Quantitative Shape Modeling in Biomedical Imaging

We propose a research consortium in shape modeling. The major emphasis is on statistical modeling of shape with high precision in cases were shape complexity and/or shape variability are larger than what standard methodologies can cope with. So far, the consortium consists of 2 universities and 4 companies, but expansions are foreseen. The work of the consortium is concentrated on industrial applications in the biomedical area, and methodological collaboration between the universities. The outcome in a three year horizon is methods for handling non-linear shape variation, methods for handling shape re-parametrization, methods for dealing with thin shapes, accurate modeling of the knee anatomy, and modeling of multi-figure shapes in pigs. Furthermore, evaluation of methodologies are essential, and quantitative evaluation is a part of the consortium work.

From the outset, the consortium has the two image analysis groups at DTU and ITU as university partners. Among the industrial partners are the three Danish companies Center for Clinical and Basic Research, Nordic Bioscience, and the Danish Meat Research Institute. Finally, the last industrial partner is Novartis from Switzerland.

1 Consortium Motivation

Shape modeling is an essential ingredient in image analysis and computer vision. Especially in the biomedical area, shapes are not man-made, are complex, and exhibit often strange and large variability. Statistical shape models are used both for inference of object shape in images and for classification in e.g. diagnosis.

Kendall introduced statistical shape analysis [Kendall, 1984] as statistics on point sets where overall translation, rotation, and scaling have been factored out. These models have been the backbone in most statistical shape modeling. In image analysis they were introduced as Active Shape Models [Cootes et al., 1995], used for inference of shapes in images. However this classical statistical shape modeling theory suffers from a number of problems when shape complexity, shape variability, and/or accuracy demands become too large:

Tangent Space Approximation The shape space is a non-flat manifold, and for practical purposes it is approximated by its tangent space round the mean shape. This give rise to inaccuracies for larger shape variations [Olsen & Nielsen, 2000].

Non-linear Shape Variation Normally, shape variation is treated by linear statistics on points on the shape surface [Cootes et al., 1995]. For complex shape variations such as bends and bulks, this leads to poor modeling and mis-classifications [Olsen & Nielsen, 2000].

Embedding Space Consistency Point sets on the surface of objects are treated with independent coordinates. In this way it is not possible to enforce constraints from the space in which shapes live such as non-self-intersection and non-overlap. This is especially a problem for thin or multi-figure objects [Joshi et al., 2002].

Shape Re-parametrization Shapes in images are defined through their contour on which clearly distinguishable point may not exist. Hence, the landmarks on which the shape modeling is built may slide along the contour of the object leading to a poor modeling. Intrinsic shape modeling must be made invariant to a re-parametrization exactly as properties of curves and surfaces are in geometry [Malladi et al., 1995].

The above mentioned approximations lead to a theoretical lower bound on the accuracy of shape modeling for any practical application. However, which of the factors that are the critical vary from application to application. At the same time, the means to overcome these limiting factors can not be introduced for free. The various advanced methods cost in computational complexity, numerical stability, and/or the amount of training data needed. Especially the latter is a major concern in 3D biomedical applications where hand annotated data are hard to obtain due to patient concerns and/or the amount of manual labor needed by expensive experts. Hence, development of theory and practice must go hand in hand.

The goal of the consortium is to develop and evaluate the descriptive power of new shape modeling techniques by solving demanding and important real world applications in the biomedical area.

So far, the consortium has identified two challenging applications:

- Modeling of the articular cartilage in human knees by 3D MR imaging for the quantitative assessment of osteo-arthritis progression. This project is described in section 2: *Quantitative Assessment of Disease Progression*. The major challenge here is to obtain sufficient precision and to model very thin shapes.
- Segmentation om pig bodies from 3D CT scans as described in section 3: *CT-scanning and Automated Segmentation of Pig Bodies*. The major challenges here lie in multi-figure modeling and inference in the case of very low signal-to-noise ratio in the images.

The work of the consortium will be organized in these two projects as well as in a third theoretical project with major contributions from the university partners.

