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Decreased sample entropy during sleep-to-wake transition in sleep apnea patients

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Abstract

Objective. This study aimed to prove that there is a sudden change in the human physiology system when switching from one sleep stage to another and physical threshold-based sample entropy (SampEn) is able to capture this transition in an RR interval time series from patients with disorders such as sleep apnea. *Approach*. Physical threshold-based SampEn was used to analyze different sleep-stage RR segments from sleep apnea subjects in the St. Vincents University Hospital/University College Dublin Sleep Apnea Database, and SampEn differences were compared between two consecutive sleep stages. Additionally, other standard heart rate variability (HRV) measures were also analyzed to make comparisons. *Main results*. The findings suggested that the sleep-to-wake transitions presented a SampEn decrease significantly larger than intra-sleep ones ($P < 0.01$), which outperformed other standard HRV measures. Moreover, significant entropy differences between sleep and subsequent wakefulness appeared when the previous sleep stage was either S1 ($P < 0.05$), S2 ($P < 0.01$) or S4 ($P < 0.05$). *Significance*. The results demonstrated that physical threshold-based SampEn has the capability of depicting physiological changes in the cardiovascular system during the sleep-to-wake transition in sleep apnea patients and it is more reliable than the other analyzed HRV measures. This noninvasive HRV measure is a potential tool for further evaluation of sleep physiological time series.

1. Introduction

Sleep regulation is a complex physiological process, which presents intricate variability and a nonlinear autonomic control mechanism. A group of neuronal interactions between the thalamus and the cortical network acts as a switch to achieve stable sleep and wakefulness, and the state transition during sleep periods is related to brain fluctuations as well as autonomic nerve activities (Somers *et al* 1993, Saper *et al* 2005). Sleep apnea syndrome (SAS) is a breathing disorder that can be interpreted as a momentary shutting of the upper parts of the human airway during sleep (Ravelo-García *et al* 2014). Among all types of this disease, obstructive sleep apnea (OSA) is the most common, characterized by cessations of respiratory flow for at least 10 s (Strollo and Rogers 1996). It is widely acknowledged that OSA leads to asphyxia, hypoxemia and awakenings; thus increasing the risk of cardiovascular diseases such as hypertension, cardiac arrhythmia, congestive heart failure, acute myocardial infarction and stroke (Yaggi *et al* 2005). In this case, understanding sleep regulation during various stages is meaningful for sleep apnea diagnosis.

Sleep scientists measure sleep electrophysiologically and the simultaneous recording of electroencephalography (EEG), the electrooculogram (EOG) and the electromyogram (EMG) are the accepted standard measures of sleep and waking, which are termed polysomnography (PSG) altogether (Wolpert 1969). Nevertheless, PSG is

quite expensive and difficult to operate, and sometimes its application affects the sleep of the trial subjects (Lee *et al* 2002). Thus, researchers have turned to uncomplicated and swift sleep-staging evaluation methods instead.

The literature has demonstrated that sleep stage classification via electrocardiogram (ECG) signals is the most recent endeavor in the field, and numerous papers have shown that sleep staging depends on ECG-related parameters (Chriskos *et al* 2020). The past decades have witnessed an increasing tendency to apply heart rate variability (HRV) to analyze ECG signal during sleep as an alternative of EEG, and the correlation between HRV and sleep stage classification has been well summarized (Vanoli *et al* 1995). As a widely used noninvasive autonomic nerve system (ANS) assessment method, HRV analyzes the interval between consecutive heartbeats, and research has proven its connection with the variation in sleep stages (Telser *et al* 2004). Given that sleep stages are classified as wakefulness, two stages of light sleep, two of deep sleep and rapid eye movement (REM) sleep, the regulation of the ANS changes with the sleep stages (Parmeggiani 1990). The average heart rate (HR) falls steadily from the wakefulness to deep sleep, since the latter is vagal-dominant. During REM, which presents a sympathetic dominance and a significant withdrawal of vagal activity, HR increases lightly and exhibits greater variability than during wakefulness. As a matter of fact, numerical methods developed for time series analysis of HRV in healthy as well as pathological people have already been applied to data from the ECG channel of the PSG, which allows characterization of various sleep stages by means of the HR (Staudacher *et al* 2005). Among all these HRV measurements, sample entropy (SampEn) is a promising nonlinear tool, which is highly adaptive for quantifying the regularity of physiological time series and eliciting valuable information about the cardiovascular system (Richman and Moorman 2000).

As a representative nonlinear feature, SampEn has been applied in massive studies for automatic sleep staging through ECG signals (Ebrahimi *et al* 2015). However, few people have paid attention to the transition process between different sleep stages. Since the alternation of sleep stages circulates across the night, specific physiological function fluctuates simultaneously, and the alternate point of two sleep stages is likely to witness a sudden change. Considering that the ANS is tightly coupled with the brain (Schiecke *et al* 2019), we assumed that a SampEn-based HRV method can capture such changes and the change in HRV index would not be strictly synchronous with that in EEG signals. Moreover, as the basic sleep regulation mechanism is similar in sleep apnea and healthy subjects (Urbanik *et al* 2018), it would be reasonable to speculate that the sudden change during sleep stage transition also exists in sleep apnea individuals. According to its internal structure, a sleep period can be roughly divided into wake, REM, and non-rapid eye movement (NREM) stages, and REM sleep is an intermediate state between NREM and wakefulness (Roehrs and Roth 2019), thus we hypothesized that the variation in SampEn value would be more obvious in sleep-to-wake transitions than intra-sleep transitions, especially from NREM sleep to wakefulness.

In previous study, a physical threshold-based SampEn was put forward to solve the inconsistency of traditional SampEn in heart failure diagnosis and experiments have verified its superiority in SampEn calculations (Xiong *et al* 2019). In this study, we continue to use the physical threshold-based SampEn, as it is more preferable than the traditional one. The aim of this work is to reveal SampEn change rules during sleep stage transitions in sleep apnea patients by analyzing the labeled RR interval time series. Since the connection between HRV and EEG during sleep has been well demonstrated, SampEn is capable to depict the changes in healthy subjects at the onset as well as the offset of the sleep. On that basis, the HRV variation during different stages for sleep apnea patients is investigated to ensure the adaptability of the SampEn change rules to pathological individuals. Comparisons between the SampEn values of the former and the latter sleep stages will be performed on the selected transition episodes to validate the hypothesis. In order to prove its consistency, experimental results with the traditional threshold are also presented.

2. Materials and methods

2.1. Physical threshold-based SampEn is able to capture the transition from sleep to wake.

As a typical nonlinear HRV measure, SampEn has been applied in numerical studies to explore the characteristics of sleep. Most research focuses on the discrimination of different sleep stages, where SampEn is selected as a feature of the RR interval time series during the sleep period. Nevertheless, such analysis does not fully exploit the potential of entropy measurement. As detecting the transitions of certain sleep stages has also been a spotlight in sleep research, we assume that the proposed physical threshold-based SampEn could also capture these sudden changes.

Sleep is not a homogeneous process, as a long period of nocturnal sleep actually comprises many short wake intervals (Lo *et al* 2002). Therefore, the complex characteristics of sleep–wake transitions might be the most worth exploring ones regarding the change-point detection during sleep. Among all the sleep–wake transitions during the total sleep time, the brief awakenings from sleep appear to be random and their durations vary greatly, making it hard to analyze the transition process (Lo *et al* 2004). Meanwhile, the transitions at the onset

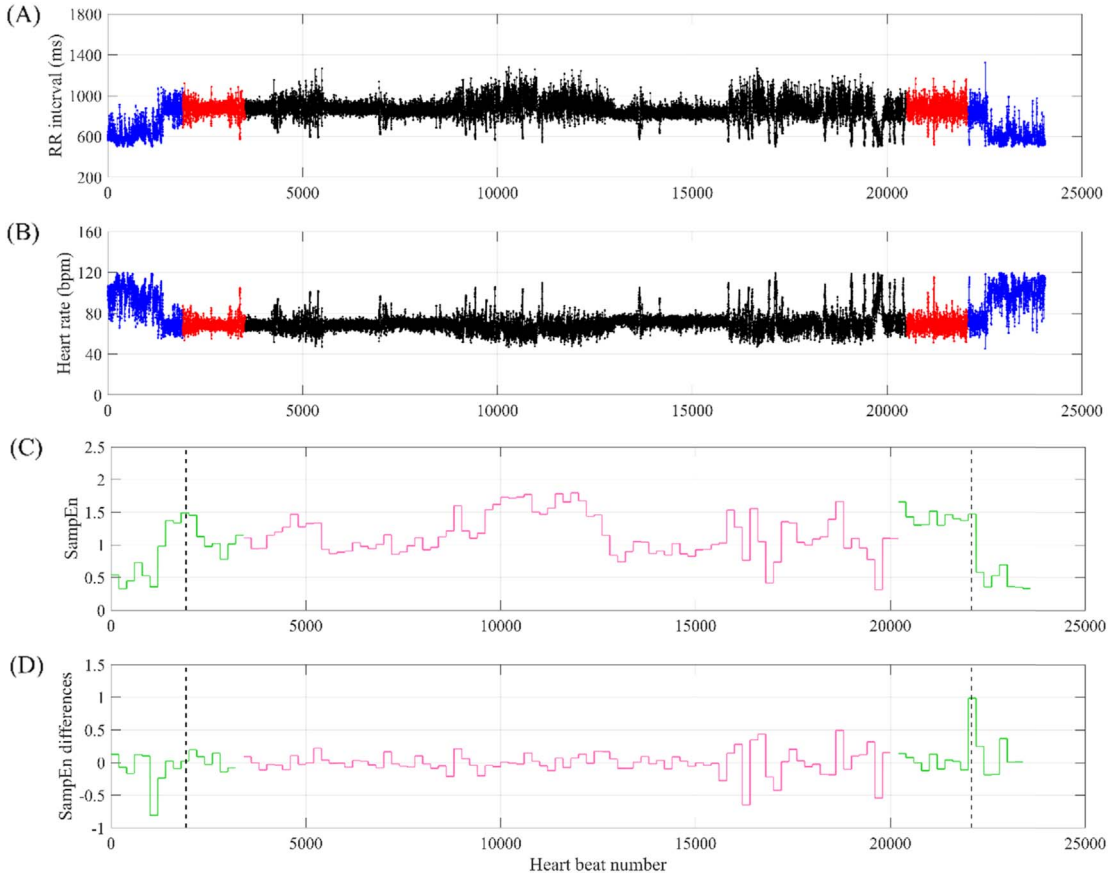

Figure 1. Presentation of (A) sleep time series, (B) sleep HR sequence, (C) SampEn results and (D) corresponding SampEn differences of subject 6 from the MMASH dataset. Herein, embedding dimension m was set as 2, physical threshold $r = 12$ ms, and segment length $N = 200$.

point as well as the offset point of nighttime sleep seem to be clearer, as the duration of the neighboring states remain long enough. Thus, the transitions of sleep onset and offset would be easier to capture.

Although sleep is characterized by sensorimotor disconnection from the environment and altered consciousness, reduced muscle activity and interactions, the brain is metabolically active during sleep, rendering it the main human organ affected by the process (Siegel 2009). The variations of sleep status are easy to observe through different frequency components in EEG signals (Chriskos *et al* 2020). Since complicated factors in the human body environment modulate the couplings between brain and heart, changes in cardiac activity lags behind the corresponding cortical one (Lueckel *et al* 2018). Given that sleep and wake are governed by complex interactions between neurons in the brain, these neurons are thought to act as a 'latch' collectively, which produces stable sleep and wakefulness (Lo *et al* 2004). In fact, brief arousals and normal wakefulness require the coordinated active of several wake-promoting cell groups located in the rostral brainstem and posterior hypothalamus, and neuronal subthreshold voltage fluctuations in wake-promoting neurons are likely the origin of spontaneous brief arousals during sleep (Dvir *et al* 2018). Such switching over is presented in the brain instantaneously, while it appears in the heart relatively late. Hence, we propose that the response of the cardiovascular system to neurons in the brain would be similar to a step response with resistance, which means there will be an obvious change in the ANS with a time delay after the switch of the 'latch' in the CNS. We also assume that the wake-to-sleep transition is likely to be a progressive process, while the sleep-to-wake transition presents a sudden change.

