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A framework for combining a motion atlas with non-motion information to learn clinically useful biomarkers: Application to cardiac resynchronisation therapy response prediction

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ABSTRACT

We present a framework for combining a cardiac motion atlas with non-motion data. The atlas represents cardiac cycle motion across a number of subjects in a common space based on rich motion descriptors capturing 3D displacement, velocity, strain and strain rate. The non-motion data are derived from a variety of sources such as imaging, electrocardiogram (ECG) and clinical reports. Once in the atlas space, we apply a novel supervised learning approach based on random projections and ensemble learning to learn the relationship between the atlas data and some desired clinical output. We apply our framework to the problem of predicting response to Cardiac Resynchronisation Therapy (CRT). Using a cohort of 34 patients selected for CRT using conventional criteria, results show that the combination of motion and non-motion data enables CRT response to be predicted with 91.2% accuracy (100% sensitivity and 62.5% specificity), which compares favourably with the current state-of-the-art in CRT response prediction.

1. Introduction

The use of spatio-temporal atlases for the statistical analysis of normal and pathological cardiac motion has gained increasing interest over the past decade. The intuition behind such approaches is that pathological changes in the heart lead to altered electromechanical behaviour, and therefore observing the mechanics of cardiac motion may lead to the uncovering of clinically useful information about the pathology. Motivated by this, machine learning based approaches have been proposed that try to identify characteristic motion 'signatures' that are linked to some desired clinical information, such as the presence of specific motion abnormalities in the left ventricle (LV) (Duchateau et al., 2012b).

At the same time, research in the clinical literature has been advancing, and more is now known about the mechanisms underlying heart failure. In addition, a wide range of data is available in clinical records, some of which are likely to be useful in forming biomarkers for different clinical problems. Some of these data are image-derived. For example, in Cardiac Resynchronisation Therapy (CRT), a number of echocardiography-based indices have been proposed for patient selection (Chung et al., 2008), although results have yet to prove conclusive. Other data are derived from the results of simple clinical tests which are often available in the clinical record, such as the six minute walk test (Enright, 2003).

Therefore, there is a wealth of potential information, both motion and non-motion based, that could be used to assist clinicians in making decisions about, for example, patient selection or treatment planning. However, to date, a methodological framework for combining and utilising such disparate sources of information has been lacking. In this paper, we propose such a framework, which facilitates the combined analysis of motion information from a spatio-temporal atlas with non-motion data derived from a variety of sources such as imaging, the electrocardiogram (ECG) or clinical reports. The framework we propose is based on the use of a spatio-temporal atlas for the normalisation of the motion information, followed by multiple kernel learning (MKL) for the combination of motion and non-motion features. We demonstrate its application to the problem of patient selection for CRT, although the framework could be applicable to the analysis of other cardiac conditions. In the following sections we first review the literature on CRT and CRT patient selection, then review relevant work from the

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field of spatio-temporal atlases and MKL, and finally we summarise our novel contributions in this context.

1.1. Cardiac resynchronisation therapy

Pathological impairment of the LV electrical conduction system typically leads to a dyssynchronous electro-mechanical activation that degrades the LV systolic performance, ultimately causing heart failure (HF) (Kirk and Kass, 2013). In the past two decades, CRT has been increasingly employed for the treatment of selected HF patients with electrical dyssynchrony. CRT aims to restore mechanical synchrony by electrically pacing the heart in a synchronised manner (Owen et al., 2009). Standard selection criteria for CRT are a New York Heart Association functional class of II to IV, a QRS duration $\geq$120 ms, and a LV ejection fraction (EF) $\leq$35% (Owen et al., 2009). However, when applying such criteria, approximately 30% and 44% of eligible patients do not show, respectively, clinical (i.e. whether the patient feels better) and volumetric (i.e. whether the LV manifests reverse remodelling) response to the treatment (Abraham et al., 2002; Bleeker et al., 2006; Kirk and Kass, 2013; Daubert et al., 2012). Improvement of the selection criteria for a better characterisation of CRT responders is therefore of great clinical interest.

Recent findings have shown that multiple independent factors correlate with treatment outcome. For instance, Bilchick et al. (2014) have shown that the presence/location of LV myocardial scar and the configuration of pacing leads can influence CRT volumetric response. A strict left bundle branch block (LBBB) (Tian et al., 2013), a type II electrical activation pattern (also known as U-shaped activation) (Sohal et al., 2013; Jackson et al., 2014) and an early activation of the septum (septal flash) (Parsai et al., 2009) have also been shown to correlate with an enhanced level of LV reverse remodelling following CRT. Several studies have also investigated the use of image-derived indices of dyssynchrony for a more accurate characterisation of CRT responders (Santaularia-Tomas and Abraham, 2009). However, to date, no single index has been shown to greatly improve the reliability of CRT patient selection, as reported in the multi-centre PROSPECT study (Chung et al., 2008). Therefore, as highlighted in Jackson et al. (2014) and Parsai et al. (2009), factors such as scar, strict LBBB and septal flash, represent some of the multiple mechanisms that influence CRT response, but may not be good predictors if considered separately.

