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Simulation of Single Cell Trapping via Hydrodynamic Manipulation

Amelia Ahmad Khalili[a], Mohd Ariffanan Mohd Basri[a], Mohd Ridzuan Ahmad[a,b*]

[a]*Dept. of Control and Mechatronic Engineering, Faculty of Electrical Eng., Universiti Teknologi Malaysia 81310 UTM Johor Bahru, Johor, Malaysia*
[b]*Institute of Ibnu Sina, Universiti Teknologi Malaysia, 81310 UTM Johor Bahru, Johor, Malaysia*

*Corresponding author: ridzuan@fke.utm.my

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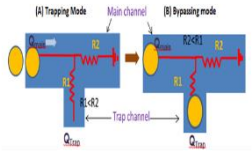
Graphical abstract



Abstract

Microfluidic devices are important for the single cell analysis such as cell mechanical and electrical characterization. Single cell characterization could be related to many significant applications including early disease diagnosis. However to perform the single cell manipulation, firstly a single cell have to be isolated and a platform for the cell manipulation have to be provided. One of the methods to trap a single cell is by using hydrodynamic trapping in the microfluidic channel. This study provides a finite element model for single cell trapping for a yeast cell model. The objectives of the simulations are to obtain the appropriate channels' geometry and optimized ratio of the fluid's inlet and suction flow rate to trap a single yeast cell. Trap channel was designed to trap a 5μm yeast cell with a suction hole placed in the end of the trap channel. Design geometry and the ratio of fluid flow rates for the cell trapping model were studied using the hydrodynamic resistance concept. The analysis was carried out using numerical solutions from the finite element ABAQUS-FEA software. Using the cell trapping model, a single yeast cell able to be trapped into the trap channel with optimized channel's suction hole's geometry and appropriate fluid's inlet and suction flow rate ratio. The appropriate Q_{Trap}/Q_{Main} ratio to perform cell trapping using hydrodynamic resistance concept is the ratio value above 1. A 5 μm yeast cell model able to be trap inside a trap channel with the height, width and length of 7 μm by manipulating the suction hole's flow rate of 1.5 and 2.0 μm of height, 7 and 3 μm of length and width, respectively which situated at the centre edge of the trap channel.

Keywords: Single cell; hydrodynamic resistance; microfluidic; cell trapping

1.0 INTRODUCTION

Biomedical and biological research nowadays has moved to a single cell approach. Previous conventional biological studies are usually being performed to study a large cell populations and these population approach prevent the investigation of an individual cell. The measurement of population based study is the summed values that can only reflect the average responses of many cells. Accessing the information inherent to single cells will allow us to resolve such heterogeneity and eventually improve our understanding of enduring problems in molecular biology, cancer diagnostics, pathology and therapy. The analysis of single cells with a sufficient number of measurement is a need to elucidate process heterogeneities which is important to obtain accurate information, hence obtaining a statistically meaningful data to reveal the properties of individual cells and cell-to-cell differences[1].

Microfluidic platforms have become an important tool for single cell analysis as they allow constructing fluidic channels in dimensions adapted to a specific cell size and provide fluidic tools for cell analysis with minimal dilution errors[2–5]. Microfluidics have advantages to overcome challenges of traditional assays used to perform medical diagnosis and able to handle small sample sizes and thus minimized the use of valuable reagents in the analysis. The main benefits of micro fabricated systems for cell studies are the capability to design cellular microenvironments, precisely control fluid flows, and to reduce the time and cost of cell culture experimentations.

Microfluidic devices can be operated using hydrodynamic flows thus exhibiting numerous advantages such as non-marker labeling, short detection time and high reproducibility based on simple and robust experimental procedure[6]. The size-based approach is relatively less invasive because it does not require any chemical or biological interactions between the cells and the device. Single cells trap should not only allow spatial localization of single cells, but also create micro-reaction chambers, where reactions with stimuli can take place[7] and manipulations could be performed.

