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PATIENT-SPECIFIC GENERATION OF THE PURKINJE NETWORK DRIVEN BY CLINICAL MEASUREMENTS: THE CASE OF PATHOLOGICAL PROPAGATIONS

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ABSTRACT

To describe the electrical activity of the left ventricle is necessary to take into account the Purkinje fibers, responsible for the fast and coordinate ventricular activation, and their interaction with the muscular propagation. The aim of this work is to propose a methodology for the generation of a patient-specific Purkinje network driven by clinical measurements of the activation times acquired during pathological propagations. In particular, we consider clinical data acquired on four subjects suffering from pathologies with different origins, from conduction problems in the muscle or in the Purkinje fibers to a pre-excitation ventricular syndrome. To assess the accuracy of the proposed method, we compare the results obtained by using the patient-specific Purkinje network with the ones obtained by using a not patient-specific network. The results showed that the mean absolute errors are reduced by a factor in the range 27%-54%, highlighting the importance of including a patient-specific Purkinje network in computational models.

INTRODUCTION

The development of biophysical patient-specific models of the human heart is crucial to gain better insight on the mechanisms regulating its activity and to provide the clinicians with a powerful instrument for diagnosis and therapeutic design. A key aspect is the study of the electrical activation, that triggers the heart contraction, and which is regulated by the cardiac conduction system (CCS), responsible for the fast and coordinated distribution of the electrical impulse in the heart [1]. In particular, the ventricular activation is regulated by the peripheral part of the CCS, the Purkinje fibers (PF), located in the inner ventricular walls of the heart, just beneath the endocardium. In a healthy propagation, the electrical signal, coming from the atrio-ventricular node, spreads rapidly in the PF and enters the ventricular wall at certain insertion sites, called Purkinje muscle junctions

(PMJ) [2]. From these sites the depolarization wave propagates in the myocardium, allowing the ventricular excitation and contraction thanks to the activation of the cardiac muscle cells [3].

Mathematical and computational models of cardiac electrophysiology can predict the electrical activity in the ventricles, thus providing useful indications to the clinicians to improve both the diagnosis [4,5] and the therapies [6, 7]. The inclusion of PF in such models is therefore essential to simulate the ventricular excitation. A computational strategy for the generation of a patient-specific Purkinje network starting from available clinical data consisting in the activation times in some points of the endocardium of the left ventricle was presented in [8]. In particular, such a method is based on locating the PMJ in such a way to improve the accordance with the clinical data. This strategy has been applied in [9] to some real cases characterized by healthy activations, highlighting the improvement of the accuracy obtained by using the patient-specific network with respect to other models known in the literature, and then the main role of PF in the description of the electrical propagation.

In this work we apply the computational algorithm for the generation of a patient-specific Purkinje network presented in [8] to patients affected by pathological propagations. In particular, we consider clinical data acquired on four subjects, one characterized by the presence of scar tissue due to an old myocardial infarction, another one suffering from dilated cardiomyopathy with a Left Bundle Branch Block (LBBB), and the last two suffering from the Wolff Parkinson White (WPW) syndrome. To assess the accuracy of the proposed method, we compare the results obtained by using the generated patient-specific network with the ones obtained by using a network generated without using the clinical data. The results show the applicability and reliability of our method also in pathological cases and the essential role played by patient-specific networks in computational models to obtain an accurate description of the electrical activation in the left ventricle.

METHODS

Patient-specific clinical measurements

Description of the patients

Four patients have been considered in this study: a 66-years-old individual with an old myocardial infarction and a characteristic apical aneurysm (subject 1); a 66-years-old individual with a dilated cardiomyopathy leading to LBBB (subject 2); a 46-years-old and a 45-years-old individuals with the WPW syndrome (subjects 3 and 4).

Both subjects 1 and 2 are characterized by an enlargement of the left ventricular chamber. For subject 1, such a condition is due to a previous myocardial infarction at the apex with a resultant scar formation and a loss of contractile function leading to a chamber dilation. For subject 2 the dilated cardiomyopathy causes the formation of fibrosis that affects the conduction property of the PF, leading to LBBB and to ventricular dyssynchrony. Subjects 3 and 4 suffered from a ventricular pre-excitation syndrome, the WPW syndrome, due to the presence of an anomalous pathway, the bundle of Kent, between the left atrium and the left ventricle, in absence of any structural heart disease.

Acquisition of imaging data and reconstruction of the endocardium geometry

Subjects 1 and 2 underwent an X-ray computed tomography (x-ray CT). The CT image of subject 1 has been acquired with a Philips CT scanner with 237 slices, with 512 × 512 pixels and voxel size equal to 0.429 × 0.429 × 0.7 mm^3. The CT image of subject 2 has been acquired with a Somatom Siemens CT scanner with 380 slices, with 512 × 512 pixels and voxel size equal to 0.429 × 0.429 × 0.6 mm^3.

Subjects 3 and 4 underwent a non-contrast enhanced 3D whole heart sequence, cardiac and respiratory gated, performed with a 1.5 Tesla MRI Unit (Magnetom Avanto, Siemens Medical Systems, Erlangen, Germany) and a 8 channel phased array torso coil. The following parameters have been used: voxel resolution=1.7x1.6x1.3 mm; TE (EchoTime)=1.46 ms; TR (repetition

Time)=269.46 ms; slice thickness=1.3 mm with 104 slices per single slab; acquisition matrix=256×173; flip angle=90°.

