Vetenskapsrådet

Application

2015-03-31

2015-05140 Lindblad, Joakim NT-19

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Project site: Inst för informationsteknologi

Information about application

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Keywords: computational microscopy, image processing, compressed sensing, spatial light modulation, biomedical applications

Funds applied for

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Descriptive data

Project info

Project title (Swedish)*

Avancerade beräkningsmetoder för högupplöst ljusmikroskopi med biomedicinska tillämpningar

Project title (English)*

Compressed sensing and sparse modelling in Fourier ptychographic microscopy for biomedical applications

Abstract (English)*

Fourier ptychographic microscopy (FPM) is a newly developed super-resolution imaging technique, which employs angularly varying illumination and a phase retrieval algorithm to surpass the diffraction limit of the objective lens. By stitching together a large number of variably illuminated, low-resolution images in Fourier space, the method produces a wide field-of-view high-resolution complex image.

This very new and rapidly advancing technique still has a number of shortcomings. Sequential imaging of hundreds of images leads to acquisition times of several minutes, as to reach good S/N ratios. Iterative solutions of the reconstruction problem are computationally demanding, imposing the need for faster and parallel algorithms. We will utilize knowledge from the field of Compressed Sensing (CS) to address these and other limitations, and further develop the FPM technique. We will utilize sparse regularization approaches in the reconstruction to further improve the quality and usefulness of FPM imaging. Optimized GPU implementations of our developed methods will provide noise resilient super-resolution reconstruction at high speed. We will by that further advance FPM as an outstanding imaging technology.

We will evaluate our theoretical work on challenging biomedical applications. We will use the phase information captured by FPM to achieve precise detection and 3D localization of individual proteins, or interacting protein pairs, in bright-field images of cells or tissue sections, facilitated by in-situ proximity ligation assays (PLA). The phase information of the FPM technique removes the need for imaging of separate z-slices and allows the direct localization of the signals in 3D. Possibility for fast and easy imaging of PLA signals in H&E stained tissue, providing excellent visualization of protein interaction together with tissue morphology, will greatly facilitate the superior ability of in situ PLA for characterizing protein events in cells and tissues to be applied to routine histopathology.

A second application of study is the early detection of cervical cancer. We expect FPM, with its phase imaging properties, high resolution and wide field-of-view (FOV), to provide an ideal tool for detecting the subtle, but diagnostically highly relevant, Malignancy Associated Changes (MAC) in the chromatin structure of cells influenced by a malignant process. The excellent price/performance ratio of FPM, combined with efficient use of phase information for improved sensitivity and reduced dependence on staining protocols, provides the potential to create a truly cost effective cancer diagnostics tool which would have a tremendous impact on global healthcare.

We aim to take advantage of this unique opportunity for creation of new groundbreaking science which is offered by the extreme potential of the FPM technique. This very rapidly developing technology will find applications throughout the field of microscopy and a successful outcome of this project would have implications on medicine and biomedicine on a global scale.

Popular scientific description (Swedish)*

Biomedicinska prover, som t.ex. celler och vävnadsprover, är ofta genomskinliga om de inte behandlats med specifika färgämnen. Strukturer i mikroskopisk skala kan ändå avbildas genom att man utnyttjar det faktum att täthetsvariationer kan mätas med hjälp av metoder som bygger på ljusets brytning. En sådan metod kallas Fourier Ptychografisk (från det grekiska ordet 'att vika') Mikroskopi (FPM), och bygger på att man belyser provet från ett antal olika håll, och sedan räknar fram en bild med hjälp av den samlade informationen. Till skillnad från de högupplösande mikroskopitekniker som tilldelades 2014 års Nobelpris är dessa metoder inte beroende av att proven är märkta med fluorescerande ämnen. Inte heller krävs särskilt avancerad utrustning; man byter helt enkelt ut lampan i ett vanligt ljusmikroskop mot ett stort antal lysdioder. Genom att ta ett hundratal bilder, som alla är belysta på olika sätt, kan man samla in både intensitets- och fas-information från relativt stora provytor. Med avancerade algoritmer kan man sedan räkna fram en bild med submikrometerupplösning. Tekniken som är helt ny, den uppfanns år 2013, har på mycket kort tid fått stor uppmärksamhet då den kringgår mikroskopets fysiska begränsningar med hjälp av beräkningsmetoder. Vi vill i detta projekt vidareutveckla dessa beräkningsmetoder och använda så kallad 'compressed sensing', som bygger på att en signal (i detta fall en bild) kan återskapas med högre upplösning än de uppmätta signalerna genom att effektivt utnyttja redundans i den insamlade informationen. Vi hoppas kunna snabba upp FPM metoden, som idag är ganska långsam, genom att på smartast möjliga vis belysa provet, så att så få bilder som möjligt behövs för att räkna ut en brusfri och högupplöst bild.

FPM tekniken har stor potential inom många tillämpningsområden. Vi har valt två viktiga områden där vi har stor erfarenhet och kommer att testa och utvärdera tekniken inom dessa områden. Först och främst vill vi använda metoden för att hitta signaler från 'Proximity Ligation Assays' (PLA); ett samlingsnamn för molekylära metoder för att identifiera specifika proteiner eller växelverkan mellan proteiner direkt i celler och vävnad. Traditionellt används fluorescerande markörer för märkning av PLA-signaler, vilket begränsar metodens användbarhet och gör det svårt att urskilja PLA märkningen vid analys av fluorescerande prover så som hjärnvävnad och biobanksvävnad som fixerats med fluorescerande ämnen. Tidigare försök att avbilda PLA signaler med vanlig ljusmikroskopi har varit beroende av att provet flyttas upp och ned i mikroskopet för att avbilda signaler i olika fokalplan. Vårt mål är att hitta PLA signaler med hjälp av Fourier ptychografisk ljusmikroskopi och utnyttja FPM dels för att få så bra upplösning som möjligt, och dels för att tekniken gör det möjligt att avbilda provytor i flera fokalplan samtidigt, utan att provet behöver flyttas fysiskt.

Högupplöst avbildning av stora provytor i flera fokalplan blir också mycket intressant för vårt andra tillämpningsområde, där målet är att öka tillförlitligheten av diagnostik av livmoderhalscancer. Livmoderhalscancer dödar fortfarande cirka en kvarts miljon kvinnor i världen varje år. Systematisk provtagning har kraftigt reducerat dödligheten i världens rikare länder, men saknas i många länder på grund av brist på expertis och för att de analyssystem som finns är för dyra. Från tidigare forskning vet vi att förändringar i den tredimensionella fördelningen av DNA i cellkärnan är en tidig indikator på en begynnande cancerutveckling. Vi tror att FPM kan vara en avgörande komponent i utvecklingen av tillförlitliga och kostnadseffektiva system för cellprovs-analys. Även i detta fall är metodens möjlighet att avbilda många bildplan ur en enda registrerad datamängd och att använda fasskillnader för att detektera variationer i täthet kopplat till möjligheterna att få hög upplösning ur förhållandevis enkel och därmed kostnadseffektiv optik av stor betydelse. Genom att optimera systemet för livmoderhalsprover kan vi fokusera på ett viktigt så väl som utmanande problem.

FPM är en ny mikroskopimetod under snabb utveckling och med många potentiella användningsområden. Med vår expertis inom digital signal- och bildbehandling ser vi stora möjligheter att vidareutveckla metoderna. Vi vill inom projektet också utvärdera och testa metoderna inom två medicinskt viktiga områden, där nya mikroskopimetoder kan förbättra noggrannheten inom klinisk diagnostik.

Project period

Number of project years*

4

Calculated project time*

2016-01-01 - 2019-12-31

Classifications

Select a minimum of one and a maximum of three SCB-codes in order of priority.

Select the SCB-code in three levels and then click the lower plus-button to save your selection.

SCB-codes*

2. Teknik > 206. Medicinteknik > 20603. Medicinsk bildbehandling

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Enter a minimum of three, and up to five, short keywords that describe your project.

Keyword 1*

computational microscopy

Keyword 2*

image processing

Keyword 3*

compressed sensing

Keyword 4

spatial light modulation

Keyword 5

biomedical applications

Research plan

Ethical considerations

Specify any ethical issues that the project (or equivalent) raises, and describe how they will be addressed in your research. Also indicate the specific considerations that might be relevant to your application.

Reporting of ethical considerations*

Image data will be provided by the collaborators and will consist of anonymized biomedical samples from patients. No patient ID information can be traced from the images. No animals will be used.

The project includes handling of personal data

No

The project includes animal experiments

No

Account of experiments on humans

No

Research plan

Compressed sensing and sparse modelling in Fourier ptychographic microscopy for biomedical applications

Illumination engineering and spatial light modulation have lately attracted a lot of attention in the field of microscopy including a Nobel prize last year. **Fourier ptychographic microscopy** (FPM) is a newly developed super-resolution imaging technique, which employs angularly varying illumination and a phase retrieval algorithm to surpass the diffraction limit of the objective lens, first suggested in [Zheng2013].

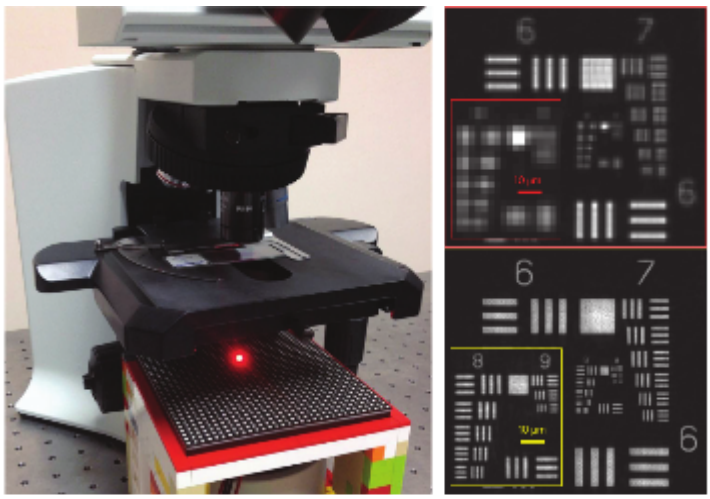

Fig. 1 Left: FPM setup with LED illumination. Right, low resolved image as captured by the microscope optics (top) and high resolution reconstructed image (bottom). [Zheng2013]

The physical scheme of Fourier ptychography (FP) is **appealingly simple**. It consists of a LED array and a conventional microscope with a low-NA objective lens (Fig. 1). By stitching together a large number of variably illuminated, low-resolution images in Fourier space, the method produces a **wide field-of-view, high-resolution complex image**. The technique has the potential to **revolutionize microscopy** since it provides gigapixel size images with sub-micrometer resolution using cheap optics. The imaging procedure transforms the general challenge of high-throughput, high-resolution microscopy from one that is coupled to the physical limitations of the system's optics to one that is solvable through computation.

This very new and rapidly advancing technique still has a number of shortcomings. Sequential imaging of hundreds of images leads to acquisition times of several minutes, as to reach good S/N ratios. Iterative solutions of the reconstruction problem are computationally demanding, imposing the need for faster and parallel algorithms. **We will utilize knowledge from the field of Compressed Sensing (CS) to address these and other limitations, and further develop the FPM technique.** Sparse regularization approaches in the reconstruction will further improve the quality and usefulness of FPM imaging.

In addition to advancing the field of FPM imaging, we will utilize the unique properties of this imaging technique to **address challenging biomedical problems**. Extending our previous work on image analysis tools for in situ **proximity ligation assays (PLA)** [Zieba2010], we will utilize the phase information captured by FPM for precise detection and 3D localization of individual proteins or interacting protein pairs in cells or tissue sections. In addition to the creation of a powerful tool for basic and clinical research, this application also provides quantitative evaluation of the FPM methods through comparison with confocal fluorescence microscopy.

A second application, where we also have a strong background is **early detection of cervical cancer** [Bengtsson2014]. We expect FPM, with its phase imaging properties, high resolution and wide field-of-view (FOV), to provide an ideal tool for detecting the subtle, but diagnostically highly relevant, Malignancy Associated Changes (MAC) in the chromatin structure of cells which are influenced by a malignant process. This would lead to reliable and cost effective cancer diagnostics.

Purpose and aims

The project will advance the state of the art of light microscopy. We will improve illumination modulation techniques and will use methods from compressed sensing (CS) together with GPU implementations for fast and noise resilient super-resolution reconstruction. We will by that further advance FPM as an outstanding imaging technology. Application driven method development will ensure practical and applicable outcomes of the project.

Aim 1, Theory: A systematic characterization of FPM, its possibilities and limitations

To improve understanding of the FPM methodology and explore how to best exploit its power. To advance the imaging technique by optimized sampling in the Fourier domain, exploiting knowledge from the CS field to provide faster and more accurate results. To improve reconstruction algorithms, fully utilizing sparse regularization approaches in combination with parallel implementation of recent and popular optimization methods such as the Alternating Direction Method of Multipliers (ADMM) and Majorization–Minimization approaches. To thereby push the reachable image resolution even further into the nano-meter range. To provide, through optimized GPU based implementations, a most useful tool for fast wide-field and accessible high-resolution imaging.

Aim 2, Application: Evaluate the FPM framework for 3D imaging of protein markers

To utilize the (improved) FPM techniques for optimized imaging and automatic 3D localization of in situ PLAs, enabling efficient and precise detection and quantification of proteins, protein interactions and modifications in fixed cells and tissue samples.

The in situ PLA enables **localized detection of individual native proteins** or interacting protein pairs in fixed cells or tissue sections, thus providing an important tool for basic and clinical research. PLA signals are usually detected by fluorescence labeling and fluorescence microscopy imaging. A major challenge for automated quantification is the prominent auto-fluorescence that occurs in many tissues, making reliable detection difficult. We have demonstrated that this problem can be avoided by basing detection on enzymatic development of a substrate and by visualizing the locations of the reaction products with bright-field microscopy [Zieba2010]. This technique can be combined with standard hematoxylin and eosin staining of tissue, thereby allowing simultaneous observation of PLA signals and tissue histopathology. The bright-field visualization of PLA signals is, however, hampered by the lack of efficient imaging of multiple z-slices, required to capture signals located at varying focal depth. FPM supported bright-field detection of PLA signals in 3D will greatly facilitate the superior ability of in situ PLA for characterizing proteins and protein complexes in cells and tissues to be applied to routine histopathology.

