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Large-scale Virtual Reality Micro-robotic Cell Injection Training

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***Abstract*—Currently the micro-robotic cell injection procedure is performed manually by professional bio-operators. It is a challenging task requiring advanced skills including the ability to precisely control the movement of a micropipette. Developing these skills requires both lengthy and intensive training, and significant practical experience. This paper extends upon our previous work in desktop Virtual Reality (VR) cell injection training to introduce a large-scale VR micro-robotic cell injection system. Through utilization of large visual displays and the large workspace INCA 6D haptic device, the proprioception related to large arm movements (and corresponding visual representation) and the resulting movement of the micropipette in relation to the cell aims to provide the user with a better understanding of the spatial relationship between the micropipette and cell. The haptic device can be operated either with or without haptic guidance. When enabled, haptic guidance is provided in the form of virtual fixtures (VFs) and force feedback to assist the user in following the ideal trajectory towards the penetration point, applying appropriate force for penetration and stopping the micropipette's tip at the suitable deposition point. A user evaluation was conducted to study the usability of the system. Eighteen participants took part in the experiments and were randomly divided into six groups based on the display and haptic guidance modes assigned. The results demonstrated that the large-scale VR micro-robotic cell injection system is a feasible and effective method for bio-operator training where it is suggested that the skills and knowledge acquired can be transferred to the real-world task.**

***Index Terms*— Micro-robot, cell injection, virtual reality, haptics, skill training.**

I. INTRODUCTION

Cell injection is a procedure where a small amount of material, such as protein, DNA, sperm or bio-molecules is injected at a suitable location inside a cell. Since introduction in the early 1900's the technology has been broadly applied to cell biology research, transgenics, toxicology, drug development and in-vitro fertilization [1]. A popular example is intracytoplasmic sperm injection (ICSI) where a sperm is injected into a mature egg to support fertilization.

Typically, micro-robotic cell injection is performed manually by expert bio-operators. In order to become an expert, trainees typically require years of intensive training and experience. Even despite this lengthy training successful cell injection is still difficult to achieve. One factor for the low success rate is that the micropipette positioning of successful injections are not easily reproducible. Furthermore due to human involvement, the manual or semi-autonomous micro-robotic cell injection suffer limitations such as poor precision [2] and low reproducibility [3].

There are a number of specific considerations for the micro-robotic cell injection procedure. The cell and the micropipette are extremely small and delicate with contact forces between the cell and micropipette ranging between mN to μN [4]. In order to perform cell injection, the bio-operator needs to be capable of precisely controlling the micropipette to achieve accurate positioning, puncturing and penetration [5, 6]. Important factors determining the success of an injection include accuracy, trajectory, speed and applied force. In an ideal injection, the tip of the micropipette should first be positioned precisely at a suitable penetration point at the cell membrane. Then appropriate force should be carefully applied enabling the micropipette to penetrate the cell membrane. Next the micropipette should be moved in a straight line path towards the deposition target (e.g. nucleus) and then the desired material deposited [7].

VR has been widely utilized in a broad range of applications including motor skills training. For the micro-robotic cell injection training application, utilization of a haptically-enabled VR system offers a flexible approach where physical equipment is not required, increasing accessibility and reducing costs associated with training. The approach also eliminates the risk of damage to the physical system which is not uncommon in the early stages of training.

The following section introduces the large-scale VR micro-robotic cell injection system as a platform for bio-operators.

II. LARGE-SCALE VR MICRO-ROBOTIC CELL INJECTION SYSTEM

In our previous work a desktop VR system for micro-robotic cell injection training was introduced [8, 9]. One of the aims was to investigate the role of the VR system in providing skills training for micro-robotic cell injection. The VR system can be used with two different input controllers, a computer keyboard or Phantom Omni (now known as Geomagic Touch [10]) haptic device. In addition to low-cost application, our earlier work introduced a reconfigurable multi-purpose haptic interface [11] designed for portability with the computer and power supply integrated inside the base of the system. It can be used with up to two Phantom Omni haptic devices for various types of applications.

