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Quantification of local changes in myocardial motion by diffeomorphic registration via currents: Application to paced hypertrophic obstructive cardiomyopathy in 2D echocardiographic sequences

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ABSTRACT

Time-to-peak measurements and single-parameter observations are cumbersome and often confusing for quantifying local changes in myocardial function. Recent spatiotemporal normalization techniques can provide a global picture of myocardial motion and strain patterns and overcome some of these limitations. Despite these advances, the quantification of pattern changes remains descriptive, which limits their relevance for longitudinal studies. Our paper provides a new perspective to the longitudinal analysis of myocardial motion. Non-rigid registration (diffeomorphic registration via currents) is used to match pairs of patterns, and pattern changes are inferred from the registration output. Scalability is added to the different components of the input patterns in order to tune up the contributions of the spatial, temporal and magnitude dimensions to data changes, which are of interest for our application. The technique is illustrated on 2D echocardiographic sequences from 15 patients with hypertrophic obstructive cardiomyopathy. These patients underwent biventricular pacing, which aims at provoking mechanical dyssynchrony to reduce left ventricular outflow tract (LVOT) obstruction. We demonstrate that our method can automatically quantify timing and magnitude changes in myocardial motion between baseline (non-paced) and 1 year follow-up (pacing on), resulting in a more robust analysis of complex patterns and subtle changes. Our method helps confirming that the reduction of LVOT pressure gradient actually comes from the induction of the type of dyssynchrony that was expected.

1. Introduction

1.1. Comparison of myocardial motion patterns

1.1.1. General context and methods

The study of cardiac function in current clinical practice and research relies on the extraction of pathophysiologically-relevant features from image sequences. Dynamic markers of common use consist of myocardial displacement, velocity, strain and strain rate (Bijnens et al., 2009, 2012). Their estimation results from the propagation of cardiac wall segmentations along the cycle. This is achieved by means of $2D/3D+t$ segmentation techniques or non-rigid registration along image sequences (Tobon-Gomez et al., 2013; De Craene et al., 2013), or speckle-tracking, which predominates in echocardiography (Duchateau et al., 2013a; Jasaityte et al., 2013). An extensive clinical review is given in Cikes et al. (2010) in the concrete case of our application: hypertrophic cardiomyopathies.

However, the complexity of the myocardial motion/strain patterns, and inter-subject differences in size and timing of the heart limit the use of such techniques (Fornwalt, 2011). Studies focus on individual qualitative descriptions or on single quantitative indices describing part of the patterns (time-to-event and regional/local single values, mainly).

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In contrast, we believe that quantitative comparison of patterns is possible at a more comprehensive level by the use of computational anatomy techniques (Miller and Qiu, 2009). This requires to normalize the studied data to a reference system of spatiotemporal coordinates, as settled in statistical atlas applications (Duchateau et al., 2011). *Anatomical normalization* generally builds upon parallel transport techniques (Qiu et al., 2009; Duchateau et al., 2012a; Lorenzi and Pennec, 2013). *Temporal normalization* addresses possible variations in the length of the cardiac cycle and its intrinsic physiological phases (Perperidis et al., 2005; Duchateau et al., 2011; Russell et al., 2012). In the present paper, we build upon these concepts for normalizing the data prior to any quantitative comparison (baseline and follow-up data, and inter-subject comparisons).

1.1.2. Voxel-based vs. pattern-based comparisons

Despite these advances, the pattern analysis is still descriptive and often performed through a voxel-based representation. On the contrary, the purpose of our application (quantifying pattern changes in longitudinal studies) requires relevant *pattern-wise representations*. Attempts towards such representations mainly take into account inter-voxel dependences. They consist of global techniques for dimensionality reduction (Ashburner and Klöppel, 2011), as also applied to myocardial motion (McLeod et al., 2013), or eventually multiscale decomposition techniques (Lorenzi et al., 2013; Bhatia et al., 2014). Neighborhood graphs have been used to represent disease evolution on a population of cardiac motion patterns (Duchateau et al., 2012b), and may serve for the study of changes under the effect of time and treatment (Duchateau et al., 2013b).

Nonetheless, none of these techniques is explicitly designed for the estimation of changes between patterns, which is our primary interest here.

