A SURE way of imaging the microvasculature

Ultrasound is an enormously valuable medical imaging tool, yet it is not currently able to image the smallest blood vessels in the body. We spoke to **Dr Charlotte Mehlin Sørensen, Professor Jørgen Arendt Jensen, Professor Erik Vilain Thomsen** and **Professor Michael Bachmann Nielsen** about their work in developing a new imaging approach designed to give clinicians insights into the microvasculature.

An ultrasound scanner is an enormously valuable tool in modern medicine, enabling doctors to image soft tissue and rapidly diagnose patients, and the technique is widely used across the world. However, currently ultrasound is relatively limited in terms of the resolution of the imaging system. "The resolution is on the order of half a millimetre, or maybe a little less. However, the smallest blood vessels in the body are actually on the micron level, down to around 10-20 microns, so we can't currently see the microvasculature," explains Jørgen Arendt Jensen, Professor of Biomedical Signal Processing at the Technical University of Denmark (DTU). This is an issue Professor Jensen is working to address as part of his work in an ERC-backed initiative. "We're trying to develop a new imaging system called SURE that can show the microvasculature," he explains.

This has previously been done by injecting small, gas-filled bubbles as contrast agents into the blood, then following them through the body. This allows medical professionals to see the smallest vessels in the body, yet it takes a long time, which is not practical for patients. "When you are measuring very small things people have to stay extremely still, which is very difficult for sustained periods," points out Professor Jensen. The SURE system takes just a couple of seconds however, while still providing highly detailed images of the microvasculature. "Our approach allows us to see vessels down to a size of maybe 25 micrometres," outlines Professor Jensen. "Then we can start observing these small vessels. How much blood do they carry, how fast does it flow? We can put on a normal ultrasound transducer, acquire data, and within seconds we can see these kinds of images."

SURE imaging

The project team are working to both develop and improve the SURE approach, and also test it with a view to its future application. In the SURE approach red blood cells – erythrocytes – are used as a target. "There are a huge amount of erythrocytes in the blood stream, around 5 million cells within just a cubic millimetre, so there are lots of targets," says Professor Jensen. Erythrocytes can't be seen directly from a normal ultrasound image however, as Professor Jensen says the signal is very weak. "The signal from the blood is often 100 times weaker than from the tissue. So it's vital for us to make a really good ultrasound image, with no movement," he explains. "We do what is called motion compensation, so that it's a completely fixed image. Then we take all the tissue signals and remove them, we essentially subtract out the tissue, which leaves the blood signal."

This approach involves isolating the blood signal, locating the blood vessel, then locating it over time. This procedure takes just a couple of seconds to provide

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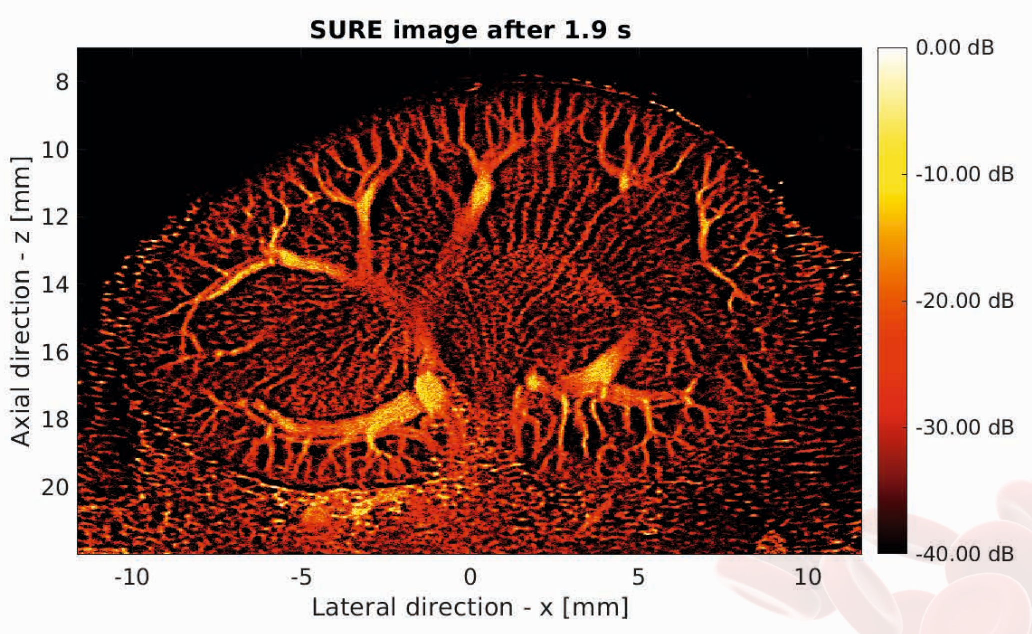
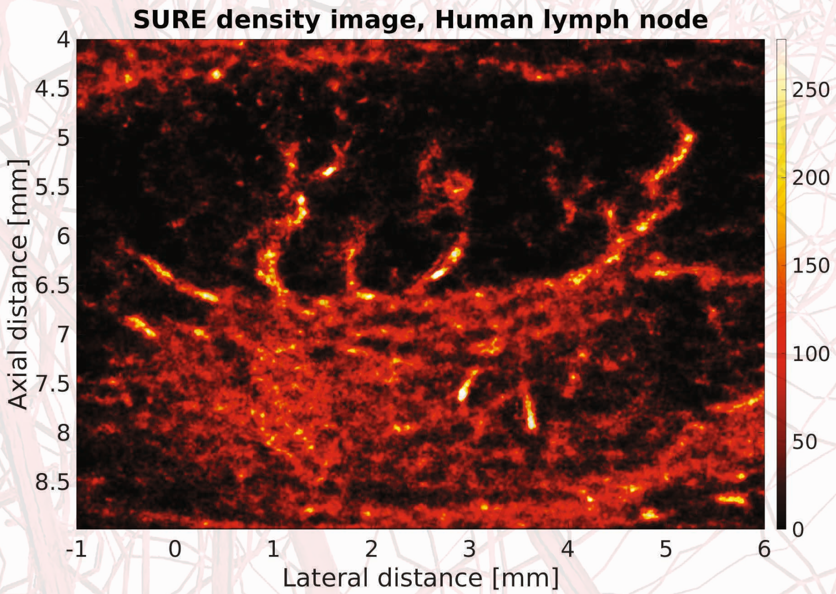
SURE image of the blood vessels in a healthy rat kidney. In the left lower corner an artery/vein pair is seen as a small and a large vessel running alongside each other from the center of the kidney towards the left side. Stretching towards the kidney surface are cortical radial arteries with a size of ~100 µm. The image is recorded over 1.9 sec without the use of contrast agents using erythrocytes as the tracking target.





