International Journal of Innovative
Computing, Information and Control
Volume **9**, Number **8**, August **2013**

ICIC International ©2013 ISSN 1349-4198
pp. **3211–3223**

QUANTIFICATION OF SUBJECT WAKEFULNESS STATE DURING ROUTINE EEG EXAMINATION

Maen Alaraj and Tadanori Fukami

Graduate School of Science and Engineering
Yamagata University
4-3-16 Jonan, Yonezawa, Yamagata 992-8510, Japan
maan_alaraj@yahoo.com; fukami@yz.yamagata-u.ac.jp

Received July 2012; revised November 2012

Abstract. *The wakefulness state of healthy subjects tends to be an early drowsy state because of the prolonged times required for electroencephalography (EEG) measurements. In such cases, clinicians should consider accurate diagnosis of the wakefulness state of the subjects in order to interpret EEG signals accurately. The aim of the present study was to quantitatively evaluate the wakefulness state (early drowsy or fully awake) of subjects using a novel index for determining the degree of alpha wave prominence and suppression in the time domain over the occipital lobe. This index was based on approximate entropy (ApEn) during routine EEG examination. EEG recordings were acquired from 45 healthy adult subjects in either fully awake or light drowsy groups. ApEn parameters were chosen based on the results that produced a statistical significant difference between the two groups. The proposed index outperformed other best conventional indices used for evaluating the wakefulness status of subjects, including relative delta sub-band power (2-4Hz) (R.δ), relative theta sub-band power (6-8Hz) (R.θ), power ratios between theta and alpha ($P_{\theta/\alpha}$) and between theta and beta band ($P_{\theta/\beta}$) over the occipital lobe. Our proposed index is superior to R.δ, R.θ, $P_{\theta/\alpha}$ and $P_{\theta/\beta}$, with 5.6%, 1.1%, 4.5%, and 20% respectively.*

Keywords: Routine EEG examination, Approximate entropy, Early drowsy and fully awake state

1. **Introduction.** Eyes opening and closing are a commonly applied test in routine EEG examination. This test is typically based on determining the degree of alpha wave prominence and suppression by eyes closing and eyes opening. However, the wakefulness state of the subjects can affect the prominence and suppression of alpha wave, and exhibits a complex behavior with multiple different EEG patterns. In this study, the complexity of the EEG signal means the unpredictability of a signal (i.e., irregularity), as well as difficulties in the physical description of a signal. In this approach, the nonlinear dynamics theory may be better than the spectrum method in characterizing the intrinsic nature of EEG signals. In this respect, the irregularity in a physiological time series is often quantified by computing the approximate entropy (ApEn). This measure is suitable for capturing the macroscopic spatial temporal dynamics of the electrical activities of the brain which makes it an attractive tool for monitoring the brain dynamics. However, calculation of ApEn requires a priori determination of three user-specified parameters. The recommended values for those parameters had been suggested by Pincus [1] who first proposed ApEn measure. Although these parameters are critical in determining the output of ApEn, no guidelines exist for optimizing their values. The recommended values for the parameters of ApEn are applicable to relatively slow dynamics signals (i.e., slow fluctuation within a narrow range) such as heart rate [2-5] and hormone secretion data

[6, 7]. Lu et al. [8] analyzed the complexity of fast dynamics of neural signals by using Monte Carlo simulations to show that the recommended range of ApEn parameters values may lead to an incorrect assessment of the complexity of a given signal, and may not always be appropriate. However, in the current study, repetitive eyes opening and closing of EEG signals instead of simulated signals were used to determine the optimal values of the ApEn parameters. Those signals were used to produce ApEn values consistent with the degree of irregularity which is typically embedded in EEG signals. The current study was based on alpha rhythm (8-13Hz) over the occipital lobe during eye closure only in healthy awake and drowsy subjects.

There are numerous reports on the use of ApEn measure for determining sleep stages [9-11]. In those studies, the authors gave strictly heed to using the recommended values of ApEn parameters, but in the current study, the values of ApEn parameters over a range wider than the previous studies typically recommended were examined in repetitive eyes opening and closing of EEG signals. Additionally, some of those reports [9, 10], reported general EEG signals that were not measured during a specific test such as eye opening and closure. In previous study, a combination of short time Fourier transform (STFT) with relative statistical values (Z-values) was used to qualitatively evaluate the drowsiness in healthy and patient subjects [12]. This study used EEG recordings where a potential bias can be noticed in the mean age of the subjects groups who participate in this study. Furthermore, this study used EEG recording from single EEG channel, and this may not always be appropriate to capture the whole information over occipital lobe. However, in the current study, the mean age of the subjects groups were almost similar and EEG recordings from two EEG channels over occipital lobe of the brain were used.

Our work makes three important contributions to the previous researches on sleep staging and quantifying works. First, the values of ApEn parameters over a range wider than the previous studies typically recommended were examined in repetitive eyes opening and closing of EEG signals, to determine a decision threshold value in complexity term that represents as a quantitative border between fully awake state and early drowsy state. Second, current study confirmed that the recommended range of one of ApEn parameters was not acceptable in EEG signals which are measured by using specific test such as eye opening and closure. Third, the proposed index outperformed other spectral measures previously reported best measures used for evaluating the wakefulness state of subjects [13]. The results of this study will aid clinicians in quantitative evaluation of the wakefulness state of healthy adult subjects during EEG measurements.

The reminder of this paper is organized as follows. Section 2 describes the EEG recordings and presents the proposed approach to determine the values of ApEn parameters; a brief description about the spectral measures is introduced. Section 3 states the biological justifications for choosing eye closure periods rather than eye opening periods for the analysis. Section 4 reports the experimental results. Section 5 analyzes the performance of the proposed index and compares it with other spectral measures previously reported best measures. Finally, the conclusions and the extensions of the current work are exposed in Section 6.

