Medical Imaging Applications: Three Case Studies

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Abstract. In this paper three case studies are briefly presented and discussed regarding medical imaging applications. We report in some detail the activity of our laboratory related to: microarray image analysis, segmentation of 3D computed tomography imagery, breast shape analysis. Some of these results are being validated by people working in the related fields of expertise, such as the surgeons of the Istituto Nazionale dei Tumori in Milan, Italy.

1 Introduction

In the last decade, the interaction between medicine and computer science has brought notable improvements to the execution of common clinical and surgical operations. Computer-assisted medical procedures allow to monitor pathologies and, above all, to evaluate the outcome of medical cares. In this scenery, digital imaging empowers physicians and scientists with a new insight on the internal and external structures of human body. Moreover, new classes of biotechnologies can help biologists to extrapolate new knowledge from experiments. Ad-hoc software can be of great help to biologist, surgeons, and physicians for scientific observation and manipulation of patients' data.

The main goal of Medical Imaging is finding solutions to problems related to the extrapolation, elaboration, visualization and retrieval of new and non-trivial knowledge from medical imagery. Effective solutions often require multidisciplinary efforts, involving computer scientists, physicians and industrial partners, to design, assess, and experiment with new techniques.

In this paper we will focus on three Medical Imaging applications in which our laboratory has been recently involved:

- Microarray Image Analysis [1][2];
- Three Dimensional segmentation of Computer Tomography data [3];
- Breast Shape Analysis [4][5][6][7].

2 Microarray Image Analysis

DNA microarray [8] is a fundamental biotechnology for gene expression profiling and biomedical studies. In a typical microarray experiment, two 16-bit images are obtained by means of microarray scanners and encoded as red and green channels of a colour image. The processing pipeline for these input data can be summarized in the following steps: gridding, segmentation, intensity extraction, and quality measurement. Gridding and segmentation are crucial steps and have a potentially large impact on subsequent analysis. Although many academic and commercial microarray image analysis techniques have been developed, human interaction is still usually required to obtain a high level of accuracy. In [1] [2] novel algorithms to solve microarray image analysis problem have been proposed. The overall image analysis pipeline is composed by three algorithms): Microarray Image Rotation Algorithm (MIRA), Microarray Image Segmentation Pipeline (MISP), Statistical GRIdding Pipeline (SGRIP).

2.1 Microarray Image Rotation Algorithm

MIRA is an algorithm based on histogram analysis to automatically detect and correct microarray images affected by a global rotation. A simple bilinear interpolation is used to reconstruct the signal after rotation. We safely assume that both input channels have the same rotation angle. The technique is designed for orthogonal grids, the most common type for microarrays.

2.2 Microarray Image Segmentation Pipeline

The microarray images obtained by MIRA are processed by Microarray Image Segmentation Pipeline (MISP) that perform all the other steps involved in microarray image analysis: gridding, segmentation and data/quality measures extraction. MISP is fully automatic. The pipeline can be ideally subdivided into two sequential modules:

- *Spot-Background separation*;
- *Foreground and Local Background identification.*

The *Spot-Background separation* module extracts the spot shape by segmenting each channel, using Statistical Region Merging (SRM [9]). The local mean intensity is used rather than a single pixel value. The shape is further refined at the intensity edges by taking into account the deviation of edge pixels from the local mean. Two binary masks, *GBin* and *RBin*, are generated.

The second module, *Foreground and Local Background identification*, identifies *GBin* and *RBin* with *Red Mask Foreground* (*RMF*) and *Green Mask Foreground* (*GMF*). It also builds as the logical OR of these two maps a *Spot Guide Mask (SGM)*.

Moreover the set of pixels belonging to *SGM* but not to *RMF* are said to be the internal background relatively to the red channel of the spot. Similarly the set of pixels belonging to *SGM* but not to *RMF* are said to be the internal background relatively to the green channel.

Let *Grid Guide Mask (GGM)* be the minimum square containing *SGM.* The difference between *GGM* and *SGM* forms the *RGBackMask*. The local background relative to the red channel is obtained augmenting *RGBackMask* with the pixels belonging to the internal background relatively to the red channel. The local background relative to the green channel is obtained similarly.

