Numerical model for the deformation of nucleated cells by optical stretchers

Ihab Sraj¹,⁴, Joshua Francois², David W M Marr³ and Charles D Eggleton²

¹ Division of Physical Sciences and Engineering, King Abdullah University of Science and Technology, Thuwal, Saudi Arabia
² Department of Mechanical Engineering, University of Maryland Baltimore County, Baltimore, Maryland 21250, USA
³ Department of Chemical and Biological Engineering, Colorado School of Mines, Golden, Colorado 80401, USA

E-mail: ihab.sraj@gmail.com, fjoshua1@umbc.edu, dmarr@mines.edu and eggleton@umbc.edu

Received 18 March 2015, revised 10 May 2015
Accepted for publication 14 May 2015
Published 2 July 2015

Abstract
In this paper, we seek to numerically study the deformation of nucleated cells by single diode-laser bar optical stretchers. We employ a recently developed computational model, the dynamic ray-tracing method, to determine the force distribution induced by optical stretchers on a cell encapsulating a nucleus of different optical properties. These optical forces are shape dependent and can deform real non-rigid objects; thus resulting in dynamically changing distributions with cell and nucleus deformation. A Chinese hamster ovary (CHO) cell is a common biological cell that is of interest to the biomedical community because of its use in recombinant protein therapeutics and is an example of a nucleated cell. To this end, we model CHO cells as two concentric three-dimensional elastic capsules immersed in a fluid where the hydrodynamic forces are calculated using the immersed boundary method. We vary the inner capsule size to simulate different nucleus sizes. Our results show that the presence of a nucleus has a major effect on the force distribution on the cell surface and consequently on its net deformation. Scattering and gradient forces are reported for different nucleus sizes and the effect of nucleus size on the cell deformation is discussed quantitatively.

Keywords: dynamic ray tracing, optical trapping, cell deformation

1. Introduction

The ability to trap particles using laser light was discovered by Arthur Ashkin in 1970 [1]. In this, gradient forces are created at the surface of transparent particles suspended in a medium of different refractive index and situated within a light gradient. In the ray-optics (RO) regime, where the particle size is much larger than the light wavelength [2], refraction of light rays of different intensities at the surface and within the particles results in a change in the total momentum between the entering and exiting light beam. These gradient forces on the order of picoNewtons are capable of drawing microscopic particles into a region of highest light intensity [3]. Scattering forces are also created that accelerate the particle in the direction of beam propagation towards its focus [4]. With these opposing mechanisms, an equilibrium position is reached and the particle is held fixed (trapped) in the center of the beam focus as the light rays passing through and exiting the particle exert forces that are balanced with no net change in momentum.

Optical traps or tweezers used to manipulate microscopic objects without any mechanical contact have become a major tool in biological research over the last 30 years. Cells have been stretched [5, 6], folded [8] and even rotated [7–9] using single and multiple optical tweezers. Recently, the technique has been extended to study the properties of cells by observing their deformation [10–12]. Guck et al developed an optical stretcher that uses two counterpropagating diverging laser beams to trap cells individually along the aligned laser beams axis [6]. This optical stretcher has also been used to deform cells and to measure their membrane properties using a simple numerical model [11]. Extending this, Sraj et al
developed a high-throughput optical stretcher using to trap and stretch bovine red blood cells (RBC) [12]. The implemented approach was able to achieve single-cell resolved measurements on larger numbers (10^3 or more). This significantly simplified optical stretcher employs an anisotropic optical trap consisting of a linear diode laser bar [13] that stretches individual cells in continuous confined microfluidic flow.

Theoretical and numerical studies have also been conducted to determine the induced optical force distribution. Using analytical solutions of the governing optical equations, Ashkin was the first to perform calculation of the total forces of a single-beam gradient laser on solid spheres in the RO regime [14]. Guck et al. determined the local optical force distribution by the dual optical stretcher on spherical cells using the RO technique before cells begin to deform [6] to determine the stiffness of RBCs [11]. In their method, the effect of subsequent deformation on the calculation of force distribution was neglected and constant rigid spherical cell morphology was assumed due to limitations in the method. Deformability of biological cells can result in a shape change under the influence of external flows or applied forces and thus the local force distribution and total trapping forces can change significantly with cell deformation [15]. To take this into account, the RO method has been improved to include different cell shapes such as oblate spheroids [16] and even cylinders [17]. As an analytical method, RO remains a difficult approach for calculating the forces on more complex cell shapes like the RBC bi-concave discoid shape and deformable cells.

