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Separation of tumor cells from the peripheral blood via a novel electro hydrodynamics model

Xin Li[1a], Yanping Liu[2], Yingcui Wang[3] and Caixia Zou[*4]

[1]School of Clinical Medicine, Weifang Medical University, Weifang 261053, Shandong, China
[2]Physical Examination Center, Qingdao Municipal Hospital (West), Qingdao 266002, Shandong, China
[3]Department of Cardiology, Qilu Hospital (Qingdao), Cheeloo College of Medicine, Shandong University, Qingdao 266035, Shandong, China
[4]Internal Medicine Nursing, Qingdao Municipal Hospital (West), Qingdao 266002, Shandong, China

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Abstract. The significant issue that has been investigated in this research due to the great clinical potential is to separate a circulating tumor cells (CTCs) from the peripheral blood and cancer treatment in advance. Nonetheless, it is difficult to detect CTCs because of the rare existence of CTCs in the middle of peripheral blood. It is found that the need of high resolution ethods is crucial because there is a similarity in size range between CTCs types such as the cells of breast cancer and the white blood cells (WBCs). This paper presents a device which can be used for tumor cells separation from the cells of blood with nonstop flow that is helped by fractionating dielectrophoresis (DEP) field-flow. The reason that leads CTCs to separate from the cells of blood is the obvious different sizes of hydrodynamics focusing and dielectrophoretic force. Numerous attempts have been made to calculate CTCs trajectories with the aid of simulating the flow speed and electric field and it reveals an accurate comparison of them with the measured results. Furthermore, the low applied voltage such 10 V_{pp} with which the represented device can be utilized. The high precision and efficiency of particle separation can be obtained by the device as well. According to the differences in size, this approach has various application for separation of other particles sorts. Based on our findings in this study, it is assumed that our device is beneficial for studying cancer and also has an excellent capability of separating tumor cells from blood cells.

Keywords: circulating tumor cell; microfluidic device; separation; dielectrophoresis; hydrodynamic flow focusing; WBCs; RBCs

1. Introduction

Numerous patients, who are diagnosed with cancer, have CTCs (circulating tumor cells) in their peripheral blood. There is the fact that CTCs numbers are extremely low (not more than 5 tumor cells can be found per blood sample mL), therefore, the detection of them is very challenging. Separation of CTCs can serve as an indicator of the effectiveness of therapeutic interventions. One of the methods of cell isolation is the effects of dielectrophoresis (Elhoseny *et al*. 2014, Metawa *et al*. 2016, Abd El Aziz *et al*. 2017, Tharwat *et al*. 2018, Devaraj *et al*. 2020). The dielectrophoretic force is due to a non-uniform electric field, in other words, if the electric field gradient is non-zero, there will be an applied force to the cells. It was concluded that some of methods because of considerable differences in cells of peripheral blood are not in good agreement with physical features of CTCs, without being affected by the type of cancer, for this reason they cause important isolation purities (Jalali *et al*. 2012, Gascoyne *et al*. 2013, Shah *et al*. 2015, Ismail *et al*. 2018, Ziaei-Nia *et al*. 2018, Alipour *et al*. 2020). Several techniques for detecting CTCs and separating them from blood cells have been employed by taking advantage of physical features such as size (Lim *et al*. 2012), deformability (Park *et al*. 2016), density (Baker *et al*. 2003), inertial (Sun *et al*. 2013, Elhoseny *et al*. 2017, Elsayed *et al*. 2018, Rizk-Allah *et al*. 2018, Hosseinabadi *et al*. 2019, Mohanty *et al*. 2020, Krishnaraj *et al*. 2021), and dielectrophoretic force (Moon *et al*. 2011) or biological (a specific statement about biomarkers (Andree *et al*. 2016, Ewees *et al*. 2017, Elhoseny *et al*. 2018, Shankar *et al*. 2020, Xu *et al*. 2020b) properties, and subsequently analyze CTCs. Totally, there are two prominent methods for producing nonuniform electric field. One of them is electrode-based (Khoshmanesh *et al*. 2011) and the other one is insulator-based dielectrophoresis (Srivastava *et al*. 2011, Lou *et al*. 2021a, Lv *et al*. 2021a). In applying electrode-based method, the nonuniformity by the use of AC electric field is created by the arrays of electrodes which are put inside the microchannel. In this approach we are deal with significant challenges such as formation of bubble, fabrication which is so complicated, and fouling of electrodes in the channel. However, in the insulator-based dielectrophoresis method, the nonuniform electric field is generated by iDEP which uses two different objects together like remote electrodes and embedded insulating inside the channel. This method is capable of operating under two AC and DC electric fields. The electron-based technique has a disadvantage such as the

*Corresponding author, Ph.D.,
E-mail: 199462000803@email.sdu.edu.cn
[a]Ph.D., E-mail: xin13021569681@163.com

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common drawbacks. Consequently, the iDEP method is more efficient than the electrode-based approach (Pang *et al*. 2019, Wang *et al*. 2019, 2020, Zhang and Liu 2019, Zou *et al*. 2019, Xu *et al*. 2020a, Wu *et al*. 2021).

