Time-series Network Analysis for Detecting Cardiac Autonomic Neuropathy using RR Interval Data

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Abstract

Cardiovascular autonomic neuropathy (CAN) is highly prevalent and a serious complication in patients with diabetes mellitus. In this study, we investigate the effect of changing the degree and data length on network properties (transition asymmetry and network efficiency) to differentiate negative CAN (NCAN) subjects from definite CAN (DCAN). Forty-one patients with Type 2 diabetes mellitus were included in the study: 15 patients had definite CAN (DCAN), whilst the remaining 26 were negative for CAN (NCAN), being without clinical signs and symptoms of CAN. Symbolic Aggregate approximation (SAX) was used as the discretization procedure to convert the heart rate variability (HRV) time-series signal to network. The optimal degree (m) and data length (n) were found to be $m_{opt} = 270$ *and* $n_{opt} = 200$ *respectively with leave-one-out accuracy of 85.37% using transition asymmetry (A(G)) and network efficiency (EF) indexes. Both, A(G) and EF indexes are found to be a potential parameter for detecting CAN in diabetes.*

1. Introduction

Cardiac autonomic neuropath (CAN) is a serious clinical complication of diabetes. CAN is found in one third of type 2 diabetes patient and causes gradual damage to the autonomic nerve fibers that innervate the heart and blood vessels, resulting in abnormalities in heart rate control and vascular dynamics [1]. The noninvasive Ewing test battery [2] is the gold standard for screening CAN at present. The Ewing test uses cardiovascular reflex responses and depends on the compliance of the participant. Therefore, alternative approach independent of patient's active participation is still on quest.

A change in heart rate variability (HRV) has been shown to be one of the early signs of CAN [3], the most common method used for CAN diagnosis is HRV analysis. However, only a few studies have applied new parameters based on nonlinear dynamics theory to HRV analysis in diabetic mellitus (DM) patients [4-6].

In the last decade, time-series network translation has been developed to understand the correlation structure and dynamical properties of the time-series signal [7-8]. This transformation also avails the tools and knowledge of graphs and networks theory to extract information from time-series data. Since HRV is a time series signal and complexity and/or dynamical information of the HRV signal has shown an association with various physiological and pathological conditions, the particular interest of this study is the application of complex network theory based HRV analysis in detecting CAN in diabetes.

Mapping of time-series signal into network is a challenging activity. Several mapping approaches capable of differentiate various time-series properties such as periodicity, fractal or chaotic dynamical behaviours are defined based on autocorrelation matrix [8-9], relative magnitude between the TS points [7], distance between phase space points [10] etc. Another simple and linear discretization approach based on symbolic aggregate approximation (SAX) method [11] was used by Tejara et al. for characterizing the complexity of HRV time-series signal in the ageing process of healthy subjects [12] and multi-scale transition asymmetry analysis of HRV signal to differentiate between normal and preeclamptic pregnancies [13]. One important parameter of this mapping procedure is the number of nodes (degree) m. It is obvious that very small value of m leads to small sized network that is computationally efficient, however the subtle fluctuation (very detailed information) of the signal could be lost. In contrast, larger m could improve the sensitivity towards subtle changes of the signal with larger computational cost. The maximum degree m_{max} of any network can be defined as: $m_{max} = \lceil (RR_{max} - RR_{min})/|\Delta RR_{min}| \rceil$, where ΔRR_{min} is the minimum difference between any two RR intervals in the HRV series. If the degree of the network is selected as $m > m_{max}$ then it confirms capturing of subtle change in the signal. However, this increases the computational cost

and does not provide any information about the minimum data length necessary for reliable feature extraction.

In this study, a detailed methodology has been shown for selecting the degree (number of nodes) of the network and minimum data length (number of RR intervals to better differentiate definite CAN (DCAN) subjects from negative CAN (NCAN) subjects using transition asymmetry and network efficiency indexes.