A variety of quality measures and useful data may be obtained gathering information inside the different masks created insofar. *SGM* is used to derive quality measures for each spot (e.g. spot area measure). *GGM* is used to assign coordinates to each spot. Other masks are used to characterize pixel belonging to *foreground/background/local background*, to calculate intensity and to extrapolate quality measures for each spot.

2.3 Statistical GRIdding Pipeline

The SGRIP module [1] detects GGM by analysing the histograms of the rows and of the columns of a binary mask of input data to obtain statistical information about the signal spatial distribution. Starting from an initial guess, the final grid mask is refined according to local considerations about typical spot acquisition problems (e.g. spot overlap, comet-tails, etc.). SGRIP is fully unsupervised and includes two steps:

- *Grid Finding – Correction;*
- *GGM Creation – Refinement.*

Grid Finding approximates the spot centres. It works on *SGM* assuming a local homogeneous background. The final output is obtained after a *Correction* step to recover spot centres that have been missed insofar. The spot centre prototypes are stored in a $m \times n$ matrix P where m and n are respectively the inferred number of rows of columns in the array.

GGM Creation uses P and *SGM* to create a first approximation: to each simple connected component in *SGM*, is assigned the minimum rectangular region containing the component. The final step (*GGM Refinement*) separates spots erroneously merged with others. We assume that SGRIP is performed on previously correctly rotated images.

2.4 Testing of Microarray Image Analysis Algorithms

To test our algorithms we have developed a framework called Microarray Image Analysis Framework (MIAF). The image dataset used for the experiments are obtained as a subarray of Whole Yeast Genome microarrays [10]. Microarray data addressed to a specific problem (segmentation, gridding, rotation) have been selected for testing.

We believe that the main strength of our approach is revealed when it is compared with techniques based on circle segmentation (fixed and adaptive). Comparisons have been carried out against the output obtained by Scanalyze [11] with the best possible choice of user-selected parameters. In particular, all of the Scanalyze parameters have been tuned to obtain optimal quality measures. MIAF is able to perform quality measurement also on imported Scanalyze grid: this makes comparison easier.

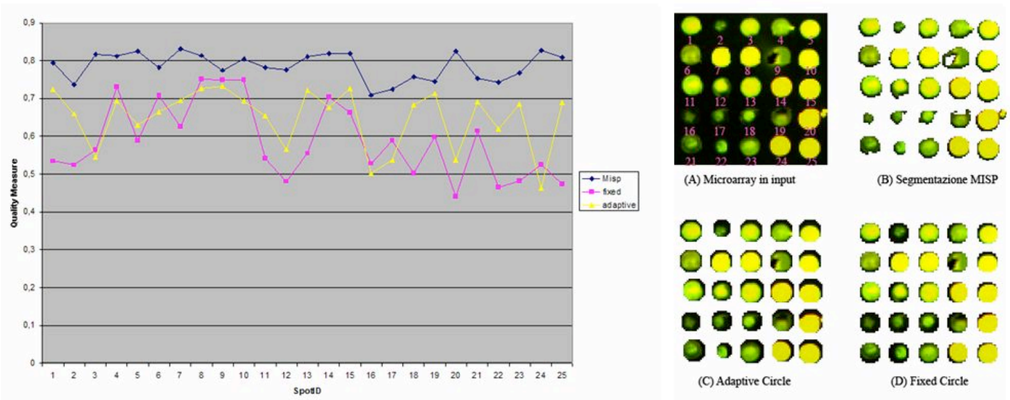


Figure 1: Results obtained using different method of segmentation on microarray test. Plot reports the quality index ($0 \leq q_{com} \leq 1$) used in [2]. Its value is proportional to the perceived quality segmentation of each spot taking into account several aspects (size, saturation, noise, etc.).

The experimental results confirm that MISP, starting from the robust gridding provided by SGRIP, performs data extraction and quality measures evaluation reliably (Figure 1). MIRA, MISP and SGRIP together allow to automatically detect microarray grid, to correct the rotation angle, to assign coordinates to each spot, to discriminate foreground, background and local background, to calculate intensity and extrapolate quality measures.

