Multi-parametric Ultrasound Imaging and Reconstruction with Deep Learning

Motivation: Deep learning (DL) has been a game changer in many signal processing and computer vision problems, and has been successfully applied for many applications involving regression and classification, and its pixel-wise spatial extension, semantic segmentation; e.g., for decision support and anatomical segmentation in radiology. Nevertheless, DL has so far had limited utilization in some problem settings with fundamentally different theoretical foundations, such as image reconstruction. Typical imaging settings involve very complex physical interactions, often with non-local, non-uniform support, which are difficult to capture using purely black-box DL models. Combined with the inherent lack of data for supervised training for these tasks, conventional black-box DL models are often subpar to traditional physics-based hand-crafted mathematical models in image reconstruction.

Goal: In this project, we aim to develop methods to combine and integrate mathematical models and physical understanding into DL systems, in a seamless and theoretically-grounded manner. This will be developed for ultrasound imaging, which involves physical interactions at multiple levels of tissue structure. With this, the aim is the ultrasound-based multi-parametric quantitative imaging of tissues at multiple levels, from macro to micro; which will allow for differentiating tissues and pathology much more precisely. This will be applied on a highly relevant clinical problem, staging fatty liver disease.

Ultrasound is a non-ionizing, portable, low-cost, and real-time medical imaging modality; therefore, commonly used for many applications in the clinic. It operates by sending acoustic waves into the tissue, and converting the received echo signals into images. Typical clinical ultrasound images contain grayscale maps of reflected echo *magnitude*, which only has a relative meaning and is not an absolute, reproducible, *quantitative* information. So, although informative for some tasks, these are not useful for other clinical tasks, e.g., for differential diagnosis of cancer or staging fatty liver disease. Ultrasound data, nonetheless, carries further valuable information that may be extracted using novel methods. For instance, we presented the assessment of microstructural tissue content that scatter ultrasonic waves, based on an inverse-problem formulation[1] and DL-based regression[2]. Alternatively, a macrostructural parameter, the tissue speed-of-sound (SoS), was imaged[3] from differential measurements of acoustic arrivals viewed from different directions, by registering these images and then approximating the physics as a linear system, to create images by solving an inverse problem of image reconstruction. SoS images yield quantitative measurements. For some applications, e.g. differential diagnosis of breast cancerous, these image tissue compositions with a higher contrast than conventional ultrasound; cf. Fig(left). We demonstrated preliminary clinical uses of our SoS imaging for breast cancer[4], breast density (for risk assessment), and sarcopenia (age-related muscle degeneration). These however use macro information so far. Furthermore, they use hand-crafted mathematical models. This project aims to describe micro- and macro-level interactions with unified models that are jointly estimated using DL techniques; aiming multi-parametric liver imaging.

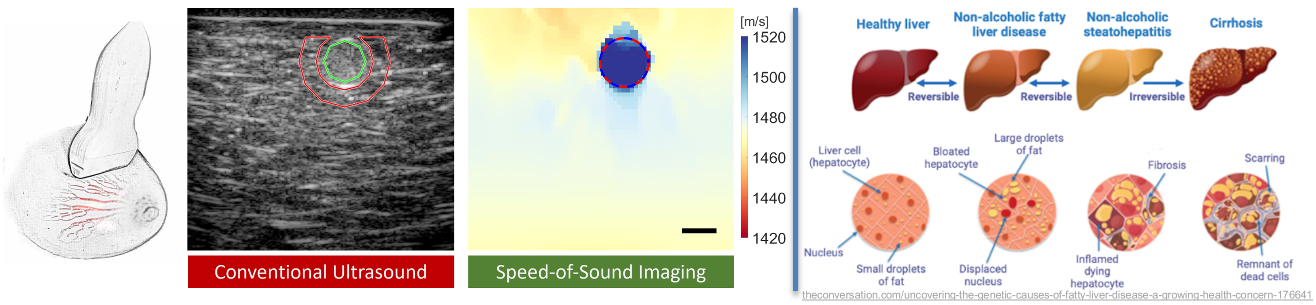

Fig.: Speed-of-sound imaging[5] (left) and the progression of NAFLD (right).