Figures 1 and 2 show the total sleep periods of two healthy subjects from the Multilevel Monitoring of Activity and Sleep in Healthy people (MMASH) dataset from http://www.physionet.org (Rossi *et al* 2020). For both figures, the sleep time series is presented in RR interval or heart rate format in the first two graphs, where the first one is the filtered time series and the second one is the filtered HR sequence, and the SampEn results as well as SampEn differences corresponding to each RR interval segment are exhibited in the last two graphs. The blue lines in subplots (A) and (B) represent the 30 min time series before sleep onset and after sleep offset, respectively; the red lines represent the 30 min time series after sleep onset and before sleep offset; and the black line is the in-between sleep period. Thus, there are two stage transitions. The transition from blue to red is a

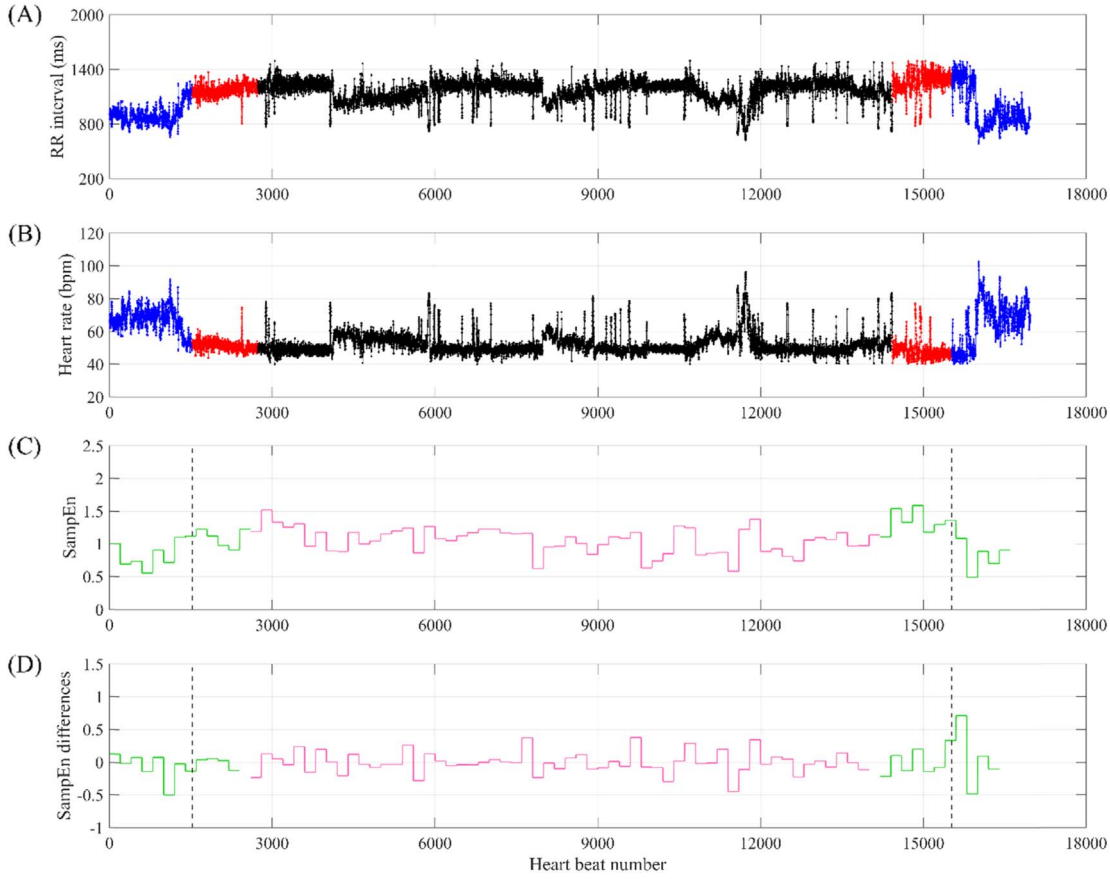

Figure 2. Presentation of (A) sleep time series, (B) sleep HR sequence, (C) SampEn results and (D) corresponding SampEn differences of subject 22 from the MMASH dataset. Herein, embedding dimension m was set as 2, physical threshold $r = 12$ ms, and segment length $N = 200$.

wake-to-sleep one and the transition from red to blue is a sleep-to-wake one. In subplots (C) and (D), the entropy values or entropy differences of these two transitions are marked in green and the onset as well as the offset point is plotted by a black dashed line. It is noticeable that the SampEn difference represents the SampEn of the former RR segment minus the latter and the total SampEn difference number is one less than the RR segment number. Herein, the embedding dimension $m = 2$ and segment length $N = 200$. Since the dataset was sampled by 1000 Hz, the physical threshold is set as 20.5 times sampling period, i.e. 20.5 ms.

As figure 1 implies, there is a progressive increase in SampEn value at the sleep onset and a sudden drop after the sleep offset point. The baseline SampEn of the total sleep period is higher than that of the wakefulness, and the transitions between sleep and wake are likely to be the outline of a step response. Furthermore, we can see that though the change in HR sequence before sleep onset is abrupt, the corresponding change in the SampEn value fluctuates, which means that the transition from wake to sleep is a tortuous process rather than a sudden change. Nevertheless, the sudden drop in SampEn with some time delay after sleep offset point illustrates that the sleep-to-wake transition is an instantaneous change, and the cardiovascular system would respond to this change with a lag. Moreover, the SampEn differences in subplot (D) reveals that there is a remarkable decrease near the onset point as well as an increase near the offset point in the SampEn difference value, while the SampEn fluctuations during other periods are relatively placid. This demonstrates that the changes in SampEn difference during the sleep onset and offset periods are more significant than the periods during sleep.

In figure 2, the RR interval time series, HR sequence, SampEn results and SampEn differences of another subject from the MMASH database are shown, and we can still observe the fluctuations in RR interval as well as the SampEn value at the sleep onset and offset points, respectively. The RR interval becomes longer, or HR accelerates when sleep begins, and RR interval shortens, or HR decelerates when sleep ends, which are clear signs of sleep onset and offset. However, fluctuations during the sleep process cause confusion. Compared to the former subject, the changes in RR interval during sleep periods seem to be more remarkable for the present one, thus interfering with the judgment of sleep onset and offset. One the other hand, the transition from wake to sleep in subject 22 is obviously a process with slow growth, where the entropy differences between adjacent segments are not so distinct. Meanwhile, the transition from sleep to wake witnesses a drop, and the SampEn

values thereafter remain at a relative low level. The SampEn values present a similar trend to the RR interval time series or HR, and subplot (D) implies that the corresponding SampEn difference depicts the sleep offset better than the onset.

Based on these findings, we have observed that sleep–wake transitions provoke a lagging step response in HR variability and SampEn with physical threshold can be used as an index to depict such transitions. Considering that wakefulness ahead of a sleep period is vulnerable to influence by uncertain external factors, we mainly focus on the sleep-to-wake transition in the following analysis. Additionally, since relevant research has pointed out that only particular transitions can be detected using certain nonlinear HRV measures (Telser *et al* 2004), the various stages in sleep need further consideration.

2.2. HRV features of different sleep stages in normal and sleep apnea subjects

According to EEG pattern-based Rechtschaffen and Kales (R&K) standards, the sleep process can be categorized into the REM stage, NREM (S1, S2, S3, S4) and the wake stage (W) (Rechtschaffen and Kales 1968). As the ANS and sleep regulatory systems, namely the CNS, are coupled anatomically and physiologically (Zambotti *et al* 2018), they play important roles in normal sleep and sleep disturbance, hence cardiovascular function varies from stage to stage . The most widely used indicators of ANS activity during sleep are HR and HRV (Otzenberger *et al* 1998). Using either time or frequency-domain indexes of HRV, massive studies have revealed that HR and HRV progressively decrease during NREM sleep and increase during REM sleep, which is be attributed to increased vagal control of HR in the NREM stage and increased sympathetic nerve system (SNS) control during the REM stage (Zemaityte *et al* 1984). Entropy-derived nonlinear indices which measure nonlinear features might be better suited to track the HRV changes associated with complicated physiological processes in humans (Seely and Macklem 2004); thus they also provide unique insights into sleep staging. NREM sleep, and slow wave sleep (SWS) in particular, presents significantly higher nonlinear HRV compared to REM sleep, which implies that the RR intervals are less regulated during the NREM period (Vigo *et al* 2010). Besides, REM is similar to a wake status as regards nonlinear HRV (Virtanen *et al* 2007).

However, as the S1 in NREM sleep represents the transition between wake and sleep (Le Bon 2020), it might not be as distinctive as deep sleep (S3 and S4) from the REM period. In addition, as NREM and REM alternate in cycles during the whole sleep period, the states before wakefulness could vary (Roehrs and Roth 2019). Therefore, it is reasonable to establish rules that apply to certain types of sleep-to-wake transitions.

Furthermore, since we have already presented the sleep–wake transitions of healthy subjects that could be captured by physical threshold-based SampEn in this paper, we wonder whether such a phenomenon still exists in sleep disorder subjects like sleep apnea patients. Since apnea occurs several hundred times overnight (Zarei and Asl 2020), the nocturnal sleep period is disrupted. Research has demonstrated that although sleep apnea subjects have a more fragmented sleep, which contains more short stages and transitions than healthy people, the robust mechanisms of sleep and wakefulness controls do not change (Penzel *et al* 2003). Spectral analysis also proves that there is no difference in changes in frequency-domain HRV parameters during different sleep stages between normal and OSA groups (Stein and Pu 2012). Thus it is reasonable to assume that entropy measurement can still characterize the stage transitions in sleep apnea. Moreover, as the fragmentation of sleep in OSA subjects arises from respiratory problems, studying sleep apnea might reveal the effect of external disturbances on sleep-stage transitions (Ivanov and Lo 2007).

2.3. Experimental design

2.3.1. Data

All data used were from the St. Vincent's University Hospital/University College Dublin sleep apnea database from http://www.physionet.org, a free-access, online archive of physiological signals (Goldberger *et al* 2000). The sleep apnea database includes overnight polysomnograms with simultaneous three-channel Holter ECG taken from 25 subjects that have sleep-disordered breathing. The subjects' age (21 males and four females) ranged from 28 to 68 (mean: 49.96 $\pm$ 9.55) and their weights ranged from 59.8 to 128.6 kg (mean: 95.02 $\pm$ 14.70 kg). Three-channel Holter ECGs (V5, CC5, V5R) were recorded using a Reynolds Lifecard CF system (Reynolds Medical, UK), and a sampling rate of 125 Hz was set for the ECG recordings of this database. In this experiment, only the ECG signals were used. Classification of the recordings was done on a 1 min basis by expert scorers according to R&K standards and each segment was assigned with a label (i.e. apnea or non-apnea). Herein, annotation 0–6 represents wake, REM, stage S1 to S4 in NREM and artifact, respectively.

