Centrality Measures from Directed Network Mapping Identify Reentries Suggesting Different Mechanisms of Atrial Flutter

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Abstract

Directed Network Mapping (DNM) models the electrical propagation within the atria using a directed graph. With DNM, reentries of different atrial flutter (AFL) mechanisms are associated with closed path in the network. Since the noise in the endocavitary recordings may hamper the identification of cycles, this study aimed to quantify whether graph-based centrality measures could identify nodes associate to reentries without the need of actual cycle identification. Endocavitary recordings from 10 patients with complex AFL of five distinct mechanisms were considered. Centrality measures included betweenness (B), harmonic centrality, and two derived from PageRank and Hyperlink-Induced Topic Search. A specific visualization called centrality map was defined by depicting the measures at all nodes. Correlation coefficients were computed between the centrality map and the counting of the cycles passing through each node. Also, centrality maps were evaluated for detecting reentries using ROC analysis. Moderate to strong correlations (> 0.5) were found between centrality and cycle count maps. Here, B resulted the most correlated and accurate measure in detecting reentries across different patients (AUC: 0.84 ± 0.05) and mechanisms (AUC: 0.81 ± 0.06). Integrating centrality measures in DNM may hold potential to characterize AFL mechanisms.

1. Introduction

Catheter ablation is considered the first-line therapy for the treatment of atrial fibrillation [1]. However, post-ablation, up to 30% of patients develop atrial flutter (AFL), requiring an additional procedure to stop the ongoing tachycardia [1]. To optimize catheter ablation, innovative tools are imperative for elucidating the arrhythmia mechanisms and assessing excitation patterns.

Network theory is a vast scientific field, which has been investigated in many applications for diverse goals. It has recently been exploited in the context of cardiac arrhythmia with the introduction of Directed Network Mapping (DNM), which models the electrical propagation across the cardiac surface using a directed graph [2, 3]. This tool has been used to detect the driving mechanisms of AFL and to recommend optimal ablation targets [4].

One of the most sensitive steps in DNM is the assignment of a directed edge between two neighboring nodes, *i.e.*, detecting electrical propagation from one site to another one. Indeed, factors such as noise in the recordings, presence of fibrotic tissue and limited number of mapping points can hamper such assignment. The error is then propagated downstream to tasks such as the detection of the type of reentrant arrhythmia in-place, and the identification of the optimal ablation strategy. In fact, DNM models reentries as cycles in the network. In order to tackle the problem, we recently proposed an algorithm tolerant to a single missing edge in a cycle [4]. While the algorithm can be extended to handle multiple missing edges, the computational cost than scales exponentially with the number of missing edges considered, making it unfeasible in complex and noisy scenarios. Therefore, investigating methodologies that can point to cycles without the need of their actual detection becomes meaningful.

Since reentries are characterized by specific pathways and propagating directions, which are encoded in the sequence of edges connecting different nodes in the network, shifting the perspective from detection of cycles to quantification of node "importance" or "relevance" (the fact that they belong to a cycle linked to a specific clinical reentry) may bring valuable information. In fact, network theory provides a plethora of algorithms to quantify the so-called "node centrality", able to highlight relevant structures and patterns at different scales in the network. To explore this idea, in this study, we considered five different centrality measures and their association to various reentrant mechanisms of AFL as modeled by DNM.

Patient	Mechanism	Atrium	Nodes of the cycles	Centrality Measures					Time [min; max] (ms)
				B	H^{in}	H^{out}	PR	hub	
1	Macro-TV	R	42 (42%)	**0.63**	**0.51**	0.28	0.37	-0.24	[1.05; 8.19]
2	Macro-TV	R	75 (54%)	**0.74**	**0.56**	0.40	**0.58**	0.15	[0.49; 1.46]
3	Macro-MV	L	30 (23%)	**0.67**	0.23	0.35	0.05	-0.13	[0.33; 5.32]
4	Macro-MV	L	33 (23%)	0.45	0.20	**0.52**	0.14	0.26	[0.54; 2.58]
5	Macro-MV	L	19 (18%)	**0.75**	0.36	0.02	**0.56**	0.16	[0.96; 3.50]
6	SAR-PVI	L	8 (6%)	0.42	0.30	-0.03	**0.59**	-0.08	[0.45; 1.43]
7	Macro-FOE	L	87 (83%)	**0.75**	0.46	0.30	**0.52**	-0.13	[0.30; 1.00]
8	Macro-FOE	L	44 (52%)	**0.62**	**0.57**	0.27	**0.69**	-0.08	[0.40; 0.72]
9	Macro-FOE	L	61 (57%)	**0.81**	0.46	0.46	**0.51**	0.18	[0.14; 0.38]
10	Macro-RPV	L	18 (16%)	0.25	0.02	0.42	-0.07	**0.53**	[0.16; 4.03]

