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Executive Summary of the Thesis

# Reconstruction of right ventricle morphology and displacements by merging time resolved MRI series

Laurea Magistrale in Biomedical Engineering - Ingegneria Biomedica

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## 1. Introduction

Cardiovascular Diseases (CVDs) represent the principal cause of death globally: their investigation can be enriched by use of computational modelling, useful for diagnostic purposes and surgical planning, especially in pathological case as Tetralogy of Fallot (ToF), characterized by anomalies in the cardiac structure that lead to dilation and dysfunction especially of cardiac right ventricle (RV). Among cardiac chambers, the most investigated is usually the left ventricle (LV): less studies have been concentrated in the past on RV, but its crucial clinical role has recently emerged. Indeed, it is involved in different clinical scenarios as reduced RV functionality in non-survivors to COVID-19 or pulmonary hypertension. Three-dimensional reconstruction of RV can be used as a tool for evaluation of its structure and functionality: clinically relevant parameters, as Ejection Fraction and Stroke Volume, can be computed, from volumes at end-systolic and end-diastolic phase, to analyze patient-specific models and *image-driven* CFD simulations can be carried out. Actually, to obtain an accurate model of RV is more challenging with respect to LV reconstruction: while left ventricle presents an ellipsoidal shape with cross-sections keeping a circular shape along the main axis, RV is more complex, having great cross-sectional variations from base to apex and triangular shape that becomes wrapped around left ventricle in the basal portion. Moreover, RV is characterized by higher volume, with thinner free-wall due to lower working pressure, more coarse trabeculations and fiber arrangement that accentuate the longitudinal shortening, with respect to rotational and torsional movement of the LV at ejection phase. 3D reconstruction is based on segmentation, corresponding to anatomical contours tracing of medical images, where the gold standard imaging technique for evaluation of cardiac function is represented by Magnetic Resonance Imaging (MRI), with respect to echocardiography that can be less accurate and Computer Tomography that uses ionizing radiation. Also, MRI can capture motion of cardiac ventricles: cine-MRI series can be obtained in standard acquisitions as Short-Axis (SA) and Long-Axis (LA) that respectively represent the cross-sectional views along the main ventricle axis and its perpendicular direction. In case of Tetralogy of Fallot, specific acquisitions can be used for monitoring of dilation of aortic structures and annulus of

tricuspid valve (TV), respectively as Short-Axis Aortic Valve (SA-AV) and Rotational-TV (TV-R). Their corresponding planes are respectively the perpendicular one with respect to the aortic valve plane and rotating planes around the axis connecting RV apex to the TV. The majority of segmentation techniques are based on exclusive use of short-axis acquisitions and usually applied to left ventricle. Given this scenario, the present work aims to obtain accurate three-dimensional reconstructions of right ventricle, in healthy and pathological cases, with merged information using multiple time-resolved cine-MRI series and increased automatization of segmentation process with use of Multi-Series Morphing technique, developed by F. Renzi at Politecnico of Milano, compared with a standard reconstruction technique, which utilizes only SA acquisitions.

## 2. Reconstruction techniques

### 2.1. Standard reconstruction techniques

Standard reconstruction techniques, which use only short-axis acquisitions (see Section 1), are usually applied on left ventricle. In this work, a general application of a standard reconstruction technique is described, inspired by the strategy used in [1] only for LV. In particular, a semi-manual segmentation is performed on slices of the SA cine-MRI series to delineate endocardium of RV: on each frame, contours are performed manually on some arbitrary slices, after which the 3D interpolation of them is performed to obtain a preliminary surface. The interpolated surface needs manual adaptation to accurately represent the ventricle: by comparison with all cine-MRI series, local modifications on the surface can be generated for this purpose. Obtained the final model, with eventual smoothing and remeshing of the surface, manual generation of tricuspid valve and pulmonary valve can be carried out. From an extraction of endocardial surfaces, tentative epicardial surfaces can be obtained and connected with suitable connection algorithm, to generate an attempted myocardial surface. From myocardial models, that can be obtained for each frame to reconstruct the whole cardiac cycle, RV motion over the cardiac cycle can be reconstructed with a registration process using the implemented algorithm in Elastix [3], based on a multi-resolution approach. Starting from generation of artificial level-set images of the 3D myocardia, a non-rigid B-spline-based transformation is used to spatially align a moving image with respect to a reference one, chosen by the user. Quality of the transformation depends on the cost function, defined by Mutual Information between reference and moving images, with an added constraint as bending energy for regularization term. As image sampler, grid with four values of spacing in a specific range is considered, with use of a Gaussian smoothing filter without downsampling applied. Adaptive stochastic gradient descent is a suitable choice as optimizer [4]. A 3d vector field represents the output of the registration procedure, that can be evaluated on every point of endocardial surfaces during the entire cardiac cycle to obtain endocardial shapes and displacements.

