Non-linear Scales of Heart Rate Variability in Anesthesia

Jia-Rong Yeh¹, Si-Hui Yang² and Shou-Zen Fan³

Abstract—Autonomic nerve system (ANS) activity is an important physiological indicator should be cared about in anesthesia. ANS activity affects heart rate, blood pressure, respiration and so on. Heart rate variability (HRV) reflects the underlying sympathetic tone and vagal modulation of human cardiac systems as an appropriate assessment for ANS activity. Moreover, ANS activity should be well managed in anesthesia, which reflects the functional response of brain stem different from the consciousness as activities in cortices. Traditional spectral analysis provides a time-frequency domain measures of HRV. Recently, nonlinear scales of short-term fractal dimension and delta entropy of HRV have been proposed and applied in the applications of ANS activity evaluation. In this study, the recordings of HRV during the courses of minor surgeries for 13 patients were investigated by spectral analysis, detrended fluctuation analysis (DFA), and delta entropy analysis for the purpose to test the performances of these nonlinear scales of HRV in anesthesia. These two nonlinear scales of short-term fractal dimension by DFA and delta entropy reflect different characteristics of dynamics for HRV in anesthesia. According our results, DFA α₁ performs a better scale for ANS activity monitoring in anesthesia than delta entropy does.

Keywords—autonomic nerve system, anesthesia, heart rate variability, fractal dimension, delta entropy, detrended fluctuation analysis.

I. INTRODUCTION

Heart rate variability (HRV) is a complicated, nonlinear, and non-stationary time series, which is dominated by many different underlying physiological mechanisms. Heart rate fluctuates over time to adapt to changing circumstances [1]. In general, HRV is dominated by vagal modulation during a non-rapid eye movement sleep [2], and ANS activity decreases during general anesthesia [3-5]. The ANS nuclei that control heart rate and blood pressure are located in the brain stem. Thus, HRV may reflect the activities of brain stem in anesthesia, which is different from the consciousness as the activities of cortices [6]. The ANS activity and consciousness should be considered as two different dimensions of anesthesia management. So far, the most of equipments for anesthesia depth monitoring focus on the level of consciousness, which is quantified using the bispectral index (BIS), state entropy (SE), and response entropy (RE) of EEG.

In this study, the ANS activity reflected by HRV is the aimed dimension of anesthesia. HRV measures derived by traditional time frequency analysis are insensitive to detect ANS activity during anesthesia [7, 8]. Recently, many nonlinear scales, such as fractal dimension and entropy, has been proposed and applied for quantifying the nonlinear properties of physiological signals. Detrended fluctuation analysis (DFA) is such a nonlinear algorithm proposed by Peng et al. for quantifying the fractal organization of nonlinear time series [9, 10]. As present reports of the investigations to dynamics of human heartbeat time series, the short-term (scale range from 4 to 11 beats) fractal organization of human heartbeat time series reflects a balance status between sympathetic and vagal modulations [11]. The short-term scaling exponent of DFA of heartbeat time series noted as DFA α₁ of HRV was used as a nonlinear scale for HRV in anesthesia. On the other hand, approximate entropy (ApEn) [12] represents the complexity of HRV as another different nonlinear scale for ANS activity [5]. In the practices of clinical application for HRV analysis in anesthesia, ApEn is interfered by low-frequency variation of HRV during light anesthesia. Therefore, a modified algorithm of ApEn is noted as delta entropy (dEn) was proposed [13].

In this investigation, 13 patients treated by minor surgeries were recruited to join this research project. The HRV recordings including overall courses of surgical operations were used as the material of this study. The surgical events, such intubation, start of surgical action, drug injection, and vital signs were recorded during the courses of surgical operations. And, the course of surgical operation was divided into 4 stages of pre-anesthesia, induction, surgical operation and after surgery for comparison. In this study, a traditional linear measure and two innovative non-linear scales are used to evaluate the ANS activity for those stages in anesthesia. According to our results, DFA α₁ performs as a good assessment for ANS activity in anesthesia.