Table 1: Correlation results between the counting of the cycles passing through each node and centrality maps of all patients along with their mechanism, atrium and number of cycle nodes. Moderate to strong correlations > 0.5 are reported in bold. Minimum and maximum computational times across all centrality measures are reported in the last column.

2. Methods

2.1. Data acquisition and study population

The work was carried out on a dataset of 10 patients with AFL, with prior ablations for atrial fibrillation and additional substrate alterations. This is the same dataset analyzed in [3,4]. The population was composed of 7 men and 3 women (age: 66 ± 5 years) who underwent electrophysiological studies and radiofrequency catheter ablation. Among all patients, different mechanisms were confirmed, comprising tricuspid valve (Macro-TV) reentry, mitral valve (Macro-MV) reentry, small area reentry (SAR-PVI) around pulmonary vein (PV) isolation lesions, figure-of-eight (Macro-FOE) macroreentry around left and right PVs and macroreentry (Macro-RPV) around right PVs. Data were acquired before the AFL ablation.

2.2. Directed network mapping and cycle identification

With the aim of characterizing the electrical propagation in the atria, DNM was performed on the endocavitary recordings routinely collected during the ablation procedure [3, 4]. For each patient, DNM produced a directed network $N = (V, E)$, where V and E represent a set of sites across the atrial surface and the directed edges corresponding to the electrical propagation from two nearby sites, respectively. The presence of a directed edge is determined using an estimate of the conduction velocity, estimated as the ratio of the distance of two nodes and the time delay between the activation times.

The reentrant mechanisms were identified as cycles in the graph through a depth-first search (DFS) algorithm tolerant to one missing edge. More details about data processing and number of cycles identified are reported in [4].

2.3. Centrality measures

Among the various topological properties defined within network theory, centrality measures highlight the relative relevance of each individual node in the network. Different definitions of relevance are available. One of the most widespread measures is the betweenness (B), which is based on the number of directed paths with minimum length (shortest) passing through a given node i. In this study, we considered the number of edges as a measure of length, with B formalized with the following equation:

$$B_i = \frac{1}{(|V|-1)(|V|-2)} \sum_{\substack{(h,j) \in V \times V \\ h \neq j, h \neq i, j \neq i}} \frac{{p_{hj}}^{(i)}}{p_{hj}} \quad (1)$$

where $|V|$ is the number of nodes, while p_{hj} and $p_{hj}^{(i)}$ are the number of shortest paths between two nodes h and j and the portion of them that pass through the node $i \in V$, respectively.

Harmonic centrality (H) is instead based on the sum of the reciprocal of the shortest distances (here, in number of nodes) between a node and all others. The distance can be computed on incoming or outgoing edges ($d_{ij}^{\text{in/out}}$). H is formalized as follows:

$$H_i^{\text{in/out}} = \sum_{(i,j) \in V \times V, j \neq i} \frac{1}{d_{ij}^{\text{in/out}}}. \quad (2)$$

Afterwards, we employed the PageRank (PR) algorithm. PR operates on the idea that the importance of a node can be determined by the number and quality of edges pointing to it. The computational process can be seen as a random walker who moves between nodes, which can be either neighbors or not (it might jump to a random node according to a damping factor δ, which is commonly set to 0.85). The rank of each node is obtained according to

