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Design of a Virtual Reality Training System for Micro-robotic Cell Injection

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Abstract

This paper discusses the design of a virtual reality (VR) training system for micro-robotic cell injection. A brief explanation of cell injection and the challenges associated with the procedure are first presented. This is followed by discussion of the skills required by the bio-operator to achieve successful injection, such as accuracy, trajectory and applied force. The design of the VR system which includes the visual display, input controllers, mapping strategies, haptic guidance and output data is then discussed. Initial evaluation of the VR system is presented including analysis and discussion based on conducted user evaluations. Finally, given the findings of the initial evaluation, this paper concludes that an effective haptically-enabled virtual cell injection training system is feasible, and recommendations for improvement and future work are given.

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Keywords: virtual reality; skills training; cell injection; haptic interface

1. Introduction

Cell injection is a procedure which involves depositing foreign material such as DNA, protein, sperm or biomolecules into a biological cell. The cell injection procedure has contributed significantly to various domains including drug development, in vitro fertilisation, toxicology, and to transgenics and cellular biological research [1]. In intracytoplasmic sperm injection (ICSI), for example, the procedure is used to inject a sperm into a matured egg to

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enable fertilisation. Conventionally, cell injection is performed manually by an expert bio-operator using a micro-robot for manoeuvring the micropipette. Aside from the widespread benefits of the procedure, there remain challenges to be overcome. Amongst these are the lengthy training and extensive hands-on experience required in order to become proficient at the task. Another challenge is the significant amount of required access to injection equipment which can be costly and also makes the equipment vulnerable to excessive use as well as accidental damage by inexperienced bio-operators. Additionally, practice injection cells can only be used once requiring a new cell for each practice attempt.

To contribute to overcoming these challenges, our recent work proposed a low-cost, portable and flexible VR micro-robotic cell injection training system [2]. The training system employed haptic interaction to provide force-based guidance and learning assistance according to different metrics. To develop the VR training system, the waterfall model (derived from [3]) was utilised. The model is a conventional software development model which has five sequential stages where each stage must be completed before the next stage can be executed as depicted by Fig. 1. The literature suggests that the waterfall model is best suited for small project development where the requirements are explicitly recognised [4, 5]. This is the case for the development of the VR micro-robotic cell injection training system where requirements are clearly defined so as to assist the bio-operator in improving their cell injection skills. These skill requirements are a function of performance against identified metrics such as injection trajectory, force and accuracy. This paper presents the development of the VR system focusing on the first four stages of the waterfall software development model, i.e. requirement, design, implementation and verification.

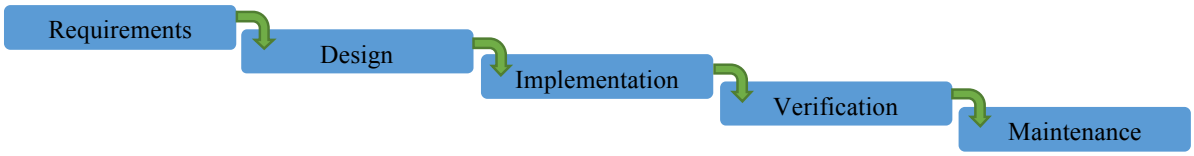

Fig. 1. Waterfall software development model

2. Cell injection skills

Injection trajectory, accuracy and force are important parameters which relate to the success of an injection [6, 7]. The skills necessary to be able to accurately control these parameters need to be mastered by the bio-operator in order to become proficient at the task and the developed VR micro-robotic cell injection training environment was designed to enhance these skills.

2.1. Trajectory

The ability for bio-operators to be able to execute a precise trajectory is important. To perform cell injection, the micropipette's tip needs to be manoeuvred to an appropriate penetration point on the cell membrane. Moving the micropipette along an optimised trajectory, from the starting location to the penetration point, will improve the chance of success and may reduce the time taken for completion. After piercing the cell membrane the micropipette needs to be moved in a straight line path along the longitudinal axis of the micropipette within the cytoplasm towards the suitable deposition point (e.g. the nucleus) [8]. This is because movement deviating from this path after piercing the cell membrane will cause slicing of the cell.

2.2. Accuracy

The penetration point needs to be accurately determined when performing the cell injection procedure. An inappropriate penetration point, e.g. too high or too low from the cell centre, can generate torque causing the cell to rotate compromising the penetration attempt [9]. It is very important to make sure that the micropipette's tip accurately stops at a suitable deposition point inside the cell, e.g. the nucleus which commonly located at the centre of a cell and carries important information such as DNA [10]. Given the relatively small size of the cell, achieving acceptable injection accuracy can be extremely challenging.