2.3.2. Physical threshold-based SampEn

Sample entropy (SampEn) is a nonlinear measurement of system complexity, which calculates the negative logarithm of the conditional probability that two sequences within a tolerance r for m points remain within r of each other at the next points (Richman and Moorman 2000). According to previous research, SampEn with a

physical threshold was taken as the baseline algorithm in this study. The calculation process of physical threshold-based SampEn is summarized as follows (Richman and Moorman 2000, Zhang *et al* 2007):

For RR segment $x(i)$ $(1 \leqslant I \leqslant N)$, given the parameters m and r, first form the vector sequences $X_{m\,i}$:

$$X_i^m = \{x(i),\ x(i+1), \cdots, x(i+m-1)\} \quad 1 \leqslant i \leqslant N-m. \tag{1}$$

The vector X_{mi} represents m consecutive $x(i)$ values. Then the distance between X_{mi} and $X_{m\,j}$ based on the maximum absolute difference is defined as

$$d_{i,j}^m = d[X_i^m, X_j^m] = \max_{0 \leqslant k \leqslant m-1} |x(i+k) - x(j+k)|. \tag{2}$$

For each X_{mi}, denote $B_{mi}(r)$ as $(N-m)^{-1}$ times the number of $X_{m\,j}$ $(1 \leqslant j \leqslant N-m)$ that meets $d_{mi,\,j} \leqslant r$. Similarly, set $A_i^m(r)$ as $(N-m)^{-1}$ times the number of $X_{m+1\,j}$ that meets $d_{i,\,j}^{m+1} \leqslant r$ for all $1 \leqslant j \leqslant N-m$. Typically, the recommended threshold r is between 0.10 and 0.25 times standard deviation (SD) (Pincus 2001). Nevertheless, when applied to heart failure detection, normal sinus rhythm (NSR) group presented higher SampEn results than those in the congestive heart failure (CHF) group when r was set to 0.10, while the outcomes reversed as r increased to 0.25 (Zhao *et al* 2015). The inverted entropy results make it hard to establish a unified standard to detect CHF subjects with a constant r value. To avoid such inconsistency, we proposed a physical threshold as multiple of sampling period and proved that it is more adaptive to CHF detection than the traditional threshold (Xiong *et al* 2019). As physiological signals were sampled at a specific frequency, the minimal time resolution of the signals was determined by the sampling rate and the distance between two vectors ought to be an integral multiple of the sampling period. Therefore, the physical threshold set as a multiple of the sampling period is able to evaluate any vector distance. On the other hand, although the physiological signals are of the same type, they vary from individual to individual. This means that the SD value of each analyzed signal segment differs greatly. As a consequence, the traditional threshold varies and it might be smaller than the minimal vector distance or larger than the maximal one, which leads to invalid entropy values in the calculation. However, the proposed physical threshold can avoid such problems, and it remains effective in cardiovascular signal processing, thus we continued to use this threshold. In this study, since the signals were sampled at 125 Hz and the sampling period was 8 ms, we set threshold r as 2.5 times sampling period, which equals 20 ms.

Then SampEn is defined by

$$SampEn(m, r, N) = -\ln\left(\sum_{i=1}^{N-m} A_i^m(r) \Big/ \sum_{i=1}^{N-m} B_i^m(r)\right). \tag{3}$$

Herein, we predefined another parameter in the calculation of entropy metrics: embedding dimension $m = 2$, aiming to avoid inefficient entropy results caused by a relatively large m. We also selected the time series length N to be 200 to capture the transient sleep stage changes, where the effectiveness of the SampEn analysis can still be guaranteed (Pincus and Huang 1992).

It is worth noticing that the SampEn difference we used in this research is defined as

$$SampEn\ difference = SampEn(n) - SampEn(n+1). \tag{4}$$

Herein, n is the order in which the entropy value appears in the time series. This setting differs from the general concept, where difference refers to SampEn$(n+1)$ – SampEn(n). However, this is merely an opposite description of the changes in SampEn value. When applying the general idea of SampEn difference, then we can say there is an increase in SampEn value during the sleep-to-wake transition.

2.3.3. Experiment scheme

The analytical procedure used in the present study contains five major steps: (1) pre-processing of each ECG interval recording; (2) calculating SampEn for each labeled RR segment and comparing the results; (3) calculating the SampEn difference between the two RR segments before and after state transition and comparing the results of sleep-to-wake transitions and intra-sleep transitions; (4) selecting transition episodes according to stage transition points and filtering out those with insufficient sleep as well as wakefulness time, calculating SampEn for the preserved episodes and analyzing the effect of refinement; (5) assessing the SampEn differences of the refined sleep-to-wake transition episodes arising from various sleep stages.

In step (1), the Pan–Tomkins algorithm was applied to the raw ECG signals to detect R waves (Pan and Tompkins 1985) and the obtained RR intervals with abnormal values were then removed (Ho *et al* 1997). For each set of five contiguous RR intervals, we computed the local mean excluding the median interval: $RR_{\mathrm{mean}[i]} = (RR_{[i-2]} + RR_{[i-1]} + RR_{[i+1]} + RR_{[i+2]})/4$. The central interval $RR_{[i]}$ is considered to be an outlier unless it lies within a 20% interval around $RR_{\mathrm{mean}[i]}$, i.e. $0.8 \times RR_{\mathrm{mean}[i]} < RR_{[i]} < 1.2 \times RR_{\mathrm{mean}[i]}$. Moreover, RR intervals either smaller than 0.5 s or larger than 1.5 s were also regarded as outliers. Any interval identified as an outlier was removed, and a new RR interval time series was rebuilt with the remaining RR intervals. The RR interval recordings and RR interval numbers before and after filtering are shown in the first part of table 1.

Table 1. Statistical results of the numbers of RR interval recordings, RR intervals and RR segments from the sleep apnea subjects in the UCD sleep apnea database.

Variables	Sleep apnea subjects
Name of RR interval recordings	ucddb002 ∼ ucddb028, with ucddb004 ucddb011, ucddb012 and ucddb016 excluded
No. of RR interval recordings	23
No. of RR intervals	654,317
No. of RR intervals after removing abnormal heartbeats	642,937
Statistical results for section 3.1	
No. of RR segments when setting $N = 200$	3,203
No. of Wake segments when setting $N = 200$	628
No. of REM segments when setting $N = 200$	466
No. of S1 segments when setting $N = 200$	566
No. of S2 segments when setting $N = 200$	1,143
No. of S3 segments when setting $N = 200$	97
No. of S4 segments when setting $N = 200$	300
No. of intra-sleep transition	742
No. of sleep-to-wake transition	163
Statistical results for section 3.2	
No. of transition episodes with insufficient duration	749
No. of transition episodes with sufficient duration	37
No. of transition episodes from REM to Wake	6
No. of transition episodes from S1 to wake	13
No. of transition episodes from S2 to Wake	11
No. of transition episodes from S4 to Wake	7

In step (2), SampEn was used to calculate the entropy values for all the sleep apnea subjects under the parameter setting embedding dimension $m = 2$ and physical threshold $r = 20$ ms. Since we aimed to capture the change in a relatively short time period, segment length $N = 200$ was used to analyze SampEn. For each RR segment, we removed the RR intervals without a 99% confidence interval (CI), (i.e. $\pm 3 \times$ SD). The state label of each RR segment was determined by the dominant labels within the 200 points. Thus each RR segment has its own label, and the entropy results were compared among wake, REM, S1, S2, S3 and S4 stages. The numbers of total RR segments as well as RR segments from different sleep stages are listed in the second part of table 1.

In step (3), we analyzed the SampEn difference of the two consecutive RR segments with different labels to evaluate nonlinear HRV features after a state switch. Herein, we classified the transitions into two types: sleep-to-wake transition where the former stage is either REM or NREM and the latter one is wakefulness; and intra-sleep transition where both former and latter periods are within REM and NREM stages. We assumed that a sleep-to-wake transition would present a more distinct change in SampEn than the intra-sleep one and the comparison between these two transitions was then implemented. The numbers of these two types of transitions are also presented in the second part of table 1.

In step (4), a refinement strategy was applied to improve the assessment of transition period. Instead of roughly deciding the state of a 200-point RR segment by the majority of the labels, we first located the change point where the physiological state of the subject has switched from sleep to wakefulness. Thus a transition episode was gained by taking the 200 points before and after this change point. To analyze SampEn under a uniform and stable condition, it is necessary to assure that both the sleep and wakefulness periods involved a sufficient time duration. Therefore transition episodes with either a sleep stage lasting less than 200 points or wakefulness lasting less than 100 pointed were excluded. Considering that the stage labels are based on EEG signals, where the sleep state of the subject was checked every 30 s, the real change point in ECG signals would not be in tune with that identified by EEG signals. Hence an optimization process was added in to improve the outcomes. We chose the 50 points before or after the original change point and searched for the one leading to the largest SampEn difference between sleep and wake periods. This point was then regarded as the actual change point in the following analysis. It is worth noting that the optimization was also performed on the transition episodes with insufficient time duration, with the aim of guaranteeing that the comparison between the preserved and exclude episodes was at an identical level. The numbers of both selected and discarded transition episodes are displayed in the last part of table 1. Moreover, to prove that SampEn has advantages over other time-

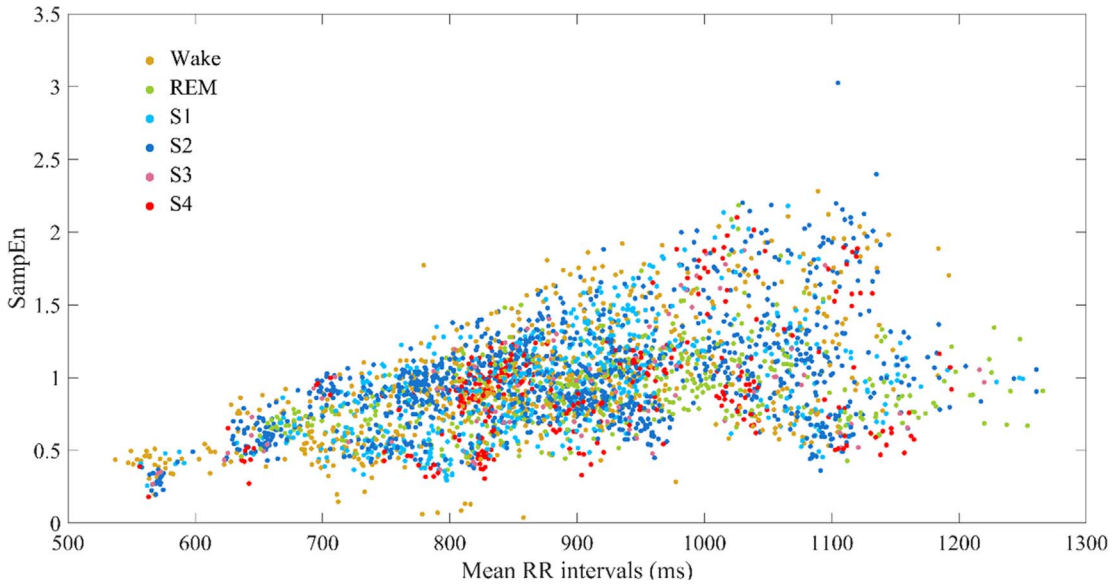

Figure 3. SampEn distribution for 23 subjects from the UCD sleep apnea dataset. Herein, embedding dimension m was set as 2, physical threshold $r = 20$ ms, and segment length $N = 200$. The x-axis is the mean RR interval for the analyzed 200-beat time window.

domain or frequency-domain HRV measures, its capability to discriminate sleep-to-wake transitions from intra-sleep transitions was analyzed and compared.

