting (12), (17), and (18) into (20) and simplifying, yields:

$$\begin{aligned} \dot{V} &= \boldsymbol{z}^T \left(-(\boldsymbol{B} + \boldsymbol{K}) \boldsymbol{z} - \boldsymbol{Y}(\ddot{\boldsymbol{s}}_r, \dot{\boldsymbol{s}}_r) \Delta \boldsymbol{\theta} - k_p \Delta \boldsymbol{\xi} \right) + \\ &+ \Delta \boldsymbol{\theta}^T \boldsymbol{Y}^T(\ddot{\boldsymbol{s}}_r, \dot{\boldsymbol{s}}_r) \boldsymbol{z} + k_p \Delta \dot{\boldsymbol{s}}^T \Delta \boldsymbol{\xi} \\ &= -\boldsymbol{z}^T (\boldsymbol{B} + \boldsymbol{K}) \boldsymbol{z} - k_p \Delta \boldsymbol{\xi}^T \Delta \boldsymbol{\xi}. \end{aligned} \tag{21}$$

Now, we can state the following theorem as follows:

Theorem. The proposed controller (16) and the update law (17) applied to the robotic stage guarantee the stability and convergence of the closed-loop control system for transportation of a caged cell to a desired region. That is, $\boldsymbol{z} \to \boldsymbol{0}$ and $\Delta \boldsymbol{\xi} \to \boldsymbol{0}$ as $t \to \infty$, the center of the cage is driven to the reference region, and thus leading to the convergence of the caged cell toward the desired region.

Proof. From (19) and (21), it is shown that V is bounded. The boundedness of V specified in (19) thus leads to the boundedness of $\boldsymbol{z}$, $\Delta \boldsymbol{\theta}$, and E. Therefore, $\Delta \boldsymbol{\xi}$ is also bounded. From (12), the boundedness of $\Delta \dot{\boldsymbol{s}}$ can be ensured from the boundedness of $\boldsymbol{z}$ and $\Delta \boldsymbol{\xi}$. Since both $\Delta \boldsymbol{\xi}$ and $\Delta \dot{\boldsymbol{s}}$ are bounded, $\Delta \dot{\boldsymbol{\xi}}$ is also bounded.
Besides, the boundedness of all $\boldsymbol{z}$, $\Delta \boldsymbol{\theta}$, and $\Delta \boldsymbol{\xi}$ also lead to the boundedness of $\dot{\boldsymbol{z}}$ from (18). As both $\Delta \dot{\boldsymbol{\xi}}$ and $\dot{\boldsymbol{z}}$ are

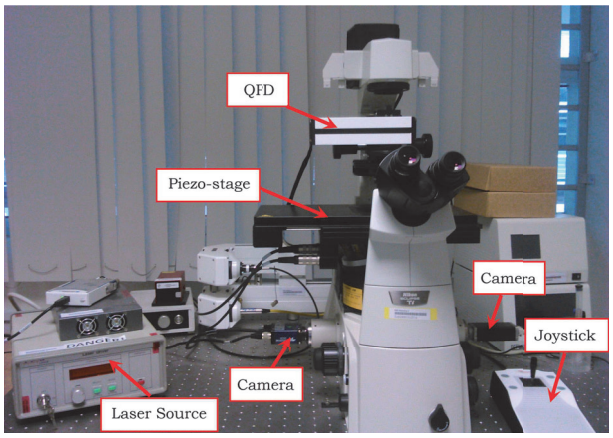

Fig. 5. An optical manipulation system. The system consists of a laser source, a robotic stage, several camera and lighting systems, an a microscope.

bounded, $\ddot{V}$ is thus bounded. Consequently, $\dot{V}$ is continuous, and therefore, $\dot{V} \to 0$ as $t \to \infty$ [13]. As a result, $\boldsymbol{z} \to \boldsymbol{0}$ and $\Delta\boldsymbol{\xi} \to \boldsymbol{0}$ as $t \to \infty$, and thus from (12), we also have that $\Delta\dot{\boldsymbol{s}} \to \boldsymbol{0}$ as $t \to \infty$.