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[1] Mattausch, Goksel: "*Image-Based Reconstruction of Tissue Scatterers Using Beam Steering …*", *IEEE Trans Med Imag*, 2018.
[2] Zhang, Vishnevskiy, Goksel: "Deep Network for Scatterer Distribution Estimation for Ultrasound …", *IEEE Trans UUFC*, 2020.
[3] Sanabria, Ozkan, Rominger, Goksel: "Spatial Domain Reconstruction for Imaging Speed-of-Sound ...", *Physics in Med & Biology*, 2018.
[4] Ruby et al.: "Breast Cancer Assessment with Pulse-Echo Speed of Sound ...: Proof-of-Concept", *Investigative Radiology*, 2019.
[5] Rau, Schweizer, Vishnevskiy, Goksel: "Speed-of-sound imaging using diverging waves", *IJ Comp Asst Radiology Surgery*, 2021.

Fatty liver disease is caused by abnormal and excessive accumulation of fat (steatosis) in the liver. Non-alcohol related fatty liver disease (NAFLD) is the most common cause of chronic liver disease worldwide, and affects 1-out-of-3 adults in the US. Exact causes of NAFLD are unknown, but are attributed to metabolic conditions (diabetes, high cholesterol, high blood pressure), some medications or steroids, or being overweight (e.g., a high fat diet). A moderate amount of fat build-up in the liver for a short time, called simple steatosis, is often benign and reversible, e.g., with simple life-style changes and medication adjustments. However, a continuous fat build-up damages the liver, causes inflammation, and the typical repair processes replace the liver tissue with non-functioning scar tissue (fibrosis), cf. Fig(right). NAFLD can eventually progress to cirrhosis, and is a precursor of liver cancer.

State of the art in diagnosing fatty liver: As one of the most common diseases of our age, and one that can be likely reversed with early detection, NAFLD largely lacks simple early-diagnostic tools that can be applied in larger populations, e.g., for screening or follow-up. Liver biopsy involves inserting long needles, and is thus invasive with risk of complications, and can only sample point-wise at a few locations. Proton density fat fraction using magnetic resonance imaging (MRI) is the most accurate non-invasive method, but it involves high costs, low accessibility, long scan times, and inability to use on patients with metal implants. Conventional ultrasound provides only qualitative visual assessment and lacks sensitivity especially in the low-grade NAFLD, for which early-detection can make the most difference. Attenuation of ultrasound in the liver and its kidney-normalized version (known as hepatorenal index) have been used as semi-quantitative metrics but with several limitations. Other ultrasound methods such as elastography can only diagnose later-stage fibrosis, thus often too late for early-stage detection before steatosis and inflammation cause irreversible liver damage.

Conventional image reconstruction, i.e., going from acquired raw sensor data to spatial images of anatomy, rely heavily on a good understanding of underlying physics, a successful mathematical modeling, and an effective numerical solution, for the particular imaging modality. For example, in ultrasound imaging, acoustic waves interact with tissues both at a macro level (e.g., with organ boundaries) that causes refractions, reflections, speed and attenuation changes; and meanwhile also at a micro level (with sub-wavelength particles, e.g., cells, large proteins, muscle fibers, and calcifications) which causes scattering and other effects. In SoS imaging, for instance, mis-registrations of scattered echo from micro-structures are used to infer the speed in bulk tissue at a macro-structural level. A unified modeling of micro- to macro-level interactions and their joint parameter estimation would allow for comprehensive multi-level quantification of tissues.

Deep Learning can provide a promising solution for the above, however conventional black-box approaches are not necessarily suitable for image reconstruction problems. Furthermore, an in-vivo ground-truth, i.e., the actual precise spatial distribution of a tissue parameter in human body, is often unknown, as an obstacle for supervised learning in image reconstruction. Learning from synthetic simulations can be an alternative, however for complex imaging processes, there is often no comprehensive simulation system available to fully represent the imaging physics, the imaging hardware, and the potential in-vivo parameter distributions. As training from simulations do not generalize well to real data, addressing domain shift via adaptation methods also become important.