Aim 3, Application: Evaluate FPM as a means for cost effective cancer diagnostics

To explore and develop the FPM techniques with an aim to improve the reliability of cervical cancer diagnostics based on PAP-smear analysis while simultaneously reducing the unit cost. Cervical cancer kills a quarter of a million women worldwide every year. Systematic screening based on visual analysis of PAP-smears is very effective in reducing cancer incidence and mortality but is only offered in richer countries due to high cost and need for skilled experts. Currently available automated screening systems are not cost effective. The FPM technique offers excellent price/performance ratio, enabling use of low cost optics for high resolution imaging. We, therefore, find the task of **sensitive and cost effective cervix cancer diagnostics** a most appropriate and highly relevant application, providing both challenging evaluation material and inspiration for further development. We will exploit the unique quantitative **phase imaging** properties of FPM, combined with its wide FOV and high resolution. Our goal is to provide a basis for a computer assisted cell detection, analysis and classification system which can be used as a screening tool worldwide without the high investment and maintenance costs associated with current systems.

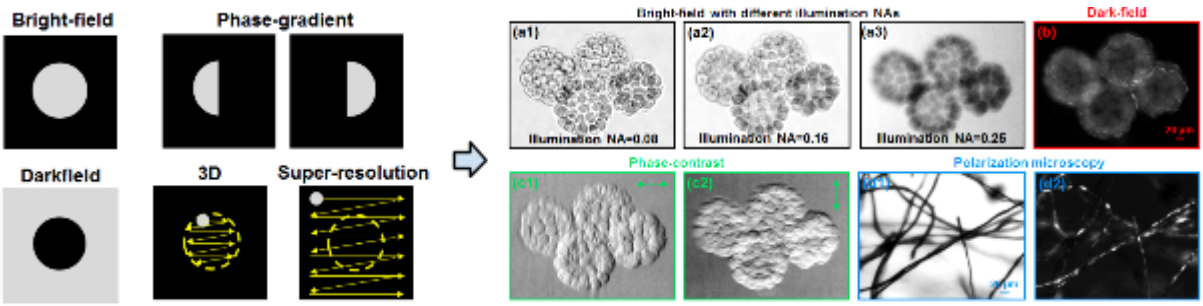

Fig. 2 By varying the illumination pattern (left), a range of different microscopy modalities can be achieved (right) [Guo2015].

Survey of the field

Fourier ptychography (FP) utilizes illumination control and computational post-processing to increase the resolution of bright-field microscopes. In effect, FP extends the numerical aperture (NA) of an objective lens to form a larger synthetic system NA, thereby **surpassing the diffraction limit** of the employed optics. Wide-field optics, together with aberration corrections to digitally extend the depth of focus, provides gigapixel colour images of histology slides with a FOV of ~120 mm^2 and a resolution-invariant depth of focus of 0.3 mm at a resolution of 0.78 µm. The recovery process of FP switches between the spatial and the Fourier domain. In the spatial domain, the captured images are used as the intensity constraint for the solution. In the Fourier domain, the confined pupil function of the objective lens is used as the support constraint for the solution.

FPM is **a very new technology**; the principal publication [Zheng2013] was published in Nature photonics in September 2013. The excellent properties of the technique have caused a great interest and recognition from scientists worldwide. Advancement of the technique, in terms of speed and applicability, extension to other modalities, etc., are being reported at a rapidly increasing rate.

The observed problem of slow acquisition speed, due to sequential imaging of hundreds of images, has already received attention [Dong2014sm,Dong2014ss,Tian2014]. FPM imaging time is, despite improvements, still measured in minutes. We will reduce the time requirements by incorporating knowledge from CS, combined with improved reconstruction algorithms. [Bian2014] report on faster reconstruction using Wirtinger flow optimization. We will explore this, and other methods for fast and reliable FP image reconstruction, within the project.

A development which allows estimation of the aberration of the imaging system during the acquisition is presented in [Ou2013]. This provides further improved image quality. Based on this and other improvements, utilizing a 40x 0.75NA objective lens and FP to synthesize a system NA of 1.45, a two-slit resolution of 335 nm is reported in [Ou2015].

The **most downloaded paper** of February 2015 in Biomedical Optics Express is [Guo2015]. The article describes how **a $15 liquid crystal display** can be used as a transparent spatial light modulator and it is shown that this provides a very versatile but still simple setup for FPM imaging. Examples of achievable imaging modalities are shown in Fig 2. We will evaluate this very promising design and compare it with the original LED illumination approach.

The original formulation of FPM imaging relies on the assumption of very thin specimens. Two directions for overcoming this restriction are suggested in the literature. A detection-path-based imaging scheme, termed aperture-scanning Fourier ptychography, is demonstrated in which [Dong2014ap]. Our interest in this approach is limited, since it significantly complicates the imaging hardware. The other, more promising approach, is presented in [Tian2015]. Keeping a simple imaging setup and using an iterative reconstruction algorithm, based on **a multislice coherent model,** the authors successfully recover the **3D** complex transmittance function of a sample at multiple depths. They demonstrate applicability of the method on

thick biological samples in a commercial microscope using a LED array setup, extending the technique's usefulness for a wide range of applications.

Compressed sensing and sparse regularization

Over the last decade compressed sensing (CS), also known as compressive sampling, has gone from a rather controversial approach, seemingly violating the Nyquist-Shannon sampling theorem, to a well established field in signal processing. CS has reached some of its greatest successes in Magnetic Resonance Imaging (MRI), where it even finds its way into commercial hardware. MRI obeys two key requirements for successful application of CS: 1) medical imagery is naturally compressible by sparse coding in an appropriate transform domain (e.g., by wavelet transform), and 2) MRI scanners naturally acquire encoded samples, rather than direct pixel samples (e.g., in spatial-frequency encoding). We observe that **these two key requirements for CS are equally well matched for FP imaging**. This motivates our main line of research.

The use of sparsity constraints has become the standard for image restoration, deblurring and denoising. The success of sparse representation owes a lot to the development of L1-norm optimization techniques, and the fact that natural images are intrinsically sparse. When assumptions about regularity of the imaging domain can be made, dictionary learning techniques have shown to provide state-of-the-art performance [Dong2011]. We will evaluate such approaches.

Own results

The team has positive experience of CS and **sparse techniques**. We have modified and accelerated the CS based Faster STORM method by parallelizing computations over multiple processor cores [Ishaq2014] and evaluated its use for signal localizations in live cell images. We have explored L1 and other sparsity promoting regularization techniques, as well as the use of potential functions for their improved performance [Lukic2011]. We have recently achieved encouraging results based on Fourier domain filtering for image enhancement [Lindblad2014,Lindblad2015] (Fig. 3). We are currently working on combining these results with sparse priors for further improved super-resolution image enhancement.

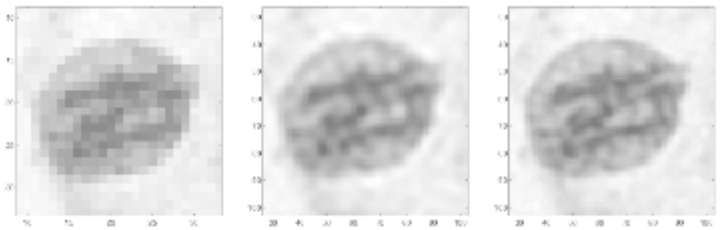

Fig. 3 Low resolution image. Enhanced image using [Lindblad2015]. Aligned high resolution reference.

It is observed that usage of a pixel size larger than the Nyquist limit in FPM may lead to a pixel aliasing problem in the Fourier domain. This significantly degrades the quality of the FP reconstruction. We expect that our extensive knowledge of **sub-pixel precise methods** [Sladoje2009,Malmberg2011] is useful for reducing the impact of discretization effects.

Protein imaging

The in situ PLA is an important tool for basic and clinical research. It allows a protein or protein complex to be represented as an amplifiable DNA molecule and enables localized detection of individual native proteins or interacting protein pairs in fixed cells or tissue sections [Söderberg2006]. We have developed image analysis techniques for improving PLA detection [Zieba2010]. This technique is widely used, provided as a national service via the Science for Life Laboratory (SciLifeLab) through its PLA Proteomics facility, and has been successfully commercialized as the Duolink In Situ kit by Olink biosciences.

PLA signals are most often detected by fluorescence labeling and imaging by fluorescence microscopy. However, one of the major challenges for detecting fluorescent probes is the prominent autofluorescence that occurs in many tissues. We have demonstrated that it is possible to avoid this problem by basing detection on enzymatic development of a substrate and visualizing the locations of the reaction products

with bright-field microscopy [Zieba2010]. Bright-field microscopy offers better visualization of tissue morphology since, unlike fluorescence, it is compatible with hematoxylin and eosin staining routinely used in the clinic.

Texture analysis for cancer diagnostics

The team has a long experience of cancer diagnostics based on PAP-smear imaging. Recent results show the importance of texture information for accurate diagnostics. In [Kim2013] we developed a new approach based on analysis of 3D texture features for detecting subtle changes in thick cancer tissue section images. Our results in [Niwas2013] show that the use of the **complex wavelet transform** gives significantly better results than the ones obtained with real valued wavelets. Our latest results on the usefulness of structural texture for PAP-smear classification are presented in [Mehnert2014].

Project description

General methodology and organization

The project is divided into three work packages (WPs) corresponding to the resp. specific aims of the project. They are designed to provide a constructive balance between theoretical and applied development of the FPM technology. The main applicant, Dr Lindblad will coordinate the project work and will together with co-applicant Prof. Wählby supervise the enrolled PhD student. Co-applicant Prof. Johansson will support the project with expertise in microengineering and wave-optics as well as hands on experience with microscope design. Co-applicants Prof. Wählby and Prof. Bengtsson will contribute with expertise and application domain knowledge regarding the two applications, protein expression characterization (WP2) and cervix cancer diagnostics (WP3). The collaborations with SciLifeLab, represented by Masood Kamali-Moghaddam and Agata Zieba-Wicher, and with the Regional Cancer Centre (RCC), Kerala, India through Dr K. Sujathan, ensure access to sample material, as well as evaluation expertise and a direct contact with the intended end-users.

WP1: A systematic characterization of FPM, its possibilities and limitations
Key resources: Prof. Stefan Johansson, Dr Joakim Lindblad

The first step will be to assemble the imaging device. With the experience from involved parties, we foresee no problems regarding this part. A great benefit of the FPM technique is its ease of implementation on a standard microscope; we have an Olympus microscope, similar to what is used in many of the published designs. Two illumination setups will be constructed, one utilizing LED illumination and one based on the very promising LCD approach, recently presented in [Guo2015]. To reduce the reported problem of low extinction ratio, we may aim for a slightly more expensive setup than the 15$ LCD that was suggested in that paper. We will proceed with implementation of several of the proposed algorithms. Again, this should not pose any complication. Methods are well documented and reasonably straight-forward to implement, some are even offered as open source [Bian2014].

Once the imaging is functional, we will begin with exploring and evaluating the properties of the FPM technique. We will evaluate the pros and cons of resp. illumination designs, possibly leading to testing new variations and a combination of the two. We will evaluate the resolving power, noise sensitivity, imaging and reconstruction speed of existing solutions and identify weak and strong sides.

Although a good understanding of the properties of the hardware is essential, the project is not hardware focused. Our main focus is on theoretical development of the FPM technique. Following on our hypothesis that CS can improve the illumination and acquisition protocol, we will start with implementing some of the most popular techniques, finding great inspiration from the approaches used for the MRI modality.

We will address the observed pixel aliasing problem considering sub-pixel and partial coverage approaches. These efforts will be combined with exploration of different sparse regularization approaches within the reconstruction. We expect that dynamic feedback from the on-line computation of the

reconstructed image can be utilized to optimize the illumination, not only for the specific specimen, but also for the current state of the reconstruction, such that at every moment an optimal image is acquired.

Evaluation will initially be performed on artificial objects, such as resolution test targets and micro-spheres. We will, at an early stage, include real image material in the evaluation procedure, connecting the different parts of the project. We will design and implement the developed algorithms to run on GPUs, providing high speed at low cost. The design of fast algorithms and parallel implementations will be greatly facilitated by the extensive experience of real-time video processing of the main applicant.

WP2: Evaluate the FPM framework for 3D imaging of protein markers

Key resources: Prof. Carolina Wählby
Collaborators: Ola Söderberg, Masood Kamali-Moghaddam, Agata Zieba-Wicher.

We have already established contact with the PLA Proteomics platform of SciLifeLab (Masood Kamali-Moghaddam and Agata Zieba-Wicher), as well as Ola Söderberg at the Dept of Immunology, Genetics and Pathology, Uppsala University, and they are very excited about new and improved imaging technologies for this alternative approach for utilizing the PLA technology.

We will integrate the FPM algorithms developed in WP1 within the existing bright-field extension of the BlobFinder software, a freely available image analysis tool for image cytometry developed at the Centre for Image Analysis, (http://www.cb.uu.se/~amin/BlobFinder/). We will evaluate the different approaches w.r.t. detection sensitivity and specificity, as well as location accuracy, and compare with reference material from fluorescence microscopy in a manner similar to [Zieba2010].

We will further explore the possibility to use illumination patterns tuned for the specific size distribution of objects of interest. This would provide effects similar to a bandpass filter, directly achieved by the used light patterns. We expect that optimized illumination patterns can be used to further enhance PLA signals of well-defined shape and size.

We have budgeted for the preparation of proof-of-principle tissue samples in collaboration with the PLA Proteomics platform, and envision that larger clinical applications will be a part of the future use of the developed technologies.

WP3: Evaluate FPM as a means for cost effective cancer diagnostics

Key resources: Prof. Ewert Bengtsson
Collaborators: Dr K. Sujathan, Regional Cancer Centre (RCC), University of Kerala, India

Problem description:

We have since 2009 a collaboration with RCC in India, aiming at the development of a cost effective cervical cancer screening system. A crucial aspect for reliable automated analysis of PAP-smears has turned out to be accurate and robust quantification of very subtle changes in the nuclear chromatin distribution through image analysis. The two most critical issues in achieving an effective, robust automated cancer screening system are: 1) high resolution imaging, and 2) consistent specimen quality. The resolution requirement leads to use of costly high NA optics, with small FOV and small depth-of-focus. This is problematic since optimal focus has to be maintained for reliable texture analysis. It is also very difficult to maintain high and consistent staining quality in clinical use in low resource settings. The Papanicolaou stain involves five dyes in three solutions and comes in several versions. However, the PAP-stain is needed for visual inspection by cytologists and pathologists.

