Analysis of Circadian Rhythm Estimation Process for Improving the Accuracy of Alzheimer Dementia Detection

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Abstract

For early detection of Alzheimer dementia (AD), this paper analyzes the features of circadian rhythm of heart rate between healthy people and AD patients, focusing on the circadian rhythm disorder in AD (i.e., unstable circadian rhythm). Focusing on the circadian rhythm estimating log of ADDUCRRaH (the AD detection method based on the stability of estimated circadian rhythms), we analyzed experiments with an elderly AD patient in five months and 21 non-AD people (age from 20-70). Through the experiments confirmed the following implications have been revealed: (1) AD and healthy people show three types of features (cancellation between the rhythms, crossing the sign of the rhythms coefficients and summation of transitions of rhythms coefficients) between unstable and stable circadian rhythms during the estimation in the one day estimated log as well as the final estimated output; (2) the features can be quantified as accumulated values and used together with existing AD detection methods to improve the accuracy of detection.

Introduction

Recently, World Health Organization reported that the number of elderly people with dementia is more than 55 million people. In addition, the report estimates that the number of new patients 10 million(Organization 2012) each year. And more than half of these dementias are classified as Alzheimer dementia (AD). However, no treatment for AD is currently available other than medication to slow its progression. And when the symptoms (due to wandering, violence, and so on) become so severe that it is difficult to care for the patient, the patient has to be hospitalized and stay in bed. For the facts, early detection is essential to slow down the progression of dementia. However, it is difficult to detect dementia early because it takes a long time (*e.g.*, ten years) for the symptoms to appear (Mioshi et al. 2010).

For earlier symptom recognition, the global standard method of dementia detection called Mini-Mental State Examination (MMSE) (Folstein, Folstein, and McHugh 1975), which is a questionnaire-based screening test, is widely employed. However, this method has problems in that the detection accuracy may decrease due to habituation when the test is taken many times. In addition, people who others have pointed out that they may have dementia are difficult to accept the fact and the test result, or are possible not to take the test.

To tackle these problems, the method that can detect AD by the biometric data from daily life can be used as the substitute for the questionnaires tests. In line with this perspective, the, we proposed the novel AD detection method, named AD Detection based on Unstable Circadian Rhythm Ratio of Heart rate (ADDUCRRaH), which focused on the circadian rhythm (approximately 24 hours cycle) of the melatonin secretion. (Matsuda, Nakari, and Takadama 2021) Concretely, the melatonin secretion of the healthy people (including the non-AD elderly persons) have stable (*i.e.*, 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) (Zhdanova and Tucci 2003). However, the melatonin secretion is hard to be obtained in the daily life. So our method focused on the fact that the circadian rhythm is also represented in heart rate (Boudreau et al. 2012)(Massin et al. 2000). Since heart rate is easily to acquire from the mattress sensor (placed under the mattress) in the daily life, it can be used to measure its circadian rhythm instead of melatonin. From these perspectives, ADDUCRRaH detects AD from the instability of the circadian rhythm estimated from the heart rate. For detail, circadian rhythms are estimated by the regression of a trigonometric function which have waves with a period of around 24 hours with the maximum likelihood estimation.

However, ADDUCRRaH has misdetected data with specific patterns in both AD patients and healthy people. Concretely, the patterns are that when misdetecting the AD patients / the healthy people, at the end of the estimation of the trigonometric function, the condition was suddenly to satisfy the conditions which the AD patients / the healthy people detected as healthy people / AD. This is because the estimation is more sensitive to the end stage (*i.e.*, just before waking) heart rate data inputed as a time series. To avoid the misdetection, it is necessary to consider data with long-term. And so this paper additionally analyzes the AD detection prosess to improve the accuracy of the AD detection of ADDUCRRaH. In particular, we will focus on the estimation transitions for the entire of data (one day sleep) in estimating the trigonometric functions and the differences in the features of those AD patients and healthy subjects.

This paper is organized as follows. The next Section “AD Detection based on Unstable Circadian Rhythm Ratio of

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Heart rate" describes the principle and the problems of ADDUCRRaH. The two analytical experiments and a human subject experiment with AD and healthy people are conducted and the results are discussed in Section "Analytical Experiment 1", "Analytical Experiment 2" and "Subject Experiment". Finally, our conclusion is given in Section "Conclusion".