2. Methods and data

2.1. Linear discretization method for mapping HRV signal to network

The linear discretization procedure used for converting time-series to a network-type process is similar to the Symbolic Aggregate Approximation (SAX) method [11]. The RR time-series extracted from the electrocardiogram (ECG) signal is considered as a numeric sequence $RR = \{rr_1, rr_2, rr_3, \cdots, rr_N\}$. The sequence is divided into m non-overlapping intervals of size $\Delta RR = (rr_{max} - rr_{min})/m$, where rr_{min} and rr_{max} represent the minimal and maximal values of the sequence. The original RR sequence is transformed in to a sequence S of m

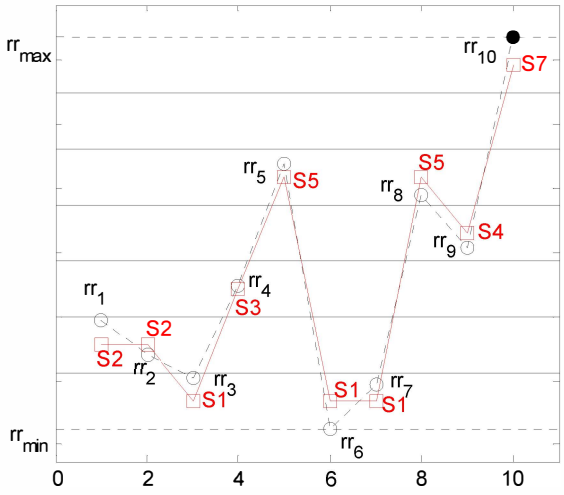

Figure 1. Example representation of the discretization process of the original RR time-series. $RR = \{rr_1, rr_2, rr_3, \cdots, rr_{10}\}$ is divided into $m = 7$ regular intervals of size ΔRR. Each element of RR is replaced by the average value of the interval and therefore RR is transformed into a new sequence S of equal length but with only seven possible values.

number of possible values that have same length as RR (Fig 1). Transformation $RR \rightarrow S$ is performed as follows:

$$\forall\, i: rr_i \in S_k : (k-1)\Delta RR \leq rr_i < k\Delta RR$$
$$S_k = RR_{min} + \frac{1}{2}(2k-1)\Delta RR \quad (1)$$

where, $k = 1, 2, \cdots, m$

Therefore all values of RR_i is replaced by the m interval average values. This m states are then considered as network nodes $V = \{v_1, v_2, v_3, \cdots, v_N\}$. Any two of these nodes v_i and v_j are connected iff $\exists\, j: j = i + 1$ in the sequence S.

2.2. Transition asymmetry ($A(G)$) and Network efficiency (EF) indexes

Simply, a transition T_{ij} indicates that the nodes v_i and v_j of network G are connected to each other. The transition frequency $F_{T_{ij}}$(total number of transitions between any two nodes) is used to generate the complete transition frequency matrix $F(m \times m)$ of network G. One interesting property of a transition map or transition frequency matrix is its symmetry. If the transition map is symmetrical then $F_{T_{ij}} = F_{T_{ji}}$ for all i and j. In contrast, if the network has some preferential nodes i.e., states with higher transitional probability then the density around these nodes increases and the network becomes asymmetric. In this study, we have used the transition asymmetry index $A(G)$, which is calculated as follows [13]:

Step 1: Define binary transition symmetry map

$$\forall\, i,j: \tau_{ij} = \begin{matrix} 1 & if\ \left|F_{T_{ij}} - F_{T_{ji}}\right| > 0 \\ 0 & Otherwise \end{matrix} \quad (2)$$

Step 2: Calculate transition asymmetry index $A(G)$ from binary transition symmetry map τ:

$$A(G) = \frac{2}{m(m-1)} \sum_{i=1}^{m-1} \sum_{j=i+1}^{m} \tau_{ij} \quad (3)$$

Network efficiency (EF) is a network centrality index and is related to the compactness of the network and degree of connectivity. Higher values of EF represent strongly connected networks, whereas a smaller value represents a loosely connected network. The network efficiency EF is defined as:

$$EF = \sum_{i=1}^{m} \sum_{j=1, j\neq i}^{m} \frac{1}{m(m-1)d_{ij}} \quad (4)$$

where, d_{ij} is the shortest distance between node v_i and v_j of the network. For simplicity, the loops in the networks are ignored and the shortest distance corresponds to topological one i.e., no weight was assigned to edges of the network.