The large-scale VR micro-robotic cell injection system presented in this section extends beyond our earlier work to introduce a large-scale training interface achieved through different configurations of up to four large projection screens and the INCA6D large scale haptic device. The utilization of the large visual display and corresponding large workspace INCA 6D haptic device is done with the intention that the proprioception related to large arm movements controlling the movement of the micropipette in relation to the cell, as viewed on the large displays, may provide the user with a better understanding of the spatial relationship between the micropipette and cell. This is proposed in a similar way to [12] where larger visual displays were shown to improve performance in spatial orientation as well as sense of presence. The use of the large workspace haptic device as the method to control the 3D movement of the micropipette, with or without haptic feedback, aims to also engage the user's proprioceptive awareness of their arms as they perform the task.

The system was implemented in the CADET VR Lab, within the School of Engineering, Deakin University. There are two different screen configurations, the CAD wall and CAVE-like, as depicted by Fig. 1.

Three of the screens, i.e. left, right and center, are known as the wall screens while the other one is known as the floor screen. A roller is fitted underneath the left and right screens allowing them to be folded in/out up to 90 degree angle. As such the screens can be set to several configurations, mainly the CAD wall and CAVE-like (see Fig. 1), to suit the desired applications. A total of four projectors designated to each of the screens. The three wall screens are rear-projected while the floor screen is overhead-projected (downwards) and all four screens have the dimensions of $3.2m \times 2.4m$.

For visual representation of the virtual environment, users can utilize one of the three display modes provided, 2D, 3D and CAVE-like. The 2D and 3D display modes utilized the CAD wall configuration where the left, center and right screens combined to form a large flat display. Meanwhile the CAVE-like display mode utilized the CAVE-like screen configuration. In this display mode, the left, center and floor screens were utilized where the left screen is folded in to be perpendicular to both the center and floor screens. While in the 2D and 3D display modes only one viewpoint of the environment is displayed to the combined three screens, the CAVE-like display mode provides three different viewpoints of the environment on each of the three screens. The multiple viewpoints can provide better understanding of the orientation and movement of the virtual objects in the 3D space virtual environment.

The setup utilizes four Barco Galaxy NW-12 stereoscopic projectors which can provide active 3D stereo display with active Infitec® technology. The active stereo features and the active Infitec technology based on 'Infitec Excellence' filters support stereoscopic images to be displayed with very fine detail. Each projector supports high light output of 12000 lumens enabling significantly high performance even in a bright environment. Other basic specifications related to the projectors' display are such as WUXGA $1920 \times 1200px$ resolution, up to $2{,}000{:}\,1$ contrast ratio, three-chip DLP and $2kW$ xenon lamp.

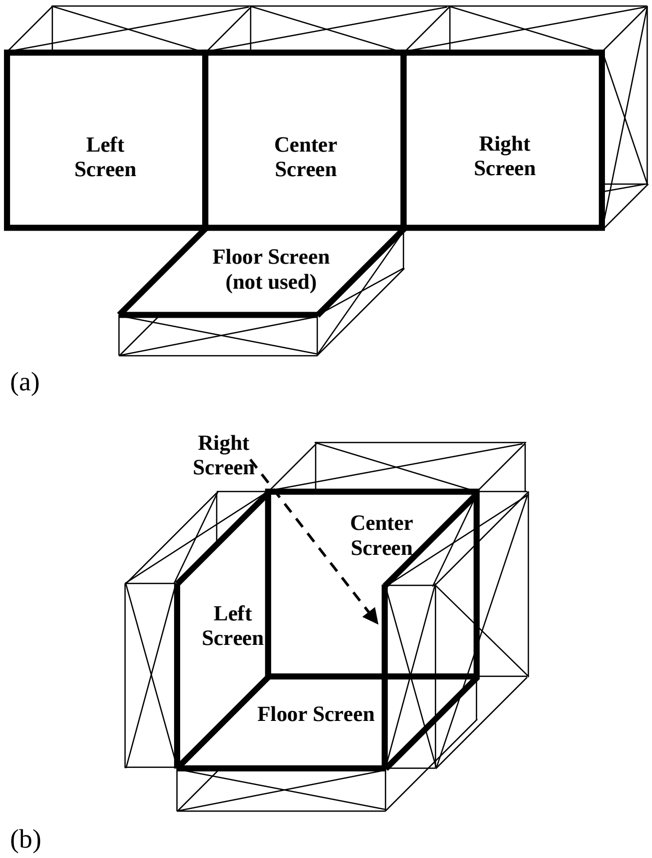

Fig. 1: Screen configurations of the large-scale system as used for the experiments (a) CAD wall configuration, (b) CAVE-like configuration