Microfluidic technology has been widely developed in particle and cell separation due to its advantages for the separation, fractionation, sortng, and purification of all classes of particles based on their physical and chemical properties because of their advantages of minimal consumption of sample and reagent, ease of use, and enabling of the integration of multicomponent for comprehensive analysis (Zhou *et al*. 2019, Ghabussi *et al*. 2020a, Zhou *et al*. 2020, 2021). The separation techniques using micro and nanofluidic devices are classified into passive and active methods, passive methods using geometries and hydrodynamic effects at micro/nanoscale, and active methods using external fields such as electric, magnetic, optical, and acoustic forces (Abdel-Basset *et al*. 2020b, Ali *et al*. 2020, El-Hasnony *et al*. 2020, Saračević *et al*. 2020, Shariati *et al*. 2020b, Uthayakumar *et al*. 2020). Gi Kye *et al*. (2019) presented a microfluidic device with dual-neodymium magnet-based negative magnetophoresis for the separation of the microparticles and cells. Kuntaegowdanahalli *et al*. (2009) proposed a simple inertial microfluidic device that used principle of Dean-coupled inertial migration in spiral microchannels for continuous, multi-particle separation. Among the all methods that are developed for particle separation, electrophoresis actuators using electric properties difference between particles, have turned out to be a powerful tool for separating (Shah *et al*. 2016, Toghroli *et al*. 2017, Nosrati *et al*. 2018, Milovancevic *et al*. 2019, Sajedi and Shariati 2019, Shariati *et al*. 2020c). A well-known and strong approach used for numerous applications is Continual dielectrophoretic separation. the analysis of water quality, a therapy based on stem cells, and cancer diagnosis are the good examples of this method. Totally, it is crucial to mix prefocusing of a particle into stream because the majority of the particles should be exposed to the identical electric field geometry existing in the separation region (Ma *et al*. 2021a, Zhao *et al*. 2021, Suhatril *et al*. 2019, Toghroli *et al*. 2020, Yazdani *et al*. 2020, Huang *et al*. 2021, Huang *et al*. 2021, Jiao *et al*. 2021, Rajaei *et al*. 2021). The mentioned focusing process needs techniques to be achieved. It needs the hydrodynamic squeezing requiring an encumbering peripheral system and a perplexing function to drive and manage the motion of the fluid and also this focusing process is dependent upon dielectrophoretic forces that are easily affected by the dielectric characterization of particles (Mohammadhassani *et al*. 2013, 2014, Toghroli *et al*. 2014, 2016, Safa *et al*. 2016, Sadeghipour Chahnasir *et al*. 2018, Sedghi *et al*. 2018, Katebi *et al*. 2019, Mansouri *et al*. 2019).

Yin *et al*. (2019) presented a microfluidic device that used microfilters and dielectrophoresis to separate micro-particle and cells. In their work the blocked particles were pushed off the filters under the negative dielectrophoretic force and drag force. Zhang *et al*. (2018) suggested an external dielectrophoretic force field and coupling it with inertial forces, they presented here an innovative hybrid DEP-inertial microfluidic platform for particle tunable separation. Yildizhan *et al*. (2017) isolated live monocytes from dead monocytes using 3D carbon-electrodes by dielectrophoretic separation. Ayala-Mar *et al*. (2019) introduced a direct current-insulator-based dielectrophoretic (DC-iDEP) approach to simultaneously capture and separate exosomes by size. Aghilinejad *et al*. (2018) studied insulator-based dielectrophoresis technique and the effects of joule heating and electrothermal flow on device performance and presented a separation plan for selective trapping of circulating tumor cells (CTCs). Zhang and Chen (2020) presented a dielectrophoresis microfluidic chip for particle separation, their device dielectric features to confirm size-based fractionation of blood cells. They computed value range of parameters by MATLAB (Jiang *et al*. 2021, Li *et al*. 2021, Lou *et al*. 2021b, Lv *et al*. 2021b, Yu *et al*. 2021) and COMSOL software simulation. Techaumnat *et al*. (2020) proposed a microfluidic device with interdigitated electrodes and a microchannel that employed discrete dielectrophoretic force to separate polystyrene particles from red blood cells. Elitas *et al*. (2019) examined the dielectrophoretic properties of the monocytes and macrophages and proposed 3D carbon-electrode dielectrophoresis as a separation tool. Zhou *et al*. (2018) examined the particle movement of the viscoelastic flow in the contraction-expansion channel. They solved the Oldroyd-B viscoelastic fluid flow field, the movement and the electric field of finite-size particles by an arbitrary Lagrangian-Eulerian (ALE) numerical method (Abdel-Basset *et al*. 2019a, Elhoseny *et al*. 2019a, Elhoseny and Shankar 2019a, b, Shankar and Elhoseny 2019, Thakur *et al*. 2019, Dutta *et al*. 2020).

