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Low Scaling Exponent during Arrhythmia: Detrended Fluctuation Analysis is a Beneficial Biomedical Computation Tool

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1. Introduction

Cardiovascular disease is one of the major social health problems. Heart attacks, in particular, are a major social concern because of the unpredictable and silent way they develop. Recently, it was reported that the incidence of myocardial infarction has decreased significantly (Yeh et al., 2010). However, some unlucky patients are unaware that they are at risk for the life threatening disease. We must acknowledge that while the default setting is good health, there is always an onset to a disease and never to a return to good health. This onset results in “silent” angina, and finally a “silent” attack can happen. In fact, Dutch researchers estimated that 43% of heart attacks went unrecognized (de Torbal et al., 2006). Our ultimate aim was to predict a heart attack, or at least to quantitatively analyze the heart condition, based on the belief that it is possible to predict a heart attack by observing fluctuations in heartbeat intervals. Fluctuation analysis first appeared in the physical literature a long time ago (Peng et al., 1995). However, strong empirical evidence of its accuracy and usefulness must still be collected.

Traditionally, cardiac studies have employed heart rate variability (HRV) to detect the onset of cardiac problems, including disorders of the autonomic nervous system. Problems arise, however, when patients are previously assumed to be healthy before the appearance of symptoms associated with HRV. An earlier marker is necessary because the early identification of symptoms aids in the prevention of the onset of chronic diseases. Detrended fluctuation analysis (DFA) (Peng et al., 1995) was proposed as a potentially useful method for detecting the signs of cardiovascular disease (See Stanley et al., 1999); although DFA has not yet been developed as a practical medical tool, such as the electrocardiogram (EKG). (We prefer the abbreviation “EKG” to “ECG,” with due respect to the inventor, Dutch physiologist, Nobel laureate, Willem Einthoven.)

We recently tested the practical usefulness of DFA by using the heart of crustacean-animal models. In the test, we successfully showed that DFA could distinguish between intact and isolated hearts (Yazawa et al., 2004). In that study, we found out that the scaling exponent of the isolated hearts shifted and approached to 0.5 without exception. In turn, the scaling exponent of the intact hearts showed a value of about 1.0 without exception. As a result, we realized that DFA was reliable and useful because DFA was likely able to accurately reflect

physiology. Unlike other methods like HRV, the value of DFA was that it has a baseline value of one (1), like a standard body temperature (37), a standard blood pH (7.4), and so on. Thus, we thought DFA was a simple tool. One (1) is nonlinearly determined a “healthy” outcome resulting from complex interactions between the structure and function of molecules, cells, and organs. Thereby, we hoped that DFA could determine the state of health “numerically.” DFA seemed to not only reflect the state of the heart itself but also the (cardiac) nervous system. We considered that DFA might be used to detect the onset of cardiac problems, including disorders of the autonomic nervous system.

In this chapter, we provide empirical evidence of the practical usefulness of DFA and a new EKG amplification device that facilitates automatic DFA computation in practical use. The fluctuation analysis (i.e., DFA) was a potentially helpful early detection tool, as it revealed information that was not provided by EKG data.

2. Materials and methods

2.1 Peak detection of the heartbeat

Interval analysis requires detection of the precise timing of the heartbeat. A consecutive and perfect detection without miscounting is desirable. According to our preliminary test, approximately 2,000 consecutive heartbeats are required to obtain a reliable scaling exponent computation. We thought that the longer recording time resulted in a more accurate diagnosis. However, we found out that recording for longer than 2,000 beats was not helpful. We first reached this conclusion in model animal experiments. The ideal number of about 2,000 consecutive heartbeats is also applicable in human subjects.

To detect the timing of the heartbeats, both EKG recording and blood flow pulse recording are useful. Figure 1 shows an example of the premature ventricular contraction registered by both EKG and finger pulse recordings. Note the difference between Figure 1 A and B. Electrical excitation of the ventricle did not produce an observable pulse at the finger (see Figure 1A); in turn, an electrical excitation of the ventricle of the identical heart sent a small pressure pulse to the finger, which is indicated by an arrowhead (see Figure 1B). No matter what recording method was used, difficulty first arose when recording the timing of the heartbeats. The baseline drift of the commercial recording system presented the primary obstacle. When we saw the drift and contaminated the electric power-line noise, we were totally unable to detect 2,000 consecutive beats.

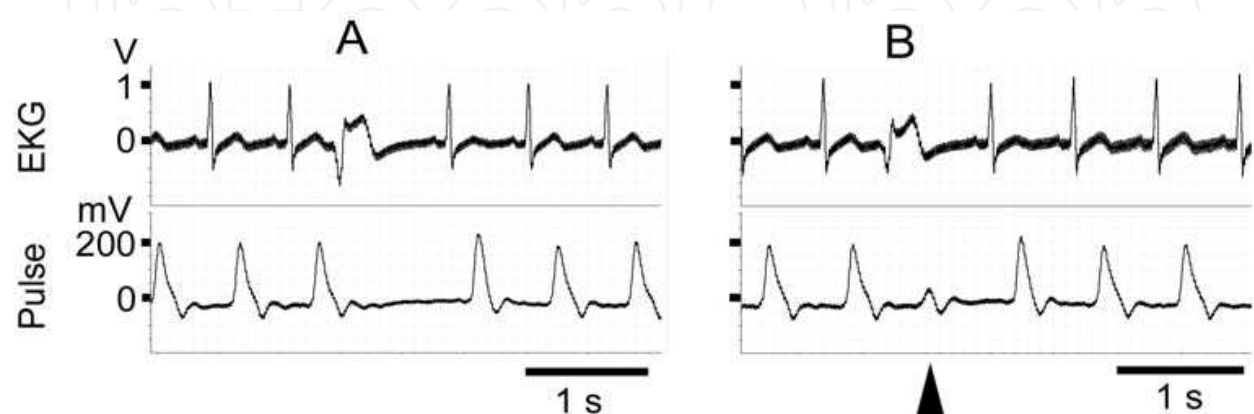


Fig. 1. Extrasystolic heartbeats in a 55-year-old man.

There was another obstacle: premature ventricular contraction (PVC). Among the “normal” subjects (age over 40 years old), about 60% of the subjects had arrhythmic heartbeats, such as PVC (Figures 1 & 2). Normally, PVC is believed to be benign arrhythmia, and, in fact, many healthy-looking people have exhibited this arrhythmia in our own experience. However, this PVC was an obstacle to the perfect detection of the timing of the heartbeat because the height of the signal was sometime very small (see Figure 1). If the baseline of the EKG recording was extremely stable, the heartbeats were automatically detectable even when irregular beats appeared sporadically (see Figure 2). However, in commercial EKG recording devices, the baseline of the recording was not as stable as shown in Figure 2. Figure 2 shows an example of peak identification. In Figure 2A, the heartbeats were not detected by visual observation but by our peak-identification program. Heartbeats No. 5 and No. 8 show PVC spikes. In Figure 2B, after the peak identification, the interval time series is constructed automatically. This is comparable to the so-called R-R interval time series in medicine. The two arrows indicate the correlation between the heartbeats in A and B.

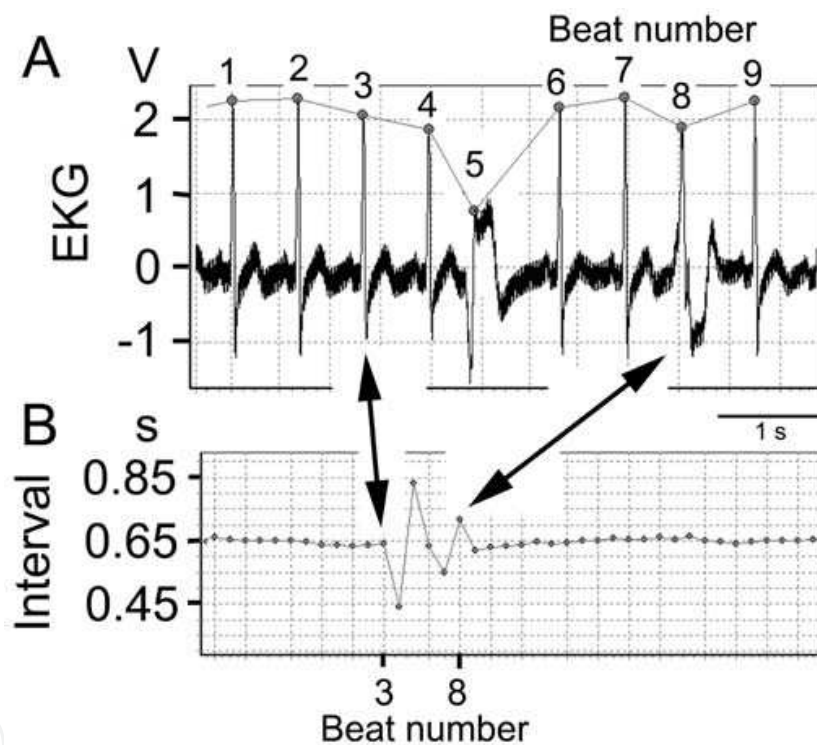


Fig. 2. An example of peak identification in a 55-year-old man.