Multi-projector integration optimization can be achieved through edge blending, DynaColor™ and linked constant light output (CLO), and warping (geometry correction) techniques. The edge blending technique produces seamless images from a multi-projector system. Fundamentally it formulates a mechanism to eliminate the visible band at the overlap region between two projected images. DynaColor™ and linked CLO are utilized to obtain consistent light and color levels across the multi-projected image. The DynaColor™ by Barco is an algorithm which aligns the digitally set primary and secondary color coordinates of each projector to a common color gamut in order to achieve color matching throughout multi-projected images. Meanwhile the Linked CLO constantly control the light output of each projector to the lowest required value regardless of their lamp life. This can ensure same light outputs across all projectors independent of lamps' lumen depreciation over time allowing mixed lamp lives usage and individual lamp replacement. Finally the image warping technique precisely adjust the projected image to be displayed across different screen surfaces or shapes and from different projection angles.

For the 3D and CAVE-like display modes, Volfoni® EDGE™ 1.2 active 3D glasses were utilized in order to view the three-dimensional virtual micro-robotic cell injection environment during the injections. The glasses provide high-quality images from all viewable angles through a pair of fast-response liquid crystal lenses. Performance-wise, the glasses offer 38% optical transmission, $> 500:1$ stereoscopic contrast, and $170 - 115$ field of vision (H,V) which are fully compatible with the display system and able to achieve optimized projected images.

A. Virtual Environment

The virtual environment displays a replication of a cell injection setup. It consists of a virtual cell and basic bio-manipulation equipment such as microscope, micro-robot, micropipette, cell holding dish, etc. The user will have a view of the environment which can be zoomed in or out to change the size of the cell visually and haptically and to concentrate on the areas of interest.

The virtual micro-robot replicates Sutter Instrument's MP285 micromanipulator which is widely used for cell injection and manipulation [13, 14]. The MP285 provides motorized 3-DOF motion usually controlled using rotary encoders. In addition to the three Cartesian axes (x, y, z), an artificial fourth axis allowing diagonal movement from the combination of any two of the three axes can be controlled.

The virtual training environment was developed on the Vizard VR software by Worldviz. In order to replicate the cell interaction in a virtual environment, an appropriate model is required. The model should be able to provide realistic visual and haptic responses to contacts made by the virtual micropipette. For this purpose we have utilized a particle-based cell model introduced in our earlier work [15]. The virtual cell is modelled to visually deform in response to micropipette contacts as well as providing interaction force estimations. These force can be haptically displayed to the user while performing the procedure.

B. Display Modes

This study introduces a large-scale VR micro-robotic cell injection system which provides an immersive virtual environment through three large screens. There are three types of large-scale display mode introduced in this study as shown in Fig. 2.

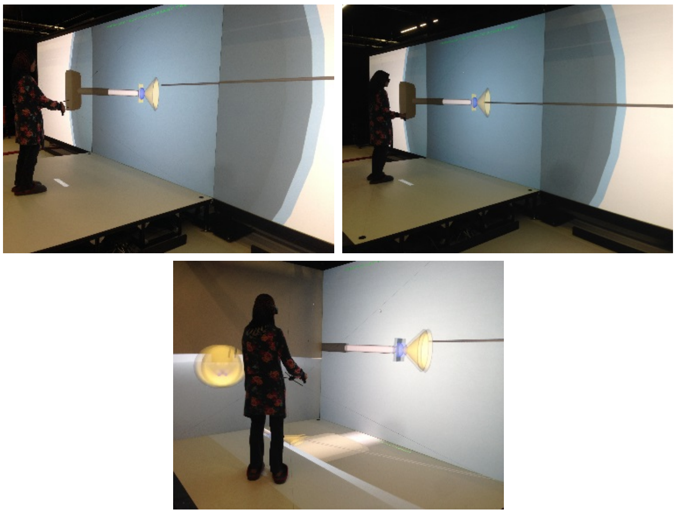

Fig. 2: 2D display mode (*upper left*), 3D display mode (*upper right*) and CAVE-like display mode (*bottom*)