A manual segmentation of such geometries has been made by using the software ITK-SNAP 2.4.0 [10]. In particular, we reconstructed the endocardium of the left ventricle of subjects 1 and 2, and the whole myocardium of subjects 3 and 4.

Acquisition of electrical data

The electrical mappings of the endocardium of the left ventricle in the four subjects have been performed by means of the Ensite NavX system. This allowed to measure at several points of the endocardium the activation times, defined as the time at which the local QRS complex starts. Such measures have been acquired for all the subjects by inserting a 7 Fr deflectable electro-catheter through the right femoral artery with a retrograde trans-aortic approach (Medtronic Enhancr II 5523/ Medtronic Conductr). Such a catheter measures a local voltage, allowing to build the whole electrical mapping of the endocardium.

For subjects 1 and 2 we acquired an electrical mapping consisting in 193 and 200 measures, respectively. Instead, for subjects 3 and 4, two electrical mappings have been acquired, one before the ablation procedure to locate and then burn the anomalous pathway, and another one after the ablation to check the success of the therapy. In this way, for these subjects we have at disposal a mapping of the pathological electrical activity in presence of the anomalous pathway, and another one of the normal propagation restored after the ablation. In particular, for subjects 3 and 4 we acquired 141 and 100 measures, respectively, before the ablation procedure, and 151 and 102 measures, respectively, after the ablation.

Patient-specific generation of the Purkinje fibers

The PF form a subendocardial network characterized by a high conduction velocity V_p (3-4 m/s) and are isolated from the muscle, except at their endpoints, the PMJ, which are located on the

endocardium. Once the electrical signal has reached the PMJ, enters the ventricle with a delay of about 10-15 ms [11,12], and then it propagates in the ventricular muscle, with a slower conduction velocity V_m (0.3-1 m/s) (orthodromic propagation).

Due to the main role of the PF in the activation of the ventricle, in [8] we developed a new methodology for the generation of a patient-specific Purkinje network by using activation times measured on the endocardium of the patient at hand. The idea is to start from an initial network generated by means of a fractal rule [13], and to adapt the locations of the PMJ by maximizing the accordance with the clinical measurements. This method is based on the following two hypotheses:

Hp1) The propagation in the PF is not influenced by the propagation in the myocardium, so that the activation wave propagates uniquely from the Purkinje network to the myocardium through the PMJ [13];

Hp2) The activation in the myocardium does not influence the activation on the endocardium.

The first hypothesis implies that the use of an explicit algorithm to treat the problem given by the coupling between the PF and the myocardium is enough, whereas the second one allows us to consider only the propagation on the endocardium in the generation of the patient-specific Purkinje network. In [8,9] it has been proposed to use the isotropic Eikonal problem on such a surface to compute the activation times to be compared with the clinical measurements.

The hypotheses Hp1 and Hp2 hold true in the case of a healthy propagation [9]. However, more in general we observe that they hold true providing that the electrical activation is characterized by a front which enters the left ventricle uniquely through the PMJ or endocardial cells, independently of the integrity of the conduction system. In the following sections, we discuss how it is possible to use the method proposed in [8] in some pathological cases.

The case of old myocardial infarction (subject 1)

If no arrhythmia or electrical disease affecting the pathway of conduction are present (as happens for subject 1), then all the sources of the muscular activation are given by the PMJ and hence we can apply the algorithm for the generation of the patient-specific network presented in [8]. However, some remarks are mandatory. In particular, the myocardium of a patient with an old myocardial infarction is characterized by the presence of scar tissue, which replaces the healthy one in the region affected by the ischemic attack. This region is characterized by a reduced blood supply, resulting in the death of the muscular cells and thus in a progressive deterioration of the electrical activity. For this reason the muscle is no longer excitable in the scar region, and then we imposed a null conduction velocity on this portion of the endocardium [4]. The location of the scar region can be estimated during the electrical mapping, since the clinicians measure a null potential at the points belonging to the scar. Moreover, we assumed that the ischemic attack affects also the conduction property of the Purkinje network located in the scar region. In particular, in this region we set $V_m=0$ and V_p about four time smaller than the physiological value, supposing that the signal propagates, even if slowly, also in the portion of PF belonging to the scar region [14]. Then, to generate the Purkinje network of subject 1, we used the method proposed in [8] with spatial dependent conduction velocities on the endocardium and in the Purkinje network.

The case of dilated cardiomyopathy with Left Bundle Branch Block (subject 2)

The LBBB arose in subject 2 due to the fibrous tissue developed as a consequence of a dilated cardiomyopathy. A natural way to model LBBB is to impose a null conduction velocity V_p in the portion of the network characterized by the block, identified thanks to the clinical measures. Moreover, due to the presence of the conduction block, in this case the signal that activates the PF does not come from the AV node, but enters the left ventricle at the septum, through the PMJ activated by the signal coming from the right ventricle. Then, all the sources for the muscular activation are given by the PMJ, so that hypotheses Hp1 and Hp2 are satisfied and we could apply

the method developed in [8]. In particular, we considered a few endocardial sources, located at the points of the septum with the smallest activation times. Such measures represent the first points of the left ventricle reached by the wave front coming from the right ventricle. Then, to generate the Purkinje network of subject 2, we used again the method proposed in [8] with a spatial dependent conduction velocity in the Purkinje network.

