

Scaling Exponent Determined by a Bio-Signal Computation for the Healthy and Diseased Heartbeat

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ABSTRACT

We analyzed heartbeat-intervals by using our own program of detrended fluctuation analysis (DFA). “Alternans” is an arrhythmia exhibiting alternating amplitude or alternating interval from heartbeat to heartbeat, which was first described in 1872 by Traube. Recently, alternans was finally recognized as the harbinger of a cardiac disease because physicians noticed that an ischemic heart exhibits alternans. To quantify irregularity of the heartbeat including alternans, we used the DFA and revealed that the alternans rhythm lowers the scaling exponent. We conclude that the scaling exponent calculated by the DFA reflects a risk for the “failing” heart. The scaling exponents could determine whether the subjects are under sick or healthy conditions on the basis of cardiac physiology.

Keywords: Alternans Heartbeat, Animal models, Crustaceans, DFA.

1. INTRODUCTION

We know that it is typical that a certain type of tree, such as the Japanese persimmon tree, bears rich fruits every other year. Global atmospheric oxygen has also bistability [1]. Therefore period-2 is an intriguing rhythm in nature and the cardiac “Alternans” is another typical period-2 as well. In cardiac period-2, the heartbeat is alternating the amplitude/interval from beat to beat on the electrocardiogram (EKG). Alternans has remained an electrocardiographic curiosity for more than three quarters of a century [2, 3]. Recently, alternans is recognized as a marker for patients at an increased risk of sudden cardiac death [2-7]. In our physiological experiments on the hearts in the 1980's, we have noticed that alternans is frequently observable with the

“isolated” hearts of crustaceans (Note: At this isolated condition the heart sooner or later dies in the experimental dish). We soon realized that alternans is a sign of future cardiac cessation. Presently, some authors believe that it is the harbinger for sudden death [2, 6]. So we came back to the crustaceans, because we know the crustaceans are outstanding models. However, details of alternans have not been studied in crustaceans. So we considered that we could study this intriguing rhythm by the detrended fluctuation analysis (DFA), since we have already demonstrated that the DFA can distinguish a normal heart (intact heart) from an unhealthy heart (isolated heart) in animal models [8]. We finally revealed that alternans and lowered scaling exponent occurred concurrently. In this report, we demonstrate that the DFA is an advantageous tool in analyzing, diagnosing and managing the dysfunction of the heart.

2. METHODS

DFA methods

Background: The DFA is an analytical method in physics, based on the concept of “scaling” [9, 28] The DFA was applied to understand a “critical phenomenon” [9-11]. Systems near critical points exhibit self-similar properties. Systems that exhibit self-similar properties are believed to be invariant under a transformation of scale. Finally the DFA was expected to apply to any biological system, which has the property of scaling. Stanley and colleagues have considered that the heartbeat fluctuation is a phenomenon, which has the property of scaling. They first applied the scaling-concept to a biological data in the late 80's to early 90's [10, 11]. They emphasized on its potential utility in life science [11]. However, although the

nonlinear method is increasingly advancing, a biomedical computation on the heart seems not to have matured technologically. Indeed we still ask us: Can we decode the fluctuations in cardiac rhythms to better diagnose a human disease?

Our own programs: We made our own programs for measuring the beat-to-beat intervals and for calculating the approximate scaling exponent of the interval time series. These DFA-computation methods have already been explained elsewhere [12]. We describe it here briefly on the most basic level.

Firstly, we obtain the heartbeat data digitized at 1 KHz. About 3,000 beats are necessary for a reliable calculation of an approximate scaling exponent. Usually a continuous record for about 50 minutes at a single testing is required. We use an EKG or finger pressure pulses.

Secondly, our own program captured pulse peaks. Using this program, we identified the true-heartbeat-peaks in terms of the time of peaks appearances. In this procedure we were able to reject unavoidable noise-false peaks. As a result we obtained a sequence of peak time $\{P_i\}$. This $\{P_i\}$ involved all true-heartbeat-peaks from the first peak to the ending peaks, usually ca. 3,000 peaks.

Practically, by eye-observation on the PC screen, all real peaks were identified and all noise peaks (by movement of the subject) were removed. Experiences on neurobiology and cardiac physiology are necessary when determining whether a spike-pulse is a cardiac signal or a noise signal. Finally our eyes confirmed, read, these entire beats.

Thirdly, using our own program, intervals of the heartbeat $\{I_i\}$, such as the R-R intervals of an EKG, were calculated, which is defined as:

$$\{P_{i+1} - P_i\} = \{I_i\} \quad (1)$$

Fourth, the mean-interval was calculated, which is defined as:

$$\langle I \rangle = \frac{1}{N} \sum_{k=1}^N I_k \quad (2)$$

where N is the total number of interval data.