The field of Computational Fluid Dynamics (CFD) is maturing fast with the ability to achieve approximate, but realistic CFD results for a wide variety of complex two- and three-dimensional viscous flows. The CFD modeling is an invaluable tool that has been applied only relatively recently in the area of micro scale cell culture that enables a better understanding of the role of the hydrodynamic environment and the factors that

modulate it. CFD is now enabling us to understand the implications of fluid flow and transport on cell function thus provides important insights into the design and optimization of microfluidic cell culture chip[8].

This study presents development of the single cell trapping in the microfluidic finite element model using hydrodynamic manipulation techniques. In this paper, we discuss the simulation of the single yeast cell trapping inside water in the microfluidic channel. The single cell trapping model was studied by performing channel's design geometry optimization and the ratio of fluid inlet and suction's flow rates to achieve success single cell trapping.

The paper is divided into five sections with the first section as introduction and second section explains the hydrodynamic trapping idea and concept of the proposed model. Third section discusses the experimental setup of the simulation, next section involves results and discussion and last section will be the conclusion.

2.0 THE IDEA AND CONCEPT OF THE MODEL

The concept of hydrodynamic trapping was originally proposed by Tan *et al*.[9]. The micro channels are designed such that: (i) when a trapping site is empty, the trapping channel has a lower flow resistance than that of the by-pass channel and beads/cells will flow into the trapping stream and subsequently into the trap; (ii) the trapped bead/cell acts as a plug, increasing the flow resistance along the trapping channel drastically; and (iii) the main flow redirects to the by-pass channel (main channel in our model) and subsequent beads/cells will flow into the by-pass stream, by-passing the filled trapping site[10]. Darcy-Weisbach equation is used to determine the pressure drop or pressure difference in a micro channel and solving the continuity and momentum equations for the Hagen-Poiseuille flow problem.

From Hagen–Poiseuille's equation, the flow rate (Q) can be defined as following equation:

$$\Delta P = Q \times \mathrm{R_h} = \mathrm{Q} \times \left(\frac{12\mu \mathrm{L}}{\mathrm{WH}^3}\right) \quad (1)$$

where ΔP is the pressure drop, Rh is the hydrodynamic flow resistance of the rectangular micro channels, μ is the fluid viscosity, L, H and W are length, height and width of the channel respectively. Considering micro channel acts as a resistive circuit, Rh is analogous to resistance in an electric circuit, this equation is an analog of Ohm's law ($V = IR$), where ΔP and Q are the analogs of V and I, respectively[11].

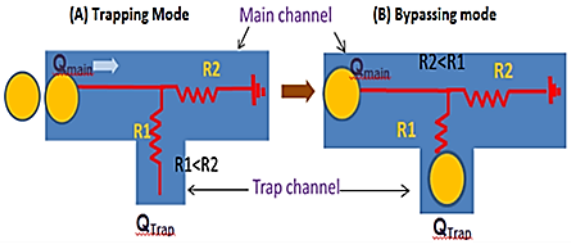


Figure 1 Simple schematic of single cell trapping channel with the hydrodynamic resistance concept

Figure 1 shows the schematic explanation of the hydrodynamic trapping concept with R1 and R2 representing the flow resistance for trapping channel and main channel, respectively. At intersection (Figure 1), the flow is divided into the trap-path and the main-path. Yellow circle denotes the yeast cells to be trapped. The flow rates of the trap-path (Q_{Trap}) and the main-path (Q_{Main}) are distributed depending on the corresponding flow resistances. By using relationships of $A = W$ x H and $P = 2(W + H)$, the hydrodynamic flow resistance can be formulated in the following equation:

$$R_h = \frac{C\mu L P^2}{A^3} \quad (2)$$

where C denotes a constant that depends on the aspect ratio (H/W), A is the cross-sectional area and P is the perimeter of the channel. The flow rate ratio between trap path and main path can be modeled as given in Equation (3), approximating that the pressure drop across main path and trap path are same[12]. For the trap to work, the flow rate along trap path must be greater than that of main path ($\mathrm{Q_{Trap}} > \mathrm{Q_{Main}}$).