We will address the two most critical issues in achieving a cost effective, robust automated cancer screening system using FPM techniques.

FPM offers high resolution wide-field imaging utilizing low cost optics. We will evaluate how well this combination of properties can be reached in practice. FPM delivers quantitative phase information which

allows dynamic refocusing as a post-processing step. We will explore how far the limits can be pushed in terms of low NA optics and wide FOV and we will design algorithms for optimal focus selection. We will evaluate how the properties of FPM can be best used to reduce the cost of microscope stage mechanics and explore the possibility for a completely stage-less microscopy setup for reliable PAP-smear imaging at a minimal cost.

We will explore whether the phase information can be successfully used to reduce the reliance on the stain, enabling increased overall robustness. We will further develop methods to utilize the phase information for improved MAC detection, providing increased sensitivity and specificity of the system. It is known that while the average phase shifts in tumor tissues and normal tissues have similar values, the detailed statistics of the spatial fluctuations of the phase shifts are completely different. We will evaluate and compare 3D texture approaches and approaches based on interference contrast, phase contrast, or dark field style imaging, all facilitated by the FPM technique, with an aim to reach cost effective and reliable cervical cancer diagnostics.

The core team

- Dr Joakim Lindblad is Head of Research and Development at Protracer AB, Stockholm. He is the main developer of their real-time tracking product. He is highly experienced in algorithm development and high throughput real-time video processing, including GPU implementations. He has significant experience in turning theoretical results into products. In parallel to that work, he has maintained academic research activity on high precision image analysis and related topics. He will coordinate the work on the project and be a driving force in both practical and theoretical research involved.
- Prof. Carolina Wählby, Centre for Image Analysis and SciLifeLab, Uppsala University, and the Broad institute of Harvard and MIT, is a 'strategic recruitment' of SciLifeLab Uppsala where she is developing image analysis tools for high content large scale quantitative microscopy analysis. She will contribute with expertise and application domain knowledge regarding quantitative analysis of microscopic images and large image based screening experiments in WP2.
- Prof. Ewert Bengtsson, Centre for Image Analysis, Uppsala University, has invaluable experience in the field of quantitative microscopy. He has more than 100 international publications on cervical cancer screening and closely related subjects. He will provide expert guidance regarding practical issues related to WP3. His wide collaborative network will further be a great resource.
- Prof. Stefan Johansson, Div. of Micro Systems Technology, Uppsala University, has previously been working with imaging techniques in materials science and is now focusing on various microsystem technologies. He has been Head of research at Piezomotor Uppsala AB and has long experience of transforming innovative solutions into commercial products. He will contribute with microsystems solutions for improved illumination devices as well as wave-optics expertise.
- A PhD student in computerized image analysis, co-supervised by Lindblad and Wählby, will be enrolled and given responsible for the majority of implementation and data analysis. The student will gradually increase competences and become involved in adjustments of existing methods to the particular task, design of appropriate evaluation, as well as development of completely new methods.

The extended team

- Masood Kamali-Moghaddam, Agata Zieba at the SciLifeLab PLA proteomics platform, together with Ola Söderberg at the Dept. of Genetics and Pathology at Uppsala University will provide PLA expertise, and samples for methods evaluation and performance testing.
- Dr K. Sujathan, Division of Cancer Research, Regional Cancer Centre, University of Kerala, Thiruvananthapuram, India, will provide samples for methods development and expertise in cervix cancer pathology.

Significance

FPM is a new and very rapidly developing technique with vast and general applicability. We aim to grab the opportunity for creating **groundbreaking new science** that is offered. A fruitful implementation of CS techniques in FP imaging has potential applications throughout the field of microscopy, with secondary implications on medicine and biomedicine as a whole.

Already the results of applications explored within the project have great significance. The novel FPM techniques could be pivotal for clinical use of PLA technologies, especially when handling highly autofluorescent samples such as those from the brain. The excellent price/performance ratio of FPM, combined with efficient use of phase information for improved sensitivity and reduced dependence on staining protocols, provides the potential to create a truly cost effective cancer diagnostics tool which would have a tremendous impact on global healthcare.

An additional important outcome of the project is to ensure that involved parties, including SciLifeLab and RCC, are able to profit from this very promising technique as early as possible. A good understanding of how to best exploit the advantages of this technique will have long lasting benefits. It is expected that positive results of this project will spawn a number of follow up projects, to properly utilize and further develop the technique.

Preliminary results

We have not had any direct access to FPM imaging devices by now. Contacts are established with Geoffrey Metcalf, Chief Commercial Officer of Clearbridge BioPhotonics and we are in the process of equipment purchasing. Relevant preliminary results related to enhancement of PAP-smear images using Fourier based methods are presented in [Lindblad2015]. Example results are shown in Fig 3.

Equipment

We have an Olympus BX51 bright-field microscope with a Hamamatsu ORCA-05G 1.4 Mpx monochrome camera. The microscope is fitted with an E-662 Piezo server controller and actuator, providing z-axis control with a 0.1 µm resolution during image acquisition. Recently the microscope was fitted with a motorized stage, enabling fully automated acquisition of a whole specimen at different focus levels, facilitating extensive and realistic testing of developed methods with minimal labour.

The different illumination and light modulation parts that we will install (LED array, LCD displays) are all relatively cheap. We will purchase a LED based FPM solution from Clearbridge BioPhotonics, including software and control electronics for approximately $5000. The required investments for the LCD based illumination approach should not exceed that level and the total investments will stay below 100 kSEK. At the second year of the project we plan an upgrade of the camera, budgeted at 50 kSEK.

International and national collaboration

In addition to already mentioned collaboration with SciLifeLab, we have a long standing collaboration with the Center for Development of Advanced Computing, CDAC, and the Regional Cancer Center, RCC, in Kerala, India.

Through our long experience of research in the field we have contacts with the majority of the researchers in the relevant fields internationally and will through conferences, organized workshops and other forms of contact seek to continue existing and establish and develop new fruitful collaborations.

Ethical considerations

Image data will be provided by the collaborators and consists of anonymized samples and cell cultures from patients. No ID information is available with the images. No animals will be used.

Other grants

To improve exchange of knowledge and experience with the research undertaken at the University of Kerala, India, we will submit an application for Swedish Research Links programme (SRL). If approved, the SRL grant will support travel as well as organization of workgroups and seminars.

Prof. Johansson will submit an application to the Swedish Research Council for development of artificial muscles. FPM may be used for materials characterization in a later stage of the project.

The research of Dr Lindblad is partially supported by the Ministry of Science and Technological development of the Republic of Serbia through Projects 174008 and III044006 of the Mathematical Institute of Serbian Academy of Sciences and Arts, Belgrade.

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Interdisciplinarity

My application is interdisciplinary

☐

An interdisciplinary research project is defined in this call for proposals as a project that can not be completed without knowledge, methods, terminology, data and researchers from more than one of the Swedish Research Councils subject areas; Medicine and health, Natural and engineering sciences, Humanities and social sciences and Educational sciences. If your research project is interdisciplinary according to this definition, you indicate and explain this here.

Click here for more information

Scientific report

Scientific report/Account for scientific activities of previous project

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Budget and research resources

Project staff

Describe the staff that will be working in the project and the salary that is applied for in the project budget. Enter the full amount, not in thousands SEK.

Participating researchers that accept an invitation to participate in the application will be displayed automatically under Dedicated time for this project. Note that it will take a few minutes before the information is updated, and that it might be necessary for the project leader to close and reopen the form.

Dedicated time for this project

	Role in the project	Name	Percent of full time
1	Applicant	Joakim Lindblad	40
2	Participating researcher	Stefan Johansson	10
3	Participating researcher	Carolina Wählby	10
4	Participating researcher	Ewert Bengtsson	10

Salaries including social fees

	Role in the project	Name	Percent of salary	2016	2017	2018	2019	Total
1	Applicant	Joakim Lindblad	40	299,578	307,067	314,744	322,612	1,244,001
2	Participating researcher	Carolina Wählby	10	93,796	96,141	98,545	101,008	389,490
3	Participating researcher	Stefan Johansson	10	89,160	91,389	93,674	96,016	370,239
4	Participating researcher	Ewert Bengtsson	10	124,824	127,945	131,143	134,422	518,334
5	Other personnel without doctoral degree	PhD student	100	478,878	493,501	500,812	530,056	2,003,247
	Total			1,086,236	1,116,043	1,138,918	1,184,114	4,525,311

Other costs

Describe the other project costs for which you apply from the Swedish Research Council. Enter the full amount, not in thousands SEK.

Premises

	Type of premises	2016	2017	2018	2019	Total
1	Office space	53,000	53,000	53,000	53,000	212,000
	Total	53,000	53,000	53,000	53,000	212,000

Running Costs

	Running Cost	Description	2016	2017	2018	2019	Total
1	Material	Sample preparation	0	20,000	20,000	20,000	60,000
2	Equipment	Work station	40,000	0	0	0	40,000
3	Equipment	Microscopy hardware	95,000	50,000	0	0	145,000
4	Travel	Conference particip.	20,000	20,000	20,000	20,000	80,000
5	Publishing	Open Access	15,000	15,000	15,000	15,000	60,000
	Total		170,000	105,000	55,000	55,000	385,000

Depreciation costs

	Depreciation cost	Description	2016	2017	2018	2019

Total project cost

Below you can see a summary of the costs in your budget, which are the costs that you apply for from the Swedish Research Council. Indirect costs are entered separately into the table.

Under Other costs you can enter which costs, aside from the ones you apply for from the Swedish Research Council, that the project includes. Add the full amounts, not in thousands of SEK.

The subtotal plus indirect costs are the total per year that you apply for.

Total budget

Specified costs	2016	2017	2018	2019	Total, applied	Other costs	Total cost
Salaries including social fees	1,086,236	1,116,043	1,138,918	1,184,114	4,525,311		4,525,311
Running costs	170,000	105,000	55,000	55,000	385,000		385,000
Depreciation costs					0		0
Premises	53,000	53,000	53,000	53,000	212,000		212,000
Subtotal	1,309,236	1,274,043	1,246,918	1,292,114	5,122,311	0	5,122,311
Indirect costs	336,371	345,313	352,175	365,734	1,399,593		1,399,593
Total project cost	1,645,607	1,619,356	1,599,093	1,657,848	6,521,904	0	6,521,904

Explanation of the proposed budget

Briefly justify each proposed cost in the stated budget.

Explanation of the proposed budget*

Motivation of suggested budget

Salary
Most of the money applied for will be spent on salaries (including LKP 48.6% and OH 30%). The main applicant will devote 40% of his time to the project and three participating researchers will devote to it 10% each. A PhD student will be employed and will dedicate 100% of his/her time on the project. The salary cost is based on the applicant's and the participants' current salaries and the median salary of a PhD student at the Dept. of IT, UU. A salary increase of 2.5 % per year is included in the budget.

Office space
Included costs are calculated in relation to the working time devoted to the project (40% , 10%, 10%, 10% and 100% respectively) of a full (J. Lindblad, C. Wählby, E. Bengtsson, and S. Johansson) and shared (PhD student) office.

Travel & conferences
Estimated costs (travel, accommodation and conference fee) for one international conference and one national conference/symposium in image analysis/pattern recognition per year are included in the budget.

Open access publication
We will strive to publish in OpenAccess journals and conference proceedings or where the papers are made open access after 6 months. However, some of the important journals in the image processing field do not apply the 6 month rule and an open access cost for 4 such publications is therefore included.

Equipment
A computer will be purchased for a PhD student.
Hardware necessary for the assembling the FP device (year 1) and for a camera upgrade (year 2) are included in the budget.
Part of the costs of preparation of tissue samples (SciLifeLab PLA proteomics platform) is included in the budget as well.

Total resources within the project
This application will cover all the expenses for the proposed project. There are no other resources that can be utilized for the research task proposed in the project. Collaborators from India will provide samples to the project by own resources.

Other funding

Describe your other project funding for the project period (applied for or granted) aside from that which you apply for from the Swedish Research Council. Write the whole sum, not thousands of SEK.

Other funding for this project

Funder	Applicant/project leader	Type of grant	Reg no or equiv.	2016	2017	2018	2019

CV

Curriculum Vitae – Joakim Lindblad

1. Higher education qualification:

1997: M.Sc. in Engineering Physics (Teknisk fysik), Uppsala University, Uppsala. M.Sc. thesis: "Image analysis for real-time quality control". Carried out at the Centre for Image Analysis, Uppsala, and CERN, Geneva, Switzerland.

2. Doctoral degree:

2003: Ph.D. in Computerized Image Analysis, Centre for Image Analysis, Uppsala University, Uppsala. Ph.D. thesis: "Development of Algorithms for Digital Image Cytometry". Supervisor: Ewert Bengtsson. Available at http://publications.uu.se/theses/abstract.xsql?isbn=91-554-5497-6.

3. Post-doctoral positions:

2004 – 2005: Post Doctoral fellow: Use of colour to improve the accuracy of image based cancer diagnostics, Cancer Imaging, BC Cancer Research Centre, Vancouver, Canada.

4. Qualifications required for appointment as a docent: -

5. Current position:

Since 2014: Head of Research and Development, Protracer AB, Stockholm, Sweden. Currently 50%. *Real time video analysis for sports TV broadcasts. Product used in TV coverage of the world's major Golf tournaments during 2008 – 2015. Golf Magazine's Innovator Award 2008.*

Since 2013: Associate professor at the Faculty of Technical Sciences, University of Novi Sad, Serbia. Currently 50%, of which 80% is research time.

6. Previous academic positions and periods of appointment:

2010 – 2013: Assistant Professor at the Faculty of Economics and Engineering Management, University Business Academy in Novi Sad, Serbia.

2006 – 2011: Assistant Professor in Computerized Image Analysis at the Centre for Image Analysis, Swedish University of Agricultural Sciences, Sweden.