In step (5), further analysis was made regarding the specific sleep stages involved in the transition episodes. According to the sleep labels, transitions arose from REM, S1, S2 and S4 stages, and their corresponding episode numbers are shown in the last part of table 1. Since the S3 stage is relatively transient among all these sleep apnea subjects, the S3-to-wake transition episode is missing here. Contrast was made among these four types of transition episodes to evaluate the impacts of the previous sleep stage on the subsequent sleep-to-wake transitions.

2.3.4. Statistical analysis

In the SampEn calculation, for each RR segment length of $N = 200$, embedding dimension $m = 2$ and physical threshold $r = 20$ ms were applied for subjects from the UCD sleep apnea dataset. The overall mean and SD values of these subjects were calculated across all RR interval recordings, and the SampEn differences between sleep periods and wake periods during sleep-to-wake transitions were also analyzed. The parametric test, Student's t-test, was used to test the statistical difference between different sleep stages. All statistical analyses were performed using MATLAB software (version R2020a, MathWorks, Natick, USA). Statistical significance was set *a priori* at $P < 0.01$. On the other hand, a receiver operating characteristic (ROC) curve was used to evaluate the discriminant ability of each HRV index. This plot displays the fraction of true positives out of positives (sensitivity) against the fraction of false positives out of the negatives (one-specificity) at different threshold settings. The optimum threshold was determined according to the Youden's criterion. Moreover, the area under the ROC curve (AUC) was also computed as an aggregate measure of performance for each metric.

3. Results

3.1. Results of different states for apnea patients

The SampEn results for every RR segment of length 200 from 23 apnea patients are shown in figure 3. The points that represent a different sleep status overlap with each other regarding their SampEn and mean RR interval values. The distribution of SampEn is so dispersed that it would be impossible to discriminate between the six sleep stages displayed in the picture. Likewise, neither can the mean RR interval of each segment classify the six sleep stages. This outcome might be attributed to the heterogeneous components of RR segments. The status label of each SampEn result is determined by its RR intervals. As we mentioned above, there are seven different labels for the experimental results of sleep monitoring, from 0 to 6 for the awake period, the REM stage, the NREM stage consisting of S1–S4, and the unknown stage (noise). For the entropy result, because 200 is selected as the segment length of the RR interval in the calculation, it is inevitable to calculate an entropy value for RR

Table 2. SampEn results for different sleep stages of 23 subjects from the UCD database with embedding dimension $m = 2$, physical threshold $r = 20$ ms and segment length $N = 200$. Data are expressed as number or mean ± standard deviation (SD).

	Sleep stage					
Record	Wake	REM	S1	S2	S3	S4
ucddb002	1.05 ± 0.15	0.81 ± 0.1	1.14 ± 0.12	1.05 ± 0.18	0.95 ± 0.17	1.04 ± 0.11
ucddb003	1.13 ± 0.21	1.3 ± 0.36	1.48 ± 0.39	1.79 ± 0.24	1.74 ± 0.11	1.81 ± 0.15
ucddb005	1.31 ± 0.25	1.11 ± 0.12	1.31 ± 0.2	1.13 ± 0.16	0.68 ± 0	0.86 ± 0.13
ucddb006	0.52 ± 0.2	0.6 ± 0.12	0.47 ± 0.11	0.52 ± 0.11	0.57 ± 0.19	0.5 ± 0.1
ucddb007	1.06 ± 0.19	1.08 ± 0.17	1.15 ± 0.18	1.09 ± 0.17	1.05 ± 0.33	0.85 ± 0.18
ucddb008	0.51 ± 0.17	0.63 ± 0.04	0.53 ± 0.13	0.53 ± 0.14	0.46 ± 0.14	0.42 ± 0.12
ucddb009	0.96 ± 0.17	0.91 ± 0.13	1.02 ± 0.2	1.12 ± 0.15	0.97 ± 0.06	0.96 ± 0.11
ucddb010	0.7 ± 0.18	0.76 ± 0.12	0.79 ± 0.16	0.9 ± 0.11	0.89 ± 0.14	0.82 ± 0.08
ucddb013	0.96 ± 0.18	0.98 ± 0.2	0.98 ± 0.13	1.06 ± 0.14	1.14 ± 0.15	1.07 ± 0.09
ucddb014	0.61 ± 0.13	0.65 ± 0.16	0.69 ± 0.14	0.83 ± 0.11	—	—
ucddb015	1.04 ± 0.23	1.07 ± 0.19	1.07 ± 0.23	1.26 ± 0.19	1.15 ± 0.16	1.07 ± 0.09
ucddb017	0.87 ± 0.13	0.9 ± 0.13	0.94 ± 0.26	0.72 ± 0.11	0.67 ± 0.11	0.72 ± 0.11
ucddb018	1.66 ± 0.33	1.6 ± 0.23	1.49 ± 0.46	1.43 ± 0.38	1.4 ± 0	0.96 ± 0.16
ucddb019	0.91 ± 0.16	1 ± 0.13	0.81 ± 0.09	0.93 ± 0.11	0.95 ± 0.07	0.92 ± 0.08
ucddb020	0.8 ± 0.21	0.76 ± 0.14	0.84 ± 0.2	0.96 ± 0.13	0.93 ± 0.16	0.84 ± 0.25
ucddb021	0.97 ± 0.18	1.05 ± 0.2	1.05 ± 0.16	1.17 ± 0.22	1.19 ± 0.1	0.99 ± 0.11
ucddb022	1.55 ± 0.2	1.21 ± 0.29	1.71 ± 0.27	1.87 ± 0.32	—	1.64 ± 0.18
ucddb023	0.51 ± 0.12	0.6 ± 0.08	0.54 ± 0.09	0.54 ± 0.07	0.53 ± 0.13	0.4 ± 0.06
ucddb024	0.71 ± 0.11	0.78 ± 0.11	0.7 ± 0.11	0.64 ± 0.11	0.58 ± 0.07	0.56 ± 0.08
ucddb025	1.15 ± 0.18	1.16 ± 0.1	1.32 ± 0.2	1.33 ± 0.14	1.54 ± 0.14	—
ucddb026	0.89 ± 0.15	1.14 ± 0.21	1.1 ± 0.3	1.07 ± 0.23	0.88 ± 0.26	1.03 ± 0.21
ucddb027	0.73 ± 0.15	0.71 ± 0.09	0.75 ± 0.12	0.92 ± 0.11	0.96 ± 0.08	0.95 ± 0.05
ucddb028	0.92 ± 0.12	0.83 ± 0.13	0.95 ± 0.14	0.9 ± 0.21	0.78 ± 0.12	0.78 ± 0.21

intervals with different sleep staging labels. Under these circumstances, a substantial part of RR segments contains diverse sleep stages, so the SampEn values would not be representative of a certain type of sleep stage.

The mean and standard deviation of the SampEn values under different labels from 23 subjects are shown in table 2. Some individuals show relatively lower SampEn values in REM and wake stages than the NREM stage, indicating that the complexity of the cardiovascular system increases as sleep deepens. However, from a statistical perspective, there is no significant difference in the SampEn values for waking and sleep stages in terms of mean and standard deviation, especially with S3 and S4 stages. This could be due to the fragmented sleep of apnea patients, whose deep sleep periods are transient and unstable, and the occasional wakefulness disturbs the equilibrium in HR dynamics.

During sleep, since the ANS controls the heart in a gradual process, adjacent RR interval segments are not independent of each other. This indicates that the former stage has an impact on the latter one. Therefore, we calculated the difference of SampEn values before and after the sleep state changes. The calculation result is shown in figure 4. Additionally, the corresponding results analyzed through RR interval differences are also presented. In subplot (A), the first group consists of the differences between sleep state and waking state, which are marked by red dots. The second group depicts intra-sleep changes, which are represented by gray dots. According to the entropy results, it is obvious that most of the red points are located in the upper part of the whole distribution and they are also more concentrated. In contrast, the distribution of the gray points is more dispersed and most of them are in the middle and lower parts. This finding builds the foundation for exploring the internal rule of the sleep-to-wake process in the following part. In subplot (B), we can see that the distribution range of sleep-to-wake transitions and intra-sleep transitions are distinctive. In fact, there is a significant difference between the two groups, and the P-value of the t-test is smaller than 0.01. Thus the transition patterns from certain sleep stages to wakefulness are quite different from those during NREM as well as REM periods. This enables us to pick out those stage transition episodes that are relatively homogeneous and stable to further analyze their characteristics via SampEn. In subplot (C), the red dots that represent sleep-to-wake transition episodes have a wider distribution range than in subplot (A), as they do not concentrate in the upper part of the picture. Now that the red dots and gray ones are mixed with each other, discriminating sleep-to-wake transitions from intra-sleep transitions via RR differences is not reliable. In subplot (D), the main parts of the two boxes are quite close and the P-value of the t-test is larger than 0.01, which is inferior compared with the result from SampEn differences analysis. Therefore, SampEn performs more effectively than RR interval in classifying these two types of episodes.

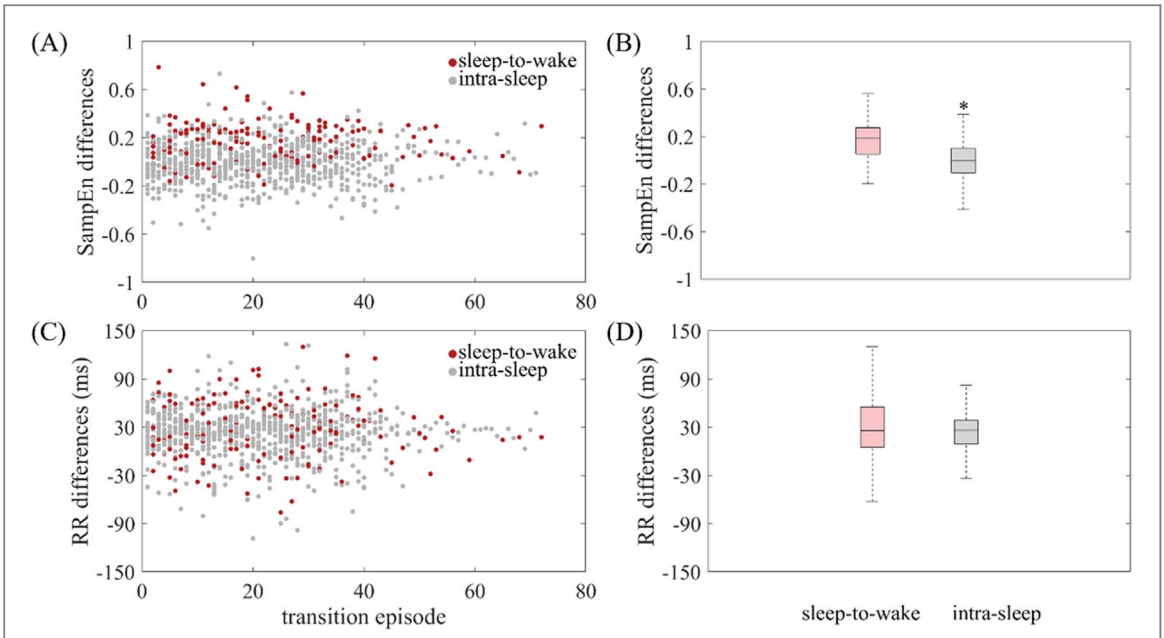

Figure 4. (A) Distribution of SampEn differences between sleep and wakefulness as well as intra-sleep changes for 23 subjects from the UCD sleep apnea dataset. (B) Distribution ranges of SampEn differences between sleep and wakefulness as well as intra-sleep changes. (C) Distribution of RR differences between sleep and wakefulness as well as intra-sleep changes. (D) Distribution ranges of RR differences between sleep and wakefulness as well as intra-sleep changes. '*' means there is a significant difference between the two groups. Herein, embedding dimension m was set as 2, physical threshold $r = 20$ ms, and segment length $N = 200$.

