Vetenskapsrådet

Application

2015-03-31

2015-04017	Avenel, Christophe	NT-14

Information about applicant

Name: Christophe Avenel

Doctorial degree: 2012-12-08

Birthdate: 19840122

Academic title: Doktor

Gender: Male

Employer: Uppsala universitet

Administrating organisation: Uppsala universitet

Project site: Inst för informationsteknologi

Information about application

Call name: Forskningsbidrag Stora utlysningen 2015 (Naturvetenskap och teknikvetenskap)

Type of grant: Projektbidrag

Focus: Unga forskare

Subject area:

Project title (english): Decision Support for the Prognostication of Prostate Cancer

Project start: 2016-01-01

Project end: 2017-12-31

Review panel applied for: NT-14, NT-19

Classification code: 20603. Medicinsk bildbehandling

Keywords: Prostate cancer, Gleason grading, Machine learning, Image analysis, Prognostication

Funds applied for

Year:	2016	2017
Amount:	1,274,000	1,027,750

Descriptive data

Project info

Project title (Swedish)*

Beslutsstöd för prognosticering av prostata cancer

Project title (English)*

Decision Support for the Prognostication of Prostate Cancer

Abstract (English)*

Prostate cancer is the leading cause of cancer death in men. The severity of prostate cancer is determined from tissue samples using Gleason grading by a pathologist using microscopic images of histological sections from biopsy or radical prostatectomy material. Gleason grading is highly subjective with significant variation between experienced pathologists; studies show that both intra- and inter-observer variations can be as high as 30-40%. Despite attempts to reach a consensus regarding the subjective rules for quantification, none have been adopted. As a result about 70% of patients with localized prostate cancer receive aggressive treatment that does not prolong life but often results in debilitating side effects. The critical prognostic factor is the proportion of Gleason grade 4 cancer in a tissue sample. Our aim is to identify Gleason grades 3 and 4 and to objectively determine the prognostic difference between cases with Gleason scores 3+4 versus 4+3.
The goal of the Decision Support System for the Prognostication of Prostate Cancer Project is a high-throughput prognostic system which correlates morphological patterns associated with malignancy to disease outcome relying on large patient cohorts available at the Uppsala University Hospital. This will identify and separate slow-growing prostate cancer from more aggressive types, and in particular identify the demarcation line between Gleason scores 3+4 and 4+3. The system will be the first of its kind in that it will help health care providers to identify the patients who will benefit from watchful waiting and those in need of radical treatment, resulting in dramatically improved patient care and at the same time improved health economy.

Popular scientific description (Swedish)*

Prostatacancer är den vanligaste orsaken till död av cancer hos män. Diagnosen och prognosen baseras på en mönsteranalys av histologiska snitt, s.k. Gleasongradering. Detta system är det vanligaste för att bedöma aggressiviteten hos tumören. Gleasongraderingen är emellertid i hög grad subjektiv vilket leder till avsevärd variation i bedömningen även av erfarna patologer. Behovet av radikal behandling av prostatacancer har visat sig överdrivet emedan över 70% av patienter som behandlats radikalt inte visar längre överlevnad än de som bara övervakats. Vårt mål är att korrekt identifiera Gleasongraderna 3 och 4 i biopsierna för att objektivt bestämma den prognostiska skillnaden mellan Gleason score 3+4 och 4+3.
Projektet syftar till att utveckla ett helt nytt beslutsstöd som hjälper patologer att skilja mellan långsamt växande prostata cancer och agressivare former genom at korrelera mönster i histologiska snitt till prognos, och speciellt identifiera skiljelinjen mellan Gleason score 3+4 och 4+3. Resultaten testas i de stora material vi samlat sedan 1990-talet med eftergranskningsdata och klinisk uppföljning. Vårt beslutssystem skall hjälpa sjukvårdsgivare att bedöma om en patient bör få en radikal behandling eller om det är bättre att avvakta. Att kunna fatta sådana beslut innebär både bättre patientvård och bättre hälsoekonomi.

Project period

Number of project years*

2

Calculated project time*

2016-01-01 - 2017-12-31

Deductible time

Deductible time

Cause	Months
Career age: 27	

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*

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

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

Keyword 1*

Prostate cancer

Keyword 2*

Gleason grading

Keyword 3*

Machine learning

Keyword 4

Image analysis

Keyword 5

Prognostication

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*

The work proposed herein is part of a larger effort in prostate cancer research for which the national ethical committee in Stockholm has given its approval.

The project includes handling of personal data

Yes

The project includes animal experiments

No

Account of experiments on humans

No

Research plan

Decision Support System for the Prognostication of Prostate Cancer

Applicant: Christophe Avenel, PhD, Post. Doc. at Uppsala University (UU).
Collaboration partners:
Ingrid Carlbom, Guest Professor, Centre for Image Analysis, Department of Information Technology, Uppsala University.
Christer Busch, Professor Emeritus in Pathology, Department of Surgical Sciences, Uppsala University Hospital.
Anna Tolf, PhD student, Department of Immunology, Genetics, and Pathology, Uppsala University, and Consultant, Clinical Pathology, Uppsala University Hospital.

Purpose and Aims

The aim of the Decision Support System for the Prognostication of Prostate Cancer is a high-throughput prognostic system for identification and separation of slow-growing prostate cancer from more aggressive types. The purpose is to help health care providers to identify the patients who will benefit from watchful waiting and those in need of radical treatment, resulting in dramatically improved patient care and at the same time improved health economy.