To overcome these issues, we recently developed and implemented a dynamic ray-tracing (DRT) approach [15] that, in addition to finding transient optical forces on deformable cells, solves for fluid–cell interactions [18, 19]. DRT offers the possibility of simulating different phenomena occurring in optical systems such as erythrocyte deformation in high-throughput optical stretchers [20] and optical levitation [21]. The approach also allows one to assess cell deformability and to investigate the optical parameters to better design traps and manipulate cells prior to performing experiments. In addition, due to the vector-based nature, DRT allows the calculations of both anisotropic and inhomogeneous structures, cases that exist in real systems.

Chinese hamster ovary (CHO) cells are the most commonly used mammalian host for industrial production of recombinant protein therapeutics [22] and have been used in related genetics studies [23]. Because of their importance, a number of previous studies have investigated the optical forces on CHO cells. For example, Wei et al. used a fiber-optic dual-beam trap to capture CHO cells and determine the associated three-dimensional (3D) optical force field [24]. Chang et al. developed a simple model to calculate the optical forces upon a solid spherically-symmetric multilayer sphere similar to the structure of a CHO cell based on RO [25]. This study showed that the magnitude of optical forces are three times smaller than that upon a polystyrene bead of the same size and that the distribution of optical forces is much different from that upon a uniform particle. Recently, Kim et al. computed the optical force on a pair of concentric spheres in a focused beam and determined the influence of refractive index differences and relative size between the inner and outer spheres on the optical force [26].

All of these studies however did not take into account the deformability of both the cell and its encapsulated nucleus. We show here how the presence of a nucleus inside deformable cells leads to alteration in the propagation of light rays due to the additional internal surface and the additional medium of different refractive index [27]. Here, the variation in the nucleus size may significantly influence the optical forces and ultimately the net deformation of both the cell and the nucleus itself.

2. Numerical method

Simulating deformation of a cell via optical stretchers requires a two-step method to first determine optical forces induced by the interaction of light with the cell surface and then model the cell–fluid interactions. Because the distribution of optical forces is dependent on the shape of the cell that in turn changes during deformation, these two steps are done alternately until a steady state shape is reached. In the case of nucleated cells, optical force calculation is additionally challenging due to the different external and internal morphologies in addition to membrane deformability. For this purpose, we resort to DRT to determine the optical forces induced on the surfaces of deformable nucleated cells by optical stretchers [12, 20]. DRT, unlike the traditional RO method, is vector-based and is capable of determining the optical forces on cells of arbitrary shape and morphology. Cell–fluid interaction and the hydrodynamics, on the other hand, are solved using the immersed boundary method (IBM). In this section we briefly describe the two methods.

2.1. Dynamic ray tracing

DRT is a vector-based method developed by Sraj et al. [15, 20] to determine optical forces on the surface of any arbitrary shaped cell including deformable cells with asymmetrical geometries [21]. Briefly, DRT considers a finite number of rays issued from a light source with given intensities and known direction. These rays are treated as vectors and traced as they intersect a surface. A ray-triangle intersection algorithm is then employed to determine the location of intersection where the surface is divided into triangular elements for this purpose. Geometrical optics laws are then applied to find the refraction and reflection angle. Consequently the vectors of the rays are updated and the procedure is repeated till each ray exits the cell. From the direction of the light rays within the cell one can calculate the trapping efficiency \( Q \), a dimensionless factor representing the amount of momentum transferred [6, 15]. The trapping efficiency \( Q \) is independent of the laser power used and depends only on the object geometry and reflectance of the medium. Elemental optical forces at any location of the cell are therefore found regardless of the initial cell shape. Rays are traced at any
surface where \( Q \) is multiplied by a factor to account for energy loss from previous refractions. Internal and external reflections within the cell are neglected as their effects rapidly diminish. Optical forces can be expressed as

\[
F_{\text{optical}} = \frac{n_m Q P}{c},
\]

where \( n_m \) is the index of refraction of the buffer medium, \( c \) the speed of light in vacuum, and \( P \) the laser power. It is important to note that the resulting optical forces are added to the Navier–Stokes equations as body forces as described below.

