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Application

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Information about application

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Descriptive data

Project info

Project title (Swedish)*

Aktiv inlärning i kohortgrafer: Kvantitativ medicinsk bildanalys av tusentals individer

Project title (English)*

Active Learning in Cohort Graphs: Scaling Quantitative Medical Image Analysis to Thousands of Subjects

Abstract (English)*

Three-dimensional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) are routinely used in medicine to generate high resolution three dimensional images of the human body. In addition to qualitative analysis performed by radiologists, digital image analysis can be used to extract quantitative information about the patient based on the image data. The ability to quickly and accurately extract quantitative information from medical images has a huge potential in clinical research and, ultimately, in everyday clinical radiological practice.

Ideally, the quantitative image analysis should be fully automatic. Despite decades of active research, however, fully automatic quantitative analysis of medical images generally remains an unsolved problem. Semi-automatic, or interactive, methods use human expert knowledge as additional input, thereby making the analysis problem more tractable. Using a combination of automatic and semi-automatic methods, many medical image analysis problems have been solved successfully for modestly sized studies, involving up to a few hundred subjects.

This project concerns the scaling of current medical image analysis methods to very large studies, involving thousands or tens of thousands of subjects. In this setting, direct application of semi-automatic methods is no longer feasible. Even a small amount of user interaction requires a prohibitive amount of time if it has to be repeated for all images in a large cohort.

Our proposed method is based on the idea that information provided by an expert user can be propagated from one subject to other, similar, subjects. The further the information is propagated, the more uncertain it becomes. We keep track of this uncertainty and utilize it to actively alert the user to subjects where additional user input may be needed, in analogy with active learning. This relieves the user from having to inspect all subjects, reducing the required interaction time to a reasonable level even for very large studies. At the same time, we maintain a high degree of user control, to ensure the correctness of the result.

The project is a close collaboration between researchers at the Department of Information Technology and the Department of Surgical Sciences, Radiolgy, at Uppsala University.

Popular scientific description (Swedish)*

Bildalstrande metoder som skiktröntgen (CT) och magnetresonanstomografi (MRI) används idag rutinmässigt på sjukhus över hela världen för att skapa högupplösta tredimensionella bilder av människokroppen. Vanligtvis analyseras dessa bilder visuellt av läkare, som gör en kvalitativ bedömning av bildinnehållet. Utöver denna kvalitativa analys kan datoriserad bildanalys användas för att utföra kvantitativa mätningar av bildinnehållet. Denna möjlighet att snabbt och med hög precision utvinna kvantitativ information om enskilda patienter har en enorm potential inom klinisk forskning.

I de flesta fall kan den kvantitativa analysen inte utföras helt automatiskt – oftast behövs viss inblandning från en läkare som styr och övervakar analysprocessen. Sådana halvautomatiska metoder används idag med stor framgång för att utföra kvantitativa bildbaserade mätningar i medelstora medicinska studier, omfattande upp till ett par hundra individer.

I takt med att tekniken för medicinsk avbildning utvecklas, ökar också möjligheterna att utföra väldigt stora medicinska studier. Pågående studier, bland annat vid Uppsala universitet, omfattar tusentals eller tiotusentals individer. Detta ger helt nya möjligheter till statistisk analys, vilket öppnar för nya medicinska upptäckter. I så stora studier är det dock inte längre görbart att använda halvautomatiska metoder för att analysera varje enskild individ.

Detta projekt syftar till att utveckla ett ramverk för att möjliggöra halvautomatisk kvantitativ bildanalys i stor skala. Grunden för vår metod är att information som läkaren angett för en viss individ kan spridas vidare till liknande individer utan större precisionsförlust. Ju fler steg informationen sprids, desto mer osäkert blir dock resultatet. Vi föreslår olika metoder för att mäta denna osäkerhet. På så sätt kan datorn automatiskt identifiera osäkra resultat, och aktivt be läkaren om mer information i dessa fall.

Projektet är ett nära samarbete mellan forskare från Institutionen för informationsteknologi och Institutionen för Kirurgiska vetenskaper, radiologi, vid Uppsala Universitet.

Project period

Number of project years*

4

Calculated project time*

2016-01-01 - 2019-12-31

Deductible time

Deductible time

	Cause	Months
1	Parental leave	5
	Total	5

Career age: 41

Career age is a description of the time from your first doctoral degree until the last day of the call. Your career age change if you have deductible time. Your career age is shown in months. For some calls there are restrictions in the career age.

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*	1. Naturvetenskap > 102. Data- och informationsvetenskap (Datateknik) > 10299. Annan data- och informationsvetenskap

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

Keyword 1*

Computerized image analysis

Keyword 2*

Image segmentation

Keyword 3*

Image registration

Keyword 4

Active learning

Keyword 5

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*

Real patient image data will be used in this project. We will observe standard protocols for keeping patient data confidential.

The project includes handling of personal data

Yes

The project includes animal experiments

No

Account of experiments on humans

No

Research plan

ACTIVE LEARNING IN COHORT GRAPHS: SCALING QUANTITATIVE MEDICAL IMAGE ANALYSIS TO THOUSANDS OF SUBJECTS

1 Purpose and Aims

Three-dimensional imaging techniques such as computed tomography (CT) and magnetic resonance imaging (MRI) are routinely used in medicine to generate high resolution three dimensional image of the human body. In addition to qualitative analysis performed by radiologists, digital image analysis can be used to extract quantitative information about the patient based on the image data. The ability to quickly and accurately extract quantitative information from medical images has a huge potential in clinical research and, ultimately, in everyday clinical radiological practice. The interest in quantitative medical image analysis is increasing with the ever-increasing amount of collected image data. For example, large scale whole-body MR image data is collected in the POEM [1], EpiHealth [2], U-CAN [3] (over 6000 individuals scanned to date), UK Biobank [4] (up to 100 000 individuals will be scanned) and German Cohort Biobank [5] (up to 30 000 volunteers will be scanned) studies. Of these examples, we are directly involved with POEM,U-CAN and EpiHealth.

