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Brief paper

Development of a collision-avoidance vector based control algorithm for automated in-vivo transportation of biological cells☆

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ABSTRACT

With the rapid development of precision medicine, the in-vivo manipulation of microparticles has attracted increased attention in recent years. Collision is a main cause of the failure of in-vivo particle transportation. In this paper, an automated control approach with obstacle avoidance function is proposed for in-vivo cell transportation. In the proposed approach, a collision-avoidance vector method is utilized to avoid obstacles during the transportation of the target cell. The proposed method integrates obstacle detection and collision avoidance into a single step, hence reducing the duration of online processing while enhancing the accuracy of obstacle detection. With the proposed approach, different collision avoidance strategies are designed to suit for different transportation environments. The proposed approach exhibits the advantages of reduced online calculation, fast response, high accuracy, and disturbance compensation. Experiments are performed to demonstrate the effectiveness of the proposed controller.

1. Introduction

The in-vivo transportation of microparticles has attracted increased attention in recent years because of its extensive applications in precision medicine, such as the induction or elimination of thrombosis (Zhong, Wei, Zhou, Wang, & Li, 2013), analysis of adhesion property and membrane deformation (Johansen, Fenaroli, Evensen, Griffiths, & Koster, 2016), delivery of drugs (Arruebo, Fernández-Pacheco, Ibarra, & Santamaría, 2007; Berry & Curtis, 2003), and precise transport of target cancer cells in metastasis research. Compared with other manipulation tools, such as *magnetically actuated system* (Arcese, Fruchard, & Ferreira, 2013; Martel et al., 2007), electron microscope (Fukuda, Nakajima, Liu, & ElShimy, 2009), and atomic force microscope (Xie, Haliyo, & Régnier, 2009), optical tweezers exhibits the advantages of precision, flexibility, and noninvasive operation in handling microparticles (Zhang & Liu, 2008). Optical tweezers has also been utilized for the manipulation of microscale objects in vivo (Johansen et al., 2016; Li, Liu et al., 2015, 2017; Zhong et al., 2013). Zhong et al. (2013) used optical tweezers to manipulate red blood cells in living mice to induce or eliminate thrombosis. Johansen et al. (2016) reported in-vivo particle manipulation in living zebrafish, demonstrating the feasibility of using optical tweezers to trap nanoparticles that are adhered on cells for the analysis of adhesion properties and membrane deformation in vivo. To date, all in-vivo manipulation studies with optical tweezers are based on manual operation, which suffer from limitations of disturbances, uncertainties, and problematic collision avoidance.

Robotics technology can help improve in-vivo manipulation. The automated robot-aided optical tweezers system integrates robotics with optical tweezers to achieve the fast, stable, and efficient manipulation of microparticles. Robotic tweezers manipulation has been widely used in a variety of in-vitro manipulation tasks, including cell transportation (Banerjee, Chowdhury, Losert, & Gupta, 2012; Chowdhury et al., 2014; Hu & Sun, 2011; Ju, Liu, Yang, & Sun, 2014; Li, Liu et al., 2015; Thakur et al., 2014), cell pairing (Xie, Wang, Feng, & Sun, 2015), cell sorting (Chapin, Germain, & Dufresne, 2006), and cell assembly (Ta & Cheah, 2017; Tanaka, Tsutsui, & Kitajima, 2013). In Li, Liu et al. (2015), a robot-tweezers cell manipulation system with a P-type controller was developed to automatically transport single red blood cells (RBCs) in living zebrafish. A disturbance compensation controller was reported in

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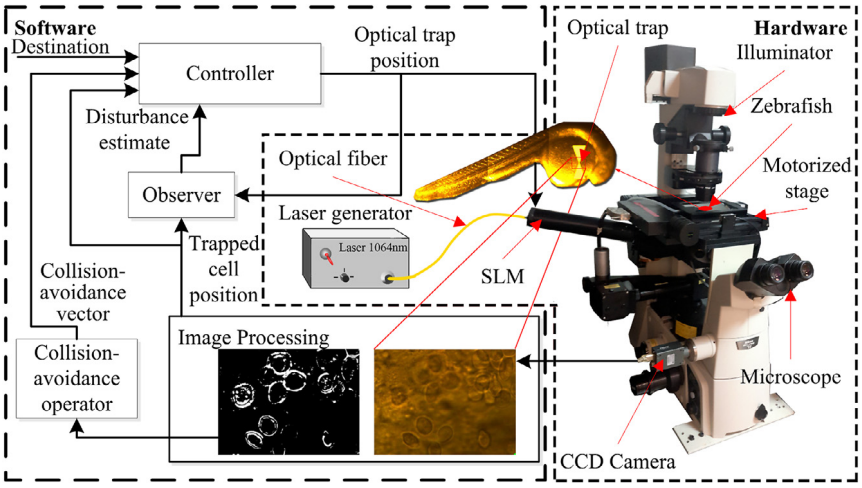

Fig. 1. Schematic of the cell transportation control system.