This method has been validated and applied to cells of different initial shapes [15] and different optical applications [20, 21]. Here, DRT is used to model nucleated cells by considering two concentric capsule, the outer one representing the cell surface and the inner one representing the nucleus. DRT is then employed to determine optical forces induced on both surfaces.

### 2.2. Immersed boundary method

The IBM is a cell–fluid interaction solver that has been used extensively to simulate biological systems such as cell adhesion [28], cell adhesion in atomic force microscopy measurements [29] and RBC motion through microvascular bifurcation [30]. IBM splits the numerical solution onto two grids: a stationary grid that has a fixed position with time representing the 3D fluid domain and a moving grid representing the two-dimensional immersed boundary.

To this end, a cell is modeled as an elastic membrane that is deformable by any applied stress. The membrane is discretized into a finite number of flat triangular elements that remain flat after deformation. This approximation is valid given that the local radius of curvature during deformation is much larger than the membrane thickness and that bending stresses are negligible. Elastic forces at the discrete membrane nodes are found from their displacement (deformation) using a finite element model. We adopt an approach developed by Charrier et al. [31] and Shrivastava and Tang [32] that uses the principle of virtual work to find those forces from an appropriate strain energy density function. These forces and any external applied forces such as the optical forces are then distributed onto the fluid grid using an appropriate discrete delta function and added to the Navier–Stokes equations as body forces. The discrete delta function ensures that only membrane nodes in the sphere of influence of the fluid grid make a contribution to the local body forces. The Navier–Stokes equations are then solved for the fluid velocity.

The no-slip boundary condition at the membrane surface is satisfied by allowing the membrane nodes to move with the local fluid velocity. The velocity of the membrane is found by summing of the velocities at the fluid grid nodes weighted by the same discrete delta function used for the distribution of body forces. This again ensures that only fluid grid nodes in the sphere of influence of the membrane node make a contribution to its velocity. Membrane nodes are then moved with the calculated velocity for one time step to a new position giving a new membrane shape. The procedure is repeated where elastic forces and optical forces are again calculated as described above to advance the flow for another time step.

### 3. Model parameters

The CHO cell is a typical example of a nucleated cell. The size of such cells vary with radius \( r_{\text{cell}} \) ranging from 5 – 7.5 \( \mu m \) [33] and nucleus radius \( r_{\text{nuc}} \) varying following the relationship [34]:

\[
r_{\text{cell}} = (1.38 \pm 0.02) r_{\text{nuc}} + (0.03 \pm 0.05).
\]

The refractive index of the cytoplasm has been measured and reported as \( n_{\text{cyl}} = 1.37 \) while that of the nucleus has been found to be slightly greater \( n_{\text{nuc}} = 1.392 \) [34]. As the size of the cell has an effect on the forces induced by optical stretchers (more surface area intuitively results in large forces) and hence on the cell deformation, we seek to investigate the impact of the presence of the nucleus and its size on the optical force distribution and resulting cellular deformation. For this purpose, we model CHO cells as two 3D concentric elastic spherical capsules. The radius of the outer capsule is fixed and taken as the CHO cell average radius \( r_{\text{cell}} = 5.6 \mu m \); however, the radius of the inner capsule representing the nucleus is varied from \( r_{\text{nuc}} = 1.1 – 5 \mu m \). The ratio of the radius of the cell to the radius of the nucleus is denoted by \( r = r_{\text{nuc}} / r_{\text{cell}} \). We note that a typical CHO cell has radii ratio of \( r = 0.72 \) from equation (2).

In our calculations, cells are assumed initially trapped and situated at the center of a laser beam created with a single linear diode bar of wavelength \( \lambda = 808 \text{ nm} \) and power \( P = 12.5 \text{ mW mm}^{-1} \). The length of the diode lies in the \( y \)-axis and the laser beam direction is along the \( z \)-axis as shown in figure 1. The cell is assumed to be immersed in an aqueous medium of refractive index \( n_m = 1.335 \) that is lower than the refractive index of both the cell and its nucleus \( (n_m < n_{\text{cyl}} < n_{\text{nuc}}) \) (figure 1).