2. **Method.**

2.1. **EEG recording.** A multichannel EEG signal was acquired using a (EEG-1100; Nihon Koden polygraph, Tokyo, Japan) with a 0.3s time constant, a cut-off frequency of 60Hz in a low-pass band filter, and a 97.5nV quantization level. EEG signals were measured from 19 electrodes on the scalp, placed according to the international 10/20 system with mono-polar derivation from bilateral reference electrodes. In this study, we

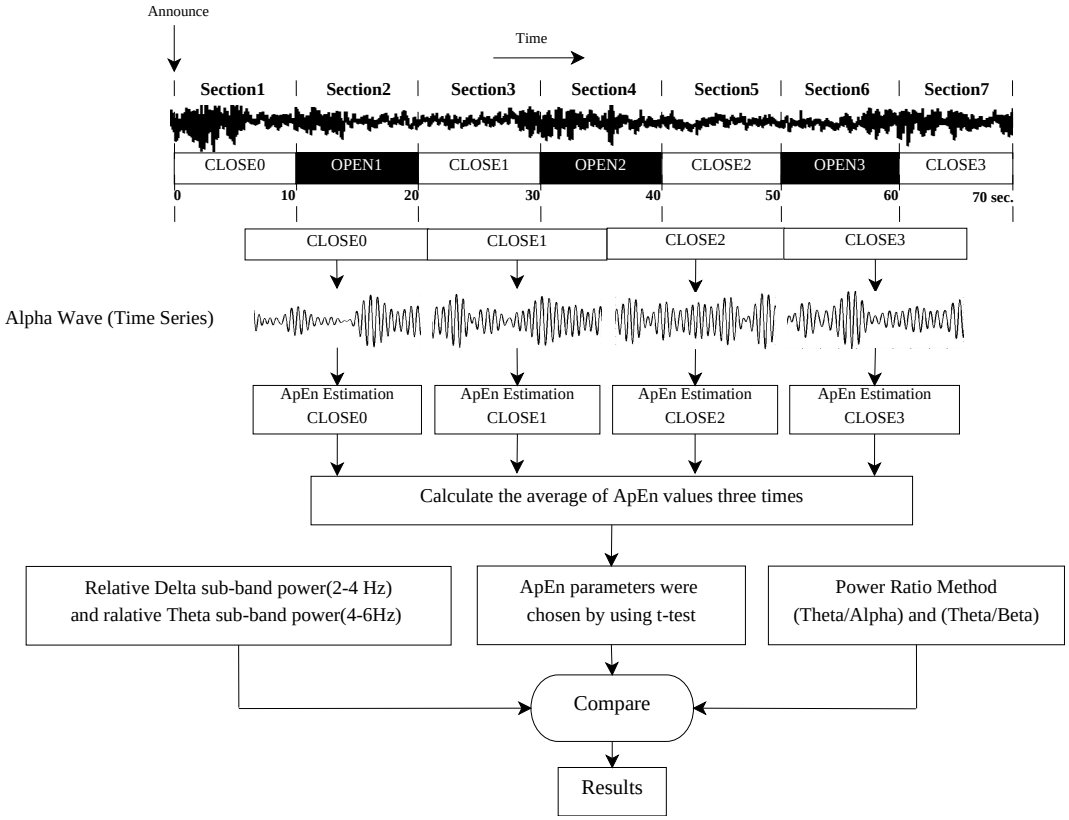

FIGURE 1. Schematic representation of the overall method

analyzed signals from the occipital lobe only, corresponding to O1 and O2. We used data from an eyes opening and closing test during a routine EEG examination. Each EEG recording period lasted for 70s, beginning with the eyes-closed test for 10s, followed by a period with eyes open for 10s. This sequence was repeated for 70s, as shown in Figure 1. Thus, each 10s period contained a section corresponding to either eyes-closed or eyes-open state. Each section was considered as a block, and each block was described as follows: "CLOSE0", "OPEN1", "CLOSE1", etc., to "CLOSE3". A clinical laboratory technician made a visual confirmation of eyes opening and closing. Additionally, an in-house computer program detected the execution of eyes opening and closing from the electrooculogram. If these two checks indicated that eyes opening and closing had not been performed correctly, the corresponding EEG was excluded from further analysis. In addition, body motions, which can cause motion artifacts, were monitored and processed accordingly. The EEG signals were digitized at a sampling frequency of 200Hz. All data were collected at Utsunomiya hospital after obtaining informed consent. EEG data were recorded from 45 healthy awake subjects and 45 healthy drowsy subjects. A full description of the conditions of the healthy subjects is shown in Table 1. Classification of the wakefulness state was based on the international classification scheme proposed by Rechtshaffen and Kales [14]. According to this scheme, EEG recordings from drowsy state subjects were considered as sleep stage 1 of non-rapid eye movement (NREM).

2.2. **Approximate entropy (ApEn).** ApEn is a measure of the complexity of a time series, and assigns a nonnegative number to a noisy time series, with larger values corresponding to more complexity (i.e., unpredicted fluctuation) and vice versa [2]. ApEn measures the (logarithmic) likelihood that runs of patterns that are close for m observations remain close on the next incremental comparisons. Calculation of ApEn requires a

TABLE 1. Number and age of subjects in the two groups

	Awake	*Drowsy*
Number	45	45
Age	23.8 ± 3.09	23.4 ± 2.30

priori determination of three user-specified parameters, m, r, and N. The parameter m determines the length of the segments (or vectors) to be compared, r is the tolerance for accepting similar patterns between two segments, and N is the length of the time series. Thus, ApEn measure can be considered as a measure that divides the signal into a series of vectors whose lengths are m. Each vector serves, in turn, as a template vector for comparison with all other vectors in the signal toward the determination of a conditional probability. This means that each vector in the given signal has an associated conditional probability. In this approach, ApEn aggregates these conditional probabilities into an ensemble measure of regularity [2].

