**Perfusion vector - a new method to quantify myocardial perfusion scintigraphy images: a simulation study with validation in patients**

Background The interpretation of myocardial perfusion scintigraphy (MPS) largely relies on visual assessment by the physician of the localization and extent of a perfusion defect. The aim of this study was to introduce the concept of the perfusion vector as a new objective quantitative method for further assisting the visual interpretation and to test the concept using simulated MPS images as well as patients. Methods The perfusion vector is based on calculating the difference between the anatomical centroid and the perfusion center of gravity of the left ventricle. Simulated MPS images were obtained using the SIMIND Monte Carlo program together with XCAT phantom. Four different-sized anterior and four lateral defects were simulated, and perfusion vector components x-, y-, and z-axes were calculated. For the patient study, 40 normal and 80 abnormal studies were included. Perfusion vectors were compared between normal and abnormal (apical, inferior, anterior, and lateral ischemia or infarction) studies and also correlated to the defect size. Results For simulated anterior defects, the stress perfusion vector component on the y-axis (anterior-inferior direction) increased in proportion to the defect size. For the simulated lateral defects, the stress perfusion vector component on the x-axis (septal-lateral direction) decreased in proportion to the defect size. When comparing normal and abnormal patients, there was a statistically significant difference for the stress perfusion vector on the x-axis for apical and lateral defects; on the y-axis for apical, inferior, and lateral defects; and on the z-axis (basal-apical direction) for apical, anterior, and lateral defects. A significant difference was shown for the difference vector magnitude (stress/rest) between normal and ischemic patients (p=0.001) but not for patients with infarction. The correlation between the defect size and stress vector magnitude was also found to be significant (p<0.001). Conclusions The concept of the perfusion vector introduced in this study is shown to have potential in assisting the visual interpretation in MPS studies. Further studies are needed to validate the concept in patients.

**General information**

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A Novel Automated Platform for Quantifying the Extent of Skeletal Tumour Involvement in Prostate Cancer Patients Using the Bone Scan Index

Background
There is little consensus on a standard approach to analysing bone scan images. The Bone Scan Index (BSI) is predictive of survival in patients with progressive prostate cancer (PCa), but the popularity of this metric is hampered by the tedium of the manual calculation.

Objective
Develop a fully automated method of quantifying the BSI and determining the clinical value of automated BSI measurements beyond conventional clinical and pathologic features. Design, setting, and participants
We conditioned a computer-assisted diagnosis system identifying metastatic lesions on a bone scan to automatically compute BSI measurements. A training group of 795 bone scans was used in the conditioning process. Independent validation of the method used bone scans obtained ≤3 mo from diagnosis of 384 PCa cases in two large population-based cohorts. An experienced analyser (blinded to case identity, prior BSI, and outcome) scored the BSI measurements twice. We measured prediction of outcome using pretreatment Gleason score, clinical stage, and prostate-specific antigen with models that also incorporated either manual or automated BSI measurements. Measurements
The agreement between methods was evaluated using Pearson's correlation coefficient. Discrimination between prognostic models was assessed using the concordance index (C-index).

Results and limitations
Manual and automated BSI measurements were strongly correlated (ρ=0.80), correlated more closely (ρ=0.93) when excluding cases with BSI scores ≥10 (1.8%), and were independently associated with PCa death (p<0.0001 for each) when added to the prediction model. Predictive accuracy of the base model (C-index: 0.768; 95% confidence interval [CI], 0.702–0.837) increased to 0.794 (95% CI, 0.727–0.860) by adding manual BSI scoring, and increased to 0.825 (95% CI, 0.754–0.881) by adding automated BSI scoring to the base model. Conclusions
Automated BSI scoring, with its 100% reproducibility, reduces turnaround time, eliminates operator-dependent subjectivity, and provides important clinical information comparable to that of manual BSI scoring.

We developed and evaluated the first unbiased, fully automated software system to systematically calculate skeletal tumour burden in patients with metastatic cancer in the bone, simplifying a valuable but cumbersome technology with shortcomings that had prevented its widespread clinical use.

