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[Daiki Nishikawa](#), [Yoshinori Seki](#), [Shigeru Tada](#) *

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Article

Modeling of Electric Field and Dielectrophoretic Force in a Parallel-Plate Cell-Separation Device with an Electrode Lid and Analytical Formulation Using Fourier Series

Daiki Nishikawa, Yoshinori Seki and Shigeru Tada *

Department of Applied Physics, National Defense Academy, Hashirimizu 1-10-20, Yokosuka city, 239-0802, Kanagawa, Japan

* Correspondence: stada@nda.ac.jp; Tel.: Tel.: +81-46-841-3810

Abstract: Dielectrophoresis (DEP) cell-separation technology is an effective means of separating rare cells. To develop highly efficient cell-separation devices, detailed analysis of the nonuniform electric field's intensity distribution within the device is needed, as it affects separation performance. Here we analytically expressed the distributions of the electric field and DEP force in a parallel-plate cell-separation DEP device by employing electrostatic analysis through the Fourier series method. The solution was approximated by extrapolating a novel approximate equation as a boundary condition for the potential between adjacent fingers of interdigitated electrodes and changed the underlying differential equation into a solvable form. The distributions of the potential and electric fields obtained by the analytical solution were compared with those from numerical simulations using finite element method software to verify their accuracy. The results showed excellent agreement. Three-dimensional fluorescence imaging analysis used live non-tumorigenic human mammary (MCF10A) cells. The distribution of cell clusters adsorbed on the interdigitated electrodes was compared with the analytically obtained distribution of the DEP force, and the mechanism underlying cell adsorption on the electrode surface was discussed. Furthermore, parametric analysis using the width and spacing of these electrodes as variables revealed that spacing is crucial for determining DEP force. The results showed that, by optimizing cell-separation devices using interdigitated electrodes, adjusting electrode spacing significantly enhances device performance.

Keywords: dielectrophoresis; cell separation; microfluidic device; electric field analysis; Fourier series expansion; three-dimensional fluorescence imaging

1. Introduction

In recent years, the development of a rapid and highly accurate method of separating and detecting specific rare cells from large numbers of diverse cell populations has become an urgent priority. For instance, the presence of circulating tumor cells (CTCs) in the blood increases as cancer progresses, underscoring the effectiveness of the rapid and accurate detection of CTCs for ultra-early cancer diagnosis. However, it is challenging to isolate and detect rare cells, including very early-stage CTCs, which exist in minute quantities in the blood. In light of these challenges, dielectrophoresis (DEP) technology has recently gained attention as an effective means of separating and detecting rare cells [1–4].

DEP is a phenomenon in which dielectric microparticles move along the gradient of a nonuniform electric field, propelled by the induction of electrical forces (DEP forces) acting on the microparticles. This results from the interaction between the dipole moment induced in the microparticles and the nonuniform electric field. In particular, using DEP with an AC electric field for cell separation offers significant advantages: it allows the separation of biological particles such as cells, viruses, and DNA with high accuracy, and is non-invasive to such particles because it does

not require pretreatments such as fluorescent labeling [5,6]. However, planar electrodes, which are widely used in DEP cell-separation technology, have a limited effective volume for processing cell samples, posing a challenge in achieving highly efficient separation of large quantities of cells [7]. Along with the increasing size of cell-separation devices and the optimization of the parallel-plate microfluidic channel structure, which has been the basis of the cell-separation device structure, devices with various shapes of microfluidic channels and electrodes have been proposed to enable the highly efficient separation of large numbers of cells [8–20]. However, issues such as increased applied voltage due to larger and more complex device structures have raised concerns about the adverse effects stemming from the generation of Joule heat and strong AC electromagnetic fields on the physiological functions of cells [21]. Therefore, there is a need to develop devices capable of highly efficient cell separation even under low-voltage loading conditions. Since the magnitude and distribution of the DEP forces acting on cells depend heavily on the electric field distribution, the precise determination of the electric field distribution will enable the optimal design of the device's internal structure, electrode arrangement, and electrode architecture. This, in turn, is expected to facilitate the development of highly efficient cell-separation devices that can operate under low-voltage conditions.

Numerous studies have aimed to rigorously determine the electric field in microfluidic devices and the DEP force induced by nonuniform electric fields. A wide range of methods exists for obtaining electric field distributions. For example, analytical approaches have utilized Fourier series [18,22–25], Green's functions [26,27], and Green's theorem [28,29], while other approaches have been based on the principle of conformal mapping, including the Schwarz–Christoffel transform [30–34], or on numerical simulations using finite element methods (FEMs) [35–39].

In this study, we derived analytical solutions for the distribution of the AC electric field and DEP forces generated in a parallel-plate cell-separation device that we proposed previously [20,40] by applying electrostatic analysis using the Fourier series method. In modeling the proposed device, whose top plate (lid) also serves as an electrode, we need to solve a mixed boundary value problem comprising three Dirichlet boundary conditions and one Neumann boundary condition for the electric potential, excluding the periodic boundary condition [41]. However, this problem differs significantly from conventional devices that have either a glass top plate or open-top interdigitated electrodes, where exact solutions are attainable, highlighting the severe challenge of obtaining closed-form solutions [12,18,29,31,33,42]. Therefore, in this study we extrapolated a newly proposed approximate equation to the potential between adjacent fingers of interdigitated electrodes, originally necessitating a Neumann boundary condition. This was replaced with the corresponding Dirichlet boundary condition to reformulate the underlying differential equation into a solvable form, thus enabling the derivation of an analytical solution. The accuracy of the distributions of the potential and electric fields was verified by comparing those obtained by the analytical solutions to the results of numerical simulations using commercially available FEM software. Three-dimensional (3D) fluorescence imaging analysis was subsequently performed using live non-tumorigenic human mammary cells (MCF10A). The analytical model was validated by comparing the distribution of live cell clusters adsorbed on the interdigitated electrode surface to the analytically obtained distribution of the DEP force. The mechanisms underlying cell adsorption and cell cluster formation at the interdigitated electrode surface were also discussed. Furthermore, a parametric analysis was performed using the electrode width and spacing of the interdigitated electrodes as variables, and the optimal electrode arrangement and architecture for highly efficient cell separation were explored and proposed.

