Identifying Characteristic Physiological Patterns of Parkinson's Disease Sufferers using Sample Entropy of Pulse Waves

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Abstract: In this study, we identify characteristic physiological patterns of Parkinson's disease patients, through analysis of the data of their pulse waves. We find that the sample entropy values of pulse waves, with certain parameters fix (In this case, we define the sample entropy value as "border of Parkinson entropy", or BPE), is statistically different between Parkinson's disease sufferers and healthy individuals. In addition, values of the largest Lyapunov exponent computed from the same data are also analysed, and significant difference between the two groups are observed. At the end, we describe an Android tablet that we developed for real-time measurement and analysis of BPE.

1 INTRODUCTION

With the aging of Japan's population advancing, incidence of various aging-related diseases is becoming increasingly frequent. Parkinson's disease is one of them (Yamawaki et al., 2009). Studies have shown that symptoms of neurological and mental disorders are common in Parkinson's disease, such as depression (Lemke et al., 2004), dementia (Emre, 2004) and autonomic nerve system dysfunction (Zesiewicz et al., 2003).

Meanwhile, in our recent studies, we have discovered indicators – the largest Lyapunov exponent (LLE) and the autonomic nerve balance (ANB), both computed from pulse wave data – for identifying mental status changes (Oyama-Higa et al., 2008; Wang et al., 2012) and mental disorders, including dementia (Oyama-Higa and Miao, 2006; Oyama-Higa et al., 2008; Pham et al., 2015) and depression (Oyama-Higa et al., 2008; Hu et al., 2011; Pham et al., 2013). A comprehensive explanation can be found in Oyama's 2012 book.

Inspired by the relevance of Parkinson's disease to mental disorders and the effectiveness of the pulse wave analysis in detecting mental disorders, we have made an attempt to observe if any characteristic patterns of Parkinson's disease sufferers exist in their pulse waves.

This study has succeeded in discovering such characteristic patterns, by comparing the sample entropy computed from the pulse wave data. More precisely, what we applied is the sample entropy with two parameters – the length of subsequences of the data sequence and the tolerance – set to certain fixed values. We define this indicator as "border of Parkinson Entropy (BPE)". Besides, in addition to BPE, statistically significant difference is also in the LLE values from the same pulse wave data.

Furthermore, we have incorporated the function of BPE computation and result display into "Alys", an application installed on an Android tablet that we developed for real-time mental health check-up (Oyama-Higa et al., 2016). With "Alys", not only status of mental health, but also risk of Parkinson's disease can be checked in a convenient and economical way.

2 COMPUTATIONAL METHODS

In this study, we mainly propose two indicators – the border of Parkinson entropy (BPE) and the largest

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Lyapunov exponent (LLE). We will start with the introduction of sample entropy.

2.1 Sample Entropy

As a conventional method for studying the complexity in biological time series, the sample entropy is defined as the reciprocal of the natural logarithm of the conditional probability that two sequences that are similar for certain points within a given tolerance still remain similar when one consecutive point is included (Richman and Moorman, 2000).

To begin with, given a time-series sequence

$$\{x\,(1), \ldots, x\,(N)\}, \tag{1}$$

its subsequence with a length of m can form a vector

$$X_m(i) = (\,x(i), x(i+1), \ldots, x(i+m\text{-}1)\,) \tag{2}$$

and, in the same fashion, an (m+1) subsequence can be denoted as

$$X_{m+1}(i) = (x(i), x(i+1), \ldots, x(i+m)\,). \tag{3}$$

Here, the range of i is from 1 to N-m so that both (2) and (3) are well-defined.

Next, the distance between two m-long subsequences $X_m(i)$ and $X_m(j)$ is defined as

$$|X_m(i) - X_m(j)| = \max_{0\le k\le m-1} |x(i+k) - x(j+k)|. \tag{4}$$

For a given $X_m(i)$, its r-neighbourhood is

$$\{X_m(j): |X_m(i) - X_m(j)| < \mathrm{r}\}. \tag{5}$$

Let $B_i^m(r)$ denote the probability that another subsequence is in its r-neighbourhood. Thus,

$$B_i^m(r) = \frac{\#\{X_m(j): |X_m(i)-X_m(j)|<\mathrm{r},1\le\mathrm{j}\le\mathrm{N-m,j}\ne\mathrm{i}\}}{N-m-1}. \tag{6}$$

