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Better with Bubbles: New Applications of the Acoustic Bubble in Medicine

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Abstract
After many years of development and a somewhat hesitant start, gas-filled microbubbles offer ultrasound imaging a clinical contrast agent with properties that are both practical and exotic, promising to propel ultrasound into new areas of therapeutic as well as diagnostic medicine. The intriguing properties of a sphere of gas oscillating in a sound field have graduated from a curiosity in physics to the core of a number of entirely new strategies in biomedicine. Bubbles can act as acoustic beacons that allow imaging of flow in the microscopic vessels that herald the onset of malignant invasion of a tumour into its host; they can be engineered to adhere to cellular and molecular markers of disease and be sent to find them by injection into the bloodstream; they can be exploited to unlock the barrier of the cell membrane and allow drugs to enter organs like the brain from which they have hitherto been banished; and they can be used to carry payloads of drugs or genetic material itself for localised acoustic release under the precise guidance of an ultrasound beam.

These developments are first a consequence of a new generation of bubble constructs - heavy gases stabilised by a shell of lipid or other biocompatible material - that are smaller than a red blood cell and so pass freely around the circulation. But they also arise from serendipity: a micron sized free gas bubble resonates radially at frequencies that happen to fall within the range of medical diagnosis. They thus have scattering cross-sections orders of magnitude larger than their physical size, and can be driven easily into nonlinear oscillation by a typical ultrasound imaging pulse. This has spawned a mass of nonlinear echo detection strategies that are now sufficiently sensitive to detect a single 3 micron bubble in a capillary more than 10 cm below the skin surface. The resulting real time perfusion images have redefined what is possible to diagnose from a medical image. Resonance also allows disruption of the bubbles remotely using the ultrasound beam and a new way to measure blood flow at the tumour tissue level, an important indicator of response to therapy. In their current form, the bubbles flow in the vascular system without interaction, but it is easy to modify their surface so that they bind to specific cellular or molecular targets on the endothelial cells lining blood vessels, signalling the presence of disease.

Our new fascination with a microbubble oscillating in a sound field has in fact been shared by a long list of distinguished scientists, starting more than a century ago with Lord Rayleigh. That a resonating bubble is able to concentrate sound energy and re-radiate an amplified echo back to the transducer, like a ringing bell, is an appealing concept which has given rise to a new generation of blood pool contrast agents with an exceptional profile for sensitivity, safety and tolerance. More extraordinary, however, is that a bubble can do the converse: transform a burst of sound into an ultra-brief event that releases energy in such a short time at such a small point in space that instantaneous temperatures exceeding that of the sun’s surface are easy to attain. Such events can porate a cell to deliver a drug through its membrane, provide shrimp with means to attack their peers, can blow up whole ships, and can open the blood brain barrier safely, focally and reversibly under imaging guidance. For diagnosis, new strategies that produce several thousand images per second can be used to track individual bubbles through vessels too small to resolve anatomically. By imaging the path of these tracks, rather than the vessels themselves, the resolution of the image, usually limited by the wavelength of sound to a fraction of a millimetre, can be cheated, showing organ vasculature and flow velocity at the level of tens of microns. For therapy, bubbles can initiate transport across cell membranes and open junctions between endothelial cells, allowing delivery of drugs, genes and nanoparticles into otherwise inaccessible tissue such as the brain. New methods for the creation of bubbles within the interstitium may have particular relevance to breaking down the extracellular matrix in solid tumours, delivering new drugs and potentiating thermal and ultrasound therapies. The ubiquity of sound and bubbles in the natural environment has meant that many of these techniques have been pre-empted by members of the animal kingdom, sometimes with surprising results: examples will be shown.