The hydrodynamics and cell mechanics are calculated using the IBM. Both fluid inside and outside the cell are assumed incompressible and Newtonian with identical density \( \rho = 1 \text{ g cm}^{-3} \) and viscosity \( \mu = 0.8 \text{ cP} \). The cell membrane is assumed of Neo–Hookean material, as appropriate for most biological cells, and can be characterized using solely its stiffness \( E_h \). Unless otherwise noted, membrane stiffness is taken as \( E_h = 0.1 \text{ dyn cm}^{-1} \). For the purpose of quantifying cell deformation from optical or hydrodynamic forces, we use the Taylor deformation parameter defined as: \( DF = (L - B) / (L + B) \), where \( L \) and \( B \) are the major and minor semi-axis of a capsule in the \( x - z \) plane. When viscous stresses, elastic forces and optical forces are balanced, cells adopt a steady state shape denoted by \( DF = 0 \). The uniform grid used for the fluid solver has 64\(^3\) nodes with a grid spacing of \( r_{\text{cell}} / 8 \) while the finite element cell grid has 20482 triangular elements. A time step of \( 10^{-3} \) was used in all computations to ensure numerical stability. The optically
induced transient deformation of the cell creates fluid flow that, in turn, leads to viscous stresses that influence the characteristic time $t_o$ for cellular deformation such that:

$$t_o = \frac{\mu r_{cell}^2}{F_{optical}}. \quad (3)$$

To this end, the transient results are presented using the dimensionless time $t^* = t/t_o$.

4. Results and discussions

4.1. Impact of nucleus size on optical forces

As a first step, we investigate the effect of nucleus size on the optical forces initially induced at the cell surface. For reference, we employ DRT to determine the forces induced on a cell that does not contain a nucleus. In this case, light rays emerging from the diode laser bar hit the front surface of the cell to create optical scattering forces along the laser beam axis whose direction is opposite to their propagation direction i.e. the negative $z$-axis direction as shown in figure 1. This is due to the momentum gained by the cell when the rays transit from a medium of lower refractive index to a medium of higher refractive index (cell cytoplasm $n_{cyt} = 1.37$) [6]. Gradient optical forces are also created with a sum equal to zero as the center of the cell is aligned with the center of the laser beam. After refraction, the rays continue to hit the back surface of the cell where they refract again and transfer momentum inducing scattering forces in the positive direction. The magnitude of the net scattering force at the back surface of the cell is, however, greater than the net scattering force at the front surface resulting in a net total scattering force in the positive $z$–axis direction. With our chosen laser, cell, and fluid properties, the magnitude of scattering force applied on the front surface is found to be 23.1 pN while on the back surface 26.7 pN with a net scattering force of 3.6 pN. The scattering forces would both stretch and translate the cell away from the light source. The net gradient forces are again equal to zero on both the front and back surface of the cell; however, if we consider the net gradient force in the perpendicular direction to the laser beam on one half of the cell we find it equal to 20.7 pN. The gradient forces contribute to the stretching of the cell as well but have no translation effect.

In the case of a cell containing a nucleus, light rays can hit up to four surfaces as shown in figure 1 before exiting the cell from the back surface. This leads to scattering and gradient optical forces at both the outer cell and the nucleus surface. At the front cell surface, scattering forces remain unchanged and independent of the nucleus size as the rays first enter the cell as described above. As the refractive index of the nucleus is higher than that of the cytoplasm, scattering forces at the front surface are also in the negative direction while the same scattering forces at the back surface are in the positive direction. However, the magnitude of the net scattering force on the nucleus is less than the net scattering force on the cell due to the smaller refractive index contrast between the nucleus and the cell compared with the cell and suspending medium $\left( \frac{n_{nuc}}{n_{m}} = \frac{1.392}{1.37} = 1.016 \right)$ versus $\left( \frac{n_{cyt}}{n_{m}} = \frac{1.37}{1.335} = 1.030 \right)$. The magnitude of these forces varies depending on the nucleus size. For instance, cells with small nucleus ($r < 0.4$) the scattering forces exerted on the nucleus are found to be negligible. This is an interesting observation as many biological cells fall in this range. For larger nuclei a different behavior is observed; a nucleus of radius $r_{nuc} = 4 \mu m \ (r = 0.71)$ experiences a scattering force of 4.54 pN on the front surface of the nucleus and a scattering force of 5.24 pN on the back surface yielding a net scattering force of 0.7 pN. This is the case of nominal CHO cell where $r = 0.72$. For even larger nuclei of radius $r_{nuc} = 5 \mu m \ (r = 0.89)$ the net scattering force increases to 8.75 pN and 10.4 pN on the front and back surfaces respectively with a net scattering force of 1.6 pN. The increase in net scattering force on the nucleus has a apparent effect on its deformation but also a significant effect of the forces induced on the cell itself as discussed next.