3.2. Results of sleep-to-wake transitions after refinement

In the last section, we performed statistical analysis of labeled RR intervals from different sleep stages. One of our goals is to capture the state transition process from sleeping to waking through the physical threshold-based SampEn algorithm. Nevertheless, according to research, every patient with apnea syndrome will experience 100 to 130 different states every night, thus some labeled sleep stages might be too transient for further calculation. In section 3.1, we also subtracted the entropy values after state transitions from those before transitions to obtain the differences, and most of the SampEn differences from sleep to wakefulness are higher than other cases. Although there is a significant difference between the distribution range of sleep-to-wake transitions and intra-sleep transitions, discriminating each single sleep-to-wake transition would still be hard, which indicates that the state transition in reality has corresponding requirements for the sequence length before and after the transition. Furthermore, since the adjustment of the ANS depends on the coordination of different systems, there will be a certain delay in the HR adjustment. As the labels of sleep stages are based on EEG signals, such delay could merely be presented in cardiovascular system. At this time, not only the RR intervals of the current state themselves, but also the regulatory factors of the previous state, such as the level of hormones, have a continuous impact on the present HRV indexes. Therefore, the delay will lead to a fuzzy transition in the RR intervals between different states. To obtain ideal state transitions, first of all, we need to ensure that the regulatory effect of the ANS has remained long enough for the RR sequences of the previous sleep state as well as the following wakefulness. Hence we analyzed the overall stage transition episodes and eliminated those whose previous stages and next stages are relatively short.

Figure 5 presents the entropy results of fine sleep-to-wake transition episodes after we have filtered out those with sufficient state duration. As a premise, we assumed that a sleep-to-wake transition is worth analyzing only when the wakefulness contains more than 100 heartbeats. In subplot (A), gray dots stand for transition episodes with insufficient duration, where the previous sleep stage is no greater than 200 points. Meanwhile, red dots represent transition episodes with previous sleep stage longer than 200 points. The distribution of SampEn differences implies that most transition episodes with sufficient duration of the previous stage show relatively large values, and those whose preceding sleep stages are transient have unpredictable SampEn differences. This indicates that only state transitions with both enduring and stable sleep as well as wakefulness stages are able to present the sudden change in SampEn values. Subplot (B) displays the distribution ranges of SampEn differences for these two groups. We can see that the entropy differences of transition episodes with sufficient sleep periods are significantly larger than the other ones ($P < 0.01$). Thus the transitions with sufficient duration of previous sleep stage are appropriate objects to further analyze the HRV changes in the sleep-to-wake process.

Furthermore, considering that the discrimination between sleep-to-wake transitions and intra-sleep transitions might be even more obvious through other HRV indexes besides SampEn, a comparison among

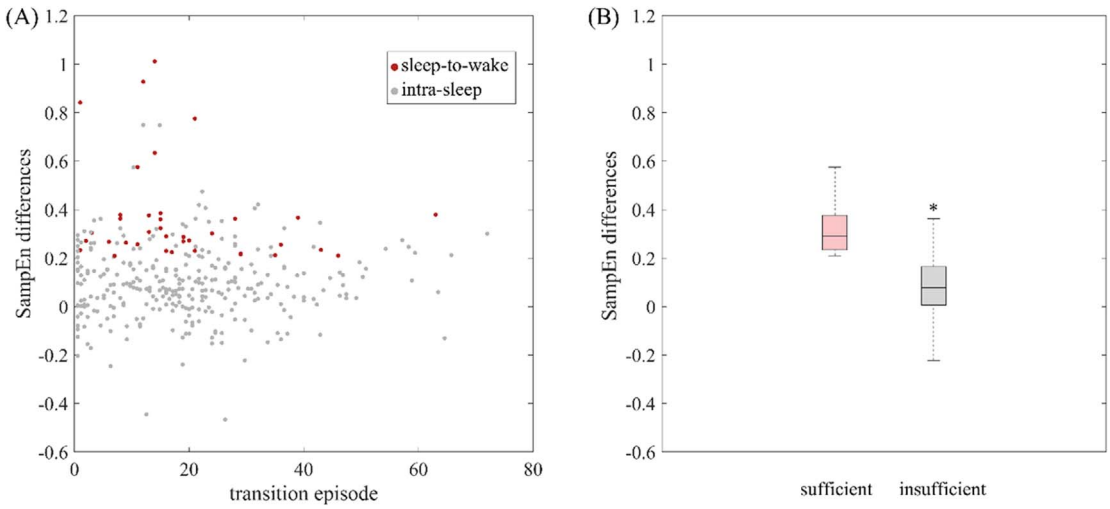

Figure 5. (A) Distribution of SampEn differences for sleep-to-wake and intra-sleep transitions with sufficient duration from 23 UCD sleep apnea subjects. (B) Distribution ranges of SampEn differences from sleep-to-wake and intra-sleep transitions with sufficient duration. '*' means there is a significant difference between the two groups. Herein, embedding dimension m was set as 2, physical threshold $r = 20$ ms, and segment length $N = 200$.

Table 3. HRV time-domain and frequency-domain measures included in the sleep-to-wake and intra-sleep transitions discrimination.

Parameter	Unit	Description
	Time-domain measures	
Mean RR	ms	Mean value of RR intervals
SDNN	ms	Standard deviation of RR intervals
RMSSD	ms	Root mean square of successive RR interval differences
pNN50	%	Percentage of successive RR intervals that differ by more than 50 ms
	Frequency-domain measures	
LF power	nu	Relative power of the low-frequency band (0.04–0.15 Hz) in normal units
LF/HF	%	Ratio of low-frequency to high-frequency power

various HRV measurements was made. Four time-domain and two frequency-domain HRV measures were included in this study. Table 3 gives an overview of the added indices. Time-domain indexes of HRV quantify the amount of variability in measurements of the inter-beat interval, which is the time period between successive heartbeats. Frequency-domain measurements estimate the distribution of absolute or relative power into different frequency bands. All these standard HRV measures provide a perspective different from the nonlinear entropy method, which aims to explore whether SampEn has an advantage in sleep-to-wake transition discrimination.

Likewise, the transition episodes with persistent sleep or wakefulness used above were analyzed via various HRV measures, and the differences between the pre-transition and post-transition segments were calculated. In accordance with the previous analysis, a segment length of 200 was used for all measures, and embedding dimension m was set as 2 and physical threshold $r = 20$ ms for SampEn. The overall results were compared with SampEn in the form of ROC curves and AUC values in figure 6. As figure shows, SampEn achieves the highest AUC value 86.85% in classifying sleep-to-wake transition episodes from the intra-sleep ones. For the four time-domain HRV indices analyzed, mean RR reaches the second highest AUC value of 78.35%, which is better than the 61.44% of SDNN, 65.7% of RMSSD and 67.79% of pNN50. As for the two frequency-domain indices, LF power achieves 63.3% and LF/HF ratio achieves 60.55%. The less preferable performance of the frequency-domain measures might be attributed to the length of the RR segments, which is not adequate for the HRV power analysis. It is worth noticing that HF power, which depicts the high-frequency band (0.15–0.4 Hz), produces complementary results with LF power when subtracting the post-transition segment from the pre-transition one, leading to the same ROC curve and AUC value, and thus is omitted in this evaluation. On the

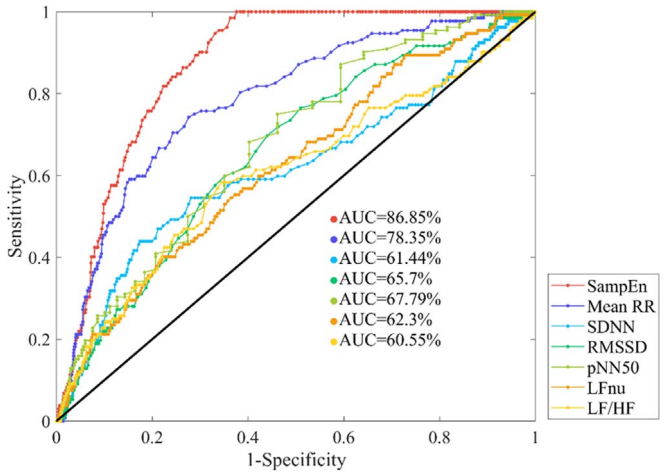

Figure 6. ROC curve plots with AUC values for classifying sleep-to-wake transitions and intra-sleep transitions through various HRV indices.

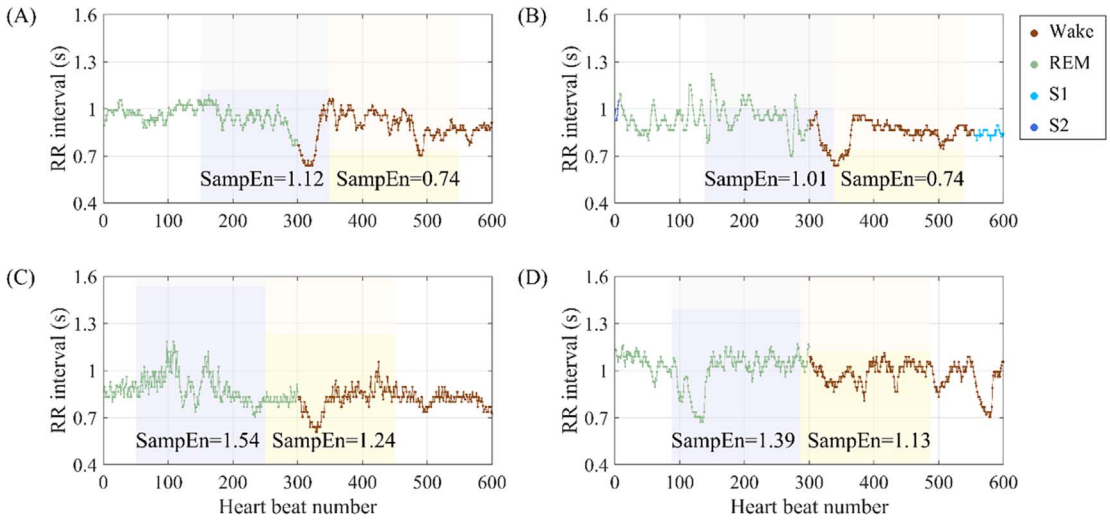

Figure 7. Presentation of transitions from REM stage to wake stage for (A) ucddb017, (B) ucddb019, (C) ucddb021 and (D) ucddb026. Herein, embedding dimension m was set as 2, physical threshold $r = 20$ ms, and segment length $N = 200$.

whole, although sleep-to-wake transitions differ from the intra-sleep ones in various HRV indices, SampEn presents such discrimination more preferably.

Now that we have selected transition episodes with lasting sleep and wake periods, studying sleep-to-wake transitions arising from different sleep stages is meaningful. According to the filtering results, among all these apnea subjects, we can observe stable wakefulness after any sleep stage except S3, which is momentary and rare in the recordings. Figure 7 exhibits four transition episodes from REM to wakefulness as an example. The RR intervals where transitions appear are plotted using different colors according to their sleep stage labels, and the two segments selected for SampEn calculation are marked in lavender and cornsilk respectively. In the first three subgraphs, there is a sharp drop at the junction of green line and brown line, corresponding to the increasing heart rate at the beginning of wakefulness. A decrease in SampEn is also observed. The two RR segments of length 200 analyzed a bit ahead or behind the transition heart beat present a declining complexity in HRV, and such alteration is out of synchronization with the stage labels specified by EEG. In subplot (D), where the stage transition point does not show an obvious decline in RR interval duration, SampEn is capable of depicting inherent information in the cardiovascular system that is not fully expressed by HR. The SampEn of the REM stage RR segment ahead of wakefulness is actually higher than that of wakefulness in spite of the fact that they look quite alike morphologically.

