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Image analysis in epidemiological applications

Abstract: A rising number of epidemiological studies apply imaging technologies. Images are not features themselves but provide raw data from which features are extracted. Different to other applications of analysis of medical images the data is analyzed statistically across the cohort. It results in unique requirements regarding the development of methods to efficiently integrate varying domain knowledge into the process without compromising comparability of results across subjects or time. Examples from two different strategies are presented and discussed.

Keywords: Epidemiology, visual analytics, medical image processing.

ACM CCS: Computing methodologies → Artificial intelligence → Computer vision → Computer vision problems → Image Segmentation

1 Introduction

Epidemiology is the science of distribution, patterns, causes and effects of health and disease in predefined populations. Incidence, i. e. the probability to develop a disease in a specified period of time, and prevalence, i. e. the percentage of the population affected by a disease, are investigated in epidemiological studies. Of special interest are group-specific variations, e. g., in socio-economic or age-specific subgroups. Images, such as microscopy or sonography, have been part of several studies for quite some time. They are often used to complement data that is acquired by other means. Recently, several studies employed extensive magnetic resonance imaging (MRI). It may provide insight into a much broader range of questions regarding anatomy and function of human organs.

Epidemiological studies may be roughly categorized into *hypothesis-driven* and *open* studies. In the former case, which is currently the predominant form, the purpose of the study and hence the potential hypothesis for gathering the data is known. Open studies only recently entered the scene. Their purpose may be rather unspecific such as studying the effects of demographic change. It is well possible and may even be intended that some research questions may be posed long after the data have been acquired. Image analysis methodology to extract features from image data should be adaptable to changing requirements arising during the potentially very long period of time in which the epidemiological data is exploited.

Image analysis in epidemiology addresses similar questions to other fields of medical imaging, i. e. reduction of artefacts, quantitation of geometry (volume, distances, etc.) and classification. However, given the unspecific nature especially of open studies, some important differences exist which we will explore in this paper. We will focus on open studies as their fairly unique requirements result in different or differently applied image analysis methodology.

Efficient analysis resulting in useful features is essential for subsequent visual analytics methods. Shape variance visualizations of segmented structures augmented with information visualization techniques for non-image data can be used to identify subject groups with unusual organ shapes and pathologies [1]. User guided assessment of local deformation changes between subject classes can be used to determine major distinctions between them [2]. For example, regions of interests specified by a domain expert can be mapped to associated anatomic covariation using tensor visualization. Extracting structure specific metrics using data mappers allow for concurrent visual analysis with non-image features [3]. However, visual analytics methods may not only be restricted to understand extracted features. If the role of the feature extraction process as part of the analysis is sufficiently understood, vi-

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sual analysis may even support development of the methods themselves.

2 Open epidemiological studies

Data acquisition for several open epidemiological studies has started or is planned to be started soon. Analysis of data from such an open study may very well be driven by a hypothesis but data is gathered with broad application fields in mind that may be subject to future scientific analysis. Usually, the cohort that took part in such study is intended to be invited again several years later providing data for longitudinal studies that investigate developments in time. Several studies, e. g., the Rotterdam study [4], the Norwegian Aging study [5] or the Study of Health in Pomerania (SHIP, [6]), qualify for this label (see [7] for details on these studies). Imaging in all these studies includes MRI and sonography. Sometimes, microscopic images generated from tissue samples and optical coherence tomography (OCT) for eye examinations are available as well. Since research questions are rather unspecific, imaging is unspecific as well. For instance, the decision for acquiring a certain kind of MRI of some body region is driven by the assumption that this kind of image may contain important information for the goal of the study in general but it is not optimized w. r. t. a specific hypothesis.

Data from an open epidemiological study will be analyzed by many different researchers in many projects. The SHIP data, for instance, has been used in more than 1500 projects since its first phase starting in 1997. Each of the projects had been motivated by a single goal (e. g., understanding a certain disease pattern) and the users were not necessarily aware of problems that may arise from re-use of data or methods. However, problems of comparability over time due to change of equipment or inter-observer variability may arise [8, 9]. The problem exists mainly for the analysis of image data as the semantics of the data elements (the pixels or voxels) is far from the information that is required for an epidemiological study. Methods to transform and reduce image data to epidemiologically meaningful entities (e. g. the volume or shape of depicted organs) are not standardized at all. Hence, each analysis request will result in its own specific method and evaluation of the method. Furthermore, with such a wide range of potential analysis goals support and management of analysis methods may become infeasible.

