

Application

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Descriptive data

Project info

Project title (Swedish)*

SIMHOR - Likhetsmått för hybridrepresentationer av objekt med tillämpningar inom biomedicinsk bildbehandling

Project title (English)*

SIMHOR - Similarity measure for hybrid object representations with applications in biomedical image processing

Abstract (English)*

We will establish the theoretical foundation, explore applicability, and evaluate performance of a novel Similarity Measure between Hybrid Objects Representations – SIMHOR. SIMHOR will aggregate heterogeneous multichannel information about observed samples into a powerful, highly specific and sensitive tool for finding, identifying and differentiating objects in images. It will enable utilization of information-rich hybrid representations, allowing objects of interest to be characterized by a multitude of heterogeneous properties. Furthermore, it will enable fast and robust matching and registration of multimodal and high-dimensional data. The smooth search space offered by the method will allow use of fast gradient based optimization for tracking and matching. The great flexibility of this similarity measure will ensure that the project results have a high impact throughout the fields of image analysis and computer vision.

Single channel object representations are not sufficiently information-rich to respond to the needs of modern image analysis applications. Fusion of information coming from different sources leads to hybrid object representations, which are becoming a necessity for reaching reliable results in pattern recognition and classification, and high-content data analysis in general. However, there is a serious lack of methods that can handle heterogeneous information-rich representations. We will address this problem by developing SIMHOR and related methods applicable to hybrid representations.

Our first aim is theoretical development of SIMHOR. To reach it, we will explore approaches for selection and fusion of discriminative features (based on shape, texture, color, etc.) to be utilized in hybrid object representations. We will evaluate SIMHOR w.r.t. noise sensitivity, and explore approaches to appropriately handle rotation, scale and contrast invariance. We will evaluate the discriminative power of SIMHOR, in combination with several pattern recognition and machine learning methods. We will generalize it to higher spatial and spectral dimensions. We will improve its performance to subpixel precision, to reduce negative effects of discretization and to achieve precise registration and accurate comparison of objects characterized by fine structures/texture, relevant in the applications we will address. We will adjust SIMHOR to applications requiring multimodal comparisons. By exploiting recent results related to fast computation of distances and sub-pixel precise level set methods in combination with GPU-based implementations, we will reach fast and highly applicable outcomes.

Our second aim is to apply and evaluate SIMHOR in three challenging research and clinical biomedical applications, where the currently used approaches are considered insufficient. We will focus on application of SIMHOR in:

- facilitated diagnosis of Cilia disorders in TEM images;
- cost efficient virus detection and classification in TEM images;
- multimodal image registration for spatially resolved gene expression profiling.

We envision equally high importance and applicability in other areas. Fast object and camera motion tracking are applications where SIMHOR has a great potential. For increased precision in stereo matching, point-based features are often combined with area-based ones. SIMHOR offers a unified framework for handling of such heterogeneous data.

The project will last four years and is divided into four work packages, corresponding to the theoretical development of SIMHOR, and each of the three applications. The project team is carefully composed to respond to all the challenges of the project, offering all required complementary competences and skills.

Popular scientific description (Swedish)*

Bilder är fantastiska förmedlare av information. De är givande inte bara för konst och underhållning, utan även för praktiska saker som materialprovning, ansiktsigenkänning, väderprognoser, och medicinska bedömningar. Inom vården tas det dagligen en enorm mängd bilder, bilder som i många fall är helt avgörande för att en läkare skall kunna ställa rätt diagnos. Den allt större mängden bilder i samhället gör att behovet av tolkning och analys av bilder bara ökar.

Det här projektet syftar till att utveckla nya matematiska metoder och algoritmer för att bättre kunna hantera kombinationer av bilder; bilder som visar samma sak men på olika sätt, men också olika aspekter av information i bilder, så som form och färg. Vi människor är experter på att kombinera olika typer av information för att dra slutsatser. Datorer och andra sidan är rätt enkelspåriga, vilket gör att många beslut blir fel. Vi vill utveckla datorprogram som kan sammanföra och utnyttja information av olika typ. Det kan vara liknande information, t.ex. bilder tagna med olika typer av kameror, eller helt olika typer av information, så som form, färg, och olika mått på mönster och struktur. Den här typen av metoder behövs för att kunna ge säkrare och mer pålitlig analys, så att användaren kan lita på vad datorn tycker sig ha sett i bilden.

Inom digital bildanalys och datorseende så används ofta olika typer av likhetsmått. Sådana mått kan användas bland annat för att hitta objekt i bilder, för att skilja på olika typer av objekt, för att matcha ihop bilder tagna från olika håll eller av objekt med olika form. Vi har nyligen utvecklat ett likhetsmått som klarar av att kombinera information om form och textur på ett bra sätt. Det här måttet har visat sig vara väldigt användbart och pålitligt; i tester som vi har gjort så visade sig vårt mått sig vara klart bättre än andra liknande mått. För att säkerställa att vår forskning verkligen är användbar kommer vi att kombinera teori med praktik. Dels så kommer vi att utveckla teorin bakom likhetsmåttet som vi jobbar med, dels så kommer vi att använda det för att lösa verkliga problem i samhället. Vi kommer att utvärdera och använda våra resultat i tre kliniska forskningsprojekt där manuell/visuell analys inte är möjlig, inte är tillräckligt exakt, eller tar alldeles för lång tid och där ett väl fungerande likhetsmått som kan kombinera olika typer av information kan göra stor nytta.

Det första problemet handlar om att hjälpa till att ställa diagnos på cilie-orörlighet. Defekter på cilier (flimmerhår) kan påverka bland annat lungornas funktion och fertilitet. För att kunna ställa diagnos analyseras högupplösta transmissionselektronmikroskopi (TEM)-bilder på prov från näsa-svalg eller sperma. Analysen av ett prov tar oftast några timmar i elektronmikroskopet för en tränad patolog; strukturerna som analyseras är så små att ett femtiotal tvärsnitt på cilier måste hittas och vägas samman för att kunna ställa diagnos.

Det andra problemet gäller virusidentifiering i TEM-bilder. Visuell analys av TEM bilder används vid misstänkta infektioner av högpatogena virus och vid krissituationer, som en första metod för att snabbt kunna vidta rätt åtgärder. Problemen med TEM är att en expert behövs för att utföra analysen vid mikroskopet, att mikroskopen är dyra, kräver specialdesignade lokaler, och är tekniskt svåra att använda. Vi kommer att använda de utvecklade likhetsmåtten både för att automatiskt detektera viruspartiklar i provet och för att identifiera vilken typ av virus som finns i provet.

Det tredje problemet handlar om biomedicinsk forskning där man försöker förstå kopplingen mellan var i vår kropp olika gener uttrycks och sjukdomsförlopp (t.ex. cancer). Vi läser av genuttryck genom upprepad färgning och mikroskopiavbildning, och många bilder behöver läggas ihop (registreras) för att vi ska kunna koppla genuttryck till strukturer i vävnaden; här kommer vi använda SIMHOR som likhetsmått.

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 > 202. Elektroteknik och elektronik > 20205. Signalbehandling
	2. Teknik > 206. Medicinteknik > 20603. Medicinsk bildbehandling
	1. Naturvetenskap > 102. Data- och informationsvetenskap (Datateknik) > 10207. Datorseende och robotik (autonoma system)

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

Keyword 1*image analysisKeyword 2*biomedical applicationsKeyword 3*similarity measureKeyword 4data fusionKeyword 5pattern recognition

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

SIMHOR - Similarity measure for hybrid object representations with applications in biomedical image processing

We will establish the theoretical foundation, explore applicability, and evaluate performance of a novel Similarity Measure between Hybrid objects Representations – SIMHOR. SIMHOR will aggregate heterogeneous multichannel information about the observed samples into a powerful, highly specific and sensitive tool for finding, identifying and differentiating objects in images. SIMHOR will enable utilization of information rich hybrid representations, allowing objects of interest to be characterized by a multitude of heterogeneous properties.

Single channel object representations are not sufficiently information rich to respond to the needs of modern image analysis applications. Fusion of information coming from different sources leads to discriminative hybrid object representations, which are becoming a necessity for reaching reliable results in pattern recognition and classification, and high-content data analysis in general. There is a lack of methods that can handle such heterogeneous information-rich representations. We will develop a class of methods applicable to hybrid representations. We will apply and evaluate them in three challenging research and clinical biomedical applications, where the currently used approaches and tools are considered insufficient.



