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Oral

Acoustophoretic manipulation of sub-micron objects enabled by density gradients

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Direct and precise manipulation of sub-micron particles such as bacteria, platelets, organelles, microvesicles, exosomes or virus particles is challenging. We describe for the first time how acoustic streaming in the bulk can be efficiently reduced by introducing a density or compressibility gradient and that this enables focusing of 500-nm-diameter particles in a standard acoustophoresis channel.

Acoustophoresis is a gentle and robust method that has been demonstrated for concentrating, trapping, washing and sorting cells [1]. Due to acoustic streaming acoustophoresis was limited to objects larger than ~2 µm but was recently extended to sub-micron particles by redirecting, but not stopping, the acoustic streaming by 2D-acoustic-wave action [2]. The method enabled concentration of bacteria, caused by the rotating acoustic streaming field, but was not applicable to separate sub-micron objects from molecules by outrunning diffusion.

Recently we introduced iso-acoustic focusing for size-insensitive separation [3]. Cells migrate in an acoustic impedance gradient to their zero acoustic contrast point. Surprisingly, cells can be retained in their iso-acoustic point longer than the typical mixing time due to acoustic streaming. We here describe how radiation forces acting directly on gradients in acoustic properties counteract acoustic streaming rolls in the bulk.

In a homogeneous fluid the time-averaged acoustic energy density E_{ac} of the standing wave is constant across the channel width, such that no time-averaged net forces act on the fluid due to the acoustic field. This is not the case in an inhomogeneous fluid, where gradients in density and compressibility lead to spatial inhomogeneity in the acoustic energy density. The acoustic body force f_{ac} acting on the fluid can be estimated as [3],

$$|f_{\mathrm{ac}}| \approx \partial_y E_{\mathrm{ac}} \approx \frac{\partial E_{\mathrm{ac}}}{\partial \rho_{\mathrm{m}}} \partial_y \rho_{\mathrm{m}} \approx E_{\mathrm{ac}}\, \partial_y \delta \quad (1)$$

where ρ_{m} is the density of the medium and δ is the position-dependent relative density and $\partial_y \delta$ is its gradient in the *y*-direction. The magnitude f_{str} of the shear-force density associated with streaming flow rolls driven by the slip-velocity v_{str} at the walls can be estimated as

$$|f_{\mathrm{str}}| \approx \eta \nabla^2 v_{\mathrm{str}} \approx \eta \frac{1}{L^2} \Psi \frac{v_{\mathrm{a}}^2}{c_s} \approx \frac{4\Psi\eta}{\rho_{\mathrm{m0}} c_s L^2} E_{\mathrm{ac}} \qquad (2)$$

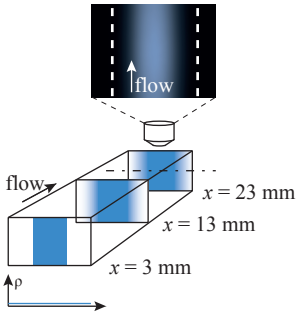
Here, v_{a} is the amplitude of the acoustic velocity field, c_s is the speed of sound, Ψ=3/8 is a geometrical pre-factor [4], $L = h/4$ is the characteristic length scale, η is dynamic viscosity and $E_{\mathrm{ac}} \approx \frac{1}{4}\rho_{\mathrm{m0}} v_{\mathrm{a}}^2$. The ratio of the destabilizing streaming force $|f_{\mathrm{str}}|$ in Eq. (1) and the stabilizing acoustic force $|f_{\mathrm{ac}}|$ in Eq. (2) becomes

$$\frac{|f_{\mathrm{str}}|}{|f_{\mathrm{ac}}|} \approx \frac{|f_{\mathrm{str}}|}{E_{\mathrm{ac}}\delta/L} \approx \frac{4\Psi\eta}{\rho_{\mathrm{m0}} c_s L \delta} \approx \frac{16\Psi\eta}{\rho_{\mathrm{m0}} c_s h \delta} \approx 10^{-4}\,. \qquad (3)$$

Our results show that even for small density variations ($\delta \approx 10\%$) acoustic streaming is greatly suppressed in the bulk of inhomogeneous fluids due to the density-gradient-induced acoustic force f_{ac}. To demonstrate this experimentally, we laminated water and FITC-labelled density modifier Ficoll in a standard acoustophoresis silicon-glass microchannel and observed the effect of reduced acoustic streaming by confocal imaging, **Figs. 1-3**. Further, we observed that 500 nm polystyrene particles agglomerate in the node of the acoustic field if a density gradient is present (**Fig. 4**), but not in the case of homogeneous density medium (**Fig. 5**).

