TU Delft
Delft University of Technology
Faculty of Applied Sciences

Department of Imaging Science & Technology
Prof. dr. I.T. Young
Lorentzweg 1
NL-2628 CJ Delft, The Netherlands
www.ist.tudelft.nl

PhD Positions in Quantitative Imaging

The following six research projects are being pursued in the Quantitative Imaging Group at the Delft University of Technology. The group is interested in finding PhD students to work on these projects. The head of the group (and department) is Professor Lucas J. van Vliet

General requirements for a PhD position in this type of research are:

- Language skills: proficient in English (TOEFL Total ≥ 90, Writing ≥ 23, Speaking ≥23)
- Scientific creativity
- Mathematics background: proficient in calculus, solving systems of equations, geometry, probability and statistics
- Excellent programming skills for image processing in Matlab and C or C++
- Outstanding research qualities

Project 1	
Title	**Novel microscopy techniques for digital pathology**
Project Leader	Dr. Sjoerd Stallinga, Delft University of Technology
Collaborators	Philips Research Laboratories, Leiden University Medical Center (LUMC)
Description	The project is motivated by the emerging field of digital pathology. The primary activity of a pathologist, making a diagnosis via microscopic examination of tissue and cells from a biopsy, is aided by the availability of digital high-resolution images of tissue slides acquired with a high-throughput automated microscope ('whole slide scanner'). This enables a number of applications such as connectivity for cooperation amongst pathologists and with other clinicians, quality control by workflow management, and the application of computer aided diagnostics. The latter application is especially relevant in case specific molecular markers are used such as in so-called immunostained tissue slides. These markers can be fluorescently labeled in order to increase detection sensitivity. From the technological point of view digital imaging opens up a whole new venue of imaging techniques and computer analyses for pathology. These novel techniques are based on the combination of optical modifications of conventional microscopes, such as new ways of illuminating the sample, with post-processing of the raw images in order to obtain a versatile high-quality digital image.

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	It is the aim of the project to develop one of these new microscopy techniques, so-called structured illumination, for application in digital pathology. This technique uses non-uniform object illumination for improving resolution and photobleaching in fluorescence imaging. The project focuses on illumination by an array of tiny spots, which is better suited to whole slide scanning than other structured illumination techniques, and in addition provides several new routes to image cells and tissue with phase contrast. This direction in novel instrumentation makes use of the method of virtual staining, in which the raw images (in phase contrast) of non-stained or minimally stained slides are post-processed to visualize cell and tissue morphology.
Required Background	Education: MSc degree in Molecular Biophysics, (Applied) Physics, or Electrical Engineering Expertise: Advanced light microscopy and spectroscopy, fluorescence, molecular biophysics, digital image processing, imaging physics Skills: Excellent experimental and engineering skills (microscopy) and programming skills formathematical modeling in Matlab and C or C++.

Project 2	
Title	Automated temporal screening for diabetic retinopathy
Project Leader	Prof. dr. ir. Lucas J. van Vliet, Delft University of Technology
Collaborators	Oogziekenhuis Rotterdam
Description	One of the most common complications in Diabetes Mellitus is Diabetic Retinopathy (DRP). If left untreated, DRP can lead to blindness. While the effects can be treated, no cure for DRP is available. Regular screening for DRP is therefore necessary to minimize damage of the retina. The screening of diabetic patients is performed by acquiring a fundus photo which is then assessed by a retinal specialist. This process is labor intensive and, given the large amount of patients that needs annual checkups, puts a significant demand on the available health care. This demand is expected to rise in the future, due to the increasing number of people affected by this disease. In order to continue screening on DRP in the future, decreasing the amount of human (and especially specialist) involvement in the screening process is required. This can be achieved by transferring part of the screening process to computer programs employing advanced image processing and pattern recognition algorithms. Automated screening may be implemented on several levels. Initially, the computer can identify suspect areas which are then assessed by the specialist. This relieves the specialist from reviewing the full image. More involved algorithms may even be able to classify the full image themselves. In contrast to most existing research on automated diagnosis of DRP, where

