A Generic Virtual Reality Training Simulator for Intracytoplasmic Sperm Injection

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***Abstract*– Cell microinjection is a well-known procedure where a fine tip micropipette is used to deliver a precise amount of substance into the cell. The procedure requires extremely high precision, depth perception and hand-eye coordination for manoeuvring the micro-pipette especially when performed using a micro-robotic system. To train users on procuring these skills, we have introduced a VR training simulator with basic training modules in our preceding paper, which is developed using a generic open-source physics engine called the Simulation Open Framework Architecture (SOFA). In this paper, we produce one advanced training module which trains the users on complete cell injection procedures. We have also introduced evaluation mechanism to evaluate learning rate of a user, which consists of important evaluation metrics, i.e, (i) trajectory, (ii) positioning accuracy, (iii) and injection force. Based on our development, we noticed that a VR training simulator for training on cell injection procedures can be very effective and feasible to facilitate independent and unsupervised learning.**

Keywords–Micro Injection, Adherent, Trajectory, Suspended, Evaluation metrics, Intra-cytoplasmic Sperm Injection

I. Introduction

Cell injection, such as intracytoplasmic sperm injection and pronuclei DNA injection, is a typical manipulation operation, where successful operation is determined greatly by positioning accuracy, trajectory and applied injection force [1]. Cell microinjection procedure is carried out with the help of a micropipette, micro injector controller and micromanipulator controller. The cell is injected with some kind of substance, i.e., sperm, drug, medicine using a micropipette. Once the material is delivered, the pipette can be removed easily [2], as shown in Fig 1.

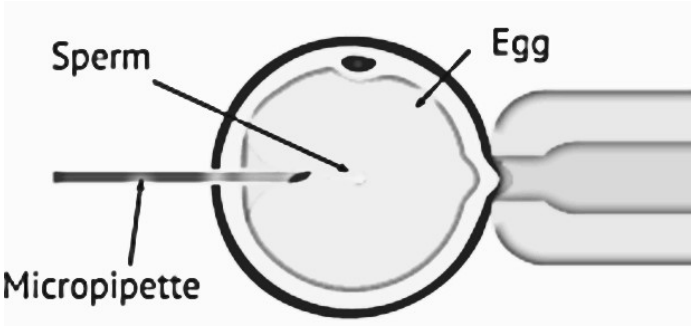

Fig. 1: Cell Microinjection Procedure

Cell injection technique has been extensively applied to the domains of cell biology, in-vitro fertilization, intracytoplasmic sperm injection and transgenics [3], [4]. In the field of medicine, it is used for the treatment of diseases, like cancer, cystic fibrosis and Alzheimer etc. [5]. However, manual cell injection is prone to errors. To overcome this, micro-robotic cell injection systems have been developed and are commonly used for these applications. They are remotely operated by humans using the video feed from the microscope displayed on a screen. The requirement of training in cell injection procedures arising due to the acquisition of non-traditional skills like hand-eye coordination, depth perception and ability to work within a confined space [6]. Amongst the most important skills for cell injection is the ability of the bio-operators to approach the cell towards a proper penetration point at the membrane, applying appropriate force to penetrate and then to position the pipette tip as close as possible to the cell centre for disposition [7]. Conventional manual training has several major hitches, where the real cell and equipment used for training is quite expensive. Once the cell is injected, it becomes useless and cannot be reused, therefore, every time a new cell is required for next attempt. Moreover, the expensive equipment is exposed to excessive use and probable mishandling by novice users during training. Apart from this, the system lacks in terms of portability and flexibility as it is placed at a specific location usually a dedicated laboratory [7].

To overcome above mentioned issues, in our previous work, we have presented a virtual reality (VR) training simulator for cell injection that enables the users to learn basic skills, i.e., movement of micropipette, targeting an object, controlling movements using manipulator and controllers, in an offline environment. This paper extends that work by providing an advanced training module which trains the user on a complete cell injection procedure with the help of micro manipulator and injector controllers. We also introduce an evaluation mechanism based upon five metrics which are important in injection procedures [2].

The rest of the paper is organized as follows: We present an overview of the literature in Section II. The simulator application is described in Section III, which is followed by the discussion of advanced training module in Section IV. Section V contains the overview of the evaluation metrics. Finally in Section VI, we conclude the paper and highlight some future directions.