The case of the Wolff-Parkinson-White syndrome (subjects 3 and 4)

The WPW syndrome is characterized by an accessory pathway between the left atrium and the left ventricle, the bundle of Kent. In this case, the hypotheses Hp1 and Hp2 are not in general satisfied, so that the algorithm proposed in [8] cannot be applied anymore. However, for subjects 3 and 4 we have at disposal also clinical measurements acquired after the ablation therapy, so related to a healthy activation. Since the therapy consists in the ablation of the anomalous path, it is reasonable to assume that the Purkinje network does not change after the therapy. Therefore, we used the clinical measurements acquired after the ablation to generate the patient-specific network with the method proposed in [8]. Then, we applied such a network to simulate WPW, by solving an anisotropic Eikonal problem in all the myocardium, accounting for the muscular fibers. Since we had no patient-specific information about the muscular fiber architectures, we generated them according to geometrical rules and anatomical knowledge [15,16,17].

Observe that the clinical measures are all located on the endocardium, so that it was not possible to use the measures to locate the intramyocardial pathway. For this reason, this has been modeled as a single activation, located in the point, among those where possibly the bundle of Kent enters the left ventricle, which guaranteed the best accordance with the measures acquired before the therapy.

We notice that for the case of WPW syndrome is important to consider also the antidromic propagation, that is the one from the muscle towards the PF, due to the premature muscular activation. This is characterized by a delay of the signal at the PMJ of about 2-3 ms [11].

RESULTS

In this section, we show the numerical results obtained by applying the strategy developed in [8] for the generation of a patient-specific Purkinje network to the pathological cases discussed above. The aim is to compare the measured activation times with those obtained by using both the patient-specific network and the network generated by means of a fractal rule, named in what follows as tentative network.

In Table 1, first two rows, we report the number of branches and PMJ for the tentative and for the patient-specific networks for each of the subjects, while in Figure 1 we depict both the networks. To obtain the tentative network we used a fractal rule where the length of the branches and the branching angle are described by Gaussian variables (mean value of the length=7.0 ± 0.3 mm for subject 1 and 4.0 ± 0.3 mm for subjects 2, 3 and 4, mean value of the angle=$60° \pm 1.8°$ for all the subjects).

In Figure 2 we show the activation times obtained by solving an Eikonal problem, and using the tentative and the patient-specific networks to provide the source terms. In particular, for subjects 1 and 2 we solved the isotropic Eikonal problem only on the endocardium, since they satisfy hypotheses Hp1 and Hp2, whereas for subjects 3 and 4 we solved the anisotropic Eikonal problem in all the myocardium, due to the presence of the anomalous pathway.

The conduction velocities in the network (V_p), on the endocardium (V_e), along the muscular fiber direction (V_f), and transverse to the muscular fiber direction (V_t), have been tuned in order to maximize the accordance with the clinical measures. Notice that for subjects 3 and 4 we did not estimate any endocardial velocity V_e, since we solved directly the Eikonal problem in the myocardium. We report for all the subjects such quantities in Table 1, third, fourth and fifth rows. We can notice that for all the subjects V_p falls in the physiological ranges 3.0-4.0 m/s, whereas only for subject 1 V_e is slightly outside the physiological range 0.3-1.0 m/s [18]. Moreover, we notice that the value of the estimated velocity along the fibers direction V_f falls in the physiological range 0.3-

1.0 m/s for patient 4, whereas it is slightly outside for subject 3. Finally, we notice that the estimated value of the velocity in the direction orthogonal to the fibers V_t satisfies for both subjects 3 and 4 the physiological condition V_f/V_t belonging to (1.5, 2.1). Regarding the muscular fibers architecture generated for subjects 3 and 4, we assumed that the transmural variation of the fiber direction is uniform, with an angle of -75° at the endocardium and +45° on the epicardium, for subject 3, and -60° at the endocardium and +45° on the epicardium, for subject 4 (an angle of +90° corresponds to a fiber pointing toward the apex of the ventricle). For subjects 1 and 2, we imposed a time delay at the PMJ of 10 ms in the orthodromic propagation, whereas for subjects 3 and 4, we imposed a time delay at the PMJ of 14 ms in the orthodromic propagation and of 3 ms in the antidromic propagation. Such values of the angles and of the delays have been chosen so to maximize the accordance with the clinical measures and are in physiological ranges reported in [16] and [12], respectively.

In order to assess the accuracy obtained by using the generated networks, for all the subjects we performed a cross-validation test. In particular, for subjects 1 and 2, we used 50% of the measures for the generation of the patient-specific network (training set), and the remaining measures to validate the networks (testing set). Instead, for subjects 3 and 4, we used all the clinical data acquired after the ablation procedure, related to a healthy activation, for the generation of the patient-specific network (training set), and the clinical data acquired before the ablation procedure for the validation of the networks, by simulating the WPW (testing set). In Figure 3 we show the absolute errors in the activation times between the measured data in the testing sets and the corresponding computed data. Moreover, in Table 2 we report the mean absolute errors in the activation time. From these results we observe that in all the cases the use of the patient-specific network allowed to improve the accuracy with respect to the one obtained with the tentative network. In particular, subject 1 highlights a very large improvement, the mean error being halved when using the patient-specific network. Regarding subjects 3 and 4, we observe a less good improvement in the accuracy when using the patient-specific network. This is strictly related to the WPW syndrome, as discussed later on.