Note that when counting the number of such subsequences in the numerator of (6), since $X_m(i)$ itself should be excluded, there are a total of N-m-1 candidates. Hence the denominator N-m-1. Regarding $X_{m+1}(i)$, we use a different notation $A_i^m(r)$ to denote the probability that another (m+1)-long subsequence is in its r-neighbourhood:

$$A_i^m(r) = \frac{\#\{X_{m+1}(j): |X_{m+1}(i)-X_{m+1}(j)|<\mathrm{r},1\le\mathrm{j}\le\mathrm{N-m,j}\ne\mathrm{i}\}}{N-m-1}. \tag{7}$$

For the whole time-series sequence (1), the probability corresponding to (6) or (7) can be given as an average taken over all subsequences, from i =1 to i =N-m, as follows.

$$B^m(r) = \frac{1}{N-m}\sum_{i=1}^{N-m} B_i^m(r) \tag{8}$$

$$A^m(r) = \frac{1}{N-m}\sum_{i=1}^{N-m} A_i^m(r) \tag{9}$$

The sample entropy with tolerance r for m-long subsequences of an N-point time-series sequence is therefore computed by the following formula.

$$SampEn(m,r,N) = -\ln\frac{A^m(r)}{B^m(r)} \tag{10}$$

In our recent studies on the indication of mental health from pulse waves, the device "Lyspect" (developed by Chaos Technology Research Laboratory) has been frequently applied (Oyama-Higa et al., 2012). We have upgraded the device to make the computation of sample entropy possible. The following shows the value of sample entropy (vertical axis) as a function of the tolerance r (horizontal axis), with the length of subsequence m fixed. A total 9 graphs are displayed, for m =2 to 10.

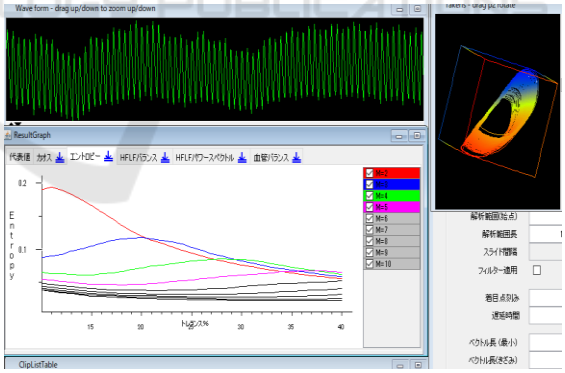

Figure 1: Display of sample entropy with "Lyspect".

2.2 Border of Parkinson Entropy

We define the border of Parkinson entropy (BPE) as the sample entropy with m=2 and r=10%, namely,

$$BPE = SampEn(2,10\%). \tag{11}$$

(The length of the time series sequence, N, is dropped for convenience.) These two parameters

were decided this way after trials and errors in search for an ideal indicator that shows statistically significant difference between Parkinson's disease sufferers and healthy individuals, as will be explained in Section 4.1.

As mentioned at the end of Section 1, we have imbedded the function of BPE computation in our device "Alys". A normalized result display is applied with a semi-circular graph, in consistency with the display of largest Lyapunov exponent and autonomic nerve balance. We will introduce this new performance in Section 5.

2.3 Largest Lyapunov Exponent

The mathematical definition and computation of the largest Lyapunov exponent (LLE) is elaborated in almost each of our papers on the indication of mental health from pulse waves (for the most updated work, refer to Oyama-Higa et al., 2016 and Oyama-Higa et al., 2017). In this article, since we mainly study the BPE, a detailed explanation on the definition of LLE is omitted.

In our devices "Lyspect" (Oyama-Higa et al., 2012) and "Alys" (Oyama-Higa et al., 2016), the value of LLE is normalized to a range of 0-10 in the result display. Our previous studies have shown that the values of LLE of a mentally healthy individual fluctuate from 2 to 7, centred at 5. When LLE is abnormally high, the mental immunity of the individual is so strong that he or she is likely to go to extremes: such individual can be easily irritated and take unexpected actions. On the other hand, when it is abnormally low, the mental immunity is so weak that the individual is prone to mental illnesses. In other words, a high LLE indicates a mental status of adapting to the external environment (we simply called it "external adaptation" in some of our previous articles), while a low LLE indicates a status of "internal focusing".

