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Using Renyi Entropy to Detect Early Cardiac Autonomic Neuropathy

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Abstract— **Cardiac Autonomic Neuropathy (CAN) is a disease that involves nerve damage leading to abnormal control of heart rate. CAN affects the correct operation of the heart and in turn leads to associated arrhythmias and heart attack. An open question is to what extent this condition is detectable by the measurement of Heart Rate Variability (HRV). An even more desirable option is to detect CAN in its early, preclinical stage, to improve treatment and outcomes. In previous work we have shown a difference in the Renyi spectrum between participants identified with well-defined CAN and controls. In this work we applied the multi-scale Renyi entropy for identification of early CAN in diabetes patients. Results suggest that Renyi entropy derived from a 20 minute, Lead-II ECG recording, forms a useful contribution to the detection of CAN even in the early stages of the disease. The positive α parameters ($1 \leq \alpha \leq 5$) associated with the Renyi distribution indicated a significant difference ($p < 0.00004$) between controls and early CAN as well as definite CAN. This is a significant achievement given the simple nature of the information collected, and raises prospects of a simple screening test and improved outcomes of patients.**

I. INTRODUCTION

The Renyi entropy has been shown to be useful in a variety of applications including chaotic dynamical systems, which characterise heart rate (HR) changes observed over time. Heart rate and its inversely related property heart rate variability represents a non-stationary non-linear system [1]. In previous work [2] we have shown that entropy measures based on Heart Rate Variability (HRV) allow people with Cardiac Autonomic Neuropathy (CAN) to be distinguished from controls with good sensitivity and specificity. Detection of CAN is difficult as current tests are invasive and labour intensive, and many people at risk of this disease are not routinely screened. Detection of CAN at an earlier stage, before the disease is well defined, would greatly assist in management of this disease. The possibility of automatic detection of early CAN from a simple measure such as HRV would be a huge leap forward in terms of detection and most importantly, in terms of improving the health outlook and quality of life for those people living with CAN. For the detection of well defined CAN, the Renyi entropy provides a high level of accuracy and should therefore be considered as a neuroendocrine test for CAN. In this work we have extended this finding to examine the possible role of Renyi entropy in detection of early CAN. Results based on actual clinical data suggest that it is possible to detect early CAN from HRV data, but requires use of a multi-spectral Renyi entropy and some care in the selection of the spectral parameter α. This result holds great promise for early detection and the benefits that flow from that in terms of better outlook and quality of life for patients with CAN.

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A. Heart Rate Variability (HRV)

A standard ECG signal is shown in Fig. 1. This type of signal has been extensively studied and the diagnostic value of the different features is well established. ECG features are referred to using letters. The large spike is referred to as the QRS complex, with R being the peak of the wave or fiducial point, while the smaller peak to the left is the P wave and to the right of the QRS is the T wave. The natural rhythm of the human heart is subject to variation that is believed to indicate the health of the cardiovascular system. HRV is commonly used in assessing the functioning of cardiac autonomic regulation [3]. The autonomic nervous system (ANS) regulates heart rate (HR) through sympathetic and parasympathetic branches. Roughly speaking, sympathetic activity increases HR and decreases HRV, whereas parasympathetic activity decreases HR and increases HRV [4].The heart rate (HR) is expressed as the number of beats per minute. The HR varies considerably between individuals, but a typical adult heart rate is 60-80 beats per minute.

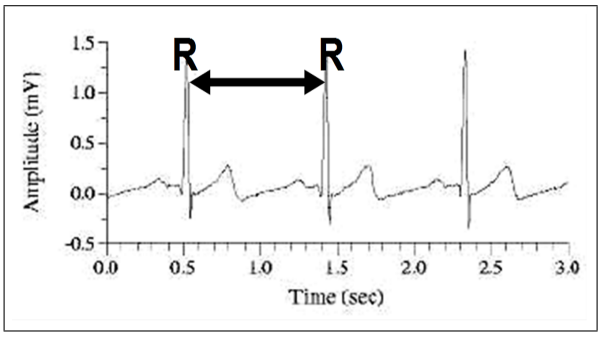

Fig. 1. Normal ECG recording showing RR interval.

