There may be bubbles ahead

DR THOMAS MATULA

The use of microbubbles in therapeutic ultrasound is set to change. **Dr Tom Matula**, based at the University of Washington, explains how his research is providing new applications for this technology

What benefits does ultrasound offer over traditional imaging and targeting methods?

Various technologies are used to image within the human body; MRI (Magnetic Resonance Imaging), CT (Computed Tomography), PET (Positron Emission Tomography), and Diagnostic Ultrasound are common technologies. The major strengths of ultrasound are that there is no ionising radiation (i.e. x-rays), it is non-invasive, very low cost, highly portable and provides real-time information to the clinician.

For example, some current diagnostic ultrasound systems are the size of cell phones, and can be easily transported to very rural areas; the images that are displayed are in real time, giving the clinician immediate feedback on what is occurring. All in all, I see ultrasound as a partial solution to two major problems in society: the rising costs of healthcare, and bringing low-cost medicine to poor and/or rural regions.

Microbubbles are already used as contrast agents in ultrasound imaging, but what other potential applications of microbubbles might there be in everyday treatment and analysis of patients?

Yes, microbubbles, termed 'Ultrasound contrast agents' are already being used to help cardiologists visualise blood flow in the heart, and in many countries they are used in general radiology applications as well. But I believe the future of microbubbles are in targeting and drug delivery. Targeting refers to microbubbles that are manufactured with 'sticky' molecules that bind to specific receptors on disease proteins. Since microbubbles are so easily visualised by ultrasound, they can be used for very early detection of disease, like cancer, which would be of great benefit for two reasons: firstly, it can help detect disease early enough so that more effective treatments can be performed; secondly, because ultrasound is less expensive than other modalities, it can help reduce health costs, both at the diagnostic stage and when therapies are applied. Ultrasound-activated microbubbles can assist drug delivery through the vasculature, making drugs more efficacious, and also more targeted, since one can 'aim' the treatment directly to the site of interest. For example, chemotherapeutic drugs can be more effective if we can 'push' the drugs through the blood vessel right at the site where they are needed, instead of having them attack the body systemically.

Why is the impact of microbubbles so much more severe within the range of the therapeutic ultrasound pressure system than in the diagnostic ultrasound based alternative?

From the diagnostic point of view, we are interested in visualising the region of interest. Microbubbles are used as 'imaging beacons' to help improve visualisation of blood flow. Very low ultrasound power is needed to achieve this benefit. On the other hand, therapeutic ultrasound uses much higher pressures than diagnostic ultrasound to force the microbubbles to interact and affect their surroundings. The higher pressures are intended to cause a mechanical effect (such as shear stress or cavitation-induced stress), or a thermal effect (heating) to induce some biological response. A mechanical effect might be useful for example to open the endothelial layer, allowing drugs to diffuse into the surrounding tissue. A thermal effect, on the other hand, is important to cauterise wounds or perhaps to kill cancerous cells. It is important to note that therapeutic ultrasound is applied to a very specific region within the body, so it only affects the part where it is aimed.

Do you believe that a balance between high acoustic pressures and minimal impact on vessels can be achieved or will alternative methods have to be found?

The major goal of therapeutic ultrasound with microbubbles is to induce a bioeffect. Although this does impact tissues within the focal zone of the ultrasound, it seems to me to be much better than open surgery, where healthy tissues must be destroyed just to get to the unhealthy tissue. It also appears to be a better alternative than systemic drugs, which end up being so diluted by the time they reach the area where they are supposed to work that you have to take much more than is actually needed. Therapeutic ultrasound may also lead to reduced incidences of infections, since the procedure will be either minimally-invasive, or non-invasive. While I believe that it is important to make therapeutic ultrasound as safe as possible, we cannot ignore the fact that many of today's therapies already impact tissues in a negative way. Therapeutic ultrasound will provide better treatments to some diseases in the future, and these are the areas we need to focus on.

Small agents of big change

Rocketing healthcare costs in the U.S and the possibility of global benefits make a closer understanding of ultrasound contrast agents a necessary and valuable tool for the future. **Dr Tom Matula's** research is set to shed light on this important area

HEALTHCARE COSTS IN the U.S. are rising at an unsustainable rate, with expenditures surpassing 2.3 trillion dollars in 2008. The need to curtail this growth has become a major priority for decision makers, employers and consumers, who are suffering from mounting healthcare bills. As the debate about U.S. healthcare reform becomes central to government policy, research that provides potential solutions and clinical applications for reducing costs is essential.