Li, Liu et al. (2017), which could reduce the influence of blood flow during in-vivo cell transportation.

The problem of collision avoidance, however, has not been sufficiently addressed in all the reported in-vivo cell transportation studies. Poor collision avoidance may cause cell transportation to fail. The problem of collision avoidance has been intensively investigated in the field of robotics. Many solutions to the collision-avoidance problem, such as rapidly exploring random tree (RRT) algorithm (Karaman, Walter, Perez, Frazzoli, & Teller, 2011; Melchior & Simmons, 2007), potential field method (Ge & Cui, 2002; Koren & Borenstein, 1991), and dynamic A* search (Likhachev, Ferguson, Gordon, Stentz, & Thrun, 2005) have been reported. For the in-vitro transportation of microparticles, several collision-avoidance approaches have been reported mainly in two categories. In the first category, path is planned first and then a controller is designed to track microparticles in moving along the designed path (Banerjee et al., 2012; Chowdhury et al., 2013; Ju et al., 2014; Wu, Sun, Huang, & Xi, 2012). This method requires identification of the obstacle position and estimation of the obstacle's motion, which is difficult to achieve in complex in vivo environment. In the second category, a controller that utilizes real-time feedback to avoid obstacles is designed (Haghighi & Cheah, 2016; Hu & Sun, 2011; Li, Yang, Wang, & Sun, 2015), which is more suitable for dynamic environment. Among all these reported works, the obstacles' positions must be identified first for the purpose of obstacle avoidance. In reality, however, identification of microparticles' positions in the in-vivo condition requires a considerable amount of processing work, which also suffers from low accuracy. As a result, existing transportation methods are difficult to be used for avoiding obstacles in a cell-dense in-vivo environment. We recently proposed direct extraction of pixel information from the image around the controlled cell, instead of the whole information of nearby obstacles, to design an obstacle avoidance strategy (Li, Chen, Wang, & Sun, 2017).

In this paper, we propose a disturbance compensation controller with collision-avoidance capability for in-vivo cell transportation. A collision-avoidance vector method is developed to solve the collision-avoidance problem encountered during automatically controlled in-vivo cell transportation. The collision-avoidance vector can be obtained by processing the image around the controlled cell with a collision-avoidance operator. In this way, the information of obstacles can be obtained with significantly reduced online computation work, and there is no need to measure the position of each obstacle. With this calculated vector, a closed-loop controller is designed to precisely drive the target cell while avoiding obstacles. With different collision-avoidance operators, the controller can have different avoidance strategies for different environments. In this paper, two types of collision-avoidance operators are introduced and three avoidance strategies are tested with these two operators. The controller prioritizes avoiding large and close-to-cell obstacles and strikes a balance between avoiding collision and moving cells forward in an environment with high cell density. The proposed controller can also compensate for the disturbance caused by blood flow. Experiments of transporting red blood cells (RBCs) in living zebrafish are performed to demonstrate the effectiveness of the proposed approach.

2. Cell manipulation system

Fig. 1 shows the schematic of the proposed cell transportation control system, which includes a holographic optical tweezers (Arryx, BioRyx200) cell manipulation system established in the City University of Hong Kong (Hu & Sun, 2011). A zebrafish is placed on an $X-Y-Z$ moving stage (Prior Scientific, ProScan). Images in the transparent zebrafish can be visualized with a microscope (Nikon TE2000) mounted on the Z-axis of the moving stage, and can be observed and captured by an IEEE 1394 CCD camera (Foculus, FO124SC). A laser with a maximum output of 3 W at a wavelength of 1064 nm is produced by a laser source (V-106C-3000 OEM J-series, Spectra Physics). An optical trap can be focused on the zebrafish by adjusting a liquid crystal spatial light modulator (SLM) and the convergence of an inverted objective (Nikon TE2000, Plan Apo 60X/1.20 WI, Japan). Internal zebrafish images, which are captured by a CCD camera, are delivered to a computer for background extraction, background segmentation, cell recognition, and target tracking. The collision-avoidance vector, which guides cell movement while avoiding collision, is calculated by processing the image around the controlled cell with the designed operator. The disturbance caused by blood flow can be estimated by the observer based on cell movement speed and optical trap position. A controller then calculates the expert position and sends the signal to SLM to generate a designed optical trap. The generated optical trap drives the target cell toward the destination while avoiding collisions during transportation.

In practice, the in-vivo image is chaotic and difficult to be directly used for cell identification. To accurately track the target cell and to avoid obstacles, the image that represents the moving cell must be extracted from the original image via the background segmentation method (Hofmann, Tiefenbacher, & Rigoll, 2012; Li, Liu et al., 2015). Fig. 2 illustrates image processing procedures. The