Characterization of myocardial motion patterns by unsupervised multiple kernel learning

Sergio Sanchez-Martinez [a,*], Nicolas Duchateau [c], Tamas Erdei [d], Alan G. Fraser [d], Bart H. Bijnens [a,b], Gemma Piella [a]

[a] *Department of Information and Communication Technologies, Universitat Pompeu Fabra, Barcelona, Spain*
[b] *ICREA, Barcelona, Spain*
[c] *Inria Asclepios research project, Sophia Antipolis, France*
[d] *Wales Heart Research Institute, Cardiff University, United Kingdom*

ABSTRACT

We propose an independent objective method to characterize different patterns of functional responses to stress in the heart failure with preserved ejection fraction (HFPEF) syndrome by combining multiple temporally-aligned myocardial velocity traces at rest and during exercise, together with temporal information on the occurrence of cardiac events (valves openings/closures and atrial activation). The method builds upon multiple kernel learning, a machine learning technique that allows the combination of data of different nature and the reduction of their dimensionality towards a meaningful representation (output space). The learning process is kept unsupervised, to study the variability of the input traces without being conditioned by data labels. To enhance the physiological interpretation of the output space, the variability that it encodes is analyzed in the space of input signals after reconstructing the velocity traces via multiscale kernel regression. The methodology was applied to 2D sequences from a stress echocardiography protocol from 55 subjects (22 healthy, 19 HFPEF and 14 breathless subjects). The results confirm that characterization of the myocardial functional response to stress in the HFPEF syndrome may be improved by the joint analysis of multiple relevant features.

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1. Introduction

Multiple feature analysis has proved to be helpful to understand the information embedded in complex data. We demonstrate the value of this kind of analysis to unravel patterns of cardiac mechanical dysfunction, focusing on the heart failure with preserved ejection fraction (HFPEF) syndrome, which is pathophysiologically heterogeneous and difficult to diagnose (Shah et al., 2014; Komajda and Lam, 2014). We illustrate the relevance of our approach to improve the understanding of this syndrome.

1.1. Multiple features analysis

Clinical guidelines provide consensus indications to guide diagnosis in daily clinical practice. However, the measurements that they suggest are kept to simple parameters that have been shown to correlate with disease status (Borlaug and Paulus, 2011; Penicka et al., 2014). The number of studies that include more advanced

statistical tools is rather limited. Multiple stepwise logistic regression was previously used within the context of our application (Mädler et al., 2003), and multiparametric approaches were proposed to predict response to cardiac resynchronization therapy (CRT) (Santaularia-Tomas and Abraham, 2009; Lafitte et al., 2009). Nonetheless, all these approaches have notable limits for the advanced diagnosis of complex diseases. Indeed, they all seek for simple key markers of the disease, such as peak measurements or specific timings, while induced changes tend to be more complex, both spatially and temporally. A more complete analysis should therefore target the study of cardiac function at the pattern level, as was previously recommended to improve the prediction of response to CRT (Fornwalt et al., 2009) and to reach a deeper understanding of myocardial mechanics and physiology (Bijnens et al., 2012). Such an analysis should also allow jointly analyzing multiple variables, eventually at different hierarchical levels.

In the computer vision community, the fusion of high-dimensional heterogeneous descriptors has become a wide field of research, successfully applied to a large variety of pattern recognition applications (object, face and handwriting recognition). However, its application to medical imaging is rather new.

Tiwari et al. (2013) quantitatively combined structural and metabolic imaging data for prostate cancer characterization. Castro et al. (2014) combined the phase and magnitude of magnetic resonance acquisitions to improve the characterization of schizophrenia. Wolz et al. (2012) fused image-derived descriptors and relevant clinical parameters to improve the classification of Alzheimer's disease and mild cognitive impairment.

Different trends have recently emerged in machine learning to address the fusion of different descriptors. The most common approach consists in directly analyzing a concatenated set of the input features (Beckmann and Smith, 2005), which can be improved by taking into account the structure of the manifold to which these features belong (Lombaert and Peyrat, 2013). However, this simple approach does not handle possible differences in the nature or distribution of the analyzed features. Besides, the possible redundancy in the different input descriptors may bias the final result. Multiset canonical correlation analysis (Correa et al., 2010) deals with redundancy by finding cross-descriptor associations and performing source separation. Nonetheless, all these linear approaches are not suitable for the type of data used in our application. Indeed, it has been pointed out that non-linear operations may be more adequate to prevent artifacts when processing medical images (Gerber et al., 2010) and more precisely cardiac motion patterns (Duchateau et al., 2012).

Kernel methods are appropriate to deal with these disadvantages, since these non-linear approaches do not make any assumption on the nature of the data. They all use a kernel-based affinity matrix that codifies pair-wise similarities between samples. The eigen decomposition of this matrix leads to a space of reduced dimension, which encodes the most relevant characteristics of the data (Yan et al., 2007).