Survey of the Field

Prostate cancer is a malignant growth originating in the epithelial cells of the prostate gland. Healthy prostate glands are uniform in size and shape, arranged in regular glandular patterns with two layers of cells (See Figure 1). When cancer progresses in degree of malignancy, the glands loose uniformity in size and shape, and the distance between them becomes more variable. With loss of cellular features such as polarity (i.e., orientation) the glands become complex, initially multilayered yet still single-luminal, but eventually multi-luminal and more aggressive. They are then considered of high grade. Low-grade cancer tends to grow slowly and spread only after a prolonged time, whereas high-grade cancer is more likely to grow aggressively or to have already metastasized at the time of diagnosis.

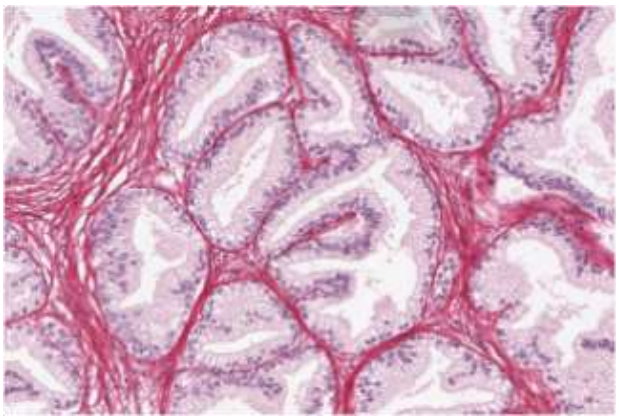

Figure 1: Normal prostate glands.

Gleason grading is the most widely used system for determining the severity of prostate cancer (1; 2; 3; 4; 5; 6), and when combined with information on tumour size it is viewed as the best indicator of long-term prognosis (7). The Gleason grade, from 1-5, is usually determined by a pathologist using microscopic images of histological sections from biopsies or radical prostatectomies at low or moderate magnification. Since Gleason proposed his grading system, much work has been devoted to identify morphological markers to form rules that characterize the five malignancy grades. The markers include the number of glandular units, their size and shape, and the intra-glandular distances. Other markers are epithelial thickness, cell polarity, cytoplasm color, and the cells' location relative to the stromal boundary. The Gleason grade is highly subjective with significant variation between experienced pathologists; studies show that both inter- and intra-observer variations can be as high as 30-40% (8; 9; 10). But despite attempts to reach a consensus regarding the rules for quantification, none have been adopted (5; 6).

Several attempts have been made to use image analysis to quantify and standardize Gleason grading from histological sections (11; 12; 13; 14; 15; 16). In contrast to these methods, we do not rely on the standard histological stain, hematoxylin-eosin, but on a stain new to prostate cancer that gives a good contrast between epithelium and stroma.

Project Description

Stain and blind color decomposition: Pathologists use multiple, contrasting stains to visually determine the grade of prostate tissue under a microscope. The most common such stain is hematoxylin-eosin (H&E), where the hematoxylin stains the cell nuclei blue, and eosin stains the cytoplasm pink and stroma in various grades of red/pink. We propose a methodology for quantitative comparisons of histological stains based on their classification and clustering performance (17). Among the stains we investigated for prostate cancer tissue, we showed that certain stains perform consistently better than others according to objective error criteria. Picro-Sirius-hematoxylin (Sir-Htx) (18) outperforms the traditional hematoxylin-eosin for classification of nuclei, cytoplasm and stroma, the most important components for Gleason grading (see Figure 2).

Color decomposition is a technique for stained tissue separation into gray-level images (density maps) with the individual contributions of the pixels from each spectral band, in this case from three channels, red, green, and blue. We have described a blind color decomposition method (BCD) (19; 20) that removes intensity variations present in the samples due to tissue preparation factors, including stain concentration, staining duration, tissue thickness, and fixation, allowing the decomposition to be based only on tissue absorption characteristics. We demonstrate both qualitatively and quantitatively that the BCD method outperforms other color decomposition methods for several types of tissue based on ground truth provided by an expert pathologist. We further showed that the color decomposition of prostate tissue stained with Sir-Htx gives a more accurate decomposition into density maps than does color decomposition of H&E-stained tissue, and thus enables a more accurate segmentation of morphological features that determine the Gleason grade (21).

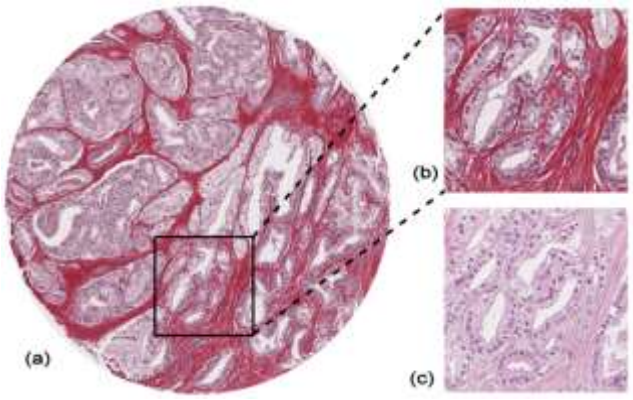

Figure 2. (a) Image of one tissue core section stained with Sir-Htx. (b) Cutout from image in (a). (c) Cutout of the corresponding tissue core section stained with H&E.

Online prostate tissue grading tool: Using our OpenSeaDragon-based (22) image selection tool we are building an image database of 650 small images from whole mount sections, where each image has one dominant pattern that represents a malignancy grade, precancerous tissue, or benign tissue. With our online grading tool, fourteen internationally prominent urological pathologists from seven countries are grading these images according to the Gleason system. (See Figure 3.)