According to the above mentioned investigation, we represent a novel microfluidic device that performs in a combination of hydrodynamic focusing and dielectrophoresis force in order to separate tumor cells from blood cells. Moreover, this device as a means of achieving dielectrophoresis field-flow-fractionation (DEP-FFF) uses a system which works in low voltage and a single state. dielectrophoretic force relies on the cell sizes that is why the separation of cells which are dependent on their size is difficult. Hence DEP-FFF is employed with low voltages to solve this problem (Gaber *et al*. 2018, Yuan *et al*. 2018).

The biggest cells are repelled by the dielectrophoretic force, because of the force is proportional to the cell volume, from one side of the channel on which the cells are focused by the presented system utilizing a buffer flow. With respect to the blood sorting where the tumor cells are much bigger than the white and the red blood and are deviated more than the white and the red blood. So in this study the classification region is of great importance and after this area, a place, which is bifurcated, separates the cells based on their location in the flow stream. Furthermore, the rates of recovery and the purity of CTCs are very efficient and obtained by this device that is able to combine other approaches to make it effective like opacity-based cell classification (Ali and Park 2016), cell coulter counting (Murali *et al*. 2009, Hassan *et al*. 2014), or cell lysis (Schilling *et al*. 2002, Chen *et al*. 2007) and also it can be used in applications named point of care.

2. Computational microfluidic device

2.1 Hydrodynamic flow focusing

Hydrodynamic flow focusing occurs when fluids with different velocities are injected side by side and is a useful technique for sample focusing and control (Golden *et al*. 2012). It might be characterized as the the sample fluid squeezing of interest using another fluid, which is called the sheath fluid. This phenomenon has been investigated for a long time and also has yielded a myriad of applications (Tripathi *et al*. 2016, Elhoseny and Shankar 2019b, Elhoseny 2020a, b, Geetha *et al*. 2021, Lydia *et al*. 2021). There are two simple methods for cell focusing, which are named, sheathless flow focusing and sheath flow focusing (Tripathi *et al*. 2015). Sheathless flow focusing uses external forces like magnetic, acoustic, dielectrophoresis, and inertial. while, Sheath flow focusing applies one or more sheath fluid named hydrodynamic focusing. In this paper, the adaption of pressures is used at the intents to calibrate the hydrodynamic focusing which causes a cells focusing to be obtained on the left side of the channel. Here, the flow focusing is used to concentrate flow streamlines to increase the effect of dielectrophoresis force (Chen *et al*. 2018, 2021, Deng *et al*. 2019, Hu *et al*. 2019, Jiang *et al*. 2020, Liu *et al*. 2020, Pan *et al*. 2020, Zhang *et al*. 2020a).

2.1 Dielectrophoresis force

The polarization of a dielectric particle is because of placing it in the electric field. In case of the used electric field is uniform, the net applied force on particle will be zero. whereas a dipole onto the particle is induced by the electric field which is non uniform, and the field gradient generates various Coulomb forces on either pole. So, the particle moves up or down the gradient in the imposed electric field, referred to as positive DEP (pDEP) or negative DEP (nDEP), depending on whether it is more or less polarizable than the suspending medium. If an applied electric field is non uniform, the net force will be obtained by the following equation (Castellanos *et al*. 2003)

$$F_{DEP} = (p \cdot \nabla)E \tag{1}$$

where p and E is the particle bipolar moment and the electric field intensity respectively. As a result, the calculated effective particle bipolar moment is shown in Eq. (1). (Castellanos *et al*. 2003)

$$P^* = v\alpha^* E \tag{2}$$

In which P^* and v and α^* are used as a complex conjugate of P and a particle volume and a particle complex polarization respectively. Consequently, Eq. (3) can be obtained by a combination of Eqs. (1) and (2), which is as follow

$$F_{DEP} = \frac{1}{4} Re[\alpha^*] \nabla |E|^2 \tag{3}$$

As it is shown, $Re[\alpha^*]$ is defined as the real part of particle polarization. A polarization for a uniform particle can be determined by Eq. (4) If the particle is assumed to be a sphere (Castellanos *et al*. 2003)

$$\alpha^*(\omega) = 3\varepsilon_m f_{CM}(\omega) \tag{4}$$

$\omega = 2\pi f$ refers to the angular frequency of electric and f_{CM} shows the Clausius-Mossotti factor that will be discussed later in detail. In addition, ε^* is determined by Eq. (5), which represents the complex permittivity coefficient

$$\varepsilon_x^* = \varepsilon_0 \varepsilon_x - j\left(\frac{\sigma_x}{\omega}\right) \quad . \quad x = p \;\; or \;\; m \tag{5}$$