Aims

Aim 1, Theoretical development: Object similarity and distance measures, which quantify the degree of similarity (or difference) between intensity patterns of two images, are among the most important tools for image analysis, computer vision and pattern recognition. They are utilized in optimization for, e.g., image registration, segmentation, template matching, and classification. Our focus is on further development of the similarity measure with excellent discriminative power, recently proposed by the main applicant [1]. This state-of-the-art measure successfully exploits spatial and intensity information contained in the observed object representations, to reach top level classification performance on, e.g., the MNIST data base of handwritten digits. The performance of

this measure in template matching is illustrated in Fig.1: the measure provides smooth search spaces, with fewer local minima than other commonly used distance measure. We will extend this measure to a true multichannel similarity measure between hybrid object representations. The resulting **SIMHOR** will enable combining and characterizing the spatial relations of contextual features.

We will explore approaches for selection and fusion of discriminative features (based on shape, texture, color, etc) to be utilized in hybrid object representations. We will evaluate SIMHOR w.r.t. noise sensitivity, and explore approaches to appropriately handle rotation, scale and contrast invariance. We will evaluate the discriminative power of SIMHOR, in combination with several pattern recognition and machine learning methods. We will generalize it to higher spatial and spectral dimensions. We will improve its performance to subpixel precision, to reduce negative effects of discretization and to achieve precise registration and accurate comparison of objects characterized by fine structures/texture, relevant in the applications we will address. We will adjust SIMHOR to applications requiring multimodal comparisons. We will, by that, develop a powerful tool for maximally specific and sensitive object description and efficient analysis of high-content data. By exploiting recent results related to fast computation of distances and sub-pixel precise level set methods, in combination with GPU-based implementations, we will reach fast and highly applicable outcomes.



Fig. 1. Performance of the distance measure [1] in template matching. The lower number of local minima, compared to one of the most often used alternative measures, is clearly visible.

Aim 2, Application of developed methods: Automated image analysis of cells and tissues becomes increasingly important in biomedical research and patient diagnostics. Huge amounts of generated data makes manual assessment tedious or infeasible, in particular when the aim is to detect very subtle, but highly relevant, characteristics of the observed specimens; this can be extremely difficult even for a trained human expert. SIMHOR will be applied to three different biomedical applications; they are selected because this general similarity measure and approach for automated comparison of objects, capturing sophisticated spatial and intensity changes, is particularly suited to address their needs. We will focus on the following highly relevant clinical biomedical microscopy applications:

- Cost-effective diagnosis of Cilia disorders utilizing fast and efficient object detection, segmentation, classification, and registration for data fusion, in TEM images;
- Fast and reliable virus identification of known and new (so-called emerging) virus species in TEM images, utilizing hybrid representations combining spatial and texture information;
- Multimodal registration in spatially resolved gene expression profiling, for fusion of information from brightfield and fluorescence microscopy images of tissues, utilizing multiple biomarkers.

Survey of the field

Hybrid shape representations

The need for highly discriminative representations of complex objects has imposed a need for hybrid representations, providing spatial encoding of perceptual information of various types. Recent

inspiring results related to such representations are presented in [2]. There proposed hybrid representations unify several types of descriptors, such as local geometry related ones and/or texture descriptors, and/or color descriptors. The work generalizes approaches utilizing local descriptors such as SIFT [3], SURF [4], and HoG [5]), and global representations, such as Active basis model and Primal sketch, into a highly discriminative representations which capture intrinsic characteristics of the objects. SIMHOR will be utilized for comparisons of this type of hybrid representations.

Distance and similarity measures

Distance measures and their reciprocal similarity measures are used to compare objects, spatially or w.r.t. some other relevant property. Most distance measures in image processing operate on objects represented as spatial sets in integer grids. Such are Hausdorff Distance, Symmetric Difference, Chamfer Matching Distance, Sum of Minimal Distances; a comparative study is presented in [6]. These distances do not consider intensities of the observed objects but only their shapes. Similarity/distance measures which do consider intensity information include Cross-Correlation (CC), Normalized Cross-Correlation (NCC), Sum of Squared Intensity Differences, Mutual Information (MI), Normalized Mutual Information (NMI), Image Euclidean Distance [7], Image Normalized Cross Correlation [8], and the Earth Mover's (Wasserstein) distance. They are, however, not well suited for comparison of complex multidimensional objects in terms of selected properties, are often defined as Minkowski or Mahalanobis distances on a space of the representation based feature vectors. These, however, are lacking spatial object information. SIMHOR provides an approach to combine both spatial and multidimensional feature-based information.

Image registration

Two excellent surveys of image registration techniques are given in [9] and [10]. Hundreds of references included in these surveys indicate the relevance and interest of the problem. Methods are based on comparison of large scale intensity patterns in images, and/or can establish correspondence between a number of especially distinct (salient) feature points. The algorithms often rely on optimization of some appropriate distance/similarity metrics defined on the image space. The properties of the metrics strongly influence the performance of registration algorithms. Most of the available metrices generate highly non-convex search spaces, which makes optimization very difficult. Registration methods can be single-modality (used for images acquired by the same sensor type) or multi-modality methods (used if images are acquired by different sensor types). Most popular similarity measures used in multimodal registration are based on MI [11] and NMI [12]. Their drawbacks have inspired a number of variations [10], addressing problems of overlap invariance, noise sensitivity and lack of spatial information included. There is a need for high-content object representations and appropriate tools for comparisons of hybrid representations.

Our own results

Distance measures: We have recently presented a powerful distance measure between images, with excellent discriminative power [1]. This measure successfully exploits spatial and intensity information contained in the object representations, to reach top level classification performance on, e.g., the MNIST data base of handwritten digits. The measure provides smooth search spaces, with fewer local minima than other commonly used distance measures; this property significantly reduces the need for good initialization compared to other similar approaches (e.g., MI), and allows utilization of simple, thus fast, optimization methods. The distance can be computed in linear time. It performs well on a difficult task of texture and shape based classification of very small objects in noisy and cluttered images. Additional relevant work includes novel distance measures applicable in pattern recognition and image registration [6] and recent results related to distance measures and distance transforms with subpixel precision [13],[14].

Object representations for robust and precise image analysis: Our results on connecting the mathematical concept of fuzzy sets and related notions with concepts in image analysis are summarized in [15]. We have proposed object representations which preserve and aggregate more information about the underlying image content than a classic crisp representation, and developed feature estimation methods characterized by increased robustness and precision [16]. Our results confirm applicability of the suggested representation and analysis model [15].

Project description

General methodology and organization

The team The project team is carefully composed to respond to all the challenges of the project. Our complementary competences and skills include experience in development of mathematical framework for representing and treating image information, (Sladoje); experience in high throughput real time video processing (Lindblad); experience in segmentation and texture analysis of viruses in electron microscopy images (Sintorn); experience with development of image analysis tools for high content large scale quantitative microscopy analysis (Wählby) and clinical experience relevant for applications related to electron-microscopy applications (Dragomir).

Organization, time-line and tasks distribution: The project is divided into four work packages.

- The main applicant, Dr Nataša Sladoje, will coordinate the work on the project. She is awarded a VINNMER Marie Curie Incoming Mobility grant and is since 2014 full time employed as a researcher at the Centre for Image Analysis, Uppsala University. She has a strong background in applied mathematics. Her work will be related to theoretical development of the SIMHOR and the related hybrid object representations as well as adjustments of the developed methods to all the applications considered within the project.
- Dr Joakim Lindblad is Head of Research and Development at Protracer AB, Stockholm, and proficient in algorithm development and high throughput real time video processing. He will collaborate in development of SIMHOR and will supervise implementations of the methods and monitor their quality (**WP1**, *Jan 2016 Dec 2018*).
- MD PhD Anca Dragomir is Head of the Surgical Pathology Electron Microscopy Unit, Uppsala University Hospital, a specialist in diagnostic histopathology and diagnostic ultrastructural pathology, and an expert in the field of Primary Ciliary Dyskinesia. She will provide clinical samples and images necessary to develop, test and evaluate, in clinical routine work, application of developed SIMHOR to Cilia disorder diagnosis (WP2, *June 2016 Dec 2017*).
- Docent Ida-Maria Sintorn, Centre for Image Analysis, SciLifeLab, Uppsala University, and Head of Research and Development at Vironova AB, is specialized in image analysis for electron microscopy imagery. She will provide expertise related to segmentation and texture analysis of viruses in TEM. Through her collaboraton with Vironova AB, the project has access to a miniTEM microscope and image data required for WP3 (*Sept 2017 Dec 2018*).
- Prof. Carolina Wählby has developed algorithms for quantitative analysis of microscopy data, both at Uppsala University and as Principal Investigator at the Imaging Platform of the Broad institute of Harvard and MIT 2009-2014. Her recent collaborative work within SciLifeLab on combining spatially resolved gene expression analysis with tissue morphology [19] will be further explored within **WP4** (*Sept 2018 Dec 2019*).
- A PhD student in computerized image analysis, to be supervised by Dr Sladoje, will be enrolled, and given responsibility for the majority of implementation and data analysis, with gradually increased involvement in the method development and evaluation.