$$\frac{Q_{Trap}}{Q_{Main}} = \left(\frac{L_M}{L_T}\right) \cdot \left(\frac{W_M + H_M}{W_T + H_T}\right)^2 \cdot \left(\frac{W_T H_T}{W_M H_M}\right)^3 \quad (3)$$

The flow rate ratio at each bifurcation could be determined by controlling the hydrodynamic resistance ratio between the main channel and test channel. The flow rate of whole fluid at the inlet could be assumed as an electric current source. Outlet which leads to the atmospheric pressure could be assumed as grounds.

In our model, the cells will be introduced into the device through the inlet with appropriate flow rate. Cell will be directed to micro-well by applying an appropriate suction force (depending Rh ratio) through the suction holes. The excess and remaining cells will be directed out through the channel's outlet by injecting cell's culture medium. The appropriate flow rates to trap single yeast cell in the specified design was studied.

3.0 SIMULATION SETUP

The analysis was carried out using finite element ABAQUS-FEA analysis software which able to perform multi-physics analysis. At first, the simulation analysis was carried out using the parameters in micro dimension properties. However due to time consumed for the simulation to converge is too long (data not shown), the parameters was appropriately scaled into meter dimension with the ratio of 1 m is proportional to 1 μm. The advantage of dimension scaling is that a simulation works could be carried out in a reasonable simulation times[13]. The approach to represents a nano scale model by giving nanometer dimensions to the geometry and using the material property values identical to the scale model suffers from two major drawbacks. Firstly, the simulation will face a very small incremental time steps which would make real time simulation prohibitively expensive if not impossible and secondly, using properties with nanometer dimensions will create numerical issues in finite element programs[10]

The single cell trapping system was modeled using Abaqus-CAE software. The fluid micro channel was modeled as 3D eulerian explicit EC3DR and an 8-node linear eulerian brick element part assigned with water properties (density, equation of state, viscosity). Figure 2A shows the different parts involved in the model; a eulerian part with the fluid channel and a three dimension (3D) deformable part of the elastic yeast cell model (5 μm in diameter) and Figure 2B shows the assembly setup with a yeast cell positioned in the main channel, near the channel's inlet (right). the The micro channel consists of two channel; the main channel with the width and depth of 7 μm and total length of 67 μm and a trap

channel with 7 μm of length, width and depth. There is one rectangular suction hole placed at the end of the trap channel with the dimension of 3 μm and 7 μm of width and length, respectively. The height of suction hole is a variable ranging from 1.0 - 2.0 μm, with 1.0 μm was set as the height for the initial simulation analysis.

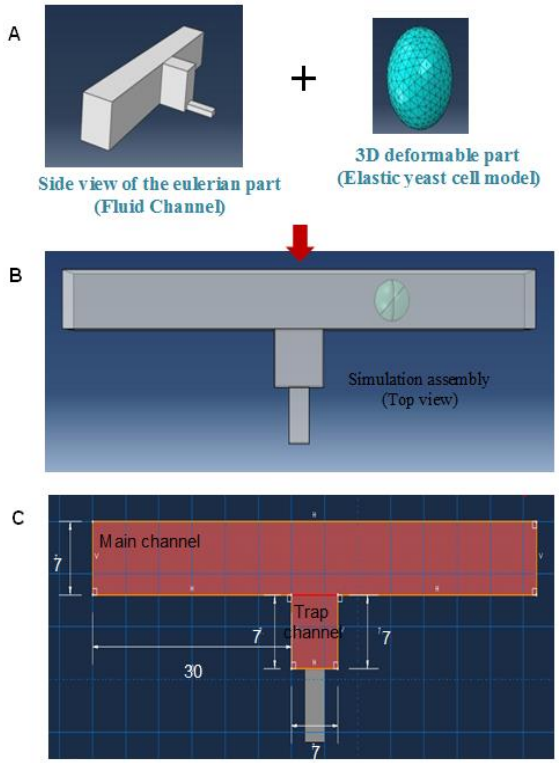


Figure 2 Construction of the finite element model of single cell trapping system. (A) Parts involved in the model. (B) Simulation assembly setup. (C) The dimensions of fluid channel (top view)