1.2. Cardiac spatio-temporal atlases

The term *spatio-temporal atlas* (or *motion atlas*) refers to the establishment of a common coordinate system in which population comparisons of motion can be carried out. The use of such atlases for the statistical analysis of normal and pathological LV motion has gained increasing interest over the past decade, showing promising results for patient stratification and for the characterisation of cardiac diseases. Following advances in mathematical tools for the parallel transport of vector fields and tensors (Rao et al., 2002, 2004; Qiu et al., 2009; Lorenzi et al., 2011), statistical spatio-temporal atlases of the LV have been derived from cardiac Magnetic Resonance (CMR) sequences (Chandrashekara et al., 2003; Rougon et al., 2004; Perperidis et al., 2005; Ardekani et al., 2009; Lu et al., 2009; Garcia-Barnes et al., 2010; De Craene et al., 2012; Medrano-Gracia et al., 2013, 2014; Bai et al., 2015), as well as from 2D echocardiography (Duchateau et al., 2011, 2012b) and Computed Tomography (CT) (Hoogendoorn et al., 2013).

Although conceptually similar, these works differ in the techniques used to estimate the LV geometry and motion, to represent the motion, and also their intended application. For instance, Medrano-Gracia et al. (2013) fitted a finite-element model to cine-CMR sequences to estimate the LV motion, and subsequently analysed the shape and motion configuration of the model to detect and quantify infarcted myocardium. With the same application, Suinesiaputra et al. (2009) employed Independent Component Analysis on the distribution of endo- and epi-cardial LV contours derived from cine-MR. These works focussed on the statistical analysis of shapes, without explicitly estimating and transporting motion fields.

A polyaffine motion model has been recently proposed for statistical analysis of LV motion in McLeod et al. (2015a,b). In this approach, the motion of the myocardium is represented as an affine transformation for each of the 17 American Heart Association (AHA) segments, and inter-subject comparisons of these transformations is facilitated by conversion to a prolate spheroidal coordinate system.

More closely related to the proposed framework is the work of Duchateau et al. (2011, 2012b) and De Craene et al. (2012), in which statistical inference on myocardial velocities was proposed to detect septal flash and LV motion abnormalities as compared to the LV motion of healthy subjects. However, in Duchateau et al. (2011, 2012b) the velocities of the LV myocardium were estimated from 2D echocardiography, therefore providing a limited description of the complex 3D mechanical contraction. De Craene et al. (2012) employed tag-CMR sequences to quantify 3D+t myocardial motion abnormalities, but the method was evaluated on only two patients. In Duchateau et al. (2011), the spatio-temporal atlas of the LV septum proposed previously in Duchateau et al. (2010) was employed to assess the changes induced by CRT on the motion of the septum. By using the velocity maps, the authors demonstrated that a correction of the septal flash due to CRT correlated with an enhanced volumetric response.

In the cardiac spatio-temporal atlas works reviewed in this section, a number of motion representations have been employed, including intensity-based (Lu et al., 2009), displacement-based (Chandrashekara et al., 2003; Perperidis et al., 2005; Garcia-Barnes et al., 2010; Bai et al., 2015), velocity-based (Duchateau et al., 2011, 2012b), momentum-based (Ardekani et al., 2009) and polyaffine (McLeod et al., 2015a,b). In Garcia-Barnes et al. (2010) a representation based on 2D strain was employed but the technique performed inter-subject comparisons in a normalised parametric domain and therefore was not a spatio-temporal atlas in the sense discussed here.

1.3. Multiple kernel learning

As well as motion and shape information, several works have attempted to combine such high dimensional data with lower dimensional data from other sources for learning tasks. An early example of this principle is the work by Costa and Hero (2005), in which class labels were used to constrain embeddings computed using non-linear dimensionality reduction. This idea was extended and applied to a medical application in Wolz et al. (2012), who used clinical meta-data to constrain a manifold learnt from MR imaging data for the purpose of Alzheimer's disease stratification.

MKL works on a similar principle to these techniques. MKL algorithms extend Support Vector Machine (SVM) methods by considering a linear or non-linear combination of multiple kernels, as opposed to the single kernel representation of SVM. In particular, MKL offers an optimal solution for the combination of information derived from different sources or modalities, addressing issues related to differences in representation, variability and dimensionality. In MKL, each kernel provides a different measure of similarity between observations, therefore enriching the description necessary to accurately perform the classification/regression task at hand.

MKL methods have been successfully employed in several applications, ranging from genetics, computer vision and medical