2.2 EKG recording with stable baseline

To capture peaks without misdetection, we first needed to know how noise disturbs general EKG recordings. Figure 3 shows how false peak identifications occur. Here, 3 EKG electrodes (+, -, and ground (Nihonkoden Co. Ltd.; disposable Model Vitrode V) were placed on the chest of the subject. The subject was asked to hit his chest with his hands during the middle of the recording. Artificial noise-like spikes (4 arrowheads) appeared by hitting. They were automatically captured as the “false” heartbeats in this figure.

We made an EKG amplifier that enabled us to perform stable baseline recordings (see Figures 4, 5, & 6). An example set is shown in Figure 4. In the photograph, AC- and DC-EKG amplifiers, a 100-times amplifier, an analogue digital converter, and a USB connector can be

seen. Nothing was special with respect to the arrangement of the parts, but the important issue was that we found out that the time constant for the input stage of the recording must be adjusted to <0.22 s (Yazawa et al., 2010a; 2010b, Yazawa & Shimoda, 2010a; 2010b).

Figure 5 shows how our amplifier works for correct peak observation. The EKG trace is very stable. Body movements appeared on the record of the Piezo-electric pressure pulse (Finger p. trace), but the movements did not disturb the stable EKG recording (EKG trace).

Figure 6 shows an example of the long-period recording needed to perform instantaneous DFA computation. Here, a 15-year-old girl sat on a chair and engaged in fun conversation for a period of about 25 min. We used the amplifiers and a small time constant for the present study. This facilitated our DFA research. However, in some cases, inevitable noises contaminated the recordings, like the data shown in Figure 3. In such case, we removed the noises by eye observation on the PC screen in making a heartbeat interval time series. However, we have already identified how this problem occurred. It was due to the electrodes partially separating from the skin caused by sweating. We can overcome this problem by ensuring low smear clean skin.

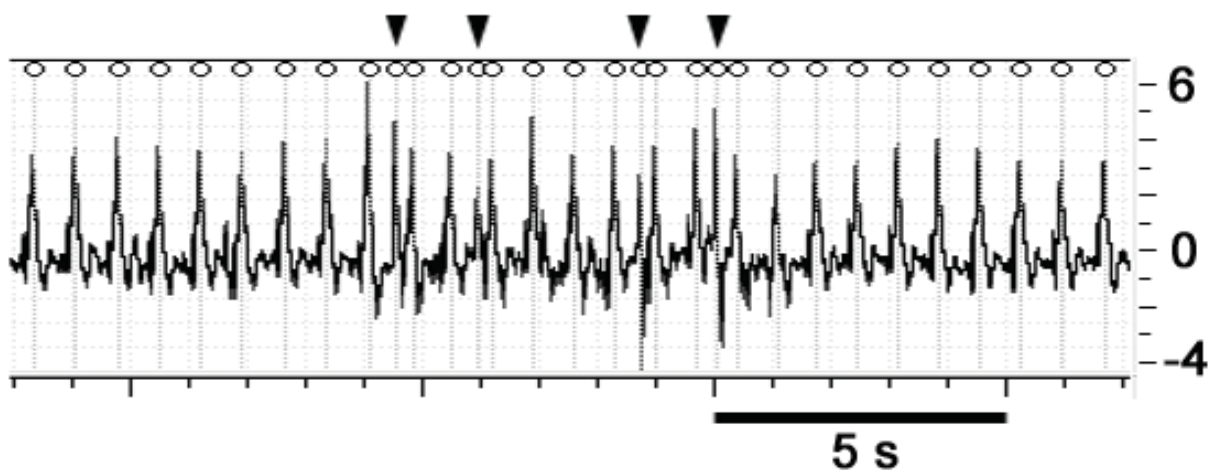


Fig. 3. False peaks incorporated into EKG in a 63-year-old man.

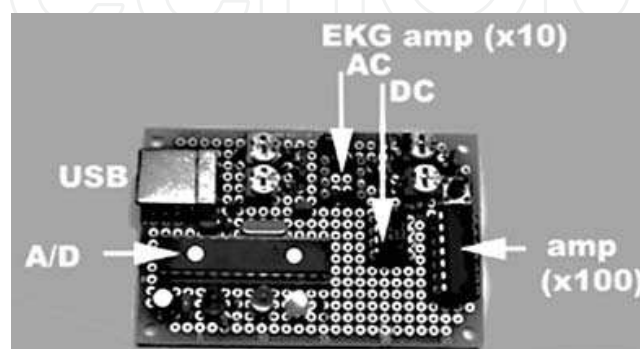


Fig. 4. An EKG amplifier.

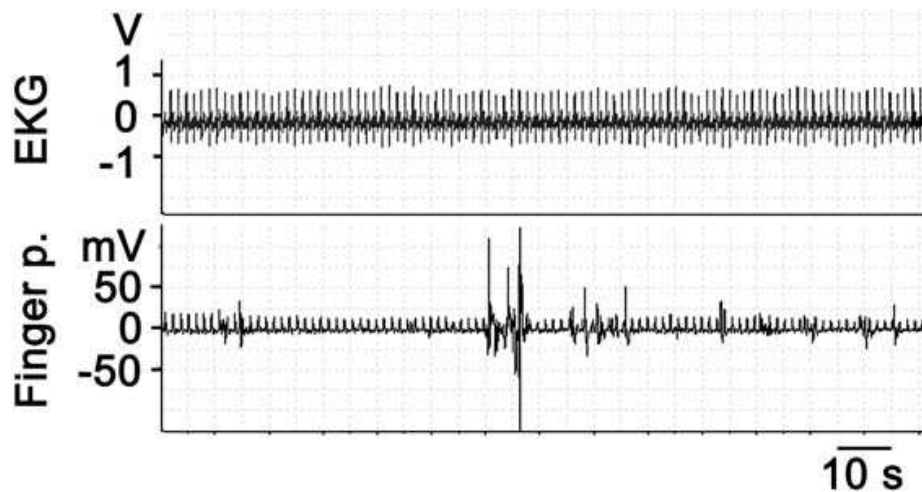


Fig. 5. Steady EKG recording during bodily movements in a 59-year-old man.

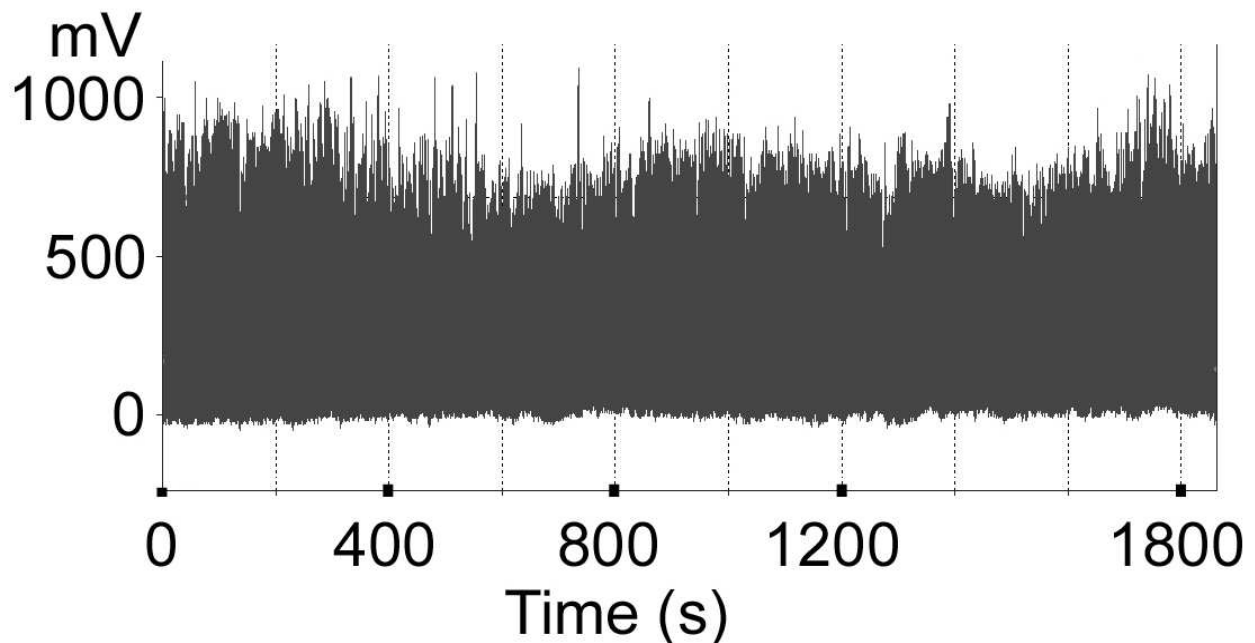


Fig. 6. A long-term EKG recording without obstacle noise in a 15-year-old girl.