Table 1. Number of branches and of PMJ, conduction velocities in the network (V_p), on the endocardium (V_e), along the muscular fiber (V_f) and transverse to the muscular fiber direction (V_t).

		Subject 1	**Subject 2**	**Subject 3**	**Subject 4**
Tentative network	**# branches**	2144	3068	2182	1500
	# PMJs	308	786	498	289
	V_p (m/s)	3.1	3.9	3.95	3.7
	V_e (m/s)	0.29	0.31	-	-
	V_f / V_t (m/s)	-	-	1.030/0.515	0.870/0.580
Patient-specific network	**# branches**	2047	2681	2121	1355
	# PMJs	211	399	437	144
	V_p (m/s)	3.1	3.9	3.95	3.7
	V_e (m/s)	0.29	0.31	-	-
	V_f / V_t (m/s)	-	-	1.030/0.515	0.945/0.630

To have a more accurate description of the error distribution, in Figure 4 we show the histograms representing the number of points N (over the total number) characterized by specific ranges of the error. These results confirm the improvement in the accuracy obtained with the patient-specific network. Again, we observe the significant improvement for subjects 1 and 2, and the less good improvement for subjects 3 and 4. For the latter subjects the points of the endocardium could be activated either by the Purkinje network or by the underlying muscle due to the anomalous pathway. Then, for such patients, we built the subset K of the testing set given by the points activated in our simulations by the networks, and the subset W given by the points activated by the front propagating from the anomalous pathway. In Table 3, we report the mean absolute errors related to each of these two subsets. These results clearly show that there is an appreciable improvement in the accuracy

when using the patient-specific network for the points activated by the PF (subset K), whereas no significant improvements are observed for the points activated by the anomalous signal (subset W).

Table 2. Mean absolute error for the four patients in the case of the tentative (up) and of the patient-specific (bottom) Purkinje networks.

	Mean absolute error (ms)			
	Subject 1	**Subject 2**	**Subject 3**	**Subject 4**
Tentative network	30.57 ± 27.91	24.85 ± 23.20	7.90 ± 6.19	9.69 ± 6.41
Patient-specific network	14.06 ± 15.52	15.44 ± 12.09	6.84 ± 5.38	7.59 ± 5.52

Table 3. Mean absolute error for the patients suffering from WPW on the subsets K and W in the case of the tentative and of the patient-specific Purkinje networks.

	Network	**Mean absolute error on K (ms)**	**Mean absolute error on W (ms)**
Subject 3	Tentative	8.76 ± 6.54	7.25 ± 5.82
	Patient-specific	6.38 ± 5.20	7.13 ± 5.47
Subject 4	Tentative	9.74 ± 6.53	9.58 ± 6.15
	Patient-specific	6.87 ± 4.99	8.68 ± 6.08

DISCUSSION

The case of old myocardial infarction

State of the art

The myocardial ischemia has been studied with computational models for over twenty years. The

first computational models of such a pathology studied the development of depressions in the ST segment of the electro-cardiogram due to the developing of ischemic currents at the interface between the damaged and the healthy cells [19,20,21]. More recent studies investigated the possibility to recover information on the size and location of the ischemic region from such depressions by solving an inverse problem [5,22]. The ischemic currents are developed during the plateau phase of the cell electrical activity, when all the muscle heart cells have been already activated. For this reason, the presence of the Purkinje network in the previous works has been neglected. Instead, if we are interested in modeling the ventricular activation to recover the QRS complex, it is mandatory to model the presence of the Purkinje network [14,23]. The only work, as far as we know, that included a (non-patient-specific) Purkinje network for the study of the ischemia is [11], where the authors studied the effect of such a network on the propagation of arrhythmias. Instead, in [3,24] surrogate models of the PF have been considered, by using a variable-in-space conduction velocity on the endocardium.

Discussion of the results

The results reported in Figures 3 and 4 and in Table 2 for subject 1 clearly show the big improvement when the patient-specific network is used to compute the activation times on the endocardium. In particular, the mean absolute error decreased by 54.0% with respect to the one obtained with the tentative network, with over 60% of the measures characterized by an absolute error less than 10 ms. Moreover, we observe the lack of PMJ in the patient-specific Purkinje network in the region opposite to the septum, just between the two big scar regions (see Figure 1, first row on the right). This probably reflects the fact that the Purkinje network is in fact a little bit damaged in that region, due to the vicinity of the infarction. Of course, the tentative network is not able to recognize such a damaged region, since it localizes the PMJ randomly. Accordingly, looking at Figure 2, first row, we can appreciate the difference in the activation pattern in the region opposite to the septum between the two networks, leading to different absolute errors in this region, as shown in

Figure 3.

These results show that our approach could be used successfully also in presence of a muscular conduction damage. In fact, we believe that really in presence of a muscular conduction problem our method could be mainly effective, since it is able to capture more evidently the specificity of the patient at hand.

The case of dilated cardiomyopathy with Left Bundle Branch Block

State of the art

The LBBB has been deeply studied computationally in the last years. In such studies the PF has been modeled either by imposing a high conduction velocity in the region of the endocardium in contact with the PF [7,25], or by an explicit construction of a (non-patient-specific) network [26,27]. In [6] the authors highlighted the importance of considering the presence of an explicit Purkinje network instead of surrogate models to obtain realistic pattern of activation also during the pacing of a cardiac resynchronization therapy device, frequently used to overcome the LBBB.