3 Three Dimensional Segmentation of Computed Tomography data

The knee joint can be severely damaged due to a variety of causes, such as arthritis or a knee injury. This can cause pain and inability to walk. In some cases, replacing parts of the joint is thus appropriate. A total knee replacement is a surgical procedure whereby the damaged knee joint is replaced with artificial shells (prostheses). An accurate clinical evaluation must be carried out before applying knee prostheses to ensure optimal outcome from surgical operations.

Most patients suffer from long-term problems, such as loosening. This occurs because either the cement crumbles or the bone melts away from the cement. In some cases, loosening can be painful and require re-operation. The results of a second operation are not as good as the first, and the risks of complication are higher.

The accurate choice of materials can improve prosthesis durability. Anyway, loosening can be mainly avoided (or at least postponed) by tailoring the implanted prosthesis to the patient's anatomical peculiarities. By acquiring a CT scan of the knee area, one can infer useful information, such as posture, that can be exploited by mechanical simulators (e.g., finite elements analysis, FEM) to estimate the forces that will be acting on the prosthesis being implanted [12].
This information can be exploited to estimate the lifespan of the implanted material and tailor the prosthesis to the patient's anatomy.

Our laboratory is involved in a project [3] that is a joint work of a multidisciplinary team including a prosthesis production company, LIMA spa [13]. Our main activity is the 3D segmentation of CT data. The aim is to devise a segmentation algorithm empowered with self-evaluation capabilities and with bounded error.

3.1 Requisites of the 3D Segmentation Algorithm

Most segmentation algorithms work only on 2D data, where every pixel is characterised by a vector of values in a specific colour domain. Segmentation can be thought as a partition of a 3D space in which the third dimension is related to colour. Conversely, CT data have three spatial dimensions in which every voxel is characterised by a 12-bit scalar in the HU domain.

Working on a per-slice basis, important features spanning over more slices might be undetected. Extending 2D segmentation algorithms to the 3D case poses some problems, mainly: efficiency in terms of memory and time resources, and definition of the shape of the neighbourhood of a voxel. In particular, defining the neighbourhood of a voxel is not straightforward since voxels are elongated in the scanning direction. Most image processing algorithms assume that pixels/voxels possess a regular shape, which is not our case. Moreover, CT data of bones possess interesting statistical properties that few algorithms exploit.

Finally, user interaction should be minimised and, most of all, must be intuitive for people who do not have a Computer Science background. To summarise, the main features of our segmentation algorithm should be:

1. Bounding/measuring the segmentation error;
2. Exploit the intrinsic structure of the 3D data by working on the whole data set, rather than on a per-slice basis;
3. Time efficiency and low memory consumption;
4. Employing a statistical model to model knee CT data;
5. Minimum and intuitive user interaction (particularly for parameter setting).

3.2 From 2D to 3D Segmentation of CT imagery

In [9] the algorithm named statistical region merging (SRM) is built from sound statistical considerations. Theorems are provided to prove that (1) only overmerging is possible, and (2) the error with respect to the best segmentation is bounded. These features make this algorithm attractive to satisfy our first requirement.

SRM is based on a region growing technique empowered with a sound statistical test for region merging. The segmentation granularity is tuned using a single intuitive parameter, Q. This simplifies the interaction with the user, fulfilling our fifth requirement. Finally, SRM is fast since it is linear with respect to the number of pixels due to its merging strategy. Its low time complexity and memory consumption, if carefully extended to the 3D case, would satisfy our third requirement.

As a straightforward extension of the SRM algorithm to cope with 3D data, one could use a local neighbourhood including pixels belonging to neighbouring slices. Anyway, CT scans are usually made up of a large number of slices. Therefore, memory occupancy is a concern.