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Automated segmentation of the skeleton in whole-body bone scans: influence of difference in atlas

Aim: Automated segmentation of the skeleton is the first step for quantitative analysis and computer-aided diagnosis (CAD) of whole-body bone scans. The purpose of this study was to examine the influence of differences in skeletal atlas on the automated segmentation of skeletons in a Japanese patient group. Methods: The study was based on a bone scan CAD system that included a skeletal atlas obtained using 10 normal bone scans from European patients and 23 normal bone scans from Japanese patients. These were incorporated into the CAD system. The performance of the skeletal segmentation, based on either the European or the Japanese Atlas, was evaluated independently by three observers in a group of 50 randomly selected bone scans from Japanese patients. Results: The skeletal segmentation was classified as correct in 41-44 of the 50 cases by the three observers using the Japanese atlas. The corresponding results were 15-18 of the 50 cases using the European atlas, and this difference was statistically significant (P

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Organisations: Department of Informatics and Mathematical Modeling, DTU Data Analysis, Kanazawa University, Gunma Prefectural Cancer Center, University of Gothenburg
Computer-aided diagnosis system for bone scintigrams from Japanese patients: importance of training database

Computer-aided diagnosis (CAD) software for bone scintigrams have recently been introduced as a clinical quality assurance tool. The purpose of this study was to compare the diagnostic accuracy of two CAD systems, one based on a European and one on a Japanese training database, in a group of bone scans from Japanese patients. The two CAD software are trained to interpret bone scans using training databases consisting of bone scans with the desired interpretation, metastatic disease or not. One software was trained using 795 bone scans from European patients and the other with 904 bone scans from Japanese patients. The two CAD softwares were evaluated using the same group of 257 Japanese patients, who underwent bone scintigraphy because of suspected metastases of malignant tumors in 2009. The final diagnostic results made by clinicians were used as gold standard. The Japanese CAD software showed a higher specificity and accuracy compared to the European CAD software [81 vs. 57 % (p <0.05) and 82 vs. 61 % (p <0.05), respectively]. The sensitivity was 90 % for the Japanese CAD software and 83 % for the European CAD software (n.s). The CAD software trained with a Japanese database showed significantly higher performance than the corresponding CAD software trained with a European database for the analysis of bone scans from Japanese patients. These results could at least partly be caused by the physical differences between Japanese and European patients resulting in less influence of attenuation in Japanese patients and possible different judgement of count intensities of hot spots.

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Normal stress databases in myocardial perfusion scintigraphy – how many subjects do you need?

Commercial normal stress databases in myocardial perfusion scintigraphy (MPS) commonly consist of 30–40 individuals. The aim of the study was to determine how many subjects are needed. Four normal stress databases were developed using patients who underwent 99mTc MPS: non-corrected images (NC) for male, NC for female, attenuation-corrected images (AC) for male and AC for female subjects. 126 male and 205 female subjects were included. The normal database was created by alternatingly computing the mean of all normal subjects and normalizing the subjects with respect to this mean, until convergence. Coefficients of variation (CV) were created for increasing number of included patients in the four different normal stress databases. Normal stress databases with <35 subjects had a high CV. Mean CV −2 standard deviations (SD) decreased with 28% between two and five included subjects, 71% between two and 35 subjects and 83% between two and 100 included subjects for NC man. We conclude that the commonly used 30–40 individuals for making a normal stress database might not be enough due to the high CV. We propose that normal stress databases should consist of more than 30–40 individuals, preferably more than 50 individuals, both for NC and AC studies.

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An Automated System for the Detection and Diagnosis of Kidney Lesions in Children from Scintigraphy Images

Designing a system for computer aided diagnosis is a complex procedure requiring an understanding of the biology of the disease, insight into hospital workflow and awareness of available technical solutions. This paper aims to show that a valuable system can be designed for diagnosing kidney lesions in children and adolescents from 99mTc- DMSA scintigraphy images. We present the chain of analysis and provide a discussion of its performance. On a per-lesion basis, the classification reached an ROC-curve area of 0.96 (sensitivity/specificity e.g. 97%/85%) measured using an independent test group consisting of 56 patients with 730 candidate lesions. We conclude that the presented system for diagnostic support has the potential of increasing the quality of care regarding this type of examination.

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Automatic Compartment Modelling and Segmentation for Dynamical Renal Scintigraphies

Time-resolved medical data has important applications in a large variety of medical applications. In this paper we study automatic analysis of dynamical renal scintigraphies. The traditional analysis pipeline for dynamical renal scintigraphies is to use manual or semiautomatic methods for segmentation of pixels into physical compartments, extract their corresponding time-activity curves and then compute the parameters that are relevant for medical assessment. In this paper we present a fully automatic system that incorporates spatial smoothing constraints, compartment modelling and positivity constraints to produce an interpretation of the full time-resolved data. The method has been tested on renal dynamical scintigraphies with promising results. It is shown that the method indeed produces more compact representations, while keeping the residual of fit low. The parameters of the time activity curve, such as peak-time and time for half activity from peak, are compared between the previous semiautomatic method and the method presented in this paper. It is also shown how to obtain new and clinically relevant features using our novel system.