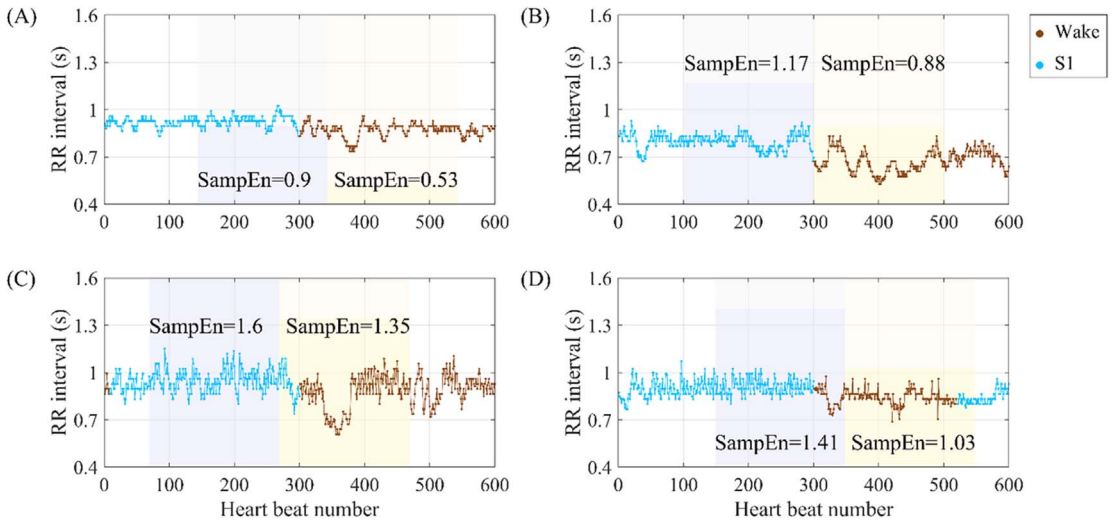

Figure 8. Presentation of transitions from S1 stage to wake stage for (A) ucddb014, (B) ucddb021, (C) ucddb022 and (D) ucddb025. Herein, embedding dimension m was set as 2, physical threshold $r = 20$ ms, and segment length $N = 200$.

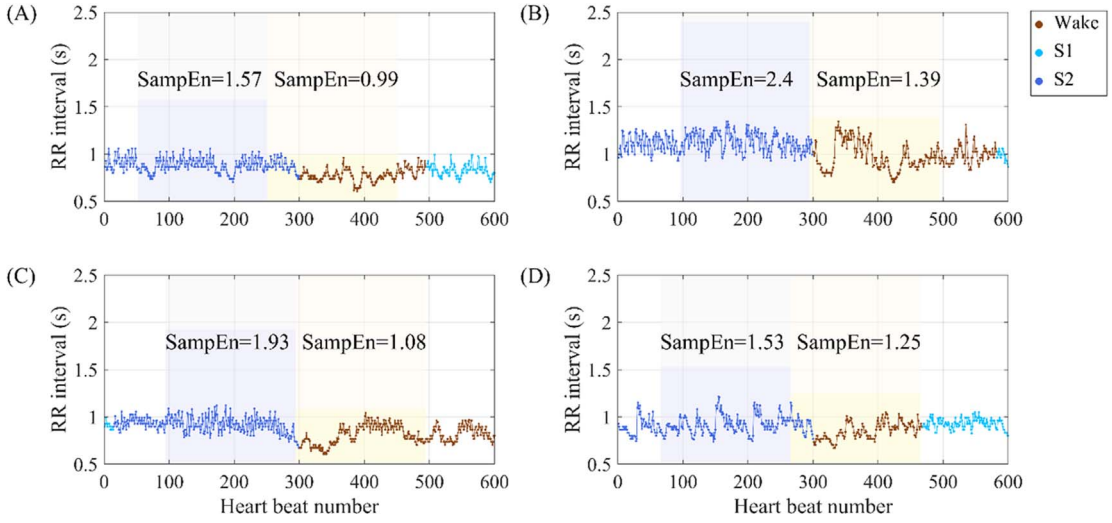

Figure 9. Presentation of transitions from S2 stage to wake stage for (A) ucddb015, (B) ucddb018, (C) ucddb022 and (D) ucddb025. Herein, embedding dimension m was set as 2, physical threshold $r = 20$ ms, and segment length $N = 200$.

Four transition episodes from S1 to wakefulness are displayed in figure 8. The RR intervals that contain transitions are plotted by two colors, where blue line corresponds to S1 stage and brown line corresponds to wake stage, and the two segments selected for SampEn calculation are marked in lavender and cornsilk respectively. At this time, the RR interval time series from S1 stage presents less volatility compared with REM stage, and the subsequent wakefulness also seems to be relative placid. It is still difficult to discriminate the wake period from the sleep period through RR interval sequences, as these two segments look quite alike, and the acceleration of HR does not always follows wakefulness in rapid succession. On the other side, a decrease in SampEn is present after the subject has switched from light sleep stage to wakefulness, thus the entropy measurement reveals the nonlinear changes inside the sleep-to-wake transition. Moreover, as the S1 stage is relatively close to the REM stage in the overall sleep cycle, the SampEn changes for both of them is not so remarkable, and the frequent transitions between REM, S1 and wakefulness in sleep apnea subjects might also interfere with the SampEn values.

Transition episodes from S2 to wakefulness are shown in figure 9. The RR intervals of the transition parts are plotted mainly by two colors, where the slate blue line corresponds to the S2 stage and the brown line corresponds to the wake stage, and the two segments selected for SampEn calculation are marked in lavender and cornsilk, respectively. In contrast to the REM and S1 stages, the RR interval time series from the S2 stage contains more small-range fluctuations and the following wake period seems to be influenced by the mode of S2

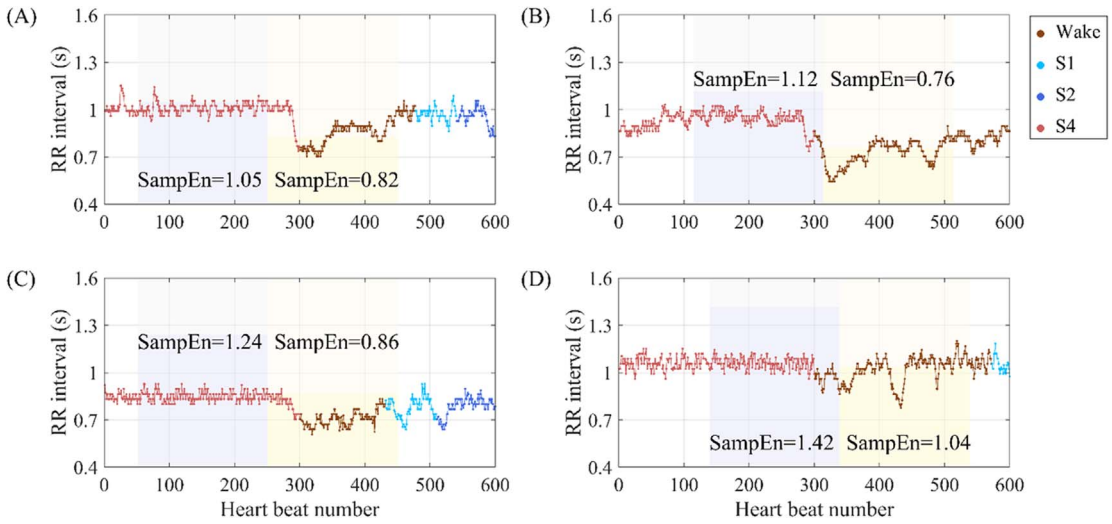

Figure 10. Presentation of transitions from S4 stage to wake stage for (A) ucddb002, (B) ucddb013, (C) ucddb021 and (D) ucddb026. Herein, embedding dimension m was set as 2, physical threshold $r = 20$ ms, and segment length $N = 200$.

stage, as it presents a placid but less regular pattern. Compared to the former two figures, in figure 9, the SampEn values of the sleep period soar to a relatively higher level as sleep deepens, and the following wake period seems to be influenced by the mode of the S2 stage, as it presents a placid but less regular pattern. In other words, the SampEn difference between sleep and wakefulness becomes more obvious under these circumstances.

Figure 10 gives four examples of transition episodes from the S4 stage to wakefulness. The RR intervals of the transition parts are plotted by two colors, where the red line corresponds to the S4 stage and the brown line corresponds to the wake stage, and the two segments selected for SampEn calculation are marked in lavender and cornsilk, respectively. It is interesting that the wakefulness is quite transient here, and the subjects go into light sleep after arousals from deep sleep. Although the RR segment of the deep sleep period appears to be less fluctuated, its SampEn still remains high and the subsequent wakefulness witnesses a sudden drop in RR interval time duration as well as in entropy value. In fact, the high entropy value of the S4 stage implies some nonlinear properties of the deep sleep stage. Albeit insensitive to external stimuli, the cardiovascular system still presents high complexity during deep sleep.

Table 4 summarizes the SampEn results of transition episodes with sufficient sleep and wakefulness duration. Besides our proposed physical threshold, we also made a comparison between the sleep stage and the wake stage for the episodes selected above using SampEn with traditional threshold $r = 0.20$, aiming to verify of the drop in entropy value still exists with recommended r (i.e. between 0.10 and 0.25 times the SD of the time series).

For physical threshold, among the four sleep stages, REM seems to be indistinguishable from the wakefulness that follows. Both transitions arising from the S1 and S4 stages show a significant difference between the sleep and wake periods. Meanwhile, the transition from the S2 stage to wakefulness is most remarkable with a P-value less than 0.01. Based on these findings, we can conclude that ensuring there are lasting sleep and wakefulness periods, the status transitions emerged from NREM sleep, S2 and S4 stages in particular, are likely to trigger a sudden decrease in physical threshold-based SampEn value. Since REM is the arousal during sleep and S1 is the transition between sleep and wake, they share more features in common with wakefulness than with light or deep sleep.

For a traditional threshold, the outcomes are similar to those of SampEn with physical threshold, as transitions from S2 stage have a P-value less than 0.01 and REM-to-wake transitions do not possess a significant difference. In the meantime, transitions from both S1 and S4 stages have a P-value a bit smaller than those using a physical threshold, implying that the discriminations are more notable. Thus, we can still claim that the traditional SampEn is able to depict the sudden decrease when switching from sleep to wakefulness.

4. Discussion

In the past decades, sleep-related research has concentrated on how various factors influence sleep and how sleep affects human physiology and cognition (Krystal *et al* 2002, Schmidt *et al* 2012). Among them, most studies have focused on automatic sleep stage classification and different variables have been considered in the experiments,

Table 4. Results of SampEn and SampEn difference before and after sleep-to-wake transitions. Herein, transitions arising from four different sleep stages were analyzed, where both sleep and wake periods have sufficient time duration. For SampEn parameters, embedding dimension m was set as 2, physical threshold $r = 20$ ms, traditional threshold $r = 0.20$, and segment length $N = 200$. P-value measured the statistical significance between sleep period and the following wakefulness. Physical threshold is expressed as r_p and traditional threshold is expressed as r_t for brevity. Data are expressed as number or mean $\pm$ standard deviation (SD). '*': statistical significance $P < 0.05$; '**': statistical significance $P < 0.01$.