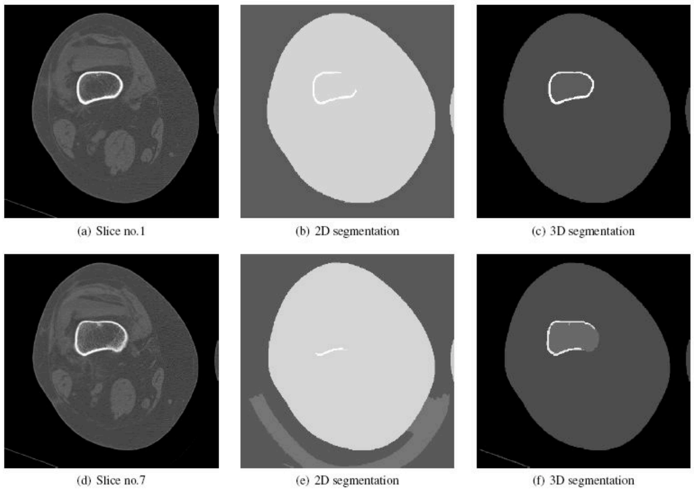


Figure 2: Segmentation results using the SRM algorithm and its straightforward extension to 3D data.

We have compared the segmentation results of the original (2D) SRM and of a modified version which merges the regions of three neighbouring slices (Figure 2). This simple extension improves the results in most cases. We expect that working on the whole dataset the results would be more robust. Unfortunately, loading the whole dataset into the main memory is unfeasible in most real cases. In order to satisfy our second requirement, we are studying a method to merge regions spanning over multiple slices, while avoiding to load the whole dataset in the main memory.

Finally, to satisfy our fourth requirement, we are trying to use statistic knowledge about the knee CT data to guide segmentation.

4 Breast Shape Analysis

Breast shape assessment in aesthetic and reconstructive surgery is a crucial step to evaluate the final outcome. Up today, visual assessment is the common practice among surgeons, since no universally accepted breast shape analysis techniques are currently available. Devising reliable methodologies to objectively analyse natural and reconstructed breast shape is an important research issue.

Several reproducible measurement methodologies have been proposed in the literature but none of them reached clinical practice. Some authors propose to analyse breast shape either by using anatomic reference points and manual linear measurements, or by measuring the volume by means of water displacement, MRI, X-rays, or thermoplastic moulding.

3D scanning technologies can be exploited to acquire useful data for accurate and reproducible analysis of breast surface. We devised a non-ambiguous segmentation of the thoraco-mammary surface, starting from the informal specifications suggested by the surgeons of INT in Milan. We also indicate a set of geometric measurements and computer graphics techniques for 3D visualisation allowing an objective evaluation of the outcome of cosmetic and reconstructive surgery.

4.1 Surgeons' Desiderata

The surgeon possesses the ability, from his experience, to recognise several anatomical points and structures of interest, in the analysis of patients. However, the tools used to gather measurements (e.g., area of breast surface, length of the path over the breast surface, and so on) are inaccurate or do not exists at all. Moreover, manual measurements heavily depend on experimental settings, such as posture of the subject and the like.

Recently, computer scientist from Catania University and surgeons from INT joined in a multidisciplinary effort to find a viable solution and explore the new technological perspective for the analysis of breast shape [4][5][6][7]. Analysis and definition of the breast shape based on clinical semantics can help plastic surgeons to objectively evaluate the outcome of reconstructive plastic operations.

The team singled out, as a starting point for this research, the following objectives that are especially relevant for common clinical practice:

1. Characterisation and segmentation of breast subunits;
2. Measure of distances between landmark points over the female thorax: these measures may be obtained as line distances in the 3D space or may be obtained as path length over the body surface;
3. Measure of areas, volumes, percentage of area subunit over the total area;
4. Angles between landmark planes.

The relevance of these measures is evident considering that the area ratios between lower and upper pole of the breast and between other clinically-meaningful surfaces are widely used parameters in reconstructive surgery, as well as distances between anatomical landmark. An important issue raised by the surgeons has been to provide a sound and objective meaning for vague but universally used terms, such as *sweet slope*, *inferior pole* and similar. To this aim visualisation in false colours of curvature and convexity is very effective. The analysis of curvature and convexity can help surgeons to achieve symmetry and the desired breast shape i.e., the main goals of breast reconstructive surgery.