2. Theory

2.1. Basic Principle of DEP

The DEP force induced in the cell subjected to a nonuniform AC electric field is given as follows,

$$\mathbf{F}_{\text{DEP}} = 2\pi \epsilon_l \left(\frac{d_c}{2} \right)^3 \text{Re}(\beta) \nabla |\mathbf{E}|^2 \quad (1)$$

where ϵ_l is the electric permittivity of the solution, d_c is the cell diameter, ∇ is the Nabla operator, and $\mathbf{E}$ is the AC electric field vector. $\text{Re}(\beta)$ denotes the real part of the Clausius–Mossotti (CM) factor

$$\beta = \frac{\epsilon_c^* - \epsilon_l^*}{\epsilon_c^* + 2\epsilon_l^*}$$

where ϵ_c is the electric permittivity of the cell. The symbol '*' represents the complex electric permittivity and is expressed as

$$\epsilon^* = \epsilon + \frac{\sigma}{j\omega}, \quad j = \sqrt{-1}$$

where σ is the electric conductivity and ω is the angular frequency of the AC electric field ($= 2\pi f$; f is the electric field frequency). For the application of the single-shell model to live mammalian cells, β can be expressed as [43]

$$\beta = \frac{\omega^2(\tau_l \tau_c^* - \tau_c \tau_l^*) + j\omega(\tau_l^* - \tau_l - \tau_c^*) - 1}{\omega^2(2\tau_l \tau_c^* - \tau_c \tau_l^*) - j\omega(\tau_l^* - 2\tau_l - \tau_c^*) - 2} \quad (2)$$

where

$$\tau_c^* = \frac{c_m d_c}{2\sigma_c'}, \quad \tau_c = \frac{\epsilon_c'}{\sigma_c'}, \quad \tau_l^* = \frac{c_m d_c}{2\sigma_l}, \quad \tau_l = \frac{\epsilon_l}{\sigma_l}.$$

Here, σ_l is the electric conductivity of the solution, ϵ_c' is the effective electric permittivity of the cell, σ_c' is the effective electric conductivity of the cell, and c_m is the capacitance of the cell membrane. As an example, Figure 1 shows the frequency spectra of the $\text{Re}(\beta)$ of live MCF10A cells for various values of σ_l . Values of the d_c and other electrical properties were taken from Ref. [44].

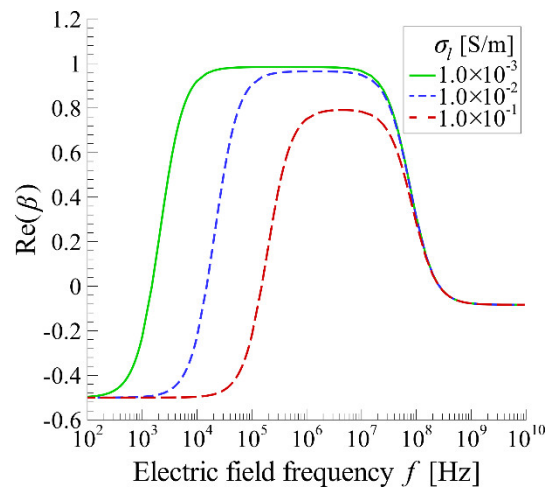


Figure 1. Frequency spectrum of $\text{Re}(\beta)$ for various σ_l .

To evaluate the magnitude of $\mathbf{F}_{\text{DEP}}$ induced on the cell, it is necessary to know the values of $\text{Re}(\beta)$ and $\nabla|\mathbf{E}|^2$. The value of $\text{Re}(\beta)$ can be obtained from Equation (2) if the values of d_c and f are known, and the value of $\nabla|\mathbf{E}|^2$ can be determined if the distribution of $\mathbf{E}$ can be obtained by some means.

2.2. Electric Field Analysis

Figure 2a shows a schematic of the cell-separation device to be analyzed. The device has a parallel-plate microfluidic channel structure consisting of interdigitated electrodes on the bottom surface and a planar electrode on the top surface. By applying AC voltage to the device, a nonuniform electric field is generated across the whole volume of the microfluidic channel. Because the fingers of the interdigitated electrodes are sufficiently long and aligned along the flow direction of the microfluidic channel, the electric field analysis model in the device can be simplified into a two-dimensional (2D) model in the cross section of the microfluidic channel, as shown in Figure 2b.

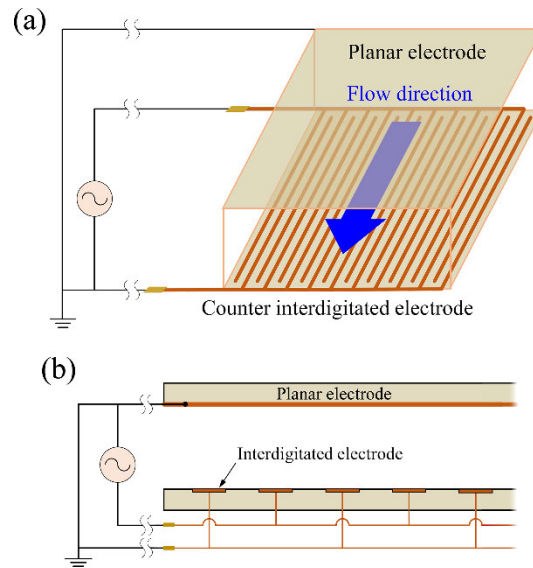


Figure 2. (a) Schematic of cell-separation device. (b) 2D model of cell-separation device.

The mathematical model of the electric field analysis is shown in Figure 3. In the present analysis, an electrostatic field analysis based on the AC effective value was adopted. The governing equation for the potential of the electrostatic field in the microfluidic channel, $\varphi(x, y)$, is the Laplace equation

$$\frac{\partial^2 \varphi(x, y)}{\partial x^2} + \frac{\partial^2 \varphi(x, y)}{\partial y^2} = 0. \quad (3)$$

The boundary conditions for the potential are

$$\varphi(x, H) = V_{\text{rms}} \quad (0 \leq x \leq w) \quad (4)$$

$$\frac{\partial \varphi(x, H)}{\partial y} = 0 \quad (w < x < L - w) \quad (5)$$

$$\varphi(x, H) = 0 \quad (L - w \leq x \leq L) \quad (6)$$

$$\varphi(x, 0) = 0 \quad (7)$$

$$\frac{\partial \varphi(0, y)}{\partial x} = 0 \quad (8)$$

$$\frac{\partial \varphi(L, y)}{\partial x} = 0 \quad (9)$$

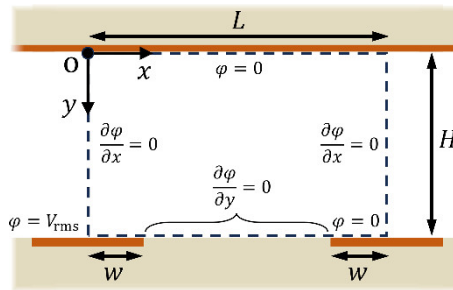


Figure 3. Mathematical model and boundary conditions.