2.3. Injection force

It is important for the bio-operator to be able to control the force exerted by the micropipette when penetrating the cell membrane. Even a slightly excessive force may damage the cell membrane, while insufficient force may not allow the micropipette to penetrate the cell membrane [11]. It is also important to stop the motion of the micropipette at a suitable deposition point inside the cell to prevent overshoot which can damage the opposite cell membrane or even the injection equipment.

3. VR training system design

The VR micro-robotic cell injection training system was designed to cater to two distinct requirements, being the provision of an appropriate level of realism and the ability to provide haptic guidance. An overarching objective was to achieve low-cost implementation and portable operation. The system's development considered five main elements; visual display, input controllers, mapping strategies, haptic guidance and output data.

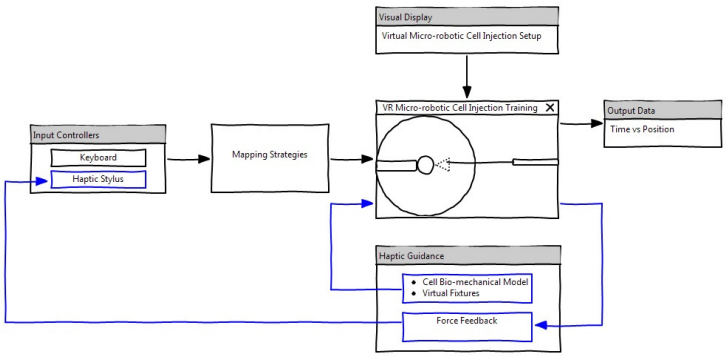

Fig. 2. Design of the VR training system for micro-robotic cell injection

3.1. Visual display

The VR environment was developed in C++ and using the OpenHaptics® toolkit designed for the Phantom® range of haptic devices, and Direct3D and OpenCV for graphics programming. The virtual environment displays a virtual cell injection setup consisting of a cell to be injected and bio-manipulation equipment including a microscope, micromanipulator, injection micropipette, holding micropipette and cell holding dish. The setup is placed on top of a rectangular table in the virtual environment. To improve the visualisation, a three dimensional view of the environment is presented to the bio-operator with the option to zoom in to focus on areas of interest.

The virtual micromanipulator replicates the actual MP285 micromanipulator by Sutter Instruments. The MP285 provides three motorised degrees of freedom (DOF) motion typically controlled using rotary optical encoders or a joystick. It can be manipulated in three (x, y, z) axes and can also provide an artificial fourth axis to achieve diagonal movement from the combination of any two of the three axes. One of the rotary encoder's dials needs to be used to control the movement of the micromanipulator along the fourth axis.

The cell in the virtual environment is displayed as a sphere that deforms in response to contact made with the micropipette. In order to achieve the replication of the cell, a suitable cell bio-mechanical model was employed. Aside from representing visual deformation, the model also provides an estimate of interaction forces which can be displayed haptically to the bio-operator as discussed in Section 3.4.

3.2. Input controllers

The VR training system was designed for use with two input controllers; the keyboard and haptic stylus. These input controllers are used to manipulate the virtual micropipette in three dimensional space. The keyboard was

chosen due to its ubiquitous use in daily computing applications. In VR systems, the keyboard is commonly used due to its simplicity and low-cost. Our earlier work suggests that skills obtained from other keyboard applications such as computer use and gaming are transferrable to the operation of the system [12]. Fig. 3(a) shows how the buttons of the numeric/directional keypad are used to control the virtual micromanipulator.

The second input controller is achieved using the stylus of a Sensable Phantom Omni® (now known as Geomagic® Touch™) haptic device. Aside from being able to provide force feedback to bio-operators, the haptic stylus also allows bio-operator to control the micropipette intuitively in 3D using a similar method to that of handheld needle insertion.

3.3. Mapping strategies

For keyboard control, the mapping was designed in such a way that the virtual micropipette moves at constant velocity in response to keystrokes. As such, bio-operators can achieve gross and fine control by holding down and tapping the key(s) respectively. The direction of the movement is based on which pre-determined key is pressed by the bio-operator (shown in Fig. 3(a)). For haptic stylus control, the position-to-position mapping framework of our earlier work was utilised [13]. Using the framework, movement of the haptic device's haptic interaction point (HIP) is mapped to the virtual micropipette's tip. The bio-operator can perform the cell injection procedure by controlling the haptic device stylus in order to move the virtual micromanipulator appropriately.