Ideally, the quantitative image analysis should be fully automatic. Despite decades of active research, however, fully automatic quantitative analysis of arbitrary images remains an unsolved problem. Semi-automatic, or interactive, methods use human expert knowledge as additional input, thereby making the analysis problem more tractable. Using a combination of automatic and semi-automatic methods, many medical image analysis problems have been solved successfully for modestly sized studies, involving up to a few hundred subjects.

This project concerns the scaling of current medical image analysis methods to very large studies, involving thousands or tens of thousands of subjects. In this setting, direct application of semi-automatic methods is no longer feasible. Even a small amount of user interaction requires a prohibitive amount of time if it has to be repeated for all images in a large cohort.

To make large scale analysis feasible, we introduce the notion of a *cohort graph* – a structure where analysis information can be propagated between subjects in the cohort. Information provided by an expert user can be propagated from one subject to other, similar, subjects. The further the information is propagated, the more uncertain it becomes. We keep track of this uncertainty and utilize it to actively alert the user to subjects where additional user input may be

[1] http://www.medsci.uu.se/poem
[2] www.epihealth.se
[3] www.u-can.uu.se
[4] http://www.ukbiobank.ac.uk/
[5] http://www.nationale-kohorte.de/

needed, in analogy with active learning [9]. When sufficient input has been given, the user may decide that the results are satisfactory also in the most uncertain parts of the cohort graph. At this point, the user indicates that the analysis is done. In this way, the procedure of evaluating the results and deciding when a correct result is achieved becomes semi-automatic. This relieves the user from having to inspect all subjects, reducing the required interaction time to a reasonable level even for very large studies. At the same time, we maintain a high degree of user control, to ensure the correctness of the result.

2 Background (including a survey of the field)

Two fundamental tasks appear in nearly all medical image analysis pipelines: *image registration* and *image segmentation*. Image registration is the task of finding a spatial transformation (a deformation field) that aligns aligns two or more images to a common coordinate system. The result is a point-to-point correspondence between the images. Image segmentation is the task of identifying and separating relevant objects and structure (e.g. organs) in an image.

Over the last decades, the segmentation and registration problems have both been the focus of active research in the image analysis community. Despite this, they are still considered the bottlenecks of most image analysis pipelines – accurate segmentation and/or registration is typically a prerequisite for further quantitative analysis.

2.1 Image segmentation

To segment an image, we assign to every image element a *label*, indicating which object or structure the element belongs to. To perform automatic recognition of objects in an image, the segmentation algorithm must somehow include prior knowledge about the problem at hand.

Segmentation is often phrased as an optimization problem. Given some prior knowledge of the objects that are to be segmented, we seek a labeling that optimizes some criterion on segmentation "goodness" while remaining consistent with the prior knowledge. For example, a segmentation may be considered good if it partitions the image into regions with homogeneous intensity, or whose boundaries coincide with salient edges in the image. The resulting optimization problems are often solved using combinatorial methods. In many cases, these can be shown to produce globally optimal results. A good overview of state of the art methods in this area is given by Couprie et al. [1].

Methods for *interactive* segmentation can be classified according to the type of input that the user provides to the method during the segmentation process. The user may for example provide correct segmentation labels for a small subset of the image elements (seed-points), indicate points on the desired segmentation boundary, or provide an approximate segmentation that is "close" to the desired one. An overview of interactive methods for image segmentation is given by Malmberg [4].

2.2 Image registration

To register two images, we seek a spatial transformation that aligns them to a common coordinate system. As there are typically substantial shape differences between different individuals, the registration is usually *non-rigid*. Commonly, registrations is phrased as an optimization problem: We seek a transformation that maximizes some measure of similarity between the images, while also satisfying certain regularity criteria. The resulting optimization problems are often solved using iterative methods, e.g. gradient descent, to find local minima. To avoid poor local minima, and for computational efficiency, multi-resolution schemes are frequently used to compute the solution. For a survey of medical image registration techniques, see e.g. [3, 10].

In a semi-automatic setting, there are several ways in which the user can guide the registration problem. A common approach is to ask the user to provide *landmarks* – a set of known correct point correspondences.

2.3 Links between segmentation and registration

Image segmentation and registration are interrelated problems. If an accurate segmentation of the same structures is available for two images, this provides valuable information for the registration of the images – in a correct registration the segmented regions should be perfectly aligned.

Conversely, if a correct segmentation is available for one image in a cohort, image registration can be used to transfer the segmentation to other images. After obtaining an accurate registration between a segmented and an unsegmented image, the segmentation label for each voxel in the unsegmented image can be determined from the corresponding point in the segmented image. This process is known as *atlas based segmentation*, and the segmented image is commonly referred to as an *atlas*. An extension of this approach is to register several individual atlases independently to a fixed image, and use label-fusion methods to combine the individual results into a single segmentation. Label fusion has been shown to give superior results, compared to using a single atlas [8].

2.4 Active confidence-based user guidance

Semi-automatic methods for segmentation and registration require the user to iteratively 1) identify errors in a current solution. 2) Provide additional input to correct the error [4].

Previous research in interactive methods has focused almost exclusively on the second task, i.e., developing methods for quickly and accurately correcting an identified error with a minimum of user input. For the first task, these methods have relied on the ability of the user to quickly spot errors. As pointed out by Straehle [11], the task of identifying errors becomes harder as we move from 2D images to the tomographic 3D images used in medicine. In large studies, involving thousands of 3D images, identifying an erroneous segmentation or registration somewhere in the cohort can require a prohibitive amount of time. In the proposed projects, we attempt to semi-automate the first task as well by actively guiding the user to locations where user input may be needed.

In the context of interactive segmentation, work in this direction has been performed by Top et al. [12, 13] and Straehle et al. [11]. To minimize the amount of user interaction required for interactive segmentation, they both propose algorithms that actively query the user for input at the most critical locations, in analogy with active learning [9]. Both methods identify critical locations by means of suitable uncertainty measures. The active learning approach significantly reduces the amount of user time required to complete a segmentation.

In this project, we propose a framework that allows active learning techniques to be applied not only to single images, but to entire cohorts. By automatically guiding the user to subjects where more user input is needed, we aim to significantly reduce the user interaction time required for analyzing the whole cohort.