2.3 DFA: Background

DFA is based on the concepts of “scaling” and “self-similarity” (Stanley, 1995). It can identify “critical” phenomena because systems near critical points exhibit self-similar fluctuations (Stanley, 1995, Peng et al., 1995, Goldberger et al., 2002), which means that recorded signals and their magnified/contracted copies are statistically similar. Self-similarity is defined as follows. In general, the statistical quantities, such as “average” and “variance,” of a fluctuating signal can be calculated by taking the average of the signal through a certain section; however, the average is not necessarily a simple average. In this study, we took an average of the data squared. The statistical quantity calculated depended on the section size. The signal was self-similar when the statistical quantity was λ^α times for a section size magnified by λ . Here, “ α ” is the “scaling exponent” and characterizes the self-similarity.

Stanley and colleagues consider that the scaling property can be detected in biological data because most biological systems are strongly nonlinear and resemble the systems in nature that exhibit critical phenomena. They applied DFA to DNA arrangement and EKG data in the late 80s and early 90s, identified the scaling property (Peng et al., 1995, Goldberger et al., 2002), and emphasized the potential utility of DFA in the life sciences (Goldberger et al., 2002). Although DFA technology has not progressed to a great extent, nonlinear technology is now widely accepted, and rapid advances are being made in this technology.

2.4 DFA: Technique

DFA computation methods have been explained elsewhere (Katsuyama et al., 2003). In brief, DFA is performed as follows:

- i. The heartbeat is recorded for 30–50 minutes in a single test because approximately 2,000 beats are required for determination of the scaling exponent. We recorded heartbeats using an EKG or finger pressure pulses.
- ii. Pulse-peak time series $\{t_i\}$ ($i = 1, 2, \dots, N + 1$) are captured from the record by using an algorithm based on the peak-detection method. To avoid false detection, we visually identified all peaks on the PC screen. Experience in neurobiology and cardiac animal physiology is occasionally necessary when determining whether a pulse-peak is a cardiac signal or noise.
- iii. Heartbeat-interval time series $\{I_i\}$, such as the R-R intervals on an EKG, are calculated as follows:

$$\{I_i\} = \{t_{i+1} - t_i\}, i = 1, 2, \dots, N \quad (1)$$

- iv. The series $\{B_k\}$, upon which we conduct the DFA, is calculated as follows:

$$\{B_k\} = \left\{ \sum_{j=1}^k [I_j - \langle I \rangle] \right\}, \quad (2)$$

where $\langle I \rangle$ is the mean interval defined as:

$$\langle I \rangle = \frac{\sum_{i=1}^N I_i}{N} \quad (3)$$

- v. The series $\{B_k\}$ is divided into smaller sections of j beats each. The section size j can range from 1 to N . To ensure efficient and reliable calculation of the scaling exponent in our program, we confirmed by test analysis that the number N should ideally exceed 1,000.
- vi. In each section, the series $\{B_k\}$ is approximated to a linear function. To find the function, we applied the least square method. This function expresses the “trend” – slow fluctuations such as increases/decreases in B_k throughout the section size. A “detrended” series $\{B'_k\}_j$ is then obtained by the subtraction of $\{B_k\}$ from the linear function.
- vii. We calculated the variance, which was defined as:

$$F^2(j) = \langle \{B'_k\}_j^2 \rangle \quad (4)$$

- viii. Steps (v) to (vii) are repeated for changing j from 1 to N . Finally, the variance is plotted against the section size j . The scaling exponent is then obtained by

$$F^2(j) \propto j^\alpha \quad (5)$$

Most of computations mentioned above, which are necessary to obtain the scaling exponent, are automated. The automatic program gives us a scaling exponent relatively quickly. The scaling exponent is approximately 1.0 for healthy hearts and is higher or lower for sick hearts. Although we cannot have a critical discussion regarding whether the exponent is precisely 1.0, our automatic program can reliably distinguish a healthy heart from a sick heart. In this article, we classified the scaling exponent into 3 types, normal, high, and low.

2.5 EKG and finger pulse

For human subjects, we used both finger pulse recordings and EKG recordings. For pulse recordings, we used a Piezo-crystal mechano-electric sensor connected to a Power Lab System (AD Instruments; Australia). For EKG, 3 AgAgCl electrodes (+, -, and ground, manufacturer mentioned above) were used. Wires from the EKG electrodes were connected to our newly made amplifier (For EKG amplifier, see above). These EKG signals were also connected to a Power Lab System.

2.6 Model animals

It is very important that animal models be healthy before an investigation. To confirm that all the animals used were healthy, we captured them from a natural habitat and examined them. We used crustacean hearts because we are familiar with the structure and function of the crustacean heart and nervous system. One of the main reasons for using invertebrates was that all these animals have a common genetic code (DNA information) for body systems such as the cardiovascular system (Gehring, 1998, Sabirzhanova et al., 2009). All animals have a pump (the heart) and a controller (the brain).

2.7 Volunteers and ethics

Subjects were selected from colleagues in our university laboratories, volunteers who willingly visited our exhibition booth and desired have their heart checked, and the staff at NOMS Co. Ltd. and Maru Hachi Co. Ltd. All subjects were treated as per the ethical control regulations of our universities, Tokyo Metropolitan University and Tokyo Women's Medical University.

3. Results

3.1 Extrasystole: PVC

Figure 7 shows an example recording of extrasystole. This recording was obtained by a finger pulse recording. Large peaks were marked (o). Two small pulses are shown (A and B), which are PVCs. Our volunteers said that a PVC is perceived as a "skipped beat" or felt as palpitations, although some experienced no special sensation. In a normal heartbeat, the ventricles contract after the atria. In a PVC, the ventricles contract first. Therefore, the ejection volume is inefficient (see Figure 7). Single beat PVC arrhythmias do not usually pose a danger and can be asymptomatic in "healthy" individuals according to physicians. However, there is no way to accurately determine if someone is a "healthy" individual, which is the problem. That is why we tested DFA as a tool.

In Figure 7, one can see that there is difference in the pulse configuration between A and B. The two beats originated from different sites (a myocardial cell or cluster of myocardial cells) inside the ventricle, or at different times from an identical site. This is a typical extrasystole arrhythmia, although we did not pay further attention to cardiac physiology like the ectopic beat characteristics. For DFA, we just needed to measure the intervals of the heartbeats. Theoretically, irregularity itself carries hidden information.

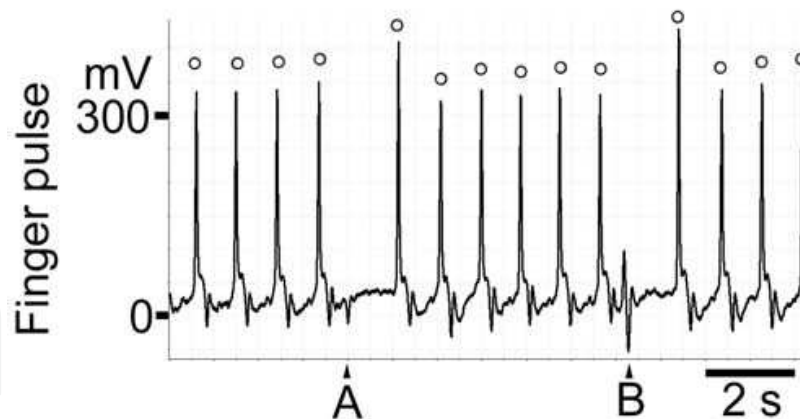


Fig. 7. An example of extrasystolic pulsations in a 65-year-old man.

During the past 4 years, we have encountered about 50 subjects who have extrasystole arrhythmia. Among all of our subjects (over 300) from age 2 to age 87, PVCs were not recorded in very young people (age < 19). One exception was a student (age 20); he showed benign PVCs. Most cases of PVCs were found in subjects over age 50 and about half were male.