Fifth, the fluctuation value was calculated by removing a mean value from each interval data, which is defined as:

$$Y_i = I_i - \langle I \rangle \quad (3)$$

Sixth, a set of beat-interval-fluctuation data $\{B_i\}$ upon which we do the DFA, was obtained by adding each value derived from the equation (3), which is defined as:

$$B_i = \sum_{k=0}^i Y_k \quad (4)$$

Here the maximum number of i is the total number of the data point, i.e., the total number of peaks in a recording. In the next step, we determine a box size, τ (TAU), which represents the numbers of beats in a box and which can range from 1 to a

maximum. Maximum TAU can be the total number of heartbeats to be studied. For the reliable calculation of the approximate scaling exponent, the number of total heartbeats is hopefully greater than 3,000. If TAU is 300, for example, we can obtain 10 boxes.

Seventh, we calculate the variance, successively, as expressed by Eqs. (5) and (6).

$$B'_i = B_i - f_{n,\tau}(i) \quad (5)$$

Here, n is the number of boxes at a box size τ (TAU). In each box, we performed the linear least-square fit with a polynomial function of 4th order. Then we made a detrended time series $\{B'_i\}$ as Eq. (5).

$$F^2(\tau) = \langle (B'_{i+\tau} - B'_i)^2 \rangle \quad (6)$$

Here we adopted a method for "standard deviation analysis." This method is probably the most natural method of variance detection [see ref 18]. Mathematically, this is a known method for studying "random walk" time-series.

Meantime, Peng et al. [10] analyzed the heartbeat as we did. But they used a different idea than ours. They considered that the behavior of the heartbeat fluctuation is a phenomena belonging to the "critical" phenomena. (A "critical" phenomenon is involved in a "Random-walk" phenomenon.) Our consideration is that the behavior of a heartbeat fluctuation is a phenomenon, involved in a "random walk" type phenomenon. Peng et al. [10] used a much a stricter concept than ours. There was no mathematical proof, whether Peng's or ours is feasible for the heartbeat analysis, since the reality of this complex system is still under study. Probably the important point will be if the heartbeat fluctuation is a "critical" phenomenon or not. What we wondered, if the physiological homeostasis is a "critical" phenomena or not. As for the biomedical computing technology, we prefer a tangible method to uncover "something is wrong with the heart" instead of "what is the causality of a failing heart." So far, no one can deny that the heartbeat fluctuation belongs to the "critical" phenomena, but also there is no proof for that. We chose technically "Random walk." The idea of "random walk" is applicable to biology; a broad area from a biochemical reaction pathway to animal's foraging strategies [27]. "Random walk time series" was made by the Eq. (4). The present DFA study is a typical example for the "random walk" analysis on the heartbeats.

Eighth, finally, we plotted a variance against the box size. Then the scaling exponent is calculated, by looking at the slope (see Fig. 8 for an example).

Most of computations mentioned above are automated although we still need, in part, keyboard manipulations on PC. Our automatic program is helpful and reliable to distinguish a normal state of heart (scaling exponent exhibits near 1.0) from a sick state of heart (high or low exponent). In this report, we mention the three categories in differentiation: Normal, high, and low.

EKG and finger pulse: From human subjects we mostly used the finger pulse recording with a Piezo-crystal mechanic-electric sensor, connected to a Power Lab System (AD Instruments, Australia). The EKG recordings from crustacean model animals were done by implanted permanent metal

electrodes, which are connected to the Power Lab System. With this recording, animals walked around in the container.

It is most important to us, that animal models are healthy before an investigation. We captured all specimens from a natural habitat by ourselves. We observed with our very own eyes that all animals, which were used, were naturally healthy, before starting any experiments.

During the decades of biological research on crustaceans, many famous invertebrate scientists (i.e. some distinguished cardiac researchers: J. S. Alexandrovicz in 1930's, C. A. G. Wiersma in 1940's, D. M. Maynard in 1950's, I. M. Cooke in 1970's, and McMahon and Wilkens in 1980's) have studied the hearts and its surrounding organs, investigating every accessible detail of its physiology and morphology, from nerves to muscles, from transmitters to hormones and from circulatory/respiratory control, to relevance and to behavioral integration. Thus it was that the crustacean cardiovascular systems have been well documented, as reviewed by Cooke [22] and Richter [23]. We, ourselves, have also been studying the heart of this animal [24].