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On the regularization path of the support vector domain description

The internet and a growing number of increasingly sophisticated measuring devices make vast amounts of data available in many applications. However, the dimensionality is often high, and the time available for manual labelling scarce. Methods for unsupervised novelty detection are a great step towards meeting these challenges, and the support vector domain description has already shown its worth in this field. The method has recently received more attention, since it has been shown that the regularization path is piece-wise linear, and can be calculated efficiently. The presented work restates the new findings in a manner which permits the calculation with $O(n(n + B))$ complexity in each iteration step instead of $O(n^2 + n^3)$, where $n$ is the number of data points and $n_B$ is the number of boundary points. This is achieved by updating and downdating the system matrix to avoid redundant calculations. We believe this will further promote the use of this method. (C) 2010 Elsevier B.V. All rights reserved.

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Small Differences in Attenuation-Corrected Images between Men and Women in Myocardial Perfusion Scintigraphy: A Novel Normal Stress Database

Aim: To develop and compare different normal stress databases for myocardial perfusion scintigraphy (MPS), with regard to men, women, attenuation-corrected (AC) images and nonattenuation-corrected (NC) images. The hypothesis was that AC images show less differences between men and women compared with NC images. Methods: Normal stress perfusion databases were developed for four different groups. A male and a female database were developed, as well as an AC and a NC database. Patients who underwent 99mTc MPS at Malmö University Hospital in 2008 were considered for inclusion. Patients were included in the study group if they had a normal test result (neither fixed nor reversible perfusion defects, normal ejection fraction (≥ 60% for women, ≥ 55% for men) and normal end diastolic volume (≤ 132 ml for women, ≤ 181 ml for men) based on the final report according to clinical routine. The EXINI heart software package was used for interpretation. Patients with diabetes, coronary artery disease, previous myocardial infarction, previous revascularization, ECG signs of myocardial infarction, presence of pre-excitation, paced rhythms and left bundle branch block were excluded. After this, 131 men and 213 women were included. Bull’s eye plots for these patients were created, and obvious ‘non-normal’ patients were excluded. Finally, 126 men and 206 women were included. The comparison method consisted both of a pixel-by-pixel analysis and a segmental analysis (anterior, septal, inferior, lateral, and apical). The following four comparisons were performed: AC vs. NC for men, AC vs. NC for women, men vs. women for AC and men vs. women for NC. Results: When comparing women within the NC and AC databases, the main finding was that the largest difference in mean counts was found in the inferior segment (lower in the NC group). The same result was found in men. For men and women in the NC group, men showed lower mean counts in the inferior segment. When comparing men and women in the AC group, the largest differences were found in the apical and lateral segments (Table 1). Conclusion: Differences in mean counts when comparing men and women in the AC group were much smaller than when comparing the other groups. The results support the hypothesis that it is possible to use gender-independent AC stress databases.

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Automated decision support for bone scintigraphy

A quantitative analysis of metastatic bone involvement can be an important prognostic indicator of survival or a tool in monitoring treatment response in patients with cancer. The purpose of this study was to develop a completely automated decision support system for whole-body bone scans using image analysis and artificial neural networks. The study population consisted of 795 whole-body bone scans. The decision support system first detects and classifies individual hotspots as being metastatic or not. A second prediction model then classifies the scan regarding metastatic disease on a patient level. The test set sensitivity and specificity was 95% and 64% respectively, corresponding to 95% area under the receiver operating characteristics curve. ©2009 IEEE.

Statistical Regularization of Deformation Fields for Atlas-Based Segmentation of Bone Scintigraphy Images
A generalization of voxel-wise procedures for highdimensional statistical inference using ridge regression

Whole-brain morphometry denotes a group of methods with the aim of relating clinical and cognitive measurements to regions of the brain. Typically, such methods require the statistical analysis of a data set with many variables (voxels and exogenous variables) paired with few observations (subjects). A common approach to this ill-posed problem is to analyze each spatial variable separately, dividing the analysis into manageable subproblems. A disadvantage of this method is that the correlation structure of the spatial variables is not taken into account. This paper investigates the use of ridge regression to address this issue, allowing for a gradual introduction of correlation information into the model. We make the connections between ridge regression and voxel-wise procedures explicit and discuss relations to other statistical methods. Results are given on an in-vivo data set of deformation based morphometry from a study of cognitive decline in an elderly population.
White matter changes contribute to corpus callosum atrophy in the elderly: The LADIS study

BACKGROUND AND PURPOSE: The corpus callosum (CC) is the most important structure involved in the transmission of interhemispheric information. The aim of this study was to investigate the potential correlation between regional age-related white matter changes (ARWMC) and atrophy of CC in elderly subjects.

