Identification of Cardiac Autonomic Neuropathy Progression from ECG Signals Using Multiscaled Crucial Events and Multifractal Analysis

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Abstract

Cardiac autonomic neuropathy (CAN) is a condition characterized by the dysfunction of autonomic neurons affecting heart rate regulation, which is often reflected in changes in ECG signals. Identifying the progression of CAN based on ECG changes requires advanced signal complexity analysis due to the subtle variations in signal features across different disease stages. This study investigates the relationship between CAN progression and complexity measures using a novel multiscale modified diffusion entropy analysis (MSMDEA) and multifractal detrended fluctuation analysis (MFDFA). ECG signals of 15-minute duration from participants of the Charles Sturt University Diabetes Complications Screening Group in Australia were classified into normal (N)(n=40), early (E)(n=42), and severe (S)(n=10) CAN stages. MSMDEA and MFDFA were applied to quantify the scaling index (δ) of crucial events identified by MDEA using the method of stripes and the fractal spectral density exponents (α), respectively. Significant differences in disease progression were observed by comparing MSMDEA δ values across 20 temporal scaling factors between each pair of groups using post hoc analysis (E/S, N/E, and S/N at $p < 0.01$). The full ranges of α spectra computed from MFDFA distinguished the three pairs of ECG signals at a post hoc test statistical significance of $p<0.01$.

1. Introduction

Cardiac Autonomic Neuropathy (CAN) is a major complication of diabetes marked by impaired heart rate regulation resulting from autonomic neuron dysfunction [1]. Timely identification and surveillance of CAN advancement are essential for averting severe cardiac events. Conventional research mostly focuses on distinguishing between healthy and abnormal ECG readings [2,3] or its progression at single-scale analyses [4,5]. Monitoring the progression of CAN can be further improved by investigating nuanced differences in ECG characteristics across multiple disease stages. The complexity of the ECG signal indicates autonomic function, and complexity measures can offer significant insights into the course of CAN [2, 6].

This study seeks to identify the progression of CAN by complexity metrics obtained from ECG data. Two advanced analysis methods were used: Multiscale Modified Diffusion Entropy Analysis (MSMDEA) [7] and Multifractal Detrended Fluctuation Analysis (MFDFA) [8]. MSMDEA facilitates the identification of significant events by evaluating signal complexity across many scales, whereas MFDFA quantifies the multifractal characteristics of ECG signals [7, 8].

Previous studies have assessed heart rate variability (HRV) and other linear and nonlinear features of ECG signals to detect autonomic dysfunction [3–5, 9], providing insights into autonomic function but were limited in capturing and explaining the multiscaled complexity of physiological signals and their associated memory and 1/f noise types [4], and linear HRV measures often do not distinguish between different stages of CAN progression [3, 9].

Recently, nonlinear methods such as entropy measures [5, 6], fractal analysis, and multifractal analysis [4] have been introduced to provide a more nuanced understanding of the autonomic nervous system's (ANS) regulation of heart rate [10]. Modified Diffusion Entropy Analysis (MDEA) [11, 12], particularly the multiscaled approach of it (MSMDEA) [7], has proven effective in uncovering the complex dynamics present in physiological signals manifested as crucial events. On a related note, multifractal analysis, quantified through Multifractal Detrended Fluctuation Analysis (MFDFA) [8], is another robust method that detects the multifractal variability of the ANS function in terms of the cardiac mechanism. However, existing research has a limited understanding of the connection between relevant complexity analyses and their physiological interpretations [13].

The present study builds on this body of work by applying Multiscale Modified Diffusion Entropy Analysis (MSMDEA) supported by MFDFA to capture the subtle variations in ECG signals at various time scales [14] attributed to different stages of CAN by first confirming the presence of anomalous scaling [12] and then identifying its type as a Type II 1/f noise [4] associated with crucial

events detected through the MDEA. Crucial events, identified by their inverse power-law (IPL) waiting time probability density function (PDF) with a scaling index (μ) less than 3, play a significant role in shaping the multifractal characteristics of heartbeat dynamics [13, 15]. The novelty lies in using these methods to analyze disease progression rather than merely differentiating between healthy and pathological states and highlighting the complementary application of both techniques. This approach provides a more comprehensive understanding of the multifractal nature of ECG signals and their changes with disease progression, with a high significance for promising clinical applications.