With more than 60% of the images graded, we see similar grade variations as seen in other studies; for example, in 43% of the cases more than three pathologists disagree. But unlike other studies on intra- and interobserver grading variation, which are based on entire biopsies or whole mounts, each image in our study contains only *one* dominant pattern, allowing us to identify patterns that cause the discrepancies. Our goal is to establish a consensus for these patterns, thereby promoting international grading standardization.

The grading is nearing its end, and we expect to have a consensus grading meeting early fall. This consensus graded database will form the basis for an automatic malignancy Gleason grading system.

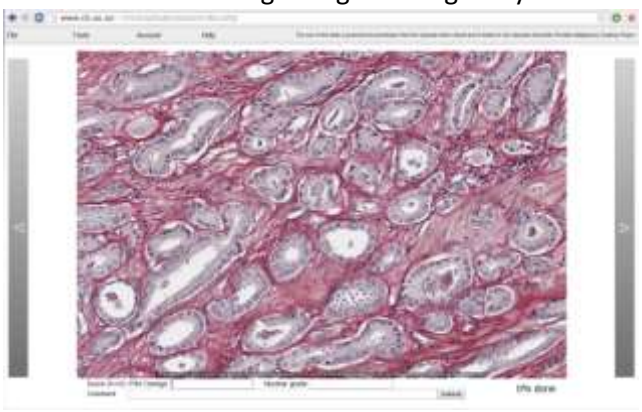

Figure 3: The user gives a Gleason Score below the image, or indicates PIN or benign as the primary pattern.

Automatic segmentation of prostate glands and nuclei: Using the stromal density map from the color decomposition of Sir-he-stained tissue, we extract the glandular structures using morphological operations combined with standard image processing operations. With the glandular units as masks, we then extract the epithelium and the lumen from the epithelial density maps. Qualitative analysis of over 5000 glands indicates that the segmentation results in highly accurate representations of the glandular shape, including the epithelium and the lumen (Figure 4).

From the epithelial density map, we use a marked point process to segment the epithelial nuclei (23). This enables us to extract nuclei as individual, joint, or overlapping objects generally without discarding overlapping parts and therefore without major loss in segmentation precision. The algorithm, which was originally developed for breast cancer tissue nuclei identification, uses simulated annealing combined with a "birth and death" process to find the best match with the density map, and was adapted to prostate tissue by pre-and-post processing methods. We have augmented the algorithm to find a more precise shape of the nuclei using a deformable circular model (Figure 5).

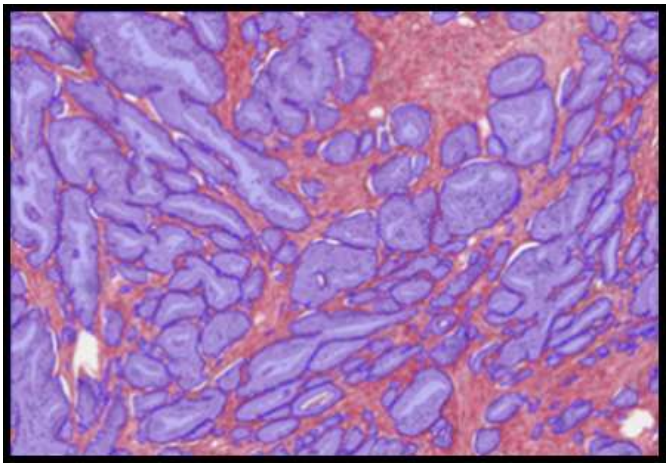

Figure 4. Segmented glands.

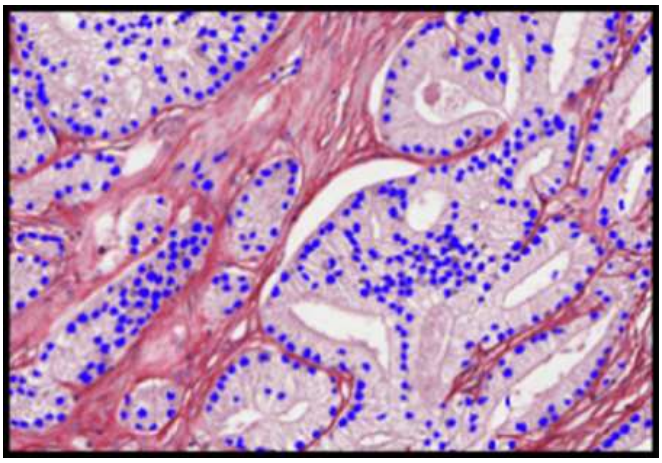

Figure 5. Segmented epithelial nuclei.

Consensus-based training dataset: Using the automatic-ally segmented glandular units, we label each gland based on the Gleason Grade produced by one pathologist. This labelling is on a finer scale than the Gleason grades; for example, grade 4 will be separated into fine caliber 4 and cribriform 4. Other grades are also divided to capture differences within the grade. To date we have labelled more than 5000 glands with one pathologist, giving us a dataset for training of our automatic grading algorithm. The labels will be updated when we reach a consensus grade with our international panel of experts.

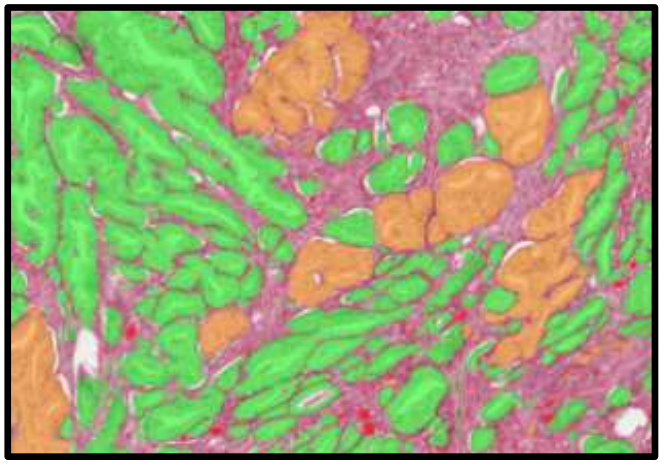

Figure 6. Gleason grades: green GG 3; orange GG 4; red GG 5.