3 Analysis of images from an open epidemiological study

Open studies using images such as the ones mentioned above have a number of attributes and goals in common:
- A large number of participants in the study
- Images from different imaging modalities and with different parameterizations for image acquisition for multiple purposes
- Potential for cross-sectional and longitudinal analysis
- Computation of quantitative norms of any kind
- Detection of sub-populations under different hypotheses

Analysis of images from these studies is difficult because of the large number of data sets that have to be processed, because a specific research question is missing and because results from image analysis may have to be compared over time. This results in the following research questions:
- How can analysis be carried out efficiently in view of the fact that often part of the domain knowledge needs to be entered interactively?
- How can methods be developed efficiently, i. e. how can it be avoided to develop a new solution for every research question that may be posed?
- How is longevity of analysis results ensured given that results may be tracked over long periods of time?

The furthest advances have been made regarding the first question. Due to the large number of subjects and potential variation within and among human readers, fully automated methods are preferred. Reader input should be minimized and it should ideally be carried out before or after an automated part.

In many cases, volumetry or other kinds of size measurements are the purpose of analysis. Examples are the work of Gloger et al [10]., who measured kidney volumes in MRI, the work of Fazekas et al [11]., who measured relative volume of MS lesions in MRI, or the work of de Laat et al [12]., who measured cortical thickness in MRI. More advanced geometrical features such as shape have been investigated as well (see Good et al [13].). These methods are fully automatic except for initial parameterization that may happen during a training phase on a subset of images (e. g. [10]).

Having many cases, however, has also advantages. A definite advantage in connection with the research questions in epidemiology is that data may also be used to gain domain knowledge. It may even provide insight into supervised training which otherwise cannot be achieved

when lacking a sufficiently large data base. For instance, questions about size and selection of training data as well as improvement of domain knowledge by added training data may be answered more precisely. Furthermore, the large number of samples provides sufficient information for outlier detection. Non-biased errors should cancel out.

Automatic methods, however, are usually tailored to some specific application (e. g. [13–15]) since automation requires inclusion of specific domain knowledge in the analysis process. This does not go well with the longevity of a large-scale cohort study and the potentially very large and to some part unknown number of possible analysis questions. It would eventually result in many different, specialized methods that need to be supported over a long period of time. Re-using methods for different research questions (e. g. adapting a volumetry method developed for livers in MRI to compute volumes of the spleen in MRI) has not been addressed by the research community. Basic methodology has been developed, of course, such as the use of level set segmentation techniques, live wire or region growing for extracting objects from the data. However, the large variability of methods in image analysis mainly stems from adding sufficient domain knowledge for each specific purpose. This knowledge is added by introducing high-level components such as active shape models and by combining several such components to counteract deficiencies of the single modules in the exact description of required domain knowledge.

Cross-sectional and longitudinal studies require *normalization* of the data w. r. t. acquisition-specific and subject-specific influences. A cross-sectional study compares a certain aspect in the subject (i. e. an organ, a group of organs, etc.) across subjects. Examples for acquisition-specific influences that need to be normalized in this case are those from image acquisition (e. g., shading in MRI) or operator influence (i. e. anything having an influence on inter- or intra-rater variability) during image analysis. An example for subject-specific influence is the registration of subject data to some reference (such as the mapping of brain images onto the MNI atlas [16]). Aspects of subject-specific normalization need to be independent of any feature that is subject of the research.

Longitudinal studies that analyze the same subject at different times need to be normalized as well. Normalization may be more difficult since imaging the same subjects several years apart will involve different imaging devices.

4 The development of an image analysis method

When developing an image analysis method for use in epidemiology, it is instructive to think of this method as part of data acquisition, hence it is not the images but the features generated from the images that are part of the epidemiological data. Images then play a similar role as stained images from protein electrophoresis of a blood test that are subjected to different analysis methods for producing a feature, such as the globulin level.

Lack of standardization

Different to biomarker analysis from blood samples, however, image analysis is far from being well standardized. There is no "volumetry" button on some analysis console that computes the volume of an imaged organ. Moreover, the feature "volume" is computed differently for different organs or different images and in most cases no established method exists. This does not pose a great problem, if images are generated and used to compute one specific feature for one specific purpose in a hypothesis-driven epidemiological study. In this case, features are determined based on the hypothesis and a method is implemented and evaluated for their extraction. This is done just once and the computed feature values are then added to the epidemiological data base.