The ECG signal is degraded by the presence of noise, so that the most reliable feature that can be obtained from low quality recordings (and therefore the most easily obtained measurement) is the interval between successive R peaks, known as the RR interval (inverse of heart rate). RR intervals are obtained from the recorded ECG and the RR variation can be subjected to further analysis through a variety of algorithms in order to yield variables with good discriminant

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power, based on the difference of RR interval variability with respect to the total recording interval. For the purposes of further analysis, the RR interval is expressed as the time between beats (measured in milliseconds), and this can be plotted against time to produce the graph shown in Fig. 2. Fig. 2 illustrates the natural variation of RR intervals over a 20 minute recording that is indicative of a healthy cardiac system, as the heart rate is continuously varied to adapt to current needs of oxygenation and perfusion. It is the absence of such a variation that can indicate cardiac disease.

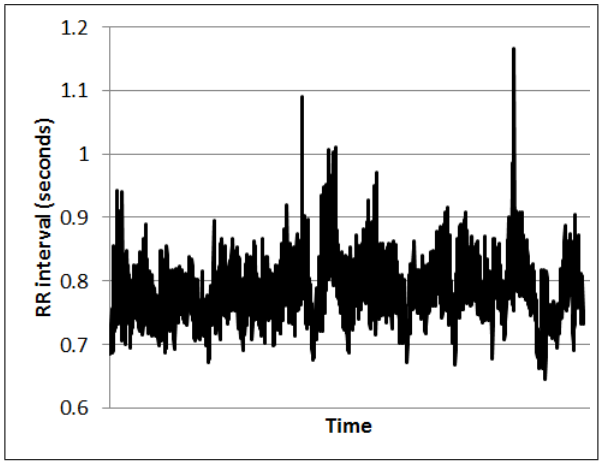

Fig. 2. Normal R-R interval graph.

HRV provides information only on the changes in the interval length between heart beats over the length of the recording. It is relatively non-invasive and easy to obtain from an ECG recording. The analysis of HRV has been the subject of extensive work using time and frequency based methods [5]. These methods have either focused on the magnitude of RR interval fluctuations around its mean, or on the magnitude of fluctuations in given frequency bands. However more recent analysis methods have shown an increased sensitivity for identifying risk of future morbidity and mortality in diverse patient groups. For example, an estimate of HRV using the standard deviation of RR intervals found that this is higher in well-functioning hearts but can be decreased in coronary artery disease, congestive heart failure and diabetic neuropathy [6]. Although HRV is useful in disease detection, when only a simple derived measure is used, such as the standard deviation of RR intervals, it is no better than the average heart rate and in fact contains less information for risk prediction after acute myocardial infarction [7]. This indicates that more advanced measures of HRV should be explored. Some of the measures derived from the RR interval fluctuations and used in this work are now discussed.

HRV is reduced in diabetes mellitus (DM) patients, suggesting dysfunction of cardiac autonomic regulation. Early assessment of cardiac autonomic neuropathy (CAN) and intervention are important for risk stratification and early treatment in preventing sudden cardiac death in diabetic patients. While HRV is recognised to carry early diagnostic value regarding CAN, reduction of HRV has been observed also in patients without evidence of CAN [8]. For the assessment of CAN using HRV analysis, standard time and frequency-domain methods as well as different non-linear methods have been proposed [9], [10].

A promising non-linear method is the Renyi entropy, which is calculated by considering the probability of sequences of RR values occurring in the HRV data. Renyi entropy has shown significant differentiation of cardiovascular disease, along with several other measures. In previous work, we have shown that Renyi entropy can distinguish CAN from controls [2]. In this work we show that it is useful in distinguishing CAN even in the early stages of the disease.

