COMPUTATIONAL VISION AND MEDICAL IMAGE PROCESSING IV

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Computational Vision and Medical Image Processing IV

Editors

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Table of contents

Computational Vision and Medical Image Processing IV – João Tavares & Natal Jorge (eds)

Preface

This book contains invited lectures and full papers presented at VipIMAGE 2013 – IV ECCOMAS Thematic Conference on Computational Vision and Medical Image Processing, which was held in Funchal, Madeira Island, Portugal, during the period 14–16 October 2013. The event had 6 invited lectures, and 74 contributed presentations originated from 17 countries: Austria, Brazil, Canada, Cuba, Czech Republic, Finland, France, Germany, Italy, Poland, Portugal, Republic of Korea, Romania, Spain, Sweden and Venezuela.

Computational methodologies of signal processing and analyses have been commonly used in our society. For instances, full automatic or semi-automatic Computational Vision systems have been increasing used in surveillance tasks, traffic analysis, recognition process, inspection purposes, human-machine interfaces, 3D vision and deformation analysis.

One of the notable aspects of the Computational Vision domain is the inter- and multi-disciplinarily. Actually, methodologies of more traditional sciences, such as Informatics, Mathematics, Statistics, Psychology, Mechanics and Physics, are regularly comprised in this domain. One of the key motives that contributes for the continually effort done in this field of the human knowledge is the high number of applications that can be easily found in Medicine. For instance, computational algorithms can be applied on medical images for shape reconstruction, motion and deformation analysis, tissue characterization or computer-assisted diagnosis and therapy.

The main objective of these ECCOMAS Thematic Conferences on Computational Vision and Medical Image Processing, initiated in 2007, is to promote a comprehensive forum for discussion on the recent advances in the related fields in order to identify potential collaboration between researchers of different sciences. Henceforth, VipIMAGE 2013 brought together researchers representing fields related to Biomechanics, Biomedical Engineering, Computational Vision, Computer Graphics, Computer Sciences, Computational Mechanics, Electrical Engineering, Mathematics, Statistics, Medical Imaging and Medicine.

The expertises spanned a broad range of techniques for Image Acquisition, Image Processing and Analysis, Signal Processing and Analysis, Data Interpolation, Registration, Acquisition and Compression, Image Segmentation, Tracking and Analysis of Motion, 3D Vision, Computer Simulation, Medical Imaging, Computer Aided Diagnosis, Surgery, Therapy, and Treatment, Computational Bio- imaging and Visualization and Telemedicine, Virtual Reality, Software Development and Applications.

The conference co-chairs would like to take this opportunity to express gratitude for the support given by The International European Community on Computational Methods in Applied Sciences and The Portuguese Association of Theoretical, Applied and Computational Mechanics, and thank to all sponsors, to all members of the Scientific Committee, to all Invited Lecturers, to all Session-Chairs and to all Authors for submitting and sharing their knowledge.

João Manuel R.S. Tavares
Renato M. Natal Jorge
(Conference co-chairs)

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Invited lecturers

During VipIMAGE 2013, were presented Invited Lectures by 6 Expertises from 3 countries:

– Daniel Cremers, *Technische Universität München, Germany*
– Daniel Rueckert, *Imperial College London, UK*
– Dimitris N. Metaxas, *Rutgers University, USA*
– James S Duncan, *Yale School of Medicine, USA*
– Milan Sonka, *The University of Iowa, USA*
– Richard Bowden, *University of Surrey, UK*

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Thematic sessions

Under the auspicious of VipIMAGE 2013, 3 Thematic Sessions were organized:

Imaging of biological flows: Trends and challenges

Alberto Gambaruto, *Instituto Superior Técnico, Portugal*
Mónica S.N. *Oliveira, University of Strathclyde, UK*
Rui Lima, *Polytechnic Institute of Bragança, Portugal*

Trabecular bone characterization: New trends and challenges

Angel Alberich-Bayarri, *Grupo Hospitalario Quirón S.A., Spain*
Waldir L. Roque, *Federal University of Rio Grande do Sul, Brazil*
Fábio Baruffaldi, *Rizzoli Ortopaedic Institut, Italy*
Zbislaw Tabor, *Cracow University of Technology, Poland*