WP1: Theoretical evaluation and development of SIMHOR

Collaborator: Dr Joakim Lindblad, Head of Research and Development, Protracer AB

We will build on our recently developed distance measure [1] which has proven to outperform most other measures with similar purpose. Particular issues that we will address are:

- Applicability of SIMHOR to hybrid object representations, integrating several types of information (shape, texture, color): We will start our studies on hybrid representations by observing performance of SIMHOR on color (e.g, H&E stained) objects and address the question how to best combine the information from different channels. We will, after that, adjust the similarity measure to hybrid object representations unifying a variety of descriptors. We will study texture descriptors (e.g, filter bank responses) encoded into spatial representations. Next, we will combine them with color descriptors, and then extend representations with a variety of other descriptors at different scales. What to integrate in the hybrid representation, and how to integrate so that SIMHOR can maximally utilize the information, are relevant questions that we will address in the project.
- Generalization to higher spatial dimensions: We will generalize the SIMHOR to objects in higher spatial dimensions. Appropriate evaluation on, e.g., textured 3D data and large-scale images from slide scanners, will be conducted.
- **Improved precision to subpixel level:** Our recently proposed distance transforms with subpixel precision [13], [14], can be directly utilized in implementation of SIMHOR to increase its precision and reduce negative effects of discretization to translation, rotation, and scale invariance. This improvement will be particularly useful as a compensation for the lost sensitivity (precision) imposed by the requirement for robustness to noise. We have shown in [1] that it is beneficial to use around 7 intensity levels for best classification results (out of possible 255), to not "preserve" noise at the same time as enhancing desirable image details. Alternative ways to preserve precision, while still maintaining robustness to noise, are of high importance.
- **Applicability to multimodal data:** Inspired by evaluation results in [1], especially regarding comparisons with standard measures used in uni-modal registration (e.g., NCC), we will evaluate and further develop SIMHOR so that it becomes a multi-modal similarity measure with radically better performance than MI-type measures, known to suffer from small regions of attraction.
- **Robustness to change of scale:** It is often desirable that object descriptors are invariant to (small) changes of scale. It is observed that hybrid object representations, combining spatial/geometric features and texture features, enable to establish some kind of continuous transformation of most dominant type of descriptor for a given scale (spatial features are dominant at high resolutions, texture at lower resolutions, and flat regions at even lower resolutions). Utilizing this, we will ensure that SIMHOR performs well under changing scale.
- Sensitivity to contrast changes: We will explore contrast sensitivity of hybrid representation, as well as of SIMHOR. We will compare utilization of contrast invariant features with the use of locally contrast-normalized features in the representations.
- **Robustness to noise:** Noise is present in every image acquired in real conditions. SIMHOR incorporates intensity information which might, if not addressed properly, increase its sensitivity to noise. The results obtained in [1] are informative, but further investigation addressing good balance between smoothing and intensity information preservation are still needed.
- Fast and efficient implementations for real applications: Initial tests show promising results of application of the distance measure [1] for detection and classification of Cilia and virus particles in TEM images. The distance creates few local minima in the search space and therefore allows utilization of simple and fast gradient based optimization methods, which contributes to overall fast computation. However, finding small objects in huge amounts of data can be accomplished only if advanced algorithmic, but also hardware (e.g., GPU), solutions are used. To achieve high applicability, we will implement the framework utilizing GPU multi-core implementation.
- **Recognition performance in combination with different classifiers:** Performed tests indicate excellent performance of the distance measure [1] for character recognition, in combination with the simple *k*NN classifier. The correct classification rate of 99.04% reached by our proposed

distance is the best reported result for a kNN classifier using only rigid transformations. We expect further performance improvement as a consequence of replacing the NN-type classifier with, e.g., support vector machines, or random forest classifier.

WP2: Application of SIMHOR for facilitated diagnosis of Cilia disorders in TEM images

Collaborator: MD PhD Anca Dragomir, Head of Electron Microscopy Diagnostics, Dept. of Surgical Pathology, Uppsala University Hospital

Clinical problem: Primary Ciliary Dyskinesia is a rare, genetically heterogeneous disorder that affects approximately 1 in 20,000 individuals. It results from dysfunction of small hair-like organelles (cilia) which clean our airways. The disorder causes severe airway disease with progressive loss of lung function. Cardiovascular and reproductive system can also be affected [17]. TEM is the only method providing a resolution sufficient for diagnosis of cilia disorders based on structural information in the samples. TEM is used on ultrathin sections of tissue samples as a routine diagnostic instrument. To set a diagnosis, at least 50 high quality imaged instances of perfectly cut Cilia need to be located and analyzed. The structures observed for diagnoses are at the single nanometer size. Cilia are often unevenly spread throughout the sample. Manual diagnostic procedure is time consuming, requiring a skilled pathologist to spend on average 2 hours per diagnosis on routine work at a microscope. Provided automated acquisition and subsequent object detection, expert pathologists can spend their time on validating candidate objects, rather than spending hours searching in different magnifications to detect a sufficient number of good quality instances of Cilia for setting a diagnosis.



Fig. 2. In our preliminary study, one instance of Cilia (framed by a green square) is used as a template. The most similar objects are automatically detected and ranked based on degree of similarity. Red circles indicate the ten most similar instances, blue mark the following ten. The ten most similar are shown as cut-outs to the right. The processing time is a couple of seconds.

Approach: We will apply SIMHOR for automated and efficient search for Cilia in TEM images, utilizing shape and texture information at multiple scales. Image data will be provided by expert pathologists from Uppsala University Hospital. We will at low magnification locate areas likely to contain Cilia, and automatically acquire images of these locations at a magnification increased to the level that Cilia become visible. Due to significantly increased speed of object detection, which relies on the properties of SIMHOR, we can search for more than 50 instances of Cilia and, hence, facilitate more accurate diagnosis. We will detect instances of Cilia in such zoomed-in images, and display a selection of the best found instances to the pathologist, for final diagnosis. An illustrative example (including our preliminary results) is shown in Fig. 2. Information from individual representative instances of Cilia will be fused by performing subpixel precise registration based on SIMHOR. We anticipate such a fused representation will display (e.g. by mean or min projection) the potential defects much clearer and hence the diagnosis will be easier and more correct.

WP3: Application of SIMHOR in cost efficient virus detection and classification in TEM images

Collaborator: Docent Ida-Maria Sintorn, Centre for Image Analysis and Science for Life Laboratory, Uppsala University, and Head of Research and Development, Vironova AB

Clinical problem: The potential havoc that lethal viral infections such as e.g., pox viruses, Dengue, Yellow Fever and Ebola can cause in modern society is enormous. TEM is an established method for detecting and identifying viral pathogens, utilized in infectious emergency situations caused by viral outbreaks, suspected bioterrorist attacks or suspected zoonoses (virus mutates to infect new species). The benefit with TEM is that it is fast (visual inspection takes $\sim 10-20$ min) once the sample has reached the microscope, and that it allows for detection of novel, mutated, or deliberately altered viruses, which may easily escape detection by other methods. The main drawbacks of TEM are the need for a specialized expert (there are very few experts in the world, only 1-2 in Sweden) to perform the analysis at the microscope, the bulkiness and requirements for hosting a TEM, the level of technical sophistication making it difficult to operate a microscope, and the cost and maintenance of TEMs [18]. To overcome these drawbacks, Vironova AB has recently developed the MiniTEM instrument for fast, easy and cost-effective TEM imaging. This shifts the focus of the problem from instrument issues to the lack of experts for analyzing and interpreting TEM images of viruses. Furthermore, it opens up the possibility to automate image acquisition and to support the interpretation process, reducing the need for an expert at the microscope. Fig. 3(b) shows a (composite) image of typical samples with virus particles, containing also lots of other particles and objects, as well as two examples of different virus textures, Fig.3(a).