In which $\varepsilon_0 = 8 \cdot 854 \times 10^{-12}\, {}^{F}\!/_{m}$ is used as a vacuum permittivity coefficient and ε_x represents the relative permittivity coefficients. Furthermore, σ_x refers to the electrical conductivity. Clausius-Mossotti factor can be determined by Eq. (6) if the uniformity of the particle is evident. But when a very thin layer covers the particle such as numerous cells, ε_P, which is determined by Eq. (6), will be obtained based on Eq. (7) that is as follow

$$f_{CM} = \frac{\varepsilon_p^* - \varepsilon_m^*}{\varepsilon_p^* + 2\varepsilon_m^*} \tag{6}$$

$$\varepsilon_p^* = \varepsilon_{mem}^* = \frac{\left(\frac{r+d}{r}\right)^3 + 2\left(\frac{\varepsilon_{int}^* - \varepsilon_{mem}^*}{\varepsilon_{int}^* + 2\varepsilon_{mem}^*}\right)}{\left(\frac{r+d}{r}\right)^3 - \left(\frac{\varepsilon_{int}^* - \varepsilon_{mem}^*}{\varepsilon_{int}^* + 2\varepsilon_{mem}^*}\right)} \tag{7}$$

where d and r are used as a thickness of the membrane and an internal layer radius respectively. The effective electric field substitutes electric field In Eq. (8) where the applied force on the particle can be determined by replacing Eqs. (4)-(7) into Eq. (3) as It is shown in the following

$$F_{DEP} = \frac{1}{2}\pi\varepsilon_m a^3 Re(f_{CM}) \nabla |E_{rms}|^2 \tag{8}$$

As it can be seen in the above equation, the force applied on particle is dependent on the radius of particle, gradient of electric field square, and by which the intensity and direction of the force applied on particle can be obtained (Morasaei *et al*. 2021, Cao *et al*. 2020, Ma *et al*. 2021b, Zhang *et al*. 2021b). In Eq. (6), it is apparent that this factor amount and sign rely on polarization of particle and its surrounding fluid. Whenever the distance between these two increases, the force applied on particle rises. If the particle polarization is lower than the surrounding fluid polarization, an occurrence of nDEP is assumed and the region with the maximum electric field gradient repulses the particles. in case the particle polarization is higher, the status of the Clausius-Mossotti factor will change to positive and also pDEP will influence the particle. hence, the absorption of particle occurs (Abdel-Basset *et al*. 2019b Elhoseny *et al*. 2019b, Lakshmanaprabu *et al*. 2019, Krishnaraj *et al*. 2020, Zaher *et al*. 2020). Fig. 1 indicates the line of electric filed and the impact of the negative and positive dielectrophoresis on the movement of the electron. there are some forces which are applied on the particles placed in the fluid such as, dielectrophoresis force, buoyancy, gravity, and drag. Eq. (9) depicts the interaction of two forces which are buoyancy and gravity, in which r, g, and p are used as radius, gravity acceleration, and density respectively (Pethig and Talary 2007).

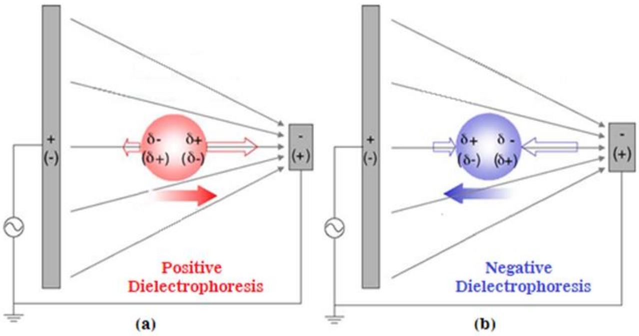

Fig. 1 It is of great significance that which polarization is higher, the particle or the fluids surrounding the particle. If the first case is true (a), there is a factor which is named Clausius-Mossotti, its status will immediately turn to positive, after that PDEP appears in order to influence the particle, as a result an area will be found with the maximum gradient of electric field in which the particles are thoroughly absorbed. In the second condition when the fluid polarization is higher (b), it is assumed that NDEP occurs and the region with the maximum electric field gradient repulses the particles.

$$F_g = (\rho_p - \rho_m)\left(\frac{4}{3}\pi r^3\right)(g) \tag{9}$$

Eq. (10) displays the drag force of a particle that is spherical and located in fluid, in which η counts for fluid viscosity and v represents fluid velocity difference vector (Amo *et al*. 2009).

$$F_{Drag} = 6\pi\eta r v \tag{10}$$

2.3 Inertial lift force

The inertial lift force consists of the wall-effect lift force and the shear-gradient lift force (Cao *et al*. 2019, Dorri *et al*. 2019, Libo *et al*. 2019, Puri *et al*. 2019, Tang and Elhoseny 2019). The shear-gradient lift force pushes the particle towards the wall while the wall-effect lift force pushes the particle towards the center. Eventually, driven by the inertial lift force, particles are focused in the equilibrium positions in the straight microchannel. In unbounded flow, a neutrally buoyant particle can experience lift due to slip (relative particle velocity), combined with shear or rotation (Gao *et al*. 2020, Ghabussi *et al*. 2020, Ma *et al*. 2020). Near a wall, the presence of the wall induces extra flow disturbances, resulting in increased lift forces. The lift forces are computed by superimposing the flow disturbance caused by ambient shear, relative motion, rotation and the presence of the walls. In wall bounded flows the highest drag is observed when the particle is in contact with wall, and decays rapidly as the distance between the particle and wall increases (Happel and Brenner 1961, Eassa *et al*. 2018, Hurrah *et al*. 2019, Muhammad *et al*. 2019, Murugan *et al*. 2019, Valayapalayam Kittusamy *et al*. 2019). In a straight microchannel, the inertial lift force on a particle can be expressed as below