Computational vision and image processing applied to dental medicine

André Correia, *Universidade do Porto, Universidade Católica Portuguesa, Portugal*
J.C. Reis Campos, *Universidade do Porto, Portugal*
Mário Vaz, *Universidade do Porto, Portugal*

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Scientific committee

All works submitted to VipIMAGE 2013 were evaluated by an International Scientific Committee composed by 84 expert researchers from recognized institutions of 17 countries:

- Ahmed El-Rafei, *Friedrich-Alexander University Erlangen-Nuremberg, Germany*
- Alberto Gambaruto, *Instituto Superior Técnico, Portugal*
- Alejandro F. Frangi, *The University of Sheffield, UK*
- Alexandre Cunha, *California Institute of Technology, USA*
- Ana Mafalda Reis, *University of Porto, Portugal*
- André Correia, *University of Porto, Portugal*
- André R.S. Marçal, *University of Porto, Portugal*
- Andrew D. Bagdanov, *University of Florence, Italy*
- Angel Alberich-Bayarri, *Grupo Hospitalario Quirón S.A., Spain*
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- Mário Vaz, *University of Porto, Portugal*
- Miguel Velhote Correia, *University of Porto, Portugal*
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- Susana Branco Silva, *Polytechnic Institute of Lisbon, Portugal*
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- Thierry Brouard, *University of Tours, France*
- Tolga Tasdizen, *University of Utah, USA*
- Waldir L. Roque, *Federal University of Rio Grande do Sul, Brazil*
- Yongjie (Jessica) Zhang, *Carnegie Mellon University, USA*
- Zbislaw Tabor, *Cracow University of Technology, Poland*
- Zeyun Yu, *University of Wisconsin at Milwaukee, USA*

Invited lectures

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Machine learning meets medical imaging: Learning and discovery of clinically useful information from images

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ABSTRACT: Three-dimensional (3D) and four-dimensional (4D) imaging plays an increasingly important role in computer-assisted diagnosis, intervention and therapy. However, in many cases the interpretation of these images is heavily dependent on the subjective assessment of the imaging data by clinicians. Over the last decades image registration has transformed the clinical workflow in many areas of medical imaging. At the same time, advances in machine learning have transformed many of the classical problems in computer vision into machine learning problems. This paper will focus on the convergence of image registration and machine learning techniques for the discovery and quantification of clinically useful information from medical images. We will illustrate this with several examples such as the segmentation of neuro-anatomical structures, the discovery of biomarkers for neurodegenerative diseases and the quantification of temporal changes such as atrophy in Alzheimer's disease.

1 INTRODUCTION

For many clinical applications the analysis of medical images represents an important aspect in decision making in the context of diagnosis, treatment planning and therapy. Different imaging modalities often provide complementary anatomical information about the underlying tissues such as the X-ray attenuation coefficients from X-ray computed tomography (CT), and proton density or proton relaxation times from magnetic resonance (MR) imaging. Medical images allow clinicians to gather information about thesize, shape and spatial relationship between anatomical structures and any pathology, if present. In addition to CT and MR, other imaging modalities provide functional information such as the blood flow or glucose metabolism from positron emission tomography (PET) or single-photon emission tomography (SPECT), and permit clinicians to study the relationship between anatomy and physiology. Finally, histological images provide another important source of information which depicts structures at a microscopiclevel of resolution.

The use of machine learning in the analysis of medical images has become increasingly important in many real-world, clinical applications ranging from the acquisition of images of moving organs such as the heart, liver and lungs to the computer-aided detection, diagnosis and therapy. For example, machine learning techniques such as clustering can be used to identify classes in the image data and classifiers may be used to differentiate clinical groups across images or tissue types within an image. These techniques may be applied to images at different levels: At the lowest level or voxel level one may be interested in classifying the voxel as part of a tissue class such as white matter or grey matter. At a more intermediate level, classification may be applied to some representation or features extracted from the images. For example, one may be interested in classifying the shape of the hippocampus as belonging to a healthy control or to a subject with dementia. At the highest level, clustering may be applied in order to classify entire images.

In the following we will discuss two particular applications of image registration and machine learning in medical imaging: (a) segmentation and (b) biomarker discovery and classification.