II. MATERIAL

Total of 13 patients treated by minor surgeries were recruited to join this research project. As the exclusion criteria, subjects with chronic diseases such as cardiopathy, hypertension, arrhythmia and diabetes were excluded in this
study. Subjects who abuse the drugs or morphine were also not included in this investigation. The courses of general anesthesia were divided into four different stages as pre-anesthesia, induction, surgical operation, and after surgery. The complete course of general anesthesia is considered to reflect the spontaneous status of ANS activity. And, this research has been approved by the Research Ethics Committee of National Taiwan University Hospital. Physiological signals, such as blood pressure, ECG, EEG, SPO2 and SE and RE of EEG, were measured by Intellivue MP60 patients monitor system, the product of Philips.

III. METHODOLOGY

3.1 A brief introduction of DFA

As the detrending process, least square lines fit data within the windows with fixed timescale of $n$ as the trends of data on a predetermined timescale. The function of fluctuation, $F(n)$, is defined as root mean square (RMS) energy of the detrended time series. Then, the power-law correlation between the timescales, $n$, and the functions of fluctuation, $F(n)$, is defined as the fractal dimension of a nonlinear and non-stationary signal. In a graphic presentation, the plot of logarithmic fluctuation functions against their corresponding logarithmic timescales, defined as DFA plot, is a straight line for a power-law correlation. The fractal dimension was defined as the scaling exponent of power-law correlation as the slope of DFA plot.

Generally, a real-world signal is with a fractal organization in a small scale range. In order to improve the fractal dimension of a real-world signal, the method of integration can be applied to enhance the fractal organization of time series [16, 17]. The integration to a time series can be expressed by the following equation:

$$y(k) = \sum_{i=1}^{k} [B(i) - B_{ave}]$$

(1)

Where $B(i)$ is the $i$th sample of heartbeat time series; $B_{ave}$ is the average of the heartbeat time series and $y(k)$ is the value of the $i$th sample of the integrated time series.

In a detrending process, least square lines are used to fit the data within windows with size of $n$ as the local trends of data for timescale of $n$. Then, the function of fluctuation, $F(n)$, for a detrended time series using the linear trends with timescale of $n$ is defined as the root mean square energy derived by the following equation:

$$F(n) = \frac{1}{N} \sum_{k=1}^{N} [y(k) - y_{ave}(k)]^2$$

(2)

where $F(n)$ is the function of fluctuation for an detrended time series using local trends with timescale of $n$; $N$ is number of heartbeats and $y_{ave}(k)$ is the $k$th sample of the local trends with timescale of $n$.

The power-law correlation between the timescales and the corresponding fluctuation functions is shown as the distribution close to a straight line on a DFA plot as shown in Figure 1. The scaling exponent of DFA is defined as the slope of DFA plot.

![Fig.1 The power-law correlation between the timescales and their corresponding fluctuation functions.](image)

The fractal dimension of heartbeat time series can be quantified by the power-law correlation between timescales and their corresponding fluctuation functions as the slope of DFA plot. According to previous studies of DFA in HRV analysis, the scaling exponent of DFA can be divided into two different timescale ranges of short-term scaling range from 4 to 11 beats and long-term scaling range above 11 beats. The short-term scaling exponent noted as DFA $\alpha_1$ performs as an assessment for the balance of vagal and sympathetic modulation. And the long-time scaling exponent $\alpha_2$, with scaling range above 11, performs as an assessment for the systemic function of human cardiac systems [14, 15].

3.2 A brief introduction of delta entropy ($\delta$En)

Delta entropy is a modified algorithm of ApEn. The only different between $\delta$En and ApEn is the operation of differential. ApEn of HRV is calculated from the time series of R-R intervals directly, and $\delta$En of HRV is calculated from the differenced time series of R-R intervals, in which the interfering effect of low-frequency variation can be eliminated [11]. The differential operation can be expressed as the following equation:

$$dRRI_n = RRI_n - RRI_{n-1}$$

(3)

Where $dRRI_n$ is the $n$-th sample of the differenced time series of R-R intervals and $RRI_n$ is the $n$-th sample of the original time series of R-R intervals.