$$F_L = \frac{\rho v_m^2 d^4}{D_h^2} f_c \tag{11}$$

where $\rho . v_m . d . D_h .\ and\ f_c$ indicate fluid density, maximum channel velocity, particle diameter, channel hydraulic diameter and lift coefficient. The inertial lift force will decrease significantly with small decrease in particle size due to the fourth-order dependence (Ghabussi *et al*. 2019, 2020a, Shariati *et al*. 2020a). In this work due to the low velocity of inlet fluid and the small size of the main channel, the effects of the wall-effect lift force and the shear-gradient lift force are avoided. Negative dielectrophoresis has some applications such as directing and assembling colloidal particles away from the edges of electrode. Here, repulsion is applied in conjunction with hydrodynamic focusing by negative dielectrophoresis which is utilized in this approach and is also carried out in solution conductivity while the opacity-based sorting only performs in low conductivity. In this study, RBCs, WBCs and CTCs undergo negative dielectrophoresis when 100 kHz is the applied frequency. Due to differences in size, the dielectrophoretic force is less powerful for the RBCs and WBCs than for CTC. Moreover, the cells on which the medium friction oppose the dielectrophoretic force that gives the whole force are studied by (Di Sia 2013, Malarkodi *et al*. 2013, Benmansour *et al*. 2019, Altabey *et al*. 2020)

$$F_{TOT} = F_{DEP} - F_{Drag} \tag{12}$$

3. Fabrication, packaging and chip design

The fabrication process is described elsewhere and is briefly defined here. The device is made on a glass whose dimensions are 4-in wide and 225 mm thick. The platinum electrodes with the two hundred nanometer thickness are sputtered on the top of a titanium adhesion layer with a 20 nm thickness and more patterned by lift-off. With use of the SU8 layer whose height is 40 μm and the wafer is cut into smaller chips which are 20 $mm \times 15\,mm$, the microchannels are made and in order to seal them a polydimethylsiloxane (PDMS) block is located on the top of the chip making the microchannels fixed and stable utilizing a plastic portion. There is also a chip holder made in acrylic on which the chips are located and are coupled to a printed circuit board for keeping the signal amplification safe and protecting the distribution to the suitable contacts. by using this setup, the outlets and inlets of the fluid, and pressure regulation with a pressure can be accessible.

The chip design is shown in Fig. 2. As it can be seen, it shows different and significant parts of this chip which involves three sections: (1) an injection region, (2) a separation region, (3) a collection region. As agreed, there is an important direction where can be seen by the cells when they are flowing in the right and left sides of channel t. A mixture of blood cells with CTCs is injected at the left inlet and buffer comes from the right inlet. Due to the small channel dimensions (only 40 μm in width), a mixture of two flows cannot be seen in the separation region because the flow is laminar in this region (Reynolds number < 0.05).

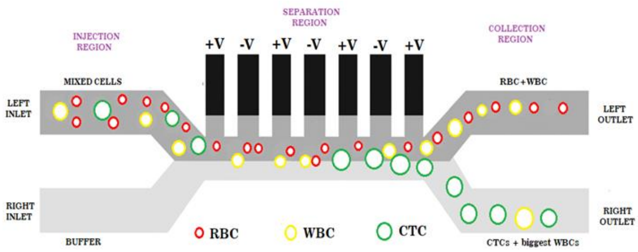

Fig. 2 This picture depicts various and main sections of a chip sketch. It gives us some useful knowledge about different functions and behavior of this system such as the CTCs, WBCs, and RBCs. One of the parts concerns with the extent of microfluidic channels which are measured 40 μm high and 40 μm wide. Another part that has been analyzed is located on the left side of these channels in the separation region named liquid electrodes on which the dielectrophoretic voltage is applied.

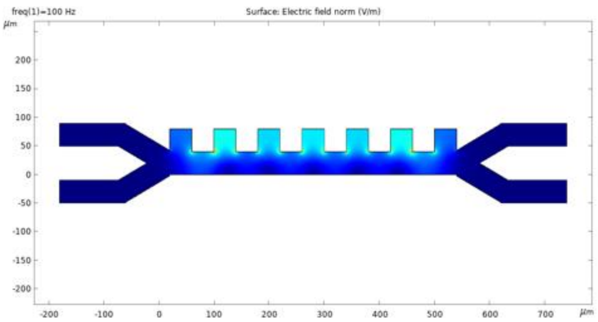

Fig. 3 The intensity of the electric field obtained by simulation in the device is shown. It is apparent that the electric field norm is at a distance from the electrodes and begins to exist in the origin of the dielectrophoretic repulsion of CTCs. In this depicted norm, in front of the electrode channels besides the lateral corners of them, There is region with higher gradient than elsewhere. Consequently, a gradual increase in the cell trajectory will occur due to the repulsion of the dielectrophoretic going to the lower section of the channel and happening at each pair of electrode on which hydrodynamics concentrate.