### 2.2. Multi-Series Morphing technique

The Multi-Series Morphing (MSMorph) technique, developed by F.Renzi, relies on the use multiple cine-MRI series to generate accurate three-dimensional models of cardiac ventricles: basing on the level of merged cine-MRI series, different variants of the technique, as MSMorph I, MSMorph II and MSMorph II, can be defined, all representing an attempt to overstep the limiting use of exclusively short-axis acquisitions of standard reconstruction techniques, described in 2.1: in the specific case of RV reconstruction, SA images (see Section 1) can be defective in detecting some characteristics as the longitudinal shortening of the RV. The MSMorph technique includes as first step the semi-automatic generation of contours and as second step the generation of the endocardial surface by morphing, as the MSMorph name suggests. Both these processes are useful to reduce the time employed in the reconstruction procedure. Considering the first step of the method, we consider that total segmentation has to be performed on each slice and for each frame of cine-MRI series included: the number of frames is given by the ratio of acquisition times $t_n$ and the time-resolution $\tau_{cMRI}$ of each series. For simplicity of exposure we consider the $k$ index as the total

number of slices at disposal, which increases as more cine-MRI series are taken into account, and the $n$ index as number of frames, variable between 0 and maximum value N= T/$\tau_{cMRI}$, with T heartbeart duration. The semi-automatic segmentation of MSMorph technique consists in an initial manual segmentation on a fixed frame $\tilde{n}$ identifying a specific acquisition time $t_{\tilde{n}}$ for each $k$ at disposal: an initial set $\Gamma_{\tilde{n}}$ is created, to be the reference configuration of the automatic registration process, with which all other contours $\gamma_{n,k}$ for every $n$ different from $\tilde{n}$ on every slice $k$ are generated. A multi-resolution approach with 4 levels is adopted in the registration process, based on a non-rigid registration algorithm implemented in the Elastix software [3]. We consider a non-rigid B-spline based transformation $T_{n,k}$ that spatially align the grey-level functions $\Upsilon_{n,k}$, with choices for registration components defined: cost function chosen to be a Mutual Information defined in [5] based on a continuous differentiable function of the parameters of registration using Parzen windows with regularization term defined by a smoothness constraint; grid-spacing can vary in a specific range in the two dimensions with Gaussian smoothing filter without down-sampling applied; standard gradient descent as most suitable optimizer. In this particular registration procedure, spatial alignment is performed on each slice backward and forward applying different transformations for respective $n$ parameter evolution with respect to $\tilde{n}$, where contours are already defined: $T_{f\,n,k}$ for forward alignment with n = $\tilde{n}$ + 1, ... , N and $T_{bn,k}$ for backward alignment with n = 0, ... , $\tilde{n}$ - 1. From the registration process, trasformation $T_{n,k}$ is obtained and applied to endocardial contours for each $k$, as represented in Figure 1. At


Figure 1: Scheme of application of the forward and backward transformations, respectively $T_{f\,n,k}$ and $T_{bn,k}$, in the procedure for automatic registration (see Section 2.2) of contours $\gamma_{n,k}$ (red lines).

the end of the registration process, $N$ total contours sets are obtained: for each n, a contours set is represented by the sum of all contours $\gamma_{n,k}$ generated for each $k$. Contours sets are then used in the second step of surface generation by morphing: the concept of morphing is based on the transformation of one object, target, into another object, source. In case of meshes, creating a vertex correspondence used to generate intermediate models. In the specific MSMorph technique each set of contours can be used, as a target surface, to morph a source template $\Sigma$ towards the same configuration. For ventricle reconstructions, a sphere can be utilized as template for each frame considered. The template is independent of $n$ index, above defined in this section. Through implementation of an iterative algorithm, defined in [4], the summarizing description of the procedure is given as follows: first, a projection of points cloud $\Gamma_n$, that generates a points cloud $\Theta_n$ defined on the source $\Sigma$ is generated. Then, is performed the computation of difference of coordinates between points of $\Gamma_n$ and closest points of the surface projection $\Theta_n$, found with point location algorithm: this step bring to the creation of vectorial array for distance field $g_{n,k}$. Progressively, a harmonic function is built on the distance field $g_{n,k}$ leading to extension of the solution to the entire surface $\Sigma$ by solving the vectorial Laplace-Beltrami problem: consequential computation of harmonic distance $d_{n,k}$ as vectorial array is performed. A moving average smoothing is applied to data: the subset size for the smoothing coincides to the element patch of each node in the Finite Elements representation. Vertex correspondence between contours set and surface is created with the projection of resulting harmonic array onto the surface. Then, warping filter based on the vertex correspondence is applied to create a deformation: a topological transformation is performed according to a scaling factor, user-defined, to obtain intermediate models. Lastly, remeshing of the intermediate model created is needed for adjustment of the surface mesh connectivity. All these steps described are executed for each $n$ for a certain number of k iterations in relation to a stopping criterion based on the maximum square distance value. As a result, N endocardial surfaces are morphed basing on the combination of contours set, eventually for each variant of the technique.