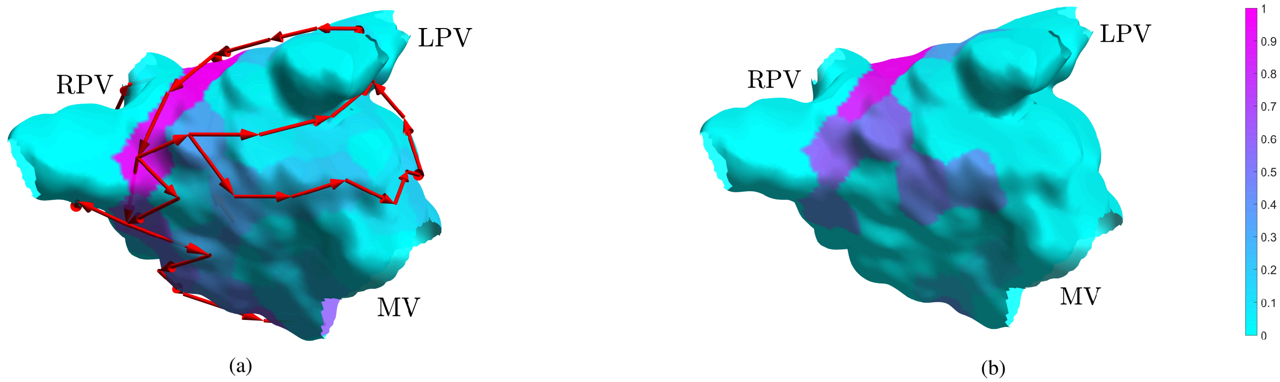

Figure 1: The cycle map (a) and the centrality map of B (b) of patient 9, characterized by Macro-FOE mechanism with gaps in previous PVIs. The red arrows show 4 detected cycles with the lowest average Menger curvature. For visualization purposes, both maps were normalized to their maximum value across nodes.

the probability that the random walker will end up on that node. The final rank is obtained iteratively and, when stable values are obtained, PR for each node satisfies:

$$PR_i = \frac{(1-\delta)}{|V|} + \delta \sum_{\substack{(i,j)\in E \\ i\neq j}} \frac{PR_j}{l_j} \qquad (3)$$

where l_j is the number of outgoing edges from $j \in V$.

Finally, we employed hub centrality (hub) computed through the Hyperlink-Induced Topic Search (HITS) algorithm. HITS is based on the concept of "hubs", *i.e.*, well-connected nodes to the others, and "authorities", *i.e.*, nodes pointed from many nodes. HITS finds a balance between hubs and authorities through the following score updates:

$$auth_i = \sum_{(j,i)\in E} hub_j \,, \qquad hub_i = \sum_{(i,j)\in E} auth_j \qquad (4)$$

All node scores are first initialized to 1 and the update steps are repeated until convergence.

2.4. Statistical assessment

Two statistical analyses were performed. The first one assessed the Pearson's correlation coefficient between the "cycle map", here defined as the count of cycles passing through each node, and each of the centrality measures ("centrality map") associated with each node described in the previous section. In the second analysis, we quantified whether the centrality measures could be used to identify nodes within a cycle. To do so, we performed a receiver operating characteristic (ROC) analysis where the rule defining a node as part of a cycle was set as centrality measure $\geq m^{\text{th}}$ percentile. Here, true positive rate (TPR) and false positive rate (FPR) were defined as the detection rate of nodes within cycles and error rate outside cycles, respectively. The analysis was performed for each of the AFL mechanisms in the dataset and the five selected centrality measures. TPR and FPR were averaged across subjects with the same underlying mechanism.

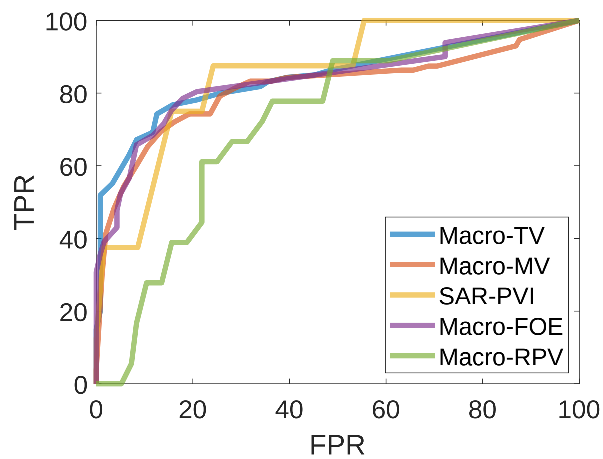

Figure 2: ROC curves for centrality measure B averaged across patients for each different mechanism.

3. Results

The correlation analysis, whose results are summarized in Table 1, highlighted moderate to strong correlations (> 0.5) in all patients between at least one centrality measure and the cycle map. More specifically, B and PR were the most correlated measures in 7 and 6 patients, respectively. B was consistently correlated in patients characterized by Macro-TV and Macro-FOE mechanisms, whereas PR was the only measure correlating in the SAR-PVI case. Furthermore, hub correlated in the Macro-RPV case, H^{in} in Macro-TV cases and H^{out} in case 4 only (Macro-MV). An example of the cycle map in comparison to the centrality map for B of patient 9 is shown in Fig. 1. By visual inspection, it is worth noting a good agreement between the two maps.

