Move Me with Your Sound: Acoustic Streaming, Its Manifestations, and Some of Its Uses

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Introduction

This article is about acoustic streaming, an intriguing phenomenon that is defined in **Acoustic Streaming**, and it has many uses, but this article emphasizes the application to enhance drug delivery to specific tissues of the body, with brief mention of other uses.

As background, the archetypal example of a wave on the surface of the water appears as a disturbance that moves across the surface without carrying the water along with it. In fact, there are several demonstrations of this on the Web, where an object experiencing the passing of a wave in a tank of water bobs up and down but does not really change its position (e.g., see bit.ly/BobUpnDn). In reality, the object does not quite return to where it started, but in most cases the motion of objects along the direction of the wave motion is too small for this discrepancy to be noticed in the short term. Over longer periods, however, sand or other materials in the water will move long distances from their original positions due to the motion of the waves because the object has drifted with the wave. This is often called the Stokes drift. See youtu.be/iPSC4Zt4l50 for a video illustrating the net motion that occurs.

There are many applications of streaming in biomedical technology. We discuss a fledgling application of enhanced drug delivery where acoustic streaming can be used to increase the concentration of the drugs to a region that might otherwise be hard to reach. We also mention other more mature applications. Due to the subtle difficulties of streaming, these applications will first require some background.

Sound is a longitudinal vibration that moves through air, water, or even solid objects. Such a vibration causes the particles in the medium to vibrate to-and-fro in the direction of the wave as the wave passes. This is different than the up-and-down motion of the water waves mentioned above that are transverse to the wave propagation direction. The drift behavior we saw with water waves can, however, also happen with sound waves traveling through air or liquids, like within tissue, blood vessels, or the fluid surrounding our brain. Fluids, unlike solids, have no fixed shape. Thus, sound waves can drive currents, causing the fluid to drift away from where it started and carrying things in it, like dust in air or dissolved drug molecules in a saline solution. The speed of drift is *much* smaller than the speed of the wave that, in turn, is essentially the speed of the *random* motion of the molecules due to the temperature of the medium, called the *thermal velocity*. On the other hand, the drift speed may well be comparable to the speed of the coherent motion of the particles due to the wave. We call the coherent motion of the fluid as a whole the *bulk velocity*. The result would then be a drift superimposed on the to-and-fro motion. Drift that occurs due to a sound wave is an example of what we call *acoustic streaming*. However, acoustic streaming is caused by an entirely different mechanism than the Stokes drift in water waves. We now discuss such matters in more detail.

Acoustic Streaming

The scientific underpinnings of streaming are fascinating, and there is still much to discover. The heyday of the twentieth-century theories of streaming was immediately after World War II, and much of the work from this period was summarized in a watershed review (Lighthill, 1978) that not only established a context but pointed out that previous studies were quite inadequate. People had treated only those cases in fluid media where the intensity

https://doi.org/10.1121/AT.2023.19.3.38

of the sound waves was often unrealistically small. Since Lighthill's review (1978), the limitations he pointed out are being overcome.

We are accustomed to thinking of an acoustic wave as a cyclic process, with pressure and displacements returning to their rest values at the end of every cycle. For example, for a pulsed acoustic disturbance in ultrasonic medical imaging, we may think of the entire pulse duration as a cycle. The oscillatory pressure is a quite small disturbance to the resting pressure that is essentially the energy density of the thermal motion of the molecules. Acoustic streaming in a fluid is a *net* displacement of the fluid particles at the end of a cycle, and this displacement accumulates over cycles. This cannot happen in an ideal (linear) sound wave in an ideal fluid. For streaming to occur, some of the energy carried by the sound wave needs to be dissipated into the fluid medium, and we need to account for fluid motions beyond the linear approximation that accounts for the familiar harmonic vibrations.

We see a natural decrease in wave intensity as the sound wave covers an ever-expanding volume of fluid, resulting in less energy per volume element. This form of the *attenuation* of sound is due to simple geometry and does not result in acoustic streaming. When dealing with fluids, it is convenient to consider a small volume that is so large that the number of fluid particles in that volume can be treated as a constant. However, that volume is so small that it is smaller than the resolution of how we measure or model it. We will call such a small volume a (fluid) *parcel*.