Previous non-academic appointments and entrepreneurial activities:

2007 – 2013: Lead Software Engineer (part time), Protracer AB, Stockholm, Sweden.
2006 – 2007: Software developer (part time), private firm, Uppsala, Sweden, on consultation basis for Protracer AB, Sweden.
2005 – 2006: Algorithm and software developer: Image analysis for quantification of seed vitality, SeedGard AB, Uppsala, Sweden.
2004 – 2005: Algorithm and software developer: Separation and extraction of microarray images, the Human Protein Atlas project, KTH Royal Institute of Technology and Uppsala University.
2001 – 2002: Algorithm developer: The RAC Image Cytometry project, Amersham Biosciences, Cardiff, Wales.
1997: Algorithm and software developer: The LHC-cable inspection project, on behalf of the CERN organization, Geneva, Switzerland.
1994 – 1995: Computer games development. Private company, on consultation basis for 21st. Century Entertainment Ltd., England.

7. Interruption in research : -

8. Completed Ph.D. Supervision:

2011: Tibor Lukic, "Regularized Problems in Image Processing", Univ. of Novi Sad.

2011: Hamid Sarve, "Evaluation of Osseointegration using Image Analysis and Visualization of 2D and 3D Image Data", SLU. Assistant supervisor.

2008: Patrick Karlsson, “Methods and models for 2D and 3D image analysis in microscopy, in particular for the study of muscle cells”, Uppsala Univ. Assistant supervisor.

9. Other information relevant for application:

Scientific publications

More than 50 fully reviewed high quality international publications in the field of Computerized Image Analysis; 746 citations, h-index 15 (Google scholar, March 2015). The published works include foundational theoretical works as well as applied works, with applications in medicine, bio-medicine, material science, and food science, and are carried out within a number of national and international projects with more than 40 collaborators.

Current funded research project participation

- “Advanced Techniques of Cryptology, Image Processing and Computational Topology for Information Security”; Grant ON 174008 of the Ministry of Science and Technological development of the Republic of Serbia.
- “Development of new information and communication technologies, based on advanced mathematical methods, with applications in medicine, telecommunications, power systems, protection of national heritage and education”; Grant III 44006 of the Ministry of Science and Technological development of the Republic of Serbia.
- “Collaborative development of methods for robust and precise image analysis for cost effective and reliable detection of cervical cancer.” Grant nr. 2014-4231, Swedish Research Council, within Swedish Research Links program.

Other merits of relevance

- Frequent reviewer of international scientific journals (IEEE Transactions on Image processing, Image and Vision Computing, Discrete Applied Mathematics, Pattern Recognition Letters, Cytometry, IEEE Transactions on Medical Imaging, Journal of Microscopy) as well as reviewed international conferences (ICPR, MICCAI, SCIA, DGCI, ISPA, IWCIA).
- Member of the reviewing and program committee of the International Workshop on Combinatorial Image Analysis. Member of the technical program committee of the International Conference on Pattern Recognition. Member of the reviewing committee of the International Conference on Discrete Geometry for Computer Imagery.
- Member of the program committee, and 2007 and 2009 organizer of the Special Session on “Digital Shape Analysis: Theory and Applications” for the International Symposium on Image and Signal Processing and Analysis.
- Expert Evaluator in the Committee of the Blanc SIMI 2 2013 program of the French National Research Agency - Agence Nationale de la Recherche.
- Invited speaker at First Croatian Computer Vision Workshop (CCVW), Zagreb, Croatia, 2012.
- 2007 – 2014: Invited lecturer at the International Summer School for Image Processing.
- 2013: Invited lecturer at IEEE SPS Summer School on Biomedical Image Processing and Analysis, Dubrovnik, Croatia.
- 2009: Invited lecturer at the Summer School on Foundations of Information Technologies, Novi Sad, Serbia.

Selected professional network

- Daniel Forsgren, CEO Protracer AB, Stockholm, Sweden.
- Dr. Miodrag Mihaljević, Mathematical Institute SANU, Belgrade, Serbia.
- Dr. Zoran Ognjanović, Mathematical Institute SANU, Belgrade, Serbia.
- Prof. Ewert Bengtsson et al., Centre for Image Analysis, Uppsala University, Sweden.
- Prof. Zoltan Kato et al., Jozsef Attila University, Szeged, Hungary.
- Dr. Calum MacAulay, Cancer Imaging, BC Cancer Research Centre, Vancouver, Canada.

CV Carolina Wählby

1. Higher Education Qualification
1993-1998 MSc in Molecular Biotechnology, Uppsala University

2. Doctoral degree
2003-10-31 PhD degree in Computerized Image Analysis, Centre for Image Analysis, Uppsala University. Thesis title: Algorithms for Applied Digital Image Cytometry. http://publications.uu.se/theses/abstract.xsql?dbid=3608. Supervisor: Ewert Bengtsson

3. Postdoctoral Position
2005-2009 (50%) Postdoctoral fellowship at the Department of Genetics & Pathology, Research Group on Molecular Medicine, Uppsala University. Supervisors Ulf Landegren and Mats Nilsson.

4. Docent Qualification
2009 Docentship in Digital Image Processing, Dept. Information Technology, Uppsala University

5. Present Positions
- Professor in Quantitative Microscopy at the Division of Visual Information and Interaction, Dept. of Information Technology, Uppsala University. (80% 20140401-present). 100% research.

6. Previous Positions and Periods of Appointment
- Principal Investigator, Imaging Platform, Broad Institute of Harvard and MIT, Cambridge, MA, USA (full time 20090501-20110630. 50% 20110701-20120630, 20% 20120701-20141231).
- Associate Professor (universitetslektor) at the Div. of Visual Information and Interaction, Dept. of Information Technology, UU. (50% 20110801-20120630, 80% 20120701-20120331).
- Assistant Professor in Digital Image Analysis at the Centre for Image Analysis, Uppsala University, Sweden (100% 2004, 50% from 2005-2009)

7. Interruption in research
Three children born 20031222, 20050914 and 20070810. Total time off after PhD degree: 16 m.

8. Supervision
- Main supervisor for Amalka Pinidiyaarachchi, PhD 2009.
- Main supervisor for Amin Allalou, PhD 2011.
- Main supervisor for Milan Gavrilovic, PhD 2011.
- Main supervisor, Martin Simonsson, PostDoc 2011-2013.
- Main supervisor Alexandra Pacureanu, PostDoc 2012-2014.
- Main supervisor for Omer Ishaq, PhD planned 2016.
- Main supervisor for Sajith Kecheril Sadanandan, PhD planed 2017.

9. Experience from operating infrastructure
The SciLifeLab has since August 2011 funded me and part of my research group as ‘strategic recruitment’ with two main tasks; to do high-end research within digital image processing, and to provide researchers with support on image analysis. This task was not new as it resembles the structure of work at the Imaging Platform of the Broad Institute of Harvard and MIT, where I started May 2009, and acted as PI 2010-2014. The combination of novel algorithm development and practical application (of novel as well as well established methods) to solve biomedical questions approached by microscopy has turned out to be very fruitful. It pushes the biomedical research forward, at the same time as it brings our focus to the most relevant problems.

CV for Ewert Bengtsson 2015

1. **Higher education qualifications:** MSc in Eng. Physics (Civ.ing. i teknisk fysik) from Uppsala University in 1974

2. **Doctoral degree:** PhD in Physics from Uppsala University, 1977. Thesis: On the Design of Systems for Computer Aided Analysis of Microscopic Images. Application to early detection of cervical cancer. Supervisor: Kai Siegbahn, (Nobel Laureate 1981) Assistant supervisors: Björn Stenkvist, Bengt Olsen

3. **Postdoctoral position:** Electrotechnical Laboratories, Tsukuba, Japan, 1983

4. **Qualifications required for appointment as a docent:** Docent in scientific computing, at Uppsala University, 1980.

5. **Current position:** Professor of Computerized image analysis at Uppsala university, since 1996, about 80% of full time available for research

6. **Previous positions and periods of appointment**
    a. Research assistant for image analysis of cervical smears 1973 - 1978.
    b. Scientific director of the Image Analysis Lab. of Uppsala Univ. 1979 -1984.
    c. Project leader for developing an automated screening microscope 1983 - 1984
    d. Head of development at IMTEC - Image Technology AB 1984 - 1989.
    e. Adjunct professor of digital image processing at Uppsala Univ. 1988-1996
    f. Chairman of the board and consultant in image processing technology for Uppsala Bildbehandling AB, 1988-1999.
    g. Director of the Centre for Image Analysis 1988-1990, 1992-1996, 2005-2010
    h. Vice rektor/rektorsråd i.e. senior advisor to the vice chancellor of Uppsala University on Information Technology, 30% of full time 1998-2011

7. **Interruption in research.** Parental leave 3 months 1984.

8. **Supervision:**

People awarded doctorates with Bengtsson as main supervisor (26):
Dahlqvist Bengt, 1988, Nordin Bo, 1989, Orbert Curt, 1993, Pedersen Finn, 1994, Thurfjell Lennart, 1994, Wester (Johansson) Tomas, 1994, Choi Heung-Kook, 1996, Jarkrans Torsten, 1996, Nyström Ingela, 1997, Ranefall Petter, 1998, Frimmel Hans, 1999, Östlund Catherine, 1999, Lundqvist Roger, 2001, Lindblad Joakim, 2003, Ammenberg Petra, 2003, Hult Roger, 2003, Wählby Carolina 2003, Hast Anders, 2004, Wehrmann Felix, 2004, Muhammed Hamed Hamid, 2005, Razifar Pascha, 2005, Åhlen Julia, 2005, Karlsson Patrick, 2008, Gedda Magnus 2010, Niazi Khalid 2011, Malm Patrik 2014

With Bengtsson as assistant supervisor (7):

Vidholm Erik, 2008, Pinidiyaarachchi Amalka 2009, Allalou Amin 2011, Gavrilovic Milan 2011, Malmberg Filip 2011, Kårsnäs Andreas 2014, Azar Jimmy 2014.

Current PhD students under my supervision (main or assistant) (9):

Olsson Pontus, Linnér Elisabeth, Wahlberg Fredrik, Lidayová Kristina, Ishaq Omer, Liu Fei, Ram Kaylan, Sadanandan Kecheril Sajith, Wilkinson Tomas.

9. Other information of relevance to the application

Distinctions

a. Member of Royal Society of Sciences at Uppsala since 2000

b. Member of the Royal Academy of Engineering Sciences, IVA since 2006

c. Recipient of the Gustaf Adolf Gold Medal from Uppsala University 2013

d. Fellow of IEEE 2015

e. Dean of the Division of Mathematics and Computer Science of the Faculty of Science and Technology at Uppsala Univ. 1996 – 1998.

Invited plenary presentations

Invited presentations about medical image analysis, mainly microscopy to international conferences during the last 8 years in: Korea, Australia, India, China, Sri Lanka, Indonesia, Canada, France, USA.

Date/place of birth: August 5, 1960 in Krylbo, Sweden
Civil status: Two children (born 1996 and 1999)
Home address/phone: Vretavägen 24, S-755 91 Uppsala, Sweden. Phone +46-70-3975256

1. Högskoleexamen

M.Sc. (Civ. Ing.) Teknisk Fysik, Uppsala University 1982

2. Doktorsexamen

Dr. Sc. (Tekn. dr.), Materials Science, Uppsala University 1988
Avhandlingens titel: "Micromechanical Properties of Silicon"
Handledare: Jan-Åke Schweitz

3. Postdoktorvistelser

Visiting professor, Institute of Solid State Electronics, Rome, Italy 1989/1990

4. Docentkompetens

Assoc. professor (Docent) in Materials Science, Uppsala University 1994

5. Nuvarande anställning

Adjunct professor in materials science, Uppsala University 2009-

6. Tidigare anställningar och förordnandetider

Graduate student, Materials Science, Uppsala University	1983-1988
Assistant professor in Materials Science, Uppsala University	1988-1989, 1990-1994
Assoc. professor (Docent) in Materials Science, Uppsala University	1994-1997
"Universitetslektor" in Materials Science, Uppsala University	1997-2000
Prof. in Materials Science (microactuator technology), Uppsala University	2000-2006

7. **Uppehåll i forskningen**

Military service, in total 12 months	1983-1984
Parental leave, part time, in total 6 months	1997-2002
Leave of absence (spin-off company), 40-50%	1999-2006
Industry (confidential) research, 80%	2006-2013

In 1997 I co-founded the spin-off company Piezomotor Uppsala AB and were head of research until 2013. To support the company full time during a critical period I had to leave my position as professor at Uppsala University 2006. I did however continue to supervise three graduate students part time during 2006-2009. Most of the research at the company concerns actuator and processing technology that cannot be published.