The results of the ROC analysis showed that B obtained the highest mean AUC and the lowest variability among all centrality measures across patients (mean ± std; B: 0.84 ± 0.05; H^{in}: 0.75 ± 0.08; H^{out}: 0.74 ± 0.13; PR: 0.73 ± 0.12; hub: 0.5 ± 0.14). When considering different mechanisms, the ROC curves obtained with B are reported in Fig. 2. Specifically, the AUCs of average ROC curves were Macro-TV: 0.85, Macro-MV: 0.82, SAR-PVI: 0.86, Macro-FOE: 0.84, Macro-RPV: 0.72.

4. Discussions and conclusions

This study explored the use of network-based centrality measures to point out the relevant areas of endocardial surface involving reentries in the context of different complex AFL. Depending on the centrality measure, we found correlations with the nodes mostly crossed by reentries. However, not all centrality measures displayed this correlation. This result poses the question about why only B and PR were found so, especially in Macro-FOE and Macro-TV reentries. It is worth considering that the tested measures were originally introduced for the characterization of networks with general topological structure (*e.g.*, PR is widely used to determine the importance of web pages). In our case, DNM provides a network which shows a specific property, *i.e.*, nodes are locally connected between each other. This characteristic might be the reason for the correlation found only for B and PR, which are mostly based on the number of times a path goes through a node. Future investigations will shed light on this aspect.

The recognition ability of the centrality measures in detecting reentries was also assessed through the AUC of their respective ROC curves. In this case, B obtained high AUC value across mechanisms, with the exception of Macro-RPV, where DNM only partially identified the mechanism [4]. In addition, this measure was the only one reporting both high correlation and AUC for Macro-FOE and Macro-TV cases. Differently, H^{in} and H^{out} displayed good recognition rates but poor correlations with cycle map. This result suggested that the identification of cycles could be performed by considering node importance.

Considering our results, the centrality measure B holds potential for the visualization of reentrant mechanisms through centrality maps, as the one depicted in Fig. 1. This measure seems to reveal valuable insights into the electrophysiology of the atria without the need of visualizing the large number of detected cycles. Further and more robust validation is needed to confirm the findings obtained, since the population size represents a major limitation of the study. Regarding the future works, centrality measures could be tested to enhance the detection of cycles and lighten the computation cost. In addition, novel measures, specifically related to cycles [5], or approaches aggregating multiple information [6], may further improve the results.

Finally, this study illustrates the potential of employing centrality measures on top of DNM for identifying reentries in different mechanisms. Their use may contribute to advance our comprehension of atrial electrophysiology, and to design efficient algorithms to include within a recommender systems, like the one we proposed in [4].

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References

[1] Calkins H, Hindricks G, Cappato R, Kim YH, Saad EBea. 2017 hrs/ehra/ecas/aphrs/solaece expert consensus statement on catheter and surgical ablation of atrial fibrillation. Europace 2017;20:e1–e160.

[2] Vandersickel N, Van Nieuwenhuyse E, Van Cleemput N, Goedgebeur J, El Haddad M, et al. Directed Networks as a Novel Way to Describe and Analyze Cardiac Excitation: Directed Graph Mapping. Front Physiol 2019;10:1138.

[3] Vila M, Rivolta MW, Luongo G, Unger LA, Luik A, Gigli L, Lombardi F, Loewe A, Sassi R. Atrial Flutter Mechanism Detection Using Directed Network Mapping. Front Physiol 2021;12:749635.

[4] Vila M, Rivolta MW, Barrios Espinosa CA, Unger LA, Luik A, Loewe A, Sassi R. Recommender system for ablation lines to treat complex atrial tachycardia. Comput Meth Prog Bio 2023;231:107406.

[5] Zhou X, Liang X, Zhao J, Zhang S. Cycle Based Network Centrality. Sci Rep 2018;8:11749.

[6] Vega-Oliveros DA, Gomes PS, E. Milios E, Berton L. A multi-centrality index for graph-based keyword extraction. Comm Com Inf Sc 2019;56:102063.

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