AD Detection based on Unstable Circadian Rhythm Ratio of Heart rate

Overview

The AD detection method, AD Detection based on Unstable Circadian Rhythm Ratio of Heart rate (ADDUCRRaH), detects AD based on the hypothesis which the circadian rhythm of the heart rate in AD patients tends to be unstable in comparison with healthy people described in Section "Introduction". This method has two steps. First, the circadian rhythm is estimated by the modified version of the real-time sleep stage estimation from heart rate data (in Section "Estimation of Circadian Rhythm of Heart rate"). Second is judging whether the estimated circadian rhythm is stable or not (described in Section "Stability of Circadian Rhythm of Heart rate" in detail). At the end of this chapter, We summarize the problems of this method as the arguments against the analysis in this paper (in Section "Problem").

Estimation of Circadian Rhythm of Heart rate

Real-time Sleep Stage Estimation (RSSE) (Harada et al. 2016) estimates six sleep stages (*i.e.*, Wake, REM, Non-REM1, 2, 3, and 4) by the regression of the heart rate.This method is based on the fact that there is a correlation between sleep stages and heart rate. The regression model $f(t)$ is computed by synthesizing the frequency waves as shown in Eq. (1), where $a_{l,i}$(*i.e.*, $i \in \{\mathrm{c}, \mathrm{s}\}$) 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 $f(t)$.

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

the likelihood function used for the maximum likelihood estimation is defined 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 heart rate at the time t), and the second term suppresses the overfitting of $a_{l,i}$ (coefficients of sine and cosine waves defined from L) by avoiding a large separation from the one time previous coefficient $\hat{a_{l,i}}$ (*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 $a_{l,i}$ 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 $d(l, L)$ is the index of l in L.

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

To estimate the circadian rhythm of heart rate, 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 $\{2^{14}/1, ..., 2^{14}/14\}$. Figure 1 shows the example of estimated $f(t)$, where the vertical and horizontal axes respectively indicate the heart rate and time, the blue line indicates the heart rate, and the orange line indicates the estimated $f(t)$ composed of the frequency waves with the L periods.

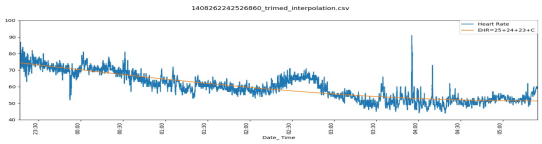

Figure 1: An example of heart rate (blue) and the estimated $f(t)$ (orange).

Stability of Circadian Rhythm of Heart rate

Figure 2 and Figure 3 respectively show the estimated $f(t)$ for one day with the stable and unstable circadian rhythms of heart rate, where the blue and orange lines in the graphs respectively indicate the heart rate and the estimated $f(t)$, and the equations under the graphs indicates the sine and cosine waves in $f(t)$. When the heart rate gradually decreases and finally increases as shown in Figure 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 heart rate repeatedly increases and decreases in a certain short periods as shown in Figure 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 Figure 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

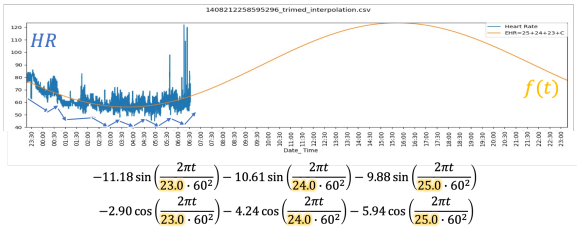

Figure 2: Stable circadian rhythm of heart rate in estimated $f(t)$.

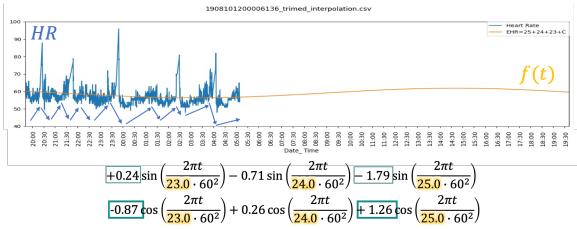

Figure 3: Unstable circadian rhythm of heart rate in estimated $f(t)$.

