Engineering 24 (2023) 13–16

Contents lists available at ScienceDirect

Engineering

journal homepage: www.elsevier.com/locate/eng

Views & Comments

Acoustic Micro-Manipulation and Its Biomedical Applications

Zhichao Ma [a,c], Peer Fischer [a,b]

[a] Max Planck Institute for Intelligent Systems, Stuttgart 70569, Germany
[b] Institute of Physical Chemistry, University of Stuttgart, Stuttgart 70569, Germany
[c] School of Biomedical Engineering, Shanghai Jiao Tong University, Shanghai 200030, China

Acoustic waves—and ultrasound waves in particular—are biocompatible, with excellent transmission through biological tissues. Furthermore, the wavelength and intensity of acoustic waves can be tuned over several orders of magnitude. Most notably, the commonly used 10–300 MHz frequency range is attractive for biomedical applications, as its wavelength in water (5–150 μm) corresponds to the cellular-length scale. Thus, acoustic micromanipulation has emerged as a promising tool for biomedical studies and clinical diagnostics. Its basis is the movement of tiny particles and objects actuated by acoustic waves, which is termed acoustophoresis. The origin of this field can be traced back to the 17th century, when Hooke described the nodal patterns formed by sand grains or flour as they spread on a vibrating drum surface [1]. The method was later extended to visualize vibrations and acoustic fields, and the patterns have since been known as Chladni figures [1]. Two centuries later, Rayleigh provided a theoretical explanation of the underlying principles—the acoustic streaming effect [2] and the acoustic radiation force [3]. Since the 1920s and the development of piezoelectric materials and electronic devices, acoustophoresis has been exploited for the manipulation of microscopic objects. For example, in 1928, Harvey and Loomis [4] reported an intracellular protoplasmic rotation actuated by ultrasonic waves.

In terms of instrumentation [5,6], acoustic waves are usually generated by applying an alternating current voltage to a piezoelectric material. According to the geometry of the piezoelectric material, the acoustic source can be classified as a bulk transducer [7], a plate transducer [8], a surface acoustic wave (SAW) transducer [9], and so forth. The acoustic energy from the transducer is transmitted to the fluid for manipulation via a waveguide, such as a glass substrate or a coupling medium.

The following discussion highlights promising applications of acoustic micro-manipulation according to its underlying mechanisms—namely, the acoustic streaming effect and the acoustic radiation force—as schematically shown in Fig. 1.

The acoustic streaming effect arises from the attenuation of acoustic waves and the concomitant induced motion of the fluid, and can be used for the manipulation of micro-objects. This effect can be generated near a vibrating fluid boundary, such as a vibrating bubble surface or a resonant microstructure surface, where the attenuation of acoustic energy induces boundary-layer streaming, also known as Schlichting streaming. The shear by this boundary-layer streaming drives a flow in the bulk fluid, which is known as Rayleigh streaming. The acoustic streaming can also be generated in the bulk of a fluid where acoustic waves propagate, in which case it is known as Eckart streaming. Particles suspended in the flow will migrate or rotate along with the acoustically induced flow due to the fluid drag. These flows enable the acoustic manipulation of micro-objects and of the fluid itself, which can be exploited for pumping [10,11], mixing [12], and rotational motion [8,13]. A typical system to realize acoustic manipulation is a microfluidic chamber, where the resonant mode of the microstructures or microbubbles is excited by acoustic waves approximately in the kilohertz range. The resultant acoustic streaming intensity and profile are dependent on the acoustic intensity and acoustic field distribution. Acoustic streaming permits the contact-free manipulation of cells and organisms, and has become a promising tool in biomedical studies.