For an open study, this is not as simple. Open studies are designed to cover a broad range of possible hypotheses, yielding complex requirements for image analysis methods. A new tool may be necessary if the current tool has been developed for a different organ, imaging device, or imaging protocol. Furthermore, an existing tool may be replaced by a more efficient or more exact tool. In both cases equivalence of feature values needs to be established. Otherwise, feature values for the same feature will have different accuracy, bias and sensitivity w. r. t. outliers.

Expert knowledge

Inclusion of domain knowledge can be complicated when adapting such tool to some task. Most image analysis methods need to be parameterized and users have to be trained in the correct setting of parameters. Furthermore, tools need to be available to different users and possibly for a long time. Since most image analysis methods are not commercial products, longevity has to be ensured on-site. This relates to adaptation to changing software or imaging environments and often results in sub-optimal solutions.

Methods from an established open or commercial software package are used simply because they promise the least development and maintenance costs.

Re-use of image analysis methods

It is not easy to suggest general strategies to deal with the aspects listed above, but some of the attributes of feature generation presented in Section 3 may help. Different methods for generating features have a lot in common since most features require separating a foreground object and quantitating geometric attributes of this object. Components that deal with the different aspects of foreground segmentation (detection, boundary computation and completion, etc.) are often similar. It may be helpful

for potential re-use, when the role of these components in the extraction of information is explicitly stated and at least an expert mode exists that allows recombination of software modules.

Re-combination has been done by [10, 17, 18] who proposed fully-automatic segmentation frameworks for kidney and liver volumetry in MR volume data. MR intensity distributions of four different MR weightings were incorporated by using linear discriminant reduction techniques followed by a Bayesian probabilistic approach to compute liver-specific probability maps. These maps were used for segmentation based on region-growing and refined, assuming a smooth liver shape (see [17]). Since subjects in epidemiological studies can show varying liver fat degrees, which bias liver intensities in MR images, the pro-
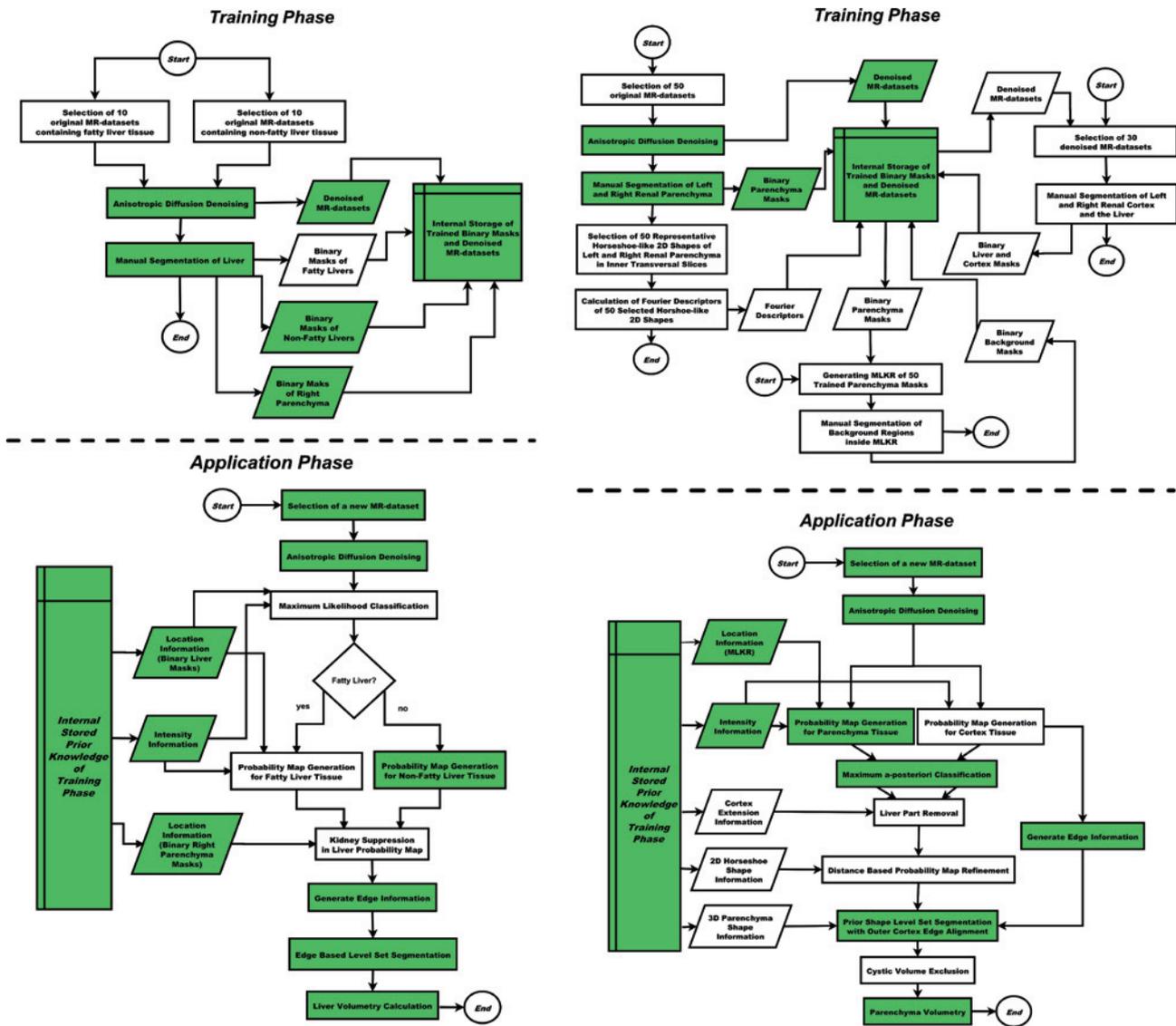