Figure 8 shows the interval time series from the subject in Figure 7. Here, we recorded 1998 beats. Only 17 PVCs can be seen as downward swings.

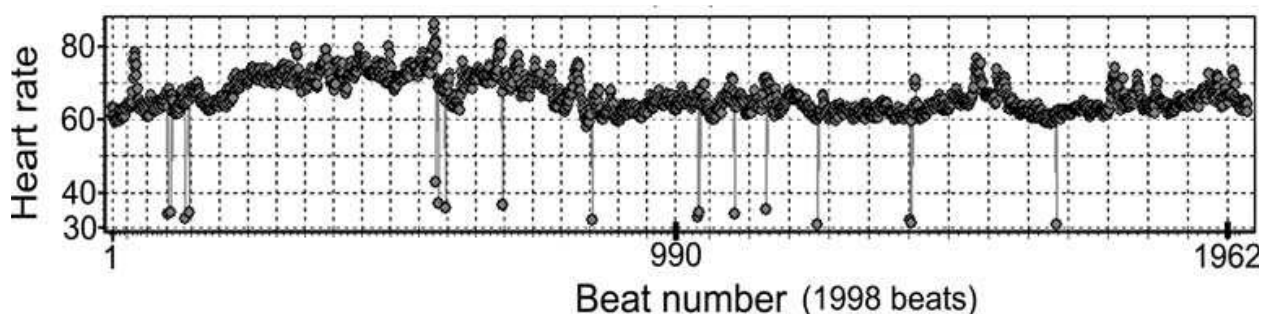


Fig. 8. A time series of the EKG with some PVCs. The same subject as in Figure 7.

We found that PVC hearts always exhibited a low scaling exponent (0.7–0.8). Figure 9 shows an example. The computation was worked out on the data of Figure 8. The slope in the graph shows a straight line, indicating that “scaling” is beautifully constituted over the entire range of the box size (10–1000). The scaling exponent for this subject was 0.8095 (see inset equation in Figure 9).

Most PVCs are benign according to physicians’ assessments so long as the PVC does not exceed over 10 times per min. The subject (male 65 years old) shown in Figures 7, 8, and 9 was a very active person. He told us he was working at a large electric company. He seemed to have no major health problems. He indicated he was not bothered by his PVC. In fact, it looked to be benign. However, on the basis of our DFA results, we do not agree that PVCs are always benign. His scaling exponent was 0.8, which is not perfect health in terms of fluctuation analysis. We would say the subject’s health is dependant upon other factors. Therefore, we should treat individuals one by one. Everyone has a unique genomic blue print (DNA). The genetic code for the structure and function of life is never the same in any 2 individuals.

Another case study involves a volunteer we worked with for over 6 years. She has so-called benign PVCs. She is a German-American (age 58) living in Virginia, USA. She often told us that her palpitations (about 10 times per one hour) were uncomfortable when they occurred

(data not shown). Her scaling exponents were 0.7–0.8. She said that the PVCs were annoying. She was very nervous to have her PVCs compared to this male subject (Figures 7, 8, and 9). It is known that repetitive PVC leads to ventricular tachycardia. We so far do not have good solution for the problem of the low exponent.

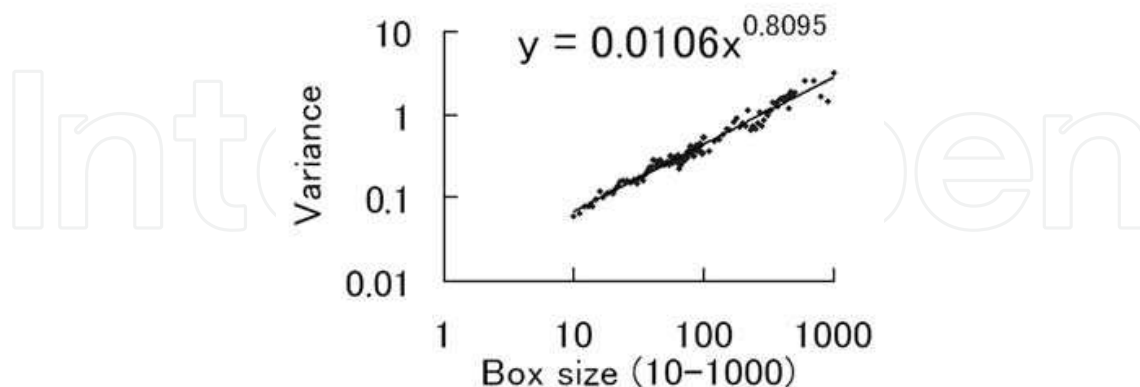


Fig. 9. DFA results for the subject shown in Figures 7 and 8.

3.2 Arrhythmia with dialysis

When we presented our work at an exhibition, Innovation Japan 2009, we met a representative from a company who had an interest in healthcare issues. According to his proposal, we recorded his EKGs and finger pulses (shown in Figures 1 & 2). We brought back his data to the university laboratory and started DFA analysis.

Figure 10 shows the results. In A, the time series data of 4265 heartbeats is shown. In B, the results of the calculation from the entire range of the box size, 10–1000, is shown. This box size is our normal calculation procedure. In C, the DFA results on a small box size of 30–110 are shown. The slope gives the scaling exponent, calculated by least mean square approximation, which was 1.1502. In D, the DFA results on a box size of 120–270 are shown. The scaling exponent was 0.6283.

We noticed that his heartbeat exhibited PVC-like arrhythmia (Figures 1, 2, & 10A). We were not 100% sure that his arrhythmia was PVC. We wondered how and why his arrhythmic beats were generated. After DFA computation was completed, we found that the slope was not a straight line (Figure 10B). The scaling exponent calculated from a small box size (30–110) was 1.15 (see Figure 10C). While 1.15 is within the normal value, we were concerned that it was a value higher than 1.0. In turn, his scaling exponent from a large box size (120–270) was extremely low, 0.6 (see Figure 10D). We could at least say that his health was not perfect; we wanted to recommend that he see a doctor.

Since he did not provide us with any personal health information about himself, we believed that he was normal when we took the recording. However, the results were not normal. It looked like PVC, but we were not sure. Then, we discussed his results in the laboratory, and decided to share our concerns about his heart. We made a telephone call to him, and stated: “I am not a physician. I am just a neurobiologist. However, I would like to suggest you visiting a cardiologist based on your data.” He then replied that he already knew that he had skipped heartbeats, and he was regularly visiting a physician three times a week. He further explained that he has been on dialysis for about 20 years. The sickness started in his early 30s. He and his doctor always talked about the state of his heart. He thanked us for contacting him.