where V_{rms} is the effective value of the applied voltage, L is the distance between the center lines of adjacent interdigitated electrodes, H is the height of the microfluidic channel, and w is half the width of the electrode. Here, the following dimensionless variables are introduced.

$$x^* = \frac{x}{L} \quad (10)$$

$$y^* = \frac{y}{H}. \quad (11)$$

Substituting Eqs. (10) and (11) into Eqs. (3)–(9) yields

$$\frac{\partial^2 \varphi(x^*, y^*)}{\partial x^{*2}} + \left(\frac{L}{H}\right)^2 \frac{\partial^2 \varphi(x^*, y^*)}{\partial y^{*2}} = 0 \quad (12)$$

$$\varphi(x^*, 1) = V_{\text{rms}} \quad \left(0 \leq x^* \leq \frac{w}{L}\right) \quad (13)$$

$$\frac{\partial \varphi(x^*, 1)}{\partial y^*} = 0 \quad \left(\frac{w}{L} < x^* < 1 - \frac{w}{L}\right) \quad (14)$$

$$\varphi(x^*, 1) = 0 \quad \left(1 - \frac{w}{L} \leq x^* \leq 1\right) \quad (15)$$

$$\varphi(x^*, 0) = 0 \quad (16)$$

$$\frac{\partial \varphi(0, y^*)}{\partial x^*} = 0 \quad (17)$$

$$\frac{\partial \varphi(1, y^*)}{\partial x^*} = 0 \quad (18)$$

Equations (12)–(18) collectively form a mixed boundary value problem. It is particularly difficult to obtain a closed-form solution in the case of this analysis. Therefore, to obtain a solution by using the quadrature method, the Neumann boundary condition in Equation (14) was replaced by a Dirichlet boundary condition

$$\varphi(x^*, 1) = V(x^*) \quad \left(\frac{w}{L} < x^* < 1 - \frac{w}{L}\right). \quad (19)$$

For an extrapolating function of $V(x^*)$ on the right-hand side of Equation (19), the expression

$$V(x^*) = \frac{V_{\text{rms}}}{\pi} \cos^{-1} x^* \quad (20)$$

was chosen. Equation (20) closely approximates the exact solution for the inter-electrode potential in the absence of a planar electrode on the top surface of the device ($y^* = 0$) [Appendix A]. To make Equation (20) integrable in the Fourier series method, the third-order terms of the McLaurin expansion of $\cos^{-1} x^*$ were considered. This was done under the conditions where $1 - 2w/L \cong 0$, resulting in the reduction of Equation (20) as

$$V(x^*) \cong \frac{V_{\text{rms}}}{\pi} \left[\frac{\pi}{2} - x^* - \frac{(x^*)^3}{6} \right] + O((x^*)^5). \quad (21)$$

Equation (21), satisfying boundary conditions, $V(w/L) = V_{\text{rms}}$ and $V(1 - w/L) = 0$, was obtained as

$$V(x^*) = \frac{V_{\text{rms}}}{\pi} \left[\frac{\pi}{2} - C \frac{x^* - \frac{1}{2}}{\frac{1}{2} - \frac{w}{L}} - \left(\frac{\pi}{2} - C \right) \frac{\left(x^* - \frac{1}{2} \right)^3}{6 \left(\frac{1}{2} - \frac{w}{L} \right)^3} \right]. \quad (22)$$

Here, C is an arbitrary constant, and its optimal value was determined by curve fitting Equation (22) to Equation (20) using the method of least squares, yielding $C = 0.75480$. Figure 4 shows the distribution of Equation (22) normalized to the value V_{rms} for various values of C when $H/L = 5$ and $w/L = 0.25$, together with the distribution of normalized Equation (20).

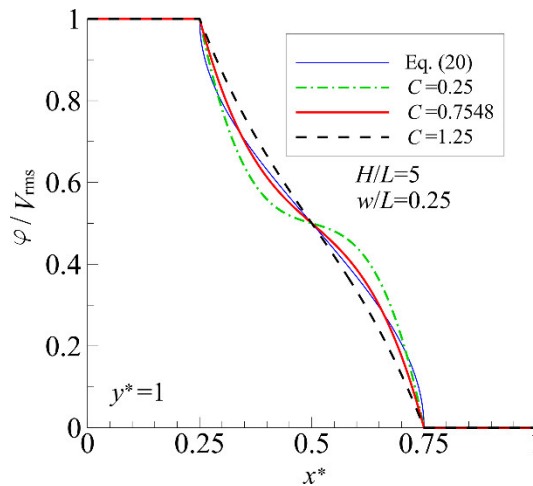


Figure 4. Distribution of $\varphi(=V(x^*))$ for various values of C .

2.3. Analytical Solution by Fourier Series Method

The solution of $\varphi = \varphi(x^*, y^*)$ is expressed as

$$\varphi = A' + B'x^* + C'y^* + D'x^*y^* + f(x^*)g(y^*) \quad (23)$$

where A' , B' , C' , and D' are unknown constants, and f and g are functions of only x^* and y^* satisfying Eqs. (13)–(18), respectively. Substituting Equation (16) into Equation (23) yields

$$A' = B' = 0 \quad (24)$$

Furthermore, substitution of Eqs. (17) and (18) into Equation (23) yields

$$D' = 0. \quad (25)$$

Using Eqs. (13), (15), (19), and (22), the functional form of φ is determined as follows, assuming $k_n = n\pi (n = 1, 2, \dots)$ [Appendix B]

$$\varphi = a_0 y^* + 2 \sum_{n=1}^{\infty} a_n \cos(k_n x^*) \sinh\left(\frac{k_n H}{L} y^*\right) \quad (26)$$

