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Brief paper

A switching controller for high speed cell transportation by using a robot-aided optical tweezers system☆

Xiangpeng Li [a,b], Hao Yang [a,b], Haibo Huang [b], Dong Sun [a,*]

[a] Department of Mechanical and Biomedical Engineering, City University of Hong Kong, Hong Kong
[b] Robotics and Microsystems Center, College of Mechanical and Electrical Engineering, Soochow University, Taiwan

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ABSTRACT

Rapid and efficient cell manipulation is critical to many cellular operations at the single-cell resolution. In this paper, we propose a new approach for high speed manipulation of a single suspended cell using a robot-aided optical tweezers cell manipulation system. A switching geometrical model for achieving automatic cell trapping, maintenance of optical trapping, and obstacle avoidance is developed based on an objective of confining the trapped cell inside the high speed transfer region, which can help attain high speed cell transportation velocity. With the switching geometrical model, a controller for high speed cell transportation is proposed to transfer the target cell to the destination efficiently. Experiments of manipulating human leukemia cancer NB-4 cells to the specific testing area for property characterization are performed to demonstrate the effectiveness of the proposed approach.

1. Introduction

Single cell analysis uncovers individual cell differences within heterogeneous cell populations, thus enhances understanding of the molecular basis of aberrant cell states and advances early diagnosis of diseases and personalized medicine (Tischler & Surani, 2013). A fundamental issue of the single-cell research relies on rapid and accurate separation and manipulation of specific cells (e.g., metastatic cancer cells, human leukemia cells or low-level bacteremia in blood) to the target positions for conducting further bioassays in the context of cancer diagnosis (Dittrich & Manz, 2006), pathogen detection (Beyor, Seo, Liu, & Mathies, 2008), and genomic testing (Cheong et al., 2008). Therefore, a rapid and efficient cellular manipulation technology, regardless of shape, size, type and elasticity of cells, is becoming highly demanded for the cellular analysis with high productivity at the single-cell level.

Several approaches to transporting micro-particles have been previously developed (Wang, Chen, Kong, Wang, Costa, Li, & Sun, 2011) based on technologies of micropipette aspiration (Lee & Lim, 2007), atomic force microscope (Onal, Ozcan, & Sitti, 2011), micro-fabricated cell pusher (Boukallel, Gauthier, Dauge, Piat, & Abadie, 2007), microinjection (Huang, Sun, Mills, Li, & Cheng, 2009), and magnetic tweezers (Bergeles, Kratochvil, & Nelson, 2012; Diller, Giltinan, & Sitti, 2013). In recent years, robot-aided micro-manipulation with optical tweezers has been emerged as a useful tool in biomedical applications, for its advantages of non-contact manipulation thus resulting in minimal damage to biological particles (Ashkin, 2000; Ramser & Hanstorp, 2009). Optical tweezers employ a tightly focused low-power laser beam, which functions as a special robot end-effector to trap and manipulate bio-particles in a non-contact manner (Ramser & Hanstorp, 2009). The optical trapping forces imposed on particles and the corresponding deformations of the particles are in the order of piconewton and nanometer, respectively. The optical trap works only when the microscopic bio-particles locate near the centroid of the focused laser beam (Stromberg, Ryttsen, Chiu, Davidson, Eriksson, Wilson, Orwar, & Zare, 2000).

Most of existing cell manipulation systems equipped with optical tweezers are operated manually. The manual operation requires long-term training of the skilled operators, and also suffers from disadvantages of low efficiency, low success rate and low accuracy. Several automatic schemes have been proposed recently, including Arai, Onda, Iitsuka, and Maruyama (2009), Chapin, Germain, and Dufresne (2006), Chowdhury, Svec, Wang,

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* Corresponding author.
E-mail addresses: licool@suda.edu.cn (X. Li), younghow@mail.ustc.edu.cn (H. Yang), hbhuang@suda.edu.cn (H. Huang), medsun@cityu.edu.hk (D. Sun).

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Seale, Wikswo, Losert, and Gupta (2013), Ju, Liu, Yang, and Sun (2014), and Wu, Sun, Huang, and Xi (2013). In all these methods, an open-loop control planner was adopted to transfer cells along pre-designed, collision-free paths. A dynamic path planner for indirect optical transportation of multiple cells was proposed by Banerjee, Chowhury, Losert, and Gupta (2012). In the study of Aguilar-Ibanez, Suarez-Castanon, and Rosas-Soriano (2010), a simple feedback control scheme was proposed to transfer micro-particles. A closed-loop control strategy developed by Hu and Sun (2011) achieved automated manipulation of single and multiple cells in an obstacle-free environment. Chen and Sun (2012) developed a region-based flocking controller to control multiple cells into formations. Cheah, Li, Yan, and Sun (2014) developed a vision-based observer to estimate cell velocity during optical manipulation with a tracking control strategy. Li, Cheah, Hu, and Sun (2013) controlled both cell trapping and cell manipulation in an obstacle-free environment. A unified controller was further developed to control cell trapping, cell manipulation and obstacle avoidance simultaneously (Li, Yang, Wang, & Sun, 2015).