ApEn is a simple algorithm used to quantify the degree of regularity and unpredictability over a complicated time series. According to the calculation of ApEn described in [16], two parameters of template length $m$ and distance coefficient $r$ should be determined first. Then, for a time series $x_i$, $i=0,...,N-1$, a set of $m$-dimensional vectors can be formulated, such that $x_i^m=[x_{i-(m-1)}, x_{i-(m-2)}, ..., x_i]$. In addition, a set of $(m+1)$-dimensional vectors can be obtained by the same way. For any $i$th $m$- and $(m+1)$-dimensional vectors, the number of all within the distance threshold of $r \times SD$ can be counted and normalized to the total number of vectors as
\[ C^n_m = \frac{1}{N - (m - 1)} \sum_{i,j \neq i} H(|x^n_i - x^n_j| - r \cdot SD) \]  \hspace{1cm} (4)

and

\[ C^{n+1}_m = \frac{1}{N - (m - 1)} \sum_{i,j \neq i} H(|x^{n+1}_i - x^{n+1}_j| - r \cdot SD) \]  \hspace{1cm} (5)

Then, ApEn can be calculated as the predictability of the \((m+1)\)th points based on the probability of \(m\)-dimensional vectors.

\[ ApEn(m, \delta, N) = \frac{1}{N - (m - 1)} \sum \log(C^n_m) - \frac{1}{N - m} \sum \log(C^{n+1}_m) \]  \hspace{1cm} (6)

Where \(H\) is the Heaviside function and \(|x^n_i - x^n_j|\) is the measure of distance between vectors \(x^n_i\) and \(x^n_j\). \(SD\) is the standard deviation of time series.

In this investigation, DFA \(\alpha_1\) and \(\delta\) entropy were calculated for a sliding window with size of 200 heartbeats and each window has 100 beats overlap with the previous and the successive windows.

**IV. RESULTS**

In this study, 3 different analysis algorithms of HRV were used to investigate linear and nonlinear scales of ANS activity. These 3 algorithms are time frequency analysis, DFA and \(\delta\)En. For these 3 different analysis methods, the time series of HRV must be pre-processed by re-sampling, integration or differential. In this investigation, the time series of HRV were re-sampled at 0.25 Hz for time frequency analysis; were integrated using equation (1) for DFA; and were differenced using equation (3) for \(\delta\)En. The profiles of the pre-processed time series of HRV are totally different as shown in Figure 2.

![Fig. 2 Examples for the re-sampled, integrated, and differenced time series of HRV](image)

The re-sampled time series of HRV keeps the time frequency domain information as the original one. An integrated HRV represents the auto-correlation property of time series and a differenced one reflects the fluctuating profile of signal. Therefore, time frequency analysis to the re-sampled time series of HRV generates a time-frequency measure for ANS activity; DFA \(\alpha_1\) represents the short-term power-law correlation of HRV; and \(\delta\)En is a measure for the regulation and unpredictability of HRV time series. Figure 3 shows an example for the overall variation of HRV during a course of surgical operation using time frequency distribution, DFA \(\alpha_1\), and \(\delta\)En.

![Fig. 3 Illustration of the overall variation of HRV during a whole course of surgical operation using DFA \(\alpha_1\), \(\delta\)En, and time frequency distribution](image)
distribution.

As shown in figure 3, both DFA $\alpha_1$ and $\delta\text{En}$ generally decrease during the induction stage and fluctuates because of stress caused by intubation. Then, DFA $\alpha_1$ and $\delta\text{En}$ calm down before the start of surgical operation. During the surgical operation, drugs and surgical stresses affect the HRV to generate the keeping low and fluctuating patterns in the assessments of DFA $\alpha_1$ and $\delta\text{En}$. The output of time frequency analysis is a time frequency distribution of HRV as shown in the 3rd row of figure 3. The time frequency analysis performed weak to defense the interfering effect of low frequency variation. Significantly, the low frequency variation is nonlinear and the spectrum at the time point that low frequency variation appears is significantly abruptly rising in comparing with the neighborhood. This result is similar to the description in the previous study of Mäenpää et al. [13]. Therefore, the nonlinear scales of HRV seem to be more reliable in HRV analysis for the ANS activity monitoring in anesthesia. Then, the statistical results of DFA $\alpha_1$ and $\delta\text{En}$ of HRV on 4 different stages of anesthesia are shown in Table 1.