II. Literature Review

Micro cell injection is a well-known procedure, a lot of research has been carried out in this context [3, 8, 9, 10]. Research shows the most important challenges in such a VR simulator is to achieve micro-level precision and rendering of deformation in cells. A cell that is to be used in VR simulators should be modeled in such a way that it exhibits deformation when the micro pipette is inserted just like the real-world injection processes. Real-time deformation is usually achieved using either mass-spring approach or Finite Element Method (FEM). The former approach is composed of a set of nodes, which sometimes leads to unstable and unrealistic behaviour. The FEM approach produces more accurate results but requires heavy computational resources [11].

In cell injection systems, the majority of the cells are derived into three categories: energetic, structural and continuum. The models related to the energetic class assume the cell compromising with certain continuum material without any insight on solid models, shell liquid core models or spherical biphasic models [12]. The second category of continuum models consider various cytoskeleton structures to the overall energy budget of cell during contraction, it comprises of percolation theory at large deformations and polymer physics models. The third category is based on tensegrity structures divided into two subclasses: cytoskeleton models and apectrinnetwork models for adherent cells [13]. Recently, cell modeling has been based on the assumption that actin cytoplasm and cell membrane are the major contributors in terms of stiffness and small deformations in the cells [12]. The shape of the cell is assumed to be semi-elliptic. A similar system for cell injection is illustrated in detail in [14].

Another crucial requirement for a VR simulator for micro manipulation systems is the human-machine interface through which a trainee would interact with the simulation module. A recent system proposed by Ladjal et al. 2013 [9], which is an improvised version of their VR simulator for the training on manual cell injection systems. The proposed methodology first observes the mechanical behaviour and structure of the cells, this information then presents the corresponding CAD model which is used as a basis for a haptic feedback simulator. Authors in [3] proposed a VR training simulator to train users on micro injection skills. This simulator uses phantom Omni for providing feedback, which is expensive which limits the cell injection procedure.

The most important need of a VR training simulator is its interface that should match the interface of the actual system. To the best of our knowledge, most of the commercially available VR training simulators do not have haptics included into their interfaces and are also similar to each other in terms of interfaces [2].

III. Simulator: An Overview

The proposed low cost and portable VR training simulator for microcell injection is discussed in this section. The training provides basic and advanced learning assistance according to different metrics. The proposed micro cell injection (MCI) system is composed of three parts: the Micro manipulator controller, the Micro injector controller and a software application running on the computer screen [2].

Our simulator application consists upon Simulation Open Framework Architecture (SOFA) [15], which allows to (1) create complex simulations by combining different algorithms available in SOFA; (2) modify different parameters related to simulation, i.e, surface representation, constraints, solver etc by editing and XML file; (3) develop complicated models using a scene graph library; (4) reuse and compare various available methods.

SOFA is a scene graph library containing various components with each component handling one specific aspect of simulation independently. The availability of these independent components provide a considerable amount of flexibility in modeling as in the implementation, one component can be replaced by another without modifying any other components in the graph. SOFA also provides modularity by modeling of collision, behavioural and rendering aspects of simulation using different topologies. SOFA provides a mechanism of mappings between different topologies as shown in Fig 2.

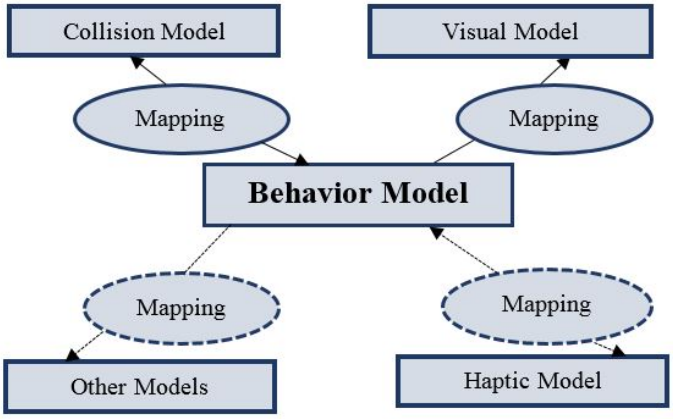

Fig. 2: Multimodal mapping in SOFA

Fig 3. uses a liver model to illustrate different models depicted in Fig. 2.