Bulk Velocity of the Sound Wave

The bulk velocity of the sound wave in the direction of the wave decreases transversely to this direction away from the axis of the sound beam. This directional change is the skewness or the shear of the velocity. As particles arrive across the shear, the skewness of the thermal velocity also increases and results in heating proportional to the kinetic energy in a parcel of the fluid. The coefficient that is needed to relate the kinetic energy of the bulk flow in a parcel to the rate of energy dissipation is called the shear viscosity. Furthermore, the sound wave alternately compresses and expands parcels of the fluid in its passage. This changes the balance of bulk velocity versus the thermal velocity. Such a change also results in dissipation due to what is sometimes called *bulk viscosity*. One result of all this is that the acceleration is no longer in phase with the force.

Another mechanism for dissipation, which also knocks acceleration and force out of phase, is due to transferring energy to the internal molecular vibrations of the fluid. This effect is mathematically of the same form as the bulk viscosity that helps in modeling these flows, although, of course, it is not physically the same at all. The sound wave over a cycle or several cycles brings in more velocity into one end of a fluid parcel than is taken out at the other end, thereby increasing the net rate of bulk momentum transfer across this parcel. This rate of change in momentum is a force, as Newton taught us, that causes some net motion called acoustical streaming. The effect is the product of two quantities oscillating in phase that does not vanish over a cycle, for example, like the square of a sine or cosine. This product is nonlinear. Consequently, acoustical streaming needs both dissipation and nonlinear considerations.

To make things even more complicated, dissipation and nonlinearity do not guarantee acoustical streaming. One reason is that while there is a transfer of momentum, we must also allow for the fluid pressure that is nothing but the energy density due to thermal motions. If the energy density can adjust itself spatially to counterbalance the bulk momentum transfer, the streaming will vanish. This can happen if the momentum transfer rate is of a certain form (Nyborg, 1965; Lighthill, 1978) or if boundary conditions force a vanishing as discussed in ***Spatial and Material Pictures***.

Manifestations of Streaming

Sound waves can be traveling waves as in an unbounded space or they can be standing waves as in a closed tube or vessel of air or water. Circulatory streaming due to standing waves is shown in **Figure 1a**. **Figure 1a**, *arrows*, represents the directions of the streaming velocities produced by the waves. This first kind of streaming ever studied was by Lord Rayleigh (Strutt, 1884), and circulatory streaming due to the boundaries in a standing wave in general is often called Rayleigh streaming.

Microstreaming Around Cells

A more extreme example of this situation is shown in **Figure 1b**, where the intensity of the sound is increased. In this case, the velocity produced results in a second