First, acoustic streaming can provide tunable fluid pumping at rates ranging from nanoliters per second to microliters per second, which otherwise might require complex and expensive mechanical pumps. Using acoustics, the pumping can be wirelessly activated and thus is potentially applicable even in implantable devices. Moreover, acoustic streaming can be used for mixing in micron-sized fluid volumes, which is needed in lab-on-a-chip devices to accelerate reactions and facilitate heat transfer, but is challenging at these small scales due to the low Reynolds number laminar flows. Intense convective flows can be generated using the acoustic streaming effect, which can further accelerate mixing. Finally, rotational control via fluid flow permits the user to reorient a sample, such as a cell or small organism (whose size ranges from ~1 μm to ~1 mm) [8,14], so that it can be imaged from all sides without having to touch the sample. Depending on the acoustic intensity, the rotation speed can be tuned from approximately 10–1000 rotations per minute (rpm). Aside from manipulation based on immobilized microstructures or bubbles, acoustic streaming has also been applied to actuate the motion of mobile microstructures, such as propelling micro-swimmers [15] and actuating miniature wireless robot arms [16].

https://doi.org/10.1016/j.eng.2022.06.006
2095-8099/© 2022 THE AUTHORS. Published by Elsevier LTD on behalf of Chinese Academy of Engineering and Higher Education Press Limited Company.
This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

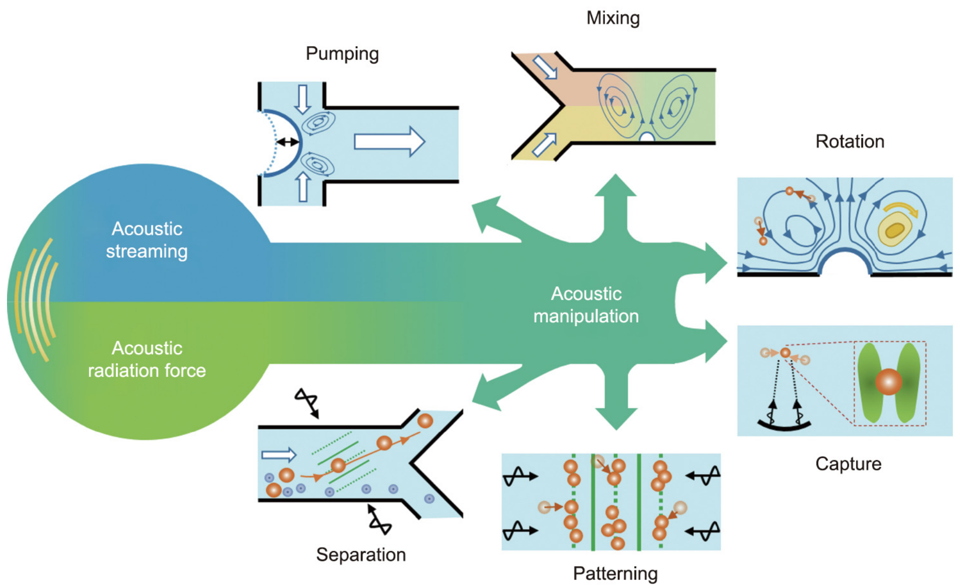

Fig. 1. Acoustic micro-manipulation and its biomedical applications.

The second key mechanism for manipulation is the acoustic radiation force, which is the time-averaged force exerted on an object due to the scattering and absorption of acoustic waves, when the object is suspended in a fluid and subject to an acoustic field. This force depends on the particles' size and acoustic properties, as well as those of the surrounding medium (e.g., the density and speed of sound). Standing waves in an acoustic resonator cause particles to move to the acoustic pressure maxima or minima, depending on the corresponding acoustic properties. The associated acoustic radiation force enables the manipulation of micro-objects, including particle separation [7,17,18], patterning [9,19], and remote capturing [20,21]. Since the acoustic radiation force depends on size, density, and compressibility, it can be used to separate microparticles that differ in one or more of these properties. This is useful in, for example, increasing the diagnostic efficiency and accuracy of bio-analysis by isolating essential biomarkers from a mixture or raw sample. In such an application, a bio-sample typically flows through a microfluidic channel, and a standing acoustic wave field redirects the analytes (i.e., cells and microparticles) into the corresponding outlets due to differences in the acoustic radiation force exerted on them. For example, cells can be separated based on their difference in size (e.g., circulating tumor cells can be separated from whole blood [17]) or in acoustic properties (e.g., the acoustic phenotyping of tumor cells and blood cells [7]). Particles ranging in size from 1 to 100 μm can commonly be separated with a corresponding acoustic frequency ranging from 1 to 100 MHz. Based on the device setup, micro-separation systems can be classified as bulk acoustic wave (BAW) [7], SAW [17], or film BAW (FBAW) devices [18]. In general, the acoustic frequency of these three types of devices increases in the following sequence: BAW (100 kHz–10 MHz), SAW (1 MHz–1 GHz), and FBAW (1–10 GHz).