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 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_{c} for the cosine wave and R_{s} for the sine 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 heart rate, while it judges as the AD patient when if $R > 1.0$ because of having the unstable circadian rhythm of heart rate.

$$R_i = \left| \frac{\sum_{l\in L} |a_{l,i}|}{\sum_{l\in L} a_{l,i}} \right| \qquad (3)$$
$$R = \frac{R_{\mathrm{c}} + R_{\mathrm{s}}}{2}$$

Analytical Experiment 1

Experimental Setup

As mentioned in the "Introduction", the factor for ADDU-CRRaH misdetection of AD patients / healthy people is found to be that when misdetecting the healthy people, at the end of the estimation of the trigonometric function, the condition was suddenly to detect the AD patients / the healthy people as healthy people / AD satisfied. For this perspective, we focused not only on the end of the estimation, but also on the its transitions, and conducted an analytical experiment on the differences in features between AD and healthy subjects. Specifically, we use the trajectory of the estimation as shown in Figure 5 and Figure 4, where the horizontal and vertical axes respectively indicate the time and the value of the estimated sine/cosine waves coefficients $a_{i,l}$ for 23, 24, and 25 hours. The upper/lower graphs are the coefficients of the sine/cosine ($a_{\mathrm{s},25}$, $a_{\mathrm{s},24}$ and $a_{\mathrm{s},23}$/$a_{\mathrm{c},25}$, $a_{\mathrm{c},24}$ and $a_{\mathrm{c},23}$). Figure 5/4 is the example of the AD patient/healthy person which detected as AD/healthy person (true positive/negative). The coefficients at the last time of the graph (red line on the right side of the graph) are used for $f(t)$ (described in "Estimation of Circadian Rhythm of Heart rate") which is used for AD detection (described in "Stability of Circadian Rhythm of Heart rate"). Figure 6 shows the relationship between the estimation transition and $f(t)$. It is possible to draw $f(t)$ from the coefficients $a_{i,l}$ at each time. Basically, $f(t)$ will follow the heart rate that you input.

This experiment employs the heart rate data of the following subjects: (a) one elderly AD patient in the care house (72 days); (b) 21 healthy (*i.e.*, non-AD) persons (20s $\sim$ 70s, 30 days in total). The ethics community of St.Marianna University and the University of Electro-Communications approved this study, and all the subjects signed their consent.

Result

Figure 8 and Figure 9 represent respectively the examples of AD patients / the healthy person data which detected as healthy people / AD because the coefficients (of the cosine waves) are emphasized each other / cancelled out at the end of the estimation (red circle on the right side of the figure). However, when focusing on the transition of the estimation, it can be seen that the coefficients crosses positive and negative many times (as shown blue circle) and occurs cancellation for a long time (as shown green arrow) in Figure 8, and the coefficients of sine waves in particular is negative and stable over a long period of time in Figure 9.

Discussion

In Figure 8, the reason why the coefficients crosses positive and negative many times and occurs long cancellation is that cancellation occurs for unstable heart rate and can occur periodically even during estimation (*i.e.*, a part of heart rate).

While, in Figure 9, the reason why the coefficient of the sine wave is negative and stable can be explained as shown in Figure 7. The top graph shows the estimated $f(t)$ for one day of a healthy person, where the blue and orange lines in the graphs respectively indicate the heart rate and the estimated $f(t)$, and the equations under the graphs indicates the sine and cosine waves in $f(t)$. The sine and cosine portions of $f(t)$ are respectively represented by the red and yellow lines in the bottom figure. The heart rate of healthy people decreases monotonically from the time they fall asleep until dawn, and the amount of decrease is gradually reduced to zero. For such the transitions, it is easy to improve the likelihood of the entire f(t) by combining cosine waves based on sine waves with negative coefficients that has the form represented by the red line. As a result, the sine waves transitions are more likely to be negative and stable for healthy people.

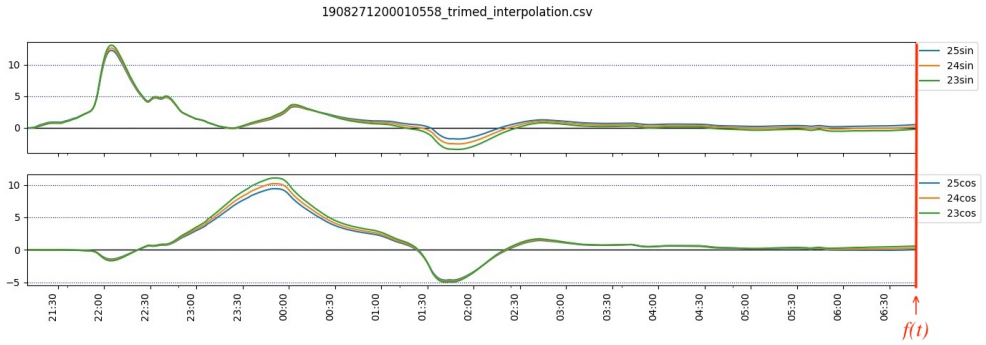

Figure 4: The exmaple of the estimation transition of the AD patients data detected as the AD (true positive).