$$a_0 = \frac{V_{\text{rms}}}{2} \quad (27)$$

$$\begin{aligned} a_n = \frac{V_{\text{rms}}}{k_n} \left\{ \left(1 - \frac{2C}{\pi}\right) - \frac{4C}{\pi k_n \frac{L-2w}{L}} \tan\left(\frac{k_n}{2} \frac{L-2w}{L}\right) \right. \\ \left. - \frac{24\left(1 - \frac{2C}{\pi}\right)}{k_n^2 \left(\frac{L-2w}{L}\right)^3} \left\{ \frac{L-2w}{L} \left[\frac{k_n^2}{24} \left(\frac{L-2w}{L}\right)^2 - 1 \right] \right. \right. \\ \left. \left. + \frac{2}{k_n} \left[\frac{k_n^2}{8} \left(\frac{L-2w}{L}\right)^2 - 1 \right] \cot\left(\frac{k_n}{2}\right) \right\} \right\} \frac{\sin\left(\frac{k_n}{2}\right) \cos\left(\frac{k_n}{2} \frac{L-2w}{L}\right)}{\sinh\left(\frac{k_n H}{L}\right)} \end{aligned} \quad (28)$$

2.4. Analytical Form of DEP Force

Since the electric field $\mathbf{E} = \mathbf{E}(x^*, y^*)$ is a vector quantity, it can be represented by the vector expression as

$$\mathbf{E} = E_x \mathbf{e}_x + E_y \mathbf{e}_y = -\text{grad}\varphi \quad (29)$$

where $\mathbf{e}_x$ and $\mathbf{e}_y$ denote the unit vectors in the x and y directions, respectively, and $E_x = E_x(x^*, y^*)$ and $E_y = E_y(x^*, y^*)$ are the x and y components of the electric field $\mathbf{E}$. Using Eqs. (26)–(28), E_x and E_y become

$$E_x = 2 \sum_{n=1}^{\infty} a_n k_n \sin(k_n x^*) \sinh\left(\frac{k_n H}{L} y^*\right) \quad (30)$$

$$E_y = \frac{V_{\text{rms}}}{2} - \frac{2H}{L} \sum_{n=1}^{\infty} a_n k_n \cos(k_n x^*) \cosh\left(\frac{k_n H}{L} y^*\right). \quad (31)$$

To find $\mathbf{F}_{\text{DEP}}$, we can utilize the mathematical relationship

$$\begin{aligned} \nabla|\mathbf{E}|^2 &= \nabla(E_x^2 + E_y^2) \\ &= 2 \left(E_x \frac{dE_x}{dx^*} + E_y \frac{dE_y}{dx^*} \right) \mathbf{e}_x + 2 \left(E_x \frac{dE_x}{dy^*} + E_y \frac{dE_y}{dy^*} \right) \mathbf{e}_y \end{aligned} \quad (32)$$

Equation (1) becomes

$$\mathbf{F}_{\text{DEP}} = 4\pi \epsilon_l \left(\frac{d_c}{2}\right)^3 \text{Re}(\beta) \left[\left(E_x \frac{dE_x}{dx^*} + E_y \frac{dE_y}{dx^*} \right) \mathbf{e}_x + \left(E_x \frac{dE_x}{dy^*} + E_y \frac{dE_y}{dy^*} \right) \mathbf{e}_y \right]. \quad (33)$$

$\mathbf{F}_{\text{DEP}}$ can be found by substituting Eqs. (30) and (31) into Equation (33).

3. Experimental

3.1. Cell Sample Preparation

Live non-tumorigenic human mammary (MCF10A) cells were used as cell samples. A culture medium consisting of 500 mL DMEM/F12 (11320033, Gibco), 20 ng/mL Human epidermal growth factor (E9644, ThermoFisher), 0.5 $\mu\text{g/mL}$ Hydrocortisone (H4001, Sigma Aldrich), 100 ng/mL Cholera

toxin (C8052, Sigma Aldrich), 5% (v/v) Horse serum (16050122, ThermoFisher), and 10 $\mu\text{g/mL}$ Human insulin (I9278, Sigma Aldrich) was used for cell cultivation. The cultured cells were incubated in a 5% CO_2 incubator for 2–3 days. Experiments were conducted using cells at passages P5–10.

3.2. Preparation of Cell Sample Solution

A cell sample solution was prepared by suspending cells in a 300 mM isotonic mannitol solution to achieve a cell density of $\phi = 8.0 \times 10^5$ cells/mL. For fluorescence imaging observations, cells were incubated with Calcein AM (C396, Dojindo; $\lambda_{\text{ex}} = 490$ nm, $\lambda_{\text{em}} = 515$ nm). Calcein AM was introduced into the cells by incubating them in a PBS(–) solution with a Calcein AM concentration of 20 μM for 30 min. The conductivity of the cell sample solution was adjusted to $\sigma_f = 1.0 \times 10^{-3}$ S/m using the culture medium.

3.3. Fabrication of Cell-Separation Device

A cell-separation device using the counter-interdigitated electrodes was fabricated, and the relationship between the distribution of cell clusters formed on the electrode surface and the DEP force distribution determined through analytical solutions was examined.

Three types of interdigitated electrodes with different electrode widths and spacings were fabricated to generate different electric field distributions under the condition of a constant applied voltage. Figure 5a shows the dimensions of the electrode substrate used in the experiment, and Figure 5b shows the dimensions of the three types of interdigitated electrode. For the electrode width or spacing, combinations of 50 μm and 75 μm were considered. The interdigitated electrodes with (width : spacing) ratios were designated as Type A (50 μm : 50 μm), Type B (50 μm : 75 μm), and Type C (75 μm : 50 μm). A standard photolithographic method was used to fabricate the interdigitated electrodes. The procedure is briefly described as follows. First, the surfaces of the glass planar plate with dimensions of 50 $\times$ 90 mm and a thickness of 0.4 mm were ultrasonically cleaned with acetone and isopropyl alcohol for 5 min each, followed by ultrapure water for 5 min. Next, a 300-nm-thick aluminum film was deposited on the glass plate surface by vacuum evaporation. Electrode patterning was achieved using a photoresist (S1805G). Pre-baking was performed at 90 $^{\circ}\text{C}$ for 3 min, followed by a 20 s exposure and 1 min of development. Post-baking was performed at 130 $^{\circ}\text{C}$ for 3 min to fix the electrode to the glass plate surface. Then, etching treatment with mixed acid was performed at 40 $^{\circ}\text{C}$ for 90 s, and the photoresist was removed using an AZ 100 remover (AZ Electronic Materials). The fingers of the interdigitated electrodes were arranged in alternating fashion with high-voltage electrodes and grounded electrodes featuring 75 pairs for Type A and 60 pairs for Types B and C.