IV. EXPERIMENT

The proposed controller for caging and transportation of biological cells using optical tweezers, which has been specified in (16) and (17), was then implemented on an optical tweezers system, as shown in Fig. 5. The positions of the biological cells or micro-objects in the working space are specified by using either a quadrant photo-diode mechanism or the camera systems with associated video-based detection technique. In the implemented optical tweezers system, transportation of trapped cells or micro-objects can be performed by either controlling the robotic stage or moving the laser traps. The proposed controller was programmed using LabVIEW, and the control input was generated to drive the robotic stage.

In the following experiment, a yeast cell with $5\mu m$ in diameter was employed to be the target cell for the caging and transportation process. Four latex beads whose refractive indexes are of 1.60 were trapped and employed as optically trapped micro-particles. The yeast cell and latex beads were then immerged into ultra-pure water, which was chosen as a fluid medium for the manipulation process.

In the experiment, four laser beams were first generated, and each laser beam was employed to trap a single micro-particle. The four optically trapped micro-particles were then spread around the target cell to form a cage that bounds the cell mobility without strictly immobilizing it. The distances between the optically trapped micro-particles were chosen to satisfy requirements (2) and (3). The caged cell was then transported to a desired circular region:

$$f(\Delta\boldsymbol{x}) = (x_1 - x_{o1})^2 + (x_2 - x_{o2})^2 - R^2 \leq 0, \qquad (22)$$

as the center of the cage being transported to a reference circular region of the form:

$$f(\Delta\boldsymbol{s}) = (s_1 - s_{o1})^2 + (s_2 - s_{o2})^2 - R^2 \leq 0, \qquad (23)$$

with a positive constant R. The power of each laser beam was chosen to be $0.1W$, and the control parameters were set at $\alpha = 1$, $\beta = 4$, $\boldsymbol{K}_z = diag(0.025, 0.025)$, $k_p = 0.01$, and $\boldsymbol{L}_\theta = 10^{-5}\boldsymbol{I}_4$ with $\boldsymbol{I}_4$ being the 4×4 identity matrix. The region error of the target cell with respect to the desired region, which is specified as $||\Delta\boldsymbol{\xi}||$, is shown in Fig. 6, and the snapshots of the control system for caging and transportation of the target cell at different time instants are shown in Fig. 7. A recorded video for caging and transportation of a yeast cell using optical tweezers can also be found in the video attachment together with the submission.

V. CONCLUSION

This paper has proposed a novel micro-manipulation technique for caging and transportation of cells. In this control technique, a cage is first formed by several optically trapped micro-particles around a target cell, and thus bounding the mobility of the cell in a fluid medium. The caged cell is then transported to a desired region by controlling the robotic stage. Formulation of the control problem has been developed with the consideration of the robotic stage's dynamics, and the stability of the control system has been investigated by using a Lyapunov-like analysis. An experiment on caging and transportation of a yeast cell has also been conducted to show the feasibility of the control technique.