4.2 Methodology of Breast Shape Study

Our analysis has been carried out on a set of breast models related to clinical cases collected in Plastic and Reconstructive Surgery Department at Istituto Nazionale Tumori in Milan, according to common cosmetic and reconstructive criteria (e.g., age, menopausal status, ptosis classification).

The recruited volunteers were seated on a chair with their back at 45 degrees, as to simulate theatre evaluation position. Three scans of the same volunteer were acquired: facing the camera and rotating the chair at 45 degrees to the left and to the right. Moreover, three more acquisitions were taken in the same positioning, but suspending the breast with a large adhesive bandage, in order to evaluate the infra-mammary fold shape. We choose not to merge the different scans because of uncontrollable physiological movements (e.g., breathing and imperceptible body torsions) during the scanning process. Although extremely precise, laser scanning requires a time lag that is not compatible with the patient breathing. Therefore, the analysis has been performed on partial views. Unsampled areas has been filled using volumetric diffusion.

In order to unambiguously define breast sub-units, we exploited the following anatomical landmarks, suggested by surgeons because of their easy reproducibility:

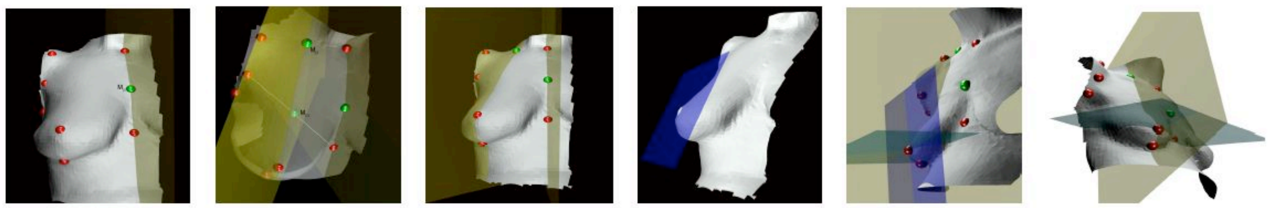
1. Sternal Notch or Jugulum (p_j)
2. Xiphoid (p_x)

3. Nipple (p_c)
4. Pectoralis insertion in the arm (p_{aa})
5. Acromial extremity of clavicle (p_s)
6. Mid-axillary point (p_{pa})
7. Lowest breast point with respect to the vertical body axis (p_d)

Accurate positioning of these landmarks is crucial for the quality of the outcome and it is difficult to automatise because the landmarks have clinical meaning. Hence, these points are interactively placed by surgeons on the model using the BSA 0.1 tool developed by our Lab.

In clinical practice, breast sub-units are manually traced and the outcome strongly depends on the experience and ability of surgeons. We aimed at defining a tracing scheme that is less dependent on the ability of the user. The proposed scheme employs simple geometric primitives such as planes, lines, and geodesics. Geometrically-defined breast partitioning guarantees a more objective and reproducible subdivision procedure and opens the way to objective quantitative measuring methods. The proposed subdivision algorithm defines four elements (Figure 3):

1. Thoraco-mammary bilateral symmetry plane (Л$_{s}$);
2. Breast meridian plane (Л$_{m,l}$ and Л$_{m,r}$ for left and right breast, respectively);
3. Breast equatorial plane (Л$_{e,l}$ and Л$_{e,r}$ for left and right breast, respectively);
4. Breast box hull.



(a) (b) (c) (d) (e) (f)

Figure 3: Planes used for breast segmentation. (a) Thoraco-mammary bilateral symmetry plane. (b) Breast meridian plane (c) Breast meridian curve obtained by intersecting the 3D model and the meridian plane. (d)Nipple-areola plane. (e) Construction of the equatorial plane. (f) Breast equatorial curve.

In order to analyse breast surface properties in compliance to surgeon specifications, an enlarged thoraco-mammary surface from the breast model has been selected as a region of interest to produce a breast box hull.