2.4 Autonomic Nerve Balance

The autonomic nerve balance (ANB) is another important indicator in our recent studies (Oyama-Higa et al., 2016 and Oyama-Higa et al., 2017). The detailed explanation is omitted here. In our devices, like LLE, we apply a 0-10 valued graph to display the result of *ANB*. $ANB < 5$ indicates predominance of parasympathetic nerve while $ANB > 5$ indicates sympathetic predominance.

3 EXPERIMENT

3.1 Devices

As usual in our recent studies, we apply an infrared sensor (UBIX Corporation) to take in pulse waves from the subjects, and "Lyspect" (Chaos Technology Research Laboratory) to analyse the data.

The pulse waves are taken in as 200 Hz analogue data, saved as text file, and then input to "Lyspect" for analysis. To reduce noise from the external environment (such as the power supply), the fast Fourier transform is applied in order that only data with frequency less than 30 Hz (It has been shown by additional trials that 8 Hz will suffice to produce the same analytical results) is to be analysed.

3.2 Subjects

Two groups of subjects, the Parkinson's disease patients and healthy individuals, are studied.

The former group consists of 45 patients diagnosed as Parkinson's disease, aged from 40 to 65. The latter group consists of 113 healthy university students, aged from 19 to 20.

3.3 Process of Measurement

Informed consent was obtained from all subjects in the measurement.

For each subject, a 2-minute measurement was performed for 2 to 3 times in a relaxed condition at room temperature (25 ℃) and the average result of measurement was used for analyse. Specifically, for the healthy students, it was sufficient to take 2 times because their results were stable, while for each of the Parkinson's disease sufferers, measurement was performed 3 times at intervals.

For a part of the Parkinson's disease sufferers, in order to reduce measurement errors due to tremor, a common symptom of the disease, the sensor was attached to the subject's earlobe instead of fingertip.

4 ANALYSIS AND RESULT

4.1 Comparison of Sample Entropy

As introduced at the end of Section 2.1, "Lyspect" can display the sample entropy values *SampEn* (*m*, *r*) as a function of *r*, for different *m*'s. We observed that as *m* increases, the range of *SampEn* (*m*, *r*) tends to concentrate and less sensitive to *r*, so we decided

to apply m=2. In the following, *SampEn* (2, r) is compared between the two groups.

The following graph shows *SampEn* (2, r) for the group of 113 healthy individuals. We observe that when the tolerance r changes from a small value over 0 to a little more than 40%, the sample entropy value with m=2 monotonically decreases and the range of *SampEn* (2, r) is bounded in (0, 0.4) for each subject of this group.

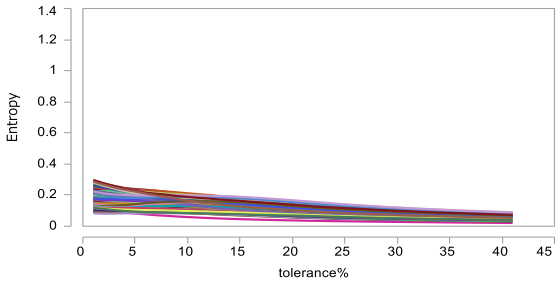

Figure 2: Graph of *SampEn* (2, r) for healthy individuals.

Similarly, *SampEn* (2, r) for the group of Parkinson's disease suffers is shown in the following graph. The tolerance changes in the same way as the above. *SampEn* (2, r) is monotonically decreasing, but the range of *SampEn* (2, r) is remarkably wider than the healthy individuals' group.

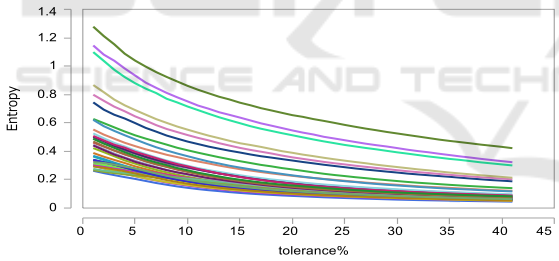

Figure 3: Graph of *SampEn* (2, r) for Parkinson's sufferers.

In hopes of finding an ideal indicator to distinguish Parkinson's disease sufferers from healthy individuals, based on the data from our measurement, we have performed analysis of variance (ANOVA) for various r's. Consequently, we found that when r = 10%, the result of ANOVA shows highly statistically significant difference in *SampEn* (2, 10%) between Parkinson's disease sufferers and healthy individuals. The basic information of *SampEn* (2, 10%) values for the analysis are given in the following table.