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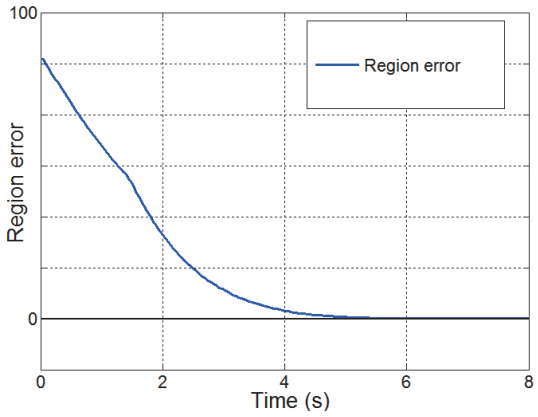
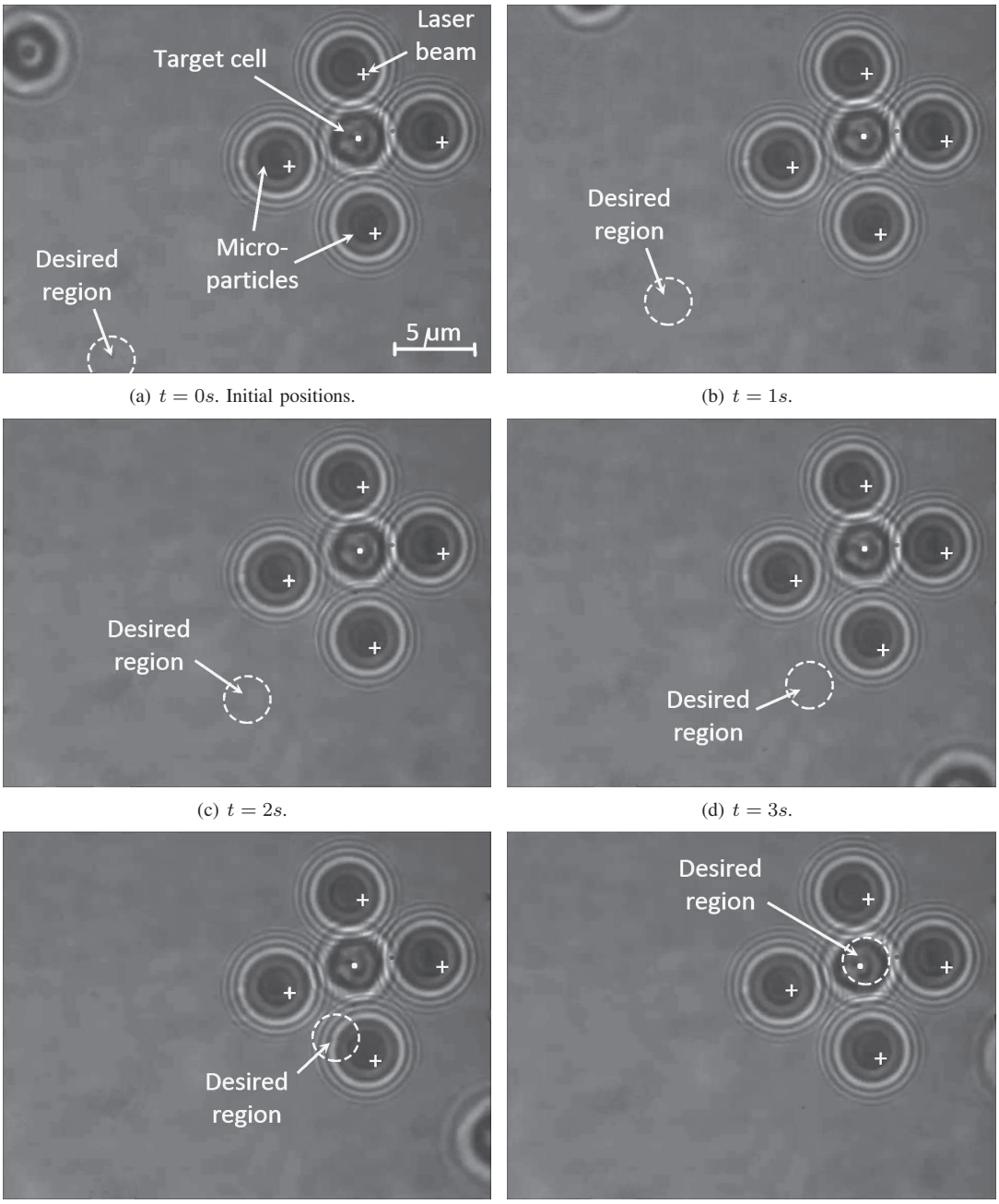


Fig. 6. Region error of the caged cell.



(a) $t = 0s$. Initial positions.

(b) $t = 1s$.

(c) $t = 2s$.

(d) $t = 3s$.

(e) $t = 4s$.

(f) $t = 6s$.

Fig. 7. Experimental result for caging and transportation of a yeast cell using optical tweezers. A cage is first formed by four optically trapped micro-particles around a target cell, and thus bounding the cell's mobility in a fluid medium. The caged cell is thus transported to a desired region by controlling the robotic stage, while fixing the cage in the camera's field of view.

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