The acoustic radiation force has also been used for cell patterning, which is an essential technique for studying intercellular interactions and building sophisticated three-dimensional (3D) cellular assemblies and organoids for tissue engineering. In the standing acoustic fields formed by oppositely placed acoustic sources or by a source and a reflector, cells will migrate to the acoustic pressure nodes and aggregate in lines. The distance between the nodes is half the wavelength, which can be tuned using the acoustic frequency.

It is also possible to capture a micro-object at a distance further from the source (at the centimeter to meter scale) using the acoustic radiation force. Benefiting from high transmission through biological tissues, acoustic waves can even control micro-objects within the human body [22,23], which is expected to be useful for noninvasive therapies. One of the most common methods is to trap a microparticle in an acoustic vortex field. In the center of a focused acoustic vortex beam, there is a region where the acoustic pressure is minimal and where microparticles—including cells [21], polymeric particles [24], and microbubbles [22]—can be trapped. Focused vortex beams can be generated with a phased transducer array [23,25], an acoustic lens [26], acoustic metamaterials [27], or SAW devices [21]. It is worth mentioning that there are other biomedical applications of acoustic radiation pressure as well, such as cell stimulation [28], neural modulation [29], and elastography [30].

The acoustic streaming effect and the acoustic radiation force always arise simultaneously; however, it is common for researchers to only speak of the most dominant effect when discussing acoustic manipulation. The dominant effect is usually determined by analyzing and comparing the scale of the acoustic radiation force and that of the streaming-induced drag force on the manipulated particles, which is a result of various factors such as particle size and acoustic properties, fluid viscosity and geometry, and the applied acoustic field. However, there are certain cases in which both phenomena are equally important and must be considered for a correct understanding. For example, the attractive acoustic radiation force may prevent the escape of particles from the acoustic streaming vortex during acoustic streaming-based rotation [8,31]. In acoustic patterning, the acoustic streaming effect has been utilized to control the vertical position of acoustically trapped cells [32] or to transport cells at a distance to the trapping position [33,34]. Acoustic streaming also expands the range of particles that can be trapped in a certain acoustic vortex beam [35].

Enabled by recent advances in acoustophoresis, contact-free and noninvasive acoustic manipulation provides versatile tools for controlling micro-objects and holds great potential for biomedical research. Recently, it has also been shown how the mutual attraction due to the secondary Bjerknes force, provided by arrays of air bubbles that interact over larger distances in a fluid, permits the precise positioning and manipulation larger objects with ultrasound [36]. In the future, the development of further technological advances will expand the range of potential applications in a number of exciting directions, including the following:

- High-frequency acoustic waves, such as hypersonic waves, are expected to be applied in acoustic micro-manipulation. Both the acoustic streaming effect and the acoustic radiation force will be enhanced as the frequency increases [37,38]. The high frequency will be important in the manipulation of submicron particles [18]. Moreover, high-frequency acoustic waves have small wavelengths, which will increase the precision of cell patterning [19].
- Developments in generating and shaping complex acoustic fields are expected to improve the various applications of acoustic manipulation, such as cell patterning, capture, and rotation [24,33,34,39,40]. Complex-shaped acoustic fields promise a breakthrough in the generation of complex-shaped cellular assemblies that will mimic natural tissue structures better than is currently possible with conventional periodic and symmetric acoustic cell-patterning methods. Developments in 3D field control will bring further advances in therapy and surgery, along with new opportunities in the acoustic assembly of cells and organoids.
- New principles for acoustic micro-manipulation are likely to play an important role in other acoustic effects, such as acoustic droplet vaporization [41], inertial cavitation [42], and piezoelectricity [43]. In addition, acoustic manipulation could be integrated with other acoustic-biological effects, such as sonoporation [44] and cell lysis [45]. Moreover, while taking advantage of the intrinsic merits of acoustic waves (e.g., high transmission, good biocompatibility, and wide tunability), the synergy of acoustic micro-manipulation with other field-driven manipulation methods (e.g., magnetic [46], optical [47], and electrical methods [48]) could open up new directions in biomedical studies.

We envisage that these developments in acoustic micro-manipulation will advance biomedical research, including sample pretreatment, biomechanics, and drug delivery. Acoustophoresis also plays a major role in any solution-based effects that use ultrasound to trigger material changes or chemical reactions, and in the use of focused ultrasound in medical applications, such as the opening of the blood–brain barrier [49]. Innovations in micro- and nanofabrication, precise acoustic field characterization, and the computational modeling of acoustic waves through complex media are expected to accelerate these advances.

Acknowledgments

The work was supported in part by the European Research Council under the ERC Advanced Grant Agreement HOLOMAN (788296) and by the Max Planck Society. Zhichao Ma acknowledges support from the Alexander von Humboldt Foundation.