The same process of generation of valve's orifices and myocardial surfaces, with achievement of shapes and displacements, used in standard reconstruction techniques (see Section 2.1), can be performed on endocardial surfaces.

## 3. Results and Discussion

Datasets and patients are presented in Section 3.1, then results are displayed and analyzed in Section 3.2. Analysis of accuracy and efficiency of Multi-Series Morphing technique (see Section 2.2) is carried out in Section 3.3.

### 3.1. Time-resolved cine-MRI series at disposal

MRI series that have been used in the segmentation process were provided by the Division of Radiology of University Hospital of Verona, Verona, Italy. The achievement of acquisition was carried out using the Achieva 1.5T (TX) - DS (Philips, Amsterdam, Netherlands) technology: the in-plane homogeneous space can vary in the different types of acquisitions from 1.15 mm to 1.25 mm while thickness ranges from 5 mm to 8 mm [4]. We identify for the present work: Patient (A) as healthy patient and Patient (B) for patient affected by Tetralogy of Fallot, surgically repaired (rToF). Cine-MRI series (see Section **??**) at disposal for Patient (A) and (B), with corresponding number of slices, are now listed:

- Patient (A)
  - Short Axis (SA) volumetric series: 21 slices.
  - Long-Axis (LA) cine MRI series: 6 slices
  - Rotational-TV (R-TV) cine-MRI series : 18 slices
  - Short-Axis Aortic Valve (SA-AV) cine-MRI series: 6 slices
- Patient (B)
  - Short Axis (SA) volumetric series: 18 slices.
  - Long-Axis (LA) cine MRI series: 6 slices

In particular for this work, given data sets at disposal, we consider MSMorph II and MSMorph III variants (see Section 2.2) as including respectively SA, LA, SA-AV and SA,LA acquisitions. For patient A, models have been obtained with these MSMorph variants and also with a standard reconstruction technique (see Section 2.1), while for Patient B only MSMorph III technique has been used.

### 3.2. Analysis of ventricle's reconstructions

Application on patient A of MSMorph II and MSMorph III (see Section 3.1) generates smoother models with respect to standard reconstruction (see Section 2.1), as can be observed in Figure 2. The tendency for all models is to increase in volume towards the diastolic phase, as expected, with an evident accentuation of the RV dilation in models of Patient B, due to the effects of Tetralogy of Fallot on the ventricle: this brings to an endocardial displacement field that is lowered with respect to the models of Patient A in the end-systolic phase. In particular, ventricular volumes in time have been carried out along the cardiac cycle for both patients A and B: as displayed in Figure 4, MSMorph applications generates less fluctuations in the evolution of volumes, reflecting a more physiological behaviour with respect to standard reconstruction technique. Also from analysis of ventricular volumes, the RV dilation is confirmed by the much higher ventricular volume of Patient B.

Clinically relevants parameters for all right ventricle's reconstructions, obtained and displayed in Table 1, resulted to be aligned, for healthy patient A, with healthy reference values found in literature, in particular referring to [2]. Parameters computed for Patient B in Table 1 defer as expected from reference values for healthy subjects with higher values of end-diastolic and end-systolic volumes and lowered ejection fraction: Tetralogy of Fallot, of which Patient B is

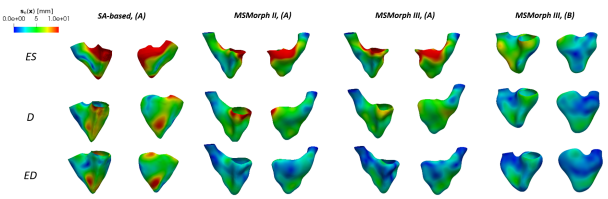


Figure 2: Reconstructions of right ventricle in three cardiac phases displayed in rows: End-Systole (ES), Diastasis (D), End-Diastole (ED). Double columns, displaying two different views, are related to different techniques, where in brackets patients (see Section 3.1) are specified. SA-based: standard reconstruction technique (see Section 2.1).