The first is a 2D display mode which projects a two-dimensional image across three large screens arranged in CAD wall. The user is provided with a magnified top view similar to what can be seen from a microscope during an injection. Similarly the second display mode, 3D provides a large-scale three-dimensional image across the three screens in CAD wall. Thirdly the CAVE-like display mode provides a three-dimensional multiple viewpoints image across three large screens in CAVE-like configuration. The front screen displays a magnified top view similar to the view provided by the 2D and 3D display modes. Meanwhile the left screen displays a view from behind the micropipette and the floor screen displays a view from side of the micropipette. With this display mode user is able to obtain a more immersive virtual environment where the display from three different angles are provided simultaneously while injection is performed. In contrast to providing images in three desktop screens the CAVE-like display mode projects large-scale displays where user can move on the floor screen to obtain more sense of presence and increased spatial awareness of the virtual environment.

C. Large Workspace Input Controller

An INCA 6D haptic device by Haption [16] was employed in the experiments to interact with the virtual environment. The INCA 6D is a cable-driven haptic device based on Spidar™ technology introduced by Sato [17]. The haptic device can provide up to 6-DOF (3 translational and 3 rotational) force feedback to user within large workspace (actual workspace depends on the motors and cables positions). The haptic device is capable to simulate heavy object handling realistically with up to $37.5N$ force feedback displays. It has $2mm$ positional resolution to be mapped to its representation in the virtual environment. The interface was achieved by mapping the orientation and position between the haptic device and the virtual micropipette as shown in Fig. 3. As such the virtual cell injection procedure can be performed by holding the haptic device handle to control the virtual micro-robot which holds the micropipette. Utilizing proprioception related to large arm movements to move the haptic device, it is suggested that this combined with the large corresponding visual display provides the user with more information to gain a better understanding of the spatial relationship between the cell and micro-robot.

Given the mapping strategy implemented to the interface user is able to experience an intuitive handling of the micropipette as if they are holding the micropipette as opposed to the traditional rotary encoders. When performing the procedure with the haptic device user have the options to either enabling or disabling the haptic guidance. The haptic guidance provided in this VR training system is discussed in the next subsection.

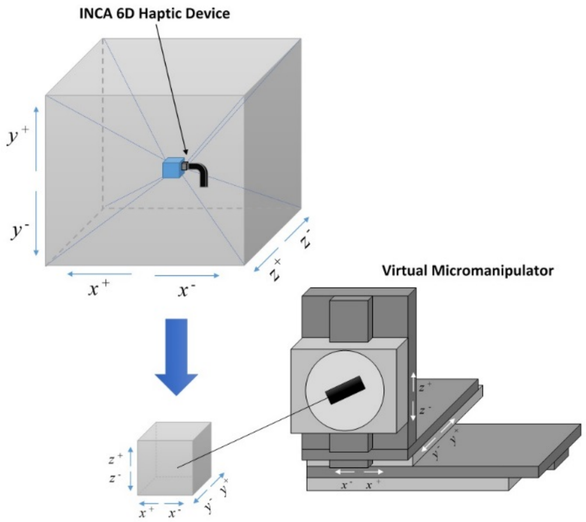

Fig. 3: Mapping strategy between INCA 6D and virtual micro-robot

In order to replicate real micro-robotic cell injection procedure, the virtual micropipette is fixed to a 30 degree offset (tilted) in the x-axis and its movement is limited to the translational x, y, z-axes (Fig. 3). As such to perform an ideal injection user should move the haptic device as straight as possible towards the deposition point.