When light rays reach the cell back surface, the forces induced are influenced by the previous two refractions at the
nucleus. As the nucleus size increases, optical forces on the nucleus increase, rays gain more energy, and we see subsequent increase in the magnitude of optical forces at the back cell surface. For a nucleus of radius $r_{\text{nuc}} = 4 \mu m$ the scattering force at the back of the cell is 27.1 pN compared to 26.7 pN for a cell of nucleus-free (and 27.4 pN for $r_{\text{nuc}} = 5 \mu m$). The increase in the back scattering force results in increase in net scatter force on the cell. The maximum increase in the net scattering forces on the cell is found to be 20.4% compared with the nucleus-free case. We finally note that the gradient forces calculated on the nucleus can increase up to 8.6 pN with increasing radius while the gradient forces calculated on the cell slightly decreases to 20.2 pN due to the presence of the nucleus for the case of $r_{\text{nuc}} = 5 \mu m$.

The variation of the net scattering and gradient forces on the cell and its nucleus with nucleus size is shown in figure 2. To this end, we clearly see the effect of the size of the nucleus on the total net force induced on the cell surface. As the nucleus size increases, the cell will be exposed to larger forces for the same laser power. The nucleus acts as a lens that focuses the light rays and leads to higher optical forces at the nucleus and cell back surfaces. We finally note that we can determine the net scattering and gradient forces on a CHO cell of nominal size from the curves in figure 2 using a vertical line (shown in magenta) that corresponds to the nominal CHO cell radius ratio of $r = 0.72$.

**4.2. Influence of nucleus size on net cell deformation**

From our calculations, it is clear that the presence of a nucleus has a significant impact on the initial optical force distribution as these forces deform and stretch CHO cells. Changes in cell shape lead to a new force distribution. To calculate these, optical forces are added as body forces to the surrounding fluid. DRT is then employed to update the optical force distribution as the cell shape is changing until steady state when the elastic and applied optical forces are equal.

The net deformation of both the cell and the nucleus is quantified using the Taylor parameter deformation $DF$ shown in figure 3. The figure indicates that in the case of small nuclei, $DF$ of the cell increases to a steady value that is higher than the reference case of no-nucleus (shown on all panels for comparison). This is due to the slight decrease in gradient forces that lead to more deformation in the z-direction and thus higher net deformation. $DF$ of the nucleus, however, is negligible due to the small magnitudes of the optical forces created.

For larger nuclei, $DF$ shows similar trends where the cell deforms until a steady state shape is reached but with net deformation lower than the nucleus-free case. In this, we see that the net deformation of the cell decreases and the net deformation of the nucleus increases with $r$.

To summarize the results discussed above, we show in figure 4 the steady state net deformation $DF_\infty$ of both the cell and the nucleus. Here, we clearly see that $DF_\infty$ of the cell is initially larger than the $DF_\infty$ of the nucleus-free case but then decreases as the radius ratio increases. At the same time, $DF_\infty$ of the nucleus increases with the radius ratio. The two curves eventually intersect when the radius of the nucleus becomes comparable to the radius of the cell. We also note here that we can determine the steady state net deformation $DF_\infty$ of a CHO cell of nominal size from the curves in figure 4 using a vertical line (shown in magenta) that corresponds to the nominal CHO cell radius ratio of $r = 0.72$.

$DF$ calculations for CHO cells show a clear relationship between the size of the nucleus and the steady state net cell and nucleus deformation. As the size of the nucleus increases, the steady state deformation increases due to the increase in the scattering forces applied at the cell surface. It is therefore expected that the corresponding deformation increases as well. Figure 4 shows also that as the size of the nucleus increases, the steady state deformation of the cell decreases. Moreover, as the size of the nucleus approaches the size of the cell, the relative deformation of the nucleus, as characterized by the Taylor deformation parameter surpasses that of the cell. The relationship between the size of the nucleus and the deformation of the cell means that cells with larger nuclei show less deformation when optically stretched than cells with smaller nuclei. Another observation is that the cell with no nucleus deformed to a steady state of $DF$ value that is
smaller than the value for the smallest radius ratio but larger than the value for the largest radius ratio.