The theoretical project will be focused on task-driven theoretical results. The university groups already have preliminary results on some of the proposed shape modeling problems [Hilger et al., 2003, Larsen & Hilger, 2003b, Stegmann & Larsen, 2003, Stegmann et al., 2003b, Darkner et al., 2004, Hilger et al., 2004, Ólafsdóttir et al., 2004, Paulsen et al., 2004, Larsen & Hilger, 2003a, Dam et al., 2004, de Bruijne & Nielsen, 2004, de Bruijne et al., 2004, Nielsen & Johansen, 2004, Pedersen, 2003, de Bruijne, 2003, Lillholm et al., 2003].

In this consortium we wish to drive the further theoretical exploration by real-world tasks where the theoretical results are needed.

2 Quantitative Assessment of Disease Progression

In this project, we wish to take computer aided diagnosis a step further by modeling the evolution of diseases. The simplest way to quantify disease progression is to monitor the patient for a period of time. However, this approach is highly problematic. Firstly, the patient is forced to wait a prolonged period before proper treatment can be determined. Secondly, clinical trials where the effect of treatment is to be established becomes lengthy and therefore extremely costly.

This is even more challenging for slowly progressing diseases where only very little change is evident over the period of, say, a couple of years. Waiting until a change is obvious is simply not feasible. It is therefore critical to either predict evolution or to establish methods that are precise and accurate enough to quantify progression over very short periods of time.

The medical application that we will focus on in this part of the consortium is quantification of articular cartilage in the knee. This is the central structure for modeling the development of Osteo-Arthritis (OA). OA causes a very slow, gradual breakdown of the thin sheet of cartilage that protects the bones in the joint and allows frictionless movement. The cartilage sheets are typically 2-3 mm and become even thinner as OA progresses over the course of decades.

2.1 Motivation

OA is a common affliction that affects the majority of people above the age of 50. It results in softening and thinning of the cartilage as well as reduces the smoothness of the cartilage surface. We focus on the cartilage in the knee joint (figure 1).

Presently, no documented, effective treatment of OA is available. A key factor is the lack of an accurate, reliable method for quantifying the progress of the disease. With an accurate quantification of the state of the cartilage, treatments may be developed and tested quantitatively.

Currently, clinical diagnosis is using x-ray to estimate the thickness of the cartilage sheets [Mazzuca & Brandt, 1999]. This is problematic for several reasons. Mostly because cartilage is invisible in x-ray and due to the information loss in the 2D projection of a 3D structure.

The medical perspective is to allow automatic quantification of the cartilage during OA. This will allow a redefinition of the golden standard for clinical trials that documents the effect of medical treatments and thereby allow development of treatments that actually help OA patients.

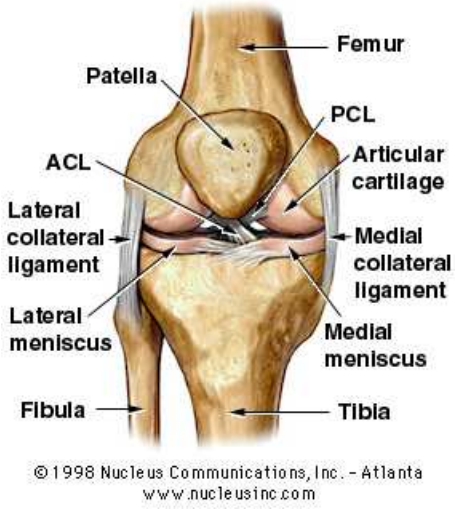

Figure 1: *The articular cartilage in the knee joint ensures smooth, low-friction bending of the joint. During osteo-arthritis the cartilage becomes softer, thinner and less smooth causing pain and reduced range of motion. From* `www.arthroscopy.com`.

2.2 Modeling and Quantification of Cartilage

The very thin sheets complicates shape modeling and the slow progression of OA makes progression quantification challenging. We propose to explore medial shape modeling in order to prevent self-intersection. Furthermore, work on multi-scale medial shape representation suggests the potential for high precision [Joshi et al., 2002].

Within the project period we hope and expect that the results of the research will lead to near-automatic quantification from MR scans of the breakdown both globally and locally (volume and thickness, respectively) and the smoothness and possibly softening of the cartilage.

Volume/Thickness These are relatively simply from a medial model with good correspondence properties.