Table 1: *SampEn* (2, 10%) data information.

Group	Number of Data Points	Mean			Standard Deviation
		Total	w/o the largest 5%	w/o the smallest 5%	
Healthy	113	0.17267	0.14588	0.19945	0.01356
Parkinson's	45	0.44105	0.39861	0.48350	0.02149

The ANOVA for the difference in *SampEn* (2, 10%) between the two groups produces the following result.

Table 2: ANOVA for the difference in *SampEn* (2, 10%).

Source	Degree of Freedom	Sum of Squares	Mean Sum of Squares	F statistic	p value
Regression	1	2.3181505	2.31815	111.5685	<.0001*
Residual	156	3.2413411	0.02078		
Total	157	5.5594916			

Since the p value is less than 0.0001, the *SampEn* (2, 10%) values between the two groups are statistically different at 0.01% significance level, or at 99.99% confidence level. This is why we call *SampEn* (2, 10%) border of Parkinson's entropy, or BPE. The distribution of BPE values for the two groups can also be compared in the following figure. One can obviously observe that the Parkinson's disease sufferers exhibit a significantly higher BPE than the healthy students.

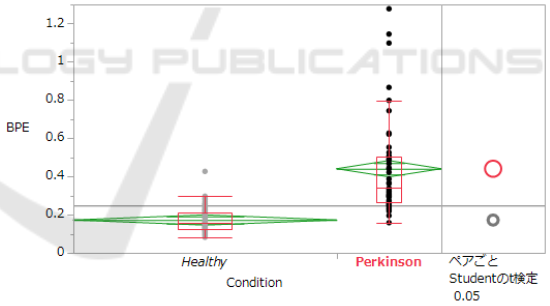

Figure 4: Comparison of distribution of BPE values.

4.2 Sample Entropy and Progression of Parkinson's Disease

Another observation made is that the sample entropy value tends to increase as the Parkinson's disease sufferer deteriorates.

The following shows the status of *SampEn* (2, r) for a same Parkinson's disease sufferer on two different dates of measurement. On July 31, 2016, there was no particular problem reported, but after 3 months, on November 1, 2016, the patient reported difficulty to move and occurrence of drooling, which interfered the patient's daily life. We clearly observe

that for each tolerance r, *SampEn* (2, r) on the latter date is higher than that on the former date.

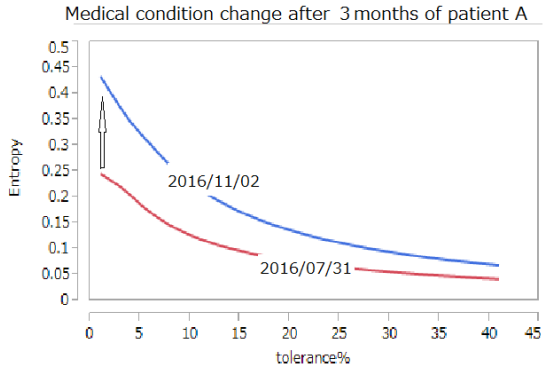

Figure 5: Graph of *SampEn* (2, r) for a Parkinson's sufferer in different condition of disease progression.

Therefore, for a same patient, BPE may be a potential indicator for checking the progression of Parkinson's disease. Doctors may refer to the BPE value when they conduct medical examination by interview.

4.3 Comparison of LLE and ANB

Since LLE has played a leading role in our studies on the indication of mental health from pulse waves, LLE values computed by "Lyspect" between the two groups are also compared and analysed.

The basic information of LLE values for the analysis are given in the following table.

Table 3: LLE data information.

Group	Number of Data Points	Mean			Standard Deviation
		Total	w/o the largest 5%	w/o the smallest 5%	
Healthy	113	4.52024	4.27080	4.76970	0.12627
Parkinson's	45	2.91475	2.51950	3.31000	0.20009

Recall from Section 2.3 that the LLE value is normalized to range from 0 to 10. Next, the result of ANOVA for the difference in LLE between the two groups is stated in the following table.

Table 4: ANOVA for the difference in LLE.