This framework can be extended to fuse high-dimensional heterogeneous descriptors. Feature space fusion and operator fusion are two approaches to tackle this problem (Cloninger et al., 2013). The first strategy consists of finding a common eigen basis to the multiple eigen spaces associated to each input feature. This can be done by joint diagonalization of Laplacians (Eynard et al., 2015; Dodero et al., 2014) or changing basis (Coifman and Hirn, 2014). However, none of these methods allows determining the relative optimal contribution of each input feature to the final result.

The approach presented in this paper belongs to the second category and consists in fusing different features at the operator level. It builds upon a recently proposed framework, known as multiple kernel learning (MKL) (Lin et al., 2011). By a combination of feature-based kernels, it allows optimally fusing heterogeneous information and weighting the contribution of each input to the final result. Several supervised examples that applied this technique to clinical applications are found in the literature (Tiwari et al., 2013; Castro et al., 2014). It has to be noted that the formulation of Lin et al. (2011) is a broad point-of-view to the MKL problem, originally introduced for the supervised problem of a support vector machine (SVM) (Lanckriet et al., 2004; Rakotomamonjy et al., 2008). Despite the high discriminative power of these kinds of approaches, unsupervised methods are more suitable for our application, for two reasons. First, they are more suitable to extract the hidden structure of the data (data spread), which has proven to correlate with disease in several applications (Wolz et al., 2012; Ye et al., 2014). Second, their result is not influenced by possibly incorrect labels from ambiguous diagnosis.

In addition, our approach allows determining the optimal weight to attribute to each feature. Other methods also pursue a similar objective. Automatic Relevance Determination (Neal, 1996) is a Bayesian approach that aims at selecting features of interest among a larger set of features. Nonetheless, its decision is categorical, while MKL proposes a relative weighting of the different features. Relevant Component Analysis (Shental et al., 2002) adopts a slightly different philosophy, being a semi-supervised approach where irrelevant data variability is reduced while the relevant one is amplified. However, it requires a priori knowledge about the content of the input, which makes this approach inappropriate for unsupervised analysis.

1.2. Heart failure with preserved ejection fraction

We apply our methodology to characterize myocardial velocities in the context of HFPEF. This syndrome presents signs of heart failure but still maintains the ejection fraction (EF) within a normal range. Left ventricular diastolic dysfunction has been identified as one of the leading mechanisms causing it (Paulus et al., 2007; Erdei et al., 2014). Nonetheless, recent studies suggest that HFPEF is a rather heterogeneous condition consisting of several pathophysiological subtypes (Lekavich et al., 2015; Shah et al., 2014). The current diagnosis relies on simple measurements (Paulus et al., 2007), such as EF and E/e' (ratio of the early transmitral flow velocity by pulsed Doppler and the early mitral annular velocity by myocardial velocity imaging). This leads to a suboptimal characterization, since these parameters do not entirely capture the complexity of the observable mechanical abnormalities (Erdei et al., 2014; Santaularia-Tomas and Abraham, 2009; Tan et al., 2009). Thus, there is still a need for an improved understanding of the syndrome. This challenge is not limited to the HFPEF syndrome, as the limitations of peak or time-to-event measurements have been largely discussed in other cardiac applications (Fornwalt et al., 2009; Fornwalt, 2011). In our work, the analyzed data are velocity traces measured from a stress protocol, where subjects are examined while performing exercise on a semi-supine bicycle. This modality has been recommended in many clinical studies to assess HFPEF (Erdei et al., 2014; Donal et al., 2016). The idea behind it is that signs and symptoms may only be revealed during exercise. In this regard, we implement a technique that enables to jointly analyze these data at different stress stages. This results in a tool to support clinical diagnosis and to uncover mechanical inter-relations, not necessarily noticed before.

1.3. Proposed approach

In this paper, we illustrate the usefulness of fusing different high-dimensional descriptors to improve the characterization of HFPEF. Our work is based upon the unsupervised MKL method introduced in (Lin et al., 2011). We explicitly detail its formulation and adapt its optimization towards the data spread rather than towards classification (e.g., healthy or diseased). This allows us to study the variability of velocity patterns—which is our primary objective. Therefore, our method differs from other supervised attempts to characterize the HFPEF syndrome (Shuai et al., 2011; Zordoky et al., 2015) since we do not compromise the learning process by involving possibly unreliable labels. In our case, the agreement with clinical labels only serves to determine the configuration and parameters of the algorithm and to check the coherence of the data spread. Previous works have derived an unsupervised formulation of the MKL problem (Tzortzis and Likas, 2012; Zhuang et al., 2011). Tzortzis et al. used it to learn a robust ensemble kernel that ultimately leads to a clustered space in which to perform classification. On the contrary, based on a Laplacian formulation, we seek to preserve the distribution of the data as a continuum, which still provides distance tools to perform inter-subject comparisons and variability analysis. Zhuang et al. used unsupervised MKL in combination with kernel PCA for dimensionality reduction. However, both the MKL and the dimensionality reduction steps were executed separately, whereas our formulation jointly optimizes them. In terms of application, Zhuang et al. also focused on classification, whereas we prioritise the variability analysis. Our method makes