Smoothness Here we plan to pursue a multi-scale approach. Seen from distance (at high scale) all cartilage sheets will look smooth, but when observed closely (at low scale) the dents and wrinkles become apparent. We plan to attack the problem of quantifying smoothness through analyzing the difference between high and low scale observations (inspired by [Lu et al., 2003]).

Softening Softening cartilage can be observed in MR scans as a cartilage area with an intensity different from the expected. We will use the statistical modeling of the training population to detect the abnormal intensity areas. When quantifying the degree of softening we can possibly generalize the theory behind recent results on quantifying aorta classification using inpainting techniques [Conrad-Hansen et al., 2004].

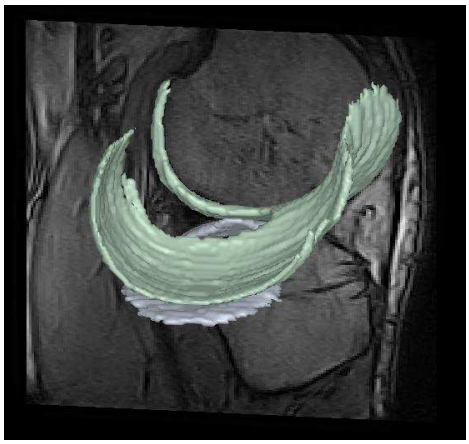

Figure 2: *Naive approach: Models of the Femoral and Tibial articular cartilage made via manual segmentations from an MR scan of a knee. From this segmentation we can approximate the total cartilage volume (14.4 cm^3 for the Femoral and 5.4 cm^3 for the Tibial) and the mean thickness in the most load-bearing part of the cartilage (2.6 mm for Femoral and 2.5 mm for Tibial).*

2.3 MR Scans and Biomarkers

MR technology allows direct visualization of the cartilage in 3D data volumes. Different MR sequences even allow focus on ensuring contrast against the different surrounding tissue types as well as visualizing the structure of the cartilage.

For the project, we will collect MR scans from 100-150 test subjects in the age range from approximately 40 to 75 with no major trauma injuries to the knees — selected to be representative for the group of people where the evolution of age-related OA can be observed. For each knee we will produce manual segmentations.

We also have a secondary source of information, namely serum and urine biomarkers. Cartilage is continuously being both worn down and regenerated. These two competing processes and the rate at which they occur may be modeled through the use of biomarkers that measures the trail of collagen-related materials in the body.

Together, the MR and biomarker based quantifications can provide the current state as well as change of the cartilage. We will investigate how well these independent measures correlate and see whether we can use the combination to predict the future state of the cartilage — thereby allowing shorter time periods in clinical trials.

2.4 Data Fusion and Resolution Enhancement

Apart from the challenges in modeling due to thinness and slow progression already mentioned, another major challenge is the resolution of the MR scans. With the available scanner, the best possible resolution is 0.7 mm isotropic voxels (or 0.35 mm with non-isotropic voxels with a slice thickness of 2-4 mm). This means that the cartilage sheet will only be approximately 3 voxels wide. Therefore, quantifying thickness with accuracy that matches the yearly thickness change in the order of 0.1 mm is no trivial task — this is the image analysis equivalent of the needle in the haystack. Currently, no validated, automatic method exists.

We attack this problem three-fold. Firstly, the MR collection has four sequences for each knee with varying contrast and resolution. We plan to fuse these images in order to achieve optimal contrast and produce information corresponding to approximately 0.35 mm isotropic voxels. Here, we will seek inspiration theory developed for movie restoration (de-interlazing [Keller et al., 2004] and inpainting [Conrad-Hansen et al., 2004]) and for non-rigid registration [Nielsen, 2002]. Secondly, when using a shape model, we can achieve regularization across the sheet and thereby estimate thickness based on a larger support than just the three voxels across. Finally, for clinical trials, statistics across the entire population allows higher precision than what the accuracy of the indiviual scan provides.

In a feasibility study on 17 knees using only the isotropic 0.7 voxel sequence, we have already achieved a segmentation based on voxel classification with sensitivity of 90% and specificity of over 99% [Folkesson et al., 2005].

2.5 Evaluation

All measures will be validated using the knee data collection. Central evaluation measures are interaction time, accuracy, and precision/reproducibility. For accuracy and precision, the aim is to perform as well as the average expert observer.