Figure 1: Block diagrams of two segmentation modules to segment liver (left) and kidney (right) from MR images of SHIP. Blocks depicted in green have been re-used in the two methods.

posed volumetric liver analysis takes subject-specific fatty and non-fatty liver tissue into account.

In a later study [18], region growing and application of the smoothness constraint were replaced by a single module using a variant of geodesic active contours from [19].

The concept was re-used again for fully automated kidney volumetry in MR volume data of SHIP (see Figure 1). The method followed the same strategy, firstly computing organ probabilities on which the segmentation is carried out. Instead of simply assuming smoothness, the level-set component of [18] was extended by a shape-term [10] and by organ edge alignment with variational level sets (see [20]) to delineate renal tissue in kidney probability maps.

The modularized segmentation framework offers potential for fast adaptation to different volumetry tasks. It should be noted, however, that an image analysis expert is required for deciding and implementing a new modular framework for a new feature extraction solution.

Since domain knowledge is so important for automatic image analysis, non-image features in the study may be used to complement knowledge in analysis. This could be, for instance, the assignment to different size classes depending on height, weight or gender of a subject, or the assignment to different age classes. Care has to be taken, however, not to bias an analysis result based on non-image and image features (e. g., by analyzing gender-related size differences when gender has been used to predict size of an organ to be extracted from the image data). If inclusion of domain knowledge can be separated from the feature extraction process, this could decrease learning cost and potentially also costs for development and maintenance of a feature extraction method, since adaptation of a method to another application would happen by adapting the domain knowledge only.

Shape, appearance and part models

Domain knowledge can be separated from the extraction process. A model is then created by user's expertise or from training that describes characteristics of the feature in the image data. The extraction process itself is independent of the model and needs not to be altered if a different feature is selected or if the feature is to be extracted from a different kind of image. Since feature generation mostly refers to the extraction of an anatomical structure from the image data, the model is used to represent expected shape and appearance of this structure. Models of this kind have been applied for quite some time for object segmentation based on trained shape variation (statistical shape models – SSM, see [21] for a review).
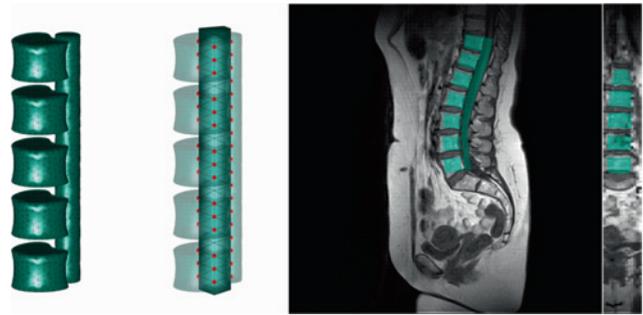

Figure 2: Deformable geometric model of vertebrae and spline. The vertebrae and the spline are connected by an auxiliary structure to represent relative positions of the parts. The picture on the right shows application of the model to MR images.