II. The Multi-Scale Renyi Entropy

The multi-scale Renyi entropy was introduced and applied to physiologic time series by [11]. Renyi entropy H_α is a generalisation of the Shannon entropy to include measures of different orders:

$$H_\alpha(X) = \frac{1}{1-\alpha} log_2 \left(\sum_{i=1}^{n} p_i^\alpha \right) \quad (1)$$

In terms of deriving a measure from a recording of RR intervals, X is the vector of RR intervals, p_i is the probability of each sub-sequence of X and α is the order of the entropy measure. The probability of each sub-sequence can be estimated by its similarity with all other sequences of the same length π [12]. Each sub-sequence is regarded as a point in a π-dimensional space, and its probability is estimated using a Parzen window density estimation with a Gaussian kernel centred on each such point [13]. Then p_i is given by this density function:

$$p_i = \sum_{j=0}^{n} exp \left(\frac{-dist_{ij}^2}{2\sigma^2} \right) \quad (2)$$

where σ is a parameter controlling the width of the density function and $dist()$ is a distance measure:

$$dist_{ij} = \sum_{k=0}^{\pi} (x_{i+k} - x_{j+k})^2 \quad (3)$$

Here, x_{i+k} is one RR sample out of sequence of length π, the pattern length over which comparison occurs. Renyi entropy may be calculated for a range of α, providing a spectrum of measures. Setting $\alpha = 0$ yields H_0 which gives simply $log_2 n$. Setting $\alpha = 1$ yields a special case of the Renyi entropy H_1, equivalent to the Shannon entropy. Setting $\alpha = 2$ yields H_2 or the Collision entropy.

III. Methodology

This work attempted the identification of early CAN in patients reviewed at the Charles Sturt Diabetes Complications Screening Group (DiScRi), Australia [14]. Participants attending the screening clinic had their lead II ECG recorded for 20 minutes and RR intervals analysed. The subjects were comparable for age, gender, and heart rate, and the same physical conditions were used for each subject. ECGs

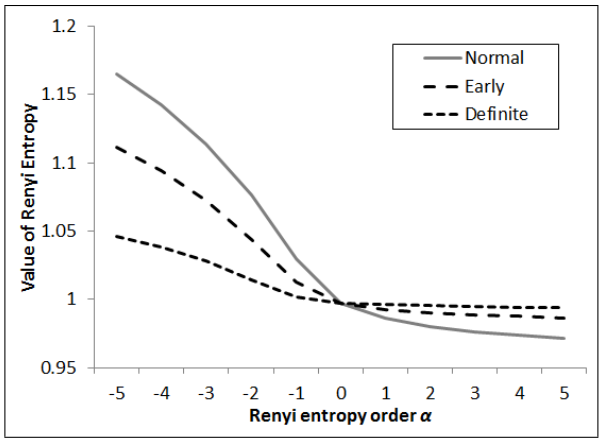

Fig. 3. Graph of the Renyi entropy for different value of the exponents α.

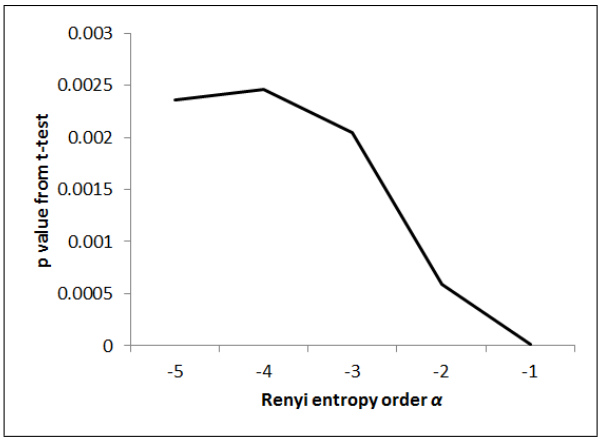

Fig. 4. Graph of p values obtained from t-tests performed on the negative part of the Renyi spectrum for the *Normal* and the *Definite* group.