Unfortunately, obtaining ground truth measurements for cartilage quantification from MR scans is highly problematic. Measures performed on cadavers are not applicable since the MR scans differ greatly from MR scans acquired from live test subjects. Practically, it would therefore require an invasive surgery where cartilage segments are extracted from the knee – an operation that invalidates the test subject. The acquisitioning of ground truth data is therefore both practically infeasible and ethically unacceptable.

As an alternative, the inclusion of biomarkers introduces an indirect means of evaluating the measures obtained from MR data.

3 CT-scanning and Automated Segmentation of Pig Bodies

The Danish slaughter houses process approximately 25 million pig carcasses every year. The Danish export of pig meat products in 2003 was 24,166 Mkr corresponding to 5.5 % of the total Danish export and 49.4 % of the Danish agricultural export.

From a pig carcass several different products or cuts can be made. The slaughter houses have a volume of orders for various amounts of various cuts/products. Since the quality of the cuts will determine the price and hence the profit it is desirable to be able to in beforehand to determine which orders should be met by cuts from a given carcass. For example longer middle cuts will fetch higher prices per weight unit. So to produce an order of middle cuts we should use carcasses with this property.

Today the optimisation of the use of the pig carcass is based on empirically determined relations between simple measurements taken on the carcass and the size/quality of the obtained cuts.

It is the purpose of this consortium project to assess the quality of the individual pig carcass in terms of parameters such as total meat percentage, total fat percentage, and the size of major muscles/musclegroups using computed tomography (CT) scanning of pig carcasses. In addition to optimising the production plan, the payment to the pig farmer may also be based on such measurements. Today the settling with the farmer is based on pig weight.

3.1 Methods and Materials

The Danish Meat Research Institute (DMRI) has recently acquired a CT scanner. In the project 2 data sets will be considered, 1) existing whole body CT scans of 40 live pigs (obtained from the Department of Chemical Engineering, DTU), on line slaughter house measurements using optical probes and subsequently determination of meat, fat and bone content by dissection; 2) scans of half pig carcasses from the DMRI CT scanner.

The project consists of the following sub tasks, 1) **3D segmentation** of CT scans in tissue classes including identification of major muscle groups; 2) **Multivariate calibration of the meat percentage** determined from scanning against simple anatomical measurements; 3) Construction of **a virtual slaughter house** - a tool for simulation of cutting of a representative set of pig carcasses and evaluation of cut quality.

The main technological challenge is the segmentation of the different muscle structures of the pig carcasses. In an operational setting, scan resolution and tissue type contrast will be balanced against time constraints. To compensate for loss in image quality, prior information of the geometry of the carcass and carcass parts must be incorporated in the image analysis. The biological variation in this geometry and the interrelations between parts calls for coupled deformable template models.

3.2 Statistical Shape Modeling

The main research theme addressed here is deformable template modelling of coupled surfaces in 3D images. Ulf Grenanders seminal work [Grenander et al., 1991] on 2D deformable template modelling was hugely popularised in the end of the nineteen-nineties by the work of Cootes and Taylor [Cootes et al., 1995, Cootes et al., 2001, Stegmann et al., 2003a], where they formulated linear models for shape variability estimated from annotated training data. Ramsay and Silverman [Ramsay & Silverman, 1997] presented seminal work of functional representations of curves.

First, in many situations linear models are likely to fail in accurately modelling natural phenomena. For instance Kendall's shape space for triangles in a plane – the simplest shape imaginable – is a sphere in $\mathbb{R}^3$. Linear approximations to the triangle shape space are only valid for low variability in triangle shape. To handle non-linear, large scale variations as occurs in nature new models are required. Developments in the statistics and machine learning fields in the new millenium have led to methods for parameterizing low dimensional manifolds in high dimensional spaces. These developments form the basis of formulating non-linear shape space models. Such as principal curves proposed by Hastie and Stuetzle [Hastie & Stuetzle, 1989]; Tenenbaum et. al [Tenenbaum et al., 2000]'s ISOMAP procedure; Roweis et al. [Roweis & Saul, 2000]'s Local Linear Embedding (LLE); Belkin and Niyogi [Belkin & Niyogi, 2002]'s Laplacian Eigenmaps; and Donoho and Grimes [Donoho & Grimes, 2003]'s Hessian Eigenmaps.