8. Huvudhandledare för personer som avlagt doktorsexamen

Mats Bexell	1998
Urban Simu	2002
Tobias Lilliehorn	2003
Niklas Snis	2008
Erik Edqvist	2009
Linda Johansson	2009

Publication list

Publication list – Joakim Lindblad

Total number of citations: 565 ***Statistics from Google Scholar 2015-03-26***
Self citations have been removed (using CIDS)

Five most cited papers

1. C. Wählby, J. Lindblad, M. Vondrus, E. Bengtsson, and L. Björkesten. Algorithms for cytoplasm segmentation of fluorescence labeled cells. Analytical Cellular Pathology, 24(2,3):101-111, 2002. Number of citations: 130
2. J. Lindblad, C. Wählby, E. Bengtsson, and A. Zaltsman. Image Analysis for Automatic Segmentation of Cytoplasms and Classification of Rac1 Activation, Cytometry Part A 57A(1):22-33, 2004. Number of citations: 77
3. E. Bengtsson, C. Wählby, and J. Lindblad. Robust Cell Image Segmentation Methods. Pattern Recognition and Image Analysis, Vol. 14, No. 2, pp. 157-167, 2004. Number of citations: 54
4. J. Lindblad. Surface Area Estimation of Digitized 3D Objects using Weighted Local Configurations. Image and Vision Computing, Vol. 23, No. 2, pp. 111-122, 2005. Number of citations: 48
5. J. Liu, A.-S. Höglund, P. Karlsson, J. Lindblad, R. Qaisar, S. Aare, E. Bengtsson, and L. Larsson. Myonuclear domain size and myosin isoform expression in muscle fibers from mammals representing a 100,000-fold difference in body size. Experimental Physiology, Vol. 94, No. 1, pp. 117-129, 2009. Number of citations: 27

Peer-reviewed original articles, 2007–2015

1. A. Tanács, J. Lindblad, N. Sladoje, and Z. Kato. Estimation of Linear Deformations of 2D and 3D Fuzzy Objects. Pattern Recognition, Vol 48, No. 4, pp. 1387-1399, 2015. Number of citations: 0
2. J. Lindblad and N. Sladoje. Linear time distances between fuzzy sets with applications to pattern matching and classification. IEEE Transactions on Image Processing. Vol. 23, No. 1, pp. 126-136, 2014. Number of citations: 2
3. V. Ćurić, J. Lindblad, N. Sladoje, H. Sarve, and G. Borgefors. A new set distance and its application to shape registration. Pattern Analysis and Applications, Vol 17, No. 1, pp 141-152, 2014. Number of citations: 3
4. * M. Gavrilovic, J. C. Azar, J. Lindblad, C. Wählby, E. Bengtsson, C. Busch, I. B. Carlbom. Blind Color Decomposition of Histological Images. IEEE Transactions on Medical Imaging, Vol. 32, No. 6, pp. 983-994, 2013. Number of citations: 11
5. J. Lindblad and N. Sladoje. Coverage Segmentation Based on Linear Unmixing and Minimization of Perimeter and Boundary Thickness. Pattern Recognition Letters. Vol. 33, No. 6, pp. 728-738, 2012. Number of citations: 1
6. * T. Lukić, J. Lindblad, and N. Sladoje. Regularized image denoising based on spectral gradient optimization. Inverse Problems. Vol. 27, No. 8, 2011. Number of citations: 6
7. F. Malmberg, J. Lindblad, C. Östlund, K.M. Almgren, E.K. Gamstedt. Measurement of fibre-fibre contact in three-dimensional images of fibrous materials obtained from X-ray

synchrotron microtomography. Nuclear Instruments and Methods in Physics Research Section A. Vol. 637,No 1, pp. 143-148, 2011. Number of citations: 5

8. H. Sarve, J. Lindblad, G. Borgefors, and C.B. Johansson. Extracting 3D Information on Bone Remodeling in the Proximity of Titanium Implants in SRμCT Image Volumes. Computer Methods and Programs in Biomedicine. Vol. 102, No 1, pp. 25-34, 2011. Number of citations: 8
9. F. Malmberg, J. Lindblad, N. Sladoje, and I. Nyström. A Graph-based Framework for Sub-pixel Image Segmentation. Theoretical Computer Science. Vol. 412, No 15, pp. 1338-1349, 2011. Number of citations: 9
10. N. Sladoje, J. Lindblad, and I. Nyström. Defuzzification of spatial fuzzy sets by feature distance minimization. Image and Vision Computing. Vol. 29, No 2-3, pp. 127-141, 2011. Number of citations: 6
11. A. Cristea, R. Qaisar, P. Karlsson Edlund, J. Lindblad, E. Bengtsson, and L. Larsson. Effects of aging and gender on the spatial organization of nuclei in single human skeletal muscle cells. Aging Cell, Vol. 9, No 5, pp. 685-697, 2010. Number of citations: 11
12. A. Cristea, P. Karlsson Edlund, J. Lindblad, R. Qaisar, E. Bengtsson, and L. Larsson. Effects of ageing and gender on the spatial organization of nuclei in single human skeletal muscle cells. Neuromuscular Disorders, Vol. 19, No. 8, pp. 605-606, 2009. Number of citations: 0
13. K.M. Almgren, E.K. Gamstedt, P. Nygård, F. Malmberg, J. Lindblad, and M. Lindström. Role of fibre-fibre and fibre-matrix adhesion in stress transfer in composites made from resin-impregnated paper sheets. International Journal of Adhesion and Adhesives. Vol. 29, No. 5, pp. 551-557, 2009. Number of citations: 12
14. N. Sladoje and J. Lindblad. High Precision Boundary Length Estimation by Utilizing Gray-Level Information. IEEE Transactions on Pattern Analysis and Machine Intelligence, Vol. 31, No. 2, pp. 357-363, 2009. Number of citations: 23
15. J. Liu, A.-S. Höglund, P. Karlsson, J. Lindblad, R. Qaisar, S. Aare, E. Bengtsson, and L. Larsson. Myonuclear domain size and myosin isoform expression in muscle fibers from mammals representing a 100,000-fold difference in body size. Experimental Physiology, Vol. 94, No. 1, pp. 117-129, 2009. Number of citations: 27
16. N. Sladoje and J. Lindblad. Representation and Reconstruction of Fuzzy Disks by Moments. Fuzzy Sets and Systems, Vol. 158, No. 5, pp. 517-534, 2007. Number of citations: 4

Peer-reviewed conference contributions, 2007–2015

1. * J. Lindblad, E. Bengtsson, and N. Sladoje. Microscopy Image Enhancement for Cost-Effective Cervical Cancer Screening. Accepted for the 19th Scandinavian Conference on Image Analysis, SCIA 2015. Number of citations: 0
2. J. Lindblad and N. Sladoje. Exact Linear Time Euclidean Distance Transforms of Grid Line Sampled Shapes. Accepted for the 12th Int. Symp.on Mathematical Morphology, ISMM 2015. Number of citations: 0
3. * B. Bajić, J. Lindblad, and N. Sladoje. An Evaluation of Potential Functions for Regularized Image Deblurring. In Proceedings Part I of the 11th International Conference on Image Analysis and Recognition (ICIAR), LNCS-8814, pp. 150-158, Vilamoura, Portugal, Oct. 2014. Number of citations: 0

4. * J. Lindblad, N. Sladoje, P. Malm, E. Bengtsson, R. Moshavegh, and A. Mehnert. Optimizing optics and imaging for pattern recognition based screening tasks. In Proceedings of the 22th International Conference on Pattern Recognition (ICPR), IEEE, pp. 3333-3338, Stockholm, Sweden, Aug. 2014. Number of citations: 0
5. K. Lidayova, J. Lindblad, N. Sladoje and H. Frimmel. Coverage segmentation of thin structures by linear unmixing and local centre of gravity attraction. In Proceedings of the 8th IEEE International Symposium on Image and Signal Processing and Analysis (ISPA). IEEE, pp. 83-88, Trieste, Italy, Sept. 2013. Number of citations: 1
6. S. Dražić, J. Lindblad, and N. Sladoje. Precise Estimation of the Projection of a Shape from a Pixel Coverage Representation. In Proceedings of the 7th IEEE International Symposium on Image and Signal Processing and Analysis (ISPA). IEEE, pp. 569-574, Dubrovnik, Croatia, Sept. 2011. Number of citations: 0
7. V. Ćurić, J. Lindblad, and N. Sladoje. Distance measures between digital fuzzy objects and their applicability in image processing. In Proceedings of the 14th International Workshop on Combinatorial Image Analysis (IWCIA), LNCS-6636, pp. 385-397, Madrid, Spain, May. 2011. Number of citations: 0
8. Tanács, J. Lindblad, N. Sladoje, and Z. Kato. Estimation of linear deformations of 3D objects. In Proceedings of International Conference on Image Processing (ICIP), IEEE, Hong Kong, China, pp. 153-156, Sept. 2010. Number of citations: 1
9. H. Sarve, J. Lindblad, C.B. Johansson, and G. Borgefors. Methods for Visualization of Bone Tissue in the Proximity of Implants. Proceedings of the International Conference on Computer Vision and Graphics (ICCVG), LNCS-6375, pp. 243-250, Warsaw, Poland, Sept. 2010. Number of citations: 0
10. J. Lindblad, N. Sladoje, and T Lukić. De-noising of SRμCT Fiber Images by Total Variation Minimization. In Proceedings of the 20th International Conference on Pattern Recognition (ICPR), IEEE, pp. 4621-4624, Istanbul, Turkey, Aug. 2010. Number of citations: 2
11. Malmberg, J. Lindblad, and I. Nyström. Sub-pixel Segmentation with the Image Foresting Transform. In Proceedings of the 13th International Workshop on Combinatorial Image Analysis (IWCIA), LNCS-5852, pp. 201-211, Playa del Carmen, Mexico, Nov. 2009. Number of citations: 9
12. J. Lindblad, V. Ćurić, and N. Sladoje. On set distances and their application to image registration. In Proceedings of the 6th International Symposium on Image and Signal Processing and Analysis (ISPA), IEEE, pp. 449-454, Salzburg, Austria, Sept. 2009. Number of citations: 0
13. N. Sladoje, J. Lindblad. Pixel coverage segmentation for improved feature estimation. In Proceedings of the 15th International Conference on Image Analysis and Processing (ICIAP), LNCS-5716, pp. 929-938, Vietri sul Mare, Italy, Sept. 2009. Number of citations: 3
14. Lindblad, N. Sladoje, V. Ćurić, H. Sarve, C.B. Johansson, and G. Borgefors. Improved quantification of bone remodelling by utilizing fuzzy based segmentation. In Proceedings of the 16th Scandinavian Conference on Image Analysis (SCIA), LNCS-5575, pp. 750-759, Oslo, Norway, June 2009. Number of citations: 0
15. H. Sarve, J. Lindblad, and C. B. Johansson. Quantification of Bone Remodeling in SRμCT Images of Implants. In Proceedings of the 16th Scandinavian Conference on Image Analysis (SCIA), LNCS-5575, pp. 770-779, Oslo, Norway, June 2009. Number of citations: 0

16. Tanács, C. Domokos, N. Sladoje, J. Lindblad, and Z. Kato. Recovering affine deformations of fuzzy shapes. In Proceedings of the 16th Scandinavian Conference on Image Analysis (SCIA), LNCS-5575, pp. 735-744, Oslo, Norway, June 2009. Number of citations: 1
17. K. Norell and J. Lindblad. Spatially-Variant Morphological Operations on Binary Images based on the Polar Distance Transform. In Proceedings of the 19th International Conference on Pattern Recognition (ICPR), IEEE, Tampa, USA, Dec. 2008. Number of citations: 1
18. H. Sarve, J. Lindblad, and C. B. Johansson. Registration of 2D Histological Images of Bone Implants with 3D SRμCT Volumes. In Proceedings of the 4th International Symposium on Advances in Visual Computing (ISVC), LNCS-5358, pp. 1071-1080, Las Vegas, USA, Dec. 2008. Number of citations: 2
19. T. Lukić, N. Sladoje, J. Lindblad. Deterministic Defuzzification based on Spectral Projected Gradient Optimization. In Proceedings of the 30th Symposium of the German Association for Pattern Recognition (DAGM), LNCS-5096, pp. 476-485, Munich, Germany, June 2008. Number of citations: 2
20. P. Karlsson Edlund, J. Lindblad. Non-uniform 3D distance transform for anisotropic signal correction in confocal image volumes of skeletal muscle cell nuclei. In Proceedings of the 5th IEEE International Symposium on Biomedical Imaging (ISBI), IEEE, pp. 1363-1366. Paris, France, May 2008. Number of citations: 0
21. J. Lindblad, T. Lukić, and N. Sladoje. Defuzzification by Feature Distance Minimization Based on DC Programming. In Proceedings of the 5th International Symposium on Image and Signal Processing and Analysis (ISPA), IEEE, pp. 373-378, Istanbul, Turkey, Sept. 2007. Number of citations: 0
22. K. Norell, J. Lindblad, and S. Svensson. Grey Weighted Polar Distance Transform for Outlining Circular and Approximately Circular Objects. In Proceedings of the 14th International Conference on Image Analysis and Processing (ICIAP), IEEE, pp. 647-652, Modena, Italy, Sept. 2007. Number of citations: 3
23. H. Sarve, J. Lindblad, C. B. Johansson, G. Borgefors, V. F. Stenport. Quantification of Bone Remodeling in the Proximity of Implants, In Proceedings of the 12th International Conference on Computer Analysis of Images and Patterns (CAIP), LNCS-4673, pp. 253-260, Vienna, Austria, Aug. 2007. Number of citations: 0

Books and book chapters

1. N. Sladoje and J. Lindblad. The coverage model and its use in image processing. Book chapter in: Selected Topics on Image Processing and Cryptology (Ed. Miodrag Mihaljević), Zbornik Radova, No 15(23), pp. 39-117, Mathematical Institute of the Serbian Academy of Sciences and Arts, Belgrade, 2012. ISSN: 0351-9406, ISBN: 978-86-80593-47-0. Number of citations: 0

* = most relevant papers for this application.

Publication list, Carolina Wählby, 19740131-0268

Citations as given by Scopus (Elsevier, scopus.com). The five publications most relevant for the project are marked with a *.