3 Project description

In this project, we focus on solving the segmentation and registration problems, as these are typically the bottlenecks of current medical image analysis pipelines. Given a cohort with a large number of imaged subjects, we seek:

- Accurate segmentations of structures of interest in all subjects.
- Accurate registrations between all pairs of subjects.

Fully automatic methods are not yet, and might never be, robust enough to solve the registration and segmentation problems in the general case. Instead we consider a combination of automatic and semi-automatic methods. For very large cohorts, with thousands of subjects, direct semi-automatic handling of all subjects is not feasible. To make semi-automatic intervention feasible in large studies, we propose to develop active learning methods for automating the identification of instances where user guidance is needed. The central concept of the proposed approach is the novel notion of a *cohort graph*, described in detail in the following sections.

3.1 Methods

3.1.1 Cohort graphs

Our proposed method is centered around the novel notion of a *cohort graph* – a graph whose node set is given by the set of subjects in a cohort. A pair of subjects are connected by an edge in the cohort graph if a (bi-directional) registration between them has been calculated. Thus, every edge in the graph represents a spatial transformation aligning the subjects representing the nodes spanned by the edge.

As stated in the previous section, one of our goals is to find a registration between all pairs of subjects, i.e. all pairs of nodes in the cohort graph. At a first glance, this seems to require the computation of a *complete* cohort graph, where every single node is connected to all other nodes. For large numbers of subjects, this would lead to an unmanageable combinatorial explosion – regarding both the time required to compute the registrations and, to a lesser extent, the space needed to store them.

Fortunately, the complete cohort graph is not required. For any path in the cohort graph, we can concatenate the transforms of the edges along the path to obtain a transform aligning the end-points of the path. Thus, we can extract a registration between any pair of subjects from the cohort graph as long there exists at least one path connecting them. The smallest cohort graph in which all subjects are connected is a spanning tree, and so a minimum of $n-1$ registrations are required to form a connected cohort graph for n subjects. See Figure 1.

If a path connecting two subjects in the cohort graphs is short, and the subjects along the path are relatively similar, then the registration obtained by composing the transforms along the path can be assumed to be of almost the same quality as an explicitly computed registration between the two subjects. Concatenating a large number of transforms, however, might lead to

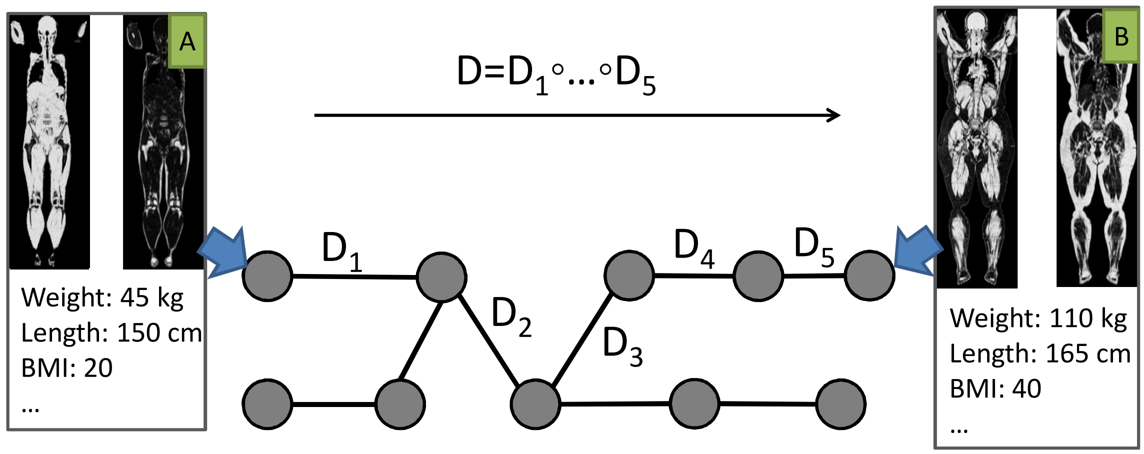

Figure 1: Illustration of the cohort graph concept. Every node in the graph represents a subject, and every edge represents a registration between two subjects. The cohort graph shown here is a tree, i.e., there is a unique path connecting every pair of subjects in the graph. A registration between subjects A and B can be obtained by concatenating the transforms $D1, \ldots, D5$ along the path between A and B.

numerical errors. If the subjects along a path are very dissimilar, small errors in the registration may also be accumulated along the path. For these reasons, it may be beneficial to add redundant edges to the cohort graph. In general, the segmentation and registration results obtained from a dense cohort graph will therefore be more accurate than those obtained from a sparse graph. Constructing a cohort graph thus implies a trade-off: we wish to construct a cohort graph that is as sparse as possible, while still producing good segmentation and registration results. It is well known that even a small number of redundant edges greatly reduces the diameter (maximum distance between any pair of nodes) of a graph [2]. Thus a relatively small number (in the order of n) of well chosen registrations is likely to be sufficient for obtaining high quality registrations between all pairs of subjects. See Figure 2.

3.1.2 Image segmentation in cohort graphs

Assume that we have computed a connected cohort graph. If a segmentation of a certain object is available for one or more subjects in the graph, then that segmentation can be propagated to all other subjects using the (multi-) atlas segmentation approach mentioned in Section 2.3.

In an ideal case, a segmentation of a single subject can be propagated to all other subjects. In practice, the accuracy of the segmentation will decrease as it is propagated further from the original segmented image. Therefore, the propagated results will need to be inspected and corrected by the user, using semi-automatic tools. A corrected segmentation can then in turn be propagated through the cohort graph, further increasing the segmentation accuracy within the whole cohort.