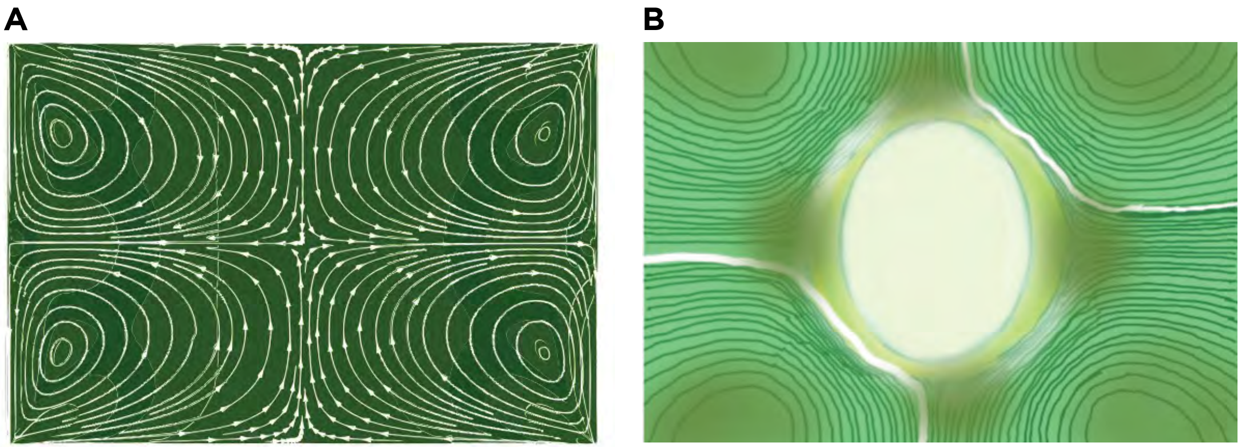


Figure 1. *Rayleigh-type acoustic streaming.* ***a:*** *Acoustic streaming in a standing wave is the form of streaming first analyzed by Lord Rayleigh.* ***Arrows:*** *directions of the streaming velocity produced by the wave.* ***b:*** *Circulatory streaming in a standing wave is the same as in* ***a*** *but at higher acoustic intensities. This is shown by four regions of circulation away from the cell (***white ellipse***) where the contours represent streamlines in these outer regions; there is also a region of circulation in the immediate vicinity of the cell whose streamlines are not apparent. It is this inner circulation that makes it different from the lower intensity in* ***a****. See text for details.*

circulatory region close to the body, where we must take into account a further term in the equations describing acoustic streaming that could be neglected for very low intensities (not shown in this article).

These are our first examples suggesting a biomedical application. The circulatory streaming from **Figure 1**, either **a** or **b**, is the norm near boundaries, particularly around cells in tissue and bubbles and is termed *microstreaming*. Microstreaming is effective in enhancing drug delivery as we describe further in **Biomedical Applications of Acoustic Streaming**.

Far away from boundaries, traveling waves can also be effective in streaming. See bit.ly/3TrdKT0 for a video of a sound transducer in a tank of water. A drop of dye introduced into the water and acted on a traveling sound wave generated by the transducer produced a velocity that moved the dye marker through the water. This is an example of a kind of acoustic streaming called *Eckart streaming*.

We now revisit our insistence that dissipation is necessary. The Stokes drift example in the video referenced in the **Introduction** illustrates an effect dependent on the phase of the wave and can happen without dissipation (but it *is* nonlinear) for a sound wave in a fluid as well. Technically speaking, this is not acoustical streaming, although it is related. To better understand these distinctions, let us examine the causes of the phenomena not related to dissipation but instead to phase.

Spatial and Material Pictures

In general, when looking at modeling a gas or a liquid such as water, we can either follow the motion of a collection of molecules or establish an imaginary grid of points fixed in space. Following the particles of fluid or the parcels is traditionally called the Lagrangian approach or material picture. Establishing the grid and keeping track of the velocity at each grid point, is called the Eulerian approach or spatial picture.

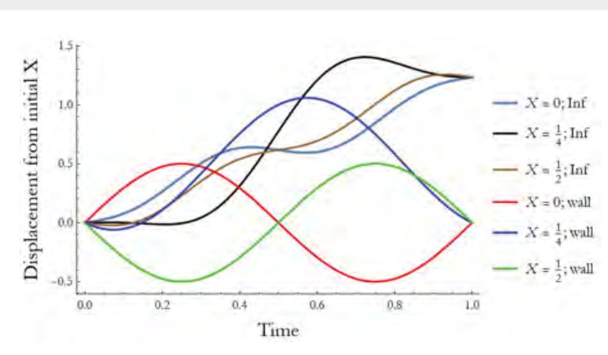
A velocity field describes the velocity at every grid point (and hence of that parcel that happens to be at that point) in a spatial picture at any given time. If we track the parcel as it is pushed by the appropriate velocity at each of the points at the appropriate times, we would be able to compute the velocity of the parcel. We refer to this as the material velocity. However, when we have a wave in the medium, not keeping the distinction between the pictures would lay traps for the unwary.

This is illustrated in **Figure 2**. The *first* case *assumes* that the spatial velocity, the velocity at a fixed point in space, is a simple harmonic (*not* attenuating) traveling wave.

Irrespective of the starting point of the three curves in this case, the fluid particle in one cycle of the wave has drifted to the right. This implies that with the passage of the wave, the fluid would just move in the direction of propagation. On the other hand, if the *spatial* velocities over a period were averaged, the averages would clearly be zero because at any point we have a simple harmonic motion. This contrasts with the cycle average of the material velocity, which does not average to zero. In other words, the spatial velocity must not be averaged or the difference between it and the material velocity must be accounted for. Stokes drift is an example of this at the surface of a body of water.