Peer-reviewed original articles (past 8 years + most cited of previous publications)

1. *B. Koos, M. Kamali-Moghaddam, L. David, M Sobrinho-Simões, A. Dimberg, M. Nilsson, **C. Wählby**, and O. Söderberg. Next generation Pathology - surveillance of tumor microecology. J Mol Biol., 2015 Feb 25. pii: S0022-2836(15)00111-4. doi: 10.1016/j.jmb.2015.02.017. Number of citations: 0
2. *R. Ke, M. Mignardi, A. Pacureanu, J. Svedlund, J. Botling, **C. Wählby**, and M. Nilsson. In situ sequencing for RNA analysis in preserved tissue and cells. Nature Methods, 2013 Jul 14. Number of citations: 18.
3. **C. Wählby**, et al. An image analysis toolbox for high-throughput *C. elegans* assays. Nature Methods, 2012 Apr 22; 9(7): 714-716. PMID: 22522656. Number of citations: 20
4. *C-M. Clausson, A. Allalou, I. Weibrecht, S. Mahmoudi, M. Farnebo, U. Landegren, **C. Wählby** and O. Söderberg. Increasing the dynamic range of *in situ* PLA. Nature Methods, 2011;8(11):892-3. Number of citations: 17
5. **C. Wählby**, I.-M. Sintorn, F. Erlandsson, G. Borgefors and E. Bengtsson. Combining intensity, edge, and shape information for 2D and 3D segmentation of cell nuclei in tissue sections. Journal of Microscopy, 215(1):67-76, July 2004. PMID: 15230877. Number of citations: 121
6. O. Ishaq, J. Elf, and **C. Wählby**. An evaluation of the faster STORM method for super-resolution microscopy. Proc IEEE ICPR 2014, 22nd Int. Conf. on Pattern Recognition, Stockholm, Sweden.
7. *M. Gavrilovic, J.C. Azar, J. Lindblad, **C. Wählby** et al. Blind color decomposition of histological images. IEEE Transactions on Medical Imaging, 2013 Jun; 32(6):983-94. Number of citations: 5
8. **C. Wählby**, A.L. Conery, M.A. Bray, L. Kamentsky, J Larkins-Ford, KL Sokolnicki, M Veneskey, K Michaels, A.E. Carpenter, and E.J. O'Rourke EJ. High- and low-throughput scoring of fat mass and body fat distribution in C. elegans. Methods, 2014 Aug 1;68(3):492-9. PMID: 24784529. Number of citations: 3
9. Allalou and **C. Wählby**. BlobFinder; a tool for fluorescence microscopy image cytometry. Computer Methods and Programs in Biomedicine, 2009 Apr;94(1):58-65. Number of citations: 50
10. M.A. Khorshidi, P.K.P. Rajeswari, **C. Wählby**, H.N. Joensson and H. Andersson Svahn. Automated analysis of dynamic behavior of single cells in picoliter droplets. Lab on a Chip, 2014(14), 931-7. Number of citations: 2
11. N.V. Kirienko,.., **C. Wählby**,.., F.M. Ausubel. Pseudomonas aeruginosa disrupts C. elegans iron homeostasis causing a hypoxic response and death. Cell Host & Microbe, 2013;13(4):406-16 Number of citations: 12
12. C. Pardo-Martin, A. Allalou, J. Medina, P.M. Eimon, **C. Wählby**, and M.F. Yanik. High-throughput hyperdimensional vertebrate phenotyping. Nature Communications, 2013 Feb 12; 4:1467, Number of citations: 6
13. A.K. Raap, …, **C. Wählby**, …,G.M.C. Janssen. Non-random mtDNA segregation patterns indicate a metastable heteroplasmic segregation unit in m.3243A>G cybrid cells. PLos One, 2012;7(12). Number of citations: 1
14. *S.I. Niwas, …, **C. Wählby**, and R. Strand. Automated classification of immunostaining patterns in breast tissue from the Human Protein Atlas. Journal of Pathology Informatics, 2013 Mar 30;4(Suppl):S14.
15. T.Y. Chang, C. Pardo-Martin, A. Allalou, **C. Wählby** and M.F. Yanik. Fully automated cellular-resolution vertebrate screening platform with parallel animal processing. Lab on a Chip, 2012;12(4):711-6. Number of citations: 26
16. Weibrecht, M. Gavrilovic, L. Lindbom, U. Landegren, **C. Wählby** and O. Söderberg. Visualising individual sequence-specific protein-DNA interactions *in situ*. New Biotechnology, 2012;29(5):589-98. Number of citations: 11

17. M. Gavrilovic, …, **C. Wählby**. Automated classification of multi-colored rolling circle products in dual-channel wide-field fluorescence microscopy. Cytometry A. 2011 79(7) 518-27. Number of citations: 3
18. **C. Wählby**, T. Riklin-Raviv, V. Ljosa, A.L. Conery, P. Golland, F.M. Ausubel, and A.E. Carpenter. Resolving clustered worms via probabilistic shape models. IEEE ISBI. 2010 Jun 21;2010:552-5. Number of citations: 7
19. A. Zieba, **C. Wählby**, et al. Bright-field microscopic visualization of proteins and protein complexes by in situ proximity ligation with peroxidase detection. Clinical Chemistry. 2010 Jan;56(1):99-110. Number of citations: 21
20. A . Allalou, A. Pinidiyaarachchi, **C. Wählby**. Robust signal detection in 3D fluorescence microscopy. Cytometry A. 2009 Sep; 77A(1):86-96. Number of citations: 2
21. M. Gavrilovic and **C. Wählby**. Quantification of colocalization and cross-talk based on spectral angles. J Microsc. 2009 Jun;234(3):311-24. Number of citations: 11
22. Pinidiyaarachchi, A. Allalou, A. Zieba, K. Pardali and **C. Wählby**. A detailed analysis of 3D subcellular signal localization. Cytometry A. 2009 Apr; 75(4):319-28. Number of citations: 2
23. J. Göransson, **C. Wählby**, M. Isaksson, M. Howell, J. Jarvius and M. Nilsson.A single molecule array for digital targeted molecular analyses. Nucleic Acids Res. 2009 Jan;37(1):e7. Number of citations: 10
24. Wählby, P. Karlsson, S. Henriksson, C. Larsson, M. Nilsson and E. Bengtsson. Finding cells, finding molecules, finding patterns. Int. J. of Signal and Imaging Systems Engineering, 1(1):11-17, 2008. Number of citations: 1
25. R.S. Jahangir Tafrechi, …, **C. Wählby**, et al. Single-cell A3243G Mitochondrial DNA Mutation Load Assays for Segregation Analysis. J. of Histochemistry and Cytochemistry, 2007 55: 1159-1166. Number of citations: 8
26. M. Jarvius, J…, **C. Wählby**, et al. In situ detection of phosphorylated PDGF receptor beta using a generalized proximity ligation method. Molecular and Cellular Proteomics, 6:1500-9, 2007. Number of citations: 105
27. J. Lindblad, **C. Wählby**, E. Bengtsson and A. Zaltsman. Image analysis for automatic segmentation of cells and classification of Rac1 activation. Cytometry, 57A(1):22-33, 2004. Number of citations: 53
28. **C. Wählby**, J. Lindblad, M. Vondrus, E. Bengtsson and L. Björkesten. Algorithms for cytoplasm segmentation of fluorescence labeled cells. Analytical Cellular Pathology, 24(2,3):101-11, 2002.Number of citations: 89

Peer-reviewed conference contributions, past 8 years

1. A. Allalou, F.M. van de Rijke, R. Jahangir Tafrechi, A.K. Raap, and **C. Wählby**. Image based measurements of single cell mtDNA mutation load. Presented at SCIA07 (Scandinavian Conference on Image Analysis), Aalborg, June 10-14, 2007. p. 631-640 (Lecture Notes in Computer Science; 4522, Springer). Available on line from http://www.springerlink.com/content/b12548446765l017/ Number of citations: 4
2. M. Gavrilovic and **C. Wählby**. Suppression of Autofluorescence based on Fuzzy Classification by Spectral Angles. Presented at MICCAI 2009, the 12th International Conference on Medical Image Computing and Computer Assisted Intervention, Workshop on Optical Tissue Image analysis in Microscopy, Histopathology and Endoscopy, September 20-24, Imperial College London, UK, 2009, pp135-146.
3. **C. Wählby**, T. Riklin-Raviv, V. Ljosa, A.L. Conery, P. Golland, F.M. Ausubel, and A.E. Carpenter. Resolving clustered worms via probabilistic shape models. Proc IEEE Int Symp Biomed Imaging. 2010 Jun 21;2010(14-17 April 2010):552-555. PMCID: PMC3048333
4. T. Riklin Raviv, V. Ljosa, A.L. Conery, F.M. Ausubel, A.E. Carpenter, P. Golland and **C. Wählby**. Morphology-Guided Graph Search for Untangling Objects: *C. elegans* Analysis. Med Image Comput Comput Assist Interv. 2010;13(Pt 3):634-41. PMCID: PMC3050593. Number of citations: 7
5. K. Althoff, …, **C. Wählby**, et al. Time-Lapse Microscopy and Classification of in Vitro Cell Migration Using Hidden Markov Modeling. IEEE Xplore; IEEE ICASSP, 2006. Number of citations: 2

6. O. Ishaq, J. Negri, M-A. Bray, A. Pacureanu, R.T. Peterson, and **C. Wählby**. Automated quantification of zebrafish tail deformation for high-throughput drug screening. IEEE Int Symp Biomed Imaging 2013: 902-5
7. A. Pacureanu, R. Ke, M. Mignardi, M. Nilsson, and **C. Wählby**. Image based in situ sequencing for RNA analysis in tissue. Proc IEEE ISBI 2014, International Society of Biomedical Imaging, 29 April - 2 May, 2014, Beijing, China.
8. O. Ishaq, J. Elf, and **C. Wählby**. An evaluation of the faster STORM method for super-resolution microscopy. Proc IEEE ICPR 2014, 22nd International Conference on Pattern Recognition, August 24-28, 2014, Stockholm, Sweden.

Patents

C. Wählby, M. Gavrilovic, E. Bengtsson, J. Lindblad: "Pixel Classification in Image Analysis", Swedish patent pending, filed 19 Feb 2008.

Open access computer programs that you have developed

1. 'Blob Finder', developed at CBA by Amin Allalou and Carolina Wählby in cooperation with Olink AB. 'BlobFinder' is freely distributed software with a graphical user interface that can perform simple calculations on cells from fluorescence microscopy images (mainly PLA). http://www.cb.uu.se/~amin/BlobFinder.
2. The WormToolbox, developed at the Imaging Platform of the Broad Institute of Harvard and MIT, and part of the free and open source CellProfiler software, downloadable from www.cellprofiler.org. Description of the software published in Wählby et al, Nature Methods, 2012 Apr 22; 9(7): 714-716.

List of Publications for Ewert Bengtsson since 2007

Total number of citations excluding self-citations: 2570

Five most cited papers (statistics from Google Scholar 2015-03-28)

1 Combining intensity, edge and shape information for 2D and 3D segmentation of cell nuclei in tissue sections. C Wählby, I Sintorn, F Erlandsson, G Borgefors, E Bengtsson. Journal of Microscopy 215:67-76, 2004. **Number of citations: 181**

2 * A Feature Set for Cytometry on Digitized Microscopic Images. K Rodenacker, E Bengtsson. Analytical Cellular Pathology, 24:1-36, 2003. N**umber of citations: 150**

3 Algorithms for cytoplasm segmentation of fluorescence labelled cells. C. Wählby, J Lindblad, M Vondrus, E Bengtsson and L Björkesten. Analytical Cellular Pathology 24:101-111, 2002. **Number of citations: 130**

4 Analysis of reproducibility of subjective grading systems for breast carcinoma. B Stenkvist, S Westman-Naeser, J Vegelius, J Holmquist, B Nordin, E Bengtsson, O Eriksson. J. of clinical pathology 32 (10), 979-985, 1979 **Number of citations: 113**

5 Cardiac glycosides and breast cancer. B Stenkvist, E Bengtsson, O Eriksson, J Holmquist, B Nordin, S Westman-Naeser, G Eklund. The Lancet 313: 563, 1979 **Number of citations: 96**

1. Peer-reviewed original journal articles, since 2007

1. Application of Underwater Hyperspectral Data for Color Correction Purposes. J Åhlen, D Sundgren, E Bengtsson. Pattern Recognition and Image Analysis, Vol 17, No 1, pp 170-173, 2007. **Number of citations: 6**

2. Finding cells, finding molecules, finding patterns. C Wählby, P Karlsson, S Henriksson, C Larsson, M Nilsson, E Bengtsson. International Journal on Signal and Imaging Systems Engineering 1(1), pp. 11–17, 2008 **Number of citations: 5**

3. Myonuclear domain size and myosin isoform expression in muscle fibres from mammals representing a 100 000-fold difference in body size. J-X Liu, A-S Höglund, P Karlsson, J Lindblad, R Qaisar, S Aare, E Bengtsson, L Larsson. Experimental Physiology, 94 (1):117-129, 2009. **Number of citations: 27**

4. Fully Automatic Heart Beat Rate Determination in Digital Video Recordings of Rat Embryos., M K K Niazi, M Nilsson, B Danielsson, E Bengsson. Transactions on Mass-Data Analysis of Images and Signals 1(2), pp. 132–146, 2009. **Number of citations: 2**

5. Performance of Principal Component Analysis and Independent Component Analysis with Respect to Signal Extraction from Noisy Positron Emission Tomography Data: a Study on Computer Simulated Images. P Razifar, H M Hamed, F Engbrant, P-E Svensson, J Olsson, E Bengtsson, B Långström, M Bergström. Open Neuroimaging Journal 1(3), pp. 1–16, 20 N**umber of citations: 1**

6. Improved methodology for identifying the teratogenic potential in early drug development of hERG channel blocking drugs. M Nilsson, C Danielsson, A Sköld, A Johansson, B Blomgren, J Wilson, K Khan , E Bengtsson, K Kultima, WS Webster, BR Danielsson. Reproductive Toxicology. 29(2):156-163, 2010. **Number of citations: 7**

7. Effects of aging and gender on the spatial organization of nuclei in single human skeletal muscle cells. A Cristea , R Qaisar, P Karlsson Edlund, J Lindblad, E Bengtsson, L Larsson. Aging Cell. 9(5):685-697,2010. **Number of citations: 11**

8. Signal Extraction and Separation in In Vivo Animal PET Studies with Masked Volumewise Principal-Component Analysis. F Engbrant, A Monazzam, P-E

Svensson, J Olsson, E Bengtsson, P Razifar. Journal of Nuclear Medicine Technology. 38(2):53-60, 2010. **Number of citations: 0**

9. Characterization and reduction of noise in dynamic PET data using masked volume wise principal component analysis. Per-Edvin Svensson, J Olsson, F Engbrant, E Bengtsson, P Razifar. Nucl Med Technol. 39(1):27-34, 2011 **Number of citations: 2**

10. Color deconvolution method for breast tissue core biopsy images cell nuclei detection and analysis using multiresolution techniques. I Niwas, S Palanisamy, E Bengtsson. International Journal of Imaging and Robotics. 2013;9(1):61-72. **Number of citations: 0**

11. Blind Color Decomposition of Histological Images. Gavrilovic, M., Azar, J., Lindblad, J., Wahlby, C., Bengtsson, E., Busch, C., Carlbom, I. IEEE Transactions on Medical Imaging, 32(6), 983-994, 2013. **Number of citations: 11**

12. * Debris removal in Pap-smear images. P Malm, R Kumar,V K. Sujathan, E Bengtsson. Computer Methods and Programs in Biomedicine, 111(1),128-138, 2013 **Number of citations: 5**