Usually, ApEn is estimated by using the widely established parameter values as suggested by Pincus [1], where $m = 1$ or 2, and a values of the r parameter were fixed between 0.1 to 0.25 times the standard deviation (STD) of the original data sequence whose length was N. However, the prescribed values of ApEn parameters are not always appropriate for neural signal as indicated by a previous study [8]. Thus, in the current study, the parameters of ApEn over wide range of values were examined in repetitive eyes opening and closing of EEG signals. ApEn is applicable to time series with at least 50 data points [15] and less than 5000 samples [2]. Calculation of ApEn was performed with software developed using MATLAB version 7.6 (MathWorks, Natick, MA, USA). A more detailed description of ApEn from the mathematical point of view can be found in [1-3]. In this study, ApEn was applied to alpha waves extracted by fast Fourier transform.

2.2.1. *Selection of dimension m.* In this study, the choice of $m = 2$ was chosen for three reasons. First, a choice of $m = 2$ is superior to $m = 1$, in that it allows more detailed reconstruction of the joint probabilistic dynamics of the process [2]. Second, ($m > 2$) typically produces poor conditional probability estimates unless r is very large, and such large r values are generally too coarse to reveal pronounced process distinctions via $ApEn(m, r)$ [2]. Finally, a higher value of m results in a higher computational time.

2.2.2. *Selection of parameters (a and N).* When small N values are used to compute ApEn, the estimates are typically inaccurate as they show a large variance. By contrast, large N values may contain abrupt changes in the amplitudes that could result in inaccurate estimates. Similarly, the value of r depends on a because ($r = a \times STD(N)$, where N is the length of data). Thus, as the a value increases, variability in ApEn decreases for the corresponding m, and vice versa [16]. To obtain an optimal value of N and a, ApEn was computed with different N and a values for the eyes-closed periods. More precisely, the selected N values were chosen to be multiple integer of 2000 samples (i.e., 50, 80, 100, 125, 200, 250, 400, 500, 1000, and 2000 samples), while the various values of a ranged from 0.05 to 1 with a step of 0.05. Occasionally the exact amount of the noise present in a data set could not be determined in advance. Thus, the estimated ApEn values were expressed by a matrix of 20×10 elements, where each element reports the value of ApEn that was estimated by different combinations of a multiplied by the STD of the analyzed section whose length is N. In the current study, the average of ApEn values were calculated three times in sequence. First average (AVG1) was calculated for the ApEn values across the sub-sections whose lengths were less than 2000 samples in

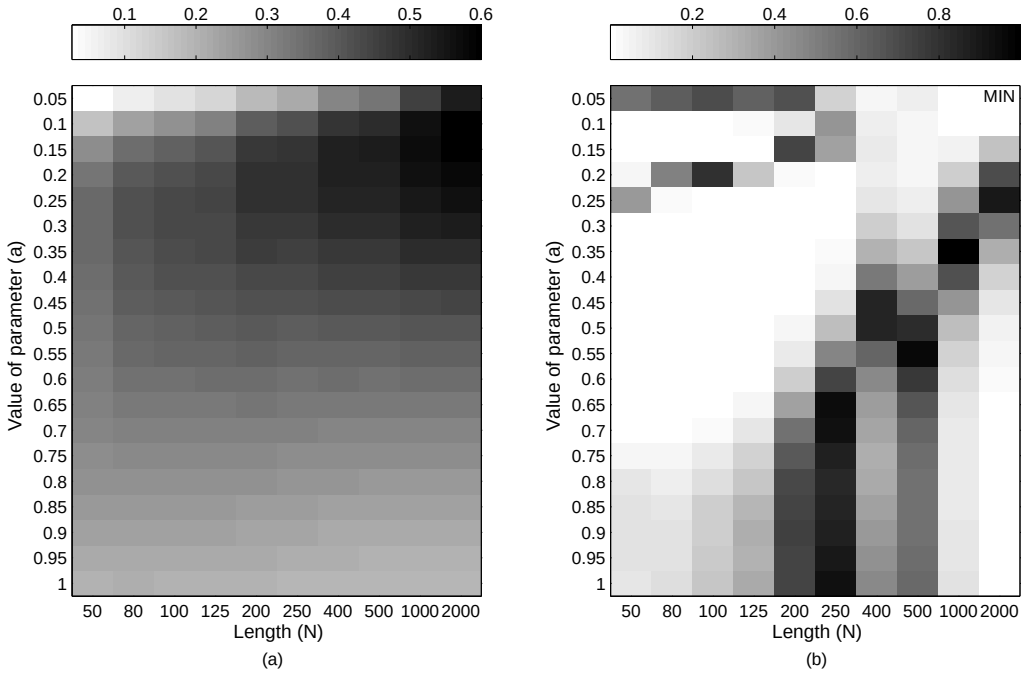

FIGURE 2. Gray scale grid of 20×10 matrix which corresponds to a combination of a and N parameters after the calculations of AVG1, AVG2 and AVG3. (a) Each element shows the value of ApEn. (b) Each element shows the p-value by two-sample Student t-test. MIN denotes to the minimum p-value.

each eye-closed period. As a consequence, all the ApEn values in the matrix 20×10 that corresponded to sub-sections whose lengths were less than 2000 samples were estimated by using AVG1. This matrix was calculated for each eye-closed period over each signal (i.e., O1 and O2) for each subject in both groups, as shown in Figure 2(a). Second average (AVG2) was calculated for the ApEn values in the aforementioned matrix across the two electrodes signals (i.e., O1 and O2) for each subject within both groups. Third average (AVG3) was calculated for the second average (AVG2) across all eyes-closed periods for each subject within the two groups. Consequently, after the calculation of AVG3, each subject within both groups could be represented by a matrix of 20×10 of ApEn values.

To test the hypothesis that the population mean of the awake subjects was significantly different from the drowsy subjects, a two-sample Student's t-test was performed between the AVG3 samples, which corresponded to the ApEn values of the awake and drowsy subjects. The ApEn values were estimated by using different combinations of a and N, as previously described. Hence, the p-value (where p-value represents the probability of t-test) of all the different combinations of a and N, which correspond to a matrix of 20×10 elements, was calculated, as shown in Figure 2(b). In this study, a significant difference was considered at p-value < 0.01. Thus, the best result that corresponds to the smallest p-value was determined with $a = 0.05$ times the SD of the data whose length was $N = 2000$ samples. The location of the smallest p-value was labeled with "MIN" (i.e., minimum p-value), as shown in Figure 2(b). Thus, $m = 2$, $a = 0.05$ and $N = 2000$ samples were chosen for the subsequent ApEn calculation, as shown in Figure 3.