(a) Templates

(b) Composite TEM

(c) Using method in [1], F1=0.98 (d) Using NCC, F1=0.87

Fig. 3. Virus detection and recognition. (a) The used templates. (b) Composite of two TEM images showing 65 virus particles. (c) **Our preliminary results** on recognition using the distance [1], and (d) Normalized Cross-Correlation (NCC). Matches are marked with circles, deviations from a correct result with squares (false negative or wrong class) and crosses (false positive). F1-score (harmonic mean of precision and recall, range in [0,1]) is used as performance measure (higher is better).

Approach: Recognition and classification of viruses is typically based on both shape and texture. This corresponds well with the hybrid object representations we intend to use. Based on promising results in [1], illustrated here in Fig. 3(c), we expect that SIMHOR will be ideal for the task of virus detection and classification, when applied to the most appropriate hybrid representations. Selection of discriminative features and their fusion that leads to best performance are therefore of high interest. We will address the issue of automatic learning of new representations/templates from images, to be able to detect unknown virus types as well. Development of smart search strategies, in addition to very fast implementations of all the observed methods, is the approach we will take. From Vironova AB, and previous research projects involving Docent Sintorn, images and grid samples of a

number of viruses, highly pathogenic, as well as common winter vomiting disease causing viruses and different influenza viruses, are available for use in the project.

WP4: Multimodal image registration in spatially resolved gene expression profiling

Collaborator: Prof. Carolina Wählby, Centre for Image Analysis and Science for Life Laboratory, Uppsala University, and the Broad institute of Harvard and MIT.

Clinical problem: Availability of advanced imaging hardware enables digitization of entire glass slides at near the optical resolution limits in only a few minutes' time, with a possibility to image fluorescence and bright field stains in parallel. Genetic analysis is rapidly evolving thanks to the impressive development of next generation sequencing technologies. However, most of today's available technologies result in a genetic analysis that is decoupled from the morphological and spatial information of the original tissue sample, while many important questions in tumor- and developmental biology require single cell spatial resolution to understand tissue heterogeneity. We have recently developed molecular and computational methods that bridge these two emerging fields by sequencing mRNA transcripts directly in tissue samples [19]. Image-based sequencing requires precise and fast registration of images from multiple staining cycles as well as registration of images from fluorescence and brightfield microscopy. So far, these alignment steps have been done manually. This is a major bottleneck in the analysis process, especially as we wish to expand the methods to handle large-scale images from slide scanners at maintained resolution for *in situ* sequencing. Automation of multi-modal image registration is pivotal for this step in development.



Fig. 4. The same tissue sample is explored both by standard H&E staining, immunostaing, and our novel in situ sequencing. We will apply SIMHOR to analyse and register data from these multiple imaging modalities in a multi-resolution fashion, enabling coupling of spatial clustering, sequencing by base-calling, extraction of morphology metrics etc, enhancing the standard H&E view.

Approach: We will apply SIMHOR to brightfield- and fluorescence microscopy images of the same tissue samples to improve sample alignment. We will explore texture descriptors common for multiple microscopy modalities (standard H&E staining, immune staining and fluorescence signals representing *in situ* sequencing, see Fig. 4) at multiple resolutions/scales to enable registration of diverse spatial representations. We will develop methods that can handle giga-pixel sized data produced by slide-scanners in an efficient way, while maintaining high enough precision to allow sequencing of signals from repeated hybridisation steps.

Significance

SIMHOR will provide a powerful, highly specific and sensitive tool for finding, identifying and differentiating objects in images. Furthermore, it will enable fast and robust matching and registration of multimodal and high-dimensional data. The smooth search space offered by the method will allow use of fast gradient based optimization for tracking and matching. The great

flexibility of the similarity measure will ensure that the project results have a high impact throughout the fields of image analysis and computer vision.

The three applications explored within the project clearly demonstrate the usefulness of SIMHOR in medicine and biomedicine. The methodology is not restricted to 2D; the benefits of a smooth search space are even greater in 3D, where the encountered optimization problems become increasingly difficult. Registration and fusion of 3D multimodal data is more and more desired. Non-rigid registration and merging of MRI and CT with quite different modalities such as PET or ultrasound, to create information rich hybrid medical atlases, is just one example.

However, we envision equally high importance and applicability in other areas. Fast object and camera motion tracking are applications where SIMHOR has a great potential. The use of hybrid representations extends on popular approaches such as SIFT or HOG, providing improved robustness and flexibility without sacrificing speed. For increased precision in stereo matching, point-based features are often combined with area-based ones. SIMHOR offers a unified framework for handling of such heterogeneous data.

Preliminary results

Excellent discriminative power of the distance measure proposed in [1] results from its property to exploit both spatial and intensity information. Its performance in template matching is **illustrated in Fig.1**; the measure provides smooth search spaces, with fewer local minima and wider catchment basins than other commonly used distance measure. We will build on these results in **theoretical development of SIMHOR in WP1**.

Initial tests related to WP2 indicate that the measure can be used to detect instances of Cilia in a TEM image. **Preliminary result is presented in Fig 2**. Further challenges are automated acquisition, subpixel registration and information fusion of the detected instances of Cilia. We will utilize SIMHOR to address these tasks.

Initial tests related to WP3 show that the distance measure [1] performs very well on a difficult task of texture and shape based classification of very small objects in noisy and cluttered TEM images. **Illustration is given in Fig.3**. We expect further improvements by utilization of SIMHOR, due to its applicability to representations utilizing complex heterogeneous information.

Equipment

The project has access to a miniTEM through Dr Sintorn's collaboration with Vironova AB. Access to image data, imaging systems, and samples for EM imaging, will be provided by our collaborator MD PhD Dragomir, via her contact with the BioVis platform, Uppsala University.

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.

Other grants and collaborations relevant for this project

Dr Sladoje is partly supported by a Marie Curie Incoming Mobility grant by VINNOVA for the project "Advanced methods for reliable and cost efficient image processing in life sciences". Collaboration with Dr Dragomir has recently been initiated through a small cross-faculty pre-study project which will result in a proof-of-concept for the approach in WP2. Dr Sintorn closely

collaborates with Vironova AB and has established a contact-network of clinical EM experts. Prof. Wählby is a PI at the Imaging Platform at the Broad Institute of Harvard and MIT, one of the leading groups in the world in quantitative, large scale microscopy analysis.

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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

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	Natasa Sladoje	50
2 Participating researcher	Ida-Maria Sintom	10
3 Participating researcher	Carolina Wählby	10
4 Participating researcher	Joakim Lindblad	10
5 PhD Student	PhD student	100

Salaries including social fees

	Role in the project	Name	Percent of salary	2016	2017	2018	2019	Total
1	Applicant	Natasa Sladoje	50	374,472	383,834	393,430	403,265	1,555,001
2	Other personnel with doctoral degree	Joakim Lindblad	10	74,894	76,767	78,686	80,653	311,000
3	Other personnel with doctoral degree	Ida-Maria Sintorn	10	74,894	76,767	78,686	80,653	311,000
4	Other personnel with doctoral degree	Carolina Wählby	10	93,796	96,141	98,545	101,008	389,490
5	Other personnel without doctoral degree	PhD student	100	478,878	493,501	500,812	530,056	2,003,247
	Total			1,096,934	1,127,010	1,150,159	1,195,635	4,569,738

Other costs

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

Pr	emises						
	Type of premises	2016	2017	2018		2019	Total
1	Office space	57,000	57,000	57,000		57,000	228,000
	Total	57,000	57,000	57,000		57,000	228,000
Rι	Inning Costs						
	Running Cost	Description	2016	2017	2018	2019	Total
1	Travel	Conference particip.	20,000	20,000	20,000	20,000	80,000
2	Publishing	Open access	15,000	15,000	15,000	15,000	60,000
3	Equipment	Work station	40,000				40,000
	Total		75,000	35,000	35,000	35,000	180,000
De	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	1,096,934	1,127,010	1,150,159	1,195,635	4,569,738		4,569,738
Running costs	75,000	35,000	35,000	35,000	180,000		180,000
Depreciation costs					0		0
Premises	57,000	57,000	57,000	57,000	228,000		228,000
Subtotal	1,228,934	1,219,010	1,242,159	1,287,635	4,977,738	0	4,977,738
Indirect costs	339,581	348,603	355,547	369,191	1,412,922		1,412,922
Total project cost	1,568,515	1,567,613	1,597,706	1,656,826	6,390,660	0	6,390,660

Explanation of the proposed budget

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Explanation of the proposed budget*

$\label{eq:model} Motivation \ of \ suggested \ budget$

Salary

Most of the money applied for will be spent on salaries (including LKP 48.6% and OH 30%). The main applicant will devote 50% of her 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. Collaborator A. Dragomir will dedicate 5-10% of her time for this project, as a part of the time she has devoted for research in her position. Her salary is not included in the budget.