Malignancy grading algorithm: With our local expert pathologists, we have identified about 20 glandular features that are associated with malignancy. These features include glandular size and shape, intra-glandular distance, epithelial thickness, cytoplasm color, and the cells' location relative to the stromal boundary. From the segmented glands and nuclei, we have developed algorithms to extract these features that will be the basis for the automatic grading. We will train classifiers on the ground truth data to give each gland a label, and then group glands with similar labels to arrive at a local grade. (See Figure 6 – note this is an illustration only – the automatic algorithm is not completed.) Once this first automatic grading system, which is based on one pathologist, is completed, we will relabel the segmented glands according to the consensus graded data and update the automatic grading system accordingly.

This is the starting point for the new VR-grant applied for herein.

As a next step we will extend our automatic malignancy grading system to find support for active surveillance or watchful waiting for patients with few positive biopsies and Gleason scores 6 or lower (24; 25; 26). It is known that a prognostic demarcation line lies between Gleason grades 3 and 4, that is patients that have a grade below this demarcation line have an excellent prognosis while the patients with a grade above this line have a much worse prognosis and require aggressive treatment (27; 28; 29). We will extend the automatic grading system to reliably identify malignancy relative to the long-term disease outcome, such as the time to cancer recurrence, metastases, PSA relapse, and death. We will characterize the morphological features that relate to the outcome. Using this information to train the classifier directly on the outcome rather than on the Gleason grade should lead to prognostication that is not obtainable when using the subjective Gleason grade alone.

At this point, we turn to validation of the algorithm. The malignancy grading prototype will be validated using data from a unique patient cohort with consensus grades and known clinical outcome. With previous grants awarded by, for example, Cancerfonden, a large group of prostate cancer patients (about 550 individuals) treated by radical prostatectomies in Uppsala during 1987-2001 (UPPALL) were followed for more than eight years. For approximately 180 of these individuals, there is a biobank with freshly frozen, histologically confirmed tumor tissue. We will produce a new data set from this cohort comprising two adjoining sections from each of the 180 cases and stain one section with Sir-Htx and the second with Sir-Htx and immune-stained basal cells.

The UPPALL cases have consensus grades, and we aim to arrive at the same grade with the automatic grading system, or to dispute the grade and arrive at an understanding of the differences and find a way to mitigate the discrepancies. We will rely on our pathologists to mitigate the discrepancies.

In some cases, it may not be possible to discriminate between normal glandular structures and infiltrating cancer. In those cases, we will use the adjoining section that has been stained with immuno-histochemical basal cells by DAB (Diaminobenzidine) to determine whether a gland is malignant or not.

Glandular units with black basal cells and a single lumen are non-cancerous and need no further processing. We expect that our highly quantitative grading method will reduce the necessity for immuno-histochemistry.

We will then develop a verified prototype of a new automatic prostate cancer prognostic tool. We will again use the UPPALL dataset which allows us to train the classifier to associate the malignancy features with the disease outcome. *This will be, to the best of our knowledge, the first attempt to create an automatic, prostate cancer prognostic cancer tool.*

Significance

In 2012 an estimated 1.1M men worldwide were diagnosed with prostate cancer, accounting for 15% of all cancers diagnosed in men. In the same year 307,000 succumbed to the disease. In the US the number of new cases of prostate cancer was 233,000 in 2012, with an estimated number of deaths at 30,000. In Europe the number of diagnoses was 345,000, with 72,000 deaths. In Sweden the prostate cancer incidence in 2012 was 11,596 with 2,444 deaths. In the US doctors perform about 400K prostate biopsies per year. At the Uppsala University Hospital, a pathologist grades about 20 biopsy cases per day (each case with 10-16 separate biopsy cores), or about 1000 biopsy cases per year (amounting to 10 000-16000 individual biopsy cores). (30)

The diagnosis and prognosis of prostate cancer is based on Gleason grading, which is the most widely used system for determining the severity of prostate cancer from tissue samples (1). The need for radical treatment of prostate cancer has been overestimated and the importance of a reliable judgement of the malignancy grade in biopsies has become urgent. However, Gleason grading is highly subjective with significant variation between experienced pathologists. As a result about 70% of patients with localized prostate cancer receive aggressive treatment that does not prolong life but often results in debilitating side effects.

A prognostic tool for prostate cancer will both prolong lives and reduce medical costs. By identifying and separating slow-growing cancer from more aggressive types, we will reduce needless radical and costly treatment. Quantitative prognostication will help lower the number of missed cancer diagnoses and give a more accurate diagnosis by eliminating inter- and intra-observer variation of under- and over-prognostication, yielding a more objective basis for a course of treatment for each patient. In the past, radical treatment has dominated in cases with clinically localized prostate cancer, but in the last few years active surveillance or watchful waiting has emerged for patients with few positive biopsies and Gleason scores 6 or lower (26). A critical problem is the diagnosis of Gleason grades 3 and 4 in biopsies and the prognostic difference between cases with Gleason score 3+4 versus 4+3. Pathologists have become more aggressive in their use of grade 4, which has resulted in confusion among urological surgeons who demand more objective grading to avoid overtreatment. We believe that our image analysis techniques will produce the needed objectivity.

