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Alzheimer Dementia Detection Based on Unstable Circadian Rhythm Waves Extracted from Heartrate

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Abstract— **This paper proposes the novel Alzheimer dementia (AD) detection method based on unstable circadian rhythm of heartrate acquired from mattress sensor. Concretely, the proposed method, UCRADD (Unstable Circadian Rhythm based Alzheimer Dementia Detection), estimates the circadian rhythm of heartrate by calculating the regression of the trigonometric functions with the maximum likelihood estimation, and judges instability of the circadian rhythm by the coefficients of the equation estimated trigonometric functions. Through the human subject experiment with one elderly AD subject in two months (*i.e.*, August and December), three elderly (age from 60-70) non-AD subjects, the ten middle-aged non-AD subjects and eight young non-AD subjects, the following implications have been revealed: (1) UCRADD succeeds to detect the AD patients in the high rate and keeps it in two months (78.9% in August and 82.4% in December), while our previous method cannot keep the rate at the same level in two months (57.9% in August and 82.4% in December). (2) the instability of circadian rhythm of heartrate has the potential of being new symptom of AD.**

I. Introduction

Recently, it has been reported that the number of elderly dementia patients in Japan will increase from 4.62 million in 2012 to 7 million in 2025. However, dementia has no complete prevention or radical cure, even though the mechanism of action of dementia has been clarified gradually (*e.g.*, the accumulation of amyloid-β in the brain causes dementia [4], and it is discharged during deep sleep [5] which suggests that sleep is important for the dementia). As the different problem, it is difficult to be aware of dementia because it takes a long time (*e.g.*, 10 years) for the symptoms to appear, which means that the condition can worsen without being noticed. From this fact, it is important to detect dementia and treat it as early as possible. For this purpose, the global standard method of dementia detection called Mini-Mental State Examination (MMSE) [6] is widely employed as one of questionnaires. However, this method burdens to the patients by asking questionnaires that doubts them dementia while it is difficult to detect the early stage of dementia.

To tackle with this problem, the method that can detect dementia in daily life (which can be substitute for questionnaries) is really needed. For this issue, Nikamalfard focused on Alzheimer dementia (AD) which is 40% of dementia, and proposed the AD detection method based on the sleep patterns estimated from the bio-vibration data obtained from the mattress sensor [1]. In detail, this method can detect AD by just sleeping in the bed because it judges AD from the viewpoint of an increase of waking time during sleep and early morning awakening due to shallow sleep, which are often found in dementia patients in comparison with non-AD persons [2].

However, it is difficult to distinguish between AD patients and non-AD elderly persons by checking the sleep duration and the number of awakening times during sleep because elderly persons tend to also suffer from sleep disorders [3], which often have similar symptoms of AD patients.

To overcome this problem, our previous research focused on the circadian rhythm (approximately 24 hours) of the melatonin secretion because the melatonin secretion of the healthy persons (including the non-AD elderly persons) have clear circadian rhythm while the AD patients have unstable circadian rhythm (*e.g.*, a phase shift of the circadian rhythm, a change of the circadian rhythm period, and a reduction of circadian rhythm amplitude) [7]. From this fact, our previous research employed the circadian rhythm of the "heartrate" instead of the "melatonin secretion" because the heartrate can be obtained from the mattress sensor (placed under the mattress) in the daily life while the melatonin secretion is hard to be obtained, and proposed Circadian Rhythm Amplitude Ratio AD Detection (CRARaADD)[8] based on the ratio between the circadian rhythm of the heartrate and its non-circadian rhythm (as a biological rhythm not related to the circadian rhythm). Such circadian and non-circadian rhythms are estimated by the regression of the trigonometric functions with the maximum likelihood estimation. CRARaADD detects AD from the viewpoint of the following two types of the circadian ratios: (1) the threshold of the ratio between the circadian rhythm of the heartrate and its non-circadian rhythm should be determined beforehand even though it is sensitive to the accuracy of AD detection; and (2) the non-circadian rhythms must be determined beforehand even though it can be any rhythms without around 24 hours, which is also sensitive to the accuracy of AD detection. To overcome the problems, this paper proposes the new AD detection method without the threshold and the non-circadian rhythm, and aims at investigating its effectiveness through the human subject experiments.

This paper is organized as follows. The next Section describes the principle of AD detection based on the circadian rhythm disorder of heartrate, the base method "Real-time Sleep Stage Estimation" and the proposed method. The human subject experiments with elderly AD patients, healthy

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elderly, middle-aged and young are conducted and the results are discussed in Section III. Finally, our conclusion is given in Section IV.