Start stage	REM		S1		S2		S4	
Threshold	r_p	r_t	r_p	r_t	r_p	r_t	r_p	r_t
Sleep stage SampEn	1.02 ± 0.40	1.06 ± 0.25	1.12 ± 0.33	1.26 ± 0.29	1.51 ± 0.46	1.52 ± 0.43	1.25 ± 0.35	1.35 ± 0.31
Wake stage SampEn	0.73 ± 0.39	0.93 ± 0.45	0.84 ± 0.35	0.97 ± 0.34	1.02 ± 0.22	1.08 ± 0.21	0.85 ± 0.25	0.94 ± 0.21
SampEn difference	0.29 ± 0.05	0.13 ± 0.30	0.29 ± 0.06	0.29 ± 0.23	0.49 ± 0.28	0.44 ± 0.43	0.40 ± 0.22	0.42 ± 0.24
P-value	0.2724	0.5965	0.0474*	0.0341*	0.0071**	0.0084**	0.0235*	0.0185*

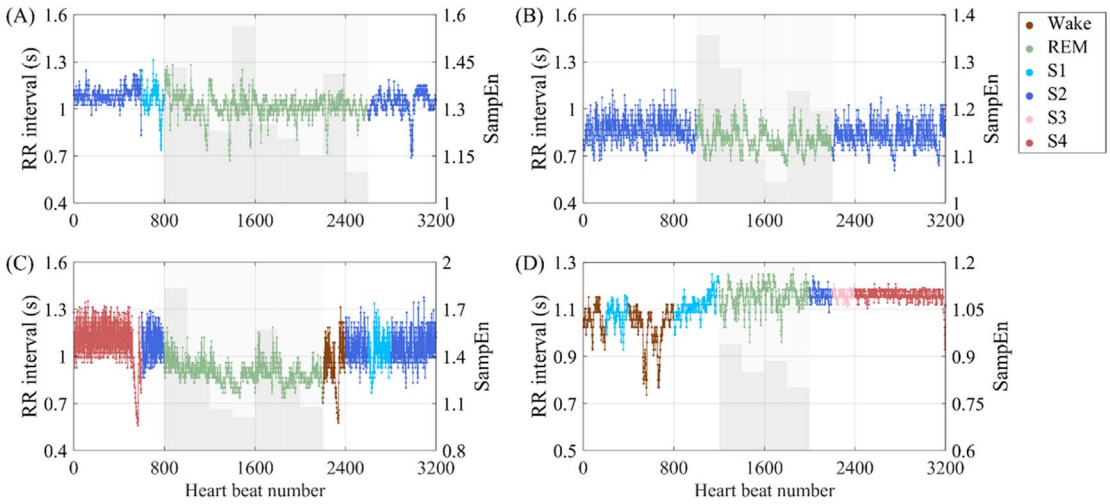

Figure 11. Presentation of REM stage RR segments for (A) ucddb007, (B) ucddb015, (C) ucddb022 and (D) ucddb024. Herein, embedding dimension m was set as 2, physical threshold $r = 20$ ms, and segment length $N = 200$.

such as aging, diurnal rhythm, sleep disorders and other diseases (Chervin *et al* 2004, Javaheri 2006). Nevertheless, the internal modes within sleep stage transitions still remain unclear and few studies have focused on sudden changes rather than stable sleep periods. While EEG signals reflect the different characteristics during sleep stages intuitively, it is also noteworthy that due to the complex operation and high cost of PSG, other biological signals including HRV, body movement and respiratory rate have been regarded as alternative measurements for reliable and low-cost sleep staging; particularly HRV, which is an index of the ANS. In fact, the technique of HRV-based sleep staging has attracted a great deal of attention. Since sleep stages are associated with activities of the ANS, HRV parameters in time, frequency as well as nonlinear domain reveal significant differences between NREM and REM sleep, and the classification results are comparable to those from EEG-based methods (Yucelbas *et al* 2018). The analysis of sleep–wake transitions through physical threshold-based SampEn in section 2 also demonstrated that the nonlinear HRV method is able to capture the transient state changes reflected in the cardiovascular time series. Moreover, sleep disorders like sleep apnea has been explored for a long time and their effects on cardiovascular autonomic function during sleep and wake has been assessed through HRV measurements. It is reported that although sleep apnea patients present sympathetic overactivity, the sleep mechanism does not change (Khoo and Blasi 2013). In this sense, it would be interesting to see whether the sleep regulation between different sleep stages, namely sleep stage transition, still has certain patterns among sleep apnea subjects. Thus we first calculated the SampEn values of RR segments from different sleep stages of sleep apnea patients and then imposed a refinement on the sleep-to-wake transition episodes to obtain discriminative SampEn differences. The results showed that when both sleep and wake stages have sufficient duration, a transition from NREM sleep to wakefulness witnesses a drop in SampEn value.

In the results section, we have analyzed the RR interval time series from the REM stage and it seems that quite a few episodes exhibit a stepwise descent in SampEn value from segment to segment. Figure 11 exhibits the REM stage RR segments from four sleep apnea subjects. Different sleep stages are expressed by lines in different colors according to the legend and the SampEn value of each REM RR segment is presented by a gray block in the background. Based on each subgraph, we can see that the consecutive REM period has a decrease in SampEn repeated for approximately three segments. This repetitive pattern is not influenced by the length of the REM stage and it appears between different individuals. Although the cause of this phenomenon is unclear, we can use it as a reference for judging REM stage in entropy-based HRV methods.

Another enlightening phenomenon in the analysis of the sleep time series is the occurrence of the intrinsic sequences. In the previous study, we assumed that an RR interval sequence with fast HR would reflect some internal characteristics of heart failure or healthy individuals, as the causes of HR acceleration for these two types of subjects were different in essence. Actually, we tried to search for episodes in the long-term ECG signals where the external disturbance has been minimized. An ideal analysis object would be sleep period, especially during the deep sleep stage, when individuals are almost completely undisturbed (Togo *et al* 2006). At that moment, the RR interval time series shows the intrinsic characteristics of the cardiovascular system, thus we regard it as an intrinsic sequence. Figure 12 gives examples of the deep sleep periods from four subjects. Similarly, different sleep stages are expressed by lines in different colors according to the legend and the SampEn values of the deep sleep RR segment and segments of other stages are presented by gray and light orange blocks, respectively. The

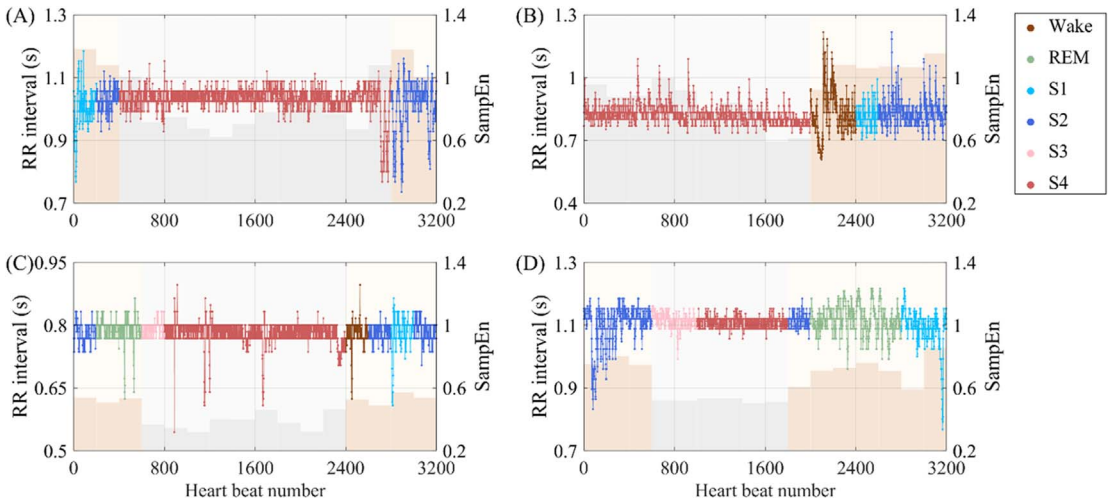

Figure 12. Presentation of deep sleep periods for (A) ucddb007, (B) ucddb018, (C) ucddb023 and (D) ucddb024. Herein, embedding dimension m was set as 2, physical threshold $r = 20$ ms, and segment length $N = 200$.

episodes from different individuals all show that the SampEn values of deep sleep segments are lower as well as more stable than adjacent RR segments from other sleep stages, which can be attributed to the less variability of RR intervals during deep sleep. If we interpret sleep as a type of stimulation, the gradual change from S1 to S4 is a process of adaptation, where SampEn first increases then decreases. As the individual has fully adapted to the stimulation, the cardiovascular system reaches a stable state and, as a consequence, SampEn becomes lower. Since the S3 stage only appears transiently, it is the S4 stage that takes dominance during the deep sleep period. Hence it would be reasonable to consider the RR interval time series from the S4 stage as the intrinsic sequence we seek. Now that such a sequence is a good reflection of the internal features, we wonder what the result would be if we use its nonlinear indexes as baselines to normalize time series from other part of the recording. It is worth exploring whether such processing could eliminate the intra-individual differences when analyzing long-term physiological time series such as 24 hour ECG signals.

The results of the present study also provoke another issue that requires consideration. Since we have demonstrated the change in HRV measurement during sleep stage transition, which proves the impact of the brain on the ANS, whether the brain control over the ANS can be captured by other physiological signals similar to ECG for different sleep apnea patients remains to be studied. If that were true, it seems possible that the state of the body can be determined by non-EEG methods. In addition, the response of the cardiovascular system to different stages is very complicated. If we regard the response of the ANS during sleep as the co-expression of multi-functions, one relevant function plays a leading role while the others are suppressed at certain sleep stages. Therefore, the regulation of the organism during different sleep stages needs to be investigated in detail in the future.

Furthermore, with the prevalence of wearable devices nowadays, actigraphy (ACT), which records movement over an extended period of time, has been widely used in sleep–wake pattern recognition (Ancoli-Israel *et al* 2015). Through an internal accelerator, ACT distinguishes sleep from wakefulness under the premise that movements are frequent and large when people are awake, but absent or small when they are asleep. Compared to PSG methods, ACT has relatively good sensitivity but poor specificity, as immobile wakefulness often leads to incorrect diagnosis (Sivertsen *et al* 2006). On the other hand, HRV indices, which perceive the sleep process via different mechanisms, have been proved to be comparable in sleep–wake pattern discrimination with the ACT ones, and studies have shown that SampEn can provide additional information related to the activity of ANS in compensation for the undetected movements during wakefulness, thus improving the low specificity of ACT methods (Aktaruzzaman *et al* 2017). In that sense, the combination of ACT indices and HRV indices such as SampEn would be a more preferable method for sleep–wake transition detection.

There are several limitations in this study. First, only subjects from the UCD sleep apnea database were used to examine our assumption and the sleep-to-wake transition episodes remained after refinement are quite limited. Thus we ought to use other sleep disorder databases to fully demonstrate the SampEn change during state transition. Second, a healthy control group with EEG-based sleep stage labels needs to be considered. Although the sleep regulation in sleep apnea subjects does not alter, disease-related symptoms such as intermittent hypoxia and arousal can really influence their cardiac rhythm. Thus it would be necessary to analyze

the corresponding transition process in healthy individuals as a reference. In this case, the rule of sleep stage transition would be more applicable. Third, since the severity of the sleep apnea subjects is different, their times series varies individually. To analyze the sleep time series from these patients more precisely, pathological indexes such as apnea hyponea index (AHI) should be taken into account. Moreover, more parameter combinations, such as larger embedding dimension m, various physical threshold r and different segment length N, should be involved in the study, to examine the consistency of the proposed SampEn algorithm in detecting state change.