One would think that fluids obligingly flow in the direction of the wave. Paradoxically, this generally does not occur. This paradox can be resolved by considering the mechanism that produces such a wave, a vibrating wall, for example. In the *second* case, let us assume that the wall vibrates with precisely the same simple harmonic velocity (displacement of the wall per unit time) as the spatial velocity of the first case discussed above. At the wall, the fluid parcel "sticks" to the wall and must move with it. Then the curves show that a fluid parcel will always return to exactly the spot that it came from. Here the average *material* velocity is zero. This is not shown here, but a calculation of the spatial velocity will show that its average does not only not vanish but is exactly the same magnitude as the material velocity of the first case but is pointing left, *opposite* to the traveling wave in the direction of the wall.

Figure 2. *Theoretical subtleties. The difference between spatial and material velocities (often called Eulerian and Lagrangian, respectively) is illustrated for a fluid through which an acoustic wave is propagating from left to right. The curves are for a fluid in an infinite medium (no boundaries;* ***inf****). There is an oscillating wall and only the fluid motion to the right of the wall is considered (****wall****). The displacements of a particle in these two geometries (starting from position X) are shown. In the open space, the particles are all displaced over a cycle (Stokes drift) and end up at a different position from the starting one (lines that end higher up). By definition, the spatial velocity has a zero average (see text for more details) and since the particles are displaced to the right, this says the material velocity average is positive. But when there is an oscillating wall and the wave propagates in the half-space, a particle returns to its original position (lines that return to the same level): the material velocity averages to zero over a cycle. The* ***horizontal short bars*** *(line segments;* ***right****) indicate the position of the wall at various times in the cycle.*



Note that this picture would also pertain to a vibrating *solid*. Namely, the material velocity must average to zero (the atoms in a solid move around a fixed equilibrium position). This automatically means that the cycle average of the *spatial* velocity, which we observe if we gaze at a fixed point and measure the velocity there, does not vanish and points opposite to the wave propagation direction. We must be aware of this difference and its effects near the surface of an acoustic source to calculate the streaming effects correctly. Note that the effects mentioned are a consequence of the conservation of mass or matter, and the distinction between liquid and solid does not appear here. (They appear in the relationship of stimulus to response: liquids flow and solids don't or, more precisely, solids can support a shear stress and liquids flow in response to such a stress.)

Biomedical Applications of Acoustic Streaming

We already mentioned one possible biomedical application of the idea of acoustical streaming to enhance drug delivery in specific tissues of the body. Perhaps the most widespread applications occur in the field of acoustofluidics (Green et al., 2014; Muller and Bruus, 2015; Rufo et al., 2022). Because a previous article in *Acoustics Today* (Nguyen et al., 2023) discussed acoustofluidics authoritatively, we do not discuss it here.

We have introduced the phenomena of microstreaming in ***Microstreaming Around Cells***. Despite its circulatory nature and its short range, it has important consequences derived from the pioneering work by Nyborg (1958). The

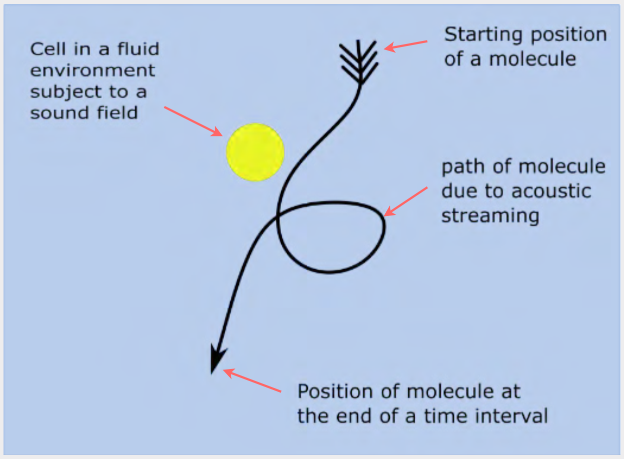


Figure 3. *Acoustic streaming in biology. Microstreaming is ubiquitous around cellular environments and plays a role in many ultrasound-assisted drug delivery applications and perhaps even in neuromodulation due to ultrasound (Kubanek et al., 2018). The movement of a marker particle near a cell (**yellow**) was followed for some time in the presence of a sound wave. The start (**tail of the arrow**) and end (**arrowhead**) positions indicate the limited time interval of observation. Inspired by Lee (2018).*