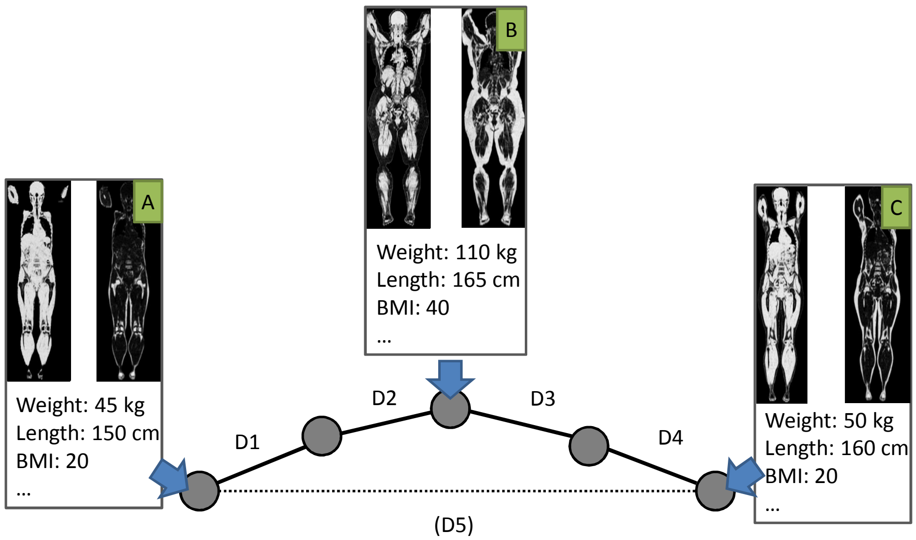

Figure 2: Introducing redundancy in a cohort graph. A registration between subjects A and C can be obtained by composition of the transforms $D1, \ldots, D4$ While subject A and C have similar body composition, subject B is quite different from both A and C. Thus, the registration between A and C obtained by concatenating the transforms along the path connecting them is likely to contain errors. To increase the accuracy of the registration result it may therefore be beneficial to register A and C directly, introducing a redundant edge with transform D5.

3.1.3 Constructing cohort graphs using active learning

We propose to construct cohort graphs using an active learning approach. While the best strategy for construction remains to be explored, we present in this section a number of promising approaches to this problem.

The difficulty of registering two subjects depends on how similar they are – subjects with similar body composition are easier to register than subjects with very different body composition. We thus make the assumption that registrations between similar subjects are relatively error free. This also extends to concatenations of transforms – if a path between subjects in the cohort graph only contains similar subjects, the registration obtained by concatenating the transforms can be assumed to be of high quality. Conversely if two subjects are similar, but the path between them in the cohort graphs contains dissimilar subjects, then it is likely that a better registration can be obtained by adding an additional edge to the cohort graph connecting those subjects directly. We intend to use this property to construct an initial cohort graph, by greedily registering similar subjects until a tree (possibly with some redundant edges) has been created. To estimate the similarity of subjects without having to register them, we plan to use available meta data about the subjects, e.g., weight, height, age, gender.

Once an initial cohort graph has been constructed, several actions can be performed to refine the graph: 1) Additional redundant edges can be added to improve the registration of subjects that are far apart in the graph. 2) Edges that no longer significantly contribute to the quality of the results can be removed. 3) Individual segmentation or registration results can be verified and/or corrected by the user, using semi-automatic methods. We plan to use an active learning approach to suggest appropriate refinement actions to the user. This requires good uncertainty measures for identifying locations where more user input is needed. There are several interesting uncertainty measures that we intend to explore:

- *Inverse consistency of registrations*. The edges of the cohort graph are bi-directional, meaning that we computed registrations between two subjects in both directions. This allows us to measure the *inverse consistency* of the registrations. The two registrations represented by an edge should ideally be inverses of each other, so that their concatenation should equal the identity transforms. If the composition of the two transforms deviates significantly from the identity transform, this is probably a sign of a poor registration result. In this case, the user can be asked to semi-automatically refine the registration of those subjects.

- *Magnitude of deformations along a path*. Registration between dissimilar subjects results in transformations with large magnitude. We assume that large transformations are more likely to contain errors than small ones. Thus, registrations and segmentation obtained by traversing paths containing large magnitude transformations may be considered more uncertain.

- *Internal consistency of the cohort graph*. In a cohort graph with redundant edges, there may exist more than one path between two subjects. The registration results obtained by traversing any of those paths should, in the ideal case, be nearly identical. If not, the user can be alerted to this inconsistency and decide which result is more accurate. Similarly, segmentation results can be propagated along multiple paths from a segmented subject to an unsegmented one. If the results are not consistent, the user may be asked to provide a semi-automatic segmentation of the unsegmented subject.

3.2 Method evaluation

As with semi-automatic methods in general, the goal of the proposed method is to minimize the user interaction time required to perform quantitative analysis of large cohorts. At the same time, we want to maintain tight user control to ensure the quality of the results.

The proposed method reduces the required interaction time by only asking the user to provide input for cases that are *critical*, as determined by an automatic algorithm. With this approach, there is of course a risk of missing errors – there may be erroneous cases that are not flagged as critical by the automatic algorithm. The evaluation of the proposed approach will therefore focus on the following two factors: 1) How much does the proposed approach reduce the user time required to complete the analysis? 2) To what extent does the result agree with results obtained by direct application of semi-automatic methods to the entire cohort?

To evaluate the first item we may, e.g., determine the fraction of subjects in the cohort for which semi-automatic analysis was performed. The second item can be evaluated by, e.g., manually inspecting the results for randomly selected subjects in the cohort. In the ideal case, the segmentation and registration results should be correct even for subjects for which no semi-automatic interventions were performed.

3.3 Example application: the POEM study

The *Prospective investigation of Obesity, Energy and Metabolism* (POEM) study is currently carried out at Uppsala University. The aim is to study pathophysiological links between obesity and vascular dysfunction and future cardiovascular disorders. The study involves 1000 middle aged subjects, plus 500 obese subjects of age 50. As part of this study, whole body MR images of all subjects are being acquired. The primary investigator for the POEM study is Lars Lind, who is also a partner in the proposed project.

We will use the POEM study as primary a testbed for the methods developed within the proposed project. Hundreds of whole body MR volume images have already been acquired, and are directly available for use within the project.

3.4 Project environment

This project is a collaboration between the Department of Information Technology, and the Department of Surgical Science, Radiology, at Uppsala University. We believe that this combination of competence in computerized image analysis and radiology is key to the success of the project.