II. Estimation of Circadian Rhythm Waves and Calculation of Stability of its Rhythms

A. Overview

Based on the report that the circadian rhythm is found in the heartrate [10], this paper hypothesizes that the circadian rhythm of the heartrate in AD patients tends to be unstable in comparison with healthy persons described in Section I. On the basis of this hypothesis, this paper proposes the AD detection method that judges whether the circadian rhythm is stable/unstable by the differences in the characteristics of the circadian rhythm (described in Section II-C in detail). The circadian rhythm is estimated by the modified version of the real-time sleep stage estimation (in Section II-B).

B. Estimation of Circadian Rhythm of Heartrate

Real-time Sleep Stage Estimation (RSSE) [9] estimates the six sleep stages (*i.e.*, Wake, REM, Non-REM1, 2, 3, and 4) according to the regression of the trigonometric functions of the heartrate by the maximum likelihood estimation. In RSSE, the estimated continuous heartrate $f(t)$ is computed by synthesizing the frequency waves from the low to high freqencies as shown in Eq. (1), where $a_{l,i}(i.e., i \in \{0,1\})$ is a coefficients of cos/sin waves, l is the period of the frequency waves (*i.e.*, $l \in L = \{2^{14}/1, ..., 2^{14}/13, 2^{14}/14\}$ [second]), and C is constant term of $f(t)$.

$$\begin{aligned} f(t) &= \sum_{l \in L} \left\{ a_{l,0} \cos m_l t + a_{l,1} \sin m_l t \right\} + C \\ m_l &= \frac{2\pi}{l} \end{aligned} \tag{1}$$

The likelihood function employed for the maximum likelihood estimation is defined as in Eq.(2), where the first term $\frac{1}{T}\sum_{t=1}^{T}\{HR(t) - f(t)\}^2$ indicates the difference between $f(t)$ and $HR(t)$ (*i.e.*, the heartrate at the time t), and the second term suppresses the overfitting of $a_{l,i}$ by avoiding a large separation from the one time previous coefficient $\hat{a_{l,0}}$ (*i.e.*, the coefficient when time is $t-1$). The λ weights the second term (in this paper, $\lambda = 1.0$ in all cases). The coefficients $a_{l,i}$ (coefficients of sine and cosine waves defined from L) and the constant term C are updated by minimizing J. The value $\gamma(T)$ weights the second term during $\Delta T_\gamma (= 600)$ seconds by changing from γ_0 (=2) to 1 (*i.e.*, $\gamma(T)$ is set to γ_0 (=2), decreases until ΔT_γ second, converges to 1 after ΔT_γ second). This is because the initial value of $a_{l,i}$ is zero and thus the value may be updated sensitively especially in the first several time during ΔT_γ second. The value $idx(l,L)$ is the index of l in L.

$$\begin{aligned} J &= \frac{1}{T}\sum_{t=1}^{T}\{HR(t) - f(t)\}^2 \\ &\quad + \frac{\lambda}{|L|}\sum_{l \in L}\gamma(T)^{idx(l,L)-1}\{(a_{l,0} - \hat{a_{l,0}})^2 + (a_{l,1} - \hat{a_{l,1}})^2\} \\ T &= |HR| \\ idx(l,L) &= \text{the index of } l \text{ in } L \\ \gamma(T) &= \max(1, (1-\gamma_0)\frac{T}{\Delta T_\gamma} + \gamma_0) \end{aligned} \tag{2}$$

To estimate the circadian rhythm of heartrate, the periods of frequency waves L in this research is set to $\{25, 24, 23\}$ hours which covers approximately 24 hours, instead of L set to $\{2^{14}/1, ..., 2^{14}/14\}$. Fig. 1 shows the example of estimated $f(t)$, where the vertical and horizontal axes respectively indicate the heartrate and time, the blue line indicates the heartrate, and the orange line indicates the estimated $f(t)$ composed of the frequency waves with the L periods.

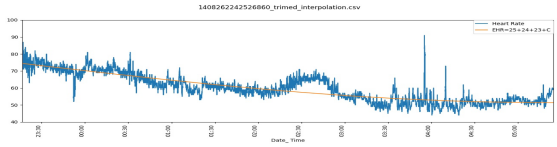
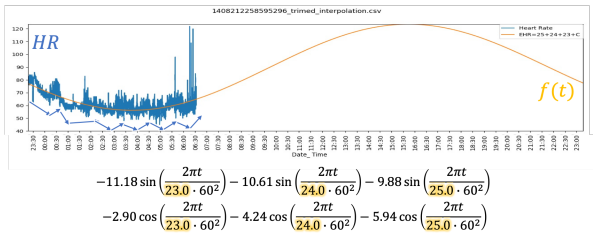


Fig. 1: An example of heartrate (blue) and the estimated $f(t)$ (orange).