Discussion of the results

The results reported in Figures 3 and 4 and in Table 2 for subject 2 show a good improvement in the accuracy when the patient-specific network is used to compute the activation times on the endocardium. In particular, the mean absolute error decreased by 37.9% with respect to the one obtained with the tentative network, with about 40.0% of the measures characterized by an absolute error less than 10 ms.

These results show that our methodology can be applied also for the case of LBBB, being capable of detecting additional abnormalities in the electrical activation of the patient. However, we observe a little deterioration in the improvement of the accuracy with respect to the previous case. We believe that this could be ascribed to the simple model we used to describe the activation front coming from the right ventricle, and consisting in a few of sources localized on the septum. To overcome this

limitation, one should consider also the propagation in the right ventricle with, possibly, its Purkinje network. This is however beyond the scope of this paper, and it will be the subject of future works.

The case of the Wolff Parkinson White syndrome

State of the art

The WPW syndrome often leads to supraventricular tachycardia that needs to be treated with an ablation therapy [28]. Computational studies related to this pathology can be founded in [29], where a model of the WPW has been presented with the aim of analyzing the relation between the location of the intramyocardial pathway and the wave form of the ECG, and in [30], where the developing of supraventricular tachycardia as a consequence of WPW has been investigated. In both the papers, simplified not patient-specific models of the PF have been considered. In particular, in [29] about one thousand of sources of activation has been used with proper activation times to model the PMJ, whereas in [30] the conduction system has been modeled with a simple network representing the bundle of His and the main bundle branches coupled with a thin layer with discrete sites of activation representing the PF and the PMJ.

Discussion of the results

The results reported in Figures 3 and 4 and in Table 2 for subjects 3 and 4 shows a less good improvement in the accuracy obtained by using the patient-specific Purkinje network with respect to the one obtained with the tentative network. In particular, for subject 3 the mean absolute error decreased by 13.4%, while for subject 4 it decreased by 21.7%.

Such a deterioration in the performance of the patient-specific network with respect to the previous cases can be ascribed to the fact that a percentage of the points of the endocardium (the subset W) is directly activated by the anomalous pathway and therefore it is not affected by the presence of the Purkinje network. For subject 3, the one with the worst improvement in accuracy, the subset W is composed by 61.0% of the data, while for subject 4 it is composed by 40.0% of the measures.

Therefore, to study the improvement in the accuracy obtained by using the patient-specific network we computed in Table 3 the mean absolute error related to the points in the subset K, those activated in our simulation by the PF. These results show a good improvement in the accuracy obtained by the patient-specific network with respect to the one obtained with the tentative network. In particular, for subject 3 the mean absolute error decreased by 27.2%, while for subject 4 it decreased by 29.5%. On the contrary, no appreciable improvement is noticed for the points activated in our simulations by the anomalous pathway.

These results highlighted that for the WPW syndrome it is important to use a patient-specific Purkinje network if we want to accurately describe the activation in the region of the endocardium far from the anomalous pathway, whereas, if we are interested only on the activation near the intramyocardial pathway, a non patient-specific network can be enough.

We conclude that the patient-specific network generated by using clinical data related to a healthy activation is able to accurately describe also the pathological activation of the same patient due to the presence of the WPW syndrome, proving again the reliability of our methodology.

CONCLUSIONS

In this work we applied the computational algorithm for the generation of a patient-specific Purkinje network presented in [8] to cases characterized by electrical pathological propagations. We compared the results obtained by using the patient-specific Purkinje network with the ones given by considering a no patient-specific (tentative) network. The numerical results highlighted:

1. The improvement in the accuracy obtained by using the patient-specific network when a cross-validation test is performed;
2. The importance of considering a patient-specific Purkinje network to detect the specificity of

the electrical propagation of the patient at hand, both in the case of a muscular conduction problem (as the myocardial ischemia) and in the case of an electrical conduction block of a portion of the PF (as the LBBB);

3. The reliability of the patient-specific Purkinje network generated with clinical measurements acquired after the ablation to accurately describe the propagation far from the anomalous muscular pathway in patients that suffered from the WPW syndrome.

These conclusions show that the method presented in [8] provides an effective tool to accurately model the activation of the left ventricle also in the case of pathological electrical propagations with different origins, from conduction problems in the PF or in the myocardium to the presence of an additional muscular pathway.

The next steps we are working on consist in the enrichment of the model to describe the LBBB by considering also the presence of the right ventricle, with the aim of studying the electrical propagation during the cardiac resynchronization therapy, and to adapt the algorithm for the generation of a patient-specific Purkinje network when only clinical data related to the WPW syndrome are available.

CONFLICT OF INTEREST

None declared.

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ETHICAL APPROVAL

This clinical study has been approved by the ethic committee of Azienda Provinciale per i Servizi Sanitari, Trento (Italy). The patients have been previously informed and gave their full consent for both the acquisition of the clinical data and for the successive mathematical analyses.