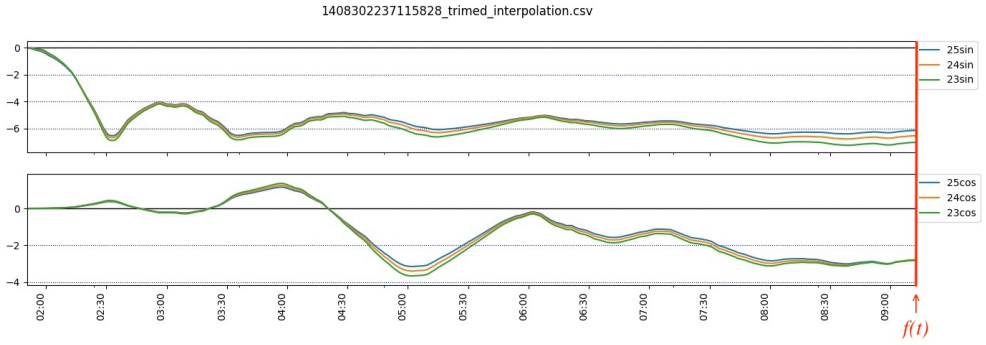

Figure 5: The exmaple of the estimation transition of the healty person data detected as the healthy person (true negative).

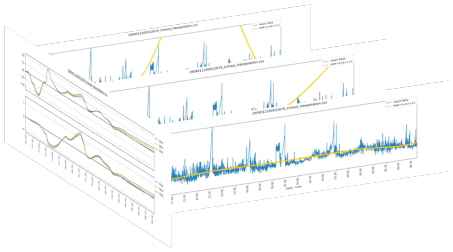

Figure 6: Relation between the estimation transition and estimating $f(t)$.

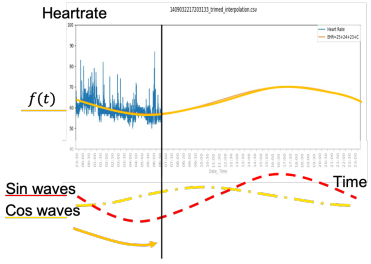

Figure 7: The reason healthy people' heart rate are easily fitted based on minus sine waves.

Analytical Experiment 2

Experimental Setup

Focusing on the features obtained from "Analysis Experiment 1", we formulate the following equation Eq.(9), Eq.(10) and Eq.(11)

$$A(x,i) = \sum_{l \in L} a_{l,i}(x) \tag{4}$$

$$AbsA(x,i) = |A(x,i)| = \left| \sum_{l \in L} a_{l,i}(x) \right| \tag{5}$$

$$AAbs(x,i) = \sum_{l \in L} |a_{l,i}(x)| \tag{6}$$

$$cancel(x,i) = \begin{cases} 1 & \frac{AAbs(x,i)}{AbsA(x,i)} > 1.0 \\ 0 & \frac{AAbs(x,i)}{AbsA(x,i)} = 1.0 \end{cases} \tag{7}$$

$$cross(x,i) = \begin{cases} 1 & (A(x,i){>}0 \wedge A(x{-}1,i){<}0) \\ & \vee (A(x,i){<}0 \wedge A(x{-}1,i){>}0) \\ 0 & \text{otherwise} \end{cases} \tag{8}$$