C. Stability of Circadian Rhythm of Heartrate

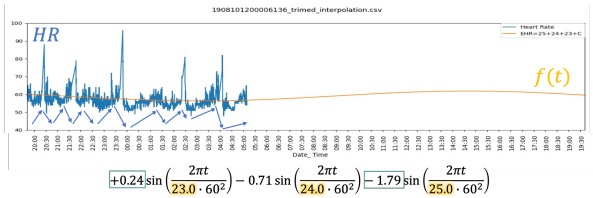
Figs. 2 and 3 respectively show the estimated $f(t)$ for one day with the stable and unstable circadian rhythms of heartrate, where the blue and orange lines in the graphs respectively indicate the heartrate and the estimated $f(t)$, and the equations under the graphs indicates the sine and cosine waves in $f(t)$. When the heartrate gradually decreases and finally increases as shown in Fig. 2, the estimated $f(t)$ shows the stable circadian rhythm and coefficients $a_{l,i}$ of the sine and cosine waves are the large enough with the same sign. When the heartrate repeatedly increases and decreases in a certain short periods as shown in Fig. 3, on the other hand, the estimated $f(t)$ shows the unstable circadian rhythm and the coefficients $a_{l,i}$ of the sine and cosine waves are relatively smaller than those in Fig. 2. In such case, these coefficients $a_{l,i}$ become the positive and negative to cancel the waves each other, which weakens the amplitude of $f(t)$.

From these differences, the proposed AD detection method evaluates the stability of the estimated circadian rhythm using the numerical value R calculated as shown in Eq.(3). R_i is calculated by the absolute value of the ratio between (i) the absolute sum of the coefficients $|a_{i,l}|$ in the fraction and (ii) the simple sum of the coefficients $a_{i,l}$ in the denominator. In the case of the stable estimated circadian rhythm which coefficients tend to have the same sign, the two types of sum values are expected to be the same, which means that R_i is expected to be 1.0. In the case of unstable ones which



$$-11.18\sin\left(\frac{2\pi t}{23.0\cdot 60^2}\right)-10.61\sin\left(\frac{2\pi t}{24.0\cdot 60^2}\right)-9.88\sin\left(\frac{2\pi t}{25.0\cdot 60^2}\right)$$
$$-2.90\cos\left(\frac{2\pi t}{23.0\cdot 60^2}\right)-4.24\cos\left(\frac{2\pi t}{24.0\cdot 60^2}\right)-5.94\cos\left(\frac{2\pi t}{25.0\cdot 60^2}\right)$$

Fig. 2: Stable circadian rhythm of heartrate in estimated $f(t)$.



$$+0.24\sin\left(\frac{2\pi t}{23.0\cdot 60^2}\right)-0.71\sin\left(\frac{2\pi t}{24.0\cdot 60^2}\right)-1.79\sin\left(\frac{2\pi t}{25.0\cdot 60^2}\right)$$
$$-0.87\cos\left(\frac{2\pi t}{23.0\cdot 60^2}\right)+0.26\cos\left(\frac{2\pi t}{24.0\cdot 60^2}\right)+1.26\cos\left(\frac{2\pi t}{25.0\cdot 60^2}\right)$$

Fig. 3: Unstable circadian rhythm of heartrate in estimated $f(t)$.

coefficients tend to have the different sign, on the other hands, the absolute sum is expected to be larger than the simple sum, which means that R_i is expected to be larger than 1.0. Considering that R is calculated by the average of R_0 for the sine wave and R_1 for the cosine wave, the proposed AD detection method judges as the non-AD person when R is 1.0 because of having the stable circadian rhythm of heartrate, while it judges as the AD patient when if $R > 1.0$ because of having the unstable circadian rhythm of heartrate.

$$R_i = \left|\frac{\sum_{l\in L}|a_{l,i}|}{\sum_{l\in L}a_{l,i}}\right|$$
$$R = \frac{R_0+R_1}{2} \tag{3}$$

D. Exclusion of Exceptional Heartrate Data

The estimated circadian rhythm is expected to decrease from 1 to 7 o'clock (and increase from 13 to 19 o'clock), but some of them do not follow the same characteristic of the circadian rhythm because of the abnormal heartrate data. From this fact, he heartrate data in one day is excluded when T_m is outside of the range of 16:00 $\pm$ 3:00 (*i.e.*, the data in the range of 0:00 $\sim$ 13:00 or 19:00 $\sim$ 24:00 is excluded), where T_m indicates the time at which the circadian rhythm gets the minimum value as shown in Eq.(4).

