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Diagnostic Capabilities of a Smartphone-Based Low-Cost Microscope

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Introduction

Microscopy enables fast and effective diagnostics. However, in many resource-limited regions it is not always accessible. Smartphone-based low-cost microscopy has the potential to compensate for this lack. In this paper, the assessment of the resolution that can be achieved by a smartphone-based microscope and the resulting diagnostic applications are presented.

Methods

The smartphone-based microscope used in this paper, consists of an inverted smartphone camera lens in front of a smartphone camera. Four different lenses with different focal lengths are examined. The resolution and the field of view (FOV) of each lens is determined by using a MIL-STD-150A USAF resolution test target and a 1 mm calibration target. A list of potentially diagnosable diseases was compiled from a literature review. By comparing the size of the pathogens to the resolution of the microscope a list of likely diagnosable diseases was created.

Results

The chosen lens achieved an average resolution of 1.23 µm and a FOV of 1.12 mm^2, thus providing a reasonable trade-off between both parameters. This resolution results in a wide range of potential applications. An overall number of 26 diseases was found that can be diagnosed with the microscope. Mainly parasitic diseases were diagnosable due to the relatively large size of their pathogens, such as Malaria and numerous neglected tropical diseases (NTD). While Malaria shows a pathogen size of 1.5 µm, some NTDs show pathogen sizes of approximately 300 µm. Furthermore, diseases like sickle-cell-anemia or hematuria with structural sizes of 7.5 µm are diagnosable.

Conclusion

In comparison to a conventional microscope, the resolution of a smartphone-based microscope is still considerably limited, thus resulting in lower diagnostic capabilities. However, the use of a smartphone-based microscope still enables a range of diagnostic applications, especially considering common diseases of resource-limited regions, while still having remarkably low costs for manufacturing and shipping.

Implant dependent local weighting for iterative CT-image reconstruction

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Introduction

High-density objects cause artifacts that appear as bright and dark streaks in the image and decrease the diagnostic value. However, not all image voxels are affected equally by these objects. Depending on the size and shape of the object, projections from different directions are affected differently. This information can be included in iterative reconstruction approaches by calculation of an implant dependent weighting matrix, which can be integrated into different regularization strategies.

Methods

Using existing measured projections, the contour of the object is calculated for each direction. Based on geometric correlations, an opening angle can be calculated for all voxels on the central beam of the respective projection. The opening angle is calculated by determining the distance of the corresponding voxel to the center of the object and the distances of the object center to the points on the contour of the object from the corresponding projection image. By repeating this for different directions, an angle value is calculated for each voxel in the image. To save calculation time, not all possible directions need to be considered as angle values can be interpolated for some voxels.

Results

A weighting matrix is calculated for different object shapes and sizes. For all objects, the calculated angle decreases with increasing voxel-object distance. However, differences in the distribution of the calculated angle values around the object depending on its shape and size can be observed.

Conclusion

The results show that by calculation of a weighting matrix depending on the metal object a more precise weighting of the regularization is possible for different image voxels depending on their relative position to the object.

Extension of the Stoichiometric Calibration of CT Hounsfield Values upon Metallic Materials

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Introduction

Today patients with metallic implants undergoing radiotherapy potentially suffer from inaccuracy due to the implant. To ensure a precise treatment plan an accurate relation between computer tomography (CT) Hounsfield values and the electron density of elements and material mixtures is indispensable.

Methods

In order to extend the stoichiometric calibration approach known for tissue-like materials to the regime of metallic materials, the basic physical equations as well as approximations in the parametrization and fitting are carefully reviewed. CT images of a standard calibration phantom and pure metallic samples up to the atomic number $Z = 29$ were acquired for various energies. Hounsfield values were determined on an extended Hounsfield scale which allows the mapping of material having high atomic number Z.

Results

It is found that from basic physics an empirical factorization of the cross–sections into a function of Z and a function of photon energy E is not allowed over a wide range of Z. Specifically, the parameterization for tissue like materials cannot be prolonged to materials with high–Z. Thus, the calibration is subdivided into regions of materials and the accuracy is quantified in each region.