$$C_i = \sum_{x=0}^{T} cancel(x,i)/T \tag{9}$$

$$O_i = \sum_{x=0}^{T} cross(x,i) \tag{10}$$

$$S_i = \frac{\sum_{x=0}^{T} A(x,i)}{T\sigma(\sum_{x=0}^{T} A(x,i))} \tag{11}$$

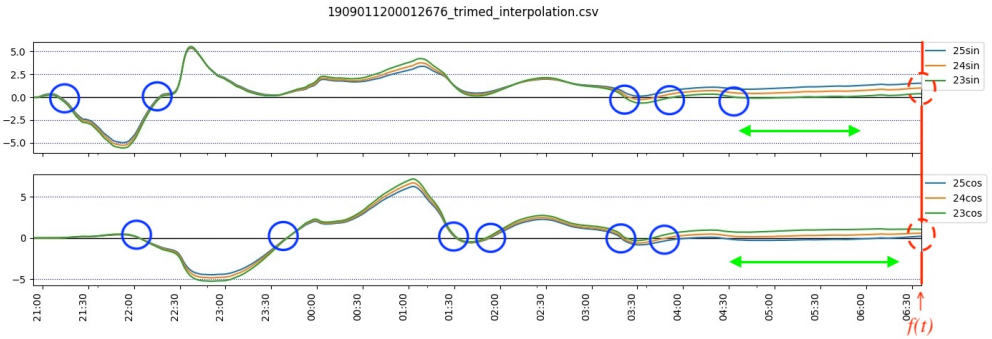

Figure 8: The exmaple of the estimation transition of the AD patients data detected as the healthy people (false negative).

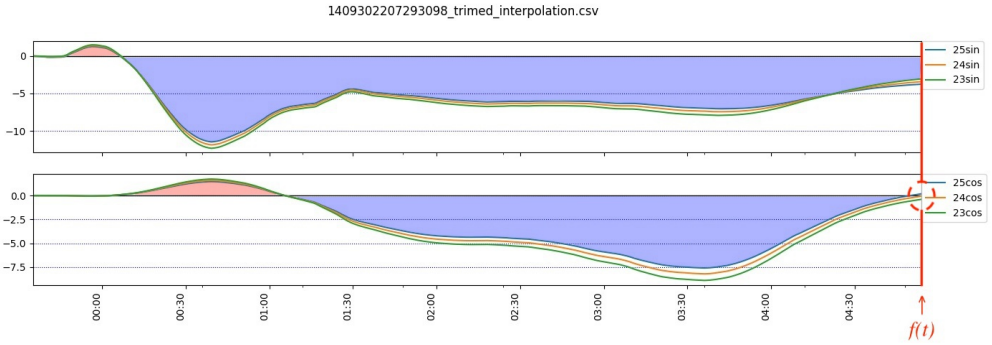

Figure 9: The exmaple of the estimation transition of the healty person data detected as the AD (false positive).

$a_{l,i}(x)$ are the extenstion of $a_{l,i}$ as the coefficients at the time x in the estimation transition. Eq.(9) is the time average of the count that cancelation (*i.e.*, i the signs of i group coefficients are different between plus and minus signs) occurred. Eq.(10) is the count that the coefficients crossed zero line (*i.e.*, the sign of the sum of i group coefficients switches). Eq.(11) is the approximately area of the red and blue regions represented in Figure 9. $a_{l,i}(t)$ is the coefficient during estimation at the time t. $S_i(i \in \{\mathrm{s}, \mathrm{c}\})$ is the area average of the sum of the coefficients divided respectively by the time T on the horizontal axes and the standard deviation $\sigma(\sum_{x=0}^{T} A(x,i))$ with the time series coefficients $a_{l,i}(x)$ $(l \in L, x = \{0, 1, ..., T\})$ on the vertical axes. A large positive value of S_i means that the coefficients are positive for a long time, and a large negative value means that they are negative for a long time.

This experiment employs the same heart rate data of "Analysis Experiment 1". And, the differences of C_i, O_i and S_i between healthy people and AD patients were analyzed.

Result

The results were as shown in Figure 10, Figure 11 and Figure 12. The horizontal axis represents each data, and the left and right sides from the black line are respectively for AD patients and healthy people, and the vertical axis represents the value of C_i (, O_i and S_i). The blue and orange bars represent respectively the C (, O and S) value of the sine waves C_s (, O_s and S_s) and that of cosine waves C_c (, O_c and S_c).

Both of C_i have large values in about half of AD patients, At least one of O_i has a possibility to reach over ten, and S_s has a large negative value in most of the data of healthy people.

Discussion

C_i and O_i tend to be higher in AD, but not enough to clearly separate it from healthy people. It is clear that S_s is able to visualize the feature of healthy people obtained from the analysis experiment as numerical values. In particular, S_s smaller than -500 was obtained only for the healthy people, which suggests that this feature can be used for AD detection. However, these features were not found in all healthy people and must be used in conjunction with other AD detection.

In addition, this feature-based detection can be added to or replaced by the second mechanism "Stability of Circadian Rhythm of Heart rate" of ADDUCRRaH. And that means that the detection by the second mechanism is also the features-based detection of the final coefficients of $f(t)$.