5. Conclusions

CHO cells are of interest to the biomedical community because of their use in recombinant protein therapeutics. Unfortunately, no experiments have been performed to stretch this line of cells in optical traps. Few experiments, however, were performed to describe deformation of cell nucleus. In these experiments researchers have studied the interaction of cells with topographically patterned material surfaces to show the changes in shape, function, and viability of the cells. Only few of these studies, however, indicated possible impact on the behavior of organelles. For instance, Dalby et al [35] quantified cell and nuclear morphology with light and fluorescence microscopy and showed a slight elongation of the

Figure 3. Evolution of net deformation $DF$ (of both a CHO cell and its nucleus) for different nucleus sizes as indicated. Evolution of net deformation of the cell with no-nucleus is also shown for reference.
nuclei in grooves. Yamauchi et al also observed the deformation of cancerous cells/nucleus and their migration in capillaries where cancer cells are able to migrate. They measured the diameter of both the cell and its nucleus for this purpose.

In our work, we modeled the deformation of CHO cells by single diode-laser bar optical stretchers. For this purpose, we extended the recently developed DRT method to determine the optical force distribution induced by optical stretchers on cells that have a nucleus. Our results showed that the presence of a nucleus has a major effect on the force distribution on the cell surface and the net deformation. We also showed and quantified the effect of nucleus size on the net applied force as well as on cell deformation. We are working effectively on setting up experiments to stretch CHO cells and compare our numerical data with experimental results.

Acknowledgments

The authors would like to acknowledge financial support provided by the National Institute of Health grant R01 AI079347-04. This work used the Extreme Science and Engineering Discovery Environment (XSEDE), which is supported by National Science Foundation grant number OCI-1053575.

References

[1] Ashkin A 1970 Acceleration and trapping of particles by radiation pressure Phys. Rev. Lett. 24 156–9
[2] van de Hulst H C 1981 Light Scattering by Small Particles (Structure of Matter Series) (New York: Dover)
[3] Ashkin A, Dziedzic J M, Bjorkholm J E and Chu S 1986 Observation of a single-beam gradient force optical trap for dielectric particles Opt. Lett. 11 288–90
[4] Ashkin A and Dziedzic J M 1971 Optical levitation by radiation pressure Appl. Phys. Lett. 19 283–5
[5] Guck J, Ananthakrishnan R, Moon T J, Cunningham C C and Käs J 2000 Optical deformability of soft biological dielectrics Phys. Rev. Lett. 84 5451–4
[6] Guck J, Ananthakrishnan R, Mahmood H, Moon T J, Cunningham C C and Käs J 2001 The optical stretcher: a novel laser tool to micromanipulate cells Biophys. J. 81 767–84
[7] Selvaggi L, Ferrari E, Moradi A, Santucci S C, Beuzyer P and Cojoc D 2010 Optimized multi-view imaging improves the observation of optically manipulated non-spherical particles J. Opt. 12 049801
[8] Gu M, Kuriakose S and Gan X 2007 A single beam near-field laser trap for optical stretching, folding and rotation of erythrocytes Opt. Express 15 1369–75
[9] Mohanty S K, Uppal A and Gupta P K 2004 Self-rotation of red blood cells in optical tweezers: prospects for high throughput malaria diagnosis Biotechnol. Lett. 26 971–4
[10] Bronkhorst P, Streekstra G, Grimbergen J, Nijhof E, Sixma J and Brakenhoff G 1995 A new method to study shape recovery of red blood cells using multiple optical trapping Biophys. J. 69 1666–73
[11] Guck J et al 2005 Optical deformability as an inherent cell marker for testing malignant transformation and metastatic competence Biophys. J. 88 3689–98
[12] Sraj I, Eggleton C D, Jimenez R, Hoover E, Squier J, Chichester J and Marr D W M 2010 Cell deformation cytometry using diode-bar optical stretchers J. Biomed. Opt. 15 047010
[13] Sraj I, Marr D W M and Eggleton C D 2010 Linear diode laser bar optical stretchers for cell deformation Biomed. Opt. Express 1 482–8
[14] Ashkin A 1992 Forces of a single-beam gradient laser trap on a dielectric sphere in the ray optics regime Biophys. J. 61 569–82
[15] Sraj I, Szatmary A C, Marr D W M and Eggleton C D 2010 Dynamic ray tracing for modeling optical cell manipulation Opt. Express 18 16702–14
[16] Sosa-Martínez H and Gutiérrez-Vega J C 2009 Optical forces on a Mie spheroidal particle arbitrarily oriented in a counterpropagating trap J. Opt. Soc. Am. B 26 2109–16
[17] Gauthier R C 1997 Theoretical investigation of the optical trapping force and torque on cylindrical micro-objects J. Opt. Soc. Am. B 14 3323–33
[18] Peskin C S and McQueen D M 1989 A three-dimensional computational method for blood flow in the heart: I. Immersed elastic fibers in a viscous incompressible fluid J. Comput. Phys. 81 372–405
[19] Eggleton C D and Popel A S 1998 Large deformation of red blood cell ghosts in a simple shear flow Phys. Fluids 10 1834–45
[20] Sraj I, Szatmary A C, Desai S A, Marr D W M and Eggleton C D 2012 Erythrocyte deformation in high-throughput optical stretchers Phys. Rev. E 85 041923
[21] Chang C B, Huang W-X, Lee K H and Sung H J 2012 Optical levitation of a non-spherical particle in a loosely focused gaussian beam Opt. Express 20 24068–84
[22] Jayapal K P, Wlaschin K F, Hu W-S and Yap M G S 2007 Recombinant protein therapeutics from CHO cells: II. Chromosomal constitution of cells in tissue culture J. Exp. Med. 108 259–68
[23] Wei M-T, Yang K-T, Karmenyan A and Chiu A 2006 Three-dimensional optical force field on a chinese hamster ovary cell in a fiber-optical dual-beam trap Opt. Express 14 3056–64
[25] Chang Y-R, Hsu L and Chi S 2006 Optical trapping of a spherically symmetric sphere in the ray-optics regime: a model for optical tweezers upon cells Appl. Opt. 45 3885–92