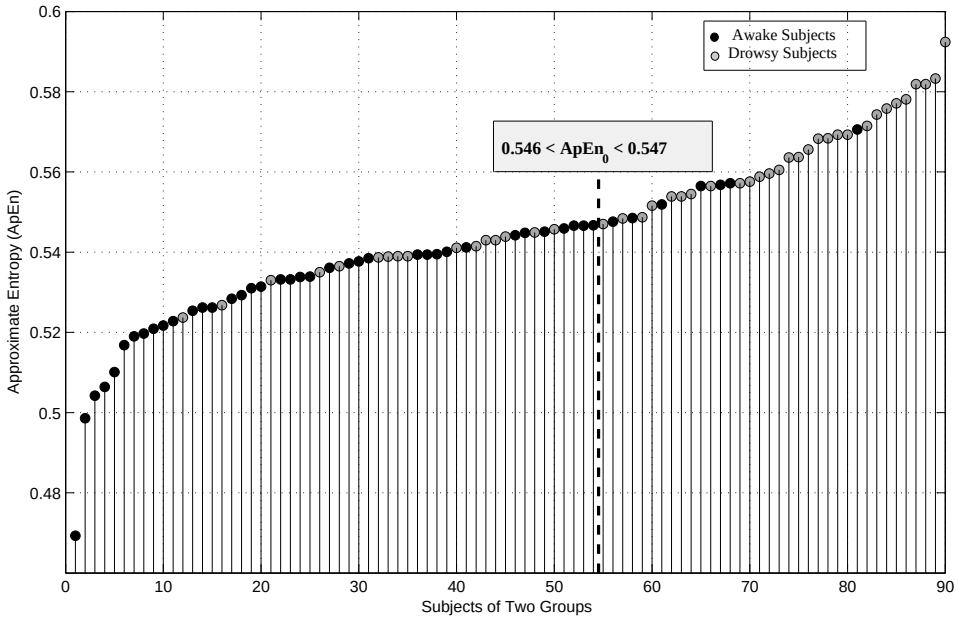

FIGURE 3. The values of ApEn ($m = 2$, $a = 0.05$, $N = 2000$) of the subjects in the two groups. The dashed line denotes the decision threshold value ($ApEn_0$).

2.3. **Spectral measures.** Spectral measures are commonly used to measure and quantify the wakefulness state of the subjects. Those measures are based on relative spectral power and power ratios between two specific EEG sub bands. More precisely, those measures are: relative delta sub-band power (2-4Hz) ($R.\delta$), relative theta sub-band power (4-6Hz) ($R.\theta$), power ratio between theta and alpha ($P_{\theta/\alpha}$), and power ratio between theta and beta ($P_{\theta/\beta}$). The frequency bands of theta and beta rhythms were 4-8Hz and 16-30Hz, respectively. All of those measures were evaluated and previously reported as best measures for distinguishing early drowsy state from the fully awake state over the occipital lobe in healthy subjects [13]. The relative spectral powers were stated as the ratios of the absolute spectral powers in specific bands to the total spectral power [13, 17]. All power spectrums were calculated using Welch averaged modified periodogram method [18] for 2000 samples corresponding to the eyes-closed period without overlapping.

Similar to AVG2 and AVG3 in ApEn, the average of the spectral measures values were not calculated only across O1 and O2 for each subject, but also across all eyes-closed periods for each subject within the two groups. Consequently, each subject within both groups had one value for each one of the spectral measures as a result from calculating AVG3. To make a comparison between the spectral measures and ApEn measure, AVG1 was not calculated for the spectral measures because those measures were calculated to the sections whose lengths were consistent with the optimal value of N parameter in ApEn (i.e., 2000 samples).

3. **Biological Justification for Choosing Eye Closure Periods.** In healthy adult subjects, alpha rhythm (8-13Hz) is typically prominent over the occipital lobe during eye closure, when the state of the subjects is relaxed and wakefulness [19, 20]. In general, the alpha rhythm can be markedly diminished by eye opening, a phenomenon termed alpha blockage. The alpha rhythm can also be attenuated when alertness decreases to

the level of drowsiness (i.e., early state of drowsiness (stage I)). However, this attenuation is often accompanied by a gradual decrease in frequency to 2-7Hz as a person falls into deep sleep [19, 20]. As a consequence, alpha rhythm in fully awake subjects is prominent during eye closure and suppressed during eye opening, but it is only suppressed during eye closure and eye opening in drowsy subjects, which may change the complexity of the alpha wave. As such, eye closure may be more suitable than eye opening for evaluating alpha prominence and suppression in awake and drowsy subjects, respectively. Therefore, eye-opening periods were not evaluated in this study.

4. **Results.** The wakefulness state discrimination of the subjects was based on decision threshold value ($ApEn_0$), which was derived from the minimum error in the discrimination rate between the two groups. To achieve this, all the ApEn values corresponding to the awake and drowsy subjects were sorted in ascending order. Next, all the possible locations of the decision threshold value were examined to enable partitioning of the ranks of ApEn values into two groups. Most of the ApEn values corresponding to the awake subjects exhibited relatively small values when compared with the ApEn values of the drowsy subjects when the ascending order was performed. Thus, to satisfy the condition of the minimum error discrimination rate between the two groups, the left side of the decision threshold value ($ApEn_0$) was considered the region of the correct discrimination of awake subjects, while the right side was considered as the region of the correct discrimination of the drowsy subjects, as shown in Figure 3. Hence, the error discrimination rate of the awake and drowsy subjects can be expressed by $ApEn_A$ and $ApEn_D$, respectively, and can be calculated by:

$$ApEn_A = \frac{ErrorDiscriminatedSubjects}{NumberAwakeSubjects} = \frac{7}{45} = 0.155 = 15.5\% \quad (1)$$

$$ApEn_D = \frac{ErrorDiscriminatedSubjects}{NumberDrowsySubjects} = \frac{16}{45} = 0.355 = 35.5\% \quad (2)$$

$$TotalError_{ApEn} = \frac{TotalErrorDiscriminatedSubjects}{TotalNumberSubjects} = \frac{23}{90} = 25.5\% \quad (3)$$