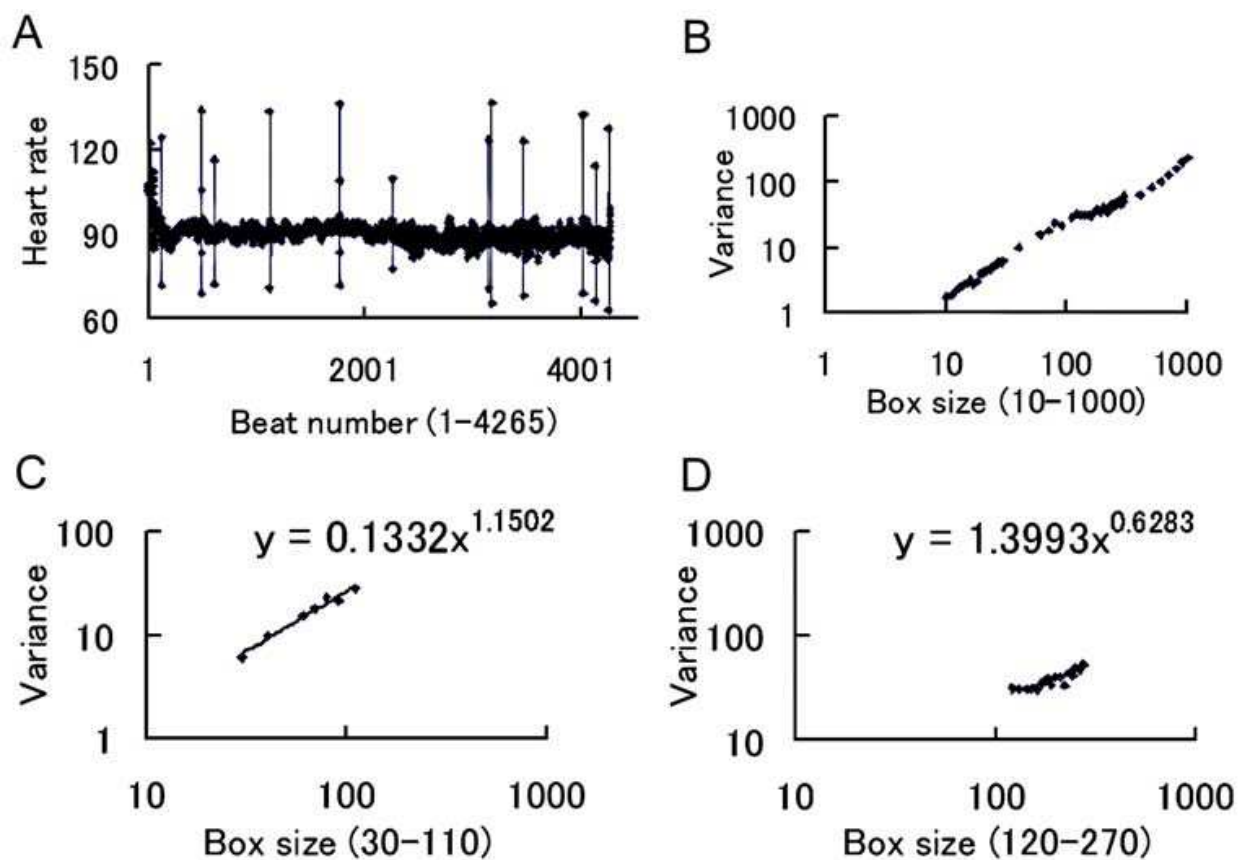


Fig. 10. DFA results from patient on dialysis. Male 55 years.

We felt that he was doubtful of our scientific skill. We passed his examination, which was set up without our knowledge. University and corporate collaboration was initiated thereafter.

3.3 PVC with smoking

Figure 11A shows that we recorded 2338 heartbeats from a subject (a friend of an author) when sitting on a chair in a coffee shop. His heartbeat showed PVCs as indicated by some short-interval beats (see downward swings in Figure 11A). Three long-interval heartbeats (Figure 11A) demonstrate a “skipped” heartbeat. These skipped beats and PVC beats were an extrasystolic phenomena. The occurrence of these arrhythmic beats did not exceed 10 per min (see Figure 11A). Therefore, we may conclude that his PVC was benign in terms of the physicians’ guidelines. However, the scaling exponent was low, 0.7288 (see Figure 12A1 and 12A2) at a normal sitting state. We confirmed that the PVC exhibited a low scaling exponent. He loved smoking cigarettes very much, although a cardiac-scientist recommended that he quit. In Figure 11B, 2433 heartbeats were recorded in the coffee shop. When he started smoking, recording also began. Skipped beats increased in number during smoking (see under-bar periods in Figure 11B). During the smoking period (Figure 11B), the total number of PVCs increased. It seemed that the intake of tobacco-related chemicals (we did not determine whether it was the nicotine, tar, etc.) into the body quickly pushed the scaling exponent toward a much lower value, i.e., from a non-smoking value of 0.7288 (Figure 12A2) to smoking-value of 0.6195 (Figure 12B2). It was apparent that DFA monitors nervous system function as well as cardiovascular function.

DFA, therefore, can measure the wellness of the entire body system. However, DFA does not tell you in detail, for example, what is wrong with the body system or what local element is reacting to the environment.

Since the results of Figures 11 & 12 were so significant and intriguing, we wanted to examine other “smoking” subjects. We finally determined that smokers’ heartbeats were not always susceptible to “smoking.”

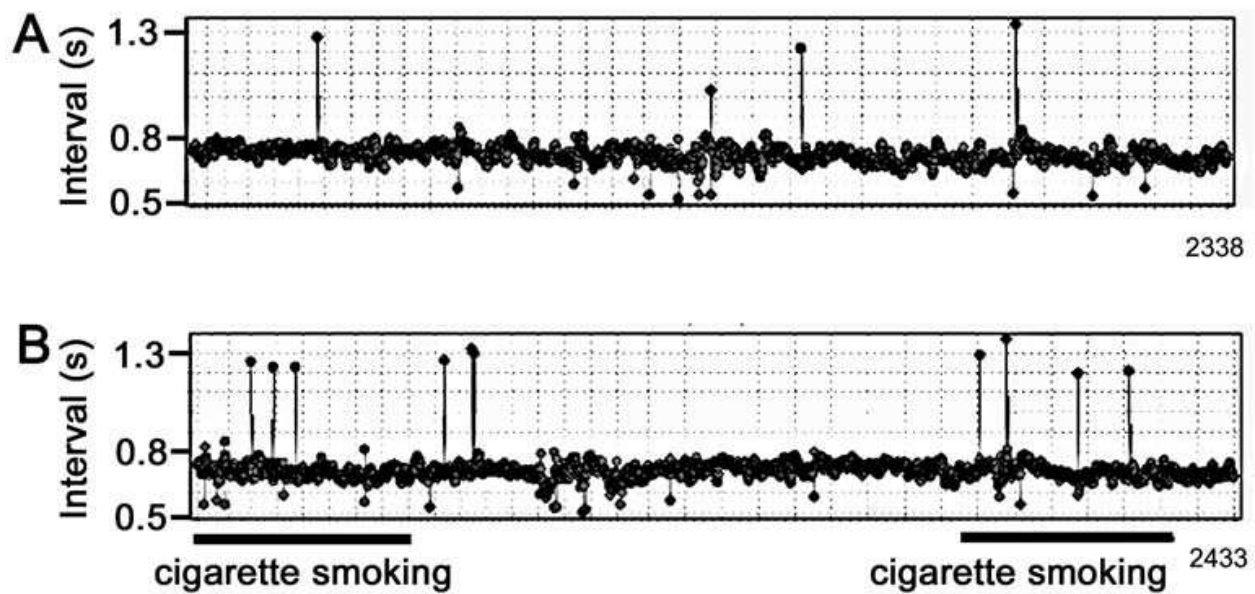


Fig. 11. Time series. A: Non smoking and B: Smoking 58-year-old man.

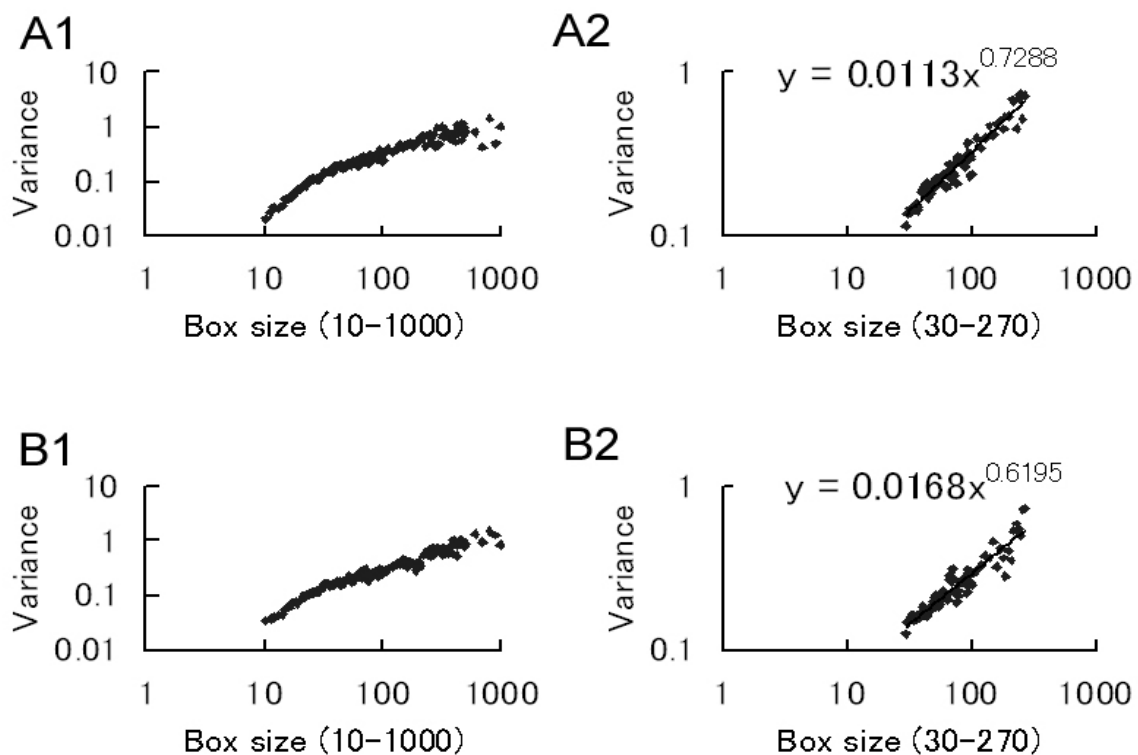


Fig. 12. DFA results on the data in Figure 11. A: Non-smoking, B: Smoking.