To transfer cells with high speed by lasers, a large trapping force by optical tweezers is needed to hold the cell, which requires a large offset between the center of the laser beam and the centroid of the trapped cell. On the other hand, to prevent the cell escape from the optical trap during transportation, the laser beam must stay closely enough to the trapped. To maintain the cell within the optical trap, most of existing approaches either employ the duration control method or generate a strong potential field to regulate the value of the offset. The duration control method (e.g., Chen & Sun, 2012; Hu & Sun, 2011) may causes a sudden switch or chattering, which is unwanted in sensitive biological applications. The potential field based approaches (e.g., Li, Cheah et al., 2013; Li et al., 2015) employ geometrical constraints to regulate the value of the offset to prevent the cell escape from the optical trap; this method, however, cannot induce high speed cell transportation.

In this paper, we develop a new switching control approach to achieving high speed cell transportation with optical tweezers while maintaining a stable optical trapping of cell. This method can significantly increase the efficiency of cell manipulation, and no similar research has ever been reported in the literature. The success of this new approach is due to the development of a new switching geometrical model that formulates automated cell trapping, maintaining the trapped cell within the optical trap in high speed motion, and obstacle avoidance in a unified manner. Based on this model, a potential field based feedback controller is developed to achieve the above goals simultaneously. Note that the approaches by Arai et al. (2009), Banerjee et al. (2012), Chen and Sun (2012), and Hu and Sun (2011) focused on the cell transportation problem only and did not discuss sufficiently how the trapped cell can be always maintained within the optical trap. Li, Cheah et al. (2013) attempted to address both the cell trapping and cell transportation problems together, but did not take the issues of high speed transfer and obstacle avoidance into consideration. Li et al. (2015) developed a geometrical model for the design of a robust unified controller, but the method suffered from disadvantages of relatively low cell transportation speed and hence low manipulation efficiency, and also, the method was incapable of automated cell trapping.

2. Dynamics and problem formulation

2.1. Dynamics

In optical tweezers system, an optical trap can be generated by focusing a laser beam with an objective lens of high numerical aperture. The optical trap can manipulate the cell without physical contact. In this paper, the cell to be transferred is an suspended cell,

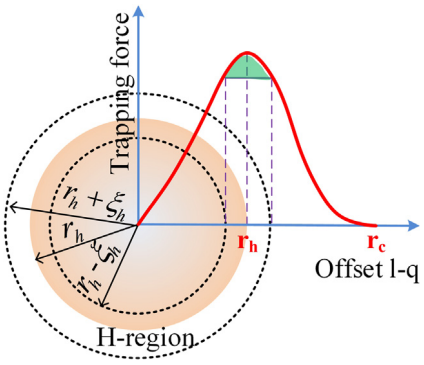

Fig. 1. The spatially variation of the trapping force.

which is denoted as a disc centered at $q(t) \in \Re^2$ with radius of R_c. The optical trap is denoted as a disc centered at $l(t) \in \Re^2$ with a radius of r. The destination is denoted as g. Following Chen and Sun (2012) and Hu and Sun (2011), the dynamics of the trapped cells is expressed as:

$$m\ddot{q} = F_{trap} - F_{drag} \tag{1}$$

where $F_{drag} = b\dot{q}$, representing the viscous drag force, and b is a positive viscous coefficient; $F_{trap} = k_t(l - q)$ denotes the trapping force applied by the optical tweezers on the trapped cell; $l - q$ denotes an offset between the centroid of the cell and the focus of the laser beam; and k_t is the trapping stiffness specified in Cheah et al. (2013) as follows:

$$k_t = \begin{cases} \hat{k}_t, & \|l - q\| \le r_h \\ \hat{k}_t e^{-(\|l-q\| - r_h)}, & \|l - q\| > r_h \end{cases} \tag{2}$$

where $\hat{k}_t$ is a positive constant. The detailed dynamics model was presented in Gauthier and Wallace (1995) and Wu, Sun, and Huang (2011).

When the cell is perfectly located at the centroid of the optical trap (i.e., zero offset), the trapping force is zero. When the offset is less than a critical value r_h, the trapping force increases as the offset increases and achieves its maximum. When the offset is greater than r_h, the trapping force decreases as the offset increases due to the attenuation of the trapping stiffness, as see in (2). The trapping force becomes zero when the offset exceeds r_c, namely, the cell is completely outside the optical trap. The spatial variation of the trapping force is illustrated in Fig. 1.

In this study, the Reynolds number is always smaller than $10^{-4} \ll 1$ in the cell manipulation environment, and hence, the effect of the inertia force $m\ddot{q}$ can be ignored. Then, the dynamics equation is simplified as

$$\dot{q} = \frac{F_{trap}}{b} = \frac{k_t}{b}(l - q) \tag{3}$$

2.2. Problem formulation

The movement of the trapped cell is proportional to the trapping force applied on it based on Eq. (3). Therefore, in order to obtain a relative large cell manipulation velocity, the offset $l - q$ is ideally to be large, e.g., close to the critical value r_h, in order to obtain a large trapping force. In other words, to attain a large cell transportation velocity, the optical trap should locate inside the annular region around the target cell (as shown in Fig. 1), which is termed as the high speed transfer region (H-region) and defined by $S_h = S_{h-o} \cap S_{h-i}$, where S_{h-o} and S_{h-i} are expressed as

$$S_{h-o} = \left\{ l \,|\, f_{h-o} = (l - q)^2 - (r_h + \xi_h)^2 \le 0 \right\}$$
$$S_{h-i} = \left\{ l \,|\, f_{h-i} = (r_h - \xi_h)^2 - (l - q)^2 \le 0 \right\},$$