The cell-separation device has a parallel-plate microfluidic channel structure with electrode substrates on the upper and lower surfaces, as shown in Figure 2. The upper electrode substrate is a 1.1-mm-thick glass planar plate coated with an indium–tin oxide (ITO) film on its surface, while the lower electrode substrate is a glass planar plate printed with interdigitated electrodes. Holes with a diameter of $\phi 1.0$ mm were drilled in the upper electrode substrate using a leutor (2307396, Sea Force) for the introduction and drainage of the cell sample solution. Polypropylene female luer fittings were bonded to the drilled holes, and a conductive epoxy resin adhesive (CW2400, Chemtronics) was used to attach lead wires to the terminals of each electrode substrate. Finally, a 0.5-mm-thick silicone rubber spacer was placed between the upper and lower electrode substrates and compressed to complete device assembly.

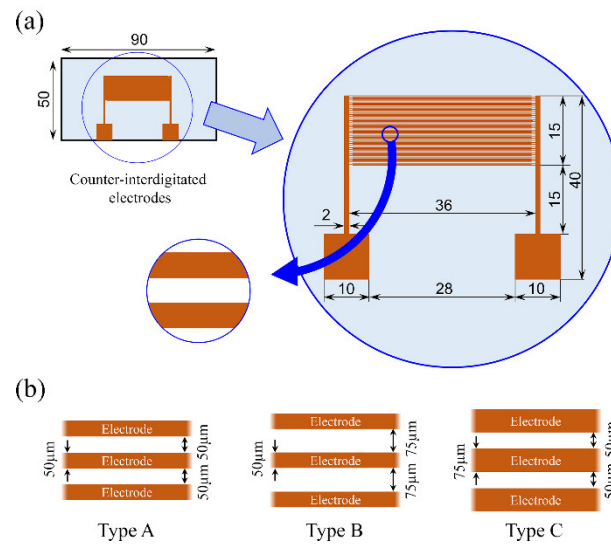


Figure 5. (a) Specifications of electrode substrate. (b) Configuration and dimensions of interdigitated electrodes.

3.4. Experimental Apparatus and Method

The experimental setup consisted primarily of the cell-separation device, a syringe pump, a waveform generator, and a confocal laser scanning microscope, as shown in Figure 6. To observe the behavior of cells in the device, the electric field frequency, f , that maximizes the value of $\text{Re}(\beta)$ in Equation (1) was calculated using Equation (2) to maximize the DEP force acting on the cells. In the case of MCF10A cells, when the solution conductivity is $\sigma_f = 1.0 \times 10^{-3}$ S/m, the frequency that gives the maximum value of the $\text{Re}(\beta)$ is $f \cong 8.5$ MHz. The value of $\text{Re}(\beta)$ is $\text{Re}(\beta) \sim 0.98$. From the above, the applied voltage was set as $V = 10V_{pp}$ with $f = 8.5$ MHz.

The experimental procedure was as follows. First, 2 mL of the cell sample solution was introduced into the device using the syringe pump, and the flow was stopped after the degassing was confirmed. Next, the waveform generator was turned on to produce a nonuniform electric field in the device. After confirming the stability of cell distribution in the device through bright-field observation under the microscope, the z-scan function of the microscope was used to capture a series of slice fluorescence 2D images of the cell clusters. A 3D image was then constructed using the accompanying image analysis program to examine the distribution of cells adsorbed on the surface of the interdigitated electrodes.

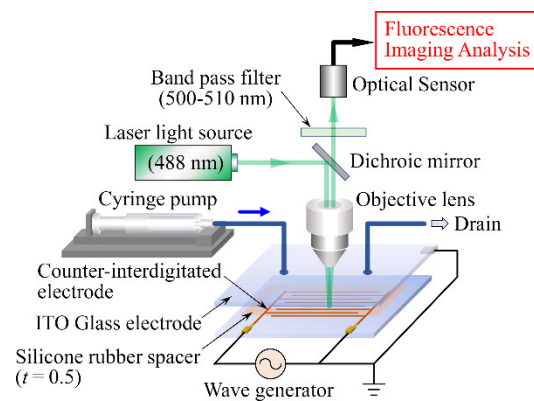


Figure 6. Schematic of the experimental setup.

4. Results and Discussion

4.1. Accuracy Verification of the Analytical Solution

To verify the accuracy of the analytical solution obtained, a numerical simulation was performed using commercially available FEM software, FEATOOLS (<https://www.featool.com>), and the results were compared. The boundary conditions for the numerical simulation model were the same as those indicated in Figure 3. The numerical simulation was performed using approximately 2.6×10^6 grid points and with a relative error of 1×10^{-6} for the convergence criterion of the iterative calculation. If the number of grid points exceeded 2.6×10^6 , the average relative error of the electric field distribution was less than 0.15% compared to, for example, results obtained with 1×10^7 grid points, except for disparities in the electric field magnitude at the electrode edges ($x^* = w/L, 1 - 2w/L$). To compute the analytical solution, FORTRAN code was written in-house, and the number of terms in the series expansion, n , was set to $n = 10000$. The aspect ratios of the calculation domain were set to match those of the Type A device, $H/L = 5$ and $w/L = 0.25$. For $n > 10000$, the error of the solution for $n = 20000$, for example, relative to that of $n = 10000$, was $\sim 3.0 \times 10^{-10}$ %. Thus, $n = 10000$ gives sufficient accuracy for the solution. Figure 7 compares the analytical solution and numerical simulation for distributions of φ and E . The effective potential value, V_{rms} , was set to $5/\sqrt{2}$ V, matching the applied voltage adopted in the experiment, and φ and E were each normalized to φ/V_{rms} and EH/V_{rms} , respectively. For φ^* and E^* at the interdigitated electrode surface ($y^* = 1$), the average relative errors, $\Delta\varphi^*$ and ΔE^* , between the numerical simulation and the analytical solutions were 6.24% and 6.29%, respectively. These results showed good agreement, affirming that the analytical solutions provided reasonable outcomes. Figure 8 compares the analytical solution and numerical simulation results for the distribution of $|\nabla E^{*2}|$ along the bottom surface of the microfluidic channel. The analytical solution overestimated the magnitude of $|\nabla E^{*2}|$ in the inter-electrode region ($0.25 < x^* < 0.75$) by about 10 % compared to the numerical simulation results. On the other hand, in the region from the electrode edge, where the value of $|\nabla E^{*2}|$ is at its maximum, extending across the entire electrode surface, the two were in relatively good agreement. From Equation (1), the magnitude of the DEP force is proportional to that of the gradient of the square of electric field, written as $|\mathbf{F}_{\text{DEP}}| = F_{\text{DEP}} \sim |\nabla E^2|$. Thus, the results demonstrated that the analytical solution of ∇E^{*2} gives a reasonable distribution of F_{DEP} . While examining the inter-electrode distribution of $|\nabla E^{*2}|$ in the numerical simulation, despite utilizing a sufficient number of grid points (2.6×10^6), strong spatial oscillations occurred, preventing the correct distribution from being obtained. This occurs due to its