The main applicant, Filip Malmberg, PhD, has a research position at the Department of Information Technology. He has a long experience developing methods for interactive image segmentation. Since June 2011, he has been working 50% at the Department of Surgical Sciences, Radiology on using interactive image segmentation in MR image segmentation.

Robin Strand, PhD, assistant professor at the Department of Information Technology, is active in the field of digital geometry, and has performed research on, e.g., theoretical properties of distance functions and segmentation. Since 2012, he has been working part time at the Department of Surgical Sciences, Radiology, focusing on image registration.

Joel Kullberg, PhD, research fellow at the Department of Surgical Sciences, Radiology, received his PhD in 2007 and is now responsible for the image analysis needs within the department.

Håkan Ahlström, MD, PhD, is chief physician and professor in radiology and head of the Department of Surgical Sciences, Radiology. He a board member of the U-CAN study.

Lars Lind, MD, PhD, is professor at the Department of Medical Sciences, Uppsala University. He is primary investigator for the POEM study, and primary investigator of the Uppsala part of the EpiHealth study.

Malmberg, Strand and Kullberg will be responsible for the technical method development within the project, while Ahlström and Lind contribute with medical knowledge and access to data from large scale imaging studies.

3.5 Time plan

- Subproject 1, year 1-4: Developing optimized methods for construction and refinement of cohort graphs.
- Subproject 2, year 1-3: Developing suitable uncertainty measures for active learning in the cohort graph.
- Subproject 3, year 2-4: Method testing and evaluation.

4 Significance

Using digital image analysis to extract quantitative information from medical images has a huge potential in clinical research and, ultimately, in everyday clinical radiological practice. Current state of the art methods for quantitative analysis involve varying degrees of user interaction. The additional information provided by an expert user is crucial, as fully automatic methods alone are usually not robust enough for precise analysis. Thus, current methods scale poorly to very large studies, involving thousands or tens of thousands of subjects. The statistical power provided by studies of this magnitude opens the door to new medical discoveries. This however, requires the availability of appropriate quantitative analysis methods.

The proposed project addresses this issue, using active learning techniques to drastically reduce the user workload required for quantitative analysis of very large cohorts. In this way, the proposed methods facilitate clinical studies that are currently not feasible due to the workload required for direct semi-automatic analysis.

5 Preliminary results

The proposed project relies heavily on the use of state of the art methods for image registrations and segmentation. The project team has a very strong background in this area. For this project, we will be able to utilize methods and software for segmentation and registration that we have previously developed in other projects.

The main applicant, Malmberg, has previously developed efficient combinatorial optimization methods for interactive segmentation [4]. Malmberg, Strand and Kullberg have jointly developed an interactive software for semi-automatic segmentation, called *SmartPaint* [5]. This software has been used in a large range of studies, covering different image modalities and segmentation targets. As a testament to the efficiency and versatility of the software, it has quickly been adopted as the tool of choice for image segmentation needs within the Department of Surgical Sciences, Radiology, at Uppsala University. SmartPaint is freely available [6], and has to date been downloaded more than 500 times. The SmartPaint software is very well suited for the segmentation needs of the proposed project.

Methods for measuring the uncertainty of multiple conflicting segmentation resuls were explored by Malmberg et al.[6].

Strand, together with Kullberg and Malmberg, has developed a robust pipeline for deformable registration of MR volume images, based on the open source software *Elastix* [7]. This pipeline also supports the inclusion of user defined landmarks, and will be used for registration within the proposed project. Additionally, a tool for semi-automatic correction of registration results was developed by Malmberg [7].

6 Independent line of research

The main applicant, Malmberg, did his PhD at the Centre for Image Analysis, Uppsala University. Since then, he has independently initiated a close interdisciplinary collaboration with

[6] http://www.cb.uu.se/~filip/SmartPaint/
[7] http://elastix.isi.uu.nl/

researchers at the Department of Surgical Sciences, Radiology, where he now is employed 50%. The proposed project continues this independent line of research, further developing the fruitful collaboration at the intersection between computer science and radiology.

References

[1] C. Couprie, L. Grady, L. Najman, and H. Talbot. Power watershed: A unifying graph-based optimization framework. *Pattern Analysis and Machine Intelligence, IEEE Transactions on*, 33(7):1384–1399, 2011.

[2] L. Grady and E. L. Schwartz. Faster graph-theoretic image processing via small-world and quadtree topologies. In *Proc. of. Computer Vision and Pattern Recognition*, volume 2, pages II–360. IEEE Computer Society; 1999, 2004.

[3] J. A. Maintz and M. A. Viergever. A survey of medical image registration. *Medical image analysis*, 2(1):1–36, 1998.

[4] F. Malmberg. *Graph-based Methods for Interactive Image Segmentation*. PhD thesis, Uppsala University, 2011.

[5] F. Malmberg, R. Nordenskjöld, R. Strand, and J. Kullberg. Smartpaint: a tool for interactive segmentation of medical volume images. *Computer Methods in Biomechanics and Biomedical Engineering: Imaging & Visualization*, (ahead-of-print):1–9, 2014.

[6] F. Malmberg, I. Nyström, A. Mehnert, C. Engstrom, and E. Bengtsson. Relaxed image foresting transforms for interactive volume image segmentation. In *Proceedings of SPIE Medical Imaging*, volume 7623, page 762340, 2010.

[7] F. Malmberg, R. Strand, R. Nordenskjold, and J. Kullberg. An interactive tool for deformable registration of volume images. In *Proceedings of Swedish symposium on image analysis 2014 (SSBA'14)*. SSBA, 2014.

[8] T. Rohlfing, R. Brandt, R. Menzel, D. Russakoff, and C. Maurer. Quo vadis, atlas-based segmentation? In J. S. Suri, D. L. Wilson, and S. Laxminarayan, editors, *Handbook of Biomedical Image Analysis*, Topics in Biomedical Engineering. International Book Series. Springer US, 2005.

[9] B. Settles. Active learning literature survey. Computer Sciences Technical Report 1648, University of Wisconsin–Madison, 2009.

[10] A. Sotiras, C. Davatzikos, and N. Paragios. Deformable medical image registration: A survey. *Medical Imaging, IEEE Transactions on*, 32(7):1153–1190, 2013.