Preliminary results

From the project description, the following points are or will be done by January 2016:

1. Stain selection of Sir-Htx and blind color decomposition, which are key to the grading and prognostication algorithms.
2. Consensus graded image database of 650 small images from whole mount sections.
3. First automatic grading system based on one expert pathologist.
4. Second automatic grading system based on the consensus graded data in the UPPALL cohort.

Independent line of research

The project has been conducted in collaboration with Professor Ingrid B. Carlbom from Uppsala University and Christer Busch from Uppsala University Hospital. It is the culmination of over 8 years of research on Prostate cancer malignancy grading. Both Professor Ingrid B. Carlbom and Christer Busch will retire in the next few years, which will allow me to take lead on the project and continue working on prostate cancer with Anna Tolf as expert pathologist, and the panel of experts from our international collaboration.

Project Timeline

Year 1: Validation of the automatic Gleason grading system to reliably identify malignancy grades using the UPPALL consensus data. Mitigate discrepancies, in some cases with the help of DAB.

Year 2: Development of a prototype automatic prostate cancer prognostic tool using the disease outcome in UPPALL.

Equipment

The Department of Pathology has access to technical assistance and equipment for sectioning and staining the described material. Likewise we have access to whole slide scanners and microscopes for digitizing microscopic images. The Centre for Image Analysis has sufficient computing resources for this project, as well as MATLAB® for algorithm development.

National and International Collaboration

The consensus grading committee has the following members:

Committee Member	**Affiliation**
Anna Tolf, MD	Uppsala University and Uppsala University Hospital, Sweden
Anna Sankila, MD, PhD	United Medix Laboratories Ltd., Helsinki, Finland
Christer Busch, MD, PhD	Professor Emeritus of University of Tromsö, Norway; Uppsala University, Sweden
Francesca Giunchi, MD	Pathology department, S.Orsola-Malpighi Hospital, Bologna, Italy
Hans Hamberg, MD, PhD	Retired uropathologist, Västerås County Hospital, Sweden
Isabell Sesterhenn	Genito-Urinary branch, Armed Forces Institute of Pathology, Washington, D.C., USA
Janos Vasko, MD, PhD	Department of Pathology, University of Umeå, Sweden
Maréne Landström, MD, PhD	Prof. of Pathology, University of Umeå, Sweden and the Ludwig Institute for Cancer Research, Uppsala University, Sweden
Massimo Loda, MD, PhD	Prof. of Pathology, Harvard Medical School; Department of Medical Oncology, Dana Farber Cancer Institute, Boston, MA, USA
Michelangelo Fiorentino, MD, PhD	Head Laboratory of Oncologic and Transplantation Molecular Pathology, Addarii Institute of Oncology, Bologna, Italy
Stig Nordling, MD, PhD	Department of Pathology, University of Helsinki, Finland

Ethical Considerations

The work proposed herein is part of a larger effort in prostate cancer research for which the national ethical committee in Stockholm has given its approval.

Gender Considerations

The results of the proposed research will benefit directly only men. However, malignancy grading is important for all types of cancer that afflict both men and women, and we expect that the results of this research can be adapted to other tumor types, given that increased aggressiveness is reflected in loss of uniformity and polarity in most malignancies.

Form of employment

Researcher in the Division of Visual Information and Interaction in the Department of Information Technology at Uppsala Universaity for two years.

Bibliography

1. Histologic Grading of Prostate Cancer: A perspective. ***Gleason, D. F.*** *March 1992, Human Pathology, Vol. 23, pp. 273-279.*
2. ***Amin, M.B., et al., et al.*** Gleason Grading of Prostate Cancer: A Contemporary Approach. *New York : Lippincott Williams and Wilkins, 2003.*
3. ***Epstein, J.*** Prostate Biopsy Interpretation. *Philadelphia, PA : Lippincott-Raven, 1995.*
4. Reproducibility of Gleason Grading of Prostate Cancer can be Improved by the Use of Reference Images. ***Egevad, L.*** *2001, Urology, Vol. 57, pp. 291-295.*
5. Recent trends in Gleason grading of prostate cancer I: Pattern Interpretation. ***Egevad, L.*** *April 2008, Analytical and Quantitative Cytology and Histology, Vol. 30, pp. 190-198.*
6. Recent Trends in Gleason Grading of Prostate Cancer II: Prognosis, Reproducibility and Reporting. ***Egevad, L.*** *April 2008, Analytical and Quantitative Cytology and Histology, Vol. 30.*
7. Biological Determinants of Cancer Progression in Men with Prostate Cancer. ***Stamey, TA., et al., et al.*** *1999, JAMA, Vol. 281, pp. 1395-1400.*
8. Update on the Gleason Grading System for Prostate Cancer: Results of an International Consensus Conference of Urologic Pathologists. ***Epstein, J.I., et al., et al.*** *January 2006, Adv. Anat. Pathol., Vol. 13, pp. 57-59.*
9. Implications of the International Society of Urological Pathology Modified Gleason Grading System. ***Egevad, L., Mazzucchelli, R. and Montironi, R.*** *April 2012, Arch Pathol Lab Med, Vol. 136, pp. 426-434.*
10. Interactive Digital Slides with Heat Maps: A Novel Method to Improve the Reproducibility of Gleason Grading. ***Egevad, L., et al., et al.*** *2011, Virchows Arch, Vol. 459, pp. 175-182.*
11. Texture Analysis of Tissues in Gleason Grading of Prostate Cancer. ***Alexandratou, E., et al., et al.*** *2008. Proc. SPIE: Imaging, Manipulation, and Analysis of Biomolecules, Cells, and Tissues. Vol. 6859.*
12. Automated Gland Segmentation and Classification for Gleason Grading of Prostate Tissue Images. ***Nguyen, K., Jain, A.K. and Allen, R.L.*** *2010. Proc. Intl Conference on Pattern Recognition (ICPR). pp. 1497-1500.*
13. Prostate Cancer Diagnosis and Gleason Grading of Histological Images. ***Tabesh, A., et al., et al.*** *October 2007, IEEE Trans. Med. Imag, Vol. 26, pp. 1366-1378.*
14. A Boosted Bayesian Multiresolution Classifier for Prostate Cancer Detection from Digitized Needle Biopsies. ***Doyle, S., et al., et al.*** *May 2012, IEEE Trans. Biomedical Engineering, Vol. 59.*
15. Computer-Aided Gleason Grading of Prostate Cancer Histopathological Images using Texton Forests. ***Khurd, P., et al., et al.*** *2010. Proc. IEEE International Symposium on Biomedical Imaging: From Nano to Macro (ISBI 2010). pp. 636 - 639.*
16. Automated Gland and Nuclei Segmentation for Grading of Prostate and Breast Cancer Histopathology. ***Naik, S., et al., et al.*** *2008. Proc. IEEE International Symposium on Biomedical Imaging: From Nano to Macro (ISBI 2008). pp. 284-287.*
17. Histological Stain Evaluation for Machine Learning Applications," 4 (11), March 2013. ***Azar, J.C., Busch, C. and Carlbom, I.B.*** *March 2013, Journal of Pathology Informatics, Vol. 4.*