MATERIALS AND METHODS: In 578 subjects with ARWMC from the Leukoaraiosis And DIStability (LADIS) study, the cross-sectional area of the CC was automatically segmented on the normalized midsagittal MR imaging section and subdivided into 5 regions. The ARWMC volumes were measured quantitatively by using a semiautomated technique and segmented into 6 brain regions.

RESULTS: Significant correlation between the area of the rostrum and splenium regions of the CC and the ARWMC load in most brain regions was identified. This correlation persisted after correction for global atrophy.

CONCLUSION: Increasing loads of ARWMC volume were significantly correlated with atrophy of the CC and its subregions in nondisabled elderly subjects with leukoaraisosis. However, the pattern of correlation between CC subregions and ARWMC was not specifically related to the topographic location of ARWMC. The results suggest that ARWMC may lead to a gradual loss of CC tissue.
Regularized Statistical Analysis of Anatomy

A path algorithm for the support vector domain description and its application to medical imaging

The support vector domain description is a one-class classification method that estimates the distributional support of a data set. A flexible closed boundary function is used to separate trustworthy data on the inside from outliers on the outside. A single regularization parameter determines the shape of the boundary and the proportion of observations that are regarded as outliers. Picking an appropriate amount of regularization is crucial in most applications but is, for computational reasons, commonly limited to a small collection of parameter values. This paper presents an algorithm where the solutions for all possible values of the regularization parameter are computed at roughly the same computational complexity previously required to obtain a single solution. Such a collection of solutions is known as a regularization path. Knowledge of the entire regularization path not only aids model selection, but may also provide new information about a data set. We illustrate this potential of the method in two applications; one where we establish a sensible ordering among a set of corpora callosa outlines, and one where ischemic segments of the myocardium are detected in patients with acute myocardial infarction.
Hierarchical linear modeling (HLM) of longitudinal brain structural and cognitive changes in alcohol-dependent individuals during sobriety

Background: Hierarchical linear modeling (HLM) can reveal complex relationships between longitudinal outcome measures and their covariates under proper consideration of potentially unequal error variances. We demonstrate the
application of FILM to the study of magnetic resonance imaging (MRI)-derived brain volume changes and cognitive changes in abstinent alcohol-dependent individuals as a function of smoking status, smoking severity, and drinking quantities. Methods: Twenty non-smoking recovering alcoholics (nsALC) and 30 age-matched smoking recovering alcoholics (sALC) underwent quantitative MRI and cognitive assessments at 1 week, 1 month, and 7 months of sobriety. Eight non-smoking light drinking controls were studied at baseline and 7 months later. Brain and ventricle volumes at each time point were quantified using MRI masks, while the boundary shift integral method measured volume changes between time points. Using HLM, we modeled volumetric and cognitive outcome measures as a function of cigarette and alcohol use variables. Results: Different hierarchical linear models with unique model structures are presented and discussed. The results show that smaller brain volumes at baseline predict faster brain volume gains, which were also related to greater smoking and drinking severities. Over 7 months of abstinence from alcohol, sALC compared to nsALC showed less improvements in visuospatial learning and memory despite larger brain volume gains and ventricular shrinkage. Conclusions: Different and unique hierarchical linear models allow assessments of the complex relationships among outcome measures of longitudinal data sets. These HLM applications suggest that chronic cigarette smoking modulates the temporal dynamics of brain structural and cognitive changes in alcoholics during prolonged sobriety.

General information
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Scopus rating (2012): SJR 1.758 SNIP 1.549 CiteScore 3.53
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Scopus rating (2010): SJR 1.952 SNIP 1.608
BFI (2009): BFI-level 1
Scopus rating (2009): SJR 2.001 SNIP 1.683
BFI (2008): BFI-level 1
Scopus rating (2008): SJR 1.856 SNIP 1.546
Scopus rating (2007): SJR 1.827 SNIP 1.606
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Scopus rating (2006): SJR 1.836 SNIP 1.715
Scopus rating (2005): SJR 1.778 SNIP 1.642
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Ischemic Segment Detection using the Support Vector Domain Description

Myocardial perfusion Magnetic Resonance (MR) imaging has proven to be a powerful method to assess coronary artery diseases. The current work presents a novel approach to the analysis of registered sequences of myocardial perfusion MR images. A previously reported AAM-based segmentation and registration of the myocardium provided pixel-wise signal intensity curves that were analyzed using the Support Vector Domain Description (SVDD). In contrast to normal SVDD, the entire regularization path was calculated and used to calculate a generalized distance. The results corresponded well to the ischemic segments found by assessment of the three common perfusion parameters; maximum upslope, peak and time-to-peak obtained pixel-wise.