Subjects Experiment

Experimental Setup

Focusing on the features obtained from "Analysis Experiment 1" and "Analysis Experiment 2", we examine an example of an AD detection method that combines the obtained

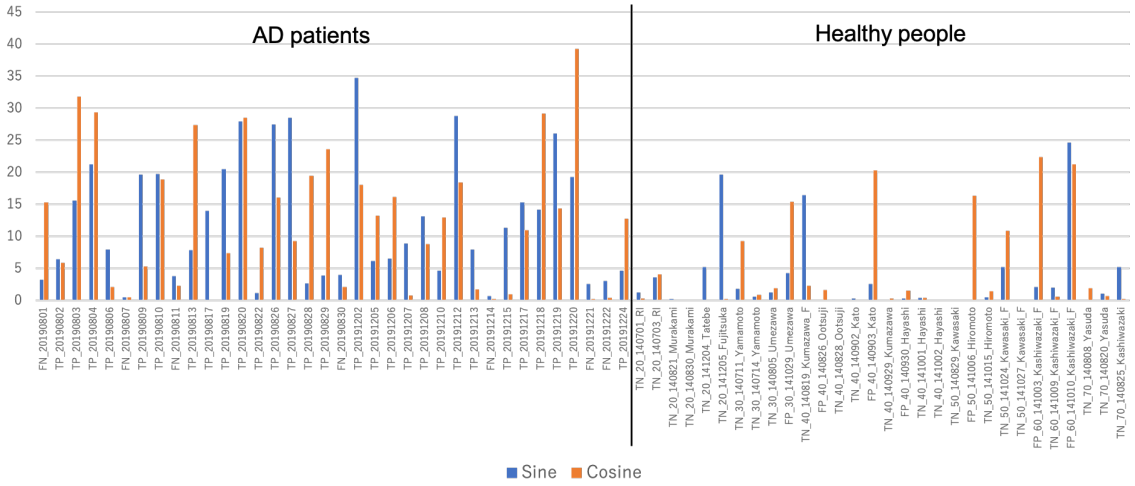

Figure 10: The calculated result of C_i of AD patients (left side) and healthy people (right side)

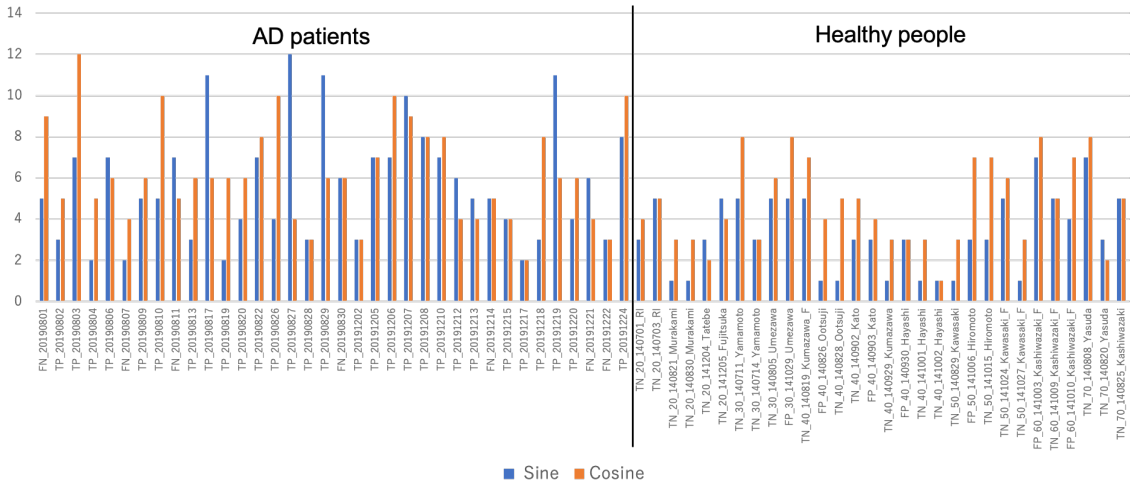

Figure 11: The calculated result of O_i of AD patients (left side) and healthy people (right side)