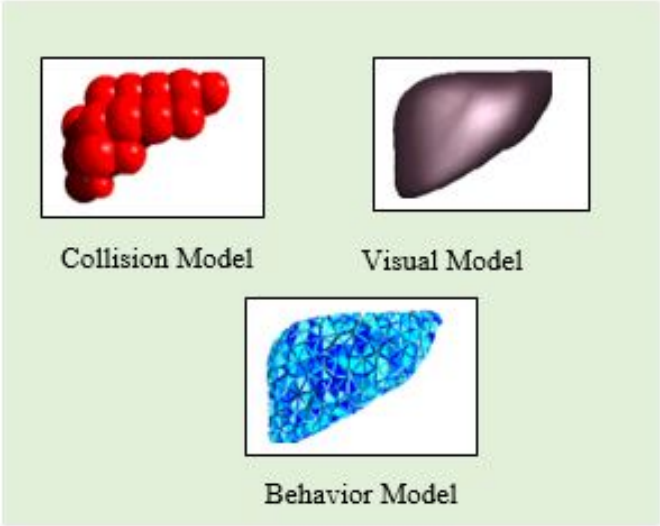

Fig. 3: Mapping representation for a liver model

The skills on which the simulator trains the users are:

1) Trajectory: The micropipette tip has to be maneuvered to the centre of the cell membrane to perform cell injection [16]. Thus, moving the pipette along with an optimized trajectory, to the central penetration point improves the success rate of injection.

2) Positioning Accuracy: The injection point should be accurately defined while injecting into the cell. An inappropriate injection or penetration point may cause damage to the cell. Due to the small size of the cell, it is very challenging to attain an acceptable accuracy [16] in this regard. The micropipette tip should be positioned at the centre of the cell to attain an ideal accuracy in the cell injection procedure. Thus, the region of interest (ROI) is defined at the central point of a cell and the accuracy is determined as the distance between pipette tip and the cell centre.

3) Injection force: A bio-operator should be able to control the force exerted by the pipette while piercing the cell. Even a slightly exerted excessive injection force damages the cell. Micropipette motion must also be stopped at an appropriate injection point, otherwise the cell membrane or the injection equipment can be damaged.

IV. Intracytoplasmic Sperm Injection (ICSI)

We had previously developed some basic training modules to train the users on attaining basic skills, like moving the micropipette along the Cartesian axis (x, y, z), rotating and controlling pressure and micro controllers respectively [2]. In this paper, we introduce a more advanced and complex training exercise, i.e., Intra cytoplasmic cell injection (ICSI), that trains the users on complete injection procedures using an injection/suction mechanism. Intra cytoplasmic cell injection (ICSI) is an in-vitro fertilization (IVF) process where a single sperm is injected into the cytoplasm of an egg. The procedure is carried out under a microscope using micro manipulation devices (micromanipulaotr, microinjector and micropipettes) as depicted in Fig 4.

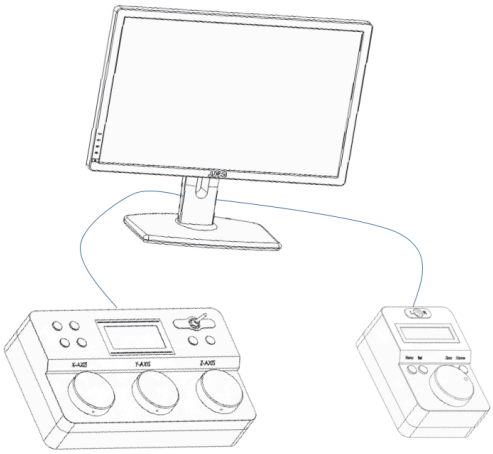

Fig. 4: *Left:* Micro-manipulator Controller *Right:* Micro-Injector Controller

Using a holding pipette, the mature oocyte is stabilized and a gentle suction is applied by a microinjector. From the opposite side of the oocyte, a micropipette with a very thin and a very fine tip is filled with sperms and is injected into the oocyte. The sperm is then released into the inner layer (cytoplasm) of the oocyte, and the micropipepette is removed. This removal is necessary as the cell may get damaged and the nucleus, that contains important information about the DNA may rapture [16].