18. Sirius red F3BA as a stain for connective tissue. ***Sweat, F., Puchtler, H. and Rosenthal, S.I.*** *1964, Arch. Pathol., Vol. 78, pp. 69-72.*

19. Blind Color Decomposition of Histological Images. ***Gavrilovic, M., et al., et al.*** *June 2013, IEEE Transactions of Medical Imaging, Vol. 32, pp. 983-994.*

20. ***Azar, J.C., et al., et al.*** *Color Decomposition in Histology.* US Patent Application Number PCT/US12/64282. *November 2012.*

21. Picro-Sirius-Htx Stain for Blind Color Decomposition of Histo-pathological Prostate Tissue. ***Carlbom, I.B., Avenel, C. and Busch, C.*** *2014. Proc. IEEE Int. Symp. Biomedical Imaging (ISBI).*

22. OpenSeadragon. [Online] http://openseadragon.github.io/.

23. Marked Point Processes with Simple and Complex Shape Objects for Cell Nuclei Extraction from Breast Cancer H&E Images. ***Avenel, C. and Kulikova, M.S.*** *2013. Proc. SPIE, Medical Imaging: Digital Pathology. Vol. 8676.*

24. Changes in Prostate Cancer Grade on Serial Biopsy in Men Undergoing Active Surveillance. ***Porten, SP., et al., et al.*** *2010, Journal of Clinical Oncology, Vol. 33, p. 134.*

25. The Potential Impact of Reproducibility of Gleason Grading in Men With Early Stage Prostate Cancer Managed by Active Surveillance: A Multi-Institutional Study. ***McKenney, JK., et al., et al.*** *2011, Journal of Urology, Vol. 186, pp. 465-469.*

26. Active Surveillance for Prostate Cancer: For Whom? ***Klotz, L.*** *2005, Journal of Clinical Oncology, Vol. 23, pp. 8165-8169.*

27. Radical Prostatectomy Versus Watchful Waiting in Localized Prostate Cancer: the Scandinavian Prostate Cancer Group-4 Randomized Trial. ***Bill-Axelson, A., et al., et al.*** *2008, JNCI J Natl Cancer Inst, Vol. 100, pp. 1144-1154.*

28. Radical Prostatectomy versus Watchful Waiting in Early Prostate Cancer. ***Bill-Axelson, A., et al., et al.*** *2011, The New England Journal of Medicine, Vol. 364, pp. 1708-1717.*

29. Low Endoglin Vascular Density and Ki67 Index in Gleason Score 6 Tumours May Identify Prostate Cancer Patients Suitable for Surveillance. ***Josefsson, A., et al., et al.*** *August 2012, Scandinavian Journal of Urology, Vol. 46, pp. 247-257.*

30. International agency for Research on Cancer. International agency for Research on Cancer. *[Online] http://globocan.iarc.fr/Pages/burden_sel.aspx.*

31. A Search for Reliable Molecular Markers of Prognosis in Prostate Cancer. A Study of 240 Cases. ***Tradonsky, A., et al., et al.*** *2012, American Journal of Clinical Pathology, Vol. 137, pp. 918-930.*

32. Improved Prediction of Prostate Cancer Recurrence Based on an Automated Tissue Image Analysis System. ***Teverovskiy, M., et al., et al.*** *2004. Proc. IEEE Int. Symp. Biomed. Imag; Nano to Macro. pp. 257-260.*

33. Multiple recognition assay reveals prostasomes as promising plasma biomarkers for prostate cancer. ***Tavoosidana, G., et al., et al.*** *2011, Proceedings of the National Academy of Sciences of the United States of America, Vol. 108(21), pp. 8809–8814.*

34. Plasma Insulin-Like Growth Factor-I, Insulin-Like Growth Factor-Binding Proteins, and Prostate Cancer Risk: a Prospective Study. ***Stattin, P., et al., et al.*** *2000, Journal of the National Cancer Institute, Vol. 92, pp. 1910–7.*