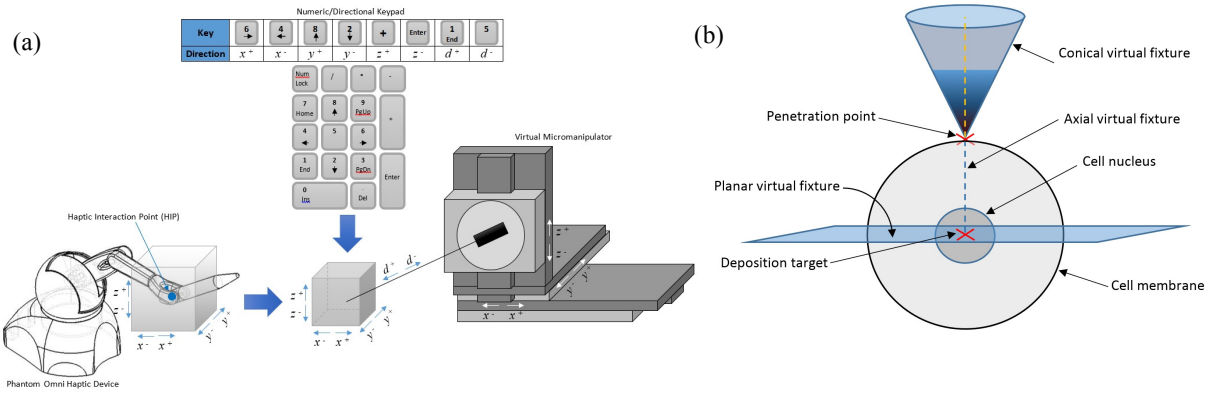

Fig. 3. (a) Mapping strategies; (b) VFs offered

3.4. Haptic guidance

The haptic guidance provided to the bio-operator is in the form of virtual fixtures (VFs), comprising conical, axial and planar VFs. The conical VF assists the bio-operator to move the micromanipulator along an optimised trajectory. The large opening of the conical VF allows the micropipette tip to simply enter the guided region, and then guide the user to advance the micropipette's tip to the penetration point located at the apex. Once the cell is penetrated, the axial VF guides the bio-operator to not deviate from the micropipette's longitudinal axis. The deposition point is located on the surface of the planar VF attempting to prevent the bio-operator from overshooting the target location. Since the maximum exertable force of the Phantom Omni® haptic device is low enough to be overridden by the bio-operator, the VFs only provide guidance and ultimate control of the movement is retained by the bio-operator. The haptic guidance and visual overlay of the VFs can be enabled/disabled as required by the bio-operator. In addition to the VFs, the bio-operator is also provided with a simulated injection force during penetration which includes the sudden force drop immediately after the cell membrane is penetrated. The simulated injection force aims to add more realism to the virtual environment as well as guiding the bio-operator to know when the cell membrane is penetrated so to arrest the momentum of the micropipette. In order to achieve the simulated injection force, a particle-based cell model as utilised in our earlier work [14] was employed. The cell model is able to

estimate cell interaction forces to be displayed haptically to the bio-operator along with the visual representation of cell deformation.

3.5. Output data

The system was designed to be able to record the data during evaluation. The position coordinates of the micropipette tip is recorded at sampling rate 60Hz. The recorded data is saved in a spreadsheet file able to be accessed and analysed using appropriate computer applications.

4. Initial evaluation

According to the waterfall model, verification logically follows system implementation. To verify that the implemented system achieves its requirements a set of user evaluations were conducted. Thirteen participants (nine males and four females) took part in the experiments. They were screened to ensure that they had no prior experience in cell injection activities. As illustrated by Fig. 4(a), participants were divided into two groups, Group 1 and 2 which comprised of three and ten participants respectively. Each group underwent different training sequences. Group 1 undertook the experiments exclusively for evaluating the keyboard control method and for this reason was a smaller group. Each experiment comprised three sessions, i.e. pre-training (PRE), training (TRA) and post-training (POS). In the PRE and POS sessions, participants were asked to perform ten trials using keyboard control. As presented in our earlier work [12], the keyboard control method, aside from providing a simple and cost effective method for micromanipulator control, can be used as a benchmark for evaluating performance progress after training using more sophisticated input controllers such as the haptically-enabled control device. The TRA session was held in between the PRE and POS sessions in which the participants underwent a systematic training programme. In the TRA session thirty trials were conducted using the input controller(s) assigned to the group. Group 1 underwent training using only keyboard control for all thirty trials while Group 2 performed 10 trials each using a passive stylus (stylus with no haptic feedback), keyboard and a haptically-enabled stylus consecutively. The selection of the input controller(s) for each group was in order to consider the performance progress after undergoing two different training regimes.