$$T_m = t_0 + t \quad (\text{when } f(t) \text{ is minimum}, 0 \le t \le 86400)$$
$$t_0 \ldots \text{measurement start time by mattress sensor} \tag{4}$$

The data excluded by the above criterion show one of the following three types of abnormalities as shown in Fig. 4, Fig. 5 and Fig. 6, where the vertical and horizontal axes respectively indicate the heartrate and time, the blue and orange lines respectively indicate the heartrate data and the estimated circadian rhythm $f(t)$: (1) the amplitude is extremely low as shown in Fig. 4, which makes it difficult to obtain the circadian rhythm component; (2) the unnatural heartrate transition marked with the red circle occurs as shown in Fig. 5 (basically, this is occurred by the influence of the temporary problems with the sensor and recording software); and (3)the heartrate always decreases during the sleep as shown in the middle graph of Fig. 6 with the mark "x", or the heartrate gradually increases and decrease as shown in the lower graph of Fig. 6 with the mark "x", which is the opposite characteristic of the usual circadian rhythm as shown in the upper graph of Fig. 6 with the mark "o".

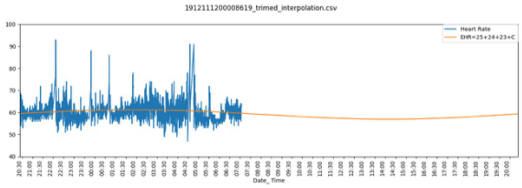


Fig. 4: abnormal pattern (1) of excluded data

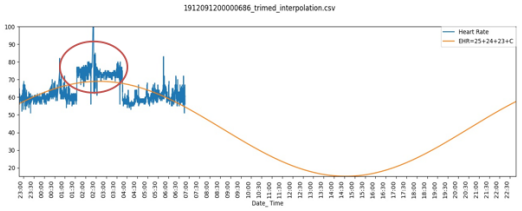


Fig. 5: abnormal pattern (2) of excluded data

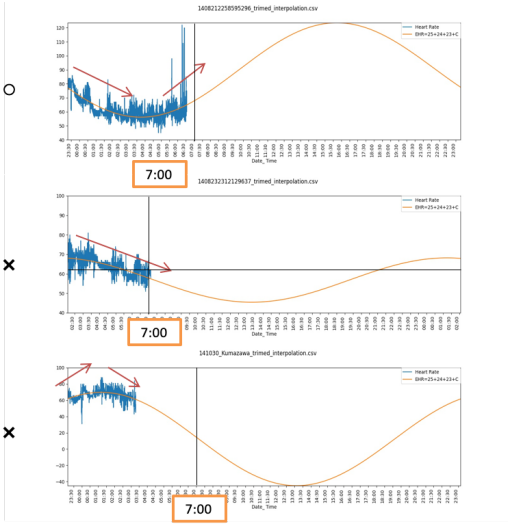


Fig. 6: abnormal pattern (3) of excluded data

III. Subject Experiment

A. Experimental Setup

To investigate the effectiveness of the proposed AD detection method, UCRADD, the human subject experiments were conducted by comparing with our previous method,

CRARaADD. The ethics community of St.Marianna University and the University of Electro-Communications approved this study, and all the subjects signed their consent. This experiment employs the heartrate data of the following subjects with excluding the data according to the criteria in Section II-D: (a) one elderly AD patient in the care house (19 days in August and 17 days in December); (b) three elderly (60s and 70s) non-AD persons (6 days in total); (c) ten middle-aged (40s and 50s) non-AD persons (14days in total); and (d) eight young (20s) non-AD persons (10 days in total). As the evaluation criteria, this experiment employs the accuracy of AD detection (*i.e.*, the percentage of AD detection for AD patients and that of the non-AD detection for healthy subjects).

B. Result

The results of UCRADD and CRARaADD are shown in Table. I and Table II, respectively. In these tables, "data_num" is the number of days for each subject groups. "detected as AD" is the number of days detected as AD. Note that the accuracy of the AD patients is the percentage of AD detection, while that of the healthy subjects is the percentage of non-AD detection. From these tables, we found that (1) the accuracy of AD patients by UCRADD (78.9% in August and 82.4% in December) is the same or higher than that by CRARaADD (57.9% in August and 82.4% in December); but (2) the overall mean accuracy of UCRADD (77.9%) is slightly lower than that of CRARaADD (83.3%).