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Robust Pseudo-Hierarchical Support Vector Clustering

Support vector clustering (SVC) has proven an efficient algorithm for clustering of noisy and high-dimensional data sets, with applications within many fields of research. An inherent problem, however, has been setting the parameters of the SVC algorithm. Using the recent emergence of a method for calculating the entire regularization path of the support vector domain description, we propose a fast method for robust pseudo-hierarchical support vector clustering (HSVC). The method is demonstrated to work well on generated data, as well as for detecting ischemic segments from multidimensional myocardial perfusion magnetic resonance imaging data, giving robust results while drastically reducing the need for parameter estimation.
Sparse Decomposition and Modeling of Anatomical Shape Variation

Recent advances in statistics have spawned powerful methods for regression and data decomposition that promote sparsity, a property that facilitates interpretation of the results. Sparse models use a small subset of the available variables and may perform as well or better than their full counterparts if constructed carefully. In most medical applications, models are required to have both good statistical performance and a relevant clinical interpretation to be of value. Morphometry of the corpus callosum is one illustrative example. This paper presents a method for relating spatial features to clinical outcome data. A set of parsimonious variables is extracted using sparse principal component analysis, producing simple yet characteristic features. The relation of these variables with clinical data is then established using a regression model. The result may be visualized as patterns of anatomical variation related to clinical outcome. In the present application, landmark-based shape data of the corpus callosum is analyzed in relation to age, gender, and clinical tests of walking speed and verbal fluency. To put the data-driven sparse principal component method into perspective, we consider two alternative techniques, one where features are derived using a model-based wavelet approach, and one where the original variables are regressed directly on the outcome.
Sparse Statistical Deformation Model for the Analysis of Craniofacial Malformations in the Crouzon Mouse

Crouzon syndrome is characterised by the premature fusion of cranial sutures. Recently the first genetic Crouzon mouse model was generated. In this study, Micro CT skull scannings of wild-type mice and Crouzon mice were investigated. Using nonrigid registration, a wild-type mouse atlas was built. The atlas was registered to all mice providing parameters controlling the deformations for each subject. Our previous PCA-based statistical deformation model on these parameters revealed only one discriminating mode of variation. Aiming at distributing the discriminating variation over more modes we built a different model using Independent Component Analysis (ICA). Here, we focus on a third method, sparse PCA (SPCA), which aims at approximating the properties of a standard PCA while introducing sparse modes of variation. This approach is compared to a standard PCA and ICA. The results show that the SPCA outperforms both ICA and PCA with respect to the Fisher discriminant.
Corpus Callosum Partitioning Schemes and Their Effect on Callosal Morphometry

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On the Alignment of Shapes Represented by Fourier Descriptors

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Sparse Modeling of Landmark and Texture Variability using the Orthomax Criterion

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Sparse PCA, a new method for unsupervised analyses of fMRI data

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Sparse Principal Component Analysis in Medical Shape Modeling

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The entire regularization path for the support vector domain description

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A Database of Registered, Textured Models of the Human Face

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Matlab implementation of LASSO, LARS, the elastic net and SPCA
There are a number of interesting variable selection methods available beside the regular forward selection and stepwise selection methods. Such approaches include LASSO (Least Absolute Shrinkage and Selection Operator), least angle regression (LARS) and elastic net (LARS-EN) regression. There also exists a method for calculating principal components with sparse loadings. This software package contains Matlab implementations of these functions. The standard implementations of these functions are available as add-on packages in S-Plus and R.

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Building a 3-D Appearance Model of the Human Face

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Automated Characterization and Recognition of 2D and 3D Brain Structure in MRI for Diagnostic Support
Department of Informatics and Mathematical Modeling
Number of participants: 5
Phd Student:
Sjöstrand, Karl (Intern)
Main Supervisor:
Larsen, Rasmus (Intern)
Examiner:
Hansen, Lars Kai (Intern)
Hastie, Trevor J. (Ekstern)
Åström, Karl (Ekstern)

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