

# Renyi Entropy in Identification of Cardiac Autonomic Neuropathy in Diabetes

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## Abstract

*Heart rate variability (HRV) has been conventionally analyzed with time- and frequency-domain methods. More recent nonlinear analysis has shown an increased sensitivity for identifying risk of future morbidity and mortality in diverse patient groups. Included in the domain of nonlinear analysis are the multiscale entropy measures. The Renyi entropy is such a measure. It is calculated by considering the probability of sequences of values occurring in the HRV data. An exponent  $\alpha$  of the probability can be varied to provide a spectrum of measures.*

*In this work we applied the multiscale Renyi entropy for identification of cardiac autonomic neuropathy (CAN) in diabetes patients. Fifteen participants were identified with CAN (dCAN) using the five-test Ewing battery and 26 were control (nCAN). The multiscale Renyi entropy was measured from  $-5 < \alpha < +5$ . The best result was obtained with  $\alpha=5$ , where the mean value for patients with CAN was 0.98 with standard deviation of 0.01, compared with a mean of 0.95 for controls with standard deviation of 0.02. The probability of the means being the same was  $p < 0.0001$ , suggesting that a significant difference between these groups was found using the Renyi entropy. Other values of  $\alpha$  also showed a significant difference.*

*Different pathologies differ in their ECG and HRV and therefore no single HRV test should be expected to be ideal for all pathologies. However, this work shows that the multiscale Renyi Entropy provides a high level of discrimination and therefore should be considered as a neuroendocrine test for CAN.*

## 1. Introduction

Heart rate variability (HRV) is the study of the variation in the beat to beat interval of the heart, usually

collected using Electrocardiography (ECG). The natural rhythm of the human heart is subject to variation that is believed to indicate the health of the cardiovascular system. RR intervals are obtained from the recorded ECG and subjected to further analysis through a variety of algorithms in order to yield variables with good discriminant power.

Time domain methods are generally variations upon the second moment of RR intervals, frequency based methods include Fourier analysis, and nonlinear methods include fractal analysis and entropy measures. For example, an estimate of HRV using the standard deviation of RR intervals found that HRV is higher in well-functioning hearts but can be decreased in coronary artery disease, congestive heart failure and diabetic neuropathy [1].

Although HRV is useful in disease detection, when only the standard deviation of RR intervals is used, it is no better than the average heart rate and in fact contains less information for risk prediction after acute myocardial infarction [2]. This indicates that more advanced measures of HRV should be explored.

More recent nonlinear analysis has shown an increased sensitivity for identifying risk of future morbidity and mortality in cardiac patients. Included in the domain of nonlinear analysis are the multiscale entropy measures, which have been indicated as associated with diabetes [3, 4]. A survey of nonlinear measures based on HRV concluded with their value in the diagnosis of cardiovascular disease [5]. In that work Renyi entropy showed significant differentiation of disease, along with several other measures.

In this work we discuss the innovation of the multiscale Renyi entropy, which was introduced and applied to physiologic time series by [6]. The innovation of this work is to explore the use of the multiscale Renyi entropy for identification of cardiac autonomic neuropathy. Here it is applied to diabetes patients reviewed at the Charles Sturt Diabetes Complications Screening Group (DiScRi), Australia [7].

## 2. Methods

### 2.1. Participant selection

Participants attending the screening clinic had their lead II ECG recorded for 20 minutes and beat-to-beat fluctuations analysed. ECGs 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 antiarrhythmic medication. Fifteen participants were identified with CAN using the five test Ewing battery and 26 were control. All ECG data were collected between 2003 to 2008.

### 2.2. Multiscale Renyi entropy

In the context of the analysis of heart rate variability, the various entropy measures can estimate the variability of the HRV. An entropy measure is typically of the form:

$$H(X) = - \sum_{i=1}^n p(x_i) \log_b p(x_i)$$

where  $p(x_i)$  is the probability of the random variable  $x$ , and  $b$  is the base of the logarithm, commonly 2. Renyi entropy  $H$  is a generalization of the Shannon entropy:

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

where  $p_i$  is the probability that  $X = x$  and  $\alpha$  is the order of the entropy measure. This is the parameter that is varied to produce the multiscale entropy. The probability can be estimated by comparing the sample  $i$  with all other samples, using the methods outlined in [8]. This involves estimating the probability density function of all other samples  $x_j$  then estimating  $p_i$  as the probability given by this density function:

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

where  $\sigma$  is a parameter controlling the width of the density function and  $dist$  is a distance measure:

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

Here,  $\pi$  is the pattern length over which comparison occurs.

The multiscale Renyi Entropy was calculated from  $-5 < \alpha < +5$ , where  $\alpha = 1$  is the Shannon entropy and  $\alpha = 2$  is the squared entropy. The Multiscale Sample Entropy (MSE) was also calculated in order to provide a comparison.