This box is made up of six surfaces detected in sequence as follows:

- Breast surface (Figure 4(a))
- Back plane, Л$_{b}$, orthogonal to the bilateral symmetry plane containing p_s (acromial extremity of clavicle) and p_{aa} (pectoralis insertion in the arm) (Figure 4(b))
- Thoraco-mammary bilateral symmetry plane Л$_{s}$ (Figure 4(a))
- Lateral plane, Л$_{l,i}$, orthogonal to the back plane and containing p_{aa} (axillary apex) and p_{pa} (pectoralis insertion) (Figure 4(c))
- Lower plane, Л$_{L}$, orthogonal to the bilateral symmetry plane passing through p_d (Figure 4(d))
- Upper plane, Л$_{U}$, orthogonal to the bilateral symmetry plane, to back plane and including p_g (sternal notch) and p_s (acromial border of the clavicle) (Figure 4(e))

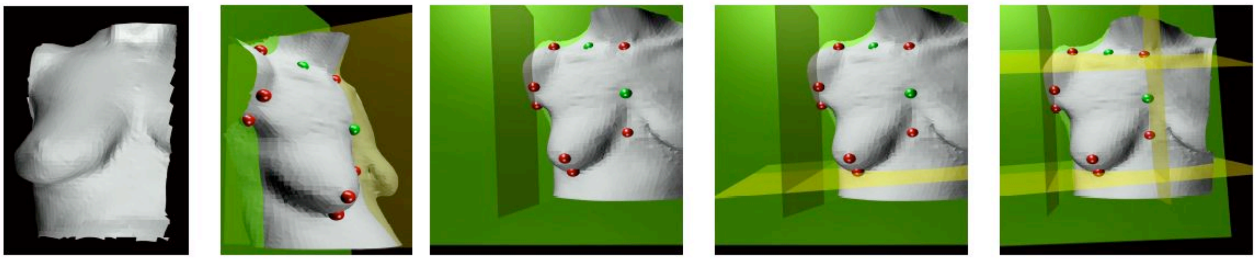


Figure 4: Surfaces involved in the Breast Box Hull. (a) Front surface. (b) Back plane, pb. (c) Lateral plane, $\text{Л}_{l,r}$. (d) Lower plane, Л_L. (e) Upper plane, Л_U.

Given this partition a number of relevant measurements can be computed:

a) Line distances between all the landmark pairs and distances between p_c and the bilateral symmetry plane, and between the nipple, p_c, and the back plane, p_b.

b) Area measurements of some relevant surfaces: the front box hull, the upper pole, the lower pole, and the sub-units defined by the intersection of the meridian plane, $\text{Л}_{m,i}$, and the equator plane, $\text{Л}_{e,i}$. Knowing the relationship between these areas can help the surgeons to understand breast shape features.

c) Angles. Let us define $O_{i,x,y,z}$ the (generally nonorthogonal) coordinate system induced by the intersection of the planes p_s, $p_{m,i}$, $p_{e,i}$, where i stands for l (left) or r (right). We compute the angle between x_i and y_i axes and the angle between x_i and z_i axes, where x_i is the axis including the nipple, p_c. The former gives a measure of the symmetry of the nipples with respect to the bilateral symmetry plane. The latter quantifies the breast ptosis.

d) Curvature and convexity. Visualising the mean curvature and convexity of the breast surface is useful to capture the concept of widely used clinical terms, such as “sweet slope” and “well defined inferior pole”. Since no unambiguous definition of breast shape features is available, surgeons found false-colour visualisation more useful than any attempt to make accurate measurements of data.

Conclusions and Future Works

We have reported some Medical Imaging applications developed in our laboratory. Some challenging issues are left open. In almost all cases we are planning further improvements and novel methodology:

- For microarray image analysis we will include the possibility to use ad-hoc techniques for common acquisition problems (e.g noise reduction).
- For 3D segmentation we are trying to use statistic knowledge to guide segmentation.
- For Breast Shape Analysis we want try to use parametric fitting of a standard breast model from few 3D anatomical landmarks and/or a low resolution scan of the body.

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