[11] C. Straehle, U. Koethe, G. Knott, K. Briggman, W. Denk, and F. A. Hamprecht. Seeded watershed cut uncertainty estimators for guided interactive segmentation. In *Proc. of. Computer Vision and Pattern Recognition*, pages 765–772. IEEE, 2012.

[12] A. Top, G. Hamarneh, and R. Abugharbieh. Active learning for interactive 3d image segmentation. In *Medical Image Computing and Computer-Assisted Intervention–MICCAI 2011*, pages 603–610. Springer, 2011.

[13] A. Top, G. Hamarneh, and R. Abugharbieh. Spotlight: Automated confidence-based user guidance for increasing efficiency in interactive 3d image segmentation. In *Medical Computer Vision. Recognition Techniques and Applications in Medical Imaging*, pages 204–213. Springer, 2011.

Interdisciplinarity

My application is interdisciplinary

☑

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

Click here for more information

Interdisciplinary research

The proposed project is interdisciplinary, and requires competence and methods from the subjects Medicine and Health and Natural and Engineering Sciences.

The researchers involved in the project have competence in computerized image analysis and radiology. This combination of competences is key to the success of the project. As the purpose of the proposed methodology is to solve medical problems, a close collaboration with medical experts is required.

The expected outcome of the project is a framework for efficient and precise quantitative analysis of medical images in very large studies. The availability of these methods will facilitate quantitative studies that are not feasible today, thereby opening the door to new medical discoveries.

A close collaboration within the interdisciplinary project team has already been established. Malmberg and Strand are both currently working 50% at the division of Radiology, Uppsala University.

The results from the project will primarily be published in journals within the image analysis field. At a later stage, results from medical studies utilizing the methods developed within the project will of course be published in medical journals.

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	Filip Malmberg	40
2	Participating researcher	Robin Strand	20
3	Participating researcher	Joel Kullberg	10
4	Participating researcher	Håkan Ahlström	5
5	Participating researcher	Lars Lind	5
6	Participating researcher	PhD Student	100

Salaries including social fees

	Role in the project	Name	Percent of salary	2016	2017	2018	2019	Total
1	Applicant	Filip Malmberg	40	249,648	255,889	262,286	268,844	1,036,667
2	Participating researcher	Robin Strand	20	139,090	142,567	146,131	149,784	577,572
3	Participating researcher	Joel Kullberg	10	80,244	82,250	84,306	86,414	333,214
4	Participating researcher	PhD student	100	478,878	493,501	500,812	530,056	2,003,247
	Total			947,860	974,207	993,535	1,035,098	3,950,700

Other costs

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

Premises

	Type of premises	2016	2017	2018	2019	Total
1	Offices	49,000	49,000	49,000	49,000	196,000
	Total	49,000	49,000	49,000	49,000	196,000

Running Costs

	Running Cost	Description	2016	2017	2018	2019	Total
1	Travels	Presenting our work at international conferences	10,000	10,000	10,000	10,000	40,000
2	Publication	Open access publication	0	15,000	15,000	15,000	45,000
	Total		10,000	25,000	25,000	25,000	85,000

Depreciation costs

	Depreciation cost	Description	2016	2017	2018	2019	Total
1	Computer	Computer for PhD Student	5,000	5,000	5,000	5,000	20,000
	Total		5,000	5,000	5,000	5,000	20,000

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	947,860	974,207	993,535	1,035,098	3,950,700		3,950,700
Running costs	10,000	25,000	25,000	25,000	85,000		85,000
Depreciation costs	5,000	5,000	5,000	5,000	20,000		20,000
Premises	49,000	49,000	49,000	49,000	196,000		196,000
Subtotal	1,011,860	1,053,207	1,072,535	1,114,098	4,251,700	0	4,251,700
Indirect costs					0		0
Total project cost	1,011,860	1,053,207	1,072,535	1,114,098	4,251,700	0	4,251,700

Explanation of the proposed budget

Briefly justify each proposed cost in the stated budget.

Explanation of the proposed budget*

Salaries:
Filip Malmberg 40% (project managment and PhD supervision)
Robin Strand 20% (PhD supervision)
Joel Kullberg 10% (PhD supervision)
PhD Student 85%

We have applied for the total cost for the involvement of Malmberg, Strand and Kullberg in this project. Ahlström and Lind will dedicate approximately 5% of their time for this project, as a part of the time they have devoted for research in their positions.

In addition to salary costs, costs for premises, open access publication, and participation in international conferences are also applied for. The PhD student will need a workstation which is depreciated over the four years.

Other funding

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

Other funding for this project

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

CV and publications

CV

Curriculum Vitae

Filip Malmberg, PhD

Adress:	Division of Visual Information and Interaction (Vi2), Department of Information Technology, Uppsala University Box 337, SE-751 05 Uppsala
E-Mail:	filip.malmberg@it.uu.se
Telephone:	+46 471 78 49

1. Higher education qualification

Master of Science (MSc) in computer science, Uppsala University (UU), February 2006.

2. Doctoral degree

Doctor of Philosophy (PhD) in computerized image processing, May 2011.

Thesis title: Graph-based Methods for Interactive Image Segmentation.

Supervisors: Ingela Nyström (main), Ewert Bengtsson

3. Post-doctoral positions

May 2011- December 2013	Post-doctoral researcher, Department of Radiology, Oncology and Radiation Science (ROS), UU.

5. Present position

Researcher, ROS and Department of Information Technology, UU

Length of appointment: December 2014 – December 2016

Amount of time for research: 80%

6. Previous positions

October 2005- December 2005	Project assistant, Department of Information technology, UU
January 2006- May 2011	Graduate student in computerized image processing, Centre for Image Analysis (CBA), UU
December 2013- December 2014	Researcher, Department of Information technology, UU

7. Supervision

Assistant supervisor for PhD-student Johan Nysjö, project: ”Interactive Image Registration for Cranio-Maxillofacial Surgery Planning”

8. Interruption in research

Reason	*Start of period*	*End of period*	*% of full time*	*Total*
Parental leave	2012-08-14	2013-01-20	100%	5 months

9. Other merits

- Reviewer for several international conferences and international scientific journals such as Pattern Recognition Letters, International Journal of Pattern Recognition and Artificial Intelligence, IEEE Transactions on Biomedical Engineering, IAPR International Conference on Pattern Recognition, IAPR International Conference on Discrete Geometry for Computer Imagery.
- Supervisor for 3 master thesis projects.
- Hosted Prof. Alexandre Falcão, University of Campinas, Brazil, when he visited Centre for Image Analysis in May 2012.