End-to-end learning of black-box functions to map sensor measurements to image reconstructions require supervision with large numbers of training samples, and are sensitive to changes in data distributions, i.e. domain shift. With variational networks (VNs) for loop unrolling, neural network layers are used to encode iterations of a general form of inverse problem, to learn the parameters that would otherwise be hand-tuned, e.g., suitable regularizers, preconditioners, numerical choices, etc. We demonstrated this for the first time in ultrasound and X-ray computed tomography (CT)[6,7], and used multiple simulation domains to increase generalizability to real data[8]. Nevertheless, it is yet an unsolved problem to develop readily generalizable methods for learned image reconstruction.

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[6] Vishnevskiy, Sanabria, Goksel: "Image Reconstruction via Variational Network for ... Sound-Speed Imaging", *MLMIR,* 2018.
[7] Vishnevskiy, Rau, Goksel: "Deep Variational Networks with Exponential Weighting for Learning Computed Tomography", *MICCAI,* 2019
[8] Bernhardt, Vishnevskiy, Rau, Goksel: "Training Variational Networks with Multi-Domain Simulations ...", *IEEE TUFFC,* 2020.

Approach: *For staging NAFLD precisely with a safe, low-cost, accessible ultrasound solution, the aim is to develop model-informed DL techniques*. For that, mathematical models of relevant acoustic and imaging phenomena that are known and to be developed will be parametrized in ways that can be learned using developed DL-based paradigms. In essence, restricting the parameter search space of learning algorithms on physically-plausible manifolds can allow robust solutions with minimal training, that can also generalize well. Also, by connecting micro- and -macro-structural models, multi-dimensional parameters of different phenomena (and hence multi-parametric images) will be estimated coherently within the same framework. We will investigate theoretical guarantees of clinical concern, such as learning bounds and confidence/uncertainty in multi-parametric reconstructions.

Significance: Methods developed for ultrasound can find applications also in other fields, such as X-ray and PET imaging, which employ tomographic image reconstructions of similar nature. Other imaging modalities also share some of the fundamental challenges tackled herein. In particular, a linear measurement / forward model for tomography only assumes generic (positive definite) matrices, where several other popular computer vision problems can be written as its special cases; e.g., magnetic-resonance imaging (MRI) using a unitary (discrete Fourier) transform; image super resolution using a fat block-diagonal matrix; and image denoising using identity transform. Hence, this work will develop solutions potentially applicable in other imaging and inverse-problem settings.

Interdisciplinarity: This project is a collaboration between the Department of Information Technology, and the Radiology section at the Department of Surgical Sciences at the university and the university hospital. While the former brings in theoretical and technical expertise, the partners from the latter are clinical experts in medical imaging, and in particular NAFLD[9]. With theoretical, computational, numerical, and clinical aspects, this project is a multi-faceted and interdisciplinary enterprise. Image reconstruction problem is rooted in mathematical foundations of information theory, signal processing, image analysis, inverse problems, optimization, function analysis, and statistics.

PhD student with a master's degree in Mathematics, Computer Science, Engineering, Image Analysis, Machine Learning, or a related field is sought, with a background and interests in mathematical foundations as well as experimental and programming aspects. A good command of optimization, learning-based systems, computer vision, and/or signal processing are preferred.

Advisors, Host Institute, and Funding

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The student will be hosted at the Image Analysis Unit within DoIT, while being cross-affiliated at the Medtech Science and Innovation Centre (https://medtech.uu.se/), facilitating the clinical translation of the project results. The position is co-funded 50% by CIM and 50% by DoIT.

[9] Alsaqal, Hockings, Ahlström, …, Ebeling Barbier: "The Combination of MR Elastography and Proton Density Fat Fraction Improves Diagnosis of Nonalcoholic Steatohepatitis", *J Magnetic Resonance Imaging,* 2022.