2 MACHINE LEARNING FOR SEGMENTATION

The amount of data produced by imaging increasingly exceeds the capacity for expert visual

analysis, resulting in a growing need for automated image analysis. In particular, accurate and reliable methods for segmentation (classifying image regions) are a key requirement for the extraction of information from images. In recent years many approaches to image segmentation have emerged that use image registration as a key component. Many of these approaches are based on so-called *atlases*. An atlas can be viewed as a map or chart of the anatomy or function, either from a single individual or from an entire population. In many cases the atlases are annotated to include geometric information about points, curves or surfaces, or label information about voxels (anatomical regions or function). Such atlases are often used in brain imaging applications (Mazziotta, Toga, Evans, Fox, & Lancaster 1995).

Atlases can be used as prior information for image segmentation. In general, an atlas A can be viewed as a mapping from a set of spatial coordinates (i.e. the voxels) to a set of labels $\Lambda = \{1, \cdots, L\}$. By warping the atlas to the target, one can make the atlas and its prior information *subject-specific* and obtain a segmentation L of image I:

$$L = A \circ \mathbf{T}_{A \to I} \tag{1}$$

Here $\mathbf{T}_{A \to I}$ denotes the transformation that maps the atlas A into the space of the image I. This transformation can be obtained using different image registration techniques, e.g. (Rueckert, Sonoda, Hayes, Hill, Leach, & Hawkes 1999).

Indeed the earliest approaches to segmentation via registration have used such approaches: By registering a labelled atlas to the target images and transforming the segmentation of the atlas into the coordinate system of the subject one can obtain a segmentation of the subject's image (Miller, Christensen, Amit, & Grenander 1993, Collins & Evans 1997). This segmentation approach is simple yet effective since the approach can segment any of the structures that are present and annotated in the atlas. However, the accuracy and robustness of the segmentation is dictated by the accuracy and robustness of the image registration. Errors in the registration process will directly affect the accuracy of the propagated segmentation.

2.1 *Multi-atlas segmentation*

In the area of machine learning it is well know that the performance of pattern recognition techniques can be boosted using combining classifiers (Kittler, Hatef, Duin, & Matas 1998). This concept can be exploited in the context of atlas-based segmentation: Assuming the availability of multiple atlases, the output of atlas-based segmentation using a particular atlas instance can be viewed the output of the classifier. Combining the output of multiple classifiers (or segmentations) into a single consensus segmentation has been show to reduce random errors in the individual atlas-to-image registration resulting in an improved segmentation (Rohlfing & Maurer Jr. 2005, Heckemann, Hajnal, Aljabar, Rueckert, & Hammers 2006). Using this method each atlas is registered to the the target image in question. The resulting transformation is thenused to transform the segmentation from the atlas into the coordinate system of the target image.

By applying classifier fusion techniques at every voxel in subject space the final consensus segmentation can be applied. Several classifier fusion techniques can be used, see (Kittler, Hatef, Duin, & Matas 1998) for a detailed review and discussion of the different classifier fusion techniques. One of the most popular techniques is the majority vote rule (Rohlfing & Maurer Jr. 2005): It simply uses a *winner-takes-all* approach in which each voxel is assigned the label that gets the most votes from the individual segmentations. Assuming K classifiers (i.e. atlases) final segmentation $L(\mathbf{p})$ can be expressed as

$$L(\mathbf{p}) = \max[f_1(\mathbf{p}), \cdots, f_L(\mathbf{p})] \tag{2}$$

where

$$f_l(\mathbf{p}) = \sum_{k=1}^{K} w_{k,l}(\mathbf{p}) \quad \text{for} \quad l = 1, \cdots, L \tag{3}$$

and

$$w_{k,l}(\mathbf{p}) = \begin{cases} 1, & \text{if } l = e_k(\mathbf{p}) \\ 0, & \text{otherwise} \end{cases} \tag{4}$$

Here e_k denotes the output or label of classifier k. An extension of multi-atlas segmentation has been proposed in (Aljabar, Heckemann, Hammers, Hajnal, & Rueckert 2009). In their work a large number of atlases are used. However, instead of using all atlases for for multi-atlas segmentation, only the most similar atlases are used: In the first step all atlases are registered to a common standard space using a coarse registration (e.g. affine registration). In addition, the target image is also aligned to the common standard space. After this initial alignment the similarity between each atlas and the target image can be determined using an image similarity measure S, e.g. sums of squared differences (SSD), cross-correlation (CC), mutual information (MI) (Collins, Evans, Holmes, & Peters 1995, Viola & Wells 1995) or normalised mutual information (NMI) (Studholme, Constable,

