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Analysis of focus shift speed for in vivo 3D corneal confocal microscopy

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Corneal confocal microscopy (CCM) allows non-invasive in vivo imaging of corneal tissue on a cellular level. For CCM we use the Heidelberg Retina Tomograph (HRT) and the Rostock Cornea Module (RCM; both Heidelberg Engineering GmbH, Heidelberg, Germany) which is originally equipped with a manual focus control. We previously developed a modified RCM_{mod}, using a computer-controlled piezo actuator to facilitate automated, fast and precise closed-loop focal plane control. With a total travel range of 500 µm, the RCM_{mod} enables expanded volume scans for 3D corneal confocal microscopy (3D-CCM) by shifting the focus with constant speed v_{focus} while simultaneously recording the image stacks with the maximum HRT frame rate of 30 fps. Decreasing v_{focus} leads to higher depth resolution of the reconstructed volume but also increased examination time. In order to minimise the patient's strain the recording time of the image stacks should be minimised by maximising v_{focus}.
For volume reconstruction, the recorded images have to be aligned. To this end, we developed special-purpose image registration algorithms, which also analyse and correct the motion induced distortions in the CCM images. This image registration process defines the upper limit $v_{focus,max}$ of the focus shift speed for 3D-CCM. If $v_{focus} > v_{focus,max}$, the reliability of the registration of consecutive CCM images decreases rapidly and the volume reconstruction fails. To evaluate $v_{focus,max}$ we analysed a total of 23,382 consecutive image pair registrations from image stacks from 11 volunteers with different values for v_{focus}. For the evaluated settings of v_{focus} = 30, 60, 120, 240, 360 and 480 µm/s we measured registration failure rates of 2.4, 2.2, 4.4, 57.3, 97.5 and 99.5 %, respectively. The failure rate of 2.4 % and 2.2 % at the two slowest speeds are mainly caused by unavoidable eye movements. While the failure rate is less than 4.4 % for $v_{focus} \leq 120$ µm/s, it increases dramatically for $v_{focus} \geq 240$ µm/s. As a result of the presented analysis, we recommend a maximum focus shift speed of 120 µm/s for reliable 3D-CCM with the HRT.

In vivo myocardial tissue characterization of all four chambers using high-resolution quantitative MRI

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Fibrosis is considered to play a role in various cardiomyopathies, such as arrhythmias. Late gadolinium enhancement cardiovascular magnetic resonance imaging (MRI) can visualize fibrosis, but requires administration of contrast agents and only focal fibrosis can be detected. Quantitative tissue characterization using native T_1 mapping can be used to assess fibrosis in the left ventricle non-invasively. Its main challenge is cardiac motion which strongly limits the achievable spatial resolution and hence does not allow to resolve small structures, as the right ventricle and atria. We demonstrate the feasibility of a multi-parametric approach, that provides cardiac motion information and native T_1 maps. The motion information is utilized to optimize data selection for T_1 mapping to ensure high-resolution (1.0x1.0 mm² in-plane) T_1 mapping of all four chambers.
Three healthy volunteers were scanned at a 3 Tesla scanner (Siemens Healthineers, Erlangen, Germany). Image acquisition using a flexible radial spoiled gradient echo scheme with multiple inversions was performed during a 25s breathhold. In a first step, cardiac motion-resolved images were reconstructed and the quiescent phase of the heart was selected for each subject separately. This optimizes motion-free data selection for T_1 mapping instead of using a predefined acquisition window. In a second step, T_1 maps were obtained from the same data by iterative model-based reconstruction which allows for image reconstruction of highly undersampled data. T_1 values were assessed by manually drawn region-of-interests in the myocardium.
In the T_1 maps of all volunteers the myocardium of the entire heart can be identified and T_1 of the atria and right ventricle were comparable to septal T_1 in the same subject.
The feasibility of native T_1 mapping of the entire heart was demonstrated for the first time. The approach could possibly serve as a non-invasive tool for myocardial tissue characterization of the entire heart in patients with cardiomyopathies.

A 3D Resolution and Aberration Test Target Design for Fluorescence Microscopic Imaging

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Fluorescence microscopic imaging has found extended applications in life science and medicine. Among different modalities, confocal laser endomicroscopy (CLE) is most promising for in-vivo diagnostic imaging, since it allows intraoperative in-situ tissue morphology at cellular resolution. These compact systems enable a field of view of less than half square millimeter with a fiber-based miniaturised probe. Due to less sophisticated optical design and small imaging volume, a test target that can assess the resolution and image quality of such systems becomes necessary. Currently there are only a few test targets exiting fluorescence contrast that is applicable for fluorescence imaging systems. Moreover, there is no test target that can measure the axial resolution of an imaging system when the axial resolution is mostly interested. We have extended the 2D bar pattern in 1951 USAF test chart to 3D structures. Together with other 3D structures, we present here as a first result that our test target can simultaneously assess the resolution in lateral and axial planes, also aberrations like field curvature and distortion can be assessed. The test structures are produced by two-photon polymerisation on microscope slides. And a fluorescence emission of the used photoresist can be excited at 488 nm. Beside research purpose, end users can use this test target to monitor and check the performance of an imaging device, while manufacturers can implement it in the quality control phase. In addition, for other fluorescence microscopic imaging modalities working in the corresponding wavelength range, this method could be applied to produce suitable test target.