1.1.3. Methods specific to the recovery of changes

A first branch of methods builds upon Dynamic Time Warping (DTW) (Sakoe and Chiba, 1978). This consists in computing a correspondence matrix between the data to match, and estimating a warping of the data from the optimal path along this matrix. Variants include improved metrics (Sakoe and Chiba, 2009), refined construction of this path (Nielsen et al., 1998), and eventually the estimation of smoother warps (Zhou and De la Torre, 2012). However, these methods present several fundamental drawbacks for our application: (i) as warping techniques, their robustness towards very different shape evolution behaviors (as encountered in our data, Section 3.2.2) may be limited; (ii) they assume that all parts of the anatomy evolve at the same speed along the cardiac cycle, which is not the case in our application. Neighboring locations along the myocardium may have a close behavior but evolve differently; and (iii) finally, they are based on landmark correspondences, while more robust features such as measures or currents have been proposed to overcome the limits of landmark matching (Glaunès, 2005).

We prefer to build upon the principles of *deformation-based morphometry* (Ashburner and Friston, 2003; Ashburner et al., 1998). This consists in analyzing the warping necessary to match different data, coming either from different subjects or from the longitudinal study of a single subject. We apply this strategy to the matching of functional data (myocardial motion), which we manage as smooth spatiotemporal shapes (Sections 2.1.1 and 2.2). We preferred a generic surface matching approach that is diffeomorphic (Trouvé, 1998) to prevent any folding in the data correspondence. Indeed, by nature, the cardiac anatomy cannot fold. The functional data patterns attached to it may change under the therapy, but such functional data still should be warped in a way compliant with the anatomy, and therefore diffeomorphic.

The registration scheme uses currents (Glaunès, 2005; Vaillant and Glaunès, 2005; Durrleman et al., 2009, 2011). In this way, surfaces are compared without the need for point-to-point correspondences. Additionally, this makes the registration robust to changes in parametrization and physiological behavior (concavity/convexity mainly, which are very likely to happen in our application).

1.1.4. Towards a generic transformation model?

Other registration-based approaches for the matching of dynamic series are extensively discussed in Durrleman et al. (2013) for atlas building purposes. The relevance of this work is twofold for our application. First, it builds upon shape warping and fitting via continuous diffeomorphic transformations from the large deformation diffeomorphic metric mapping (LDDMM) framework (Beg et al., 2005; Miller et al., 2002). This aspect is shared by the registration via currents that we use (Glaunès, 2005). Then, it settles the foundations of a generic framework for the statistical analysis of dynamic shape evolutions. The objectives of our study (comparison of individual shape evolutions between baseline and follow-up) present similarities with the comparison of growth scenarios targeted in Durrleman et al. (2013).

For the comparison of growth scenarios, the authors recommend a subject-specific approach. This leads to a transform model that separates the problem into the recovery of a purely spatial transform $\Phi_{space}(\mathbf{x})$ and a purely temporal one $\Phi_{time}(t)$, namely: $\Phi(\mathbf{x},t) = \left(\Phi_{space}(\mathbf{x}), \Phi_{time}(t)\right)$. This model seems adequate for longitudinal studies in neuroimaging or evolution scenarios, where one can assume that $\Phi_{time}(\mathbf{x},t) \approx \Phi_{time}(t)$, namely that different parts of the anatomy evolve at the same speed (e.g. age or time along the longitudinal study). The spatial transform is assumed independent from time, namely: $\Phi_{space}(\mathbf{x},t) \approx \Phi_{space}(\mathbf{x})$. Such hypotheses are not valid for our application: for the study of changes along cardiac sequences, different parts of the anatomy may clearly evolve at different speeds (e.g. the septal and lateral walls). Thus, we think that considering spatial and timing changes together, with the most general form of transformations $\Phi(\mathbf{x},t)$ can be more relevant to our application.

Nonetheless, this model has higher complexity, and cannot be directly used as such for a statistical analysis. Thus, we introduce a priori to our model through scaling factors on each dimension of the input data. This serves for conditioning the problem to solutions relevant for our application, as detailed further in Section 2.

1.2. Hypertrophic obstructive cardiomyopathy

Hypertrophic cardiomyopathy (Gersh et al., 2011) is a genetic disease that alters the cellular contractility of the cardiac muscle, leading to myocyte hypertrophy and larger wall thickness of the myocardium, typically at the left ventricle. Altered contractility first implies a decrease in the local myocardial contraction, and is accompanied by changes in the myocardial geometry (hypertrophy of affected segments). The hypertrophic septum may provoke in some patients a severe obstruction of the left ventricular outflow tract (LVOT). This may severely alter the cardiac pump performance, increase LV pressure and wall stress, and the risk of sudden death due to myocardial fibrosis and arrhythmia induction (Maron et al., 2003).

Biventricular pacing has been suggested as a potential alternative to surgery to reduce the obstruction (Berruezo et al., 2011; Vatasescu et al., 2012). This is the treatment received by the patients of our study. The aim of this process is to provoke a controlled mechanical dyssynchrony in the ventricles, so that the local geometry at the LVOT is changed, and the temporal window