Source	Degree of Freedom	Sum of Squares	Mean Sum of Squares	F statistic	p value
Regression	1	82.95642	82.9564	46.0469	<.0001*
Residual	156	281.04406	1.8016		
Total	157	364.00048			

Since the p value is less than 0.0001, the LLE values between the two groups are statistically different at 0.01% significance level, or at 99.99% confidence level. The following figure compares the distribution of LLE values between the two groups. Obviously, the LLE of the group of Parkinson's disease patients is significantly lower than that of the healthy individuals' group.

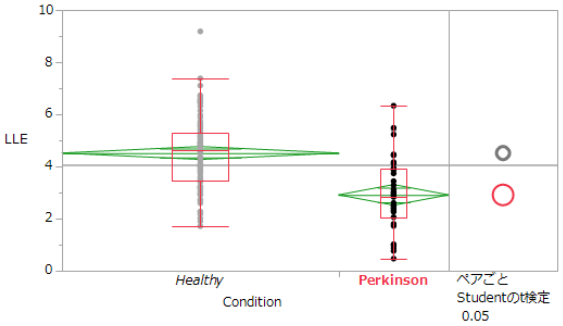

Figure 6: Comparison of distribution of LLE values.

The above result is consistent with the fact that depression is a common symptom of Parkinson's disease (Lemke et al., 2004) and the result we have obtained in our recent studies that a low LLE indicates weakness in mental immunity which leads to depression (Oyama, 2012).

In addition, we have also looked over ANB computed from the same data. Like in BPE and LLE, we have obtained statistically significant difference in the ANB values between the two groups. However, since medicine that the patients are taking can affect the nervous system and thus influence the result of ANB, we withhold further analysis.

4.4 Discriminant Analysis of BPE

As presented in Section 4.1, the BPE can provide as an indicator for identifying Parkinson's disease sufferers. Next, discriminant analysis is carried out, with the help of statistical software, in order to determine critical values of BPE to distinguish Parkinson's disease sufferers from healthy individuals. The process and result of the discriminant analysis are shown below.

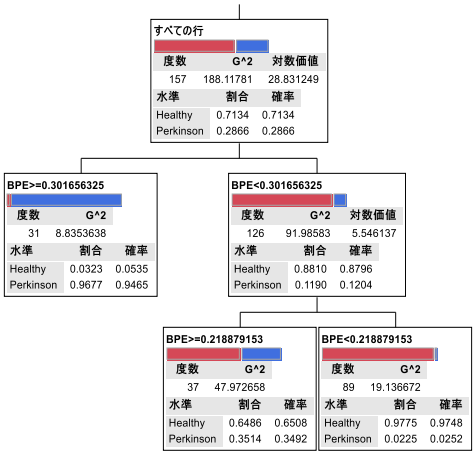

Figure 7: Process of discriminant analysis of BPE.

Table 5: Result of discriminant analysis of BPE.

BPE range	Ratio (Healthy)	Ratio (Parkison's)
BPE> = 0.301656325	5.35%	94.65%
BPE< 0.301656325 & BPE> = 0.218879153	65.08%	34.92%
BPE< 0.301656325 & BPE< 0.218879153	97.48%	2.52%

From the result, we conclude that our pulse wave data infer that if BPE $\geq$ 0.3017, the probability of suffering Parkinson's disease is 94.65%, and if BPE $<$ 0.2189, the probability of not suffering Parkinson's disease is 97.48%.

5 CHECKING BPE WITH "ALYS"

In this section, we introduce our upgraded version of "Alys", with which the analysis and result display of BPE have become possible. We explain the procedure of visualizing BPE with "Alys".

1. Start "Alys".

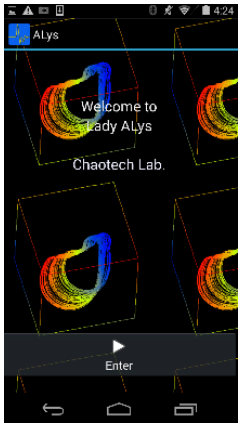

Figure 8: The welcoming window of "Alys".

2. Connect the sensor to the tablet through a USB connector.

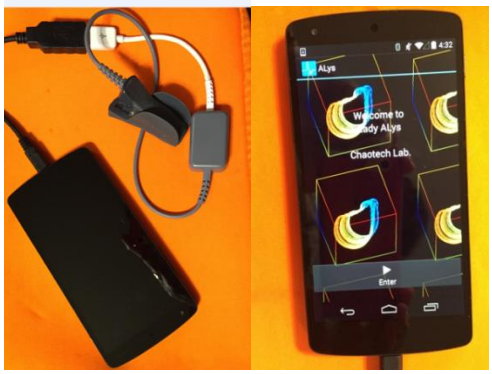

Figure 9: Connection of the sensor and the tablet.