13. * Analysis of nuclei textures of fine needle aspirated cytology images for breast cancer diagnosis using Complex Daubechies wavelets.S Issac Niwas, P Palanisamy, K Sujathan, E Bengtsson, Signal Processing 93 (10), 2828-2837, 2013. **Number of citations: 9**

14. Image Segmentation and Identification of Paired Antibodies in Breast Tissue. J C Azar, M Simonsson, E Bengtsson, A Hast. Computational & Mathematical Methods in Medicine, 11p. 2014. **Number of citations: 0**

15. Screening for Cervical Cancer Using Automated Analysis of PAP-Smears. E Bengtsson, P Malm Journal: Computational and Mathematical Methods in Medicine, 12p. 2014. **Number of citations: 0**

16. 3D Texture Analysis in Renal Cell Carcinoma Tissue Image Grading Authors: T-Y Kim, N-H Cho, G-B Jeong, E Bengtsson, H-K Choi. Computational and Mathematical Methods in Medicine, 12p.2014. **Number of citations: 0**

17. Simulation of bright-field microscopy images depicting pap-smear specimen P Malm, A Brun, E Bengtsson - Cytometry Part A, 2015. **Number of citations: 0**

2. Peer-reviewed Conference Contributions since 2007

1. The spatial distribution of nuclei in single skeletal muscle cells as visualised by 3-D images: the differences in organisation between species and between healthy cells and cells affected by disease Authors: Höglund, A.-S., Liu, J.,Karlsson, P., Lindblad, J., Borgefors, G., Bengtsson, E., Larsson, L. Biophysical Society, 51st annual meeting, Baltimore ML. Biophysical Journal 637A Suppl. S. 2007, **Number of citations: 0**

2. Hardware-accelerated volume visualization of parametrically mapped dynamic breast MRI data Authors: Vidholm, E., Mehnert, A.,Bengtsson, E., Wildermoth, M., McMahon, K., Wilson, S., Crozier, S.. Proceedings of Workshop on Interaction in medical Image analysis and visualization at 10th International Conference on Medical Image Computing and Computer Assisted Intervention , MICCAI, pp. 33–40, 2007. **Number of citations: 2**

3. Segmentation and Visualization of 3D Medical Images through Haptic Rendering. Ingela Nyström, Malmberg, Filip, Vidholm, Erik, Bengtsson, Ewert. 10th International Conference on Pattern Recognition and Information Processing, Minsk, Belarus (PRIP'09), pp. 43–48, 2009. **Number of citations: 4**

4. Vectorized table driven algorithms for double precision elementary functions using Taylor expansions. Tony Barrera, D Spångberg, Anders Hast, Ewert Bengtsson. In:

8th International Conference on Applied Mathematics (APLIMAT), 231-245, 2009.
Number of citations: 0

5. Image-Based Comparison of Pre-modern Coins and Medals. J Hedrich, D Paulus, H Mäkeler, E Bengtsson 16 Workshop Farbbildverarbeitung, 156-169, 2010

   Number of citations: 0

6. Two Non-linear Parametric Models of Contrast Enhancement for DCE-MRI of the Breast Amenable to Fitting Using Linear Least Squares. A Mehnert, M Wildermoth, S Crozier, E Bengtsson, D Kennedy. In: Proceedings 2010 International Conference on Digital Image Computing: Techniques and Applications (DICTA 2010). IEEE Computer Society; p. 611-616, 2010. **Number of citations: 0**
7. Relaxed Image Foresting Transforms for Interactive Volume Image Segmentation. F Malmberg, I Nyström, A Mehnert, C Engstrom, E Bengtsson. Proceedings of SPIE, 6p. 2010. **Number of citations: 5**
8. Papsynth: Simulated bright-field images of cervical smears. P Malm, A Brun, E Bengtsson. ISBI 2010, IEEE Symposium on Biomedical Imaging: From Nano to Macro, Rotterdam, 4p. 2010. **Number of citations: 2**
9. Recognizing signs of malignancy: The quest for computer assisted cancer screening and diagnosis systems. E Bengtsson. In: Int. Conference on Computational Intelligence and Computing Research (ICCIC), IEEE Explore, pp. 1–6, 2010.
   Number of citations: 4
10. Automated segmentation of free-lying cell nuclei in Pap smears for malignancy-associated change analysis. R Moshavegh, B E Bejnordi, A Mehnert, K Sujathan, P Malm, E Bengtsson. In: Proceedings of the Annual International Conference of the IEEE Engineering in Medicine and Biology Society, EMBS. 2012. p. 5372-5375.

    Number of citations: 3
11. Smart Paint -- A New Interactive Segmentation Method. Applied to MR Prostate Segmentation. Malmberg F, Strand R, Kullberg J, Nordenskjöld R, Bengtsson E. In: Prostate MR Image Segmentation Grand Challenge (PROMISE'12), MICCAI 2012, the 15th International Conference on Medical Image Computing and Computer Assisted Intervention. 2012 **Number of citations: 0**
12. Cluster detection in cytology images using the cellgraph method. P S Chandran, N B Byju, R U Deepak, R Kumar, S Sudhamony, P Malm, E Bengtsson. In: Proceedings of International Symposium on Information Technologies in Medicine and Education, ITME 2012, p. 923-92 **Number of citations: 0**
13. Cluster detection and field-of-view quality rating - Applied to automated Pap-smear analysis. M Astruc, P Malm, R Kumar, E Bengtsson. In Proceedings of ICPRAM 2013 - 2nd International Conference on Pattern Recognition Applications and Methods. 2013. **Number of citations: 0**
14. An algorithm for parallel calculation of trigonometric and exponential functions. T Barrera, A Hast, E Bengtsson. Proceedings of the ACM International Conference on Computing Frontiers, 8, 2013 **Number of citations: 0**
15. * Novel chromatin texture features for the classification of pap smears. BE Bejnordi, R Moshavegh, K Sujathan, P Malm, E Bengtsson, A Mehnert. SPIE Medical Imaging, 867608-867608-8, 3, 2013 **Number of citations: 0**
16. Quantitative and Automated Microscopy - Where Do We Stand after 80 Years of Research? Author: E Bengtsson. In Proceedings: IEEE 11th International Symposium on Biomedical Imaging (ISBI), pages 274-277, 2014.
    Number of citations: 0
17. * Optimizing Optics and Imaging for Pattern Recognition Based Screening Tasks Authors: J Lindblad, N Sladoje, P Malm, E Bengtsson, R Moshavegh, A Mehnert. In Proceeding of ICPR, 3333-3338, 2014 **Number of citations: 0**
18. A Structural Texture Approach for Characterising Malignancy Associated Changes in Pap Smears Based on Mean-Shift and the Watershed Transform Authors: A

Mehnert, R Moshavegh, K. Sujathan, P Malm, E Bengtsson. In Proceeding of ICPR, 2014. **Number of citations: 0**

3. Monographs

None

4. Research review articles, since 2007

1. * Screening for Cervical Cancer Using Automated Analysis of PAP-Smears. E Bengtsson, P Malm. Computational and Mathematical Methods in Medicine, 12 pages, 2014

Number of citations: 0

5. Books and book chapters, since 2007

1. Interaction in Medical Image Analysis and Visualization Edited conference proceeding: Smedby, Ö., Bengtsson, E., Persson, A. Workshop at 10th International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI 2007), Brisbane, Australia, 2007. 96 pages. **Number of citations: 0**

2. Trigonometric Splines. Barrera Tony, Hast Anders, Bengtsson Ewert. Game Programming Gems 7, Scott Jacobs (ed). Charles River Media, 2008, 191-198. **Number of citations: 1**

3. An alternative model for shading diffuse light for rough materials. Barrera Tony, Hast Anders, Bengtsson Ewert. Game Programming Gems 7, Scott Jacobs (ed). Charles River Media, 2008, 373-380. **Number of citations: 0**

4. Rapid prototyping of image analysis applications. Luengo Hendriks, Cris L, Malm, Patrik, Bengtsson, Ewert. In: Medical Image Processing: Techniques and Applications, Editor G. Dougherty. Springer Biomedical Engineering Series p 5-25, 2011. **Number of citations: 0**

6. Patents

I have been granted one patent on use of color information in microscopy but it is no longer maintained. I am currently part of one patent application relating to cervical cancer screening.

7. Open access computer programs or databases you have developed

We have developed a number of generations of software for image analysis over the years which has been openly available. Currently we have a software system for simulating cell images, and an associated database publicly available (see journal paper 17)

8. Popular science articles and presentations

I am frequently, typically at least every month, asked to give longer or shorter popular presentations on image analysis or general IT aspects. I have also over the last several years been invited to give plenary presentations at regional and international conferences. Sometimes those are also written down but there is no compiled list of all those contributions. The annual report of CBA, available at www.cb.uu.se gives a listing of these events.

* = most relevant papers for this application

Please note that I have had extensive publishing restrictions regarding microactuators and piezoelectric materials the last 8 years due to contractual and shareholder agreements. Some restrictions relieved 2014.

Most of the 3D additive manufacturing research was made prior to 2007 (still as valid). The most important publications are mentioned in the project plan (only three * in the list below). The development of high precision equipment has to a major part not been published.

Most cited articles (citations from Google Scholar – self-citations removed)

S. Johansson, J.-Å. Schweitz, L. Tenerz, J. Tirén
"Fracture testing of silicon microelements in-situ in a Scanning Electron Microscope"
J. Appl. Phys. **63** (1988) 4799-4803
"Number of citations: 220"

M. Evander, L. Johansson, T. Lilliehorn, J. Piskur, M. Lindvall , S. Johansson, M. Almqvist, T. Laurell and J. Nilsson
"Non-invasive acoustic cell trapping in a microfluidic perfusion system for on-line bioassays
Analytical Chemistry **79** (2007**)** 2984-2991,
"Number of citations: 147"

S. Greek, F. Ericson,S. Johansson, M. Fürtsch and A. Rump
"Mechanical characterisation of thick polysilicon films:Young's modulus and fracture strength evaluated with microstructures"
J. Micromech. Microeng. 9 (1999) 245-51
"Number of citations: 125"

T. Lilliehorn, U. Simu, M. Nilsson, M. Almqvist, T. Stepinski, T. Laurell, J. Nilsson, S.Johansson
"Trapping of microparticles in the near field of an ultrasonic transducer"
Ultrasonics **43**, 5 (2005) 289-299,
"Number of citations: 118".

* S. Greek, F. Ericson, S. Johansson, and J. -Å. Schweitz
"In situ Tensile Strength Measurment and Weibull Analysis of Thick Film and Thin Film Micromachined Polysilicon Structures"
Thin Solid Films **292** (1997) 247-254
"Number of citations: 102"

PUBLICATIONS 2007-2015

1. Peer-reviewed original articles

(citations from Google Scholar – self-citations removed)

1. M. Evander, L. Johansson, T. Lilliehorn, J. Piskur, M. Lindvall , S. Johansson, M. Almqvist, T. Laurell and J. Nilsson
Non-invasive acoustic cell trapping in a microfluidic perfusion system for on-line bioassays
Analytical Chemistry **79** (2007**)** 2984-2991,
"Number of citations: 147"

2. * N. Snis, E. Edqvist, U. Simu and S. Johansson
Monolithic fabrication of multilayer P(VDF-TrFE) cantilevers
Sensors and Actuators **A144** (2008) 314-320,
"Number of citations: 14"

3. * Erik Edqvist, Niklas Snis and Stefan Johansson
Gentle dry etching of P(VDF-TrFE) multilayer micro actuator micro actuator structures by use of an inductive coupled plasma
Journal of micromech. microeng. **18** (2008) ,
"Number of citations: 8"

4. A. Arbat, E. Edqvist, R. Casanova, J. Brufau, J. Canals, J. Samitier, S. Johansson, and A. Diéguez
"*Design and Validation of the Control Circuits for a Micro-cantilever Tool for a Micro-robot"*
Sensors and Actuators **153** (2009) 76-83,
"Number of citations: 7"

5. J. Olofsson, F. Lindberg, S. Johansson, S. Jacobson
On the role of tribofilm formation on the alumina drive components of an ultrasonic motor
Wear **267** (2009) 1295–1300,
"Number of citations: 0"

6. L. Johansson, S. Johansson, F. Nikolajeff and S. Thorslund
"Effective mixing of laminar flows at a density interface by an integrated ultrasonic transducer"
Lab on a Chip, **9** (2009) 297-303,
"Number of citations: 25"

7. L. Johansson, F. Nikolajeff, S. Johansson and S. Thorslund
"On-chip fluorescence activated cell sorting by an integrated miniaturized ultrasonic transducer"
Analytical Chemistry **81** (2009) 5188-5196,
"Number of citations: 23"

8. Erik Edqvist, Niklas Snis, Raimon Casanova Mohr, Oliver Scholz, Paolo Corradi, Jianbo Gao, Angel Diéguez, Nicolas Wyrsch and Stefan Johansson
"Evaluation of building technology for mass producible millimetre-sized robots using flexible printed circuit boards"
J. Micromech. Microeng. **19** (2009) 075011,
"Number of citations: 23"

9. Johanna Olofsson, S. Johansson and S. Jacobsson
"Influence from humidity on the alumina friction drive system of an ultrasonic motor"
Tribology International, 42 (2009) 1467-1477
"Number of citations: 1"

10. L. Johansson, J. Enlund, S. Johansson, I. Katardjiev, M. Wiklund and V. Yantchev
"Surface Acoustic wave-induced precise particle manipulation in a trapezoidal glass microfuidic channel"
J. Micromechanics and Microengineering **22** (2012) 025018
"Number of citations: 8"

11. L. Johansson, M. Evander, T. Lilliehorn, M. Almqvist, J. Nilsson, T. Laurell, S. Johansson,
"Temperature and trapping characterization of an acoustic trap with miniaturized integrated transducer – towards in-trap temperature regulation"
Ultrasonics **53** (2013) 1020-32
"Number of citations: 4"

2. Peer-reviewed conference contributions

(citations from Google Scholar – self-citations removed)

12. E. Edqvist, N. Snis, M. Sjölund, T. Murase, A. Söderbärg and S. Johansson
"The assembly of millimeter sized mass producible autonomous robots"
Proc. Actuators 2008, p 304-307
"Number of citations: 3"

13. Olsson, P.; Johansson, S.; Nysjö, F.; Carlbom, I.
"Rendering stiffness with a prototype haptic glove actuated by an integrated piezoelectric motor", Proc. Int. conf. Haptics: Perception, devices, mobility and Communication, Tampere, Finland, 2012, p 361-72.
"Number of citations: 1"

14. S. Johansson and N. Snis
"An ultrasonic motor for high-precision positioning"
Proc. Actuators 2014, p 647-650
"Number of citations: ?"