D. Haptic Guidance

When the haptic feedback is enabled, the VR training system provides two forms of haptic guidance, virtual fixtures (VFs) and force feedback. There are two VFs provided by the system that serves as physical guidance of user's control of the micro-robot so that the micropipette tip achieved the appropriate penetration and deposition point at the membrane and center of the cell respectively. The first is a cone-shaped VF which guides the user to follow ideal trajectory where it allows the micropipette to move inside its conical guided region. Once the micropipette entered the guided region the conical wall prevents the micropipette from going through it. As such, as the user commands the micropipette to approach the cell, the conical VF encourages them to follow an optimized trajectory to the penetration point on the cell membrane. Once the micropipette's tip has reached the penetration point, and the user attempts to pierce the cell membrane they will feel a simulated reaction force, followed by a sudden force drop representing the rupture and penetration of the cell membrane. The user then needs to move the micropipette straightly along its longitudinal axis towards the deposition point inside the cell. To guide the user's movement along this path an axial VF is provided. In order to prevent the user from overshooting the deposition point, which can cause damage to the cell, a planar VF is provided. The planar VF attempts to prevent the user's control of the micropipette from passing the deposition point at the cell center. Once the micropipette's tip reaches the deposition point, the virtual cell becomes inactive and the system can be reset to perform a new trial. It is important to remember that the VFs only provide haptic guidance, and given the maximum amount of force set to be displayed by the haptic device, the user remains in full control of the injection process. The virtual fixtures can be used with or without visual overlay and can be turned off based on user's preference.

III. USER EVALUATION

A set of experiments using human participants was conducted at VR Lab, Deakin University in order to evaluate the effectiveness of the VR system as a training tool for micro-robotic cell injection. Participants' performance in terms of their success rate was considered in the evaluation.

The evaluation was granted a low risk human research ethics approval by the Human Ethics Advisory Group (HEAG), Faculty of Science, Engineering & Built Environment, Deakin University. Eighteen participants (eleven male and eight female) were recruited for the experiments and screened to ensure that they had no prior exposure to any physical cell injection activity. Their demographic data were also obtained to be used in the analysis. Participants' performance was measured and evaluated as discussed in the next section. Participants were also video recorded and interviewed during the experiments in order to obtain useful qualitative data.

A. Experimental Design

The participants were randomly divided into six groups, named as follows and explained below: 2DN, 2DH, 3DN, 3DH, CAN and CAH. Each group comprised of three participants, based on the display mode and haptic guidance mode they used in the experiments. Participants were asked to perform ten injections while the time and position of the virtual micropipette tip were recorded at a $50Hz$ sampling rate. The 2DN and 2DH performed virtual cell injections in two-dimensional display with haptic guidance disabled and enabled respectively. Likewise the 3DN and 3DH performed injections with haptic guidance disabled and enabled respectively, except they were provided with three-dimensional display. The participants in CAN and CAH were provided with a three-dimensional display with multiple viewpoints across three large screens as shown in Fig. 2. It is anticipated that the additional viewpoints provided will contribute to better understanding of the micropipette's orientation and depth estimation as well as improving participants' spatial awareness. The CAN group performed injections with haptic guidance disabled while the CAH group performed injections with haptic guidance enabled.

The parameter used to measure performance was the success rate, S. The success of an injection was considered based on the final position of the micropipette tip, F. In an injection F is self-determined by the participant, by pressing a button on the haptic device, when they think they have reached the best deposition point and are ready for the deposition. An injection was considered successful when F is located inside the cell, indicating that the participant managed to penetrate the cell membrane and stop inside the cell for deposition.

For this evaluation the virtual cell diameter was assumed as $2\mu m$ which is considered a small cell based on the fact that real cell diameters range from 1 to $100\mu m$ [18]. The virtual cell was designed to be 2 spatial units in diameter where a spatial unit in the virtual environment relates to $1\mu m$ in real world. As such the virtual cell had a radius of $1\mu m$ which is centered at the origin $(0,0,0)$. The selection of a small cell size is useful in order to evaluate performance accurately.