5. Conclusion

The current study has discovered the SampEn decrease phenomenon during sleep-to-wake transition for sleep apnea patients. Significant entropy differences have been observed when analyzing state changes during the sleep process, especially from sleep to wakefulness. In order to further evaluate the ANS regulation during sleep-to-wake transition, a refinement was applied to filter out transition episodes without sufficient duration, and the remaining episodes presented a significant drop in SampEn value after the state switch. Therefore, the study provides a new way to analyze human sleep state based on non-EEG signals and simultaneously opens up new ideas for assessing the ANS function in daily physiological activities.

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Conflicts of interest

The authors declare no conflict of interest.

References

Aktaruzzaman M, Rivolta M W, Karmacharya R, Scarabottolo N, Pugnetti L, Garegnani M, Bovi G, Scalera G, Ferrarin M and Sassi R 2017 Performance comparison between wrist and chest actigraphy in combination with heart rate variability for sleep classification *Comput. Biol. Med.* **89** 212–21

Ancoli-Israel S, Martin J L, Blackwell T, Buenaver L, Liu L Q, Meltzer L J, Sadeh A, Spira A P and Taylor D J 2015 The SBSM guide to actigraphy monitoring: clinical and research applications *Behavioral Sleep Medicine* **13** S4–38

Chervin R D, Burns J W, Subotic N S, Roussi C, Thelen B and Ruzicka D L 2004 Correlates of respiratory cycle-related EEG changes in children with sleep-disordered breathing *Sleep* **27** 116–21

Chriskos P, Frantzidis C A, Nday C M, Gkivogkli P T, Bamidis P D and Kourtidou-Papadeli C 2020 A review on current trends in automatic sleep staging through bio-signal recordings and future challenges *Sleep Med. Rev.* **55** 101377

Dvir H, Elbaz I, Havlin S, Appelbaum L, Ivanov P C and Bartsch R P 2018 Neuronal noise as an origin of sleep arousals and its role in sudden infant death syndrome *Sci. Adv.* **4** eaar6277

Ebrahimi F, Setarehdan S K and Nazeran H 2015 Automatic sleep staging by simultaneous analysis of ECG and respiratory signals in long epochs *Biomed. Signal Process. Control* **18** 69–79

Goldberger A L, Amaral L A, Glass L, Hausdorff J M, Ivanov P C, Mark R G, Mietus J E, Moody G B, Peng C K and Stanley H E 2000 PhysioBank, PhysioToolkit, and PhysioNet: components of a new research resource for complex physiologic signals *Circulation* **101** 215–20

Ho K K L, Moody G B, Peng C K, Mietus J E, Larson M G, Levy D and Goldberger A L 1997 Predicting survival in heart failure case and control subjects by use of fully automated methods for deriving nonlinear and conventional indices of heart rate dynamics *Circulation* **96** 842–8

Ivanov P C and Lo C C 2007 Quantification of sleep fragmentation through the analysis of sleep-stage transitions(arXiv:cond-mat/0305660)

Javaheri S 2006 Sleep disorders in systolic heart failure: a prospective study of 100 male patients *The final report Int. J. Cardiol.* **106** 21–8

Khoo M C K and Blasi A 2013 Sleep-related changes in autonomic control in obstructive sleep apnea: a model-based perspective *Respir. Physiol. Neuro.* **188** 267–76

Krystal A D, Edinger J D, Wohlgemuth W K and Marsh G R 2002 NREM sleep EEG frequency spectral correlates of sleep complaints in primary insomnia subtypes *Sleep* **25** 630–40

Le Bon O 2020 Relationships between REM and NREM in the NREM-REM sleep cycle: a review on competing concepts *Sleep Med.* **70** 6–16

Lee J M, Kim D J, Kim I Y, Park K S and Kim S I 2002 Detrended fluctuation analysis of EEG in sleep apnea using MIT/BIH polysomnography data *Comput. Biol. Med.* **32** 37–47

Lo C C, Amaral L A N, Havlin S, Ivanov P C, Penzel T, Peter J H and Stanley H E 2002 Dynamics of sleep-wake transitions during sleep *Europhys. Lett.* **57** 625–31
Lo C C, Chou T, Penzel T, Scammell T E, Strecker R E, Stanley H E and Ivanov P C 2004 Common scale-invariant patterns of sleep-wake transitions across mammalian species *Proc. Natl. Acad. Sci. U. S. A.* **101** 17545–8
Lueckel M, Panitz C, Nater U M and Mueller E M 2018 Reliability and robustness of feedback-evoked brain-heart coupling after placebo, dopamine, and noradrenaline challenge *Int. J. Psychophysiol.* **132** 298–310
Otzenberger H, Gronfier C, Simon C, Charloux A, Ehrhart J, Piquard F and Brandenberger G 1998 Dynamic heart rate variability: a tool for exploring sympathovagal balance continuously during sleep in men *Am. J. Physiol. Heart. Circ. Physiol.* **275** H946–50
Pan J and Tompkins W J 1985 A real-time QRS detection algorithm *IEEE Trans. Biomed. Eng.* **32** 230–6
Parmeggiani P L 1990 *Central Regulation of Autonomic Functions* ed A D Loewy and K M Spyer (New York, NY: Oxford University Press) pp 367–82
Penzel T, Kantelhardt J W, Lo C, Voigt K and Vogelmeier C 2003 Dynamics of heart rate and sleep stages in normals and patients with sleep apnea *Neuropsychopharmacology* **28** S48–53
Pincus S M 2001 Assessing serial irregularity and its implications for health *Ann. N. Y. Acad. Sci.* **954** 245–67
Pincus S M and Huang W M 1992 Approximate entropy: Statistical properties and applications *Commun. Stat. Theory Methods* **21** 3061–77
Ravelo-García A G, Saavedra-Santana P, Juliá-Serdá G, Navarro-Mesa J L, Navarro-Esteva J, Álvarez-López X, Gapelyuk A, Penzel T and Wessel N 2014 Symbolic dynamics marker of heart rate variability combined with clinical variables enhance obstructive sleep apnea screening *Chaos* **24** 249–62
Rechtschaffen A and Kales A 1968 A manual of standardized terminology, technique and scoring system for sleep stages of human subjects (Washington, D.C: U.S. Government Printing Office)
Richman J S and Moorman J R 2000 Physiological time-series analysis using approximate entropy and sample entropy *Am. J. Physiol. Heart. Circ. Physiol.* **278** H2039–49
Roehrs T and Roth T 2019 *The Behavioral, Molecular, Pharmacological, and Clinical Basis of the Sleep-Wake Cycle* ed E Murillo-Rodríguez (Salt Lake City, UT: Academic Press) pp 1–16
Rossi A, Da Pozzo E, Menicagli D, Tremolanti C, Priami C, Sirbu A, Clifton D, Martini C and Morelli D 2020 A public dataset of 24 h multi-levels psycho-physiological responses in young healthy adults *Data* **5** 91
Saper C B, Scammell T E and Lu J 2005 Hypothalamic regulation of sleep and circadian rhythms *Nature* **437** 1257–63
Schiecke K, Schumann A, Benninger F, Feucht M, Baer K and Schlattmann P 2019 Brain–heart interactions considering complex physiological data: processing schemes for time-variant, frequency-dependent, topographical and statistical examination of directed interactions by convergent cross mapping *Physiol. Meas.* **40** 114001
Schmidt C, Peigneux P and Cajochen C 2012 Age-related changes in sleep and circadian rhythms: impact on cognitive performance and underlying neuroanatomical networks *Front. Neurol.* **3** 118-
Seely A J E and Macklem P T 2004 Complex systems and the technology of variability analysis *Crit. Care* **8** R367–84
Siegel J M 2009 Sleep viewed as a state of adaptive inactivity *Nat. Rev. Neurosci.* **10** 747–53
Sivertsen B, Omvik S, Havik O E, Pallesen S, Bjorvatn B, Nielsen G H, Straume S and Norchus I H 2006 A comparison of actigraphy and polysomnography in older adults treated for chronic primary insomnia *Sleep* **29** 1353–8
Somers V K, Dyken M E, Mark A L and Abboud F M 1993 Sympathetic-nerve activity during sleep in normal subjects *N. Engl. J. Med.* **328** 303–7
Staudacher M, Telser S, Amann A, Hinterhuber H and Ritsch-Marte M 2005 A new method for change-point detection developed for on-line analysis of the heart beat variability during sleep *Physica.* A **349** 582–96
Stein P K and Pu Y C 2012 Heart rate variability, sleep and sleep disorders *Sleep Med. Rev.* **16** 47–66
Strollo P J and Rogers R M 1996 Obstructive sleep apnea *N. Engl. J. Med.* **334** 99–104
Telser S, Staudacher M, Ploner Y, Amann A and Ritsch-Marte M 2004 Can one detect sleep stage transitions for On-Line sleep scoring by monitoring the heart rate variability? *Somnologie* **8** 33–41
Togo F, Kiyono K, Struzik Z R and Yamamoto Y 2006 Unique very low-frequency heart rate variability during deep sleep in humans *IEEE Trans. Biomed. Eng.* **53** 28–34
Urbanik D, Gać P, Martynowicz H, Poręba M, Podgórski M, Negrusz-Kawecka M, Mazur G, Sobieszczańska M and Poręba R 2018 Obstructive sleep apnea as a predictor of reduced heart rate variability *Sleep Med.* **54** 8–15
Vanoli E, Adamson P B, Lin B, Pinna G D, Lazzara R and Orr W C 1995 Heart rate variability during specific sleep stages. A comparison of healthy subjects with patients after myocardial infarction *Circulation* **91** 1918–22
Vigo D E, Dominguez J, Guinjoan S M, Scaramal M, Ruffa E, Solerno J, Siri L N and Cardinali D P 2010 Nonlinear analysis of heart rate variability within independent frequency components during the sleep-wake cycle *Auton. Neurosci-Basic Clin.* **154** 84–8
Virtanen I, Eeva E C, Polo-Kantola P and Huikuri H 2007 Sleep stage dependent patterns of nonlinear heart rate dynamics in postmenopausal women *Auton. Neurosci-Basic Clin.* **134** 74–80
Wolpert E A 1969 A manual of standardized terminology, techniques and scoring system for sleep stages of human subjects *Arch. Gen. Psychiatry* **20** 246–7
Xiong J, Liang X, Zhu T, Zhao L, Li J and Liu C 2019 A new physically meaningful threshold of sample entropy for detecting cardiovascular diseases *Entropy* **21** 830
Yaggi H K, Concato J, Kernan W N, Lichtman J H, Brass L M and Mohsenin V 2005 Obstructive sleep apnea as a risk factor for stroke and death *N. Engl. J. Med.* **353** 2034–41
Yucelbas S, Yucelbas C, Tezel G, Ozsen S and Yosunkaya S 2018 Automatic sleep staging based on SVD, VMD, HHT and morphological features of single-lead ECG signal *Expert Syst. Appl.* **102** 193–206
Zambotti M D, Trinder J, Silvani A, Colrain I M and Baker F C 2018 Dynamic coupling between the central and autonomic nervous systems during sleep: a review *Neurosci. Biobehav. Rev.* **90** 84–103
Zarei A and Asl B M 2020 Automatic classification of apnea and normal subjects using new features extracted from HRV and ECG-derived respiration signals *Biomed. Signal Process. Control* **59** 101927
Zemaityte D, Varoneckas G and Sokolov E 1984 Heart rhythm control during sleep *Psychophysiology* **21** 279–89
Zhang T, Yang Z and Coote J H 2007 Cross-sample entropy statistic as a measure of complexity and regularity of renal sympathetic nerve activity in the rat *Exp. Physiol.* **92** 659–69
Zhao L N, Wei S S, Zhang C Q, Zhang Y T, Jiang X E, Liu F and Liu C Y 2015 Determination of sample entropy and fuzzy measure entropy parameters for distinguishing congestive heart failure from normal sinus rhythm subjects *Entropy* **17** 6270–88