Publication list

Publications, Filip Malmberg

Citation counts are taken from Google Scholar.

PhD thesis

1. Filip Malmberg, Graph-based Methods for Interactive Image Segmentation, ACTA UNIVERSITATIS UPSALIENSIS, Digital Comprehensive Summaries of Uppsala Dissertations from the Faculty of Science and Technology, ISSN 1651-6214; 813, ISBN 978-91-554-8037-0.
   Number of citations: 6.

Peer-reviewed articles in journals

2. R. Nordenskjöld, F. Malmberg, E.-M. Larsson, A. Simmons, H. Ahlström, L. Johansson, J. Kullberg
   Intracranial volume normalization methods: considerations when investigating gender differences in regional brain volume
   Psychiatry research: Neuroimaging, in press, 2014.
   Number of citations: 0.

3. F. Malmberg, R. Nordenskjöld, R. Strand and J. Kullberg
   *SmartPaint – A Tool for Interactive Segmentation of Medical Volume Images **
   Computer Methods in Biomechanics and Biomedical Engineering: Imaging & Visualization, in press, 2014
   Number of citations: 0.

4. F. Malmberg and C. L. Luengo Hendriks
   *An Efficient Algorithm for Exact Evaluation of Stochastic Watersheds **
   Pattern Recognition Letters (Volume 47, pages 80–84), 2014
   Number of citations: 4.

5. K. C. Ciesielski, R. Strand, F. Malmberg and P. K. Saha.
   *Efficient algorithm for finding the exact minimum barrier distance **
   Computer Vision and Image Understanding, in press.
   Number of citations: 2.

6. A. Gifford, J. Kullberg, J. Berglund, F. Malmberg, K. C. Coate, P. E. Williams, A. D. Cherrington, M. J. Avison and E. B. Welch.
   Canine Body Composition Quantification using 3 Tesla Fat-Water MRI
   Journal of Magnetic Resonance Imaging (Volume 39, Issue 2, pages 485–491), 2014.
   Number of citations: 0.

7. G. Litjens, R. Toth, W. van de Ven, C. Hoeks, S. Kerkstra, B. van Ginneken, L. Reisaeter, V. Graham, G. Guillard, N. Birbeck, J. Zhang, R. Strand, F. Malmberg, Y. Ou, C. Davatzikos, M. Kirschner, F. Jung, J. Yuan, W. Qui, Q. Gao, P. Edwards, B. Maan, F. van der Heijden, S. Ghose, J. Mitra, J. Dowling, D. Barratt, H. Huisman, and A. Madabhushi
   Evaluation of prostate segmentation algorithms for MRI: the PROMISE12 challenge
   Medical Image Analysis (Volume 18, Issue 2, pp. 359–373), 2013.
   Number of citations: 17.

8. R. Nordenskjöld, F. Malmberg, E.-M. Larsson, A. Simmons, S. J. Brooks, L. Lind, H. Ahlström, L. Johansson, J. Kullberg.
*Intracranial volume estimated with commonly used methods could introduce bias in studies including brain volume measurements **
Neuroimage (Vol. 83, pp. 355–360), 2013.
Number of citations: 14.

9. R.H. Khonsari, M. Friess, J. Nysjö, G. Odri, F. Malmberg, I. Nyström, E. Messo, J.M. Hirsch, E.A.M. Cabanis, K.H. Kunzelmann, J.M. Salagnac, P. Corre, A. Ohazama, P.T. Sharpe, P. Charlier and R. Olszewski.
Shape and Volume of Craniofacial Cavities in Intentional Skull Deformations
American Journal of Physical Anthropology (Vol. 151, Issue 1, pp. 110–119), 2013.
Number of citations: 2.

10. M. Rönn, P. M. Lind, H. Karlsson, K. Cvek, J. Berglund, F. Malmberg, J. Örberg, L. Lind, F. Ortiz-Nieto, J. Kullberg.
Quantification of total and visceral adipose tissue in fructose-fed rats using water-fat separated single Echo MRI.
Obesity (Vol. 21, Issue 9, pp. E388–E395), 2013.
Number of citations: 4.

11. R. Strand, K. C. Ciesielski, F. Malmberg, P. K. Saha.
The Minimum Barrier Distance
Computer Vision and Image Understanding (Vol. 117, Issue 4, pp. 429–437), 2013.
Number of citations: 7.

12. M. Rönn, J. Kullberg, H. Karlsson, J. Berglund, F. Malmberg , J. Örberg, L. Lind, H. Ahlström.
Bisphenol A exposure increases liver fat in juvenile fructose-fed Fischer 344 rats
Toxicology (Vol. 303, pp 125–132, 2013)
Number of citations: 15.

13. F. Malmberg, J. Lindblad, N. Sladoje and I. Nyström.
*A Graph-based Framework for Sub-pixel Image Segmentation **
Theoretical Computer Science (Vol. 412, Issue 15, pp. 1338–1349, 2011)
Ranked number 4 of Top 25 Hottest Articles in Theoretical Computer Science, 2011 (`http://top25.sciencedirect.com/subject/computer-science/7/journal/theoretical-computer-science/03043975/archive/36/`).
Number of citations: 16.

14. F. Malmberg, J. Lindblad, C. Östlund, K.M. Almgren, E.K. Gamstedt.
Measurement of fibre-fibre contact in three-dimensional images of fibrous materials obtained from X-ray synchrotron microtomography
Nuclear Instruments and Methods in Physics Research Section A: Accelerators, Spectrometers, Detectors and Associated Equipment (Vol 637, No 1, pp. 143–148, 2011)
Number of citations: 5.