Conclusion

The accuracy and robustness depends, among others, on the knowledge of the X–ray photon spectra, the segmentation of the material samples, e.g. beam hardening, and the empirical parameterization of the linear–attenuation coefficient.

Compact Microscope Module for High-Throughput Microscopy

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Introduction

Microscopy is a prevalent used tool in research and science. However, it is still cost and resource consuming. Low-cost approaches already led to promising results for simple recordings of samples on conventional specimen slides. A small and low-cost microscope module would enable basic microscopy for various research projects/setups. In this paper, a Compact Microscope Module (CMM) for versatile application is presented. As a first application, the usage in a High-Throughput Microscope (HTM) for scanning samples in microtiter plates is shown.

Methods

The optical setup of the CMM consists of an inverted smartphone camera lens and a Raspberry Pi camera module (Raspberry Pi Foundation, UK). While both lenses have focal lengths in the same order of magnitude, only limited optical magnifications can be achieved. However, a digital magnification is enabled due to the high number of camera pixels. Two different smartphone camera lenses were used, enabling adaption of resolution, field of view (FOV) and working distance for different applications.

Results

A CMM was developed with dimension of 9 x 9 x 11 mm^3 providing a resolution of 2.46 µm while enabling a FOV of 3.5 mm^2 and a working distance of 0.3 mm. The electronics needed for controlling the camera are placed further back to ensure a compact size of the microscope module. As a first application, the use of eight combined microscope modules in a HTM was accomplished, enabling scanning of a 96-well microtiter plate with a resolution of 3.48 µm, a FOV of 21.2 mm^2 and a working distance of 1.0 mm.

Conclusion

A Compact Microscope Module was developed to enable versatile use of microscopy in research projects. This was demonstrated by successfully using the module for an HTM. However, in case of a larger required working distance, a remarkable trade-off in image resolution occurred which should be addressed in further investigations.

Validation of iterative CT reconstruction by inter and intra observer performance assessment of artificial lung foci

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Introduction

We investigate the suitability of statistical and model-based iterative reconstruction (IR) algorithm strengths and their influence on image quality and diagnostic performance in low-dose computer tomography (CT) protocols for lung-cancer screening procedures. We evaluate the inter- and intra-observer performance for the assessment of iterative CT reconstruction.

Methods

Artificial lung foci shaped as spheres and spicules made from material with calibrated Hounsfield units were pressed within layered granules in lung lobes of an anthropomorphic phantom. Adaptively, a soft-tissue- and fat-extension ring were attached. The phantom with foci was scanned using standard high contrast, low-dose and ultra low-dose protocols. For reconstruction the IR algorithm ADMIRE at four different strength levels were used. Two ranking tests and Friedman statistics were performed. Fleiss κ and modified Cohen's κ were used to quantify inter-- and intra--observer performance.

Results

In conjunction with the standard lung kernel BL75 radiologists evaluated medium to high IR strength, with preference to S4, as suitable for lung foci detection. When varying reconstruction kernels the ranking became more random than with varying phantom diameter. The inter-observer reliability shows poor to slight agreement expressed by $\kappa < 0$ and κ= 0-0.20. For the intra-observer reliability non-agreement with κ_{ney}= 0-0.20 and moderate agreement with κ_{ney}= 0.60-0.79 for the first ranking test, and almost perfect agreement with $\kappa_{ney} > 0.90$ for the second ranking test was observed.

Conclusion

In conclusion, our validation suggests radiological preference of medium to high iteration strengths, especially S4, for lung foci detection. An investigation of the correlation between diagnostic experience and the subjective perception of IR reconstructed CT images still needs to be investigated.

Increased Phase-Amplitude Coupling in Parkinson's Disease: Evidence from Source Localized Electroencephalography

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Introduction

Enhanced phase-amplitude coupling (PAC) between beta (13-30Hz) and broadband gamma (50-150Hz) oscillations has been suggested to be a biomarker of Parkinson's disease (PD). It can be measured with non-invasive scalp EEG. However, the spatial origin of PAC is still obscure, limiting the possible use for understanding and treating PD.