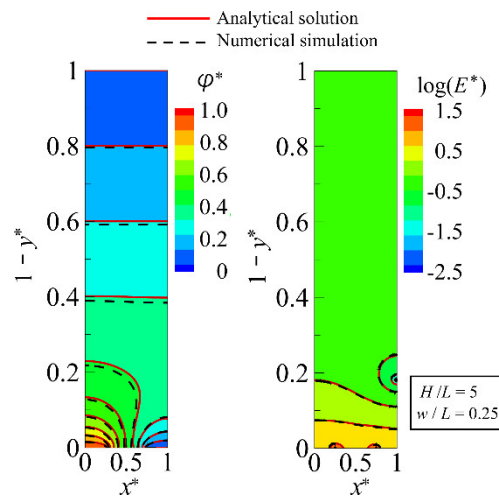


Figure 7. Comparison of analytical and numerical results for distributions of (left) electric potential and (right) electric field intensity.

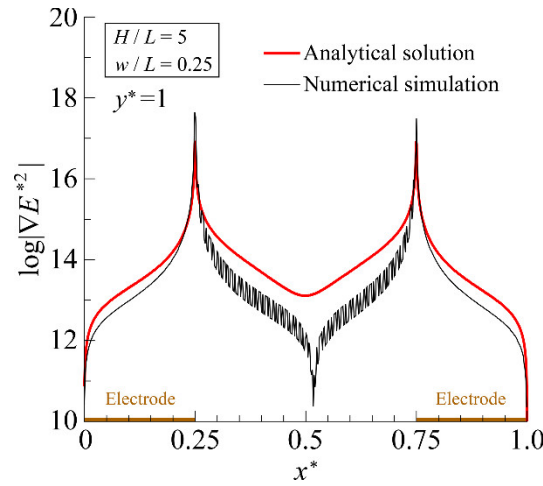


Figure 8. Distribution of $|\nabla E^{*2}|$ on the interdigitated electrode surface ($y^* = 1$).

proximity to the two electrode edges, which align with the mathematical singular points, making the numerical integration extremely unstable. For example, the numerical integration generally gives a spatially continuous solution for F_{DEP} , a function of the second-order derivative of the potential, but it does not always guarantee the smooth continuity of the solution. The effect is particularly pronounced in regions where local values change rapidly, such as positions near the singular point. The solution either has strong spatial oscillations or diverges without convergence. Spurious oscillations in the distribution of F_{DEP} are inevitable even when other commercial FEM software is used [22,45]. On the other hand, the analytical solution is particularly useful for examining the force field in the DEP device, because it always gives a smooth and stable solution for physical quantities expressed in terms of the second- or higher orders derivative of φ , such as ∇E^2 .

4.2. Distribution of DEP Force

Figure 9 shows the distributions of F_{DEP} ($= |\mathbf{F}_{\text{DEP}}|$) induced in cells by means of the three types of devices, Types A, B, and C. Note that F_{DEP} is normalized as $F_{\text{DEP}}^* = F_{\text{DEP}}/F_R$. The F_R represents the magnitude of the DEP force, defined as $F_R = 2\pi \epsilon_l (d_c/2)^3 \text{Re}(\beta) \varphi^2/H^3$. The analysis conditions are listed in Table 1. For all types of interdigitated electrodes, an extremely strong force field was created around the electrode edges. The strength of F_{DEP}^* was significant at the electrode surface and hardly decayed from the electrode surface to a height of $\sim 20 \mu\text{m}$, equivalent to the size of one or two cells. The value of F_{DEP}^* began to decay rapidly as the distance from the electrode surface increased, occurring at an approximate height of over $20 \mu\text{m}$. At a height of $\sim 30 \mu\text{m}$, the value of F_{DEP}^* decayed by two to three orders of magnitude. The F_{DEP}^* reached a minimum value at the midpoint between two adjacent electrodes because the x^* axis components of $\mathbf{F}_{\text{DEP}}^*$ generated by these two electrodes acting on the cell at this position canceled each other out. Therefore, F_{DEP}^* is an even function with respect to the vertical axis passing through this center position, leading to F_{DEP}^* satisfying $\partial^2 F_{\text{DEP}}^*/\partial x^{*2} = 0$. Figure 8 shows that the analytical solution satisfies this condition ($\partial^2 \log(\nabla E^{*2})/\partial x^{*2} = 0$) at $x^* = 0.5$, but the numerical simulation does not produce the correct distribution due to spatial oscillations.

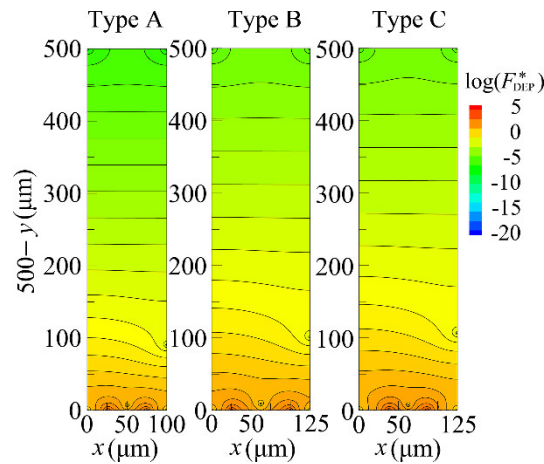


Figure 9. Distribution of DEP forces generated by three types of interdigitated electrodes.