An injection is considered successful only when the magnitude of F is less than $1\mu m$ which is the radius of the cell. As such S was determined as below

$$\begin{aligned} if\ |F| &= \sqrt{{x_F}^2 + {y_F}^2 + {z_F}^2} < 1\mu m\,; S = 1 \\ if\ |F| &= \sqrt{{x_F}^2 + {y_F}^2 + {z_F}^2} \geq 1\mu m\,; S = 0 \end{aligned} \quad (1)$$

Additionally, once the cell is penetrated, the micropipette is not allowed to be moved (retracted or pushed forward) beyond the cell membrane in any direction to avoid damage. Therefore, observation was made to verify that no multiple penetrations were made in either inward or outward direction. Apart from observing every injection, position data were also examined to ensure no multiple penetrations were made during an injection.

B. Data Analysis and Results

An evaluation was carried out for a binary completion task parameter where the success rate of every group was considered. The success of an injection, S, was a binary measurement where it involved a pass/fail option based on the final position of the micropipette, F. An injection was considered successful, $S = 1$, when the magnitude of F, $|F|$ was less than $1\mu m$. The success for every injection of a group were accumulated to calculate the success rate in terms of percentage as depicted in Fig. 4.

All six groups demonstrated promising results in terms of their success rate where four of the six groups, 2DH, 3DH, CAN and CAH achieved 100%. Meanwhile another two groups, 2DN and 3DN achieved 90% and 73% respectively. From the total of thirty injections for each group, the 2DN and 3DN groups achieved twenty seven and twenty two successful injections respectively. Despite not achieving 100% success rates, the two groups are considered to demonstrate favorable performance based on the fact that participants in both groups received no haptic guidance and other instruction than initial briefing before the session started.

For the groups with haptic guidance enabled, i.e. 2DH, 3DH and CAH, the 100% success rate may be attributable to the haptic guidance provided.

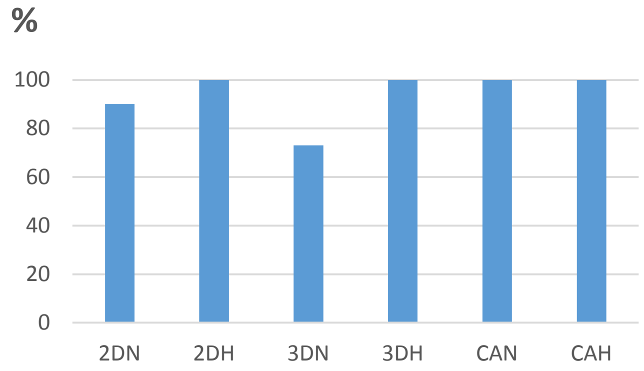

Fig. 4: Mean success rate for all groups

Interestingly, the CAN group who performed injections in CAVE-like display mode with haptic guidance disabled also achieved 100%. The visual feedback provided to the group consisted of multiple viewpoints of the virtual environment in an attempt to enhance users' understanding of the three-dimensional space, unlike the 2D and 3D display modes which only provided the top view of the cell and micropipette. The two viewpoints in addition to the top view provided by the CAVE-like display mode aims to assist user in understanding the micropipette's orientation and movements during injection.

It is interesting to consider the real cell injection task, where although the bio-operator is not able to see the contact between the micropipette and the cell in real task, they are able to look at the micropipette directly (without using the microscope) from different angles such as side, behind and front. The CAVE-like display mode provides similar views.

The observed success rates indicate potential of this method for training users for cell injection operation. Future work will further investigate how these results relate to the effectiveness of training to the real task.

IV. Conclusion

This paper introduces a large-scale VR micro-robotic cell injection system where the user is presented with a large visual display mode and uses a large workspace haptic device to control a micropipette with the intention of providing a better understanding of the micropipette's movements and orientation in a three-dimensional space. The haptic device can be used either with or without haptic guidance. The haptic guidance, in the form of VFs and force feedback, provides physical support to user in following the ideal trajectory towards appropriate penetration point at the cell membrane, apply accurate force for penetration and then stopping at the suitable deposition point at the cell center. The three display modes, 2D, 3D and CAVE-like provide large-scale and immersive graphical representation of the environment each of which is at different technology advancement level. The preliminary results indicate that there is significant potential of the approach to be utilized as a training tool for bio-operators where it is suggested that the skills acquired and understandings gained are transferrable to real-world physical task.

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