Dr Tom Matula is readdressing ultrasound technology as a possible vehicle for reducing costs. His research group from the University of Washington are studying the dynamic and vascular effects of ultrasound contrast agents, also known as 'Microbubbles'.

Ultrasound has become a routine method of generating images for both medical examination and diagnosis. This form of imaging has significant benefits, including low cost and real-time feedback, and with new approaches taken by Matula, this method could be made even more effective.

Microbubbles are used as gas based contrast agents to dramatically improve an ultrasound image, since they provide a contrast between what the technician is trying to image, and the adjacent tissue. These bubbles can be as small as red blood cells and can offer clinicians valuable data about localised blood flow.

However, ultrasound contrast agents are unstable under conventional diagnostic ultrasound conditions, with the shells often experiencing high shear stresses, which can lead to shell failure and gas loss. Matula and his team are aiming to explore the direct interactions between bubbles and tissue boundaries, especially through blood vessel walls as a means of combating these problems and providing fresh solutions.

THE RESEARCH

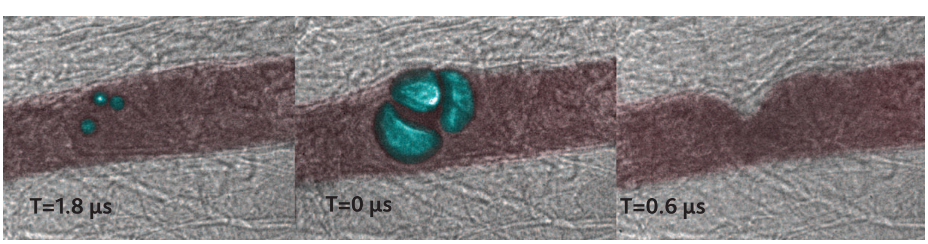
One approach Matula and his team have taken to explore these direct interactions between microbubbles and blood vessels has been to observe microvessels subjected to mega-hertz ultrasound pulses. They were able to find that the vessel wall moved outward toward the surrounding tissue (vessel distention) during the expansion of the bubble, whilst it was seen to move inward into the vessel lumen (vessel invagination) during bubble collapse. This established that microbubble oscillation is responsible for adjoining microvessel dilation, invagination and even rupture on a sub-microsecond time scale. Matula's research also revealed that the degree of this interaction depends on how close the microbubble is to the vessel wall, when subjected to both low and high pressure levels.

Understanding these interactions between acoustically activated microbubbles and microvessels is an essential part in the effective design, imaging and targeting of these contrast agents. Moreover, and crucially, this research enhances the safe use of microbubbles.

For Matula's team, the need to quantify displacements of the vessel wall at the maximum distension and invagination has proved to be another challenging aspect of their research. They achieved this by developing an algorithm to quantify displacements of the vessel and surrounding tissue, and then calculating the maximum circumferential strain in the vessel wall.

Matula points out that both distension and invagination can disrupt the endothelium, which is the lining of the blood vessel, but he has also observed that invagination appears to generate higher localised strains and stresses, and therefore may be the first place where disruption occurs.

THREE MICROBUBBLES within a 46 micron diameter vessel are subjected to 7 MPa peak negative pressure. As they grow, they distend the nearest vessel wall. During collapse, the vessel wall and surrounding tissue invaginate into the lumen



CLINICAL APPLICATIONS

This disruption of the endothelium could be used by high intensity ultrasound to purposefully damage the blood vessel in a localised region so that drugs can be pushed out of the vessel and into the surrounding tissue matrix. This could be very important for the application of this method, since lots of drugs are too large to enter the surrounding tissue via the blood vessel. "In some cases," Matula therefore remarks, "it can be desirable to generate damage."

By selectively opening up the endothelial layer at specific locations, the delivery of genes and drugs may be enhanced. In other cases, high pressures generate a cascading biological response that leads to healing of chronic conditions. No one is yet quite sure what causes the healing effect, but it may be that the ultrasound causes microdamage to very small regions and the body's repair mechanism responds by healing these areas, and in so doing the body also heals the chronic condition.