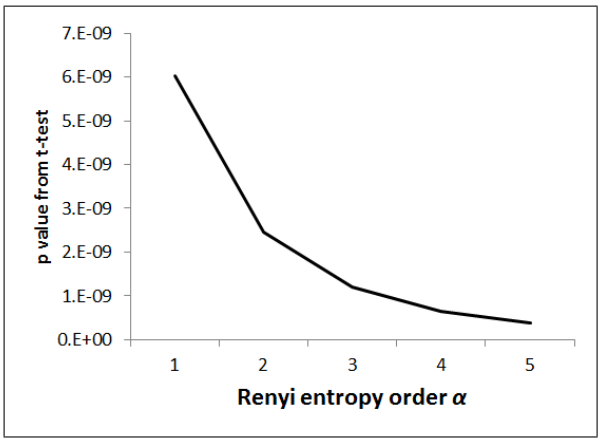

Fig. 5. Graph of p values obtained from t-tests performed on the positive part of the Renyi spectrum for the *Normal* and the *Definite* group.

were recorded using a Maclab Pro with Chart 5 software (ADInstruments). Initial screening of participants led to the exclusion of those with severe heart disease, presence of a pacemaker, kidney disease or polypharmacy including multiple anti-arrhythmic medication. The study was approved by the Charles Sturt University Human Ethics Committee and written informed consent was obtained from all participants.

This study used the Ewing battery of tests to identify the presence of early CAN [15], [9]. 11 participants with definite CAN, 67 participants with early CAN, and 71 without CAN attending the screening clinic had their beat-to-beat fluctuations analysed using the Renyi entropy described above. From the 20-minute recording, a 15 minute segment was taken from the middle of the original recording to remove start-up artefacts and movement artefacts at the end of the recording. Only the RR intervals were retained, and no other information from the ECG were utilised in this study. The baseline was removed by subtracting the mean value of the RR interval from the RR data. The Renyi entropy was calculated for exponents $-5 < \alpha < +5$. For each class of patients, the mean Renyi entropy was calculated for each value of α. Confidence intervals were also calculated for each class to allow comparison of the mean value of each class.

IV. Results

The mean value of Renyi entropy for each of the three groups of patients in the study is shown in Fig. 3. Only the mean values of each group are shown, but it can be seen that they appear distinct, especially in the region of negative α. All three groups have Renyi entropy close to 1 for all values of α. All patients have higher values for negative α but lower values for positive α. However this graph does not show the range of variation, and that is better explored through statistical comparison.

To understand better which values of the Renyi spectrum are the most successful in separating the various groups, we performed t-tests comparing the Renyi entropy for *Normal* and *Definite* groups, and for *Normal* and *Early* groups. Results are shown separately for the negative and positive parts of the Renyi spectrum because of the large difference in scale, and results are not shown for H_0 as none of these were significant even at the 0.05 level.

Fig. 4 shows p-values from the t-tests for the negative part of the Renyi spectrum ($\alpha < 0$) comparing the *Normal* and the *Definite* group. All the values for Renyi entropy shown are below 0.0025, suggesting that these groups can be easily separated using these measures, with a confidence level of less than 0.0025. The entropy H_{-1} appears to provide the best separation, with a p value of $1.318E-05$, suggesting that H_{-1} is a better measure than the others to distinguish *Normal* and the *Definite* groups. Results are shown for the positive part of the Renyi spectrum in Fig. 5. These values are all below $6E-9$, indicating a much more promising set of measures than those for $\alpha < 0$. The Shannon entropy H_1 appears least able to separate the groups compared to the other measures in the positive part of the spectrum. The highest H_5 provided the lowest p value, suggesting that higher values of α are superior for the detection of definite CAN from controls. These results are consistent with our previous findings.