4.3. Experimental Results

Figure 10 shows fluorescence images of the distribution of cells around the interdigitated electrodes of Types A, B, and C. For all three types, it can be seen that the cells were adsorbed along the electrode edges. This is because the F_{DEP} induced in the cells at each electrode edge was extremely large, and the cells that approached the electrode were

attracted to this position first and then adsorbed. In addition, the cause of the low adsorption of cells to the central area of the electrode surface is that F_{DEP} was weaker there because $E_x = 0$. Comparing the distribution of F_{DEP} in Figure 9 with the distribution of cells in Figure 10, it can be seen that they are generally similar to each other. When Type A and Type C are compared, no significant difference in the cell distribution is found. This is likely due to the similarity in the F_{DEP} distribution within the inter-electrode region between the two types, as illustrated in Figure 9. Next, when comparing Types A and B, Type A showed cell adsorption in the inter-electrode region, while Type B showed almost no cell adsorption in the inter-electrode region. This is because, as shown in Figure 9, F_{DEP} between electrodes was weaker in Type B than in Type A. As indicated above, cells tend to adsorb in the inter-electrode region rather than on the electrode surface, highlighting that the amount of cell adsorption, which determines the device's cell-separation performance, is affected more by adjusting the electrode spacing than by changing the electrode width.

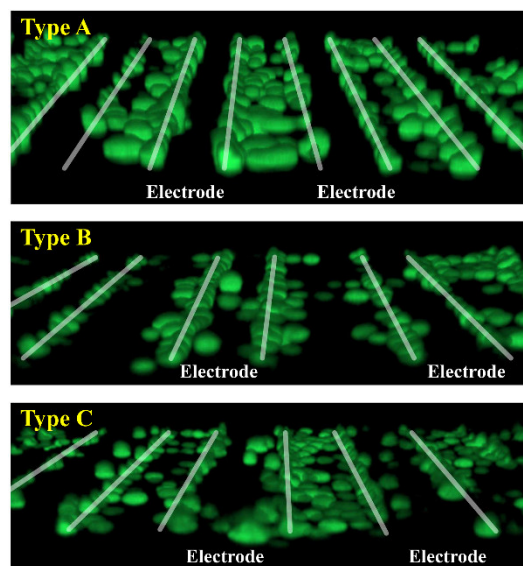


Figure 10. 3D fluorescent imaging of live cell distribution.

4.4. Relationship between DEP Force and Electrode Width and Spacing

To investigate the effect of electrode architecture on DEP force, electrode width ($2w$) and electrode spacing

$$d = L - 2w \tag{34}$$

were used as variables in the parametric analysis. The physical properties used in this analysis are shown in Table 1. Figure 11 shows a bird's-eye view of the change in the average value of F_{DEP} on the interdigitated electrode surface as d and w were changed independently from $5\text{ }\mu\text{m}$ to $60\text{ }\mu\text{m}$ in 200-point increments. As the figure shows, the value of F_{DEP} changed more sensitively in response to changes in d than in response to changes in w . In addition, considering the connection between the distribution of F_{DEP} and that of w , it is thought that optimizing a device for highly efficient cell separation entails electrode spacing (d) of $30\text{--}50\text{ }\mu\text{m}$. This design accounts for the sizes of the cells, particularly for cells of a size similar to MCF10A cells ($d_c\sim15\text{ }\mu\text{m}$) used in this study.

Table 1. Analysis conditions.

Symbol	Values	
RMS voltage V_{rms}	$5/\sqrt{2}\text{ V}$	
electric permittivity of the solution ϵ_l	$6.9 \times 10^{-10}\text{ F/m}$	
electric conductivity of the solution σ_l	$1.0 \times 10^{-3}\text{ S/m}$	
cell diameter d_c	$15\text{ }\mu\text{m}$	
height of the microchannel H	$500\text{ }\mu\text{m}$	
real part of the CM factor $\text{Re}(\beta)$	0.98	
number of terms of the series expansion n	100,000	
electrode width and spacing ($2w : d$)	Type A	($50\text{ }\mu\text{m} : 50\text{ }\mu\text{m}$)
	Type B	($50\text{ }\mu\text{m} : 75\text{ }\mu\text{m}$)
	Type C	($75\text{ }\mu\text{m} : 50\text{ }\mu\text{m}$)

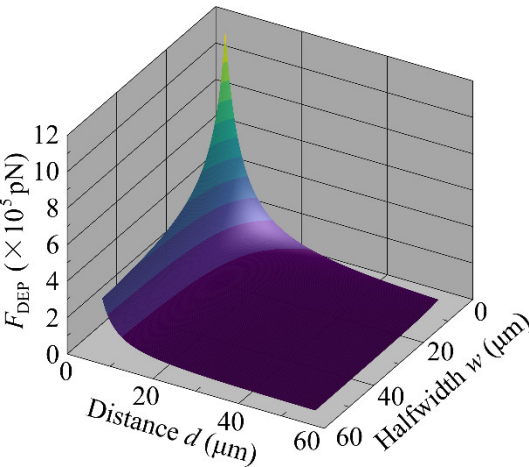


Figure 11. Variation of DEP force with variations in electrode width and spacing.

5. Conclusions

To investigate the distributions of the electric field intensity and DEP force within the newly proposed parallel-plate cell-separation device, we obtained analytical solutions using the Fourier series method. By extrapolating the inter-electrode potential with a newly proposed approximation, the boundary condition, initially given in Neumann type, was replaced by Dirichlet type. This adjustment allowed for the integration of the governing equations to derive an approximate solution. To verify the accuracy of the obtained solution, a comparison with numerical simulations was performed, demonstrating excellent agreement for both the potential and electric field intensity distributions. In addition, 3D fluorescence imaging analysis of the cell distribution in the cell-

separation device was performed. The distribution of live cells near the interdigitated electrode surface was compared with that of the DEP force obtained by the analytical solution. This comparison revealed that the distribution of live cells was very similar to that of the DEP forces. In addition, a parametric analysis involving the electrode width and spacing as variables revealed for the first time that electrode spacing was the key parameter influencing the level of cell adsorption onto the electrode. In cell-separation processes utilizing devices with interdigitated electrodes, electrode width is not very important for highly efficient cell separation. For example, when separating human cells with a diameter of about 15 μm , electrode spacing of 30–50 μm is desirable.