The training exercise developed for the training of ICSI procedure is shown in Fig 5. The holding pipette, depicted in black, is used to stabilize the oocyte, while the thin micropipette shown on opposite side is filled with a sperm. The injection procedure is carried out with the help of a micro injector and a controller as shown in Fig. 4

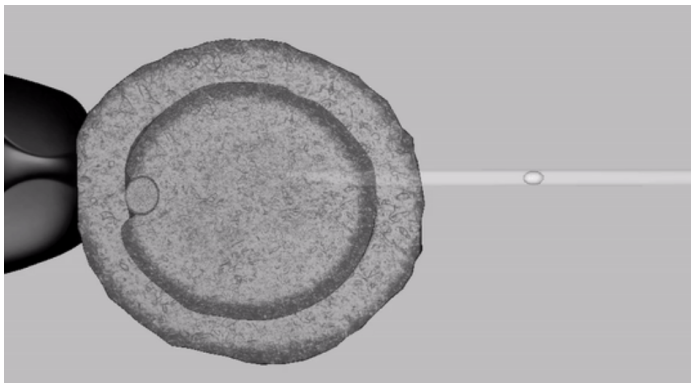

Fig. 5: Training module for ICSI

The procedure is done as follows:

Step 1. The oocyte is held with the help of a holding pipette while controlling the pressure using pressure controllers. The pressure mechanism works in such a way that when user rotates the knobs presented on controller, the activation rays are omitted from the pipette and the oocyte is held or stabilized. This is necessary as we have to make injection at a specific point, without using this holding mechanism, the successful injection cannot be achieved.

Step 2. Once the oocyte is held, the micropipette is moved in a desired trajectory (axis towards the centre of the oocyte) using micro manipulators which provide movement in three Cartesian axis (x, y, z), the pipette is moved towards the oocyte.

Step 3. The micropipette is controlled to inject the liquid into the oocyte, now the rotary knobs on pressure controllers are rotated opposite direction and the sperm is injected into the oocyte.

Step 4. The injection micro pipette is moved out of the cell. This completes the injection process.

V. Evaluation metric

The skills required to train users are; trajectory, injection force and positioning accuracy. We will discuss about the trajectory metric here, which is the distance covered by the pipette towards the cell. The desired trajectory is the straight line in axis from pipette to the central point of the oocyte. Expert users adapt this desired trajectory and avoid collision with other objects. The trajectory is measured in our proposed simulator by examining the initial indices (x,y,z) of the injecting pipette and adding the square root of the sum of the squares of three axis positions every time there is a change in the movement as follows:

$$|P|_{new} = |P|_{old} + \sqrt{x^2 + y^2 + z^2} \quad (1)$$

x, y, z are the current locations of the pipette at (0,1,1) indices respectively. The new distance travelled by the pipette is added into the old distance, angle and distances tell us whether the pipette is moving in a desired trajectory or not. This skill is required to move micropipette in the axis aligned with the trajectory of the cell, because movement deviating from this trajectory after piercing the cell membrane will cause slicing of the cell [3].

VI. Conclusion and future work

Virtual Reality training simulators are replacing the traditional training mechanism as it is portable, flexible and no ethical concerns related to the use of real cells in training, as the cells are artificially modeled to mimic the real cells. VR training simulators are being extensively used not only in the fields of cell injections, but in Laparoscopic surgical training where training is given on skills like cutting, grasping, and suturing. In the field of cell injections, VR simulators are used to provide training on injection procedures to acquire skills like trajectory, accuracy, precision and handling of different controllers, micropipettes and related tools. An idea of such a simulator is proposed in our previous paper, where training is given on basic skills. Here we have provided a basic overview of the system. The advanced training module is described in detail along with an evaluation metric. This training module provides training on complete injection procedure with the user-friendly easily moveable rotary knobs using microcontrollers and pressure controllers. In this paper we have measured the performance using an evaluation metric; trajectory. The remaining evaluation metrics and advanced training modules are set as our future directions. Moreover, there are different cultures of the cell, i.e, suspended and adherent. Suspended cells need a medium like a container where they use to float while adherent cells do not need any medium, as they are adherent in nature and are stuck with the surface, however, a deformed behaviour can be observed while piercing them. In future we will work on these cell cultures, where injection will be performed on adherent and suspended cells.

References

[1] Sun and B. Nelson, "Biological cell injection using an autonomous microrobotic system," *The International Journal of Robotics Research*, vol. 21, no. 10-11, pp. 861–868, 2002.