3.4 Alternans arrhythmia

Alternans (a period-2 rhythm) was first documented in 1872 by Traube. However, alternans did not receive particular attention from doctors until recently; in fact, alternans was previously referred to as the harbinger of death (Bragaa et al., 2004, Pieske & Kochskamper, 2002, Rosenbaum et al., 1994). The phenomenon of alternans is of continuing interest nowadays particularly because of its association with myocardial ischemia and cardiac arrhythmias. In animal models, we have already reported that the alternans heartbeat exhibits a low scaling exponent. This was measured on the heartbeats of crustacean animals such as crabs and lobsters ($n = 13$) (Yazawa et al., 2009). We also encountered human alternans subjects ($n = 8$, 5 Japanese and 3 Americans). Their scaling exponents were low (Yazawa et al., 2009).

Figure 13 shows an example of alternans in which the subject's heartbeats showed a period-2 rhythm (Figure 13A). We met him in 2007 at an exhibition called Innovation Japan 2007. At that time, he at first told us that he knew that his heart was not normal, and he regularly went to see a doctor. He visited us because we presented our DFA method at the exhibition. We recorded his heartbeat (Figure 13A). His scaling exponent in September 2007 was 0.6709 (see Figure 13B and 13C). We explained to him that he had alternans, and we explained the condition to the best of our knowledge.

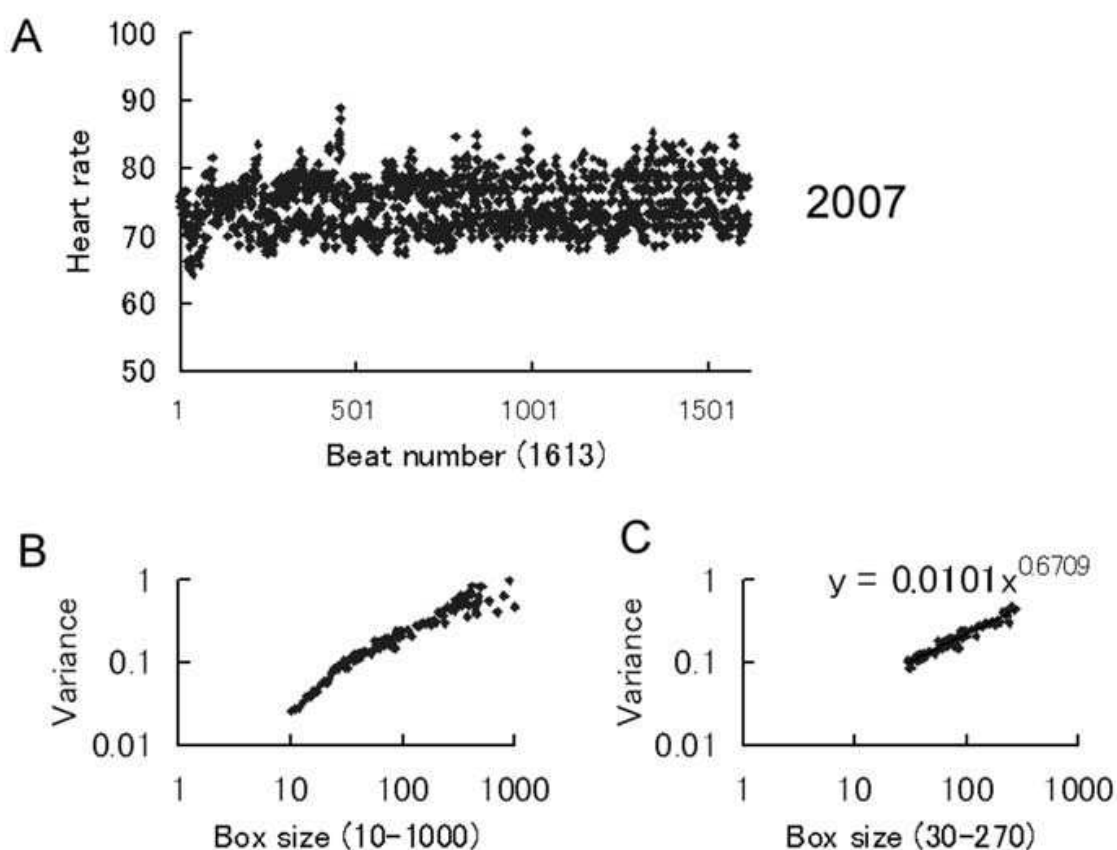


Fig. 13. DFA of alternans. Recorded in September 2007 in Tokyo. Subject was in his 60s.

Two years later, in September in 2009, we returned to the exhibition. We did not expect him to visit us again, but he came. We recorded his heartbeat and calculated his scaling exponent (Figure 14). To our surprise, the alternans was almost gone, and his scaling exponent was higher than in 2007 (see Figure 14A). In fact, there was a noticeable difference in the time

series data between 2007 (Figure 13A) and 2009 (Figure 14A). He said that since learning the results shown in Figure 13A in 2007, he had been walking to work instead of driving.

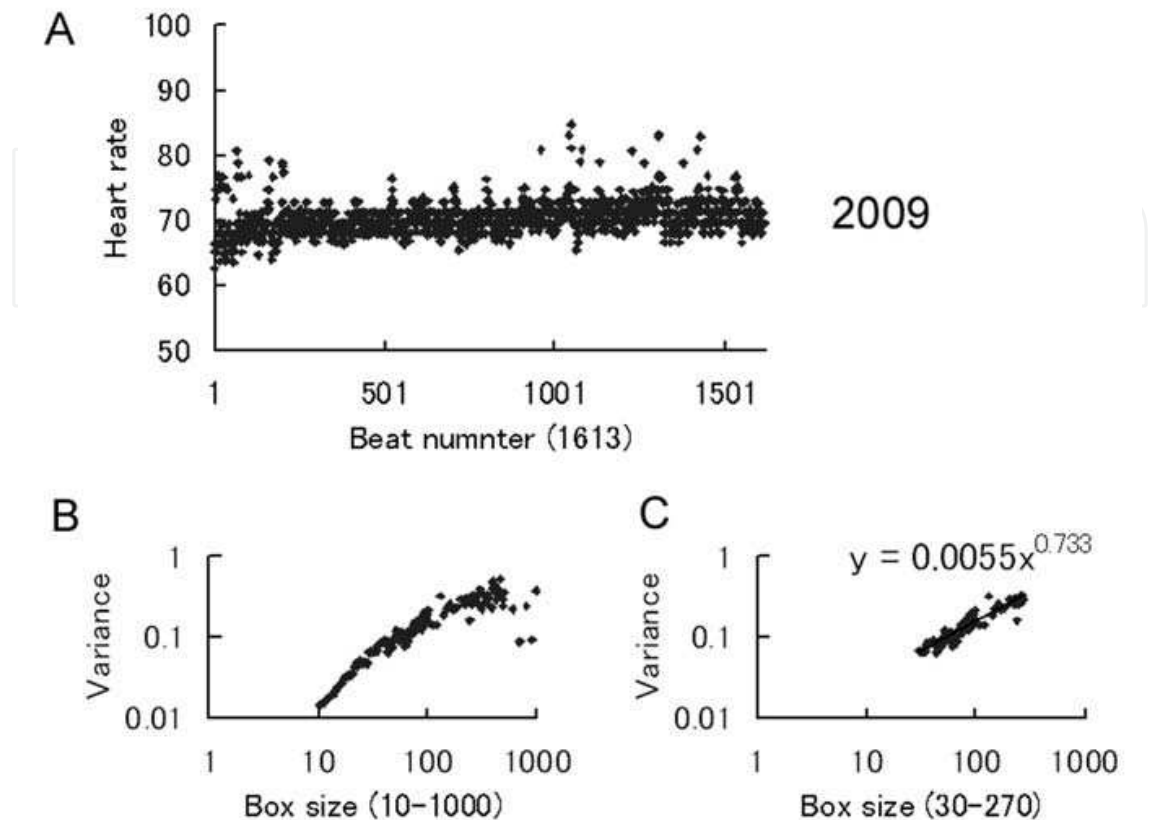


Fig. 14. DFA of alternans. Recorded again in September 2009 in Tokyo.

His scaling exponents are compared in Table 1. Three different DFA computations at different box sizes are shown. Years 2007 and 2009 are compared. The table shows that his scaling exponents were improved in all three areas. The exponents shifted toward the good health state, which is ultimately 1.0.