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Appendix A

The exact solution for the inter-electrode potential in the absence of the planar electrode on the top surface ($y^* = 0$) is expressed by an incomplete elliptic integral of the first kind with an elliptical modulus $k(= (1 - 2w) / L)$ [33]

$$F(\lambda, k) = \int_0^\lambda \frac{d\theta}{\sqrt{1 - k^2 \sin^2 \theta}} \quad (\text{A1})$$

Since the integration of $F(\lambda, k)$ by the quadrature method is difficult, we will seek an approximate solution in integrable form. The function $F(\lambda, k)$ can be expressed by using the inverse function of Jacobi's elliptic function, Sn , as

$$F(\lambda, k) = \text{Sn}^{-1}(\sin \lambda, k) \quad (\text{A2})$$

If $\lambda = \sin^{-1} x'$, then for $k \rightarrow 0$, i.e., $1 - 2d/L \rightarrow 0$, we have

$$\text{Sn}(x', 0) \cong \sin x' \quad (\text{A3})$$

Therefore, Equation (A2) can be approximated as

$$F(\lambda, k) \cong \sin^{-1} x' \quad (\text{A4})$$

Equation (20) is obtained by performing the variable transformation $x' \rightarrow x^*$ in Equation (A4) and applying the appropriate similarity transformation to satisfy the boundary conditions Eqs. (13) and (15). To evaluate the accuracy of Equation (20), the inter-electrode potential obtained using it was compared with numerical simulation results obtained using commercial FEM software. The distribution of $\varphi = \varphi(x^*, 1)$ obtained from the exact solution of Equation (A2) and that obtained from Equation (20) are shown in Fig. A1. For comparison, distributions of φ

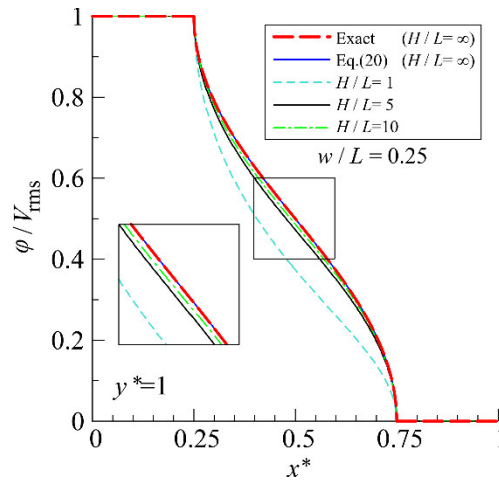


Figure A1. Inter-electrode potential distribution.

obtained by numerical simulations with three different aspect ratios, H/L , in Figure 3 are also shown. The results of the exact solution and Equation (20) show remarkable agreement. Equation (20) gives a good approximation of the inter-electrode potential when $H/L > 5$, exhibiting relative errors within 5% of the commercial FEM software results (not shown).

Appendix B

When the Laplace equation, Equation (3), is solved analytically through the separation-of-variables technique, the general form of $f(x^*)g(y^*)$ on the right-hand side of Equation (23) is expressed as

$$f(x^*)g(y^*) = \sum_{n=1}^{\infty} (a_n \cos k_n x^* + b_n \sin k_n x^*) (c_n e^{k_n y^*} + d_n e^{-k_n y^*}) \quad (\text{B1})$$

where a_n, b_n, c_n, d_n and k_n are arbitrary coefficients. From Eqs. (17) and (18)

$$b_n = 0 \quad (\text{B2})$$

$$k_n = n\pi \quad (\text{B3})$$

Furthermore, from Equation (16)

$$c_n = -d_n \quad (\text{B4})$$

and therefore, Equation (B1) becomes

$$f(x^*)g(y^*) = 2 \sum_{n=1}^{\infty} a_n \cos(k_n x^*) \sinh\left(\frac{k_n H}{L} y^*\right) \quad (\text{B5})$$

Using Eqs. (13), (15), (19), and (22), the functional form of $\varphi(x^*, y^*)$ is determined as

$$\varphi(x^*, y^*) = a_0 y^* + 2 \sum_{n=1}^{\infty} a_n \cos(k_n x^*) \sinh\left(\frac{k_n H}{L} y^*\right) \quad (\text{B6})$$

where a_0 and a_n are the Fourier coefficients. Because $\varphi(x^*, 1)$ is a periodic function of period $x^* = 1$, the Fourier coefficient a_0 can be expressed as

$$a_0 = \int_0^1 \varphi(x^*, 1) dx^* \quad (\text{B7})$$

Because the right-hand side of Equation (B7) is equal to the area of the figure bounded by the curve of potential $\varphi(x^*, 1)$ and the x^* and y^* axes shown in Figure 4, a_0 can be readily obtained as

$$a_0 = V_{\text{rms}} \frac{w}{L} + \frac{1}{2} V_{\text{rms}} \left(1 - \frac{w}{L} - \frac{w}{L}\right) = \frac{V_{\text{rms}}}{2} \quad (\text{B8})$$

For a_n , if $y^* = 1$ in Equation (B6), further multiplying both sides by $\cos k_m x^*$ and integrating over the interval $[0, 1]$ yields

$$\int_0^1 \varphi(x^*, 1) \cos(k_m x^*) dx^* = \int_0^1 a_0 \cos(k_m x^*) dx^* + 2 \int_0^1 \sum_{n=1}^{\infty} a_n \cos(k_n x^*) \sinh\left(\frac{k_n H}{L}\right) \cos(k_m x^*) dx^* \quad (\text{B9})$$

Due to the periodicity and orthogonality of trigonometric functions

$$\begin{aligned}
\int_0^1 a_0 \cos(k_n x^*) dx^* &= 0 \\
2 \int_0^1 \sum_{n=1}^{\infty} a_n \cos(k_n x^*) \sinh\left(\frac{k_n H}{L}\right) \cos(k_m x^*) dx^* \\
&= 2a_n \sinh\left(\frac{k_n H}{L}\right) \int_0^1 \cos^2(k_n x^*) dx^* \\
&= a_n \sinh\left(\frac{k_n H}{L}\right)
\end{aligned} \tag{B10}$$

Since it is required that a_n is

$$a_n = \frac{1}{\sinh\left(\frac{k_n H}{L}\right)} \int_0^1 \varphi(x^*, 1) \cos(k_n x^*) dx^* \tag{B11}$$

substituting Eqs. (13), (15), (19), and (22) into Equation (B11) yields Equation (28).

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