2. Methodology

This study employed data sourced from the Charles Sturt University Diabetes Complications Screening Group (DiScRi) in Australia [16]. The Human Ethics Committee at Charles Sturt University approved the research, and all participants provided written informed consent. Participants at the clinic underwent a 20-minute ECG recording using the lead II configuration. The recordings were acquired utilizing a Maclab Pro in conjunction with Chart 7 software (ADInstruments, Sydney). Each record features a sampling rate of 400 Hz, comprising approximately 480,000 sample points, which corresponds to a duration of 20 minutes. Participants with cardiac pathology, pacemakers, kidney disease, or those on anti-arrhythmic medications were excluded from the analysis. The classification of cardiac autonomic neuropathy (CAN) was determined using the Ewing battery criteria as described in earlier research [2]. The participants exhibited comparable characteristics regarding age, gender, and heart rate. Each participant was classified into one of three groups: those without CAN (n=40), those with early CAN (n=42), or those with definite severe CAN (n=10).

A 15-minute segment was selected from the midpoint of the 20-minute recording to eliminate any initial artifacts and movements occurring towards the conclusion of the recording period. The ECG series for each subject underwent fundamental pre-processing, including baseline wander correction and normalization. The management of ectopic and other abnormal beats utilized a simple artifact correction algorithm grounded in the single dependent rank ordered mean (SDROM) algorithm, complemented by an adaptive filtering technique (ADF) [17]. All methods were implemented using MATLAB R2023a.

2.1. Multiscale Modified Diffusion Entropy Analysis (MSMDEA)

The MSMDEA method involves initially coarse-graining the time series, employing the second-moment standard deviation σ as a measure of spread. This process generates a set of time series across different time scales [18]

The time coarse-grained ECG series was then subjected to MDEA, as outlined in [7,12]. Scaling indices were computed for each individual time series. The data series was normalized and divided into intervals of [0, 1] using parallel stripes spaced at 0.01. A power-law scaling index δ of 0.5 suggests that the process adheres to a random Poisson distribution [4]. The scaling index obtained from crucial events in a process exhibiting higher complexity exceeds 0.5 when the IPL complexity index μ meets the condition $2 < \mu < 3$, as indicated in (5).

$$\delta = \frac{1}{\mu - 1} \tag{1}$$

2.2. Manneville validation

The results from the clinical data were validated through a surrogate time series generated via the Manneville map [19]. The surrogate time series matched the length of the ECG signals and was assessed to establish a baseline signal through standard complexity metrics [15]. The baseline null hypothesis denotes a surrogate Manneville time series characterized by a mean of 3 and a standard deviation σ of 0.5, indicative of random noise. Simulations were conducted at two additional complexity levels, μ = 2.5 and μ = 2, to represent medium and high complexity, respectively (Figure 1). Prior studies have shown that pathological physiological signals exhibit a lack of complexity and crucial events, akin to random Poisson processes. Healthy physiological signals demonstrate complex dynamics and crucial events [4]. The Manneville surrogate signal provides a reliable simulation for validating the proposed methodology and comprehending its implications in clinical settings associated with health and disease.

2.3. Multifractal Detrended Fluctuation Analysis (MFDFA)

In this study, the direct estimation method of Multifractal Detrended Fluctuation Analysis (MFDFA) to estimate the multifractal spectrum from ECG time series was used, focusing on the local fluctuations directly rather than using a q-order extension of RMS (Root Mean Square). Unlike traditional MFDFA, where the q-order fluctuation function is used, the direct method estimates the local Hurst exponent at each time point [8]. The local Hurst exponent captures the scale-invariant nature of fluctuations in the time series, and its probability distribution is used to compute the multifractal spectrum directly:

$$D(h) = 1 - \frac{\ln P(h)}{-\ln s} \tag{2}$$

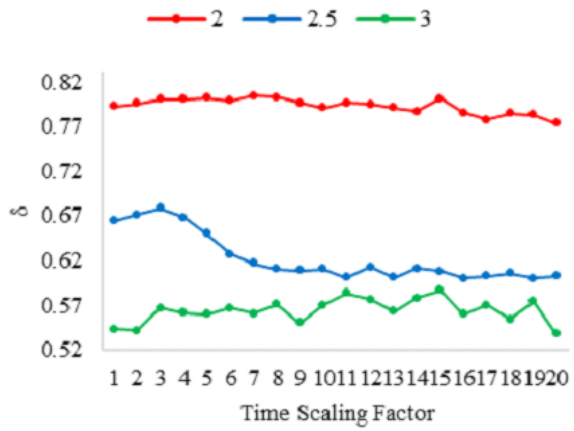

Figure 1. Scaling indices δ of the surrogate Manneville-based signals spanning 20 temporal scaling factors with three distinct complexity defined by known values of μ representing highest (μ=2), medium (μ=2.5), and minimal (μ=3) difficulties.