Turning now to the comparison of the *Normal* and *Early* groups, Fig. 6 shows the p-values from the t-tests for the negative part of the Renyi spectrum ($\alpha < 0$). These values

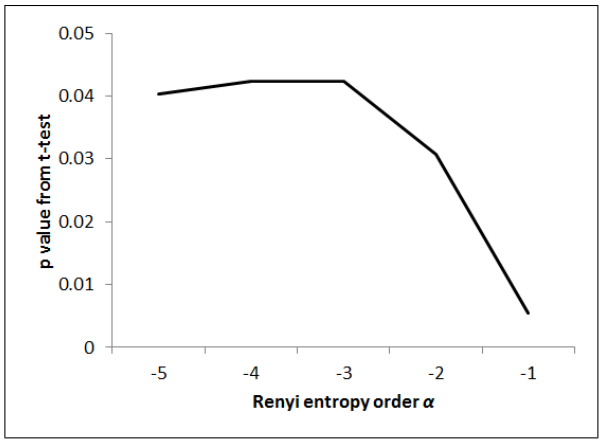

Fig. 6. Graph of p values obtained from t-tests performed on the negative part of the Renyi spectrum for the *Normal* and the *Early* group.

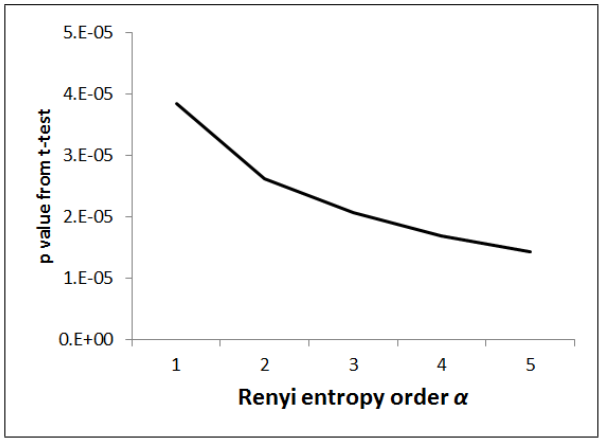

Fig. 7. Graph of p values obtained from t-tests performed on the positive part of the Renyi spectrum for the *Normal* and the *Early* group.

are higher than those for the *Normal* versus *Definite* groups, but are nevertheless all below 0.05, indicating a significant result at least at the 95% level. As noted in the previous discussion, the entropy H_{-1} appears to provide the best separation, with a p value of 0.0055, suggesting that H_{-1} is superior as a measure to distinguish the *Normal* and *Early* groups. Results are shown for the positive part of the Renyi spectrum in Fig. 7. These values are all below $4E-5$, which represents a high degree of confidence in the ability of these measures to discriminate these groups. Once again, the Shannon entropy H_1 is the least significant out of the positive part of the spectrum, and higher order measures appear to perform better, with H_5 providing a p value of $1.426E-05$.

V. CONCLUSIONS

Renyi entropy has the potential to distinguish not only between normal patients and those with definite CAN, but also between normal patients and early CAN, using measures based on HRV alone. Definite CAN was separated from controls with higher confidence ($p = 3.8E-10$ for H_5) than the separation between early CAN and controls ($p = 1.426E-05$ for H_5). The positive part of the Renyi spectrum ($\alpha > 1$) provided better separation in all cases, while H_0 was of no use as a discriminant measure. Out of the Renyi entropy measures in the positive part of the spectrum, the special case Shannon entropy (H_1) performed the most poorly and higher order Renyi entropy provided a superior result. The multi-spectrum Renyi entropy is able to provide a range of measures that can be pursued to easily discriminate between people with early CAN and controls. This is an important finding and gives hope of a simple and relatively non-invasive test for early CAN with all the benefits that implies for better prognosis and quality of life for those people developing this disease.

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