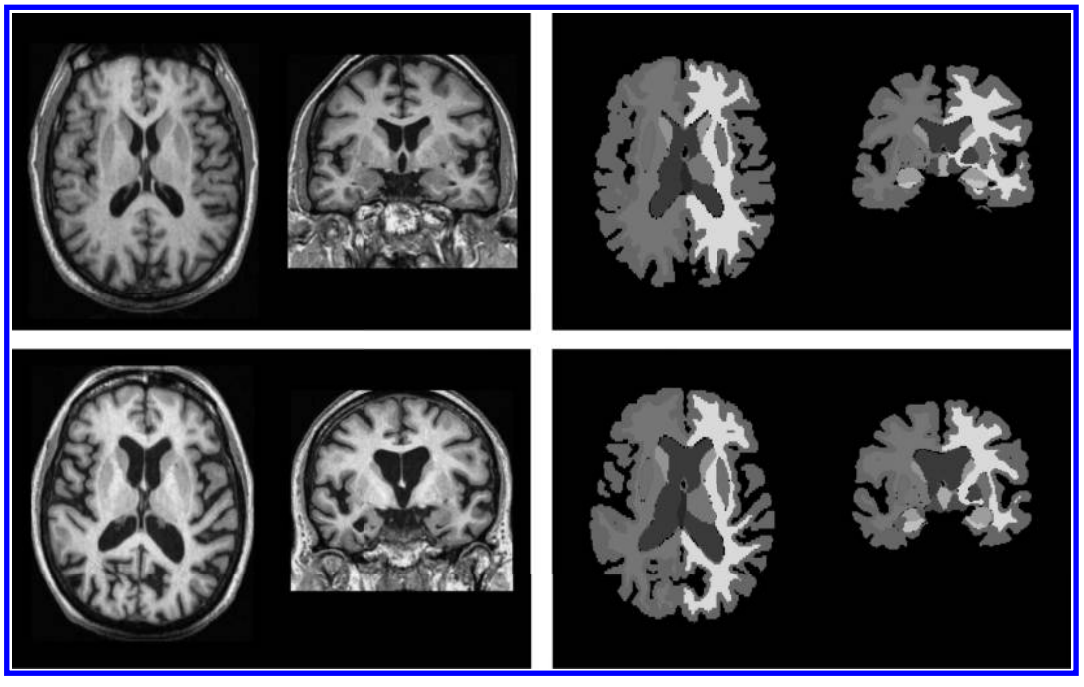

Figure 1. Result of multi-atlas segmentation of brain MR images from a normal control subject (top) and subject with Alzheimer's disease (bottom).

& Duncan 1999). This allows the ranking of all atlases with respect to the similarity to the target image. The m top-ranked atlases are then registered non-rigidly to the target image and as before a classifier fusion framework is applied to obtain a final consensus segmentation.

The use of a common standard space allows the pre-registration of all atlases to the standard common space avoiding the necessity for performing registration of each atlas to the target image for atlas selection. In principle it is also possible to rank atlases based on meta-information available from the atlases and the target image. Such meta-information can include gender, age, handedness and clinical status. In this case atlas selection can be carried out independently from the actual image data and does not require any initial registration for the atlas selections step.

Instead of ranking atlases based on their similarity to the target image and using the top m atlases for classifier fusion, it is possible to weight each atlas according to its similarity to the target image. In this case the weight w can be written as

$$w_{k,l}(\mathbf{p}) = \begin{cases} S, & \text{if } l = e_k(\mathbf{p}) \\ 0, & \text{otherwise} \end{cases} \tag{5}$$

where S measures the similarity between atlas A_k and the target image. It should be noted that the atlas selection scheme can be viewed as a special case of the weighted atlas fusion scheme described above where $w = 1$ for the top-ranked atlasesand $w = 0$ for all other atlases.