A sphere-shaped yeast cell (5 μm in diameter) was model as an elastic 3D standard solid deformable C3D8R and an 8-node linear brick 3D part with the yeast properties (Young's Modulus, Poisson's Ratio, density, etc.) obtained from literature[14-21]. The develop parts was assembled to develop the finite element model for the proposed system (Figure 2B). Figure 2C shows the dimensions of the proposed channel. The fluid channel and cell was meshed using hexahedron and tetrahedron mesh type, respectively. No-inflow and non-reflecting outflow eulerian boundary condition were to the walls of channel. Inflow velocity of 0.3 μms^{-1} was applied to the inlet and atmosphere pressure was applied to the outlet of the channel. Various suction velocities ranging from 4 to 400 μms^{-1} was applied (depending on the flow rate ratio of main channel and trap channel, Q_{Trap}/Q_{Main}) to the suction hole in the trap channel. The interaction between objects and water was set as general contact with rough tangential behaviour and the interaction between cell surface and channel's wall was set as frictionless.

4.0 RESULTS AND DISCUSSION

According to the hydrodynamic trapping concept, cell/particle trapping should able to be achieved if Q_{Trap}/Q_{Main} ratio is more than 1[9] . To verify whether the concept works in the proposed device, finite simulation analysis was carried out. Flow rates and hydrodynamic resistance analysis was carried out to the cell trapping model designed with a specific dimensions starting with the suction hole's height of 1 μm. Results obtained showed that the concept didn't work for the proposed device after the Q_{Trap}/Q_{Main} ratio of 1 to 50 were tested. Cell movement was found not directed to the trap channel and move passed through the trap channel (data not shown). This result shows the trap hole's height of 1 μm is not suitable for the specified trap channel dimension (7 μm of width, height and length). The design failed to follow the hydrodynamic trapping concept probably due to the small suction hole and its position situated at the bottom-end of the trap channel. Uneven distribution of fluid velocity produced in the trap channel (low velocity: dark blue, high velocity: grey).caused the pressure drop produced was not enough to capture cell inside the trap channel (Figure 3A).

A very high suction rate (Q_{Trap}/Q_{Main} ratio of 60) is needed to produce wide velocity distribution inside the trap hole (Figure 3B). Cell was found able to be trapped when the ratio of Q_{Trap}/Q_{Main} is 60 and above. Suction rate required is quite high for the application micro channel, as it may cause the micro channel's deformation[22, 23]. Therefore, another strategy such as increasing the suction hole size have been carried out in the subsequent analysis to produce the appropriate pressure drop with a lower suction rate. The height of suction hole was increased to 1.5 and 2.0 μm (Figure 4).

Subsequent simulation is carried out using the design with suction hole's height of 2.0 μm. Results obtained show that cell was able to be trapped into the trap hole using the modified design (Figure 5). The hydrodynamic concept was found able to be applied in the modified design. The verification using the modified model proved that the hydrodynamic concept works accordingly (trapping was successful when $Q_{Trap}/Q_{Main} > 1$).