Second, natural phenomena can often be explained by a set of few underlying parameters. This property has been used in many years in statistics, e.g. in factor rotation [Harman, 1967] for easier interpretation. In recent years sparsity has been used as design criterion to overcome the problem of the dimensionality of measurements vastly exceeding the number of observations available. Mathematically sparsity is envoked by putting a L_0 penalty of the parameters. However, this is computationally intractable. Fortunately, in many situation the L_1 penalty - for which computationally feasible solution are available - can work as a proxy for the L_0 penalty as is used for instance in LASSO and LARS regression [Tibshirani, 1996, Efron et al., 2003].

In the project the theorectical contribution will be concentrated in 3 tasks: 1) functional representation of shape models; 2) non linear manifold learning to estimate shape models; 3) shape models based on parameter sparsity.

4 Theoretical Project

As mentioned in the consortium motivation, the theoretical exploration is application-driven and we have therefore included the theoretical challenges and proposed paths in the two previous projects.

Overall, the two image analysis groups have some competence overlaps but a major difference is that the ITU group excell in geometry whereas the DTU group excell in statistics. The combination should be excellent for exploring the challenges in statistics of shape that are outlined in the consortium motivation.

5 Consortium Partners

The six consortium partners and their main roles are as follows:

ITU Image Analysis group

The Image Analysis group is situated in the Department of Innovation at the IT University of Copenhagen and spans 3 faculty members, 5 post docs, and 7 Ph.D. students. Like the IT University, the Image Analysis group is young but with an international reputation that recently resulted in securing the role as host for MICCAI 2006 (the 9th international conference on Medical Image Computing and Computer-Assisted Intervention) in collaboration with the DTU group below.

The research in the group has a main focus on scale-space theory, shape modeling, segmentation, and recently pattern recognition — with applications in medical image analysis.

The Image Analysis group will perform the research within the methods for automatically quantifying the state of the cartilage from MR scans and the post.doc. and the Ph.D. student of the project will be located at ITU.

DTU Image Analysis and Computer Graphics group

The image analysis and computer graphics group at the Institute for Mathematical Modeling at the Danish Technical University encompasses 7 faculty members, 3 senior researchers, and 10 Ph.D. students. Within the field of image analysis the two main research themes are biological shape and texture modelling and vision system optimisation. In the past decade a series of companies have spun of the activities in the group, the most prominent of which are Videometer, 3Shape, Visiopharm, Image Metrology, Trishape. The proposed project has obvious synergies with 3 other current medical image analysis projects concerning volume segmentation of structures such as brains and human hearts. The project will also benefit from activities concerned with vision system optimisation. Finally, the virtual slaughter house sub task will utilize local expertise in computer graphics for visualisation.

The group will be responsible for the research in the *CT-scanning and Automated Segmentation of Pig Bodies* project and the project Ph.D. student will be located at IMM.

Center for Clinical and Basic Research

CCBR (`www.ccbr.com`) is a private research institute with a current focus on osteo-porosis. CCBR also performs contract research for international pharmaceutical where new treatments are tested in the five CCBR centers located in Ballerup, Vejle, Aalborg, Tallinn, and Rio de Janeiro.

CCBR has performed world-leading research within osteo-porosis for the last 12 years. Their results on how to quantify the current state of the bone from x-ray imaging has lead to definition of protocols for clinical studies [Hansen et al., 1990, Svendsen et al., 1992]. In 2002, CCBR was 5th in a survey on the most cited Danish research institutions overall [MM2, 2002].

CCBR will provide the MR scanner, the radiographer, and the radiologist resources for producing the annotated collection of MR scans for more than 100 test subjects. In addition x-ray images will be acquired in order to be able to compare with the current golden standard.

Nordic Bioscience Diagnostics A/S

Nordic Bioscience (`www.nordicbioscience.com`) is among the world leaders within the field of diagnostics of bone and cartilage diseases such as osteo-porosis, bone metastasis, and arthritis [Christgau et al., 1998, Rosenquist et al., 1998, Fledelius et al., 1997]. These biomarkers quantify the growth and break-down of bone tissue. Recently Nordic Bioscience has also started performing research on biomarkers for osteo-arthritis [Mouritzen et al., 2003, Garnero et al., 2003].