While weighted voting allows the incorporation of a notation of atlas similarity into the classifier fusion, it does not account for the fact that images can be dissimilar at a global level but similar at a local level and vice versa. For example, two brain MR images may have ventricles that are very different in size and shape but their hippocampi may have similar shape and size. Since the ventricle is much larger than the hippocampus, its appearance will dominate the similarity calculations. A more flexible approach is to measure image similarity locally and to adjust the weighting function accordingly:

$$w_{k,l}(\mathbf{p}) = \begin{cases} S(\mathbf{p}), & \text{if } l = e_k(\mathbf{p}) \\ 0, & \text{otherwise} \end{cases} \tag{6}$$

Another approach is based on simultaneous truth and performance level estimation (STAPLE) (Warfield, Zhou, &Wells 2004). The STAPLE framework was initially created in order to

fuse several manual or automated segmentations of the same image. More specifically it computesa probabilistic estimate of the true segmentation as a measure of the performance level represented by each segmentation in an expectation-maximization (EM) framework. This framework has extended to account for spatially varying performance by extending the performance level parameters to account for a smooth, voxelwise performance level field that is unique to each atlas-based segmentation (Commowick, Akhondi-Asl, & Warfield 2012, Asman & Landman 2012).

3 MACHINE LEARNING FOR BIOMARKER DISCOVERY AND CLASSIFICATION

A biomarker is a measurement or physical sign used as a substitute for a clinically meaningful endpoint that measures directly how a patient feels, functions, or survives. Changes induced by a therapy on a surrogate endpoint are expected to reflect changes on a clinically meaningful endpoint. A practical example of a biomarker could be the volume of region of interest (ROI) such as the hippocampus. However, this requires a-priori information about what anatomical ROI maybe affected by a particular disease. An alternative approach is to learn the biomarker directly from the images without any a-priori knowledge.

One of the key challenges in applying machine learning techniques for biomarker discovery in medical images is the fact that medical images are often represented as data points in a very high-dimensional space, yet they only occupy a small part of this space. Another key challenge that is often faced is commonly referred to as the small sample size problem: While the data lives in a very high-dimensional space we often only have a comparatively small number of images from which to learn. In this context manifold learning techniques (Aljabar,Wolz, & Rueckert 2012) offer a powerful approach to find a representation of images or image-derived features that facilitates the application of machine learning techniques such as clustering or regression.

The basic idea of manifold learning is closely related to that of dimensionality reduction techniques such as Principal Component Analysis (PCA). The key assumption in applying manifold learning techniques is that dimensionality of the original data can be reduced with a negligible loss of information. For example, a 3D brain image with $256 \times 256 \times 128$ voxels may be viewed as a point in a more than 8 million dimensional vector space. However, brain images from different subjects have a large degree of similarity in their appearance. Thus, most regions of this high-dimensional space correspond to images that have no similarity to brain images. Instead the assumption is that the images are data points on a low dimensional manifold, which is embedded in the high-dimensional space. The goal of manifold learning algorithms is to uncover or learn this low dimensional manifold directly from the data.

A good example of the application of manifold learning to biomarker discovery can be found in (Wolz, Aljabar, Hajnal, & Rueckert 2010): In their work, the MR brain images from a population of subjects with and without Alzheimer's disease were analysed using a manifold learning approach based on Laplacian eigenmaps (Belkin & Niyogi 2003):: The set of images $\{\mathbf{x}_1,...,\mathbf{x}_n\}$ is described by N images $\mathbf{x}_i \in R$, each being defined as a vector of intensities, where D is the number of voxels per image or region of interest. Assuming that $\{\mathbf{x}_1,...,\mathbf{x}_n\}$ lie on or near a d-dimensional manifold M embedded in R^D and $d << D$, it is possible to learn a new, low dimensional representation $\{y_1,...,\mathbf{y}_n\}$ with $\mathbf{y}_i \in R$, of the input images. In Laplacian eigenmaps a set of weights w_{ij} are defined as the similarities between images within a local neighborhood and are set to zero for all other pairings. Similarities can be derived from distances d_{ij} using a heat kernel such as

$$w_{ij} = e^{-\frac{d_{ij}^2}{t}} \tag{7}$$

where t defines the width of the kernel. The Laplacian eigenmap embedding is obtained by minimizing the objective function

$$\phi(\mathbf{Y}) = \sum_{ij} \| \mathbf{y}_i - \mathbf{y}_j \|^2 \, w_{ij} = 2\mathbf{Y}^T\mathbf{L}\mathbf{Y} \tag{8}$$