Methods

We recorded 5min EEG (64-channels) from 19 PD patients and 20 age and sex matched healthy controls at rest. EEG signals were then projected to the individual cortical surfaces by a least-square minimum variance beamformer. Twenty-six regions of interests (ROIs) over the whole brain were defined according to Human Connectome Project atlas. For each ROI, independent component analysis (ICA) was applied for separating temporally independent components. Pairwise PAC values were calculated by Kullback-Leibler-based modulation index (MI) among the ICA components and then mean MI weighted by the percent variances of ICA components was computed in each ROI.

Results

Compared to healthy subjects, excessive beta-gamma PAC was detected in dosalateral prefrontal cortex (DLPFC), premotor cortex (PMC), primary motor cortex (M1), primary somatosensory cortex (BA3) and primary somatosensory complex (BA1&2), contralateral to the more symptomatic hand side of PD patient. Besides, enhanced PAC was presented among ICA components from identical, but also from the interaction between different components. Importantly, in the regions of PMC, M1, BA3 and BA1&2, the PAC strengths from the interaction between different components were correlated with the clinical severity, as indexed by the UPDRS III hemibody scores.

Conclusion

Findings suggest that enhanced PAC is extended over several brain regions involved in motor control, and is not exclusively tied to brain regions with monosynaptic projections to the subthalamic nucleus. Besides, the results also suggest that abnormal PAC from pathological interaction among different independent networks play an essensial role in generating Parkinsonian motor impairment.

EEG beamformer for correlated brain sources localization in realistic head models

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Electroencephalography (EEG) is a non-invasive technique for recording electric potentials with electrodes placed on the scalp. Adaptive beamformers have emerged as an effective way to solve the inverse problem where the neuronal current sources are localized from the measured EEG signals, which are generated by the current sources themselves. Due to the impractical assumption of uncorrelated brain sources in conventional beamformers, it is essential to develop a beamformer capable of localizing correlated brain sources. In this work, we have examined the performance of a multiple correlated sources model beamformer (MCSMB) for perfectly correlated brain sources using a realistic head model constructed from an MRI image.

To accurately incorporate the effects of the head anatomy on EEG signals, the finite difference method is used to solve the governing Poisson's equation for a realistic head model constructed from an MRI image. Conventional beamformers fail to localize multiple brain sources with high correlation coefficients. The MCSMB is capable of identifying correlated sources under low signal-to-noise-ratio (SNR) conditions. The number of active brain sources is input to the beamformer to initiate the brain-source searching. A recursive algorithm is then applied by first computing the lead field matrix for the region of interest, followed by computing the normalized output power for every node inside this region. The source location is obtained as the global maximum of the output power. The region of interest is then updated by imposing a hard null for constraining the source location obtained, and the recursive algorithm is invoked again to obtain the next source location.

The realistic head model constructed from an MRI image with 177×240×256 voxels and a resolution of 1 mm is used to evaluate the source localization accuracy for the MCSMB along with the conventional beamformers. The dipole localization error, as well as the power distribution maps, are used to demonstrate the higher accuracy of MCSMB in localizing correlated sources.

Determination of the Cavitation Pressure Threshold of Focused Ultrasound on Sonosensitive and Biocompatible Nanoparticles for Drug Delivery Applications

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Introduction

Nanoparticles are of interest as carriers of pharmaceutically active ingredients, which can be released in certain target areas ("drug delivery"). One application is localized chemotherapy of tumor diseases which reduces unwanted side effects. Nanoparticles can utilize the so-called EPR effect (Enhanced Permeability and Retention) because of their small size, as opposed to larger microbubbles. This effect could lead to a stronger penetration into the tumor tissue. “Sonosensitive” nanostructures allow the local release of drugs by focused ultrasound (FUS) via the effect of inertial cavitation (IC). So far, IC could be stimulated on sonosensitive nanoparticles of suitable size at low ultrasonic frequencies only, which do not permit sufficient focusing limited to the target tissue region.

Methods

We designed new poly-L-lactid acid particles (spheres and capsules) with diameters around 120 nm, which show IC also at higher, well focusable ultrasound frequencies (0.5 – 1 MHz). This can be verified by measuring the acoustical cavitation noise emission. One aim of our project is now to optimize the FUS operation towards efficient cavitation activity and optimal drug release with, at the same time, minimal thermal and mechanical exposure of the tissue. This includes a proper design of the focused ultrasound signal properties like waveform, duration, spectrum, level, etc.