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FIGURES

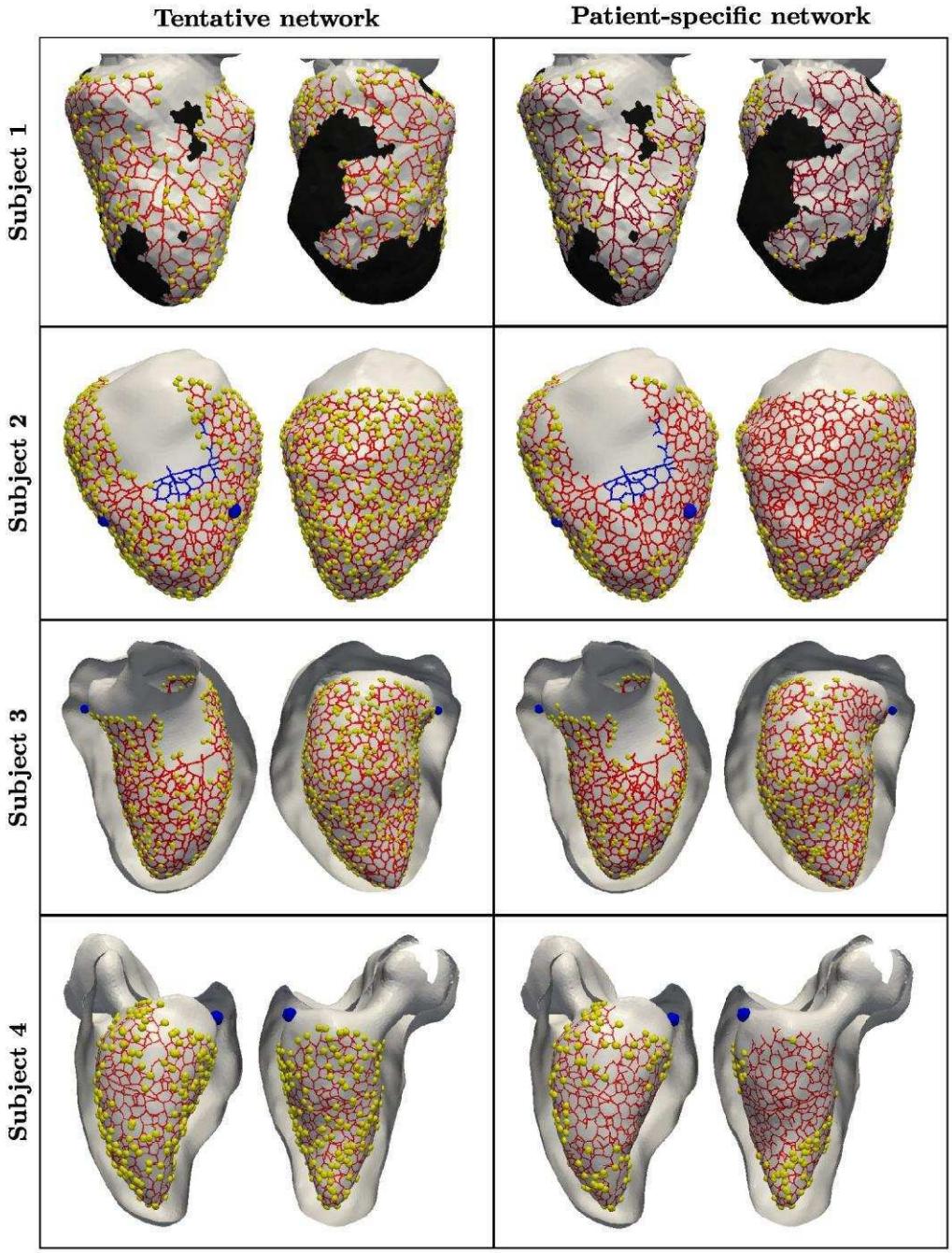

Fig. 1 Tentative (left) and patient-specific (right) networks for the four subjects. Each row represents a different subject. In yellow we depict the PMJ. For the first two subjects we depict only the endocardium, while for subjects 3 and 4 all the myocardium. For subject 1 (first row) we depict in black the region of endocardium identified with the scar, for subject 2 (second row) we depict in

blue the portion of the network affected by the block and the two endocardial sources, and for subject 3 and 4 (third and fourth rows) we depict in blue the anomalous source due to the WPW syndrome.