**TABLE I: THE STATISTICAL RESULTS OF DFA $\alpha_1$ AND $\delta\text{En}$ FOR 4 STAGES OF ANESTHESIA.**

<table>
<thead>
<tr>
<th>stage</th>
<th>Pre-anesthesia</th>
<th>induction</th>
<th>Surgical operation</th>
<th>After surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>DFA $\alpha_1$</td>
<td>1.127± 0.213</td>
<td>0.932± 0.103</td>
<td>0.899± 0.158</td>
<td>0.876± 0.137</td>
</tr>
<tr>
<td>$\delta\text{En}$</td>
<td>1.138± 0.342</td>
<td>1.025± 0.434</td>
<td>1.195± 0.263</td>
<td>1.100± 0.361</td>
</tr>
</tbody>
</table>

Furthermore, one-way analysis of variance (ANOVA) was used to test the performances of DFA $\alpha_1$ and $\delta\text{En}$. Analysis results of ANOVA show a $p$-value of 0.0006 (the results of ANOVA as shown in Table 2) for DFA $\alpha_1$ and a $p$-value of 0.6687 (the results of ANOVA as shown in Table 3) for $\delta\text{En}$.

**TABLE II ANOVA TABLE FOR DFA $\alpha_1$**

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Columns</td>
<td>0.51392</td>
<td>3</td>
<td>0.17131</td>
<td>6.84</td>
<td>0.0006</td>
</tr>
<tr>
<td>Error</td>
<td>1.20171</td>
<td>48</td>
<td>0.02504</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>1.71563</td>
<td>51</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE III ANOVA TABLE FOR $\delta\text{En}$**

<table>
<thead>
<tr>
<th>Source</th>
<th>SS</th>
<th>df</th>
<th>MS</th>
<th>F</th>
<th>$p$-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Columns</td>
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<td>0.06604</td>
<td>0.52</td>
<td>0.6687</td>
</tr>
<tr>
<td>Error</td>
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<td>48</td>
<td>0.12632</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>6.26142</td>
<td>51</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

The statistical results of ANOVA show that DFA $\alpha_1$ is a better nonlinear scale for ANS activity in the application for distinguishing the 4 different stages of anesthesia in comparing with $\delta\text{En}$. In fact, the ANS activity of induction and surgical operation stages are complicated. During the induction stage, intubation performs a kind of surgical stress for patients. And, the surgical actions and the clinical situations are complicated during the course of surgical operation. It is still unknown which scale is more sensitive for monitoring the surgical stresses and drug effects than the other one.

V. DISCUSSIONS AND CONCLUSIONS

In this study, two different nonlinear scales of HRV were used to evaluate the ANS activity during the courses of surgical operations. DFA $\alpha_1$ is a parameter using fractal dimension to quantify the auto-correlation of heartbeat time series and $\delta\text{En}$ performs as a different parameter to quantify the regularity and unpredictability of heartbeat intervals. These two parameters represent the profile of the dynamics of heartbeat time series on different views. The measure of $\delta\text{En}$ represents a degree of complexity. Generally, the degree of complexity of heartbeat time series should decrease in anesthesia. According to our observations, $\delta\text{En}$ actually decreases during anesthesia in comparing with that on awakening stage. However, $\delta\text{En}$ of heart beat time series reflects significant differences among individuals. Standard deviations of $\delta\text{En}$ on 4 different stages of anesthesia as shown in Table 1 reflect that the individual differences are significant. Because the influences of individual differences are stronger than the variation for different stages, the result of ANOVA reflects an insignificant difference in statistics for $\delta\text{En}$ as shown in Table 3.

Different from $\delta\text{En}$, DFA $\alpha_1$ reflects the sympathetic tone and vagal modulation of HRV. The individual difference is not significant within the subjects recruited in this research project. DFA $\alpha_1$ actually performs a good assessment for this application. As the activity of ANS in brain stem is suppressed in anesthesia, DFA $\alpha_1$ works well to reflect the suppression of ANS activity. Therefore, in comparing the performances & the underlying mechanisms of these two nonlinear scales, DFA $\alpha_1$ seems to be a better assessment for ANS activity monitoring in anesthesia than $\delta\text{En}$ does.

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