3. Click the tool mark on the upper right, select "Set Properties" and then select "Compute BPE" from the "Execution of Analysis Mode"

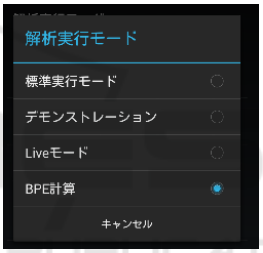

Figure 10: Option list of "Execution of Analysis Mode".

We may observe that the "Compute BPE" option is at the bottom of the option list of "Execution of Analysis Mode", as it is a newly added function.

4. Back to the "Set Properties" menu, set the measurement time (in second) and determine the critical value of BPE that is to be normalised to 5.0 in the result display. When this setting is done once, it will be saved so users need not set each time.

Figure 11: Option list of "Set Properties".

We have improved the system so that analytical result of BPE can be obtained with as short as 5 seconds of measurement.

Concerning the critical value of BPE, from the result of discriminant analysis in Section 4.4, we may use 0.31 (slightly higher than 0.3017) as the critical value corresponding to 5.0, the central value of the normalized BPE.

5. Start to take the pulse from a fingertip.

When the measurement time set in the previous step has elapsed, the measurement will end and a semi-circular graph will be displayed.

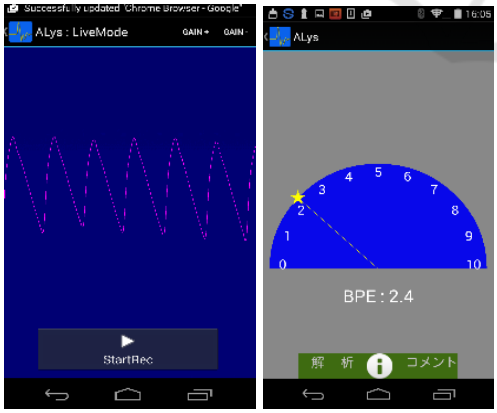

Figure 12: (Left) Display of waveform during a measurement; (Right) Graph for normalized BPE.

The BPE is normalized to range from 0 to 10, centred at 5.0, which corresponds to the critical BPE value set at the previous step. From the above figure we observe that the subject's normalized BPE is 2.4, which is less than 5.0, so this subject may not be a Parkinson's disease sufferer.

6. Other options.

Users may view their records of BPE values taken in the past in both "List Mode" and "Graph Mode". The former makes a list of all recent records, while the latter displays all results on the same semi-circular graph.

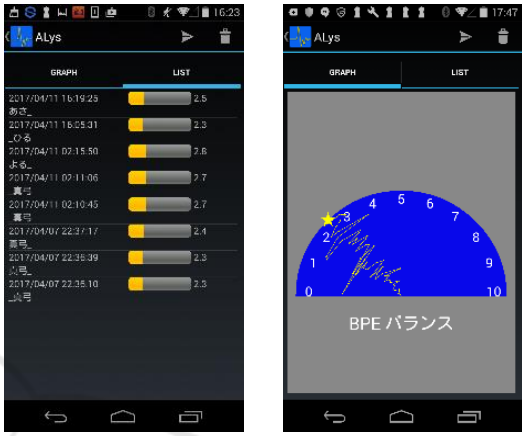

Figure 13: Display of past records in "List Mode" (left) and "Graph Mode" (right).

Moreover, the data saved in the tablet can be sent through email.

6 CONCLUSION AND REMARK

In this study, we have proposed a new indicator, the border of Parkinson's entropy (BPE), for identifying Parkinson's disease sufferers. We have collected a considerable number of pulse wave data, computed the BPE values with our system, and performed statistical analysis to obtain persuasive result. We conclude that the BPE can provide as a potentially effective indicator of Parkinson's disease. However, since this indicator is newly proposed, there is still room for improvement regarding the parameters of the sample entropy. We will strive to collect and analyse more data in the future.

As to the upgraded "Alys", since 5 seconds will suffice to produce analytical result, we believe it can enable users to conduct self-check in a convenient and economical way, without time and space limitation. We are now improving the tablet to make its size smaller. We hope that "Alys" can contribute to promoting better medical care.

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