Sensitivity Enhancement in Magnetic Particle Imaging

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Magnetic Particle Imaging (MPI) has shown great potential in temporal and spatial resolution. In addition, a high sensitivity is wanted to either allow for cell tracing or to improve the general image quality for higher iron dose. In theory, MPI should provide an exceptional sensitivity due to the large magnetic moment of the tracer used. However, the theoretical limit is still not reached by the instrumention and particle system. In this work a custom receive chain was designed together with a mouse sized receive coil that can be mounted within the 12 cm bore of the preclinical MPI Scanner located at the UKE in Hamburg. The receive coil is build following a gradiometer design consisting of a measurement coil and two cancellation coils to supress the direct feedthrough. With the setup an *in-vitro* analysis was performed to define the sensitivity level of the system, which were found at 5 ng iron content in 1 μl. With this knowledge an *in-vivo* measurement of a healthy mouse model was performed showing the inflow of a bolus in the heart of a mouse at a very low dose of only 512 ng iron in 10 μl. Using a higher iron dose it was possible to image all phases of the heart beat as well as the lung veins. In addition, one can see the phase shift of the atrium and ventricle of the heart when inspecting the time series of the respective region of interest. The results mark the lowest iron dose imaged with MPI *in-vivo* so far and in turn demonstrate the capabilities of the MPI technology.

Smartphone-based low-cost microscope with monolithic focusing mechanism

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Microscopy enables fast and effective diagnostics. However, its functionality is not accessible to everyone. Smartphone-based low-cost microscopes could be a powerful tool for diagnostics and educational purposes. Current smartphone-based microscopy approaches struggle with high cost, poor image quality and/or insufficient smartphone compatibility. In this paper, a very feasible and effective low-cost microscope is presented which addresses these issues. According to a conventional setup of a digital microscope, our device consists of an objective lens (formed by an inverted external smartphone lens) and a tube lens plus sensor (formed by the smartphone camera system). Due to the good cost-benefit ratio, the optical module of the Apple iPhone 5s was selected as the objective lens. To minimize cost, a monolithic foldable structure is designed for production by injection molding. The planar microscope can be folded into a spatial structure which is connected by seven dovetail joints. Using solid-state hinges and two leaf spring elements, a parallel guidance system of the specimen slide is achieved. The design has a high order of functional integration, minimizing the number of components, while still enabling micrometer focusing accuracy. Additive manufacturing was used to produce a fully operational prototype. A wide variety of current smartphone models can be clamped in different positions, depending on the relative position of their camera. In addition, illumination with the internal flash is possible in case of poor light situations. The microscope system costs a total of 29.08 € (Inc. tax) if 3D printed, including material costs, electricity costs and the depreciation of the printer. However, if produced by method of injection molding (10,000 units) the overall costs are estimated to be only 8.24 € (Inc. tax). In addition, the planar and lightweight design allows all components of the microscope to be shipped in a standard DIN A4 envelope.

New Tracer for Magnetic Particle Imaging - SPIONs encapsulated in RBCs

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Superparamagnetic iron oxide nanoparticles, so called SPIONs, are used as tracers in medical imaging, e. g. for magnetic particle imaging (MPI) or magnetic resonance imaging (MRI). Since the half-life time of the SPIONs in the bloodstream is quite short because they are quickly absorbed by the reticuloendothelial system (RES), the particles are introduced into human red blood cells (RBCs) to increase their half-life time in the blood circulation. The hypotonic swelling procedure is used to incorporate the particles into the RBCs. Before the SPIONs are introduced into the RBCs, they are fluorescent labelled. To evaluate the result transmission electron microscopy, magnetic particle spectroscopy and fluorescence microscopy are used. Fluorescein isothiocyanate and rose Bengal were chosen as fluorescent dyes because their biocompatibility is guaranteed. The results suggest that the method hypotonic swelling can be used to successfully introduce the nanoparticles into RBCs and that the magnetic properties of the particles which are necessary for imaging are not influenced.

Monte-Carlo Simulation of Light Tissue Interaction in Medical Hyperspectral Imaging Applications

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In Hyperspectral imaging (HSI) applications in medicine a uniform illumination is used and the illuminated surface is recorded with a camera with spectral resolution. Unlike in tissue reflectance spectroscopy with fixed light source – detector distances, in HSI the contribution of the influence of different tissue layers to the absorption signal is poorly understood.
In this work a Monte-Carlo simulation is implemented which simulates the specific HSI illumination and detector geometry. A four-layer tissue model with variable blood volume fraction and oxygen saturation is used. With 5 % blood volume fraction and 75 % oxygen saturation, SaO2, of surrounding tissue, saturation changes in 1 mm and 2 mm deep layers lead to a change in remission of up to 3 % and up to 1 % respectively. Changes in deeper layers are hardly detectable. Further simulations will be focused on different tissue models as the depth resolution is expected to vary with tissue parameters like blood volume fraction.