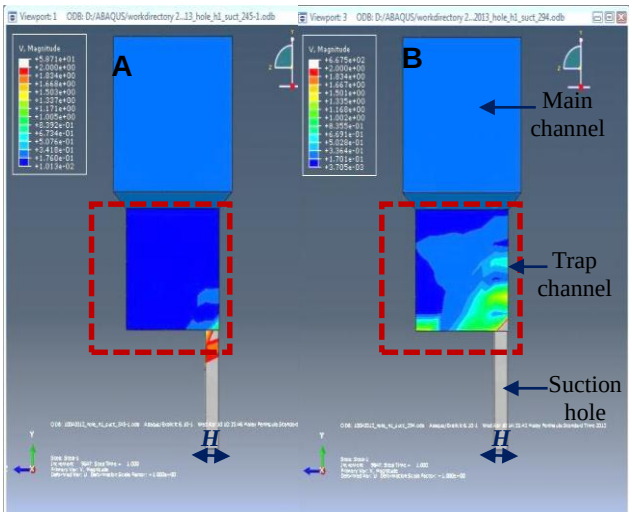


Figure 3 Simulation results show the distribution of fluid velocity inside trap channel (side view) for Q_{Trap}/Q_{Main} ratio of 3 (A) and 60 (B)

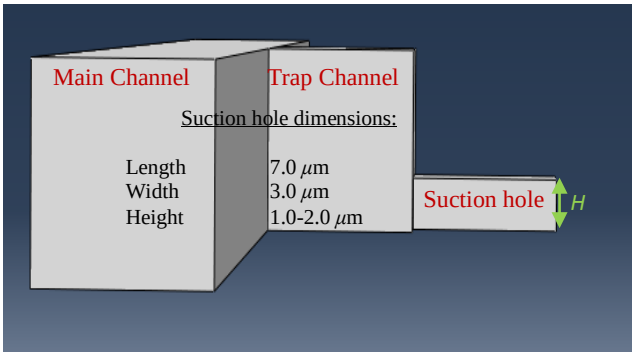


Figure 4 Suction hole's height modification (side view)

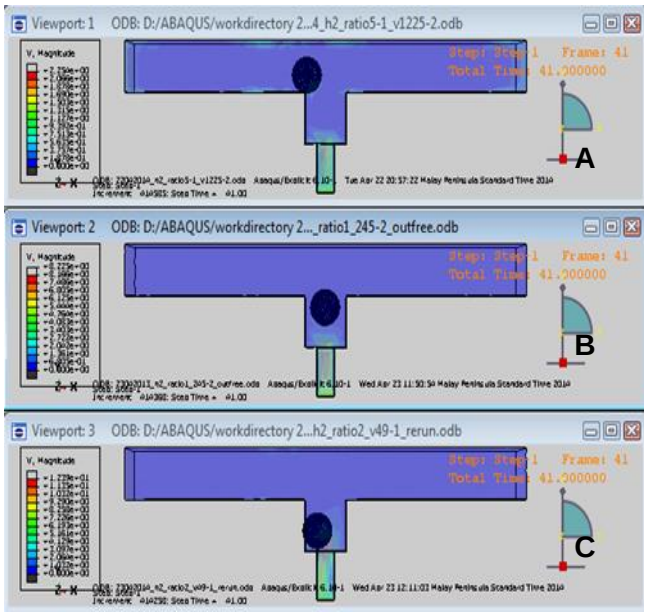


Figure 5 Simulation results (top view) of the modified's design (suction hole's height 2 µm) for Q_{Trap}/Q_{Main} ratio of (A) 0.5 (B) 1.01 (C) 2.0