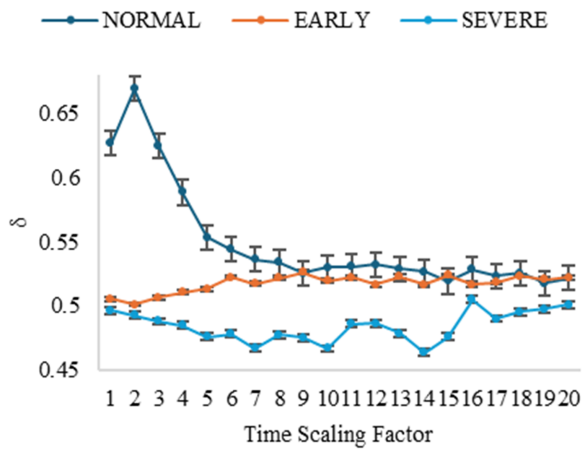

Figure 2. Scaling indices δ (y-axis) across 20 temporal scaling factors (x-axis) for the three groups of normal, early, and severe CAN progressions

where $P(h)$ is the probability distribution of the local Hurst exponents, $D(h)$ is the multifractal spectrum, and s is the scale.

3. Results and Discussion

Significant differences in CAN progression were observed via MSMDEA by analyzing the δ values across 20 temporal scaling factors between each group pair, through applying non-parametric ANOVA (Kruskal-Wallis) and Dunn's post hoc analysis ($p < 0.01$). Normal ECG signals exhibited greater complexity (values closer to critical value δ=1), suggesting healthy autonomic function, while pathological signals displayed diminished complexity, as shown in figure 2. As δ deviates from this critical value, the system approaches Gaussian behavior, suggesting increased pathology and reduced complexity [4].

Similarly, MFDFA showed statistical significance in differentiating disease stages based on the α spectra (Figure 3). Comparing the complete range of α spectra was highly effective in distinguishing the three groups of ECG signals (N, E, S) with a post hoc test statistical significance of $p < 0.01$.

The analysis revealed that complexity dynamics are more effectively distinguished at multiple temporal and fractal scales than single scale identification, highlighting the importance of temporal multiscaling and multifractality in differentiating ECG signals [4]. The findings additionally support the neural criticality hypothesis, indicating that cardiac function and pathology are linked to self-organized criticality processes [20, 21].

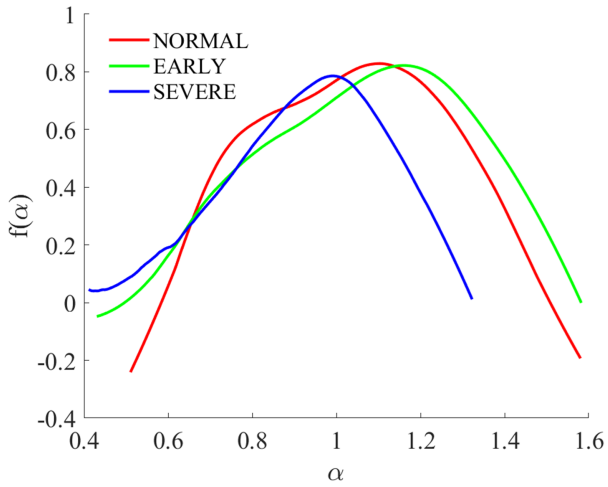

Figure 3. Multifractal spectra of CAN progression

Since it has been established that crucial events contribute to the multifractal nature of heartbeat dynamics [13], the presence and influence of these events, as opposed to uncorrelated Poisson-like events, directly correlate with a broader multifractal spectrum, signaling healthier HRV.

Hence, while MSMDEA and MFDFA differ in analyzing the complexity of heart signals, with MSMDEA targeting the non-stationarity of the signals [7], the presence of renewal events and different types of 1/f noise [4, 12] and MFDFA targeting long-range correlations regardless of their stationairty or non-stationarity [8], multifractal analysis offers a significant support to characterizing the progression of CAN by confirming the presence of anomalous scaling in the heart signals [13], the type of which is further identified through MSMDEA.

The use of MSMDEA and MFDFA has demonstrated a clear potential for enhancing the diagnosis and monitoring of CAN at higher significance than earlier methods that focused on single-scale analysis of entropy-based measures[2, 4] or linear measures [9]. The findings also indicate that complexity analysis using these methods provides complementary insightful information on the progression of CAN. MSMDEA, in particular, is valuable for understanding the multifractal nature of ECG signals by detecting crucial events that represent the heart's multifractal processes and type of anomalous scaling that drive the dynamics of cardiac autonomic regulation. These methods showed at ta high level of significance, the heterogeneous and scale-dependent behavior within ECG data in CAN progression, which is crucial for improved modeling, forecasting, and clinical decision-making.

4. Conclusion

The integration of MSMDEA and MFDFA in analyzing ECG signals offers a more nuanced understanding of CAN progression. By examining the complexity and multifractal characteristics of ECG signals, these methods enhance the accuracy and robustness of CAN classification. This study contributes to the development of advanced diagnostic tools in precision cardiology, ultimately aiding in better clinical management of patients with CAN.

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