35. Virchows Archive. ***Richardsen, E., et al., et al.*** *2003, Vol. 442, pp. 329–335.*

36. Metabolic alterations and targeted therapies in prostate cancer. ***Richard Flavin, Giorgia Zadra and Massimo Loda.*** *2011, Journal of Pathology, Vol. 223(2), pp. 283-294.*

37. Atypical Protein Kinase CI Is an Oncogene in Human Non–Small Cell Lung Cancer. ***Regala, RP., et al., et al.*** *2005, Cancer Research, Vol. 65(19), pp. 8905-11.*

38. α-Methylacyl-CoA Racemase A New Molecular Marker for Prostate Cancer. ***Luo, J., et al., et al.*** *2002, Cancer Research, Vol. 62, p. 2220.*

39. Three-Dimensional Modeling of Biopsy Protocols for Localized Prostate Cancer. ***Loughlin, M., et al., et al.*** *1998, Computerized Medical Imaging and Graphics, Vol. 22, pp. 229-238.*

40. Mechanism of TGF β signaling to growth arrest, apoptosis and epithelial-mesenchymal transition. ***Heldin, C-H., Landstrom, M. and Moustakas, A.*** *2009, Current Opinion in Cell Biology, Vol. 21, pp. 1-11.*

41. Three-Dimensional Computer Reconstruction of Prostate Cancer from Radical Prostatectomy Specimens. Evaluation of the Model by Core Biopsy Simulation. ***Egevad, L., et al., et al.*** *1999, Urology, Vol. 53, pp. 192-198.*

42. Down-regulation of CEACAM1 in human prostate cancer: correlation with loss of cell polarity, increased proliferation rate, and Gleason grade 3 to 4 transition. ***Busch, C., et al., et al.*** *2002, Hum Pathol., Vol. 33(3), pp. 290-8.*

43. TRAF6 ubiquitinates TGFb type I receptor to promote its cleavage and nuclear translocation in cancer. ***Mu, Y., et al., et al.*** *330, 2011, Nature Communications, Vol. 2.*

44. Regulation of the polarity protein Par6 by TGFbeta receptors controls epithelial cell plasticity. ***Ozdamar, B., et al., et al.*** *307, March 2005, Science, Vol. 11, pp. 1603-1609.*

45. Atypical protein kinase C phosphorylates Par6 and facilitates transforming growth factor β-induced epithelial-to-mesenchymal transition. ***Gunaratne, A., Thai, BL. and Di Guglielmo, GM.*** *5, March 2013, Molecular Cell Biology, Vol. 33, pp. 874-886.*

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

This application spans Natural and Engineering Sciences and Medicine and Health.

The overall aim of the Decision Support System for the Prognostication of Prostate Cancer is to develop a high-throughput prognostic system in order to identify and separate slow-growing prostate cancer from more aggressive types. It relies on techniques from machine vision and image analysis to automate and standardize malignancy grading and prognostication of prostate cancer tissue. Today the severity and prognostication of prostate cancer is determined from tissue samples according to Gleason by a pathologist using microscopic images of histological sections from biopsy or radical prostatectomy material.

The automatic algorithm relies on a training dataset of features associated with malignancy. The training dataset is extracted from whole mount tissue images from prostatectomies. This tissue is prepared at the Uppsala University Hospital pathology department. Then the pathologists grade the tissue and identify features in the tissue images associated with malignancy.

The test dataset comprises 180 images from prostatectomies whole mounts from the UPPALL cohort. The Uppsala University Hospital pathology department will section, stain and scan the images. The pathologists will help validate the results of the application of our algorithm to the test dataset.

Thus it is thus important that this project is carried out in very close collaboration with pathologists.

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	Christophe Avenel	75
2	Other personnel with doctoral degree	Christer Busch	20
3	Other personnel with doctoral degree	Ingrid Carlbom	20
4	Other personnel without doctoral degree	Anna Tolf	10

Salaries including social fees

	Role in the project	Name	Percent of salary	2016	2017	Total
1	Applicant	Christophe Avenel	75	490,272	502,529	992,801
2	Other personnel with doctoral degree	Christer Busch	10	126,070	129,183	255,253
3	Other personnel with doctoral degree	Ingrid Carlbom	10	126,070	129,183	255,253
	Total			742,412	760,895	1,503,307

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	Total
1	Office	20,000	20,000	40,000
	Total	20,000	20,000	40,000

Running Costs

	Running Cost	Description	2016	2017	Total
1	Travel expenses, conferences		20,000	20,000	40,000
2	Publications, OA		10,000	10,000	20,000
3	Tissue preparation		270,000		270,000
	Total		300,000	30,000	330,000

Depreciation costs

	Depreciation cost	Description	2016	2017

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	Total, applied	Other costs	Total cost
Salaries including social fees	742,412	760,895	1,503,307	739,300	2,242,607
Running costs	300,000	30,000	330,000		330,000
Depreciation costs			0		0
Premises	20,000	20,000	40,000		40,000
Subtotal	1,062,412	810,895	1,873,307	739,300	2,612,607
Indirect costs	211,588	216,855	428,443	210,700	639,143
Total project cost	1,274,000	1,027,750	2,301,750	950,000	3,251,750

Explanation of the proposed budget

Briefly justify each proposed cost in the stated budget.

Explanation of the proposed budget*

Salaries:
- Christophe Avenel: 75% of main applicant's salary including social fees and university overhead.
- Christer Busch: senior uropathologist, 10% of salary including university overhead.
- Ingrid Carlbom: senior image analyst, with 8 years of experience with prostate cancer, 10% of salary including university overhead.

Premises: office for Christophe Avenel.