Similar to that for ApEn, all the values of AVG3 that are related to $R.\delta$, $R.\theta$, $P_{\theta/\alpha}$, and $P_{\theta/\beta}$ were sorted into ascending order, and the best decision threshold value was chosen based on the minimum error of the discrimination rate between the two groups. More precisely, the condition of the minimum error discrimination rate was satisfied when the right side of the decision threshold value ($R.\delta_0$) and ($R.\theta_0$) represented the region of correct discrimination of the awake subjects, and when the left side represented the region of correct discrimination of the drowsy subjects, as shown in Figures 4 and 5, respectively. By contrast, the condition of the minimum error discrimination rate was satisfied when the left side of the decision threshold value ($P_{\theta 0/\alpha 0}$) and ($P_{\theta 0/\beta 0}$) represented the region of correct discrimination of the awake subjects, and the right side represented the region of the correct discrimination of the drowsy subjects, as shown in Figures 6 and 7, respectively.

The exact locations of all the best decision threshold values that are related to the spectral measures are shown in Figures 4-7. The best decision threshold value of $R.\delta$, $R.\theta$, $P_{\theta/\alpha}$ and $P_{\theta/\beta}$ were denoted by $R.\delta_0$, $R.\theta_0$, $P_{\theta 0/\alpha 0}$ and $P_{\theta 0/\beta 0}$ respectively. The error discrimination rate of the awake and drowsy subjects, and the total error that is related to $R.\delta$, $R.\theta$, $P_{\theta/\alpha}$, and $P_{\theta/\beta}$, were calculated using Equations (1)-(3), as shown in Table 2.

5. **Discussion.** EEG measurements are typically acquired from healthy and patient subjects and this procedure lasts for prolonged times. In such cases, the wakefulness state of the subjects tends to be an early drowsy state, particulary in healthy subjects. Usually,

TABLE 2. Quantitative comparisons among the rates of all the measures. ApEn: approximate entropy, $R.\delta$: Relative delta sub-band (2-4Hz) power, $R.\theta$: Relative theta sub-band power (4-6Hz), $P_{\theta/\alpha}$: power ratio between theta and alpha band, $P_{\theta/\beta}$: power ratio between theta and beta band.

	$ApEn$	$R.\delta$	$R.\theta$	$P_{\theta/\alpha}$	$P_{\theta/\beta}$
$AwakeSubjects$	15.5%	37.7%	28.8%	13.3%	28.8%
$DrowsySubjects$	35.5%	24.4%	24.4%	46.6%	62.2%
$TotalError$	25.5%	31.1%	26.6%	30%	45.5%

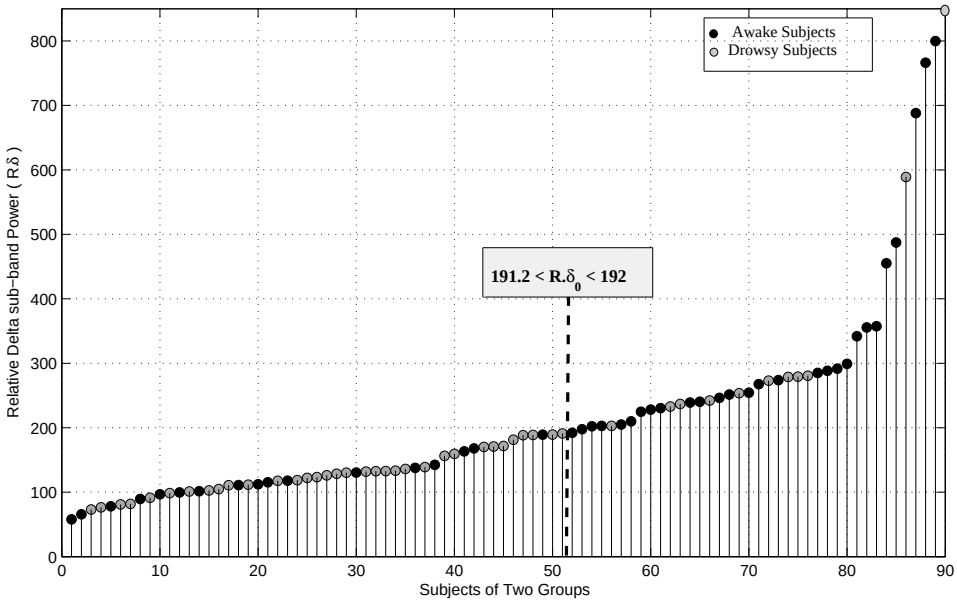

FIGURE 4. The values of $R.\delta$ for the subjects of two groups. The dashed line denotes the decision threshold value ($R.\delta_0$).

this transition from fully awake state to early drowsy state can complicate the interpretation of EEG signals. In such cases, the wakefulness state of the subjects during EEG measurements should be determined in advance for more precise interpretation. However, the transition to the early drowsy state (stage I) is still unclear [19] as it represents a mixture of alertness and sleep [13]. Thus, a system for quantitative evaluation for the wakefulness state of the subjects is needed. Such system can be based on a proper index to evaluate the wakefulness state of the subjects. In this respect, routine electroencephalography (EEG) examination was used to examine the proposed index in healthy adults subjects.