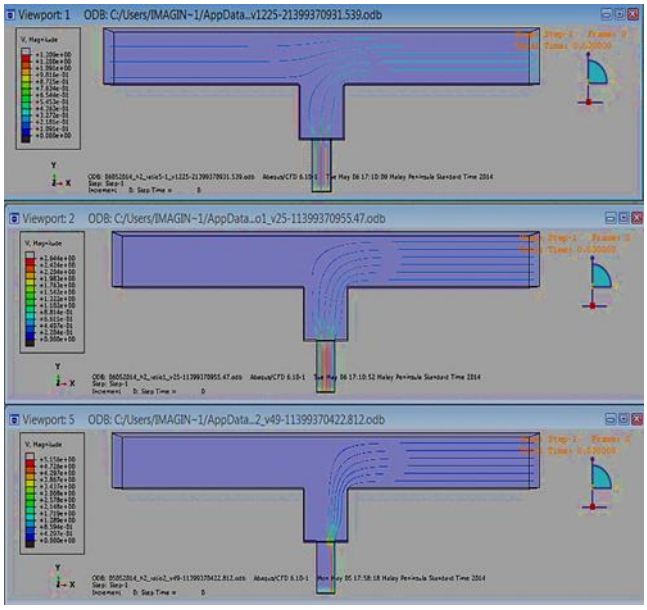


Figure 6 Streamline velocity field of the modified's design (top view) suction hole's height of 2 µm for Q_{Trap}/Q_{Main} ratio of (A) 0.5 (B) 1.01 (C) 2.0

Streamline plots of the modified design's with suction hole's height of 2 µm were obtained for Q_{Trap}/Q_{Main} ratio of 0.5 to 2.0 are shown in Figure 6. The streamline velocity field for Q_{Trap}/Q_{Main} ratio above 1 (Figure 6 B and C) show that the flow diverged from main channel to the trap channel and all the streamlines are directed towards the trap channel. In contrast to the Q_{Trap}/Q_{Main} below 1 (Figure 6A), the velocity streamlines are not fully directed to the trap channel as portions of the streamlines are directed pass through the main channel and towards the trap channel. The velocity streamlines obtained are not fully focusing towards trapping hole and unable to produced not enough force to trap the cell into trapping channel.

Simulation analysis was preceded further with other Q_{Trap}/Q_{Main} ratio value and by using different suction hole's height (1.5 μm). Table 1 summarized the simulation findings for all 3 different suction hole's height 1.0, 1.5 and 2.0 μm. Both design with suction hole's height of 1.5 μm and 2.0 μm able to obey the hydrodynamic trapping concept as cell was found able to be trap into the trap hole when Q_{Trap}/Q_{Main} ratio is more than 1 (Figure 8 down images). However design with the suction hole's height of 1 μm failed to trap cell when the Q_{Trap}/Q_{Main} ratio is more than 1.

Figure 8 shows the distribution of fluid velocity inside the channels and the trapping of the cell. Colour contours in the results (upper images) show different velocity from low (dark blue) to high (grey). The distribution of fluid velocity from suction hole to the whole trap channel for both suction hole's height of 1.5 and 2.0 μm are almost the same although the height is different (Figure 8B and 8C upper images). This results show that both design produced almost the same pressure drop for the cell to be trapped. Therefore design for suction hole's height of 1.5 μm was chosen for subsequent analysis due to the size is not too big and enough to trap single cell and to minimize access stress from executing the trapped cell.

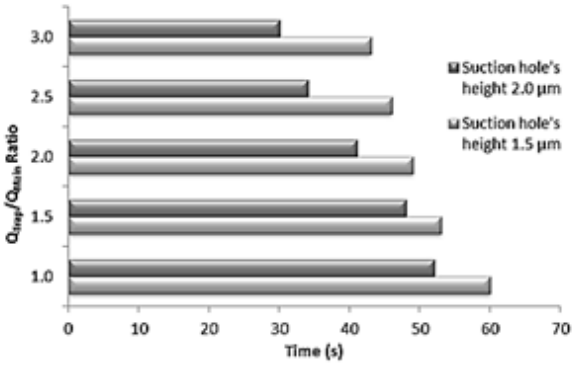


Figure 7 Simulation results of cell trapping time for different Q_{Trap} / Q_{Main} ratio of 1 to 3 for channel suction hole's height of 1.5 and 2.0 μm

Table 1 Simulation findings for the optimization of suction hole's height

Ratio of Q_{Trap}/Q_{Main}	Ability to trap cell		
	H : 1.0 μm	H : 1.5 μm	H : 2.0 μm
0.5	x	x	x
1.0	x	yes	yes
1.5	x	yes	yes
2.0	x	yes	yes
2.5	x	yes	yes
3.0	x	yes	yes