SURE image of a healthy human lymph node recorded over 2 sec. The image shows the blood perfusion running in straight healthy blood vessels. This differentiates a healthy node from a diseased node, where the blood vessels will appear more irregular and tortuous and not only appear from the central hilus (center of image).

a detailed picture of the condition of a patient's microvasculature. "A computer detects the erythrocyte peaks and they are brought together to produce an image of the blood vessels. Then we can find out more about the blood flow, including the velocity and the direction it is flowing in," outlines Professor Jensen. This will provide a deeper picture of how much blood flows to different sites and organs within the body, which is an important indicator of their overall health. "For example, if more blood is flowing to a particular area of the brain then that often means there is more activity going on there, and the same goes for other organs," says Professor Jensen.

A variety of applications of the SURE approach are being explored in the project, for example in identifying kidney problems before they become more severe. This is a prominent issue, with the incidence of kidney problems set to rise in line with an increase in the number of people with diabetes. "We know that about 25 percent of diabetic patients will have kidney problems," explains Dr Charlotte Mehlin Sørensen, Associate Professor in the Department of Biomedical Sciences at the University of Copenhagen. However, it's not clear which diabetic patients will go on to develop kidney problems, and current clinical markers only show kidney problems when they are already at an advanced stage. "A technique that could show a decline in the function of the kidney, but before damage has actually happened, would be highly valuable," stresses Dr Sørensen.

Diabetic kidney disease

The project team are exploring the potential of the SURE approach in this respect, and they have already been able to show a decrease in vascular density in diabetic rats before the clinical markers showed that they had kidney problems. The hope is that this technique could help researchers understand the underlying mechanisms behind diabetic kidney disease, which Dr Sørensen says could then open up wider possibilities. "That could then pave the way towards finding new treatment targets for diabetic kidney disease," she says. Another area of interest in the project is knee injuries, which lead to increased blood flow to the affected area. "We're conducting a long-term experiment on knee tendons, looking at the microvasculature and blood flow into the tendons," outlines Professor Jensen.

A number of other applications are also the subject of investigation in the project, such as in diagnosing lymph node cancer, with work in this area ongoing. However, the full range of applications is by nature difficult to foresee, and depends to a large degree on the technical specifications of the SURE approach, which researchers are still striving to improve and refine. "We're pushing the boundaries of the SURE approach on several different levels. We are working on animal and clinical studies, while we are also developing ultrasound probes and doing the processing," explains Professor Jensen.

Highly specialized row-column probes are developed by Professor Erik Vilain Thomsen at the MEMS group at DTU. Advanced silicon fabrication techniques are employed to construct capacitve micro-machined transducers at DTU's clean room for silicon chips with up to a million elements. This will make it possible to translate SURE imaging to 3-D volumes. "The project is backed by a synergy grant, and involves collaboration between researchers in a variety of different fields, which enables us to tackle highly complex challenges," says Professor Jensen.

The scope of the project has also widened over time, for example in building a deeper picture of what the microvasculature looks like. The project's research is breaking new ground, so there isn't a clear basis for comparison, to validate images of blood flow in tiny vessels in the body. "We then need to go to other fields where they use very high resolution imaging techniques," says Michael Bachmann Nielsen, Professor in the Department of Clinical Medicine at Copenhagen University Hospital. This challenge was tackled by tapping into specialist expertise in micro-CT scans. "We put a contrast agent in the kidney of a rat, euthanized it and gave the kidney to our colleagues who work with micro CT techniques," says Professor Jensen. "We could see that images of the microvasculature from our SURE scan were the same as we could see with a micro-CT."