2.3. ROC area analysis

Receiver-operating curve (ROC) analysis was used to determine the accuracy of classification [14], with the

area under the curve for each feature represented by the ROC area. An ROC area value of 0.5 indicates that the distributions of the features are similar in the two groups (NCAN & DCAN) with no discriminatory power. Conversely, a ROC area value of 1.0 would mean that the distribution of the features of the two groups do not overlap at all. The area under the ROC curve was approximated numerically using the trapezoidal rules [14] where a larger ROC area represents better discriminatory performance.

2.4. Degree and data length analysis

The degree m of the network (G) was varied from 2 to 400 and features ($A(G)$ and EF) of all subjects of DCAN and NCAN groups were calculated for each m. The optimal degree was selected as the minimum degree for which the maximum ROC area was found i.e., $m_{opt} = \min\left(\arg\max_{m} ROC\ area\right)$. After selection of the optimal degree (m_{opt}), the minimum data length was selected by varying data length (number of beats) from 100 to 800. For each data length, both $A(G)$ and EF were calculated for all subjects of subjects and the classification accuracy was calculated as the ROC area between DCAN and NCAN groups. Finally, the minimum data length was selected as $n_{opt} = \min\left(\arg\max_{n} ROC\ area\right)$. After selection of optimal degree and data length, features ($A(G)$ and EF) were calculated and leave-one-out accuracy was determined using linear discriminant (LD) classifier for each feature.

2.5. Data

Total 41 patients with Type 2 diabetes mellitus were included in the study: 15 patients had definite CAN (DCAN), whilst the remaining 26 were negative for CAN (NCAN), being without clinical signs and symptoms of CAN. The detail exclusion criteria, fiducial point (R wave) detection procedure, removal of ectopic beat and procedure for determining DCAN can be found in [20]. In this study, we have used the first 800 RR intervals of each subject from both groups for feature extraction.

3. Results and discussion

The ROC area (classification accuracy) between NCAN and DCAN groups for tansition asymmetry (A(G)) and network efficiency (EF) features with varying degree of networks (m) is shown in Figure 1. The ROC area is low with higher fluctuation for $m < 70$ and for $70 \leq m \leq 270$ ROC shows an increasing AUC trend with increasing m value. The fluctuation in the AUC values indicates higher variation in feature values, which indicates larger and rapid changes in network topology with increasing m at lower range ($2 < m < 70$) of the network. In contrast, the increasing trend in ROC area for $70 \geq m \geq 270$ may indicate toplogical changes , which include subtle changes of the signal to improve capturing dynamics of RR interval signal. The ROC area remains constant for $m > 270$, which indicates that further increasing of degree of the network does not affect the topology of the network. The optimal degree, $m_{opt} = 270$ was found from Figure 2 and used in data length analysis.

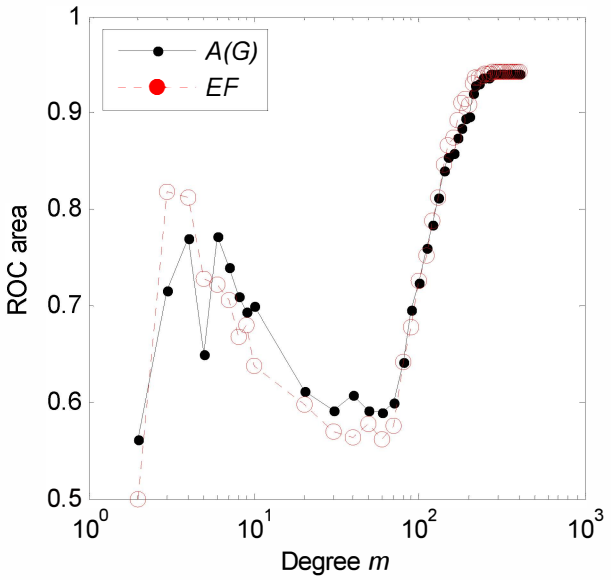

Figure 2. ROC area between NCAN and DCAN groups with varying degree of network $2 \leq m \leq 400$. Degree of network (m) is shown in *log* scale. All features are calculated for data length $n = 800$.