15. K.M. Almgren, E.K. Gamstedt, P. Nygård, F. Malmberg, J. Lindblad, and M. Lindström.
Role of fibre-fibre and fibre-matrix adhesion in stress transfer in composites made from resin-impregnated paper sheets.
International Journal of Adhesion and Adhesives (Vol. 29, no. 5, pp. 551–557, 2009)
Number of citations: 16.

Peer-reviewed articles in conference proceedings with full paper review

16. F. Malmberg, B. Selig, C. L. Luengo Hendriks
Exact Evaluation of Stochastic Watersheds: From Trees to General Graphs
Discrete Geometry for Computer Imagery. Lecture Notes in Computer Science Volume 8668, 2014, pp 309–319
Number of citations: 0.

17. R. Strand, F. Malmberg, P. K. Saha and E. Linnér
The Minimum Barrier Distance - Stability to seed point position
Discrete Geometry for Computer Imagery. Lecture Notes in Computer Science Volume 8668, 2014, pp 111–121
Number of citations: 0.

18. F. Malmberg and R. Strand
Faster Fuzzy Connectedness via Precomputation
Mathematical Morphology and Its Applications to Signal and Image Processing. Lecture Notes in Computer Science Volume 7883, 2013, pp 476–483
Number of citations: 1.

19. F. Malmberg, R. Strand, R. Nordenskjöld, J. Kullberg, E. Bengtsson
Smart Paint - A New Interactive Segmentation Method Applied to MR Prostate Segmentation
In Prostate MR Image Segmentation Grand Challenge (PROMISE'12), a MICCAI 2012 workshop.
Number of citations: 11.

20. F. Malmberg, R. Strand, R. Nordenskjöld, J. Kullberg
Seeded Segmentation Based on Object Homogeneity
In Proceedings of International Conference on Pattern Recognition (ICPR), 2012.
Number of citations: 0.

21. J. Nysjö, A.Christersson, F. Malmberg, I.-M. Sintorn, I. Nyström
Towards User-Guided Quantitative Evaluation of Wrist Fractures in CT Images
In Proceedings of International Conference on Computer Vision and Graphics (ICCVG), 2012.
Number of citations: 2.

22. I. Nyström, J. Nysjö, F. Malmberg
Visualization and Haptics for Interactive Medical Image Analysis: Image Segmentation in Cranio-Maxillofacial Surgery Planning
In Proceedings of the 2nd International Visual Informatics Conference (IVIC), 2011. Lecture Notes in Computer Science, 2011, Vol. 7066, 2011, pages 1–12, (Invited paper)
Number of citations: 7.

23. F. Malmberg, R. Strand, I. Nyström
Generalized Hard Constraints for Graph Segmentation
In Proceedings of the 17th Scandinavian Conference on Image Analysis (SCIA 2011). Lecture Notes In Computer Science (LNCS) Vol. 6688, 2011, pages 36–47.
Number of citations: 6.

24. F. Malmberg
Image Foresting Transform: On-the-fly Computation of Segmentation Boundaries
In Proceedings of the 17th Scandinavian Conference on Image Analysis (SCIA 2011). Lecture Notes In Computer Science (LNCS) Vol. 6688, 2011, pages 616–624.
Number of citations: 2.

25. F. Malmberg, J. Lindblad, I. Nyström
Sub-pixel Segmentation with the Image Foresting Transform
In Proceedings of the 13th International Workshop on Combinatorial Image Analysis (IWCIA'09) , Lecture Notes In Computer Science (LNCS) Vol. 5852, 2009, pages 201–211.
Number of citations: 16.

26. I. Nyström, F.Malmberg, E.Vidholm, E. Bengtsson
Segmentation and Visualization of 3D Medical Images through Haptic Rendering
In Proceedings of the 10th International Conference on Pattern Recognition and Information Processing (PRIP 2009), pages 43–48. Publishing Center of BSU, Minsk, Belarus, 2009. (Invited paper)
Number of citations: 6.

27. F. Malmberg, C. Östlund, G. Borgefors
Binarization of Phase Contrast Volume Images of Fibrous Materials: A Case Study
In Proceedings of International Conference on Computer Vision Theory and Applications (VISAPP 2009)
Number of citations: 3.

28. R. Strand, F. Malmberg, S. Svensson
Minimal Cost-Path for Path-Based Distances
In IEEE Proceedings, International Symposium on Image and Signal Processing and Analysis (ISPA 2007), pages 379–384, 2007.
Number of citations: 9.

Peer-reviewed articles in conference proceedings with abstract review

29. F. Malmberg, I. Nyström, A. Mehnert, C. Engstrom and E. Bengtsson.
Relaxed Image Foresting Transforms for Interactive Volume Image Segmentation
In Proceedings of SPIE Medical Imaging 2010.
Number of citations: 7.

Open access computer programs

30. SmartPaint - A tool for interactive segmentation of medical volume images
`http://www.cb.uu.se/~filip/SmartPaint/`

31. Exact evaluation of stochastic waterheds
`http://www.cb.uu.se/~filip/StochasticWatershed/`

Popular science

32. E. Vidholm, F. Malmberg, I. Nystrm
Läkarens känsel hjälper datorn
Forskning & Framsteg, nr 1, 2009, page. 62

CV

Name: Filip Malmberg	**Doctorial degree:** 2011-05-06
Birthdate: 19800806	**Academic title:** Doktor
Gender: Male	**Employer:** Uppsala universitet

Research education

Dissertation title (swe)
Grafbaserade metoder för interaktiv bildsegmentering

Dissertation title (en)
Graph-based Methods for Interactive Image Segmentation

Organisation	Unit	Supervisor
Uppsala universitet, Sweden Sweden - Higher education Institutes	Centrum för Bildanalys	Ingela Nyström

Subject doctors degree	ISSN/ISBN-number	Date doctoral exam
10299. Annan data- och informationsvetenskap	978-91-554-8037-0	2011-05-06

Publications

Name: Filip Malmberg	**Doctorial degree:** 2011-05-06
Birthdate: 19800806	**Academic title:** Doktor
Gender: Male	**Employer:** Uppsala universitet

Malmberg, Filip 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.