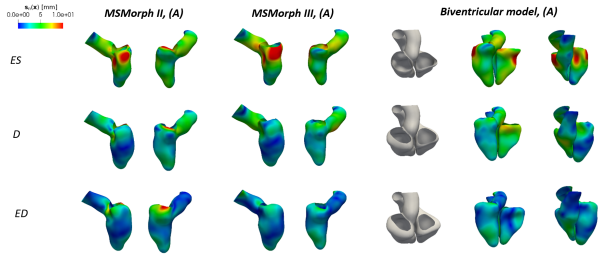


Figure 3: Patient A, left ventricle and biventricular model:in rows from top to bottom are displayed models in three cardiac phases as End-Systole (ES), Diastasis (D), End-Diastole (ED). Double columns, displaying two different views of endocardial displacement, are related to MSMorph II and MSMorph III. The three columns on the right display the biventricular model in three different views: a morphological representation (left) and two views of displacement field (center and right).

affected, causes RV dilation with impaired RV systolic function. For Patient A, introduced in

| Index | SA,(A) | II,(A) | III,(A) | III,(B) |
|---|---|---|---|---|
| $EDVi[mL/m^2]$ | 94.1 | 92.5 | 90.2 | 178.7 |
| $ESVi[mL/m^2]$ | 51.2 | 57.1 | 55.6 | 127.5 |
| $SVi[mL/m^2]$ | 42.8 | 35.4 | 34.6 | 51.2 |
| $EF[\%]$ | 45.5 | 38.3 | 38.3 | 28.6 |

Table 1: RV clinical parameters. EDVi: End-Diastolic Volume indexed, as EDV normalized by BSA. ESVi: End-Systolic Volume indexed, as ESV normalized by BSA. SVi: Stroke Volume indexed, as SV normalized by BSA. In first row, symbols of the technique applied are present, each followed by the letter defining the patient (see Section 3.1) in brackets: II for MSMorph II, III for MSMorph III and SA for standard reconstruction. SA-based: standard reconstruction technique.

Section 3.1, as MSMorph II and MSMorph III were applied also to left ventricle (LV), biventricular models could be obtained: shape and displacement field of LV and biventricular models are displayed in Figure : the same tendency of increased volume in end-diastolic phase and increased endocardial displacement is observed. Time evolution of LV ventricle models is also obtained and displayed in Figure 5, with less fluctuations in MSMorph II with respect MSMorph III due to the majority of information merged.

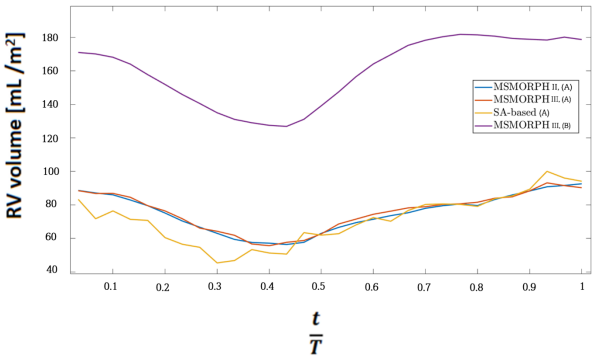


Figure 4: Time-evolution of RV volumes, normalized by Body Surface Area (BSA). The x axis represents the acquisition times normalized by heartbeat duration (T). The legend represents the name of the technique applied, followed by patients (see Section 3.1) in brackets. SA-based: standard reconstruction technique (see Section 2.1).