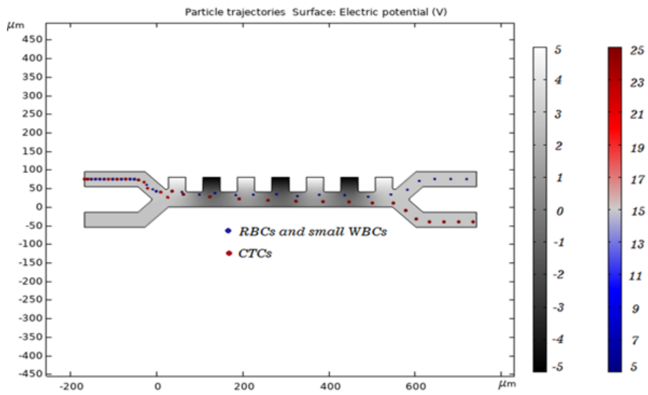

Fig. 4 With the help of CTCs trajectory and blood cells simulation, the deviation of big cells is evident and the relatively total CTCs (big cells) are collected at the right channel. While the cells which are smaller as shown above such as RBCs and small WBCs leave the device at the left channel. The amount of 10 V_{PP} voltage between adjacent electrodes is applied and after doing the flow speed calculation, figured out that the lowest part of the inlet is higher than the top of it.

The well-known “liquid electrodes” that are described as planar electrodes placed in an exactly vertical position to the main channel are utilized in this device. these liquid electrodes, on which Dielectrophoresis signals applied, are located on the left side of the channel. In addition, an uniform electric field all over the height of channel is supplied by liquid electrodes which keep a process flow as simple as possible using a single planar metal layer. The dielectrophoretic force repels the circulating tumor cells (CTCs) and the biggest WBCs leave the device at the right channel, while the deviation of the cells which are smaller like RBCs and WBCs are not sufficient and collected at the left channel. PDMS is realized to be nonthrombogenic. Utilizing a powerful and reversible anticoagulant causes the lower SU-8 and barely glass hemocompatibility to be compensated. Any time that leads to activation is much longer than the constancy time which is related to on-chip cells. Ultimately, there are lots of methods for cells to be kept safe from being involved in the contact by liquid electrodes using metal and also they are exposed to high electrical fields. The solution which provides benefits in this study is phosphate buffer saline(PBS) diluting in the sucrose solution with the aim of achieving the conductivity of 55 mS/m as controlling am osmolarity of 300 $mOsm/l$. The microchannel walls are the parts on which the cells adhesion is minimized by adding 1% bovine serum albumin (BSA). It has been concluded that EDTA is a powerful and reversible anticoagulant which prevents the process of blood forming a clot by the removal calcium from the blood without influencing the morphological variation in the cells. The blood sample infected with CTCs and WBCs are in low concentration. By means of pipetting at the inlets that are fluidic, the buffer and sample are injected. In addition, using a reversed microscope is of great importance, under which the sorting can be seen easily.

4. Numerical simulations

Comsol is a simulation software based on real and objective applications. The overall goal of comsol simulation is to get as close as possible to the effects we see in the environment, whether in the scientific or engineering fields. Here, both dielectrophoretic force and hydrodynamic flow focusing, which are applied on cells, are assessed by the quantitative simulations that are carefully executed.

The software package COMSOL multiphysics are used for analyzing elements that have two dimensions like the microchannels which are in 40 μm height and in 40 μm width and this analysis makes the distribution of the electric field and the flow reappear again inside the device. As evidence, Fig. 3 Depicts the electric field norm. In simulation the dielectrophoresis and drag force are applied on the device.

For a given applied voltage and frequency Fig. 4,

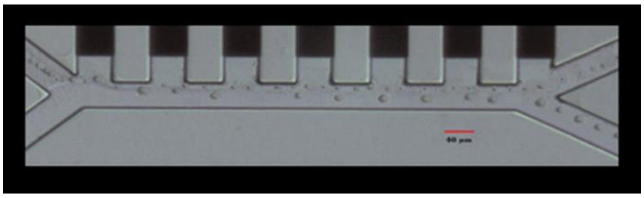

Fig. 5 Using superposition of consecutive video frames led to obtain some specific trajectories in the device like the trajectory of CTCs, RBCs, and WBCs. The studied flow speed represents that the bottom part of the inlet is higher than the top of it. In order to depict the separation properly, the typical number of CTCs should be lower than the concentration of them in blood. It is important to mention that at the frequency of 100 kHz, the voltage of 10 V_{PP} is utilized between electrodes which are adjacent.