Box size	2007	2009
30-110	0.703	0.839
70-140	0.743	0.878
30-270	0.671	0.733

Table 1. Comparison of the scaling exponents at different box sizes. Computed from the data obtained from the subject shown in Figures 13 and 14.

Based on these results, we can conclude that DFA was useful in determining that his condition had improved.

3.5 Normal healthy rhythm

Several volunteers have helped conduct our follow-up test that has lasted for several years. The volunteers include the authors, their family members, and university colleagues. Figure 15 shows an example. A young woman, 26 years old in 2006, who was working in the

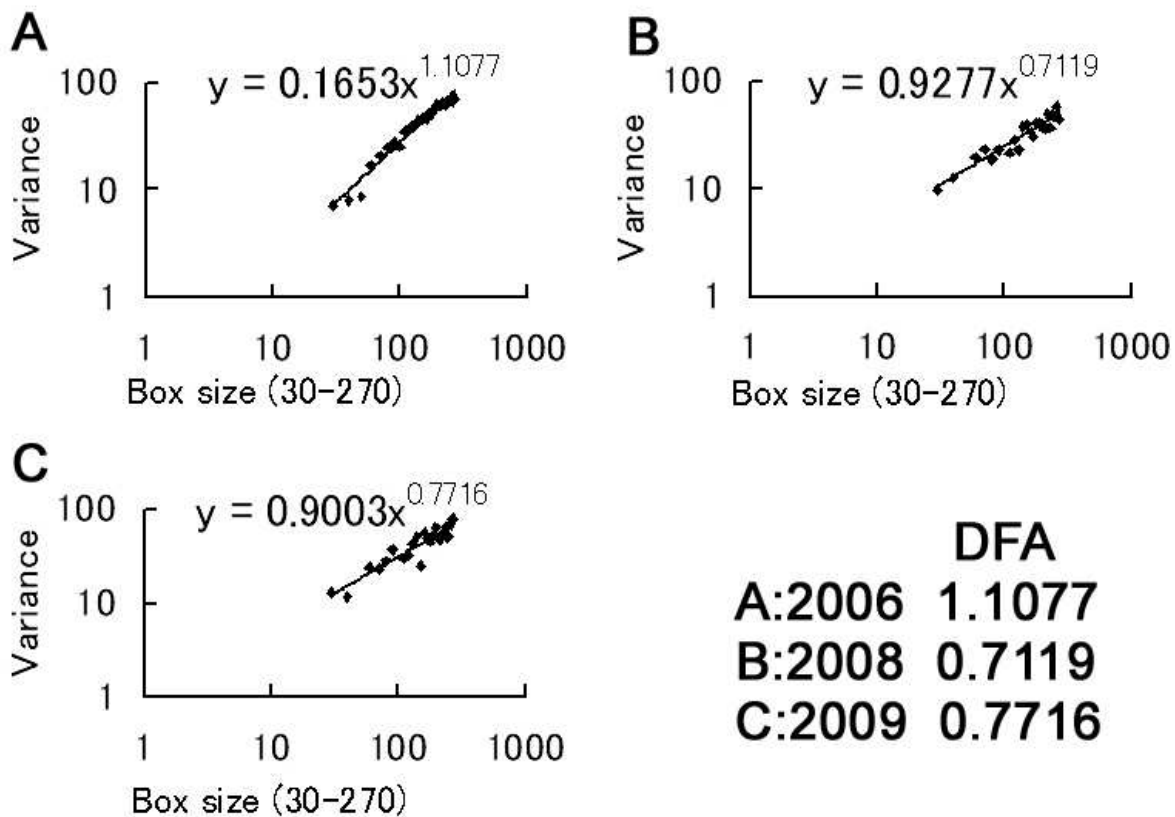


Fig. 15. DFA follow-up on a healthy subject. Female 27 years old in 2006.

university's intellectual property office, was willing to help us as a volunteer for long-range follow-up. Since we often worked together, we could obtain information about her everyday life if we needed.

Her scaling exponents have shifted toward a lower value over the course of 4 years. Herein, we have described our interpretation of why her scaling exponents gradually changed. This case study indicated how and why a once perfectly healthy subject gradually experienced stress.

In 2006, we submitted our patent regarding our DFA method from the university's intellectual property office. At that time, she was a newcomer. She supported us greatly. Her heartbeat exhibited a normal scaling exponent of 1.1077 (Figure 15A, in September 2006). One could argue that the value of 1.1 is higher than the normal perfect value 1.0. However, according to our preliminary guideline, 1.1 is normal. We recorded her heartbeat in September of 2006. She was pretty, active in her job, and she was thoughtful to colleagues. Most importantly, her exponent was fine.

In 2008, she lost a loved one. One day, she told us that her grandmother had become seriously ill. She returned to her hometown immediately. Her hometown was not located a short distance from Tokyo and, therefore, she could not commute back and forth. She stayed in her hometown for a while to take care of her grandmother. She only visited the workplace occasionally. We did not know the details about her life at that time. Therefore, we just took her heartbeat data as usual in September of 2008. Later, we learned that her loved one had recently passed away.

In September 2009, we again recorded her heartbeat as usual. The Innovation Japan exhibition was held in September as well. During the 30 min period of recording of her

heartbeat, we talked. While she had recovered from her grandmother's death, she found her present job to be boring. She wanted to be a skilful patent manager and wanted to quit her ordinary office job. At the end of the year 2009, she abruptly notified to us that she would be leaving since she had accepted another job. Although her salary would decrease, she would have the opportunity to perform much higher-level work involving the patent business.

When we measured her heartbeat in 2006, her exponents were always near 1.0. We believed for long time that she represented the perfect scaling exponent. Her EKG data from 2008 and 2009 were stored deep inside the PC and remained there without receiving attention. Recently, we accidentally analyzed her hidden data in August 2010. We discovered that her exponents correlated with a shift in her psychology.

The results are shown in Figure 15. We can trace back what has happened in her life, as mentioned above. We can interpret a correlation between the shift of her scaling exponent and the shift of her psychological states. In the year 2006, she was a fresh worker after finishing her master's degree, and she had a healthy scaling exponent (Figure 15A, see also inset of Figure 15). In the year 2008, she had hard days, and she had stress. In those days, her scaling exponent was the worst we had measured (Figure 15B). In the year 2009, she seemed to be recovered although she did not tell us so. However, her scaling exponent was not fully recovered to 1.0 (Figure 15C). We now know that she was trying to get a promotion, although she never told us until she succeeded in getting a new job. In the spring of 2010, she disappeared and we lost contact with her. Nonetheless, her data can explain how and why her healthy scaling exponent has shifted.

This story suggests that DFA measurements might be helpful for monitoring the functioning of the entire body system function, including wellness, sickness, and psychology. It is apparent that we need to conduct further investigations with additional subjects before declaring DFA's power and ability are great and beyond what we have experienced before in the community of health care, medicine, biology, and physics. Biomedical computation is a growing field of science.

4. Discussion

Heart and skeletal muscle are structurally similar; both exhibit striations. However, unlike skeletal muscle, the heart muscle exhibits automaticity—the property of spontaneous contractions in the absence of nerve stimuli. Furthermore, the spontaneous contractions are generated regularly at their own rate like a clock, or so-called pacemaker. Spontaneity and regularity are the most advanced characteristics of myocardial cells, which have been achieved in evolution. To alter its robust rhythm, actions by the nerves and hormones to the pacemaker are necessary. The force of the action is determined by the number of demands coming from the cells in the body via nerves and hormones. Since the cell is the ultimate element composing the living body, interaction between cells is a key function in a multicellular organism. While all of the elements are nonlinearly connected to each other, the interaction is never the same in any 2 individuals because each individual has his/her own genome. For example, different cells (individual) respond differently to an antibiotic; thus, some are highly resistant, and some are less resistant (Lee et al., 2010). Here is another example showing that everybody has their own genetic code: It is believed that a medication, clopidogrel, reduces the rate of major vascular events among patients with acute coronary syndromes and atrial fibrillation. A recent study implied that the benefits of clopidogrel were attenuated in patients with genetic variants (Paré et al., 2010). Thus,

everyone must be checked and considered independently when applying DFA. If we find a single exception, we should throw out our theory because it should not happen in terms of a nonlinear way of thinking. We so far have confirmed that PVC subjects have a low scaling exponent. There have been no cases where a PVC subject had a value higher than 1.0. We could not accept such a discrepancy. We have so far never found a paradox. We are able to explain all data under the criterion that 1.0 means wellness and a variation from 1.0 means sickness. However, there is a problem with the criterion: the border between wellness and sickness has not yet been established. Everlasting investigation is the only solution for confirming our theory is accurate.