### 3.3. Analysis of accuracy and efficiency of Multi-Series Morphing technique

Analysis of accuracy and efficiency of MSMorph technique were carried out considering models of Patient A (see Section 3.1): accuracy is analyzed considering the discrepancy between MSMorph (see Section 2.2) results, both contours sets and models, and gold standard contours, traced completely manually for Patient A and provided by F. Renzi; efficiency was evaluated comparing time employed for reconstruction process for MSMorph variants and a standard reconstruction technique (see Section 2.1). For accuracy evaluation, distance between contours sets obtained with MSMorph technique and gold standard contours is evaluated: Mean Square Distance (MSD) is computed to evaluate accuracy of the automatically obtained set of contours, with evolution in time displayed in Figure 6. Also, Time Average Mean Square Value was computed to evaluated the accuracy of morphed surface with respect to gold standard contours sets: values of TAMSD are shown in Table 2. Values of TAMSD and MSD obtained are both close to the in-slice resolution of 1.15 mm, with better accuracy obtained for MSMorph variants with respect to standard technique (SA-based). If the discrepancy in the accuracy is slight, the efficiency of the MSMorph technique was evaluated in terms of reconstruction time employed,

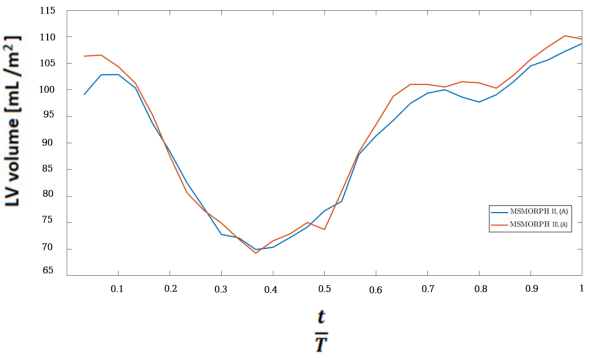


Figure 5: Time-evolution of LV volumes, normalized by Body Surface Area (BSA). The x axis represents the acquisition times normalized by heartbeat duration (T). The legend represents the name of the technique applied, followed by patients (see Section 3.1) in brackets. SA-based: standard reconstruction technique (see Section 2.1).

| SA-based | MSMorph III | MSMorph III |
|---|---|---|
| 1.75 mm | 1.61 mm | 1.57 mm |

Table 2: Values of square root of TAMSD computed for different techniques. SA-based: standard reconstruction technique (see Section 2.1; MSMorph II, III: variants of MSMorph technique (see Section 2.2).

only for endocardial surface reconstruction in particular as other processes are common in the two methods of MSMorph technique and standard reconstruction technique (see Sections 2.1 and 2.2). Accounting for SA-based technique, the total amount of time needed for generation of models of the whole cardiac cycle was computed to be 30 hours, with, for each of the 30 surfaces, 15 minutes for manual contouring and 45 minutes for manual adaptation. A decreased value of 10.5 hours and 13.5 hours was used for application of MSMorph III and MSMorph II techniques respectively: carried out with a virtual machine with 2 processor cores and 4GB of RAM, the first step of manual contouring and registration process the MSMorph technique (see section 2.2) took respectively 8 hours and 11 hours while second step of surface generation by morphing was computed to be about 2,5 hours for each variant. Given this analysis, MSMorph variants reduced the reconstruction time of nearly 55%-65% with respect to a standard technique.

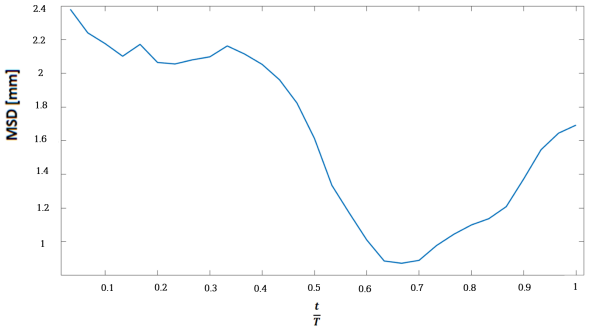


Figure 6: Time evolution of the Mean Square Distance between gold standard contours (see Section 3.3) and semi-automatically obtained contours with MSMorph technique (see Section 2.2) along the cardiac cycle. The x axis represents the acquisition times normalized by heartbeat duration (T).

## 4. Conclusions

Right ventricle's reconstruction represent an active and challenging field of research for morphological complexity of this cardiac chamber: accurate three-dimensional models can be obtained using the efficient Multi-Series Morphing (MSMorph) method that relies on multiple use of time resolved MRI series to obtain endocardial shape and displacement field. The efficiency of the MSMorph technique, increased by the use of semi-automatic segmentation process, allowed also to generate specific biventricular models, useful for analysis of inter-ventricular interactions. Moreover, the utilization of only short-axis acquisition typical of standard reconstruction techniques, potentially defective for RV reconstruction especially in presence of Tetralogy of Fallot, can be overcome by merging different cine-MRI series. Further improvements could be introduced with application of the MSMorph technique to a bigger cohort of patients and performing of image-driven CFD simulations on the models obtained.

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