Although, we did not use eyes-opening periods for evaluating our proposed index, eyes opening and closing test can be considered more appropriate than continuous eye closure test in quantifying early drowsy state (stage I), because the early state of drowsiness typically contains several forms of eyes closing and eyes opening, ranging from complete eyes closing to incomplete closing. However, such transitions from eyes closing to eyes opening may affect on the complexity of the EEG signals during early state of drowsiness and make it be close to that in the wakefulness state [11]. As a consequence, the task of distinguishing fully awake state from early drowsy states quantitatively during repetitive eyes opening and closing is more difficult than distinguishing in continuous eye closure,

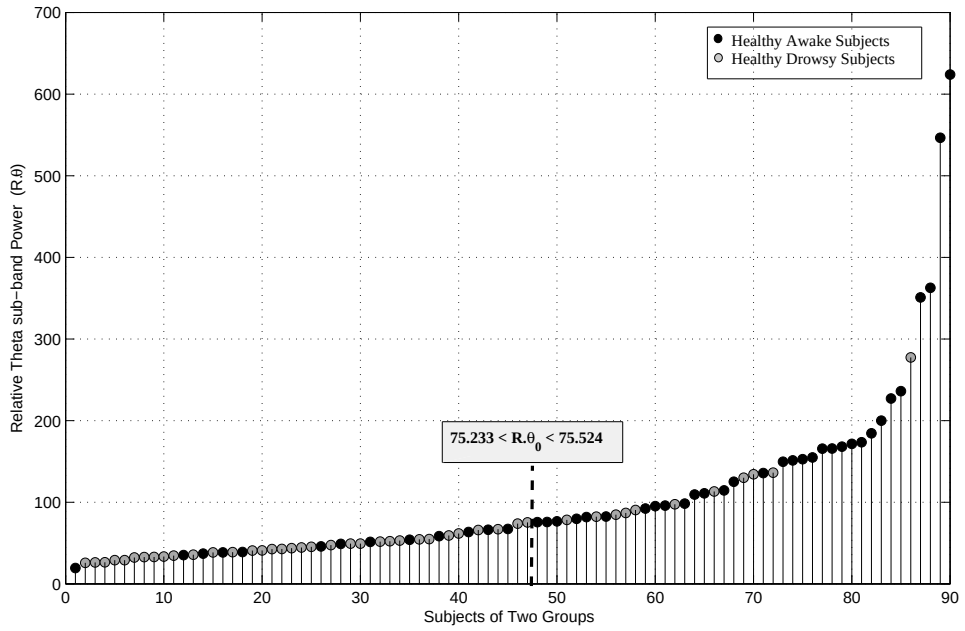

FIGURE 5. The values of $R.\theta$ for the subjects of the two groups. The dashed line denotes the decision threshold value ($R.\theta_0$).

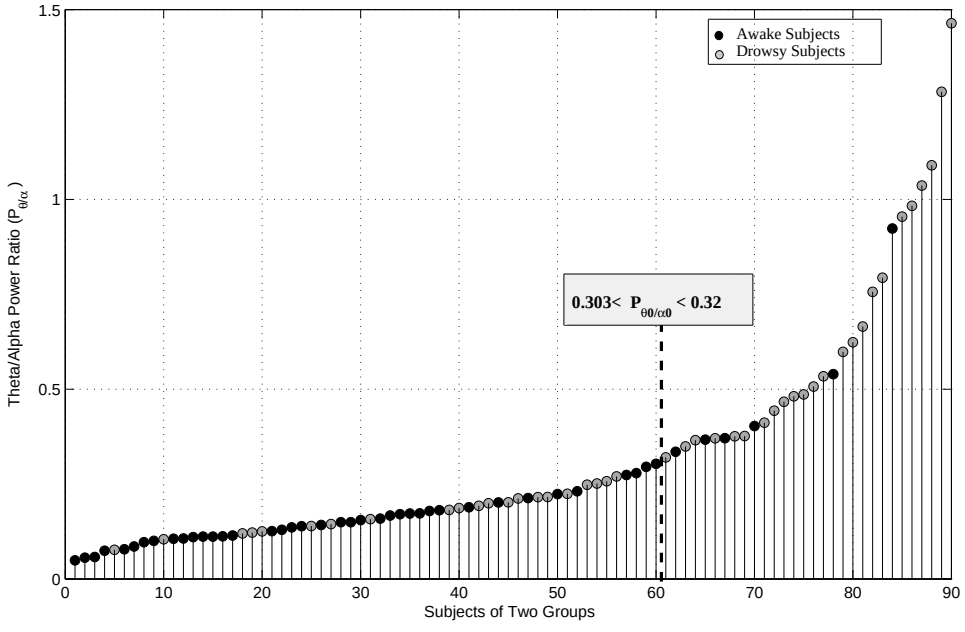

FIGURE 6. The values of $P_{\theta/\alpha}$ for the subjects of the two groups. The dashed line denotes the decision threshold value ($P_{(\theta 0/\alpha 0)}$).

as reported by [9, 10]. Thus, the current study would solve this problem by determining a distinct quantitative border by using best decision threshold value that satisfies the minimum error in the discrimination rate, to aid clinicians for more precise interpretation of EEG signals.