References

[1] Wade NJ. Sound and sight: acoustic figures and visual phenomena. Perception 2005;34(10):1275–90.
[2] Strutt JW. On the circulation of air observed in Kundt's tubes, and on some allied acoustical problems. Proc R Soc Lond 1883;36(228–31):10–1.
[3] Rayleigh L. On the pressure of vibrations. Lond Edinb Philos Mag J Sci 1902;3(15):338–46.
[4] Harvey EN, Loomis AL. High frequency sound waves of small intensity and their biological effects. Nature 1928;121(3051):622–4.
[5] Friend J, Yeo LY. Microscale acoustofluidics: microfluidics driven via acoustics and ultrasonics. Rev Mod Phys 2011;83(2):647–704.
[6] Ozcelik A, Rufo J, Guo F, Gu Y, Li P, Lata J, et al. Acoustic tweezers for the life sciences. Nat Methods 2018;15(12):1021–8.
[7] Augustsson P, Karlsen JT, Su HW, Bruus H, Voldman J. Iso-acoustic focusing of cells for size-insensitive acousto–mechanical phenotyping. Nat Commun 2016;7:11556.
[8] Ahmed D, Ozcelik A, Bojanala N, Nama N, Upadhyay A, Chen Y, et al. Rotational manipulation of single cells and organisms using acoustic waves. Nat Commun 2016;7(1):11085.
[9] Shi J, Ahmed D, Mao X, Lin SCS, Lawit A, Huang TJ. Acoustic tweezers: patterning cells and microparticles using standing surface acoustic waves (SSAW). Lab Chip 2009;9(20):2890–5.
[10] Huang PH, Nama N, Mao Z, Li P, Rufo J, Chen Y, et al. A reliable and programmable acoustofluidic pump powered by oscillating sharp-edge structures. Lab Chip 2014;14(22):4319–23.
[11] Ryu K, Chung SK, Cho SK. Micropumping by an acoustically excited oscillating bubble for automated implantable microfluidic devices. J Assoc Lab Autom 2010;15(3):163–71.
[12] Ahmed D, Mao X, Shi J, Juluri BK, Huang TJ. A millisecond micromixer via single-bubble-based acoustic streaming. Lab Chip 2009;9(18):2738–41.
[13] Hayakawa T, Sakuma S, Arai F. On-chip 3D rotation of oocyte based on a vibration-induced local whirling flow. Microsyst Nanoeng 2015;1:15001.
[14] Feng L, Song B, Chen Y, Liang S, Dai Y, Zhou Q, et al. On-chip rotational manipulation of microbeads and oocytes using acoustic microstreaming generated by oscillating asymmetrical microstructures. Biomicrofluidics 2019;13(6):064103.
[15] Feng J, Yuan J, Cho SK. Micropropulsion by an acoustic bubble for navigating microfluidic spaces. Lab Chip 2015;15(6):1554–62.
[16] Qiu T, Adams F, Palagi S, Melde K, Mark A, Wetterauer U, et al. Wireless acoustic-surface actuators for miniaturized endoscopes. ACS Appl Mater Interfaces 2017;9(49):42536–43.
[17] Li P, Mao Z, Peng Z, Zhou L, Chen Y, Huang PH, et al. Acoustic separation of circulating tumor cells. Proc Natl Acad Sci USA 2015;112(16):4970–5.
[18] Cui W, Mu L, Duan X, Pang W, Reed MA. Trapping of sub-100 nm nanoparticles using gigahertz acoustofluidic tweezers for biosensing applications. Nanoscale 2019;11(31):14625–34.
[19] Collins DJ, Morahan B, Garcia-Bustos J, Doerig C, Plebanski M, Neild A. Two-dimensional single-cell patterning with one cell per well driven by surface acoustic waves. Nat Commun 2015;6:8686.
[20] Baresch D, Thomas JL, Marchiano R. Observation of a single-beam gradient force acoustical trap for elastic particles: acoustical tweezers. Phys Rev Lett 2016;116(2):24301.
[21] Baudoin M, Thomas JL, Sahely RA, Gerbedoen JC, Gong Z, Sivery A, et al. Spatially selective manipulation of cells with single-beam acoustical tweezers. Nat Commun 2020;11(1):4244.
[22] Lo WC, Fan CH, Ho YJ, Lin CW, Yeh CK. Tornado-inspired acoustic vortex tweezer for trapping and manipulating microbubbles. Proc Natl Acad Sci USA 2021;118(4):e2023188118.
[23] Ghanem MA, Maxwell AD, Wang YN, Cunitz BW, Khokhlova VA, Sapozhnikov OA, et al. Noninvasive acoustic manipulation of objects in a living body. Proc Natl Acad Sci USA 2020;117(29):16848–55.
[24] Yang Y, Ma T, Li S, Zhang Q, Huang J, Liu Y, et al. Self-navigated 3D acoustic tweezers in complex media based on time reversal. Research 2021;2021:9781394.
[25] Cai H, Ao Z, Hu L, Moon Y, Wu Z, Lu HC, et al. Acoustofluidic assembly of 3D neurospheroids to model Alzheimer's disease. Analyst 2020;145(19):6243–53.
[26] Jiménez-Gambín S, Jiménez N, Benlloch JM, Camarena F. Generating Bessel beams with broad depth-of-field by using phase-only acoustic holograms. Sci Rep 2019;9:20104.
[27] Esfahlani H, Lissek H, Mosig JR. Generation of acoustic helical wavefronts using metasurfaces. Phys Rev B 2017;95(2):24312.
[28] Pan Y, Yoon S, Sun J, Huang Z, Lee C, Allen M, et al. Mechanogenetics for the remote and noninvasive control of cancer immunotherapy. Proc Natl Acad Sci USA 2018;115(5):992–7.
[29] Tyler WJ, Lani SW, Hwang GM. Ultrasonic modulation of neural circuit activity. Curr Opin Neurobiol 2018;50:222–31.
[30] Gennisson JL, Deffieux T, Fink M, Tanter M. Ultrasound elastography: principles and techniques. Diagn Interv Imaging 2013;94(5):487–95.
[31] Bai X, Song B, Chen Z, Zhang W, Chen D, Dai Y, et al. Postoperative evaluation of tumors based on label-free acoustic separation of circulating tumor cells by microstreaming. Lab Chip 2021;21(14):2721–9.
[32] Guo F, Mao Z, Chen Y, Xie Z, Lata JP, Li P, et al. Three-dimensional manipulation of single cells using surface acoustic waves. Proc Natl Acad Sci USA 2016;113(6):1522–7.
[33] Ma Z, Holle AW, Melde K, Qiu T, Poeppel K, Kadiri VM, et al. Acoustic holographic cell patterning in a biocompatible hydrogel. Adv Mater 2020;32(4):1904181.
[34] Ren T, Chen P, Gu L, Ogut MG, Demirci U. Soft ring-shaped cellu-robots with simultaneous locomotion in batches. Adv Mater 2020;32(8):1905713.
[35] Li J, Crivoi A, Peng X, Shen L, Pu Y, Fan Z, et al. Three dimensional acoustic tweezers with vortex streaming. Commun Phys 2021;4(1):113.
[36] Goyal R, Athanassiadis AG, Ma Z, Fischer P. Amplification of acoustic forces using microbubble arrays enables manipulation of centimeter-scale objects. Phys Rev Lett 2022;128(25):254502.
[37] Dentry MB, Yeo LY, Friend JR. Frequency effects on the scale and behavior of acoustic streaming. Phys Rev E 2016;94(5):59901.