	the aim is to classify a single fundus photo, this proposal is aimed at automating the screening process by comparing the new fundus photo to an earlier acquired photo of the same patient. This reduces problems due to the large inter-individual variability in retinal morphology, because only changes within a patient's series have to be detected. In addition, this approach is more in line with the clinical demand for monitoring the effects of DRP on the retina. The proposed approach first compensates for technical differences between the images in a series of fundus photos, such as differences in the included area and changes in illumination. Then, the remaining differences will be classified as pathological, such as aneurysms or neovascularization, or non-pathological, such as floaters. Finally, those changes that are flagged as pathological are reviewed by the retinal specialist for the final diagnosis. This approach will be evaluated by comparing it to the current, fully manual method.
Required Background	*Education*: MSc degree in (Applied) Physics, Electrical Engineering, or Computer Science *Expertise*: advanced digital image processing, statistical pattern recognition, linear systems and signal processing

Project 3	
Title	Towards soft-tissue quantification in patients with high-precision and reduced radiation dose using novel x-ray imaging techniques
Project Leader	Professor dr. ir. Lucas J. van Vliet, Delft University of Technology
Collaborators	Erasmus Medical Center
Description	Since Röntgen's discovery of X-rays in 1895, almost all x-ray images have been obtained and interpreted on the basis of absorption contrast. Notwithstanding major technological improvements, the limitations that are intrinsic to the absorption-contrast x-ray imaging (ACI) method remained, i.e. visualizing the structure of soft-tissues remained impossible. In 1995 phase contrast x-ray imaging (PCI) was demonstrated, which offers greatly enhanced contrast resolution compared to ACI allowing the observation of the inner structure of biological soft tissues with a spatial resolution of a few micrometers, but without the need for contrast agents. This is particularly interesting for cardiovascular research, since there is increasing evidence that the risk of cardiovascular events such as stroke and heart attack are primarily related to the microscopic composition of the atherosclerotic plaque in the vessel wall. The aim of this project is the experimental development, optimization, and proof-of-principle demonstration of a laboratory set-up for propagation-based (PB) PCI with polychromatic high-energy (HE) x-rays for the in-vitro visualization and quantification of atherosclerotic plaque components in carotid arteries. This requires the development of fundamentally different feed-forward and reconstruction algorithms for PCI compared to ACI. The phase component

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	of the observed signal is not only entangled with absorption contrast in a non-trivial way, but the model should also be fully 3D. The experimental results of PB-PCI will be compared to in vivo magnetic resonance imaging (MRI) and computed tomography (CT) of patients with the same atherosclerotic plaque in the carotid bifurcation. Furthermore, the PCI-results of an atherosclerotic plaque after surgical removal is also compared with micro-CT and in-vitro MRI. The results from all imaging modalities will be compared with histology, which is the gold standard. It is expected that with PCI plaque components can be detected and quantified with higher precision.
Required Background	*Education*: MSc degree in (Applied) Physics, Electrical Engineering *Expertise*: advanced wave propagation in optics (level of text book Hecht), x-ray source and x-ray detector technology, 3D tomographic reconstruction, advanced digital image processing, linear systems and signal processing, physics of imaging *Skills*: excellent experimental skills (beamline construction and experimental work) and programming skills (forward modeling & 3D reconstruction) in Matlab and C or C++.

Project 4	
Title	Tethered gold nano-particles for the ultra-sensitive detection of tuberculosis nucleic acid
Project Leader	Dr. Bernd Rieger, Delft University of Technology
Collaborators	Royal Tropical Institute (KIT), Amsterdam
Description	Although infectious disease diagnostics based on the detection of pathogen specific nucleic acid can be performed with excellent sensitivity and specificity, they currently require dedicated laboratory facilities or complex expensive devices. A major obstacle to the development of practical so called "near patient" or "bed side" nucleic acid diagnostics is the requirement for an enzymatic amplification step prior to detection. If the sensitivity of the detection method could be increased 100· - 1000·, the need for amplification could be eliminated for many applications. This could revolutionize the provision of nuclear acid based diagnostic assays. We propose to use a dark-field microscope to monitor the motion of many single tethered gold nano-particles in liquid. The tether consists of specific DNA that matches the nucleic acids that are to be detected. In our tests it will be characteristic for our model disease Mycobacterium tuberculosis . Changes in the motion of the gold nano-particle can be observed if the tether and illumination are properly designed. Such a single molecule experiment is suitable for multiplexing and could form the basis of an exquisitely sensitive method of detecting the presence of nucleic acids derived from human pathogens directly from patient material.
Required	*Education*: MSc degree in (Applied) Physics, Electrical Engineering, or