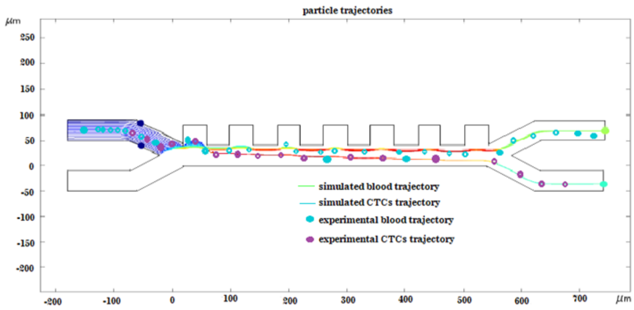

Fig. 6 An accurate comparison of the measured trajectories of WBCs, CTCs, and RBCs with the calculated ones has been carefully made. It should be pointed out that a considerable overlap exists between experiment and model data.

indicates the theoretical cells trajectory achieved inside the device. It is apparent that there is a probability to choose a mixture of nDEP and sheath focusing so that the small WBCs and the RBCs remain on the left side of the channel, whereas the deviation of the CTCs is adequate to travel to the right side of the channel. In this study, one of the advantages of bifurcation is to function as a laminar splitter.

5. Results

In this paper, the separation of CTCs from blood cells can be performed by the represented device with the aid of DEP-FFF. The blood sample in a combination of PBS are injected in the related inlets. The adaption of the pressures, which is used at the inlets, calibrates the hydrodynamic focusing in order to obtain a cells focusing on the left side of the channel. Based on a test, a validation of device function is performed applying the dielectrophoretic voltage which is 10 V_{PP} between adjacent liquid electrodes at 100 kHz. Fig. 5 indicates that the separation region in which superposition of consecutive video frames that is recorded with the help of a camera fixed firmly to the microscope at 20 frames per second in an attempt to achieve the WBCs, RBCs trajectory and CTCs in the device geometry, One of the useful result from our experimental work is that an

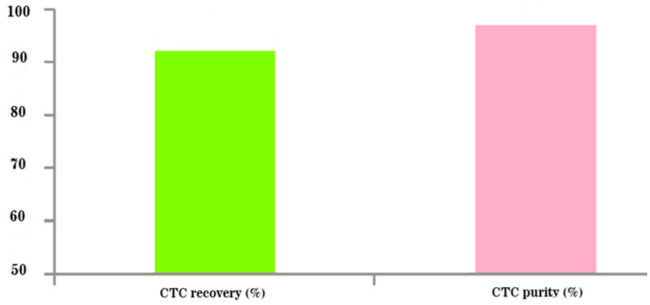

Fig. 7 Represented collection channels in which the counts of CTC purity and CTC recovery are shown. They are giving helpful information for three experiments such as the average and standard deviation as a consequence of using just a total amount of 4000 analyzed cells which are obtained by video analysis. Because of the high rates of recovery and purity of CTCs and capability of being regenerated, it can be put to use for the purpose of CTCs separation from blood.

obvious CTCs repulsion from the electrode is observed because of the negative dielectrophoresis which leads the big cells to leave the separation region on the right channel. It is shown that there is a track on the left side of the channel which depicts the blood cells trajectory. As it was mentioned, the blood cells are powerfully repelled and they also remain on the left side of the channel with the laminar flow due to their small size. As a result, they go out the separation region in the left collection channel.

Based on our first experiment, the flow speed at different parts of the inlet is various. For example, the flow speed which is utilized at the top of the inlet is lower the flow speed used at the bottom of the inlet. used at the bottom inlet is higher than the flow speed at the top inlet. the cells should be concentrated at the center of the inlet because the flow profile is parabolic. This experiment demonstrates the concept of cell sorting is thoroughly feasible due to their size and also that the CTCs and blood cells can be obtained in the various parts of the channel. Fig. 6. indicates that the comparison of experimental results reveals a good agreement with the simulation of cells trajectory.

To prove that the system is efficient enough, different methods have been applied. The properly arranged populations have been statistically analyzed and the identical concentration of these populations is applied in blood cells and CTCs and a DEP voltage whose amount is 10 V_{PP} at 100 kHz. The cell count is shown in Fig. 7. with the aid of video analysis at the various parts of the collection channel. This analysis performs in the separation region using the entire number of 4000 cells for three different experiments. The purity obtained at the CTCs collection channel is reproducible and very high (91.7%), the majority of CTCs are coming from the sample including a recovery rate higher than 91%, recovery rate is a ratio of the CTCs number existing at the right channel and their total number and the presence of WBCs that are the same size as CTCs.

In Fig. 8 presents the impacts of dielectrophoresis on the

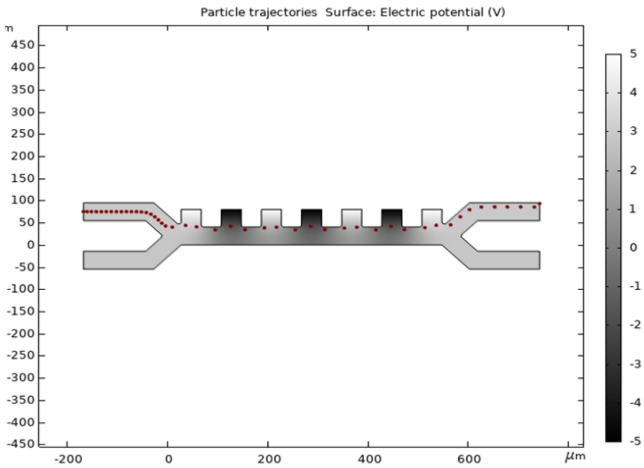

Fig. 8 Displaying the effects of excluding the dielectrophoresi force in the device. Subsequently, any separation cannot be seen in the cell trajectory without no applying voltage.