THE FUTURE

Matula and his group are very encouraged by their discoveries, and are hopeful about possible new developments that this could lead to. They see a need to quantify how much 'damage' is done by single microbubbles and the scale of the 'hole' they make (to determine what size of nanoparticles will extravasate into the surrounding tissue). Furthermore, they would like to measure the number of acoustic pulses that are needed to generate a significant effect. This research will enable a better understanding of the conditions necessary to permeablise the endothelium for drug and gene delivery, important for future individualised molecular therapy applications.

In the long term, Matula's target is to examine further the possibility of fixing targeted microbubbles to the vessel wall, and measuring the force needed to remove or break them. This research could therefore promote the use of microbubbles in molecular imaging and therapy. Matula is enthusiastic about such promising developments: "The quality of results that we are currently getting are remarkable," he states. "They are re-defining just how a microbubble interacts with its surroundings."

THE IMPORTANCE OF COLLABORATION

Matula's research has benefited substantially from employing a collaborative approach. The team at the Center for Industrial and Medical Ultrasound features scientists from diverse backgrounds in medical research, from expertise in the basic physics of bubbles to theoretical modelling; from experimental science to signal analysis; and even to prototyping and technology development. On the importance of collaboration Matula is unequivocal: "The field is much too complicated for any one person to understand," he explains, believing that team work is an essential driver of ideas, experiments and results.

By way of example, Matula points to the different aspects of the team's work on microbubble interactions within blood vessels: "We design a set of experiments based on a close collaboration of several researchers, including a biologist, an MD, and a couple of experimentalists, as well as an animal technician who performs the actual surgeries," he explains. This type of interdisciplinary and collaborative approach is key to the advancement of research its subsequent clinical applications.

Matula's research into the effects of microbubbles has raised many interesting and helpful points. The benefits that an increased understanding of microbubbles could bring to ultrasound technology, is something that has great potential value in the field of medical science worldwide. The convenient size of ultrasound equipment and its easy portability means that it can be delivered and used in rural areas where it is greatly needed. The important partnership between telemedicine and portable ultrasound also allows the results to be received anywhere in the world. This brings together the global medical community, as well as patients and specialists. It has unlimited possibilities and applications, not only for a variety of medical problems but also for the massive disparities that exist globally in medical treatment. This technique could more effectively treat patients but more importantly bridge the social and political gaps, and could be one step closer to the harmonisation of worldwide healthcare.

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THE MAIN COLLABORATORS ON THIS INITIATIVE

The major concepts and ideas for the initial project were developed by Matula and his co-PI Dr Andrew Brayman. Hong Chen (PhD student) was hired to fine-tune the experimental system and obtain the data. Wayne Kreider (Postdoc) helped analyse the data and he also developed a simple model for explaining the influence of microbubbles on vessel walls. Frank Starr (Animal Technician) managed the animals (rats), and performed the surgeries. Mike Bailey and Joo Ha Hwang, MD helped to interpret the data with Drs Brayman and Matula. Finally, Fran Olson (engineer) helped build the experimental apparatus that has worked so well in our experiments. Matula is keen to give most of the credit to his student Hong Chen; he never realised that imaging the interaction of microbubbles with real tissues this way would be so difficult, but Chen has been very tenacious and has made it work.

INTELLIGENCE

ULTRASOUND CONTRAST AGENT DYNAMICS AND VASCULAR EFFECTS

OBJECTIVES

The specific project objectives are to better understand microbubble interactions with the incident acoustic field and with the surrounding tissue. This includes: (1) to probe the coupled sub-microsecond interaction between blood vessels and microbubbles insonified by ultrasound pulses using high-speed optical imaging; (2) to correlate microbubble behaviour inside blood vessels directly with vascular bioeffects; and (3) determine microbubble shell parameters using light scattering techniques. The long-term objectives are to develop and implement microbubbles in molecular imaging and therapy applications.

TEAM MEMBERS

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THOMAS J MATULA received his PhD from Washington State University, and is now Director of the Center for Industrial and Medical Ultrasound (CIMU) within the Applied Physics Laboratory, at the University of Washington, Seattle. He is a past recipient of the Presidential Early Career Award, and the Department of Energy Young Scientist Award. He has several patents and patents pending, and actively participates in international societies. His diverse range of interests include both fundamental and translational research, usually focused on cavitation and bubble behaviour in physical, chemical and biological systems.