TABLE I: Results of UCRADD

	data_num	detected as AD	accuracy
AD patients (August)	19	15	78.9%
AD patients (December)	17	14	82.4%
Young persons	10	1	90.0%
MIddle-aged persons	14	4	71.4%
Elderly persons	6	2	66.7%

TABLE II: Results of CRARaADD

	data_num	detected as AD	accuracy
AD patients (August)	19	11	57.9%
AD patients (December)	17	14	82.4%
Young persons	10	0	100.0%
Middle-aged persons	14	1	92.9%
Elderly persons	6	1	83.3%

C. Discussion

The accuracy of AD patients by CRARaADD gradually increases from 57.9% to 82.4% from August to December, whereas the accuracy of AD patients by UCRADD keeps around 80% in both August and December. This result implies that UCRADD has the potential of detecting the early stage of AD in comparison with CRARaADD because of the following reasons: (1) UCRADD does not employ the non-circadian rhythm, while CRARaADD employs it even if the non-circadian rhythm is sensitive to the result by determining the its hours (*i.e.*, $\{11.5, 12, 12.5\}$ hours in CRARaADD); (2) the instability of circadian rhythm of AD patients can be easily detected by UCRADD which checks whether the waves of the estimated circadian rhythm are canceled in comparison with CRARaADD which checks how the estimated non-circadian rhythm differs from the estimated non-circadian rhythm.

When focusing on the overall mean accuracy of AD detection, CRARaADD is 5.4% higher than UCRADD. This is because that the overall accuracy of AD detection in healthy subjects (specificity) is larger in CRARaADD, and the number of non-AD subjects is larger than AD subjects. It means that if the method tends to detect as non-AD subjects, the overall accuracy will be high. However, from the perspective of being able to detect AD subjects as AD, wrong detection for non-AD subjects is better than wrong detection for AD subjects. When trying to improve the accuracy of the detection for non-AD subjects, the combination of the two methods can be considered.

IV. Conclusion

This paper proposed the AD detection method based on the instability of the circadian rhythm estimated from heartrate. The analysis of the human subject experiments revealed the following implications: (1) the accuracy of AD detection for AD patients by UCRADD was higher than that by CRARaADD; and (2) the instability of circadian rhythm of heartrate has the potential of being new symptom of AD.

The future works include that (1) an analysis of data between August and December to generalize our results; and (2) an investigation of the combination of UCRADD and CRARaADD to improve the accuracy of the AD detection for both AD patients and healthy persons.

References

[1] H. Nikamalfard, et al.: "A sleep pattern analysis and visualization system to support people with early dementia", *The fifth International Conference on Pervasive Computing Technologies for Healthcare and Workshops*, pp. 510-513, 2011.

[2] S. Bombois, et al.: "Sleep disorders in aging and dementia", *The journal of nutrition, health & aging Vol.14*, pp. 212-217, 2010.

[3] K. Crowley.: "Sleep and Sleep Disorders in Older Adults", *Neuropsychol Rev Vol.21*, pp. 41-53, 2011.

[4] S. Sadigh-Eteghad, et al.: "Amyloid-Beta: A Crucial Factor in Alzheimerś Disease", *Med Princ Pract Vol. 24*, pp. 1-10, 2015.

[5] N.E. Fultz, et al.: "Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep", *Science, Vol. 366, Issue. 6465*, pp. 628-631, 2019.

[6] Marshal F.FolsteinSusan E.FolsteinPaul R.McHugh, et al.: " " Mini-mental state " : A practical method for grading the cognitive state of patients for the clinician", *Journal of Psychiatric Research, Vol. 12, Issue. 3*, pp. 189-198, 1975.

[7] I.V. Zhdanova, et al.: "Melatonin, circadian rhythms, and sleep", *Current Treatment Options in Neurology, Vol. 5*, pp. 225-229, 2003.

[8] N. Matsuda, et al.: "Alzheimer Dementia Detection based on Circadian Rhythm Disorder of Heartrate", *IEEE 3rd Global Conference on Life Sciences and Technologies*, pp. 364-368, 2021.

[9] T. Harada, et al.: "Real-Time Sleep Stage Estimation from Biological Data with Trigonometric Function Regression Model", *AAAI Spring Symposium*, pp.348-353, 2016.

[10] M. Massin, et al.: "Circadian rhythm of heartrate and heartrate variability", *Archives of Disease in Childhood, Vol. 83*, pp. 179-182, 2000.

[11] P. Gehrman, et al.: "The relationship between dementia severity and rest/activity circadian rhythms", *Neuropsychiatric Disease and Treatment*, pp. 155-163, 2005.