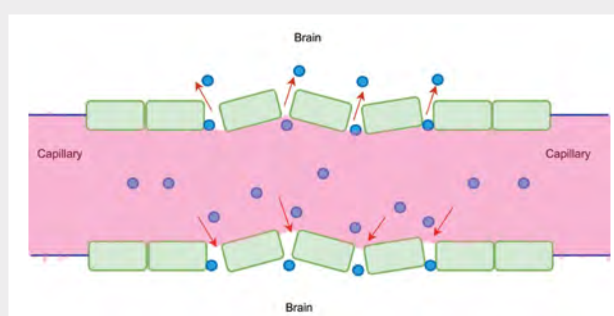
movement of a marker particle near a cell was followed for some time in the presence of a sound wave (**Figure 3**) (Lee, 2018). The start and end positions indicate the limited time interval of observation. The path is not random. Rather, it is characteristic of the complicated interaction of sound with the fluid medium. The path may develop a diffusion-type mixing if the medium consists of many cells whose placements are not regular. If this is the case, then the circulating path of a particle will not be closed (as in the case of the highly symmetrical situation in **Figure 1**) but will bifurcate so that its spread is effectively described as diffusivity enhanced by the streaming. The name for this is hydrodynamic dispersion (Bear, 1988).

One form of microstreaming used in drug delivery is called *sonophoresis*. It is believed (Collis et al., 2010) that the interaction of the sound waves with lipids in the cells opens a pathway in the cell membrane due to shear stresses, so that drugs can more easily enter the cell. Microstreaming may also play a role in opening the blood-brain barrier (BBB) for drug delivery (Konefagou, 2017) and in enhancing the delivery across it in the presence of microbubbles (Mo et al., 2012) (**Figure 4**). The microbubbles (between 1 and 10 micrometers) resonate strongly in acoustical fields used in biomedical systems. In **Figure 4**, the permeability of the capillary wall cells is represented by the gaps between the cells.

A biomedical application actively being investigated is enhancing drug delivery by the advection of therapeutic particles by a fluid streaming due to sonication. We now turn to such applications that will vastly extend the initial results such as those shown in **Figure 5**. This figure shows an example of a commercial sonicated catheter (Ekosonic Mach4). A drug was delivered via pores throughout the length of the catheter shown but sonicated only in the distal half; a color-coded concentration map of a contrast reagent shows greater radial penetration in the sonicated half.

Some delivery applications use the fact that particles such as drug molecules suspended or dissolved in a fluid can be carried by the fluid flow, called *advection*. The drug in suspension or solution with such a fluid carrier is directly delivered into tissue from a catheter port or ports by such advection. Such a process is called convection-enhanced delivery (CED) (Raghavan and Brady, 2011), and the driving force is the excess pressure from a pump used in infusing the fluid carrying the drug into the tissue. Biological tissues have a great deal of resistance to such flow due to various mechanisms (Brady et al., 2020). We may

Figure 4. *Ultrasound delivery across a blood-brain barrier (BBB). Microstreaming likely plays a role in the burgeoning field of disrupting the BBB to deliver drugs to the brain. Here we see how the sounds part the barrier, allowing a drug to pass through it. See text for references and explanation of the figure. **Blue circles:** microbubbles. **Light green rectangles:** capillary wall cells with their permeability represented by the gaps between the cells*



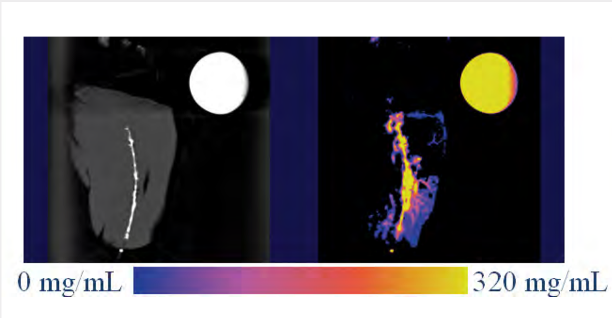


Figure 5. *Endovascular ultrasonic catheter. This example is from a catheter inserted into a blood vessel of a pig's liver ex vivo. The catheter is connected to a pump (not visible) and has ports along the side that can infuse fluid into which a contrast agent has been introduced. A contrast agent is a substance that shows up well in a CT scan.* ***Left:*** *black-and-white CT image of the catheter before the infusion. A calibration vial contains a known concentration of the contrast agent (****white circle****).* ***Right:*** *color-coded CT image of the infusion from a pump after 90 minutes. The concentration of the contrast agent is displayed (****yellow circle****), and the* ***color code*** *shows how colors match to concentrations. The bluish part of the background should be ignored as noise. In the distal (lower) half of the catheter are small ultrasound sources (not visible). The increased width around the middle of the catheter shows the increased spread of the agent due to sonication.*