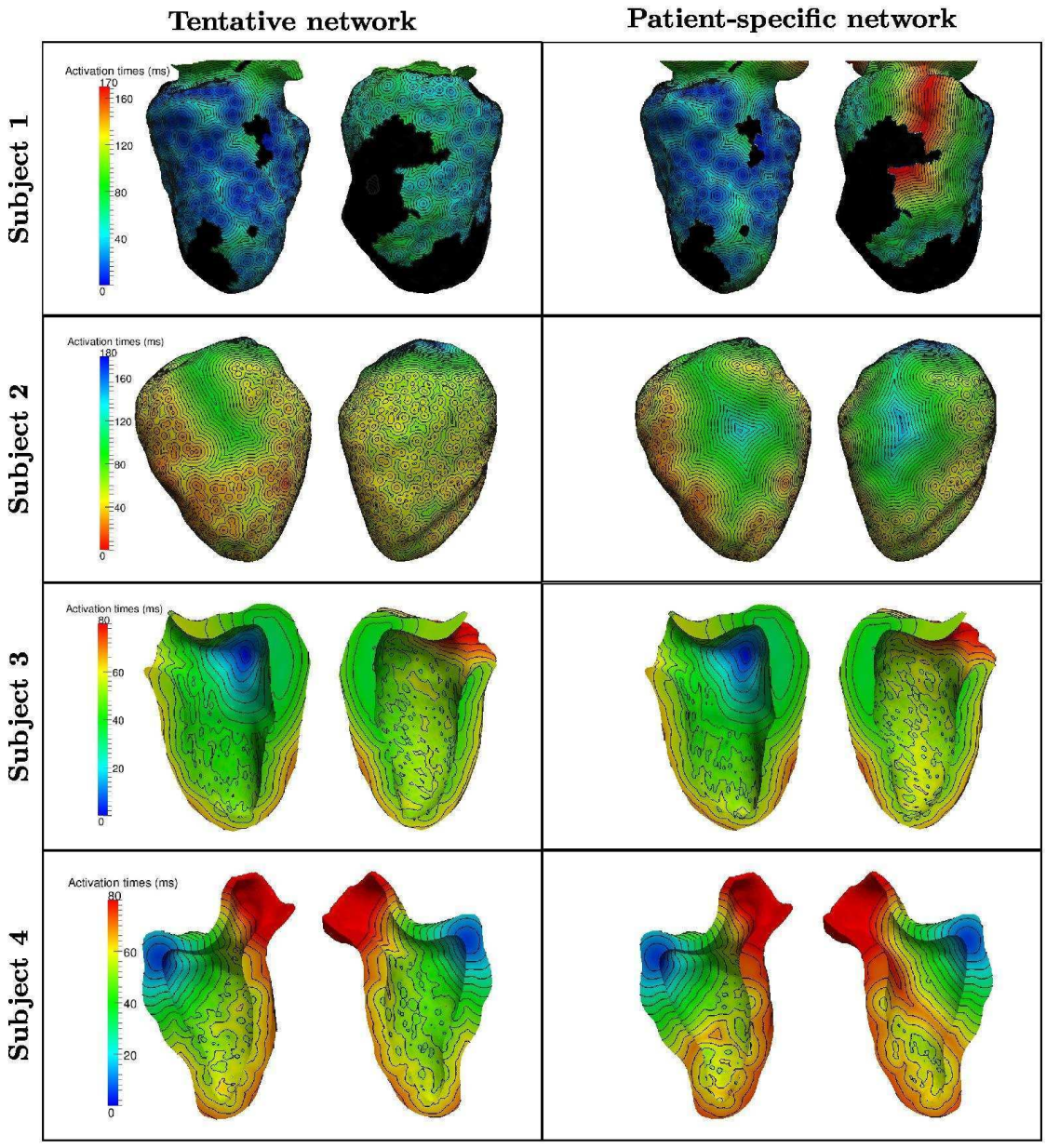

Fig. 2 Computed activation times for the four subjects. Each row represents a different subject. Left: tentative network. Right: patient-specific network.