This shows that direct manipulation using weak density gradients and acoustic fields enables concentrating, washing or sorting of sub-micron biological particles.

Word Count: 493



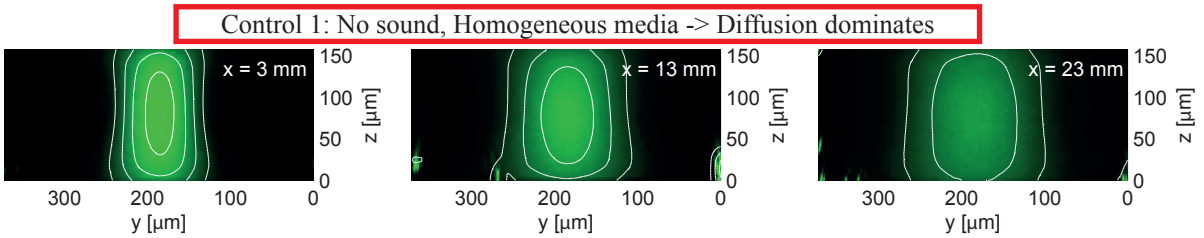
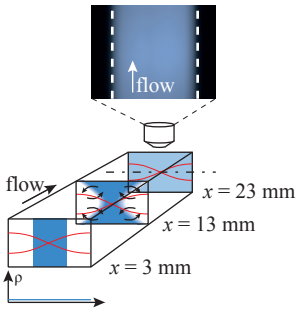


Figure 1. Confocal images along the flow of the plane transverse to the flow of a fluorecent tracer (green) and water (black). The density is uniform in the channel. The tracer broadens by diffusion.



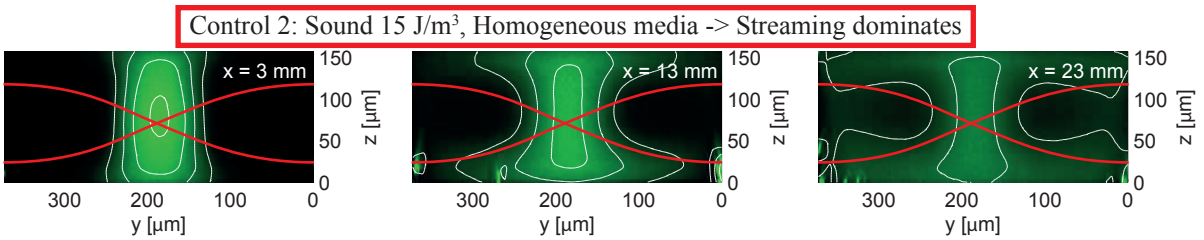
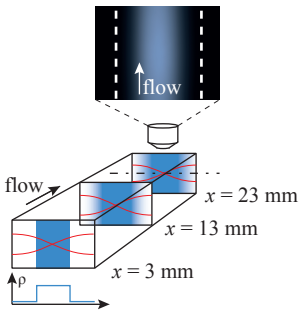


Figure 2. Same as in Fig. 1, but a half wavelength standing acoustic wave (red lines) is acting across the flow. Acoustic streaming convect the flourescent tracer faster than the diffusion broadening.