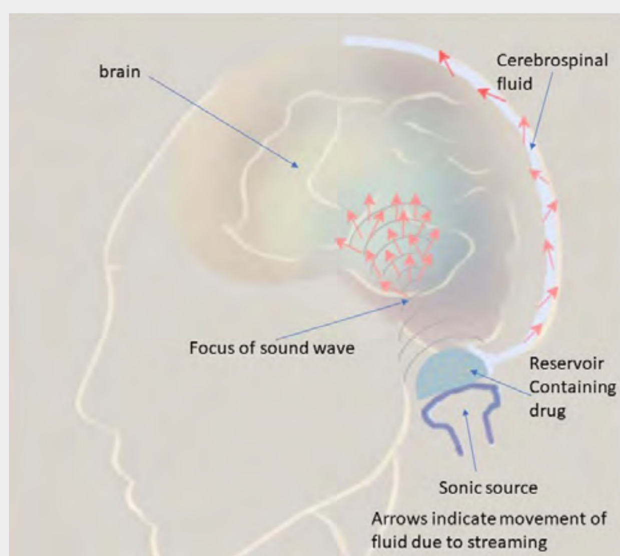
enhance the advection of the drug in the fluid by streaming driven by an acoustic beam. A stark difference from CED is that here the streaming force may be focused with adequate intensity anywhere, such as the regions further away from the catheter tip to where the CED is relatively ineffective because the pressure falls off very rapidly away from the infusion catheter. Using focused beams and steering the focus offers a way to enhance the spread of the drug (Raghavan, 2018), and this is the central promise of streaming for drug delivery. Delivery into the cerebrospinal fluid (CSF) spaces surrounding the brain known as intrathecal delivery is now becoming more widespread and streaming is expected to enhance this as well (Yoo et al., 2022).

Figure 6 shows, in schematic form, the potential application of such an enhanced delivery system, although it should not be taken literally. A source of ultrasound generates waves going into both the tissue and the CSF, generating streaming therein to aid in drug delivery.

To make this quantitative, **Figure 7a** shows approximate calculations of streaming for in-tissue delivery, whereas **Figure 7b** shows this for delivery into the CSF, both in a "spherical" brain. We have used a simple model for the acoustic intensity patterns: a beam whose intensity follows a Gaussian distribution (see Kino, 1987, pp. 206-210). The plots are cycle averages of the *material* velocities of fluid in these respective spaces; see ***Spatial and Material Pictures***. A drug that floats in the fluid will be transported by these streaming speeds. The main message of these calculations (which need to be confirmed by experiment) is that therapeutic molecules, which would be advected by the fluid, can indeed be transported. Moreover, by varying the focus, it will be possible to attain higher fluid velocities throughout the desired region.

Let us recall the importance of boundary conditions. For results such as those shown in **Figure 7**, it is presupposed that a reservoir of fluid (containing the drug) is available for the process. In other words, a pump is not delivering a fixed amount of fluid per second but rather allows as much fluid to enter as the pressure conditions allow. We have also calculated (not shown here) fluid flow in the cochlea, proposed for drug delivery into the inner ear (Sumner et al., 2021) as well as for air into

Figure 6. *Future applications of streaming in medicine? This is an illustration of potential drug delivery in the brain enhanced by acoustic streaming. The fluid velocities that are the result of the acoustic streaming are quantified in* ***Figure 7****.*