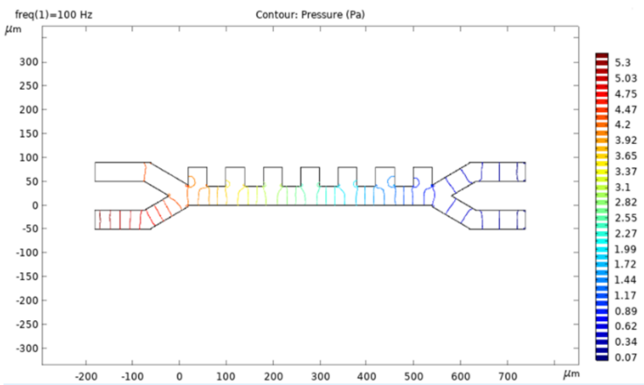

Fig. 9 This model Indicates the device where the pressure is higher than elsewhere in one region placed in the bottom of the inlet.

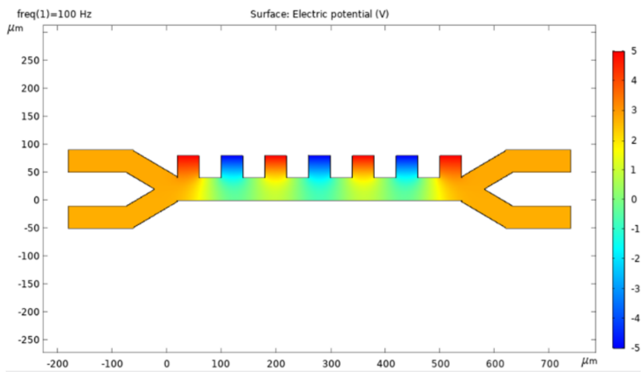

Fig. 10 According to the electric potential shown in the ab ove chip, the amount of voltage between ±5 is illustrated.

quality of separation process. According to Fig. 8 without DEP voltage, there is no deviation in the path of the cells which are moving toward the left collection channel, but the separation will occur when the voltage is applied.

According to the results, the represented device has an excellent robustness. In addition, the high efficiency of CTCs separation with high rates of recovery and purity can

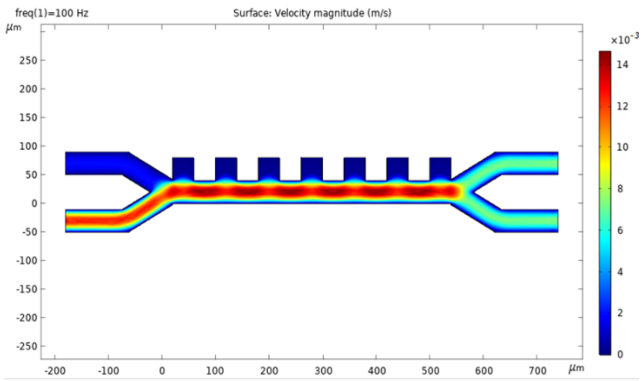

Fig. 11 fluid velocity is higher than other regions in two areas: One of them is between the electrodes and the other one is placed in the bottom inlet which can be seen in the chip as well.

be obtained by the device whose simple technology and operated low voltage causes the device adaption to a platform capable of being transported for point-of-care applications. Figs. 9, 10, and 11 show distribution of pressure, electric potential, and fluid velocity in the device. Accordingly, the following counters and information about the pressure, electric potential, and fluid velocity encounter us with a condition for having the separation process with the highest purity.

6. Conclusions

In the present work, we propose a device that has the ability to separate tumor cells from blood cells in continuous flow with the help of dielectrophoresis field-flow-fractionation. With the aid of hydrodynamics focusing together with the benefit of a dielectrophoretic force causes the separation of tumor cells from blood cell because of their size difference. Here, the flow speed and the electrical field simulate the cell trajectory whose calculations reveals a good agreement with the experimental results. The essential results of this paper are as follows

- The presented device can be used with low applied voltage such 10 V_{pp} and the theoretical cell has been obtained by numerical simulations of the flow speed and electrical field.
- The obtained separation is very efficient, the device being able to achieve a very high purity of CTCs of 91.7% with less than 9% cell loss.
- The high efficiency of separation is achieved and the device can obtain a very accurate particle separation.
- This method can also be used to separate other types of particles based on size differences.
- From the results, we believe our device possesses a high potential for separation of CTCs from blood and aiding future cancer research.
- information about the pressure, electric potential, and fluid velocity encounter us with a condition for having the separation process with the highest purity.

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