Subsequent analysis was carried out using the single cell trapping model with suction hole's height of 1.5 μm to study the velocity of fluid at the path between the main channel and trap channel. Three different nodes were selected to obtained fluid's velocity data (Figure 9A and 9B) and the averaged velocity of the nodes were used to plot the graph of fluid's velocity with respect of time (Figure 9C). Inlet fluid's velocity of 0.3 μms^{-1} was used through all analysis. From the result, significant increases in the fluid's velocity were observed with greater Q_{Trap}/Q_{Main} ratio and this trend was attributed to a change in the fluid's hydrodynamic resistance ratio. A greater Q_{Trap}/Q_{Main} ratio could provide a lower hydrodynamic resistance and could transfer the fluid at a faster rate. The minimum fluid's velocity of 0.5 μms^{-1} is needed at the path

between main channel and trap channel (refer nodes position in Figure 9A and 9B). The Q_{Trap}/Q_{Main} ratio value above 1 able to produce the minimum fluid's velocity which appropriate for trapping.

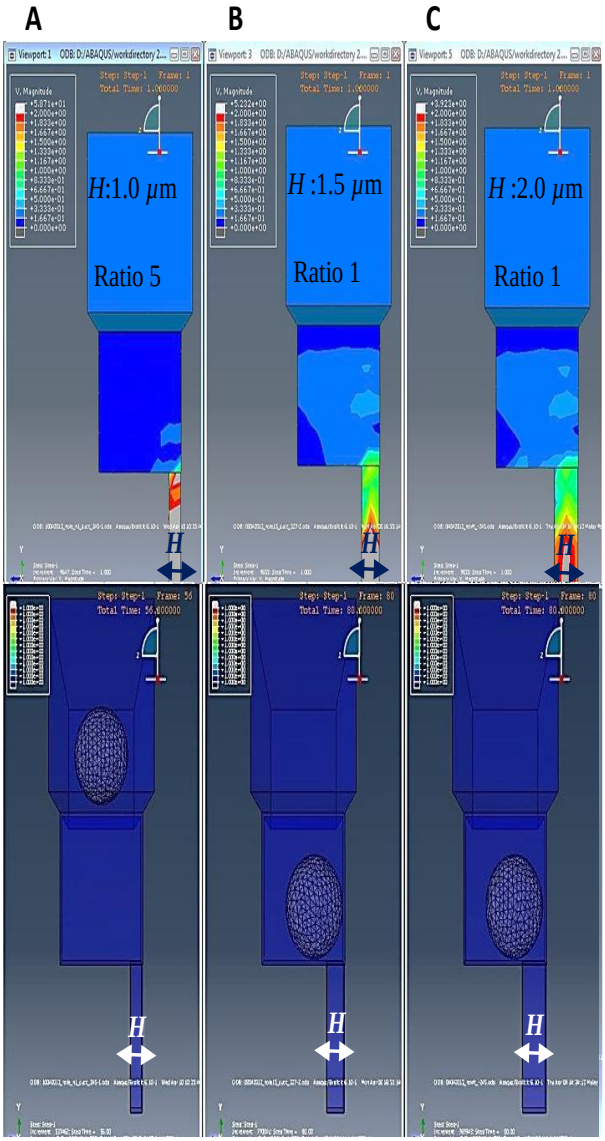


Figure 8 Simulation findings for suction hole's height optimization. Upper figures shows the velocity color contour in the fluid channel (side view) and down figures show the cell trapping result. (A) Suction height 1.0 μm with Q_{Trap}/Q_{Main} ratio = 5. (B) Suction height 1.5 μm with Q_{Trap}/Q_{Main} ratio = 1.01. (C) Suction height 2.0 μm with Q_{Trap}/Q_{Main} ratio = 1.01

Trap channel with suction hole's position in the centre channel surface was chosen to avoid inconsistency of trapped cell's position and to prevent position variable of the trapped cell. This is important in providing a good platform for cell manipulation in studying the biological, biophysical or biomedical aspect of the cells and in also achieving accurate and consistence result. Optimization of the trap channel suction hole's height able to be carried out by analyzing the fluid's (water) velocity distribution and by observing the success of cell trapping into trap hole in the analyzed model. Suction hole's height of 1.5 μm should be chosen to carry out single cell analysis because the size is not too big and enough to trap single cell and to minimize access stress from executing the trapped cell. However, the size of suction hole to be chosen is dependent on the type of cell and type of experiment or analysis and how will it be performed.