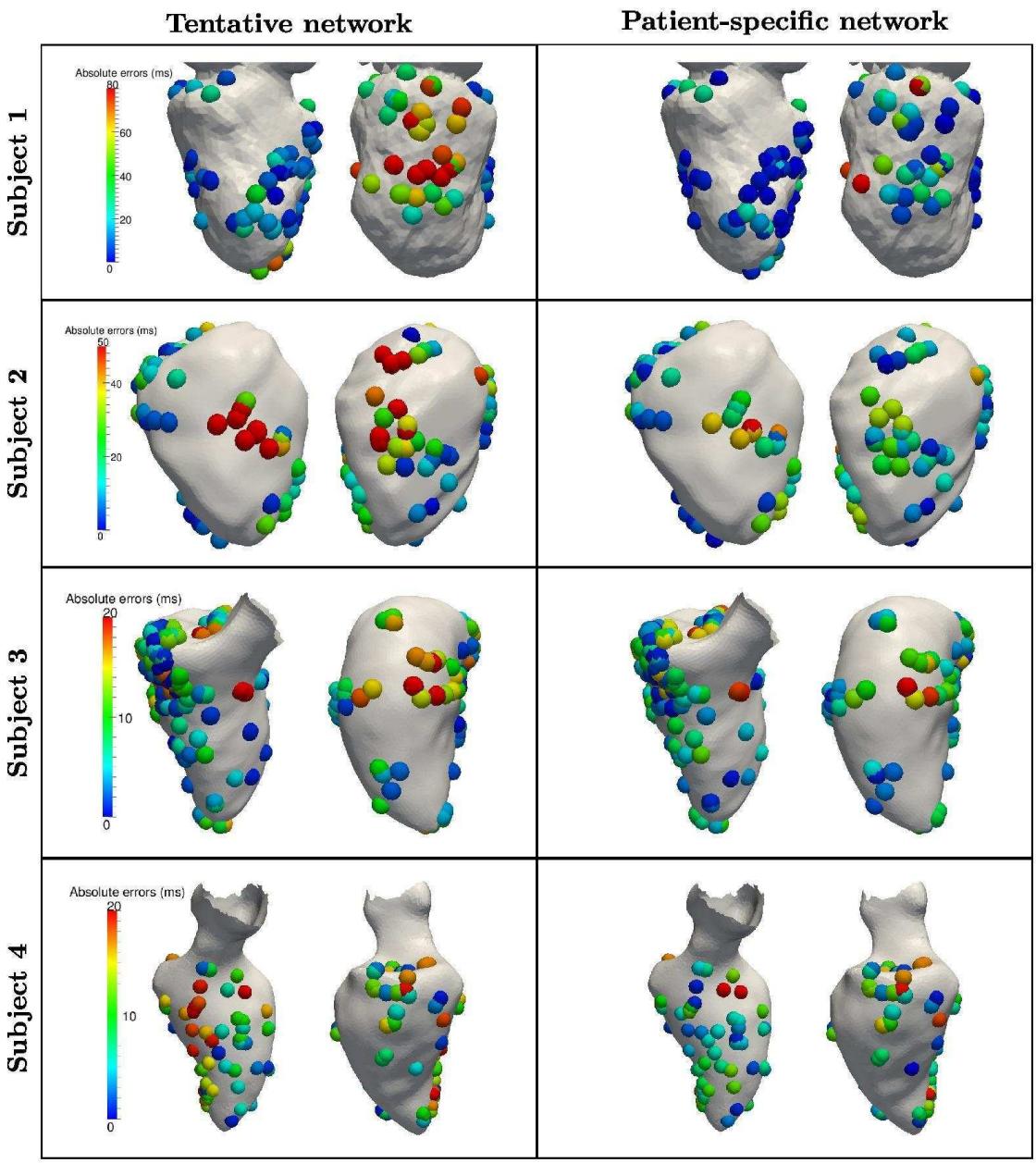

Fig. 3 Absolute errors in the activation times between the measured data in the testing set and the corresponding computed data for the four subjects, represented by spheres located in the points where the measures have been acquired. Each row of the figure depicts the results of a subject obtained with the tentative (left) and with the patient-specific (right) networks.

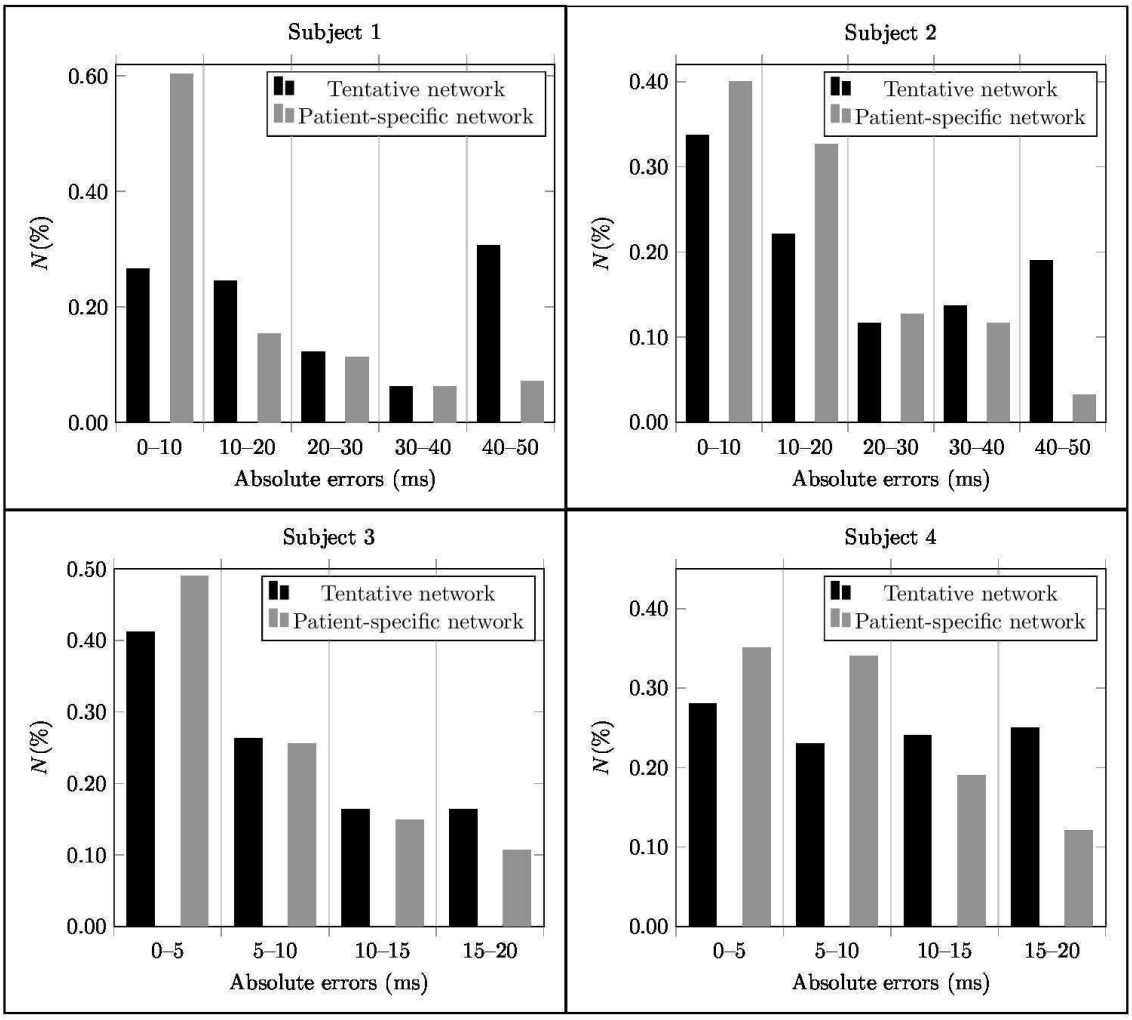

Fig. 4 Histograms of the absolute errors.

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