What is wellness of life? Wellness is the state in which an individual can generate $1/f$ rhythm from the heartbeat (Kobayashi and Musha, 1993). The important point is whether the rhythm is $1/f$ or not. In this article, we showed that DFA works without exception. If you have a scaling exponent of 1.0, then you are healthy. If your scaling exponent is higher or lower than 1.0, something is wrong with you. The scaling exponent of 1.0 is the perfect state of life. To our surprise, only 10% of our subjects belonged to the perfect state ($n = 300$, human; the number was greater in animal models including lobsters, crabs, frogs, and insects).

Synchronous contractions of the cardiac muscles are a fundamental functional requirement for the heart to work as a pump. Further, this synchrony is established by electric coupling between the muscle cells. This synchronous and regular automaticity assures a constant flow of circulation and is widely observable throughout the animal kingdom, from invertebrates to vertebrates, i.e., from insects and lobsters to humans. This explains why our experiments on model animals were successful and useful for human physiology.

Our experiments on crustacean hearts (Yazawa et al., 2004) led us to the conclusion that DFA distinguished isolated hearts from intact hearts. From this conclusion, we deduced that DFA was useful for detecting the preliminary stage of sickness of the cardiovascular system. The present case studies verified this deduction.

The periodicity of contractions is a common and important characteristic of the heart. If regularity is disturbed for some reason, clotting/coagulation of the blood cells easily occurs. Thus, irregularity is a disadvantage for wellness. Rate change in the heartbeat normally occurs in a gradual manner in various time courses, either in a slow response or quick response. A mixture of the various time courses is required for wellness. In principle, DFA looks at the degree of mixture of the time courses. Skipping heartbeats (PVC) and alternans (2 beats) exhibited less dynamical changes in rate. This was well sensed by DFA as a low scaling exponent.

A gradually and dynamically changing heart rate is proof of wellness and a healthy scaling exponent of 1.0. Uncomfortable and adverse stimulation from the environment can interfere with the periodicity of cardiac contractions, e.g., stress-induced arrhythmic heartbeats. A typical example of stress-induced arrhythmia is a sudden reflexive slow-down in the rate of the heartbeat observed during a shadow stimulation (Mashimo et al., 1976, Yazawsa et al., 1977, see also Gwilliam, 1963 for shadow reflex). Changes in rate naturally reflect changes in external and internal environments. Dynamic change is itself normal. However, if interactions between the nerve signals (neurotransmitters/hormones) and muscle receptors are not normal, skipping beats, deficit beats, unstable intervals, and extremely fast beatings may occur. This is well sensed by DFA, and DFA will calculate a low scaling exponent as described in the present investigations.

We declare that DFA can distinguish wellness and sickness. If the scaling exponent is near 1.0, wellness is confirmed. If the scaling exponents are considerably higher or lower than 1.0, a masked condition is a possibility. Unfortunately, we must admit that DFA cannot tell what cells or what organ is the origin of that poor state. We cannot determine what is wrong with the subject. We admit that there is such a limit in DFA. However, DFA makes a “good” or “bad” judgement of health in a quantitative way.

Myocardial pacemaker cells produce the periodicity of cardiac contractions. The pace is determined by the rate of action potentials, which requires strictly controlled ionic flows. The ionic flows are controlled by ionic channels equipped on the myocardial cellular membrane. The millions of ionic channels work with quasi synchronously in the myocardial membrane. However, synchrony is not perfect among the millions of channels. Fundamentally, the ionic channels in the cells have electrical properties comprised of 2 states – open and closed. The consequences of modification/distortion of the open vs. closed states are arrhythmic heartbeats, i.e., heartbeat fluctuations. The fluctuation occurs within a millisecond in the time scale. From this consideration, we adopted a sampling rate of 1 kHz when we recorded heartbeat data. This was a key factor of the recording method, and it led us to a successful DFA analysis for determining whether or not subjects were healthy. The origin of arrhythmia, therefore, is the membrane of the ionic channels. Sodium (Na) and potassium (K) are the major ions that contribute to the rate of cardiac action potentials since these ions are present in the blood (and tissue fluid) at the highest concentrations. Other ions, such as calcium (Ca), are present in the blood at relatively low concentrations. Therefore, the rate of flow of Na/K ions is the key factor determining the heart rate. (We do not, however, ignore the contribution of Ca to heart rate.) The equilibrium potential of each ion and the membrane potential of the myocardium are important factors for determining heart rate. Without any changes in the equilibrium or membrane potentials, the heart rate cannot be changed in a constant temperature environment. The pace making mechanism is fundamentally robust in function because millions of channels work together in a quasi-synchronous way. To change this robust pacing function, chemicals (neurotransmitters and hormones) must act on receptor-ionic channels (complex molecules). Taken together, ionic balance and chemical balance (hormones and neurotransmitters) are the key variables for determining the heart rate. DFA indirectly examines this fundamental molecular mechanism. Ultimately, wellness and sickness are related to the ionic mechanism of nerves and muscles that receive influences from the chemical ingredients in the blood. We trust that the state of the blood and nerves plays a pivotal role in the state of wellness.

Gradual changes from wellness to sickness are invisible on ordinary EKG recordings. Nevertheless, pumping hearts may carry hidden information about wellness or sickness, and we can extract this information from the pattern of the heartbeats. Extremely irregular heartbeats may indicate sickness, the worst-case scenario being a heart attack.

Heart attacks do not recur with the precision of a timed life cycle, or have the signature of sudden psychological shock. However, we believe that they obey the laws of physics, which means that we should be able to predict their recurrence. For this purpose, we must employ physics and mathematics in addition to biology and medicine. In Chinese medicine, physicians feel the pulse of patients to make diagnoses. A skilled physician’s nervous system seems to function like a computer and performs miraculous feats. This fact indicates that pulses and heartbeats carry hidden information about a patient’s wellness or sickness. However, man-made machines have not been able to mimic this ability of physicians, even

though more than a hundred years have elapsed since the inception of the industrial revolution. Despite the historical challenges, we hope to design a machine that can be used to detect irregularities in cardiac periodicity. Our new EKG amplifier belongs to such efforts. It is almost noise free so long as subjects do not make extremely hard movements of the body, the details of which were documented in the present article.

Based upon our preliminary guidelines, 0.9–1.19 indicates health, 1.2–1.5 indicates sudden death, and 0.5–0.89 indicates natural death. In our study, and in the study conducted by Peng et al., (1995), the “normal” state has been associated with a scaling exponent of 0.9–1.19 (our study) and 1.0 (Peng et al.). In the present article, we showed that PVC, a typical arrhythmia involving extrasystoles, exclusively lowered the scaling exponent; and alternans, an abnormal heart rhythm also known as the “harbinger of death,” also exclusively lowered the scaling exponent of heartbeat fluctuation dynamics.

Moreover, we already found that transplanted human hearts ($n = 3$) exhibit a scaling exponent as high as 1.2 (Yazawa et al., 2006), and hearts with ischemic disease ($n = 5$) exhibit a scaling exponent of 1.2–1.4 (Yazawa et al., 2008, Yazawa and Tanaka, 2009). However, we have made some intriguing observations among our volunteers. We have met a volunteer subject (subject was in his late 60s, our colleague in Tokyo) who had received emergency medical care for ischemic heart disease. He received a stent placement. He had no myocardial cell damage according to his surgeon. We found that he had a normal scaling exponent (1.0). In this case, his wife was smart enough to notice her husband’s sickness and made the quick decision to call an ambulance; in fact, she protected her husband from serious myocardial damage from coronary ischemia. Defibrillator implantation and continuous medication for atrial arrhythmia were also associated with a normal scaling exponent (subject in his 40s from in Nagoya City, subject in his 60s from Kawasaki City). Thus, the scaling exponent may indicate whether defibrillators and/or medications are working properly. Therefore, we consider that DFA will aid diagnostic decisions in patients with cardiovascular disorders. More case studies are required, although our guideline has thus far proved adequate, and we have found no exceptions to it, such as ischemic heart disease being associated with a high scaling exponent.

In this article, we have provided empirical proof of the practical usefulness of DFA. By presenting several case studies, we explained how the wellness of subjects could be evaluated using heartbeat recordings. Our purpose was to determine whether DFA is a useful method for the evaluation of the quality of a normal, healthy state. Our crucial target of this successive investigation was to discover the contradictions, if any, of our theory. Our preliminary guidelines for the interpretation of scaling exponents are as follows: 1, ideal state (wellness); >1 , the heart is ready to stop any time; and <1 , the heart is stressed, and its ionic balance and nerve activity are not ideal.

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