Office space

Included costs are calculated in relation to the working time devoted to the project (50%, 10%, 10%, 10%, 10% and 100% respectively) of a full (N. Sladoje, I.-M. Sintorn, J. Lindblad, and C. Wählby) 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 6months. 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.

A computer will be purchased for the PhD student.

Total resources within the project

This application will cover all the expenses for the proposed project. N. Sladoje is currently employed as a researcher at the Centre for Image Analysis, Uppsala, based on the Incoming Marie Curie mobility grant by VINNOVA, which covers 50% of her salary and will end in August 2016. Preliminary results for this project were partly obtained with a support of that grant, and partly during her employment as an associate professor at the University of Novi Sad, Serbia, before she moved to Sweden. There are no other funds that can be used for the development and evaluation of SIMHOR – Similarity measure for hybrid object representations proposed in this project

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.

0	ther fundin	g for this project							
	Funder	Applicant/project leader	Type of grant	Reg no or equiv.	2016	2017	2018	2019	Total
1	VINNOVA	Natasa Sladoje	Marie Curie Incom. mobility	2014-01432	445,556				445,556
	Total				445,556	0	0	0	445,556

CV and publications

cv

1. Education

- Ph.D. degree in Image Analysis from the Centre for Image Analysis, Swedish University of Agricultural Sciences, Uppsala, Sweden, 2005.
- M.Sc. degree in Mathematics (Discrete Mathematics and Programming) from the Faculty of Science, University of Novi Sad, Yugoslavia, 1998.
- B.Sc. degree in Mathematics (Numerical Mathematics and Cybernetics) from the Faculty of Science, University of Novi Sad, Yugoslavia, 1992.

2. Ph.D. Thesis

 On Analysis of Discrete Spatial Fuzzy Sets in 2 and 3 Dimensions Centre for Image Analysis, SLU, Uppsala, Sweden, 2005.
 Supervisors: Prof. Gunilla Borgefors and Prof. Ingela Nyström

The thesis was awarded the Benzelius Prize for Mathematics and Physics for 2007, from The Royal Society of Sciences. It was also one of the two Swedish candidates for The Nordic Award for the Best PhD Thesis in Pattern Recognition in 2005-2006.

3. Post-doctoral positions -

Qualifications required for appointment as a docent: Docent lecture (Computerized Image Processing) scheduled for 2015-04-10, by invitation from the Docent Committee, Uppsala Univ.

4. Specialist certification or equivalent -

5. Present position

Since 2014 – Researcher at the Dept. of Information Technology, Uppsala University, 100% research time

- 6. Previous positions and periods of appointment
- since 2011 Associate professor at the Faculty of Engineering, University of Novi Sad, Serbia
- 2006 2011 Assistant professor at the Faculty of Engineering, University of Novi Sad, Serbia
- 1992 2006 Teaching assistant at the Faculty of Engineering, University of Novi Sad, Serbia
- 7. Interruption in research

Parental leave 2 years, in 1996, and in 1998-1999.

8. Ph.D. Supervision

- Completed:
 - o Dr. Tibor Lukic, "Regularized Problems in Image Processing", University of Novi Sad, 2011.
 - Dr Vladimir Curic, "Distance Functions and Their Use in Adaptive Mathematical Morphology", Uppsala University, 2014. (co-supervisor)
- Currently supervising four Ph.D. students at the Univ. of Novi Sad, and co-supervising one Ph.D. student at Uppsala University.

9. Other information relevant for application

Scientific publications

More than 40 fully reviewed high quality international publications in the field of Computerized Image Analysis. Published works include fundamental theoretical works in discrete mathematics, as well as applied works within medicine and bio-medicine, and are carried out within a number of national and international projects.

Current funded research project participation

- Project leader: "Advanced methods for reliable and cost efficient image processing in life sciences"; VINNMER Marie Curie Incoming grant nr. 2014-01432 (2014-2016)
- Co-applicant: "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.
- Participant: "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.
- Participant: "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.
- Co-applicant: "Image Processing, Information Engineering & Interdisciplinary Knowledge Exchange"; Project CIII-AT-0042-10-1415 of the CEEPUS III program.
- Participant: "Colour and Space in Cultural Heritage (COSCH)", Management committee member; COST Action TD1201.

Other merits of relevance

- Since 2011, Associate Editor of the Pattern Recognition Letters journal (Elsevier).
- Frequent reviewer of international scientific journals (IEEE Trans. on Image Processing, Image and Vision Computing, Discr. Appl. Math, Patt. Rec. Lett.) as well as reviewed international conferences (ICPR, MICCAI, SCIA, DGCI, ISPA, IWCIA).
- 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.
- Member of the International Association of Pattern Recognition (IAPR), and the Swedish Society for Automated Images Analysis since 1997.
- Invited speaker at the First Croatian Computer Vision Workshop (CCVW), Zagreb, Croatia, 2012 and the 84th Annual meeting of the International Association of Applied Mathematics and Mechanics (GAMM), Novi Sad, 2013.
- Visiting researcher at the Centre for Image Analysis, 3 months stay during 2012/2013.
- Several times invited to give seminar talks (Univ. Of Szeged, Univ. Of Zagreb, Debrecen Univ., Graz Univ., Univ. of Cluj-Napoca).

Ph.D. examination committee membership

- Anders Landström: Thesis: "Elliptical Adaptive Structuring Elements for Mathematical Morphology", 2014, Luleå University of Technology
- Lennart Svennson; Thesis: "Image Analysis and Interactive Visualization Techniques for Electron Microscopy Tomograms", 2014, Swedish University of Agricultural Sciences
- Laszlo Rusko; Thesis: "Automated segmentation methods for liver analysis in oncology applications", 2014, University of Szeged, Hungary (official reporter)
- Magnus Gedda; Thesis: "Contributions to 3D Image Analysis using Discrete Methods and Fuzzy Techniques : With Focus on Images from Cryo-Electron Tomography", 2010, Uppsala University

CV IDA-MARIA SINTORN, 19761205-5926

1. Higher Education Degree

2000 MSc in Molecular Biotechnology Engineering, Uppsala University, MSc Thesis: *3D* reconstruction and optical density measurements of TEM micrographs of GPG treated HIV-1, Dept. of Biochemistry and Centre for Image Analysis, Uppsala University

2. Doctoral degree

2005 PhD(teknologiedoktor) in Image Analysis and Remote Sensing, Swedish University of Agricultural Sciences, Uppsala, Sweden,

Title: Segmentation methods and shape descriptions in digital images - applications in 2D and 3D microscopy,

Main supervisor: Prof. Gunilla Borgefors Assistant supervisor: Prof. Ingela Nyström

3. Postdoctoral positions

4. Docent level

Sept. 2012, subject: Computerized Image Processing, Uppsala University

5. Present positions

- Associate Senior Lecturer, SciLifeLab & Centre for Image Analysis, Dept. of Information Technology, Uppsala University (60%: 90% research, 10% teaching)
- Head of R&D, Vironova AB, Stockholm (40%: management, strategy, group leader)

6. Previous positions

- 2008-2014 Assistant Professor, Centre for Image Analysis, Swedish University of Agricultural Sciences (10%-50%, 100% research)
- **2008 2009** Researcher (50%), Centre for Image Analysis, Uppsala University (100% research)
- 2005 2007 Research Scientist (Image Analyst), Biotech Imaging, CSIRO Mathematical and Information Sciences, Sydney, Australia (research/development)
- 2000 2005 PhD student, Centre for Image Analysis, Swedish University of Agricultural Sciences, Uppsala, Sweden (research)

7. PhD student supervision

- Main supervisor for Gustaf Kylberg, Automated image acquisition and virus identification using -TEM, PhD 2014
- Main supervisor for Lennart Svensson, *Interactive visualization and segmentation of proteins in situ imaged by cryo electron tomography*, PhD 2014
- Main supervisor for Damian Matuszewski, *Digital image processing with applications in quantitative microscopy*, PhD planned 2018
- Main supervisor for Amit Suveer, *Texture analysis with applications in microscopy*, PhD planned 2019
- Assistant supervisor for Amin Allalou, *Methods for 2D and 3D quantitative microscopy of biological samples*, PhD 2011
- Assistant supervisor for Johan Nysjö, *Interactive image registration for cranio-maxillofacial surgery planning*, PhD planned 2016

8. Interruption in research

15 months of parental leave for two children born 2008 and 2010.