[2] N. Kamal, Z. A. Khan, A. Hameed, and O. Hasan, "A modular and generic virtual reality training framework for micro-robotic cell injection systems," in *Systems Conference (SysCon), 2018 Annual IEEE International*, pp. 1–8, IEEE, 2018.

[3] S. Faroque, B. Horan, H. Adam, and S. Thomas, "Design of a virtual reality training system for micro-robotic cell injection," *Procedia Technology*, vol. 20, pp. 185–190, 2015.

[4] F. Alwadani and M. S. Morsi, "Pixeye virtual reality training has the potential of enhancing proficiency of laser trabeculoplasty performed by medical students: A pilot study," *Middle East African journal of ophthalmology*, vol. 19, no. 1, p. 120, 2012.

[5] L. Mattos, E. Grant, and R. Thresher, "Semi-automated blastocyst microinjection.," in *ICRA*, pp. 1780–1785, 2006.

[6] Z. A. Khan, N. Kamal, A. Hameed, A. Mahmood, R. Zainab, B. Sadia, S. B. Mansoor, and O. Hasan, "Smartsim-a virtual reality simulator for laparoscopy training using a generic physics engine," *The International Journal of Medical Robotics and Computer Assisted Surgery*, vol. 13, no. 3, p. e1771, 2017.

[7] S. Faroque, B. Horan, M. Mortimer, and M. Pangestu, "Towards large-scale haptic virtual reality training for micro-robotic cell injection," in *Wireless Networks and Embedded Systems (WECON), 2016 5th International Conference on*, pp. 1–5, IEEE, 2016.

[8] Gurusamy, Aggarwal, Palanivelu, and B. Davidson, "Systematic review of randomized controlled trials on the effectiveness of virtual reality training for laparoscopic surgery," *British Journal of Surgery*, vol. 95, no. 9, pp. 1088–1097, 2008.

[9] H. Ladjal, J.-L. Hanus, and A. Ferreira, "Intracytoplasmic sperm injection simulator using biomechanical models," *Computer Methods in Biomechanics and Biomedical Engineering*, vol. 14, no. sup1, pp. 155–157, 2011.

[10] S. F. Shakur, C. J. Luciano, P. Kania, B. Z. Roitberg, P. P. Banerjee, K. V. Slavin, J. Sorenson, F. T. Charbel, and A. Alaraj, "Usefulness of a virtual reality percutaneous trigeminal rhizotomy simulator in neurosurgical training," *Operative Neurosurgery*, vol. 11, no. 3, pp. 420–425, 2015.

[11] H. Ladjal, J.-L. Hanus, and A. Ferreira, "Micro-to-nano biomechanical modeling for assisted biological cell injection," *IEEE Transactions on Biomedical Engineering*, vol. 60, no. 9, pp. 2461–2471, 2013.

[12] Tartibi, Liu, G.-Y. Liu, and Komvopoulos, "Single-cell mechanics–an experimental–computational method for quantifying the membrane–cytoskeleton elasticity of cells," *Acta biomaterialia*, vol. 27, pp. 224–235, 2015.

[13] H. Ladjal, J.-L. Hanus, and A. Ferreira, "Methodologies of dynamic cell injection techniques using fem biomechanical modeling," in *Biomedical Robotics and Biomechatronics, 2008. BioRob 2008. 2nd IEEE RAS & EMBS International Conference on*, pp. 631–636, IEEE, 2008.

[14] M. Ammi and A. Ferreira, "Realistic visual and haptic rendering for biological-cell injection," in *Robotics and Automation, 2005. ICRA 2005. Proceedings of the 2005 IEEE International Conference on*, pp. 918–923, IEEE, 2005.

[15] J. Allard, S. Cotin, F. Faure, P.-J. Bensoussan, F. Poyer, C. Duriez, H. Delingette, and L. Grisoni, "Sofa-an open source framework for medical simulation," in *MMVR 15-Medicine Meets Virtual Reality*, vol. 125, pp. 13–18, IOP Press, 2007.

[16] S. Faroque, M. Mortimer, M. Pangestu, M. Seyedmahmoudian, and B. Horan, "Evaluation of a new virtual reality micro-robotic cell injection training system," *Computers & Electrical Engineering*, vol. 67, pp. 656–671, 2018.