This study provides a finite element model for single cell trapping for a yeast cell model. Trap channel's was design to specifically trap a 5 μm yeast cell via hydrodynamic resistance manipulation using a suction hole placed in the end of the trap channel. The channel's geometry was optimized and ratio of fluid flow rates was applied by referring to the hydrodynamic concept. The single cell trapping finite element model was found able to trap a single yeast cell into the trap channel with optimized channel's suction hole's geometry and appropriate fluid's inlet and suction flow rate ratio.

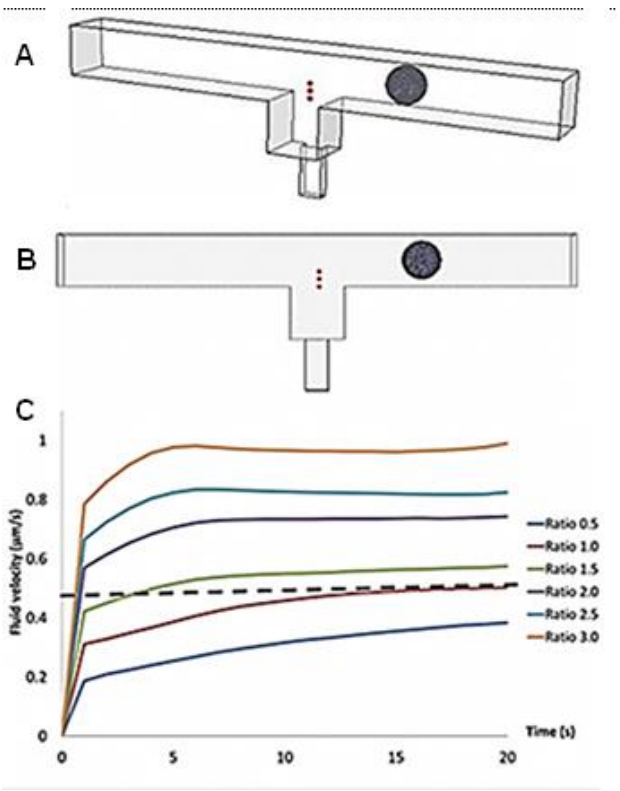


Figure 9 (A) 3D view and (B) Front view of single cell trapping model with the position of 3 nodes (red dots) selected for fluid's velocity data. (C) Graph of velocity of fluid versus time for Q_{Trap}/Q_{Main} ratio from 0.5 to 3.0. Dashed black lines represent the minimum of fluid velocity needed (average velocity of 3 nodes) at the nodes shown in upper figures to trap cell into the trap channel for a flid's inlet's velocity of 0.3 μms^{-1}.

5.0 CONCLUSION

This study presents the finite element model of single cell trapping inside microfluidic channel. This single cell trapping system able to be constructed using Abaqus-FEA™ software. The single cell trapping model able to obey the hydrodynamic resistance trapping concept as the appropriate Q_{Trap}/Q_{Main} ratio to perform cell trapping using hydrodynamic resistance concept is the ratio value above than 1. A 5 μm yeast cell model able to be trap inside a trap channel with height, width and length of 7 μm by manipulating the suction hole's flow rate with the size of 1.5 and 2.0 μm of height, 7 and 3 μm of length and width, respectively which situated at the centre edge of the trap channel. This cell trapping model able to isolate an individual yeast cell inside fluidic environment thus provide a platform to further study the mechanical or biological behaviour of single cell. Single cell manipulation such as chemical and

biophysical treatments and also mechanical characterization could be performed inside the microfluidic channel using this system.

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