The results were compared by taking mean and variance of each type (dCAN and nCAN) then applying a

t-test for unequal sample size and variance as follows:

$$t = \frac{\bar{X}_d - \bar{X}_n}{\sqrt{\frac{S_d^2}{n_d} + \frac{S_n^2}{n_n}}}$$

where  $\bar{X}_d$  is the mean of samples for type dCAN,  $S_d^2$  is the variance for dCAN,  $n_d$  is the sample size for dCAN (which was 15) and similarly for nCAN (where  $n_n = 26$ ).

## 3. Results

Fig. 1 shows the Renyi coefficients of plotted against the entropy order  $\alpha$ , with cardiac autonomic neuropathy (CAN) results indicated by black lines and control results indicated by the grey lines. For most values of  $\alpha$  the results appear to be well separated from the controls.

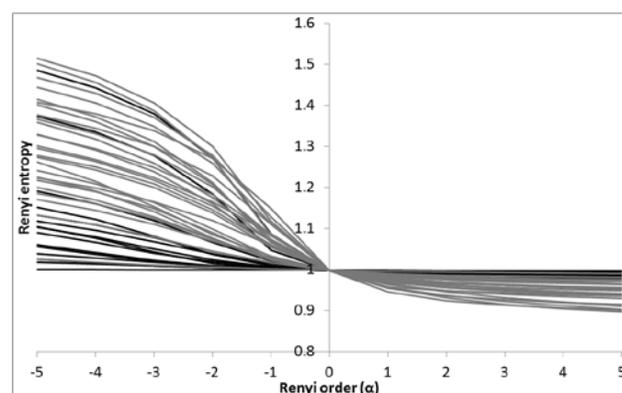


Fig.1. Renyi entropy estimated from CAN (black) and controls (grey) for various values of  $\alpha$ .

Table 1 shows the figures for 11 Renyi coefficients from  $-5$  to  $+5$ . Rows are provided for the mean and variance of dCAN, mean and variance of nCAN, the value of the t statistic and the corresponding probability of the means being equal. The table shows that for every value of  $\alpha$  except for  $\alpha=1$ , the means are different with a probability well below 99%.

Table 2 shows the results from a similar analysis carried out with Multiscale Sample Entropy (MSE) instead of Renyi entropy. Rows are similar to those in Table 1. The main difference is that the probability of accepting the null hypothesis (that is, that means are the same for CAN and controls) is much higher, and in nearly all cases is too high to justify any diagnostic value, except for the case where pattern length = 7, here it is below 95%.

Table 1. Results comparing Renyi coefficients for dCAN and nCAN types using Welch's t-test.

$\alpha$	dCAN		nCAN		$\Delta^*$	
	$\bar{X}_d$	$s_d^2$	$\bar{X}_n$	$s_n^2$	$t$	$p$
-5	0.99	0.03	0.95	0.03	5.28	< 0.0001
-4	1.13	0.14	1.31	0.12	4.23	0.0003
-3	1.11	0.13	1.27	0.11	4.25	0.0002
-2	1.08	0.11	1.23	0.10	4.26	0.0002
-1	1.05	0.08	1.16	0.08	4.28	0.0002
0	1.01	0.02	1.06	0.04	5.22	< 0.0001
1	1.00	0.00	1.00	0.00	0.36	0.73
2	0.99	0.00	0.97	0.01	7.12	< 0.0001
3	0.99	0.01	0.96	0.02	7.29	< 0.0001
4	0.99	0.01	0.96	0.02	7.34	< 0.0001
5	0.99	0.01	0.95	0.02	7.37	< 0.0001

\*  $\Delta$  = difference

Table 2. Results comparing Sample Entropy (with pattern length  $m$ ) for dCAN and nCAN types using Welch's t-test.

$m$	dCAN		nCAN		$\Delta^*$	
	$\bar{X}_d$	$s_d^2$	$\bar{X}_n$	$s_n^2$	$t$	$p$
2	1.56	0.27	1.68	0.34	1.33	0.19
3	1.47	0.27	1.57	0.34	1.06	0.30
4	1.41	0.32	1.49	0.40	0.70	0.49
5	1.36	0.35	1.90	2.56	1.06	0.30
6	2.97	4.67	3.39	4.73	0.27	0.79
7	3.07	4.64	6.77	6.57	2.11	0.04
8	8.24	6.91	9.21	6.65	0.44	0.66
9	10.0	6.48	10.7	5.96	0.33	0.74
10	11.8	5.46	12.7	4.38	0.59	0.56

\*  $\Delta$  = difference

#### 4. Conclusion

Renyi has several advantages compared to other entropy measures and when extended to a multiscale measure provides improved results. Many HRV measures have been suggested in the past, however it needs to be considered that the pathology that is being investigated will be characterized by certain specific features in the ECG and therefore no single HRV test should be expected to be ideal for all pathologies. The Multiscale Renyi Entropy performs at a high level of accuracy and should be included as a neuroendocrine test for CAN.

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