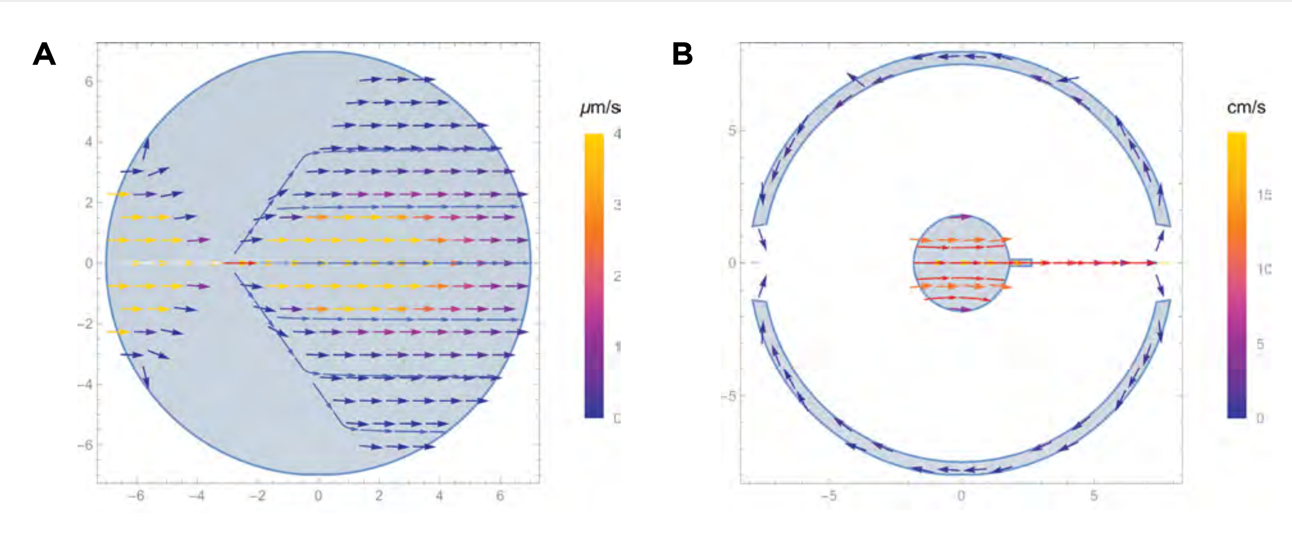


Figure 7. *Acoustic streaming calculations in tissue and in the cerebrospinal fluid (CSF).* ***a:*** *Acoustic beam focused in brain tissue.* ***b:*** *Beam in lateral ventricle to spread in the CSF. These simulated sonications are predicted to result in significant fluid flow that could be used to advect drugs in many therapies for the brain. Note the dramatic differences in speeds in liquid (**b**) and in tissue (**a**). These speeds are **color-coded arrows**, with the coding to speed matched with the bar.*

the trachea (Han et al., 2016). These calculations show more than adequate speeds of transport for safe-enough sound intensities. Although the latter application has not been realized (Meyers et al., 2019), there is potential for such development.

Many of the applications we have discussed are still in the research phase; thus, their efficacy is unverified. Although ultrasound disruption of the BBB has been known since the 1950s, the method is reaching the clinic only now because of the large investments made in the needed research and the development of monitoring technology (Flame et al., 2012). Similarly, the correlation between the promise of enhanced delivery due to acoustic streaming and the process of disease cure remains to be established. The first goal in establishing such a correlation would be to set a target and demonstrate a quantifiable improvement in coverage of the target region by a streamed drug compared with currently available delivery methods. The challenges are considerable; computing the sound fields in the environment of a living being is very difficult. Add to that further complication of predicting, not to mention calculating, the attendant streaming accurately is daunting enough. It seems inevitable that modern computational methods will play an increasingly important role in predicting the streaming. If efforts are initially promising, the entire process can be continually improved. However, just as in the case of BBB disruption, necessary investment into these improvements will be needed.

Conclusions

We have briefly reviewed the context within which acoustic streaming is situated as a nonlinear effect and the interesting mechanisms that underlie it. Although much progress has been made to treat nonlinearities (Sadhal, 2014; Catarino et al., 2016; Joergensen and Bruus, 2021) (for nonperiodic acoustic sources, see Perelomova, and Wojda, 2009), a unifying theoretical treatment of the phenomena and its varied manifestations is still lacking. We described some of its biomedical applications. Lighthill's authoritative discussion (1978) was the start of newer aspects of acoustic streaming. We hope that the impetus from new technologies and new modeling methods in this millennium that will be brought to studies of streaming will also yield interesting and useful developments.

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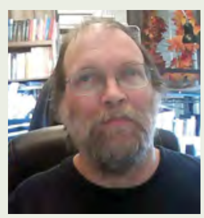

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