Table 1. Transition asymmetry and network efficiency indexes for NCAN and DCAN subjects.

Network Properties	NCAN Mean ± SD	DCAN Mean ± SD	Acc (%)
$A(G)$*	4.56E-3 ± 5.08E-4	3.26E-3 ± 7.68E-4	85.37
EF*	2.01E-2 ± 5.51E-3	9.86E-3 ± 3.70E-3	85.37

* index values are significantly ($p<0.01$) different between groups using Mann-Whitney U-test.

With optimal degree of the network, the data length n was varied from 100 to 800 RR intervals to determine the optimal data length n_{opt}. The ROC area obtained with varying data length is shown in Figure 3. The ROC area for both features remains above 0.90 for data length $n >= 200$ with small fluctuations. Moreover, maximum ROC area of 0.941 and 0.936 were found for $A(G)$ and EF respectively for data length $n_{opt} = 200$. Therefore, the optimal degree and data length selected for differentiating DCAN from NCAN subjects are determined as $m_{opt} = 270$ and $n_{opt} = 200$. These

parameters were used to generate the final network topology to extract features for classifying two groups.

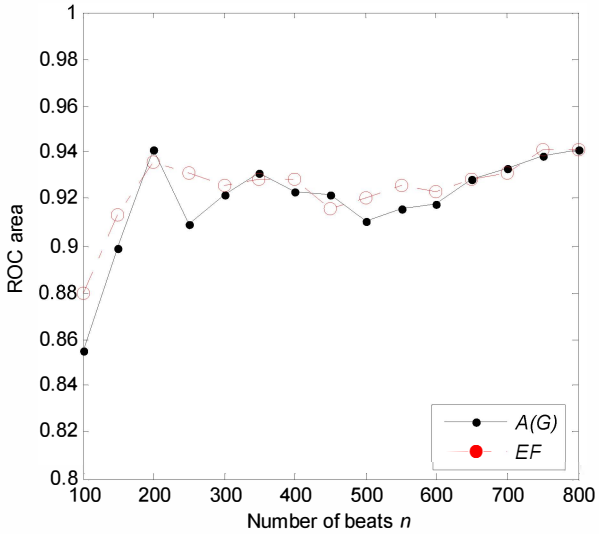

Figure 3. ROC area between NCAN and DCAN groups with varying data length $100 <= n <= 800$. All features are calculated for optimal degree $m_{opt} = 270$.

The Mean ± SD values of transition asymmetry ($A(G)$) and network efficiency (EF) indexes for NCAN and DCAN subjects for optimal degree and data length is shown in Table 1. Acc represent the leave-one-out classifying accuracy using linear discriminant (LD) classifier. Transition asymmetry of NCAN group was higher than DCAN group, which was linked with the higher variations in dynamics of HRV signal in NCAN groups compared to DCAN. Similarly, the network efficiency is also higher in NCAN group, which means that the network topology of NCAN group is strongly connected compared to DCAN group. Moreover, both A(G) and EF were found equally strong in classifying NCAN and DCAN group with an accuracy 85.37%.

4. Conclusion

In this study, the effect of degree and data length on network properties was analysed for cardiac autonomic neuropathy detection in diabetes using heart rate variability signal. A systematic approach has been presented for selecting optimal degree and data length for using complex network based HRV analysis. Transition asymmetry and network efficiency indexes are used to analyse the network and both are found potential feature for classifying NCAN and DCAN subjects using short length HRV signal. In future, it would be interesting to look at impact of degree and data length on other network properties as well as in different pathological conditions.

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