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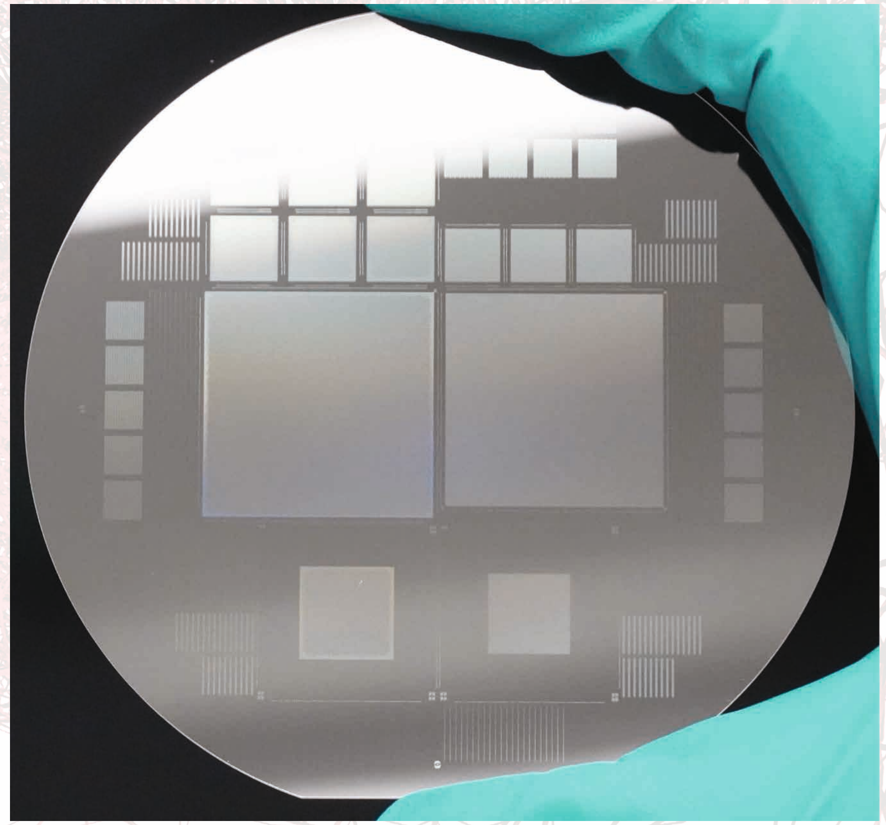

Silicon wafer with several capacitive micromachined ultrasonic transducers (CMUT) based ultrasound transducers fabricated in the SURE project. The two large arrays are row-column transducers with 512 rows and 512 columns having in total 262144 small sound emitters.

Bringing SURE to clinics

The long-term aim is to make the SURE approach available in clinics, and researchers are working to improve and refine the system while still retaining the key attributes of ultrasound, such as its interactive nature and its mobility. While the SURE approach involves a new scanning technique and some quite intensive data processing, with graphics processing units (GPUs) running in parallel to provide computational power, this doesn't lead to any changes in the outward appearance of the ultrasound scanner. "The scanner that the patients see will be the same," says Professor Jensen. A scanner can be essentially rolled to a patient's bedside, and it will rapidly provide a picture of their microvasculature. "You can take in a patient, put the probe on, push a button and see the result. We are trying to preserve the interactive nature of ultrasound," continues Professor Jensen.

This work also helps to extend the range of ultrasound imaging, with the project team looking to open up new possibilities for clinicians. Access to a wide range of imaging techniques helps clinicians understand the condition of individual patients, and Professor Jensen says ultrasound is an important tool in the bag. "Ultrasound is very functional. You can look at flow, you can see whether things are hard or soft, you can look from different viewpoints. It's a really good interactive tool," he stresses.

Breaking new ground in research requires a large team of very talented people from different research fields. The SURE team on their annual summer meeting where mile stone and project plans are discussed.

SURE

SUper Resolution ultrasound imaging using Erythrocytes

Project Objectives

Current ultrasound techniques are not able to provide a picture of the microvasculature, the smallest blood vessels in the human body. The team behind the SURE project aim to overcome existing limitations by developing a new imaging approach, using red blood cells as targets, which will allow clinicians to see vessels down to a size of 25 micrometres, opening up new possibilities in diagnosing different conditions.

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Project Partners

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Charlotte Mehlin Sørensen, Erik Vilain Thomsen, Michael Bachmann Nielsen, and Jørgen Arendt Jensen (left to right)

Charlotte Mehlin Sørensen is an Associate Professor in the Department of Biomedical Sciences at the University of Copenhagen. Her research focuses on kidney hemodynamics, diabetic kidney disease and incretin hormones.

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