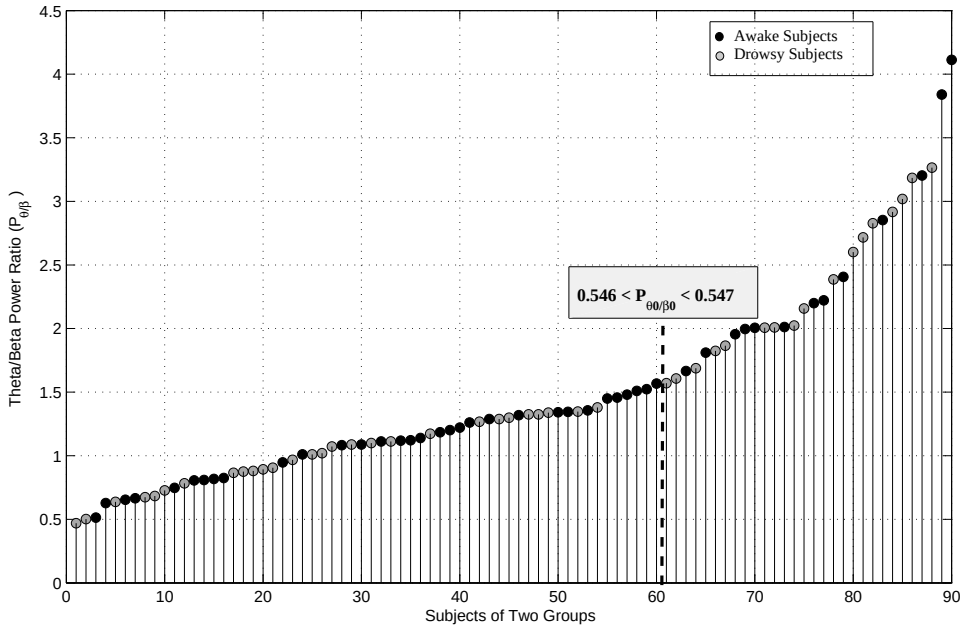

FIGURE 7. The values of $PwrRatio_{\theta/\beta}$ for the subjects of the two groups. The dashed line denotes the decision threshold value ($P_{(\theta 0/\beta 0)}$).

In the current study, we did not use any automated classifier or any feature extraction techniques. Although, a classifier may improve the discrimination performance, the results would be affected by the performance of the chosen feature extraction technique.

The best decision threshold value that corresponds to ApEn ($ApEn_0$) was determined after a careful examination for the values of ApEn parameters over a range wider than the previous studies typically recommended. The best values for ApEn parameters as we described earlier were: $m = 2$, $a = 0.05$ and $N = 2000$ samples. The value of N indicates that the calculation of AVG1 was not included in the estimation of ApEn values which were used to constitute the two sample sets of ApEn values for statistical test. By calculating AVG2 and AVG3, we were able to eliminate the differences that might have existed between O1 and O2, and differences that might have existed among the eyes-closed periods. Thus, the reported results in the current study can be considered more reliable than other results where the average values were not used, as reported by [9, 10, 13].

To examine the superiority of proposed index quantitatively, we compared our proposed index with the spectral measures which were evaluated as best measures in distinguishing fully awake state from early drowsy state (stage I) over the occipital lobe (i.e., O1 and O2) in healthy subjects [13], by using decision threshold value which satisfies the minimum error in the discrimination rate. Thus, other measures reported as best measures in either O1 or O2 alone were not evaluated in the current study. Although the error discrimination rate of the ApEn method was higher than that of $P_{\theta/\alpha}$ and ($R.\delta$ and $R.\theta$) for evaluating the fully awake and early drowsy states, respectively, the total error of $P_{\theta/\alpha}$, $R.\delta$ and $R.\theta$ was still higher than that for the ApEn method, as shown in Table 2. All the values that related to the total error in Table 2 indicate that the proposed index has more superiority than spectral analysis-based indices. In order to illustrate that the proposed index based on ApEn measure is more efficient than spectral analysis-based indices in evaluating the subject's wakefulness state, we evaluated the overall discrimination power (i.e., performance) that is related to the ApEn and the spectral measures in quantifying

the early drowsy state and fully awake state over occipital lobe by using receiver operating characteristics curve (ROC) [21]. ROC, is used to examine the performance of a diagnostic test (i.e., ApEn and spectral measures) by using different thresholds or cut-off points (i.e., different ApEn and spectral thresholds as shown in Figures 3-7) and calculates the sensetivity/specficity pair for each one of those points to show the overall discrimination power for the given measure. Sensitivity (i.e., the true positive rate) is the percentage of drowsy subjects who are correctly discriminated, whereas specificity (i.e., the true negative rate) represents the percentage of fully awake subjects who are correctly discriminated. The area under ROC curve (AUC) is a measure of the probability of correctly identifying the wakefulness state of the subjects. Thus, diagnostic measure with higher AUC value indicates that this measure has more discrimination power than diagnostic measure with lower AUC value. A rough guide to classify the precision of the diagnostic measure [22] that is related to AUC is as follows: with values between 0.9 and 1, the precision of the diagnostic measure is considered to be excellent, good for the values between 0.8 and 0.89, fair for the values between 0.7 and 0.79, poor for the values between 0.6 and 0.69, and bad for the values below than 0.6. Thus, the results of ApEn measure over occipital lobe can be considered good. All the values of AUC for ApEn measure and spectral measures are shown in Table 3.

TABLE 3. The values of area under ROC curve (AUC) for all the measures. ApEn: approximate entropy, $R.\delta$: Relative delta sub-band (2-4Hz) power, $R.\theta$: Relative theta sub-band power (4-6Hz), $P_{\theta/\alpha}$: power ratio between theta and alpha band, $P_{\theta/\beta}$: power ratio between theta and beta band.

	$ApEn$	$R.\delta$	$R.\theta$	$P_{\theta/\alpha}$	$P_{\theta/\beta}$
AUC	0.82	0.64	0.77	0.78	0.5

Although, ApEn measure could show relative small improvement for evaluating the wakefulness state of the subjects over spectral measures, ApEn has more potential widespread utility for practical data analysis and clinical application due to its ability to elucidate specific transit-temporal patterns of EEG signals called unclear significant patterns [11, 19]. In general, these patterns are normal findings in healthy adults subjects and have many types. Usually, these patterns associate with a specific EEG band frequency including alpha band and their durations were ranging from brief of seconds to several seconds depending on the type of these patterns [19]. Particular types of these patterns are close associated with alpha band over occipital lobe during eye closure when the wakefulness state of the subjects is fully awake state. More precisely, the types of those patterns are called alpha squeak and alpha variant and can be easily characterized by their distinctly characteristic shapes [19]. Comparing the durations of those patterns with the relative short periods of eyes-closing in our EEG data set, revealed that those types of patterns may affect the complexity of the time series as they have distinct characteristic shapes. Although these patterns have not appeared in each trial of eye closure, their effects on the complexity can be used as a proper indicator for the wakefulness state of the subjects.