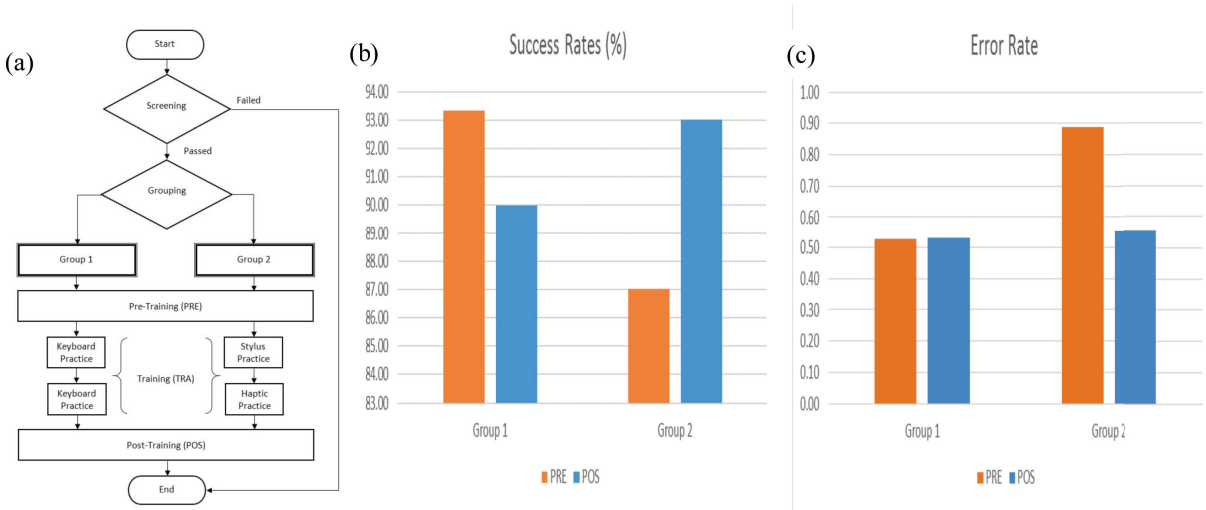

Fig. 4. (a) Experiment flow charts; (b) Mean success rate results; (c) Mean error rate results

Data such as time and positions of the virtual micropipette tip were recorded during the experiments. Two parameters were analysed in order to measure performance, i.e. success rate and injection error. An injection was considered successful when the bio-operator managed to penetrate the cell membrane and stop the micropipette tip inside the cell. An ideal injection was considered to be when the micropipette tip was positioned at the centre of the

cell for deposition. As such the injection error is measured by the distance between micropipette tip stop point and the centre of the cell. Therefore as such it is worthwhile to note that in this evaluation the injection accuracy was considered as the inverse of the injection error where the smaller the error value, the better the accuracy.

As shown in Figs. 4(b) and (c), the success rate of Group 1 deteriorated from 93% in PRE to 90% in POS while the error remained unchanged at 0.53 units. Group 2, on the other hand, showed more consistent results where performance improvement was observed against both parameters. The success rate improved from 87% in PRE to 93% in POS and the error declined from 0.89 units to 0.56 units. Based on the results it is observed that by utilising the haptic stylus as supplementary to keyboard in training resulted in better bio-operator performance. This may be because of the nature of the haptic stylus where its usage can provide more immersive training and enhance bio-operators' spatial awareness. The success rate drop observed for keyboard training was less significant and may be due to demotivation after excessive performance of the repetitive task.

It is worth mentioning that after completion of the verification stage, it is the authors' intention to take the system through the maintenance stage which involves troubleshooting such as finding bugs and resolving defects as well as non-corrective maintenance such as upgrades.

5. Conclusion

This paper presents the development process of a VR training system for micro-robotic cell injection considering the system's requirements, design, implementation and verification. Important skills relating to injection trajectory, accuracy and force are considered. The VR training system was developed based on five major elements, i.e. visual display, input controllers, mapping strategies, haptic guidance and output data. Based on the initial evaluation carried out it is suggested that the VR micro-robotic cell injection training system is feasible as an alternative to the physical system training. Further exploration on optimising haptic technologies to provide more immersive representation and guidance to bio-operator is recommended as upgrade of the existing system design.

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