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Background	Computer Science *Expertise*: advanced digital image processing, statistical pattern recognition, physics of MRI imaging, linear systems and signal processing

Project 5	
Title	Computer aided detection of gastrointestinal disorders: colorectal cancer and Crohn's disease
Project Leader	Dr. Frans Vos, Delft University of Technology
Collaborators	Academic Medical Center (AMC), Amsterdam
Description	(Ileo)colonoscopy is the standard method for detecting colorectal polyps/cancer and monitoring Crohn's disease. However, it is invasive and requires an extensive preparation (laxation), which is perceived as very burdensome by most patients. MRI colonography is a non-invasive alternative for the detection of colorectal polyps/cancer, but relevant lesions are sometimes missed due to so-called perceptual errors. Such an error concerns a lesion not detected prospectively, but visible retrospectively. MRI is also employed for diagnosing Crohn's disease, but a current limitation is the lack of an objective and reproducible method to quantify disease activity. This research project aims at developing new instruments to solve these problems. The instruments comprise Computer Aided Detection algorithms to facilitate (I) a reduction of the perceptual errors regarding colorectal polyps/cancer and (II) quantification of the severity of Crohn's disease. The design of such methods is technologically challenging particularly due to global as well as local signal fluctuation in MRI data. There are currently no CAD systems for detecting colorectal polyps/cancer or for Crohn's disease in MRI. We envisage that the detection algorithm for colorectal polyps/cancer delivers highly suspicious sites that are objectively ordered. Such a facility may sustain early detection of cancer. To facilitate practical application, the techniques will be developed in the context of large clinical studies involving hundreds of patients.
Required Background	*Education*: MSc degree in (Applied) Physics, Electrical Engineering, or Computer Science *Expertise*: advanced digital image processing, statistical pattern recognition, physics of MRI imaging, linear systems and signal processing

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Project 6	
Title	A longitudinal 4D Diffusion Tensor MRI study on consequences of early onset heavy drinking in a sample of 10 year old boys
Project Leader	Dr. Frans Vos, Delft University of Technology
Collaborators	Academic Medical Center (AMC), Amsterdam
Description	Research of alcohol effects on the developing brain is still in its infancy. Preclinical and clinical studies suggest that alcohol use in early adolescence distinctly affects white matter (WM) pathways known to be actively developing during adolescence. However, the causality of the neurobiological consequences is still unknown. The primary objective of this project is to investigate sensitive methods for the statistical analysis of longitudinal Diffusion Tensor MRI data of the brain (4D-DTI). DTI data and other neuroimaging parameters of alcohol-induced neurotoxicity (volume, brain neurochemistry, functionality) will be prospectively assessed on two time points in 300 alcohol-naïve adolescents (aged 10 years) sampled in Amsterdam through the Municipal Health Service in Amsterdam (GGD). Four years later (aged 14 years) the 50 most heavy drinkers ('Binge drinkers': 5 or more drinks per occasion) will be assessed again, along with 50 matched controls of persistent alcohol-naïve adolescents. The research project is expected to provide a decisive answer regarding the nature and the extent of the effect that early onset heavy drinking has on actively developing brain regions. Policies advocating alcohol abstinence during early adolescence would be supported by findings indicating augmented adverse alcohol effects on brain development and brain function. Investigating analysis techniques (4D-DTI) for longitudinal DTI data is scientifically challenging and very innovative from an image analysis point of view, and is expected to provide extremely powerful measures for neuroscientific research and clinical management of neurodegenerative diseases.
Required Background	*Education*: MSc degree in Molecular Biophysics, (Applied) Physics, or Electrical Engineering *Expertise*: Advanced light microscopy, single molecule techniques, Fluorescence, Molecular biophysics, Digital image processing *Skills*: Excellent experimental skills (single molecule microscopy) and programming skills for mathematical modeling in Matlab and C or C++, wetlab experience