Selected research/project management education and experience

- 2015 PI: Regional Orthogonal Moments for Texture Analysis: Applications in Microscopy Image Analysis, Vetenskapsrådet Research Grant
- 2008- Head of R&D at Vironova AB: image analysis/IT group leader and member of management team
- 2011 2014 Image Analysis Project Leader: *MiniTEM- Development of benchtop equipment for automated characterization of viruses and other biological nanoparticles*, a 3-year 1.7M€ Eurostars project involving 3 partners, Delong Instruments, Vironova AB, Centre for Image Analysis
- 2011 Guest researcher, Imaging Platform, BROAD Institute of Harvard and MIT, Cambridge, MA, USA
- 2008 2011 Technical coordinator: *Rapid detection and identification of highly pathogenic viruses* (*PanViruShield*), a 3-year 20 MSEK project involving 3 partners, Vironova AB, Centre for Image Analysis, Swedish Institute for Infectious Disease Control.
- **2008 2012** Project Leader: *Strengthening Academic and Industrial Image Analysis Collaboration through Meriting*, a 3-year project to enhance female academic and industrial careers.
- **2009 2012** Project Leader: *Protein Visualization-ProViz*, a 3-year project involving academia and industry with the goal to develop a demonstrator for visualization and analysis tools and haptic interaction of tomography data of proteins and molecules in situ.
- 2009 1-week Course: To be a director and leader, Rolf Olofsson Organisationsutveckling AB & Uppsala University
- 2009 1-week Course: Practical project management, Wenell Management AB & Uppsala University

Selected commissions of trust

- 2013 Member of grading PhD grading committees: Isaac Niwas, National Institute of Technology, Tiruchirappalli, India (2013), Patrik Malm, Dept. IT Uppsala University (2014), Carl-Magnus Clausson, Dept. Immunology Genetics and Pathology, Uppsala University (2014), Peter Andersson, Dept. Physics and Astronomy, Uppsala University (2014), Obaid Aftab, Dept. Medical Sciences, Uppsala University (2014).
- 2008 Board member: Swedish society for Automated Image Analysis, treasurer 2009-
- **2010** Reviewer of Research Grant Applications to the VINNOVA/MSB programme: *"Säkerhetslösningar med IKT"*
- **2009** Reviewer of Research Grant Applications to the VINNOVA programme: "*Innovationer för framtidens hälsa*"

Awards & acknowledgements

- 2007 CSIRO Bonus Award
- 2005 M. Homman, I. Sintorn, M. Ryner, M. Homman, *Automated image analysis of virus production*, the city of Stockholm's innovation award, 2005.
- 2004 M. Homman, I. Sintorn, M. Ryner, *Identification, quantification and analysis of viral production using image analysis,* 2nd price innovation competition, 2004.

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.

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.

Publication list – Dr Nataša Sladoje

Total number of citations: 283(statistics from Google Scholar 2015-03-27)Listed are numbers of citations without auto-citations

Five most cited papers

- *N. Sladoje and J. Lindblad. High Precision Boundary Length Estimation by Utilizing Gray-Level Information. IEEE Trans. on Pattern Analysis and Machine Intelligence, Vol. 31, No. 2, pp. 357-363, 2009. Number of citations: 23
- N. Sladoje, I. Nyström, and P.K. Saha. Measurements of digitized objects with fuzzy borders in 2D and 3D. Image and Vision Computing, Vol. 23, pp 123-132, 2005. Number of citations: 21
- J. Zunic and N. Sladoje. Efficiency of Characterizing Ellipses and Ellipsoids by Discrete Moments. IEEE Trans. Pattern Analysis and Machine Intelligence, Vol.22, No.4, pp. 407-414, 2000. Number of citations: 14
- J. Chanussot, I. Nyström and N. Sladoje. Shape Signatures of Fuzzy Star-shaped Sets Based on Distance from the Centroid. Pattern Recognition Letters, Vol. 26(6), pp. 735-746, 2005. Number of citations: 14
- 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

Peer-reviewed articles, 2007 – 2015

- A. Tanács, J. Lindblad, N. Sladoje, and Z. Kato. Estimation of Linear Deformations of 2D and 3D Fuzzy Objects. Pattern Recognition, Vol. 48(4), pp.1387–1399, 2015. Number of citations: 0
- * J. Lindblad and N. Sladoje. Linear time distances between fuzzy sets with applications to pattern matching and classification. IEEE Trans. on Image Processing, Vol. 23, No 1, pp. 126-136, 2014.
 Number of citations: 2
- * 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.
- 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
- 5. T. Lukić, J. Lindblad, N. Sladoje. Regularized image denoising based on spectral gradient optimization. Inverse Problems, Vol. 27, No. 8, 085010, 2011.

Number of citations: 6

- 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
- * 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
- * N. Sladoje and J. Lindblad. High Precision Boundary Length Estimation by Utilizing Gray-Level Information. IEEE Trans. on Pattern Analysis and Machine Intelligence, Vol. 31, No. 2, pp. 357-363, 2009. Number of citations: 23
- 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 – 2014

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, Copenhagen, Denmark, LNCS, 2015.

Number of citations: 0

- * 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), Reykjavik, Island, LNCS, 2015. Number of citations: 0
- B. Bajić, J. Lindblad, and N. Sladoje. An Evaluation of Potential Functions for Regularized Image Deblurring. In Proc. of the International Conference on Image Analysis and Recognition (ICIAR), Algarve, Portugal. Lecture Notes in Computer Science, Vol. 8814, pp. 150–158, Springer, 2014 Number of citations: 0
- J. Lindblad, N. Sladoje, P. Malm, E. Bengtsson, R. Moshavegh, and A. Mehnert. Optimizing optics and imaging for pattern recognition based screening tasks. Accepted for the 22nd Intern. Conf. on Pattern Recognition (ICPR), Stockholm, Sweden, 2014.
- K. Lidayova, J. Lindblad, N. Sladoje and H. Frimmel. Coverage segmentation of thin structures by linear unmixing and local centre of gravity attraction. In Proc.of the 8th IEEE Intern. Symp. on Image and Signal Processing and Analysis (ISPA), Trieste, Italy, pp. 83-88, 2013.
- S. Dražić, J. Lindblad, N. Sladoje. Precise Estimation of the Projection of a Shape from a Pixel Coverage Representation. In Proc. of 7th IEEE Intern. Symp. on Image and Signal Processing and Analysis (ISPA), Dubrovnik, Croatia. IEEE, pp. 569-574, 2011. Number of citations: 0
- V. Ćurić, J. Lindblad, N. Sladoje. Distance measures between digital fuzzy objects and their applicability in image processing. In Proc. of 14th Intern. Workshop on Combinatorial Image Analysis (IWCIA), Madrid, Spain. Lecture Notes in Computer Science, Vol. 6636, pp. 385-395, 2011. Number of citations: 0
- A. Tanács, J. Lindblad, N. Sladoje, and Z. Kato. Estimation of linear deformations of 3D objects. In Proc. of Intern. Conf. of Image Processing (ICIP), Hong Kong, China. IEEE, pp. 153-156, 2010. Number of citations: 1

- J. Lindblad, N. Sladoje, and T Lukić. De-noising of SRµCT Fiber Images by Total Variation Minimization. In Proc. of 20th Intern. Conf. on Pattern Recognition (ICPR), Istanbul, Turkey. IEEE, pp. 4621-4624, 2010. Number of citations: 2
- J. Lindblad, V. Ćurić, and N. Sladoje. On set distances and their application to image registration. In Proc. of 6th Intern. Symp. on Image and Signal Processing and Analysis (ISPA), Salzburg, Austria. IEEE, pp. 449-454, 2009.

Number of citations: 0

- N. Sladoje, J. Lindblad. Pixel coverage segmentation for improved feature estimation. In Proc. of 15th Intern. Conf. of Image Analysis and Processing (ICIAP), Vietri sul Mare, Italy. Lecture Notes in Computer Science, Vol. 5716, pp. 929-938, 2009. Number of citations: 3
- J. Lindblad, N. Sladoje, V. Ćurić, H. Sarve, C.B. Johansson, and G. Borgefors. Improved quantification of bone remodelling by utilizing fuzzy based segmentation. In Proc. of 16th Scandinavian Conf. of Image Analysis (SCIA), Oslo, Norway. Lecture Notes in Computer Science, Vol. 5575, pp. 750-759, 2009.