Training, however, can be tedious and still does not guarantee that the trained model describes the correct probabilities for shape and appearance variation. Hence, we replaced the trained SSM by a user-specified prototypical part-based model. It allows generating a hierarchy of sub-shapes with simpler variation than the overall shape. Variation can then be described by few, user-specified parameters [22]. We applied this strategy to images from SHIP in [23], to define the characteristics of the lumbar column (spine) and its appearance in MRI data (see Figure 2).

Parts in the part-based model are the vertebrae and the spinal canal. They are modeled by elastic material, which adapts to image structures via appropriate image-derived forces. Spatial relations among parts (as is the natural arrangement of vertebrae and canal) are realized by additional layers of elastic material, being connected to the part models by joints. The inherent natural variability of parts and relations can be parameterized by a handful of intuitive (physics-derived) material parameters.

This framework allows exploiting knowledge of shape and appearance for complex structures in a black box fashion, using different elastic models and different sets of likelihood functions for each recognition task at hand. Klemm et al [24]. then used the obtained mid-level information to relate non-image features to clusters of subjects based on the geometry of their spinal canal.

This approach is a step towards re-usable feature computation. However, there are still open questions. Currently, all models have been built by image analysis specialists based on model segmentations and simple geometric components. It would be preferable if this task, at least in part, could be carried out by the domain expert. It would let the domain expert understand limitations of the method and thus possible consequences regarding the quality of computed features.

5 Discussion and conclusions

We analyzed requirements for image analysis methods in epidemiology. The methods described above represent two strategies to construct feature extraction methods for image data with re-usable components. At present, both strategies just hint at a good solution since concepts of re-usability were executed by image analysis specialists and not by domain experts.

Visual analytics could help the domain expert in deciding whether to use a feature generation method and also how to adapt it to some specific purpose. It would mean that the domain expert is supported to create an extraction method aided by visualized properties of this method. There are a number of characteristics of a method for which visualization would be useful to the domain expert:

- Influence of parameterization on the quality of results and dependencies among parameters
- Integrated domain knowledge and its influence on results
- Extent of redundancy between domain knowledge and data information
- Reliability of trained parameters and potential gain by additional training

Of these aspects, parameter tuning has received some attention [25], where the influence of a shape model on segmentation has been visualized. This certainly provides insight into the contribution of the model to the segmentation success. However, fully automatic object extraction often consists of a sequence of several modules of which each introduces a different kind of domain knowledge.

Instead of extending the approach of [25] to visualize the behavior of all the kinds of information w. r. t. segmentation result it would be simpler to investigate each module independently (similar to [25]) and to assess the impact of the interaction between modules on the final result. The role of each module is specified by the developer (e. g. to compute an initial guess for the location of a searched object in the image). Hence expected input and output of each module can be characterized.

Visualizing the effects of variation within the range of expected outputs (or even exceeding it) of a giving module on the input of a receiving module would allow the user to assess potential sources of error. It should also give insight into the contribution of each module to the final result.

Visualizing the effect on the expected result using training data would allow assessing the importance of a module in the analysis system. Data from open studies are particularly suited as they are searching for markers of a general population usually excluding pathological cases. Hence, a small amount of training data is more likely to be representative for variation in the entirety of the data.

Such an approach based on principles of visual analytics can be a first step to understand the behavior of a set of combined modules. It could help to pinpoint potential non-robust input but also potentially redundancy when domain knowledge is included.

Hence, we will investigate the modular approach of [10, 18] for defining modules that can be parameterized but not changed otherwise so that it becomes simpler to represent (and potentially visualize) behavior of each module. Further adaptation of this framework will also help to understand the role of the modules in the system.

For the shape-model driven segmentation of [23], just one aspect (the geometric model) can be adapted. Hence, we will explore how aspects such as the need for multiple prototypes, the appropriateness of a given decomposition into parts or the redundancy between data knowledge and domain knowledge in the model can be analyzed through methods of visual analytics.

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