Results/Conclusion

For minimizing the risk of tissue lesions caused by mechanical effects, it is important to instigate IC at moderate peak rarefaction pressure amplitudes. We determine the cavitation pressure threshold by calculating the standard deviation (STD) of the cavitation activity at various peak rarefaction pressures. The maximum STD might be a reliable value for indicating the cavitation threshold. We will present the investigation of the cavitation pressure threshold of sinusoidal burst signal sequences for cavitation stimulation at different frequencies.
Future measurements and investigations will help to further confirm this approach and will also include other waveforms.

Preliminary Simulation and Characterization of Capacitive Micromachined Ultrasonic Transducers for Targeted Cell Ablation Applications

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Introduction

Capacitive Micromachined Ultrasound Transducers (CMUT) is an evolving technology which holds promise for non or minimally invasive diagnostic and therapeutic procedures. Compared to their bulk piezo based counterparts, CMUTs can offer superior performance in terms of bandwidth and self-heating. Furthermore, CMUTs are manufactured using silicon fabrication technologies, thus, offer a wealth of options to the developers for miniaturization, batch processing and monolithic integration with the driving electronics. Although medical imaging remains the mainstream application, this technology could potentially be used in therapeutic applications such as cell ablation if sufficient thermal dose can be obtained. In this paper, we present the design and fabrication process of a single array unfocused CMUT and report on the simulation and characterization results to evaluate ultrasound induced heat.

Methods

The fabrication technology was based on silicon direct bonding of two individually processed wafers: membrane and cavity wafers. The fabricated devices were diced from the bonded pair (after membrane release) and mounted either on test PCBs or packages for characterization. To measure the acoustic pressure an acoustic test setup was arranged using a calibrated hydrophone. The measurements were conducted with the devices immersed in liquids. Pressure field, pressure intensity and temperature range were simulated assuming a tissue-like layer as the target and a coupling medium between the device and the tissue.

Results

Since the devices were unfocused, achieving a so-called hot spot in the pressure field proved to be challenging. The measured pressures at distances of 20 mm were below 15 kPa. The simulation results showed some minor degrees of temperature rise.

Conclusion

This work served as the first step to acquire an adequate understanding of the fabricated CMUTs' performance for ultrasound induced heat therapeutic applications. Improvements in terms of the device output pressure and focusing mechanisms will be considered in the next steps to increase the performance.

In Vivo Study on Magnetomotive Ultrasound Imaging in the Framework of Nanoparticle based Magnetic Drug Targeting

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Magnetic Drug Targeting is a cancer treatment technique that enables local chemotherapy: chemotherapeutic drugs are bound to magnetic nanoparticles, which can be accumulated in the tumor area by employing an external static magnetic field. To control the particle concentration in the cancerous tissue, an imaging system to monitor the particle accumulation is required. Unfortunately, the common ultrasonic pulse-echo imaging modes are not capable of displaying nanoparticles due to their weak backscattering. Therefore, an alternative imaging mode, called Magnetomotive Ultrasound (MMUS), has been established. MMUS visualizes particle-induced time-variable tissue movements, excited by an alternating magnetic field.

For clinical applications, it is reasonable that the magnet used for MDT shall also be employed during MMUS. This request raises two problems: on the one hand, the aim of an MDT magnet design is to create a static magnetic field for the particle accumulation. Consequently, the MMUS procedure is limited to low-frequency fields for the tissue movement excitation in order to limit eddy current losses in the magnet. In the low-frequency range, however, there are also other movements such as respiratory movements, which makes it difficult to identify the particle-induced tissue motions. On the other hand, due to the geometrical arrangement of the magnet and the ultrasonic transducer, both components perceive the target tissue under different directions, which may even disable the detection of the particle-induced tissue movements via MMUS. This study aims at showing a suitable clinical setup to monitor the particle accumulation via MMUS in the framework of Magnetic Drug Targeting, using an appropriate MDT magnet design. Moreover, we verify the configuration in vivo with iron-oxide nanoparticles applied to a rabbit. With the measurements conducted in this contribution it was possible to observe the accumulation of iron-oxide nanoparticles during a Magnetic Drug Targeting treatment for the first time.