Running costs
- Travel: one to two conferences per year.
- Publication: fees for open access and for page charges.
- Tissue preparation: preparation of 180 scanned whole mount sections stained with Sir-Htx, and 180 with Sir-Htx + DAB.

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

CV

CHRISTOPHE AVENEL, PH.D.

Address: Frodegatan 16B, 75327 Uppsala, SWEDEN
Telephone: +46 70 040 71 62
Email: cavenel@gmail.com
Nationality: French
Date of Birth: 1984-22-01

HIGHER EDUCATIONAL QUALIFICATIONS

École Normale Supérieure de Cachan - Antenne de Bretagne
Master 2, Research in computer science **2006**
Majors Telecommunication

Université de Paris XI
Master 1, in Computer science **2005**

Université de Paris XI
Licence, in Computer science **2002 – 2004**

DOCTORAL DEGREE

PhD at Université Rennes 1 **Sep. 2008 – Dec. 2011**
Tracked closed curves with non-linear stochastic filters
We introduce a non-linear stochastic filtering technique to track the state of a free curve from image data. To that purpose, we designed a continuous-time dynamics that allows us to infer inter-frame deformations. The curve is defined by an implicit level-set representation and the stochastic dynamics is expressed as a level-set function.

CURRENT POSITION

Postdoctoral fellow at Uppsala University **2013 -**
Building an automatic prostate malignancy grading system.

PREVIOUS POSITIONS

Postdoctoral fellow at LIP6 / ANR TaMaDi **Mar. 2013 – Aug. 2013**
Parallelized the Table Maker's Dilemma.

Postdoctoral fellow at LIP6 / ANR MICO **Mar. 2012 – Mar. 2013**
Created algorithms for cell nuclei in breast cancer histological images and deployed these algorithms on many-core architectures.
In the ANR MICO framework: implementation of an effective and operational segmentation algorithm on GPUs and on multicore CPUs, in order to reach real time-detection of nuclei in very large images.

Internship at INRIA (France) **2007**
Tracked closed curves with non-linear stochastic filters.

Internship at LRI (Laboratoire de Recherche en Informatique) **2006**
Wrote software for graphical display (in Caml + Tcl/Tk) of a synchronous language.

SUPERVISION

Master student: **Yassine Guareb** **Sep. 2012 – Mar. 2013**
Aadaptation of matlab code on breast cancer grading for faster
Implementation on python.

Publication list

Christophe Avenel – Publication list

PEER-REVIEWED ORIGINAL ARTICLES

[1] C. Avenel, E. Mémin, and P. Pérez.
Stochastic level set dynamics to track closed curves through image data.
In Journal of Mathematical Imaging and Vision, In Press, 2013.

PEER-REVIEWED CONFERENCE PAPERS

[1] C. Avenel, and I.B. Carlbom
Blur detection and visualization in histological whole slide images
In International Conference on Mass Data Analysis of Images and Signals (MDA), In Press, 2015.

[2] I.B. Carlbom, C. Avenel, and C. Busch
Picro-Sirius-Htx Stain for Blind Color Decomposition of Histo-pathological Prostate Tissue
In Proc. IEEE Int. Symp. Biomedical Imaging (ISBI), Beijing, China, April 2014.

[3] C. Avenel, P. Fortin, and D. Béréziat.
Massively parallel birth and death process for cell nuclei extraction in histopathology images..
In International Conference on Parallel Processing, In Press, 2013.

[4] C. Avenel, and M. S. Kulikova.
Marked Point Processes with Simple and Complex Shape Objects for Cell Nuclei Extraction from Breast Cancer H&E Images.
In SPIE Medical Image, 2012.

[5] C. Avenel, E. Mémin, and P. Pérez.
Stochastic filtering of level sets for curve tracking.
In International Conference on Pattern Recognition (ICPR'10), Istanbul, Turkey, 2010.

[6] C. Avenel, E. Mémin, and P. Pérez.
Tracking levels representation driven by a stochastic dynamics.
In 7th International Conference on Curves and Surfaces, Avignon, France, June 2010.

[7] C. Avenel, E. Mémin, and P. Pérez.
Tracking closed curves with non-linear stochastic filters.
In Conf. on Scale Space and Variational Methods (SSVM'09), Voss, Norway, June 2009.

RESEARCH REVIEW ARTICLES

[1] P. Ranefall, A. Pacureanu, C. Avenel, A.E Carpenter and C. Wählby
The Giga-pixel Challenge: Full Resolution Image Analysis - Without Losing the Big Picture : An open-source approach for multi-scale analysis and visualization of slide-scanner data details
In Symposium of the Swedish Society for Automated Image Analysis (SSBA), 2014.

[2] I.B. Carlbom, C. Avenel, and C. Busch.
Presented the "Uppsala Automatic Prostate Malignancy Grading System".
at the Prostate Cancer Research Meeting, sponsored by Karolinska Institut, 25 Nov. 2015

CV

Name: Christophe Avenel	**Doctorial degree:** 2012-12-08
Birthdate: 19840122	**Academic title:** Doktor
Gender: Male	**Employer:** Uppsala universitet

Research education

Dissertation title (swe)

Dissertation title (en)

Tracking closed curves with non-linear stochastic filters

Organisation	Unit	Supervisor
Rennes 1 University, France Not Sweden - Higher Education institutes		
Subject doctors degree	**ISSN/ISBN-number**	**Date doctoral exam**
10207. Datorseende och robotik (autonoma system)		2012-12-21

Publications

Name: Christophe Avenel	**Doctorial degree:** 2012-12-08
Birthdate: 19840122	**Academic title:** Doktor
Gender: Male	**Employer:** Uppsala universitet

Avenel, Christophe 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.