[38] Hasegawa T, Yosioka K. Acoustic-radiation force on a solid elastic sphere. J Acoust Soc Am 1969;46(5B):1139–43.
[39] Gu Y, Chen C, Rufo J, Shen C, Wang Z, Huang PH, et al. Acoustofluidic holography for micro- to nanoscale particle manipulation. ACS Nano 2020;14 (11):14635–45.
[40] Melde K, Mark AG, Qiu T, Fischer P. Holograms for acoustics. Nature 2016;537 (7621):518–22.
[41] Soto F, Martin A, Ibsen S, Vaidyanathan M, Garcia-Gradilla V, Levin Y, et al. Acoustic microcannons: toward advanced microballistics. ACS Nano 2016;10(1): 1522–8.
[42] Miller DL, Thomas RM. Ultrasound contrast agents nucleate inertial cavitation *in vitro*. Ultrasound Med Biol 1995;21(8):1059–65.
[43] Zhu P, Chen Y, Shi J. Piezocatalytic tumor therapy by ultrasound-triggered and $BaTiO_3$-mediated piezoelectricity. Adv Mater 2020;32(29):2001976.
[44] Meng L, Liu X, Wang Y, Zhang W, Zhou W, Cai F, et al. Sonoporation of cells by a parallel stable cavitation microbubble array. Adv Sci 2019;6(17):1900557.
[45] Wang Z, Huang PH, Chen C, Bachman H, Zhao S, Yang S, et al. Cell lysis via acoustically oscillating sharp edges. Lab Chip 2019;19(24):4021–32.
[46] Parfenov VA, Koudan EV, Krokhmal AA, Annenkova EA, Petrov SV, Pereira FDAS, et al. Biofabrication of a functional tubular construct from tissue spheroids using magnetoacoustic levitational directed assembly. Adv Healthc Mater 2020;9(24):2000721.
[47] Shin JH, Seo J, Hong J, Chung SK. Hybrid optothermal and acoustic manipulations of microbubbles for precise and on-demand handling of micro-objects. Sens Actuators B 2017;246:415–20.
[48] Ma Z, Guo J, Liu YJ, Ai Y. The patterning mechanism of carbon nanotubes using surface acoustic waves: the acoustic radiation effect or the dielectrophoretic effect. Nanoscale 2015;7(33):14047–54.
[49] Jiménez-Gambín S, Jiménez N, Pouliopoulos AN, Benlloch JM, Konofagou EE, Camarena F. Acoustic holograms for bilateral blood–brain barrier opening in a mouse model. IEEE Trans Biomed Eng 2022;69 (4):1359–68.