In the cartilage project, the medical doctors and researchers from Nordic Bioscience will plan the acquisitioning of urine and blood samples for the data collection. Furthermore, Nordic Bioscience will perform research in defining biomarkers that measure the generation and break-down of articular cartilage and correlation of these with MR measurements.

Danish Meat Research Institute

DMRI (`www.dmri.com`) is the research center for the cooperation of Danish slaugther houses.

They will provide CT data of pig carcases for the data collection. Furthermore, they will as provide expertise on the anatomy and physiology of pigs and of the quality and value of different cuts.

Novartis Pharma Ltd

Switzerland-based Novartis (`www.novartis.com`) is among the five largest pharmaceutical companies in the world. They have developed and performed clinical trials for numerous treatment methods of most common diseases.

Novartis has immense experience in designing quantification methods and protocols for clinical trials. It is the hope and expectation of Novartis to be able to use cartilage quantification method resulting from early results from this consortium in phase II trials of osteo-arthritis treatment already in 2005.

5.1 Consortium Organization

The consortium will be managed through half-yearly meetings by a steering committee with a representative from each partner: Professor Mads Nielsen, Ph.D., ITU, Chairman; Associate Professor Rasmus Larsen, Ph.D., DTU; Dr. Claus Christiansen, MD, Center for Clinical and Basic Research; Per Qvist, Ph.D., Nordic Bioscience Diagnostics; Lars Bager Christensen, Ph.D., Danish Meat Research Institute; Professor Moïse Azria, MD, Novartis.

Each industrial project will be lead by the relevant subgroup from the steering comittee through quarterly meetings. The cartilage project steering group will also contain Associate Professor Ole Fogh Olsen and the pig project steering group will include Associate Professor Bjarne Ersbøll. Both project steering groups will supplement with additional members if appropriate.

The theoretical project will organize bi-monthly meetings with all members of the project group from both university groups.

6 Consortium Milestones & Success Criteria

A full project time table with planned tasks and milestones is enclosed. The milestones with corresponding success criteria are as follows (where IDs refer to tasks on the time table). Below, "publication" means that the milestones should result in a publication in an internationally leading conference or journal. It is our clear expectation that the research carried out in the consortium will result in at least one patent on cartilage quantification. In addition to these milestones, the consortium will produce half-yearly progress reports.

ID	Milestone	Success Criterium
3	Acquire scans	MR collection acquired
5	Annotate Femoral cartilage	MR collection annotated
12	Thickness ready for phase II trial	Quantification of cartilage thickness ready Patent or publication
13	Cross validate against biomarkers	MR and biomarker quantification correlate Patent or publication
15	Multi-scale smoothness quantif.	Patent or publication
19	Intra-patient registration of scans	Technical report or publication
20	Super-resolution (fusion)	MR scans can be fused Technical report or publication
23	Validate Tibial segmentation	Method validated on main collection Publication
38	Segmentation of selected structures	Carcass subset can be segmented Technical report or publication
40	Full pig segmentation	Full carcass can be segmented Technical report or publication
44	Virtual slaugther house	Virtual environment slaughter house ready Publication or interactive demonstration
50	Full carcass collection	Full pig carcass data set ready
16,45	Dissertation	Ph.D. students hand in dissertations

7 Beyond the Consortium Partners

Both the two Ph.D. students will participate in the Copenhagen Image and Signal Processing Graduate School (CISP) led by Professor Lars Kai Hansen, IMM, DTU. CISP is a joint effort between the two participating university groups and the Department of Computer Science, University of Copenhagen. It encompasses the majority of image analysis graduate students in the Copenhagen area. The two university groups also collaborate on teaching at graduate and master level and coordinate and exchange their courses.The latest collaboration was a joint Ph.D. course entitled *Shape Modeling in Medical Imaging*.

In general, there are active ties between the two groups. In 2002 they organized *European Conference on Computer Vision* and in 2006 they will organize *MICCAI*, both in Copenhagen. They also are in an EU Network of Excellence together.

Both university groups are members of the Øresund IT Academy and thereby have direct access to 40 computer vision oriented companies in the Øresund region. It is our expectation that the consortium will be expanded with more industrial partners.

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