Number of citations: 0

- A. Tanács, C. Domokos, N. Sladoje, J. Lindblad, and Z. Kato. Recovering affine deformations of fuzzy shapes. In Proc. of 16th Scandinavian Conf. of Image Analysis (SCIA), Oslo, Norway. Lecture Notes in Computer Science, Vol. 5575, pp. 735-744, 2009. Number of citations: 1
- T. Lukić, N. Sladoje, J. Lindblad. Deterministic Defuzzification based on Spectral Projected Gradient Optimization. In Proc. of 30th Symp. of the German Association for Pattern Recognition (DAGM), Munich, Germany. Lecture Notes in Computer Science, Vol. 5096, pp. 476-485, 2008. Number of citations: 2
- J. Lindblad, T. Lukić, and N. Sladoje. Defuzzification by Feature Distance Minimization Based on DC Programming. In Proc. of 5th Intern. Symp. on Image and Signal Processing and Analysis (ISPA), Istanbul, Turkey. IEEE, pp. 373-378, 2007. Number of citations: 0

Review articles, book chapters, books, 2007 - 2014

 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

List of Publications, IDA-MARIA SINTORN 19761205-5926

Comments:

- List contains all publications from 2007 + 5 most cited
- The five most important publications for this project are marked with an asterix.
- Google Scholars + CID (Citation Impact Discerning Self-citations) was used to get the number of citations excluding self-citations
- The"gap" in publications in publications between 2005-2009 is due to time in industry and industrial research.

1. Peer-reviewed international journal articles

- P. Tammela, Z. Wang, S. Fryklund, P. Zhang, I. Sintorn, L. Nyholm, M. Strømme. Asymmetric supercapacitors based on carbon nanofibre and polypyrrole/nanocellulose composite electrodes, *RSC Advances, Vol 21, pp. 16405-16413, 2015.* Number of citations:-
- *G. Kylberg, I. Sintorn, Evaluation of Noise Robust Local Binary Pattern Descriptors for Texture Classification, *EURASIP Journal on Image and Video Processing* 2013:17, 2013.
 Number of citations: 11
- K.B. Bernander, K. Gustavsson, B. Selig, I. Sintorn, C.L. Luengo Hendriks, Improving the Stochastic Watershed, *Pattern Recognition Letters*, *Vol.34(9)*, pp. 993-1000, 2013. Number of citations: 4
- *G. Kylberg, M. Uppström, K. Hedlund, G. Borgefors, I. Sintorn, Segmentation of Virus Particle Candidates in Transmission Electron Microscopy Images, *Journal of Microscopy*, 245: 140-147, 2012. Number of citations: 7
- 5) I. Sintorn, L. Bischof, P. Jackway, S. Haggarty, M. Buckley, Gradient based intensity normalization, *Journal of Microscopy*, Vol. 240 (3), pp. 249-258, 2010. Number of citations: 3
- 6) I. Sintorn, G. Borgefors, Weighted distance transforms for volume images digitized in elongated voxel grids, *Pattern Recognition Letters*, Vol. 25, pp. 571-580, 2004. Number of citations: 24
- 7) I. Sintorn, M. Homman, C. Söderberg-Naucler, G. Borgefors, A Refined Circular Template Matching Method for Classification of Human Cytomegalovirus Capsids in TEM Images, *Computer Methods and Programs in Biomedicine, Vol. 76, No. 2, pp.* 95-102, 2004. Number of citations: 20
- *C. Wählby, I. 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, Vol. 215, pp. 67-76, 2004*. Number of citations: 181

9) S. Höglund, J. Su, S. Reneby, A. Vegvari, S. Hjerten, I. Sintorn, H. Foster, Y. Wu, I. Nyström, A. Vahlne, Tripeptide interference with Human Immunodeficiency Virus Type 1 Morphogenesis, Antimicr. Agents and Chemotherapy, pp. 3597-3605, 2002. Number of citations: 35

2. Peer-reviewed international conference articles

- 10) *I. Sintorn, G. Kylberg, Virus Recognition Based on Local Texture, in Proc IEEE 22nd International Conference on Pattern Recognition (ICPR), Stockholm, Sweden, pp 1635-1638, 2014. Number of citations: -
- 11) J. Nysjö, A. Christersson, I. Sintorn, I. Nyström, S. Larsson, F. Malmberg, Precise 3D Angle Measurements in CT Wrist Images, in Proc 17th International Conference on Image Analysis and Processing, Naples, Italy, Lecture Notes in Computer Science vol. 8157, pp. 479-488, 2013. Number of citations: -
- 12) L. Svensson, I. Sintorn, A probabilistic template model for finding macromolecules in MET volume images, in Proc. 6th Iberian Conference on Pattern Recognition and Image Analysis, Madeira, Portugal, Lecture Notes in Computer Science, vol. 7887, pp. 855-862, 2013.

Number of citations: -

- 13) I. Sintorn, G. Kylberg, Regional Zernike Moments for Texture Recognition, in Proc. IEEE 21st International Conference on Pattern Recognition (ICPR), Tsukuba, Japan, pp. 1635-1638, 2012. Number of citations: 4
- 14) J. Nysjö, A. Christersson, F. Malmberg, I. Sintorn, I. Nyström, Towards User-Guided Quantitative Evaluation of Wrist Fractures in CT Images, in Proc. International Conference on Computer Vision and Graphics (ICCVG), Poland, Lecture Notes in Computer Science, vol. 7594, pp. 204-2011, 2012. Number of citations: 1
- 15) *L. Svensson, J. Nysjö, A. Brun, I. Nyström, I. Sintorn, Rigid Template Registration in MET images using CUDA, in Proc. 7th Int. Joint Conf. on Computer Vision, Imaging and Computer Graphics Theory and Applications (VISIGRAPP), Rome, Italy, Volume 2, pp. 418-422, 2012. Number of citations: 1
- 16) G. Kylberg, M. Uppström, I. Sintorn, Virus Texture Analysis Using Local Binary Patterns and Radial Density Profiles, in Proc. 16'th Iberoamerican Congress on Pattern Recognition (CIARP), Pucón, Chile, Lecture Notes in Computer Science, vol. 7042, pp. 573-580, 2011. Number of citations: 11
- 17) L. Svensson, A. Brun, I. Nyström, I. Sintorn, Registration Parameter Spaces for Molecular Electron Tomography Images, in Proc. 16th Int. Conf. on Image Analysis and Processing (ICIAP), Ravenna, Italy, Part I, Lecture Notes in Computer Science, vol. 6978, pp. 403-412, 2011. Number of citations: -

- 18) L. Svensson, I. Nyström, S. Svensson, I. Sintorn, Investigating measures for transfer function generation for MET biomedical data, in Proc. 19'th International Conference on Computer Graphics, Visualization and Computer Vision 2011, WSCG'2011, Plzen, Czech Republic, pp. 113-120, 2011. Number of citations: -
- 19) G. Kylberg, I. Sintorn, M. Uppström, M. Ryner, Local intensity and PCA based detection of virus particle candidates in transmission electron microscopy images, *in Proc. IEEE Int. Symposium on Image and Signal Processing and Analysis, Salzburg, Austria, pp.* 426-431, 2009.
 Number of citations: 4
- 20) G. Kylberg, I. Sintorn, G. Borgefors, Towards Automated TEM for Virus Diagnostics: Segmentation of Grid Squares and Detection of Regions of Interest, *in Proc. Scand. Conf. on Image Analysis, Oslo, Norway, Lecture Notes in Computer Science, vol. 5575, pp. 169-178, 2009.* Number of citations: 2
- 21) I. Sintorn, G. Borgefors, Weighted distance transforms for images using elongated voxel grids, *in Proc. International Conference on Discrete Geometry for Computer Imagery (DGCI 2002), Bordeaux, France, LNCS 2301, pp. 244-254, 2002.* Number of citations: 13

3. –

4. Patent

Method of analyzing cell structures and their components, US patent 8218834, Mohammed Homman and Ida-Maria Sintorn

5. Open-access computer programs

ProViz demonstrator, <u>http://www.cb.uu.se/research/proviz/</u> software for interactive visualization of in situ 3D protein images (developed with small group of researchers at Centre for Image Analysis)

Spatstat - R package for spatial statistics, <u>http://www.spatstat.org/spatstat/</u> (minor contribution)

6. -

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)