It is important to note that the frequency bands of the EEG signals in our study were similar to the frequency bands as defined by Susmakova and Krakovska [13], except for the alpha band. In our study, the alpha band was considered as 8-13Hz, as reported by a wide range of medical and clinical studies [12, 17, 19, 20, 22]. By contrast, the alpha band was considered as 8-12Hz in [13]. Nevertheless, this difference in the frequency band of the alpha rhythm would not significantly affect our new analysis method. In

order to generalize the proposed index to be used in other applications, rather than only during the eyes-closed test in routine EEG examination, future studies are required using a preprocessing step performed in advance.

6. **Conclusions.** Due to the nonlinear nature of physiological systems, ApEn is a powerful tool for revealing hidden characteristics of various biological signals. We used ApEn with new values for its parameters as a new index for quantitative evaluation of the wakefulness state in healthy adults subjects, as the alpha rhythm is known to occur over the occipital lobe during eye closure. We observed an increment in the amount of the fluctuation in the time series and spectrum components of alpha waves in drowsy subjects. Using this approach, we determined the optimal values of the ApEn parameter that allowed quantitative evaluation of the wakefulness state of a subject. The choice of ApEn parameters was performed based on a two-sample Student t-test where a statistical significant difference could be obtained between the awake and drowsy subjects. The proposed index was superior to other spectral analysis-based indices for quantitative evaluation of wakefulness state of subjects.

Acknowledgment. The authors thank Dr. Fumito Ishikawa in Utsunomiya Hospital for supplying EEG data and for his support to the results.

REFERENCES

[1] S. M. Pincus, Approximate entropy as a measure of system complexity, *Proc. of National Academy of Sciences of the United State of America*, vol.88, pp.2297-2301, 1991.
[2] S. M. Pincus and A. L. Goldberger, Physiological time series analysis: What does regularity quantify?, *American J. of Physiology*, vol.266, pp.1643-1656, 1994.
[3] S. M. Pincus, Assessing serial irregularity and its implications for health, *Annals of New York Academy of Sciences*, vol.954, pp.245-267, 2001.
[4] D. T. Kaplan, M. I. Furman, S. M. Pincus, L. A. Ryan and A. L. Goldberger, Aging and complexity of cardiovascular dynamics, *Biophysics J.*, vol.59, pp.945-949, 1991.
[5] K. Ho, G. Moody, C. Peng, J. Mietus, M. Larson, D. Levy and A. L. Goldberger, 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 J.*, vol.96, pp.842-848, 1997.
[6] S. M. Pincus and D. L. Keefe, Quantification of hormone pulsatility via an approximate entropy algorithm, *American J. of Physiology*, vol.262, pp.741-754, 1992.
[7] S. M. Pincus, M. L. Hartman, F. Roelfsema, M. O. Thorner and J. D. Veldhuis, Hormone pulsatility discrimination via coarse and short time sampling, *American J. of Physiology*, vol.277, pp.948-957, 1999.
[8] S. Lu, X. Chen, J. Kanters, I. Solomon and K. Chon, Automatic selection of the threshold value r for approximate entropy, *IEEE Trans. Biomedical Engineering*, vol.55, pp.1966-1972, 2008.
[9] R. Acharya, O. Faust, N. Kannathal, T. Chua and S. Laminarayan, Nonlinear analysis of EEG signals at various sleep stages, *J. Computer Methods and Programs in Biomedicine*, vol.80, pp.37-45, 2005.
[10] N. Burioka, M. Miyata, G. Cornelissen, F. Halberg, T. Takeshima, D. Kaplen et al., Approximate entropy in the electroencephalogram during wake and sleep, *J. Clin. EEG Neurosci.*, vol.36, pp.21-24, 2005.
[11] M. Alaraj, T. Fukami and F. Ishikawa, Effects of subject's wakefulness state and health status on approximated entropy during eye opening and closure test of routine EEG examination, *J. Biomedical Science and Engineering*, vol.5, pp.75-94, 2012.
[12] T. Fukami, F. Ishikawa, B. Ishikawa and Y. Saito, Quantitative evaluation of eyes opening and closure with time variation in routine EEG examination, *International Journal of Innovative Computing, Information and Control*, vol.7, no.9, pp.5529-5540, 2011.
[13] K. Susmakova and A. Krakovska, Discrimination ability of individual measures used in sleep stages classification, *J. Artificial Intelligence in Medicine*, vol.44, pp.261-277, 2008.

[14] A. Rechtshaffen and A. Kales, *A Manual of Standardized Terminology, Techniques and Scoring System for Sleep Stages of Human Subjects*, UCLA Brain Information Service/Brain Research Institute, the University of California, Los Angeles, 1968.
[15] R. Hornero, D. Abasolo, J. Mc and B. Goldstein, Interpretation of approximate entropy: Analysis of intracranial pressure approximate entropy during acute intracranial hypertension, *IEEE Trans. Biomedical Engineering*, vol.52, pp.1671-1679, 2005.
[16] R. Yan and R. Gao, Approximate entropy as a diagnostic tool for machine health monitoring, *J. Mechanical Systems and Signal Processing*, vol.21, pp.824-839, 2007.
[17] H. Schwilden, Concepts of EEG processing: From power spectrum to bispectrum, fractals, entropies and all that, *J. Best Practice and Research Clinical Anaesthesiology*, vol.20, pp.31-48, 2006.
[18] A. V. Oppenheim and R. W. Schafer, *Discrete-Time Signal Processing*, Prentice-Hall, 1989.
[19] D. Schomer and F. Lopes da Silva, *Niedermeyer's Electroencephalography: Basic Principals, Clinical Applications, and Related Fields*, Lippincott Williams and Wilkins, USA, 2011.
[20] C. John, T. Louis and B. Gary, *Hand Book of Physiology*, Cambridge University Press, UK, 2007.
[21] M. Zweig and G. Campbell, Receiver-operating characteristic (ROC) plots: A fundamental evaluation tool in clinical medicine, *J. Clin. Chem.*, vol.39, pp.561-577, 1993.
[22] D. Abasolo, R. Hornero, P. Espino, J. Poza, C. Sanchez and R. de la Rosa, Analysis of regularity in the EEG background activity of Alzheimer's disease patients with approximate entropy, *Clinical Neurophysiology*, vol.116, pp.1826-1834, 2005.