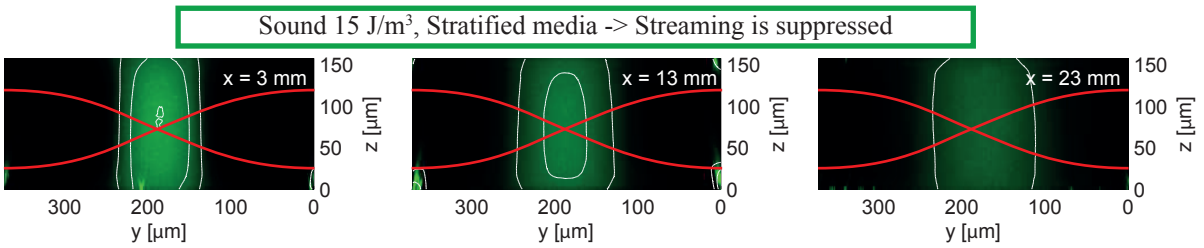


Figure 3. The density of the central flow stream is elevated by 10% adding Ficoll. Radiation forces acting on the density gradient counteracts any convective flow in the bulk caused by acoustic streaming (compare Fig. 2) and the broadening of the fluorescent tracer is once again diffusion dominated (compare Fig. 1).

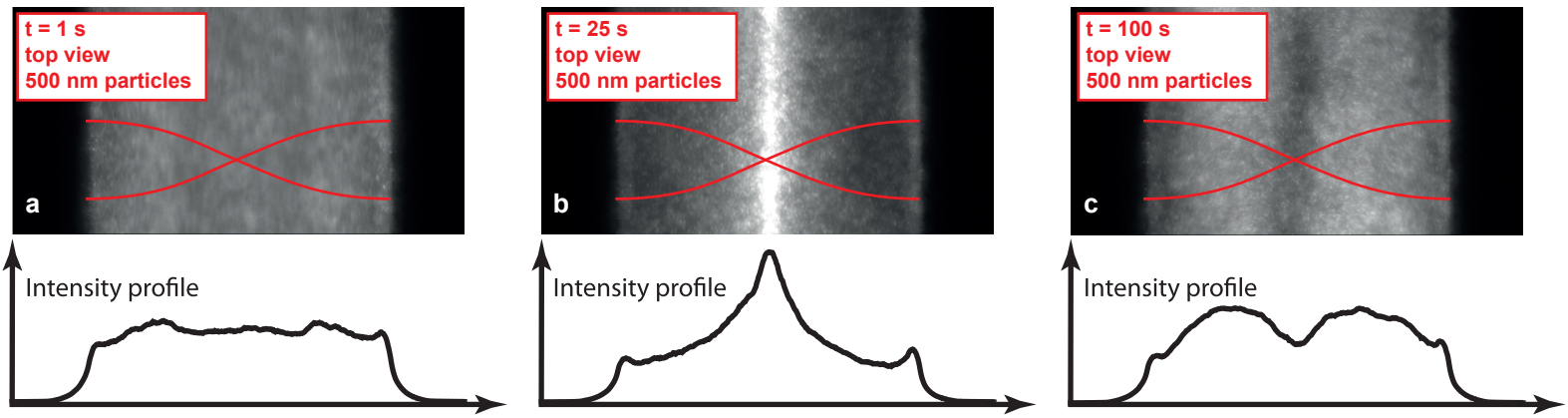


Figure 4. Focusing of 500 nm diameter polystyrene beads in the presence of a 10 % density gradient (compare Fig. 3). (a) The flow is stopped and the sound actuated at t = 0. Initially beads are uniformly distributed and (b) after 25 s of actuation the beads have aglomerated at the central pressure node (red lines). (c) After 100 s of actuation the density gradient has flatttened due to diffusion, and mixing due to acoustic streaming dominates the bead motion. The acoustic radietion acting on the density gradient thus enables the beads, for a time, to outrun the diffusing Ficoll molecules.

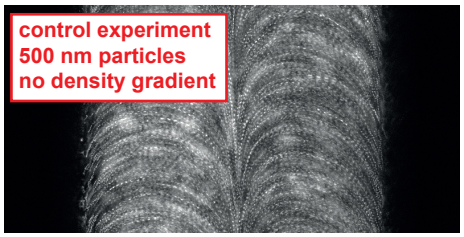


Figure 5. Control experiment for homogeneous media showing an overaly of 20 frames acquired over the first 5 seconds after onset of sound such that a single bead will appear at multiple locations. From the images acosutic streaming velocities were estimated to be on the order of 20 µm/s. This does not allow beads to aglomerate to the node. Compare to Fig. 4 where particles focus at ~4 µm/s (i.e. ~100 µm in 25 s).

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