- *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. <u>J Mol Biol.</u>, 2015 Feb 25. pii: S0022-2836(15)00111-4. doi: 10.1016/j.jmb.2015.02.017. Number of citations: 0
- *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. <u>Nature Methods</u>, 2013 Jul 14. Number of citations: 18.
- 3. **C. Wählby**, et al. An image analysis toolbox for high-throughput *C. elegans* assays. <u>Nature Methods</u>, 2012 Apr 22; 9(7): 714-716. PMID: 22522656. Number of citations: 20
- *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. <u>Nature Methods</u>, 2011;8(11):892-3. Number of citations: 17
- 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. <u>Journal of</u> <u>Microscopy</u>, 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. <u>Proc IEEE ICPR 2014</u>, 22nd Int. Conf. on Pattern Recognition, Stockholm, Sweden.
- *M. Gavrilovic, J.C. Azar, J. Lindblad, C. Wählby et al. Blind color decomposition of histological images. <u>IEEE Transactions on Medical Imaging</u>, 2013 Jun; 32(6):983-94. Number of citations: 5
- 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. <u>Methods</u>, 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. <u>Computer</u> <u>Methods and Programs in Biomedicine</u>, 2009 Apr;94(1):58-65. Number of citations: 50
- 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. <u>Lab on a Chip</u>, 2014(14), 931-7. Number of citations: 2
- N.V. Kirienko,.., C. Wählby,.., F.M. Ausubel. Pseudomonas aeruginosa disrupts C. elegans iron homeostasis causing a hypoxic response and death. <u>Cell Host & Microbe</u>, 2013;13(4):406-16 Number of citations: 12
- C. Pardo-Martin, A. Allalou, J. Medina, P.M. Eimon, C. Wählby, and M.F. Yanik. High-throughput hyperdimensional vertebrate phenotyping. <u>Nature Communications</u>, 2013 Feb 12; 4:1467, Number of citations: 6
- 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. <u>PLos One</u>, 2012;7(12). Number of citations: 1
- *S.I. Niwas, ..., C. Wählby, and R. Strand. Automated classification of immunostaining patterns in breast tissue from the Human Protein Atlas. <u>Journal of Pathology Informatics</u>, 2013 Mar 30;4(Suppl):S14.
- T.Y. Chang, C. Pardo-Martin, A. Allalou, C. Wählby and M.F. Yanik. Fully automated cellularresolution vertebrate screening platform with parallel animal processing. <u>Lab on a Chip</u>, 2012;12(4):711-6. Number of citations: 26

- Weibrecht, M. Gavrilovic, L. Lindbom, U. Landegren, C. Wählby and O. Söderberg. Visualising individual sequence-specific protein-DNA interactions *in situ*. <u>New Biotechnology</u>, 2012;29(5):589-98. Number of citations: 11
- 17. M. Gavrilovic, ..., **C. Wählby**. Automated classification of multi-colored rolling circle products in dualchannel wide-field fluorescence microscopy. <u>Cytometry A</u>. 2011 79(7) 518-27. Number of citations: 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. <u>IEEE ISBI</u>. 2010 Jun 21;2010:552-5. Number of citations: 7
- A. Zieba, C. Wählby, et al. Bright-field microscopic visualization of proteins and protein complexes by in situ proximity ligation with peroxidase detection. <u>Clinical Chemistry</u>. 2010 Jan;56(1):99-110. Number of citations: 21
- 20. A . Allalou, A. Pinidiyaarachchi, **C. Wählby**. Robust signal detection in 3D fluorescence microscopy. <u>Cytometry A.</u> 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. <u>Cytometry A.</u> 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. <u>Nucleic Acids Res.</u> 2009 Jan;37(1):e7. Number of citations: 10
- Wählby, P. Karlsson, S. Henriksson, C. Larsson, M. Nilsson and E. Bengtsson. Finding cells, finding molecules, finding patterns. <u>Int. J. of Signal and Imaging Systems Engineering</u>, 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
- M. Jarvius, J..., C. Wählby, et al. In situ detection of phosphorylated PDGF receptor beta using a generalized proximity ligation method. <u>Molecular and Cellular Proteomics</u>, 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. <u>Cytometry</u>, 57A(1):22-33, 2004. Number of citations: 53
- C. Wählby, J. Lindblad, M. Vondrus, E. Bengtsson and L. Björkesten. Algorithms for cytoplasm segmentation of fluorescence labeled cells. <u>Analytical Cellular Pathology</u>, 24(2,3):101-11, 2002.Number of citations: 89

Peer-reviewed conference contributions, past 8 years

 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

- M. Gavrilovic and C. Wählby. Suppression of Autofluorescence based on Fuzzy Classification by Spectral Angles. Presented at <u>MICCAI 2009</u>, 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.
- 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. <u>Proc IEEE Int Symp Biomed Imaging</u>. 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. <u>Med Image</u>

Comput Comput Assist Interv. 2010;13(Pt 3):634-41. PMCID: PMC3050593. Number of citations: 7

- K. Althoff, ..., C. Wählby, et al. Time-Lapse Microscopy and Classification of in Vitro Cell Migration Using Hidden Markov Modeling. <u>IEEE Xplore</u>; IEEE ICASSP, 2006. Number of citations: 2
- 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. <u>IEEE Int Symp</u> <u>Biomed Imaging</u> 2013: 902-5
- A. Pacureanu, R. Ke, M. Mignardi, M. Nilsson, and C. Wählby. Image based in situ sequencing for RNA analysis in tissue. <u>Proc IEEE ISBI 2014</u>, International Society of Biomedical Imaging, 29 April -2 May, 2014, Beijing, China.
- O. Ishaq, J. Elf, and C. Wählby. An evaluation of the faster STORM method for super-resolution microscopy. <u>Proc IEEE ICPR 2014</u>, 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

 '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). <u>http://www.cb.uu.se/~amin/BlobFinder</u>.

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 <u>www.cellprofiler.org</u>. Description of the software published in Wählby et al, <u>Nature Methods</u>, 2012 Apr 22; 9(7): 714-716.

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

- 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
- 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.
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- * 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.
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- * 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.
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- * 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
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- 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, Number of citations: 0 Stockholm, Sweden, Aug. 2014.
- 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, Number of citations: 1 pp. 83-88, Trieste, Italy, Sept. 2013.
- 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
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- 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
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- 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

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Number of citations: 2

- 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
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 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.

Name:Natasa Sladoje Birthdate: 19680504 Gender: Female

Doctorial degree: 2005-11-25 Academic title: Doktor Employer: Uppsala universitet

Dissertation title (swe) Analys av diskreta spatiella oskarpa mängder i 2 och 3 dimensioner Dissertation title (en)				
On Analysis of Discrete Spatial Fuzzy	/ Sets in 2 and 3 Dimensions			
Organisation	Unit	Supervisor		
Sveriges Lantbruksuniversitet,		Gunilla Borgefors		
Sweden				
Sweden - Higher education Institutes				
Subject doctors degree	ISSN/ISBN-number	Date doctoral exam		
10104. Diskret matematik	1652-6880/91-576-6911-2	2005-11-25		
CV				

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

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	Inst för informationsteknologi	Ewert Bengtsson
Sweden - Higher education Institutes		
Subject doctors degree	ISSN/ISBN-number	Date doctoral exam
20603, Medicinsk bildbehandling	91-554-5759-2	2003-10-31

cv

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

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	Inst för informationsteknologi	Ewert Bengtsson
Sweden - Higher education Institutes		
Subject doctors degree	ISSN/ISBN-number	Date doctoral exam
20603. Medicinsk bildbehandling	91-554-5497-6	2003-01-17

cv

Name:Ida-Maria Sintorn	Doctorial degree: 2005-04-01
Birthdate: 19761205	Academic title: Docent
Gender: Female	Employer: No current employer

Dissertation title (swe)			
Dissertation title (en) Segmentation methods and shape of	descriptions in digita	l images - app	plications in 2D and 3D microscopy
Organisation Sveriges Lantbruksuniversitet, Sweden Sweden - Higher education Institut	Unit es		Supervisor Gunilla Borgefors
Subject doctors degree 10299. Annan data- och informationsvetenskap	ISSN/ISBN-number 1652-6880/91-576-7019-6		Date doctoral exam 2005-04-01
Publications			
Name:Natasa Sladoje Birthdate: 19680504 Gender: Female		Doctorial degree: 2005-11-25 Academic title: Doktor Employer: Uppsala universitet	

Sladoje, Natasa has not added any publications to the application.

Publications

Name:Carolina Wählby Birthdate: 19740131 Gender: Female Doctorial degree: 2003-10-31 Academic title: Professor Employer: No current employer Wählby, Carolina has not added any publications to the application.

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:Ida-Maria Sintorn Birthdate: 19761205 Gender: Female Doctorial degree: 2005-04-01 Academic title: Docent Employer: No current employer Sintorn, Ida-Maria 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.