where $\mathbf{L} = \mathbf{DW}$ is the graph Laplacian matrix which is derived from the weight matrix $\mathbf{W}$ and the diagonal degree matrix $\mathbf{D}$ where $\mathbf{D}_{ii} = \sum_j w_{ij}$. The Laplacian eigenmap objective function is optimized under the constraint that $\mathbf{y}^T\,\mathbf{Dy} = 1$ which removes an arbitrary scaling factor in the embedding and prevents the trivial solution where all $\mathbf{y}_i$ are zero. The $\mathbf{y}_i$ that optimize the objective function are defined by the eigenvectors corresponding to the smallest nonzero eigenvaluesof the generalized eigenvalue problem $\mathbf{Lv} = \lambda\mathbf{Dv}$.

An example of a manifold constructed from brain MR images using Laplacian eigenmaps is shown in Figure 2: In this example a set of baseline and follow-up MR images from the ADNI study have been embedded into a two-dimensional manifold. In this manifold each pair of baseline and follow-up images correspond to a pair of points in the manifold connected by a line. The line indicates the magnitude and direction of movement of

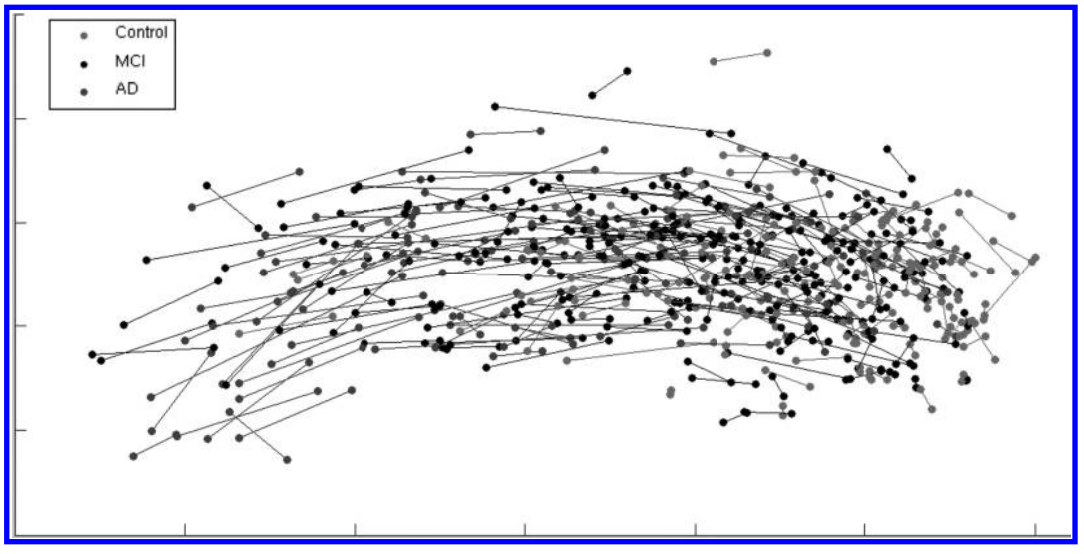

Figure 2. Example of manifold learning for biomarker discovery and classification (Wolz, Aljabar, Hajnal, & Rueckert 2010): A set of baseline and follow-up MR images from the ADNI study is embedded into a two-dimensional manifold: The figure clearly shows the difference in the longitudinal trajectory between healthy controls and subjects with AD.

each subject between baseline and follow-up (in this case 24 months after baseline). Using the position, magnitude and direction of movement in the manifold as features for a linear SVM it is possible to achieve classification rates of up-to 86% for the classification of controls and subjects with AD (Wolz, Aljabar, Hajnal, & Rueckert 2010).

4 SUMMARY AND CONCLUSIONS

Machine learning is becoming increasingly important in the context of medical imaging. In this article we have described two different exemplar applications of machine learning for image segmentation and biomarker discovery/classification. There are many more potential applications for machine learning in this area. However, one of the challenges is that the application of machine learning usually requires a large number of training datasets. In medical imaging it is often very costly and time-consuming to acquire such large number of training datasets. In future this challenge may be overcome as shared data repositories become more widely available.

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