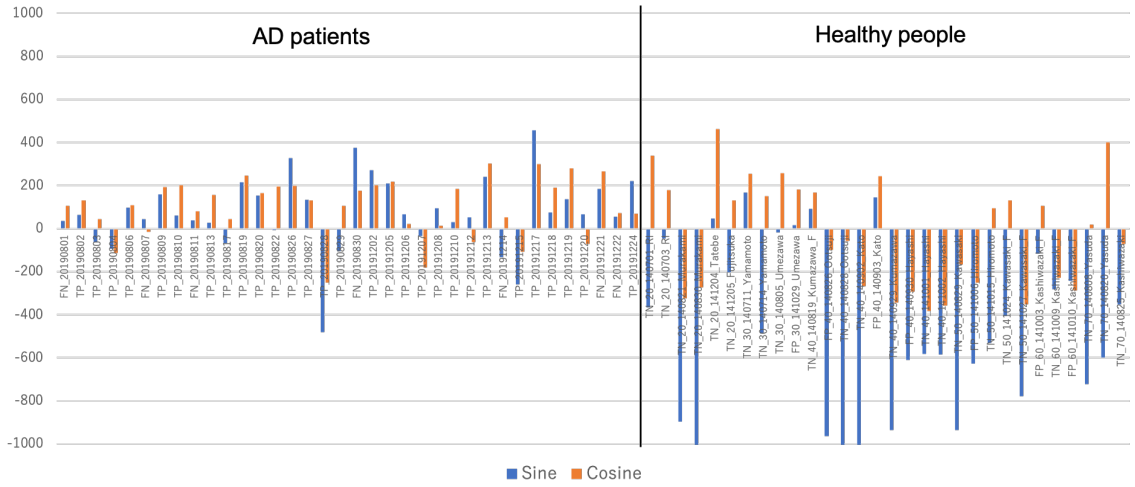

Figure 12: The calculated result of S_i of AD patients (left side) and healthy people (right side)

features (C , O and S) and that of the second mechanism of ADDUCRRaH R. Specifically, the following procedure is used to detect AD.

1. A_{s} and $f(t)$ are estimated with the ADDUCRaH's first mechanism "Estimation of Circadian Rhythm of Heart rate"
2. C_i, O_i and S_{s} are calculated.
3. If $C_{\mathrm{s}} > 5 \wedge C_{\mathrm{c}} > 5$ then the input data is detected as AD. If not, move on to the next step.
4. If $O_{\mathrm{s}} \geq 10 \vee O_{\mathrm{c}} \geq 10$ then the input data is detected as AD. If not, move on to the next step.
5. If $S_{\mathrm{s}} < -500$ then the input data is detected as a healthy person. If not, move on to the next step.
6. R is calculated by Eq.(3)
7. If $R = 1.0$ then the input data is detected as a healthy person. If not, it is detected as a AD patient.

To investigate the effectiveness of this AD detection method the human subject experiments were conducted by comparing with our previous method, ADDUCRRaH. This experiment employs the same heart rate data of "Analysis Experiment 1" and "Analysis Experiment 2". 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).

Result

Figure 13 shows the accuracy of AD detection of healthy people (blue bar) and ADDUCRRaH (orange bar). 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 this figure, we found that both of the features-based accuracies of AD and healthy people (76.4% and 83.3%) is higher than those of ADDUCRRaH (66.7% and 76.7%) and the accuracies are improved.

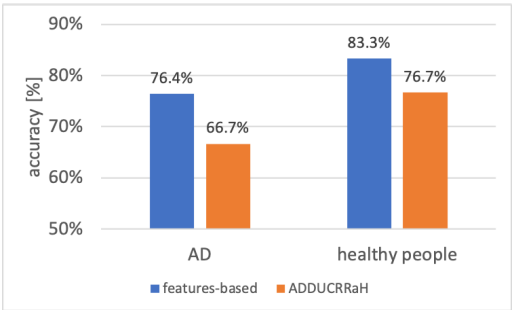

Figure 13: The accuracy of AD detection.

Conclusion

In this paper, since the misdetection of ADDUCRRaH occurred at the end of the estimation of $f(t)$, we focused on the transition of the estimation of its coefficients $a_{l,i}(t)$ and analyzed the difference between healthy people and AD patients. The analysis experiments revealed the following implications: (1) unstable heart rate in AD patients causes continuous censoring and zero line crossing; (2) the coefficients of the sine waves continue to be negative because they fit the stable heart rate of healthy people; and (3) it is possible that these features can be quantified and utilized for AD detection.

The future works include that (1) an analysis of new features of coefficient transitions; and (2) a consideration of an AD detection method that summarize the obtained features, especially non-threshold detection.

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