3. Book chapters

15. S. Johansson
"Micro- and nanomanipulation for nanomanufacturing"
In: Bhushan B. (Ed.) Encyclopedia of Nanotechnology 2nd edition: SpringerReference, Springer-Verlag, Berlin, Heidelberg, In process for online publication 2015

4. Patents

16. A. Jansson, S. Johansson, O. Johansson and J. Eriksson, Near-resonance wide-range operating electromechanical motor, US7,157,830, 2007-01-02, Issued
17. S. Johansson, Peristaltic electromechanical actuator, US7,161,278,2007-01-09, Issued
18. S. Johansson, M. Bexell and A. Jansson, Wide frequency range electromechanical actuator, KR20070004629, 2007-01-09, Issued

19. S. Johansson, O. Johansson, C. Mattsson, A. Jansson and J. Eriksson, Near-resonance electromechanical motor, KR100701722, 2007-03-23, Issued
20. A. Danell, S. Johansson, J. Abrahamsson and J. Eriksson, Electromechanical drive element, US7,208,861, 2007-04-24, Issued
21. C. Mattson, S. Johansson and A. Jansson, Digital camera system with piezoelectric actuators, US 7,212,358, 2007-05-01, Issued
22. S. Johansson and M. Bexell, Piezoelectric actuator or motor, method therefor and method for fabrication thereof, JP3980646,2007-07-06, Issued
23. S. Johansson, Double electromechanical element, CN100344007, 2007-10-17, Issued
24. J. Rouvinen, I. Kauhanieimi, P. Ahlgren, S. Johansson and C. Mattsson, Digital camera system with piezoelectric actuators, US7,298,564,2007-11-20, Issued
25. C. Mattson and S. Johansson, Robust electromechanical motor, US7,348,710,2008-03-25, Issued
26. S. Johansson, J. Abrahamsson and R. Sunnerberg, Wide frequency range electromechanical actuator,US7,355,325,2008-04-08, Issued
27. S. Johansson, O. Johansson, C. Mattsson, A. Jansson and J. Eriksson, Near-resonance electromechanical motor, CN100403570, 2008-07-16, Issued
28. S. Johansson, Heat efficient micromotor, US7,420,321,2008-09-02, Issued
29. A. Jansson, K. Håkansson and S. Johansson, Energy recovery in electromechanical motors, KR0857945, 2008-09-30, Issued
30. S. Johansson, M. Bexell and P.-O. Lithell, Walking actuator,DE1310038,2009-01-09, Issued
31. S. Johansson, M. Bexell and P.-O. Lithell, Walking actuator,KR0895914,2009-04-24, Issued
32. S. Johansson, M. Bexell and A. Jansson, Wide frequency range electromechanical actuator,DE (EP1726049, 2009-08-26), Issued
33. H. Schneider, T. Trietz, G. Schmid, M. Wilmer, S. Johansson and A. Larsson, Shock recognition system in a doorlock, US2009243434, 2009-10-01, Published
34. S. Johansson, O. Johansson, C. Mattsson, A. Jansson and J. Eriksson, Near-resonance electromechanical motor, JP4354909,2009-10-28,Issued
35. H. Schneider, T. Trietz, G. Schmid, M. Wilmer, S. Johansson and A. Larsson, Shock recognition system in a doorlock, JP2009254229,2009-10-29,Published
36. A. Jansson, S. Johansson, O. Johansson and J. Eriksson, Near-resonance wide-range operating electromechanical motor, CN100566119, 2009-12-02,Issued
37. S. Johansson, Electromechanical actuators and manufacturing method therefore, EP2148380,2010-01-27,Published
38. S. Johansson, M. Bexell and A. Jansson, Fine control of electromechanical motors, JP4455329,2010-04-21, Issued
39. S. Johansson and C. Mattsson, Piezoelectric electromechanic drive unit, JP4452276,2010-04-21, Issued
40. S. Johansson, Heat efficient micromotor,EP1994574,2010-10-27, Granted
41. S. Johansson and C. Mattsson, Piezoelectric electromechanic drive unit, KR0996521,2010-11-24, Issued
42. C. Mattsson and S. Johansson, Robust electromechanical motor, DE (EP1943722, 2010-12-22), Issued
43. S. Johansson, Flat resonating electromechanical drive unit, JP4628363,2011-02-09, Issued
44. S. Johansson, Peristaltic electromechanical actuator, JP4637112,2011-02-23, Issued
45. A. Jansson, S. Johansson, O. Johansson and J. Eriksson, Near-resonance wide-range operating electromechanical motor, JP4698580,2011-03-11, Issued

46. S. Johansson, J. Abrahamsson and R. Sunnerberg, Wide frequency range electromechanical actuator, EP2036139,2011-04-13, Issued
47. A. Danell, S. Johansson, J. Abrahamsson and J. Eriksson, Electromechanical drive element, JP4714225,2011-06-29, Issued
48. S. Johansson, Double electromechanical element, EP1350275,2011-07-20, Issued
49. C. Mattsson, M. Bexell, S. Johansson, O. Johansson, J. Eriksson and S. Lindmark, Electromechanical motor and assembling method therefore, KR10-1058304,2011-08-12, Issued
50. S. Johansson, Electromechanical actuators and manufacturing method therefore, US7,999,443,2011-08-16, Issued
51. N. Snis and S. Johansson, Noiseless electromechanical motor, PCT/EP2011/064095,2011-08-16, Filed
52. S. Johansson, Double electromechanical element, DE1350275,2011-08-24, Issued
53. C. Mattsson, M. Bexell, S. Johansson, O. Johansson, J. Eriksson and S. Lindmark, Electromechanical motor and assembling method therefore, JP4767174,2011-09-07, Issued
54. H. Schneider, T. Trietz, G. Schmid, M. Wilmer, S. Johansson and A. Larsson, Shock recognition system in a doorlock, EP2107622,2011-11-02, Issued
55. S. Johansson, M. Bexell and A. Jansson, Fine control of electromechanical motors, KR101086912,2011-11-29, Issued
56. S. Johansson, O. Johansson, C. Mattsson, A. Jansson and J. Eriksson, Near-resonance electromechanical motor ,DE (EP1523777), 2011-10-26, Issued
57. A. Jansson, S. Johansson, O. Johansson and J. Eriksson, Near-resonance wide-range operating electromechanical motor, DE1620939,2011-12-14, Issued
58. A. Jansson, S. Johansson, O. Johansson and J. Eriksson, Near-resonance wide-range operating electromechanical motor,EP1620939,2011-12-14, Issued
59. S. Johansson and C. Mattsson, Piezoelectric electromechanic drive unit, DE (EP1636898, 2011-12-21), Issued
60. S. Johansson, Flat resonating electromechanical drive unit, KR101100484, 2011-12-30, Issued
61. S. Johansson, M. Bexell and A. Jansson, Wide frequency range electromechanical actuator, JP4955406,2012-03-23, Issued
62. S. Johansson and N. Snis, Electromechanical motor, WO2012087193,2012-06-28, Published
63. S. Johansson, M. Bexell and P.-O. Lithell, Walking actuator, JP5102929,2012-10-05, Issued
64. S. Johansson, Electromechanical motor, KR20120112354,2012-10-11, Published
65. A. Danell, S. Johansson, J. Abrahamsson and J. Eriksson, Electromechanical drive element, KR1193656,2012-10-16, Issued
66. S. Johansson, J. Abrahamsson and R. Sunnerberg, Wide frequency range electromechanical actuator, DE2341565,2012-10-17, Issued
67. S. Johansson, J. Abrahamsson and R. Sunnerberg, Wide frequency range electromechanical actuator, JP5114476,2012-10-19, Issued
68. A. Danell, S. Johansson, J. Abrahamsson and J. Eriksson, Electromechanical drive element, EP1847011,2012-11-28, Issued
69. S. Johansson, Electromechanical motor, JP2012531177, 2012-12-06, Published
70. S. Johansson, M. Bexell and P.-O. Lithell, Multi-set fine walking actuator, EP2053669,2013-06-26, Issued
71. P. Benkowski and S. Johansson, Provision of normal force to an electromechanical motor, DE112009005360, 2013-07-18, Published
72. S. Johansson, Heat efficient micromotor, JP5283512, 2013-09-04, Issued

73. S. Johansson and N. Snis, Electromechanical motor, DE112010006073, 2013-10-10, Filed
74. S. Johansson, Heat efficient micromotor, KR20080107459, 2013-11-11, Issued
75. C. Mattson and S. Johansson, Robust electromechanical motor, JP2009514501, 2013-12-11, Issued
76. C. Mattson and S. Johansson, Robust electromechanical motor, KR20080074917, 2014-01-21, Issued
77. S. Johansson, Flat resonating electromechanical drive unit, EP1676326, 2014-06-18, Issued
78. C. Mattsson, M. Bexell, S. Johansson, O. Johansson, J. Eriksson and S. Lindmark, Electromechanical motor and assembling method therefore, EP1698001, 2014-07-30, Issued
79. S. Johansson,Electromechanical motor, US8,912,708, 2014-12-16, Issued
80. N. Snis and S. Johansson, Noiseless electromechanical motor, US2014210311, 2014-07-31, Published

CV

Name: Joakim Lindblad	**Doctorial degree:** 2003-01-17
Birthdate: 19730320	**Academic title:** Doktor
Gender: Male	**Employer:** No current employer

Research education

Dissertation title (swe)
Utveckling av algoritmer för digital bildbaserad cytometri

Dissertation title (en)
Development of Algorithms for Digital Image Cytometry

Organisation	Unit	Supervisor
Uppsala universitet, Sweden Sweden - Higher education Institutes	Inst för informationsteknologi	Ewert Bengtsson

Subject doctors degree	ISSN/ISBN-number	Date doctoral exam
20603. Medicinsk bildbehandling	91-554-5497-6	2003-01-17

CV

Name: Stefan Johansson	**Doctorial degree:** 1988-05-20
Birthdate: 19600805	**Academic title:** Professor
Gender: Male	**Employer:** No current employer

Research education

Dissertation title (swe)
Mikromekaniska egenskaper hos kisel

Dissertation title (en)
Micromechanical properties of silicon

Organisation	Unit	Supervisor
Uppsala universitet, Sweden Sweden - Higher education Institutes	Inst för teknikvetenskaper	Jan-Åke Schweitz

Subject doctors degree	ISSN/ISBN-number	Date doctoral exam
20599. Annan materialteknik	0282-7468/91-554-2223-3	1988-05-20

CV

Name: Carolina Wählby	**Doctorial degree:** 2003-10-31
Birthdate: 19740131	**Academic title:** Professor
Gender: Female	**Employer:** No current employer

Research education

Dissertation title (swe)
Algoritmer för digital bildbehandling med tilämpningar inom cellmätning.

Dissertation title (en)
Algorithms for Applied Digital Image Cytometry

Organisation	Unit	Supervisor
Uppsala universitet, Sweden Sweden - Higher education Institutes	Inst för informationsteknologi	Ewert Bengtsson

Subject doctors degree	ISSN/ISBN-number	Date doctoral exam
20603. Medicinsk bildbehandling	91-554-5759-2	2003-10-31

CV

Name: Ewert Bengtsson	**Doctorial degree:** 1977-05-26
Birthdate: 19480526	**Academic title:** Professor
Gender: Male	**Employer:** Uppsala universitet

Research education

Dissertation title (swe)

Om utveckling av system för datorstödd analys av mikroskopibilder. Tillämpning på tidig upptäckt av livmoderhalscancer.

Dissertation title (en)

On the Design of Systems for Computer Aided Analysis of Microscopic Images. Application to early detection of cervical cancer.

Organisation	Unit	Supervisor
Uppsala universitet, Sweden Sweden - Higher education Institutes	Inst för fysik och astronomi	Kai Siegbahn

Subject doctors degree	ISSN/ISBN-number	Date doctoral exam
10399. Annan fysik	91-554-0643-2	1977-05-26

Publications

Name: Joakim Lindblad	**Doctorial degree:** 2003-01-17
Birthdate: 19730320	**Academic title:** Doktor
Gender: Male	**Employer:** No current employer

Lindblad, Joakim has not added any publications to the application.

Publications

Name: Stefan Johansson	**Doctorial degree:** 1988-05-20
Birthdate: 19600805	**Academic title:** Professor
Gender: Male	**Employer:** No current employer

Johansson, Stefan has not added any publications to the application.

Publications

Name: Carolina Wählby	**Doctorial degree:** 2003-10-31
Birthdate: 19740131	**Academic title:** Professor
Gender: Female	**Employer:** No current employer

Wählby, Carolina has not added any publications to the application.

Publications

Name: Ewert Bengtsson	**Doctorial degree:** 1977-05-26
Birthdate: 19480526	**Academic title:** Professor
Gender: Male	**Employer:** Uppsala universitet

Bengtsson, Ewert has not added any publications to the application.

Register

Terms and conditions

The application must be signed by the applicant as well as the authorised representative of the administrating organisation. The representative is normally the department head of the institution where the research is to be conducted, but may in some instances be e.g. the vice-chancellor. This is specified in the call for proposals.

The signature*from the applicant*confirms that:

- the information in the application is correct and according to the instructions form the Swedish Research Council
- any additional professional activities or commercial ties have been reported to the administrating organisation, and that no conflicts have arisen that would conflict with good research practice
- that the necessary permits and approvals are in place at the start of the project e.g. regarding ethical review.

The signature *from the administrating organisation* confirms that:

- the research, employment and equipment indicated will be accommodated in the institution during the time, and to the extent, described in the application
- the institution approves the cost-estimate in the application
- the research is conducted according to Swedish legislation.

The above-mentioned points must have been discussed between the parties before the representative of the administrating organisation approves and signs the application.

Project out lines are not signed by the administrating organisation. The administrating organisation only sign the application if the project outline is accepted for step two.

Applications with an organisation as applicant is automatically signed when the application is registered.