[26] Kim S B, Lee K H, Kim S S and Sung H J 2012 Optical force on a pair of concentric spheres in a focused laser beam: ray-optics regime J. Opt. Soc. Am. B 29 2531–41

[27] Meyer R and Brunsting A 1975 Light scattering from nucleated biological cells Biophys. J. 15 191–203

[28] Gupta V, Sraj I, Konstantopoulos K and Eggleton C 2010 Multi-scale simulation of 1-selectin-psgl-1-dependent homotypic leukocyte binding and rupture Biomech. Model. Mechanobiol. 9 613–27

[29] Sraj I, Chan K Y, Konstantopoulos K and Eggleton C D 2011 A numerical study of the influence of cellular adhesion on prestress in atomic force microscopy measurements J. Adv. Microsc. Res. 6 89–96

[30] Xiong W and Zhang J 2012 Two-dimensional lattice Boltzmann study of red blood cell motion through microvascular bifurcation: cell deformability and suspending viscosity effects Biomech. Model. Mechanobiol. 11 575–83

[31] Charrier J M, Shrivastava S and Wu R 1989 Free and constrained inflation of elastic membranes in relation to thermoforming non-axisymmetric problems J. Strain Anal. Eng. Des. 24 55–74

[32] Shrivastava S and Tang J 1993 Large deformation finite element analysis of non-linear viscoelastic membranes with reference to thermoforming J. Strain Anal. Eng. Des. 28 31–51

[33] Han Y, Liu X-M, Liu H, Li S-C, Wu B-C, Ye L-L, Wang Q-W and Chen Z-L 2006 Cultivation of recombinant chinese hamster ovary cells grown as suspended aggregates in stirred vessels J. Biosci. Bioeng. 102 430–5

[34] Brunsting A and Mullaney P F 1974 Differential light scattering from spherical mammalian cells Biophys. J. 14 439–53

[35] Dalby M J, Riehle M O, Yarwood S J, Wilkinson C D and Curtis A S 2003 Nucleus alignment and cell signaling in fibroblasts: response to a micro-grooved topography Exp. Cell Res. 284 272–80

[36] Yamauchi K, Yang M, Jiang P, Yamamoto N, Xu M, Amoh Y, Tsuji K, Bouvet M, Tsuchiya H, Tomita K, Moossa A and Hoffman R M 2005 Real-time in vivo dual-color imaging of intracapillary cancer cell and nucleus deformation and migration Cancer Res. 65 4246–52