3. RESULTS

It is well known that the human heart rate goes up to over 200 beats per min. when a life comes to an end (Dr. Umeda, Tokyo Univ. Med.; Dr. Shimoda, Tokyo Women Med. Univ., personal communication). Literally, a similar observation has been reported during this period accompanied by a brain death (see Fig.1 of ref 13).

In an animal model, we observed an increase of heart rates during the dying period (Fig. 1). At terminal condition (see N, O, and P in Fig. 1), the heart rate attained over 300 beats per min. This model experiment indeed demonstrated a strong resemblance of a cardiac control mechanism, between lower animals and humans.

The aforementioned examples give evidence that: "Animals are models of humans." The similarity (a general idea that animals evolved from a common ancestor) was first noticed by a German scientist, Ernst Haeckel. There is another reason to use lower animals. Ethics is of course a big requisition. But we know Gehring's discovery of a gene, named homeobox: To our surprise at that time, an identical gene named "pax-6" was found to work in both, in fly's eyes and mouse's eyes at a embryonic stage for developing an optical sensory organ [14, 15]. In 2007, further strong evidence has been presented with a new data of the origin of the central nervous system: The role of genes, which patterns the nervous system in embryos of choldates (like humans) and annelids (a lower animal) are surprisingly similar and the mechanism is inherited almost unchanged from lower animals to higher animals through a long period of geology [16, 17].

In this isopod specimen (Fig. 1), interestingly, a significant alternans is seen when they are dying (H, I, J, and K, Fig. 1). Its alternans lasted for not long, therefore we did not perform the DFA on this data.

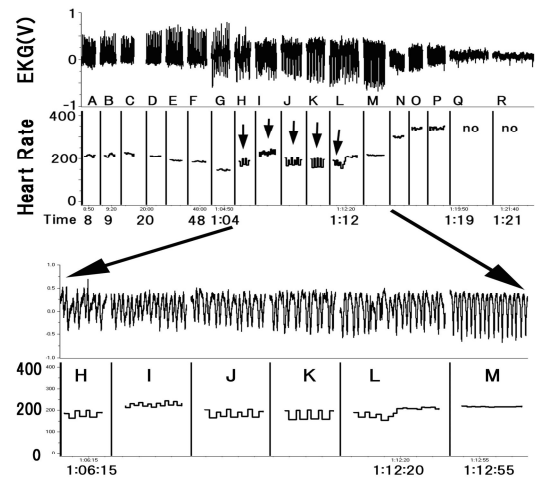


Figure1. Changes in heart rate of a dying crustacean, isopods, *Ligia exotica*. Two metal electrodes, 200 micrometer in diameter, were placed on the heart by penetrating them through the dorsal carapace. A sticky tape on a cardboard immobilized the animal. Records are shown intermittently for about one hour and 20 minutes. From H to M, the EKG and heart rates are enlarged. Small 5 arrows indicate alternans, which is observable at H-L. From Q to R, no prominent EKG signals were observed. Only small sized signals with sporadically appearance were seen.

Finally, we succeeded to calculate the scaling exponent of "alternans." The DFA revealed that the alternans exhibits a low approximate scaling exponent (Fig. 2).

The crab had a normal/healthy-scaling exponent (Fig. 3, which is 11 days before Fig. 2) when an EKG recording was first done, right after its collection in the South Pacific, on Bonin Island. Therefore, alternans and low exponents would be a sign of illness.

In models, we found that the isolated heart, which can repeat contractions for hours in a dish, often exhibits alternans (Fig. 4). The DFA again revealed that the scaling exponent of alternans is low (Fig. 4). We therefore tested three other isolated hearts of these lobster species, all of which exhibited alternans (data not shown), and the scaling exponent of the alternans' heart was low. A healthy lobster before a dissection, however, exhibits a normal scaling exponent (Fig. 5).

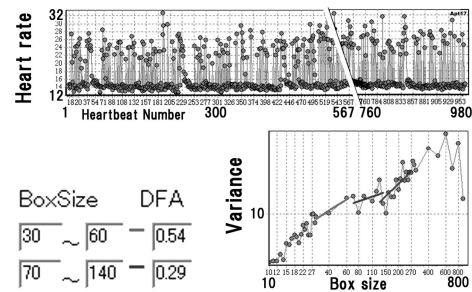


Figure 2. Mitten crab DFA. This crab was sick and did not move actively, because its heart was beating irregularly (period-2 type, thus its pattern is alternans). The approximate scaling exponent for alternans was low. Short-term box-size "30 beat ~ 60 beat" and "70 beat ~ 140 beat" were calculated, 0.54 and 0.29, respectively.

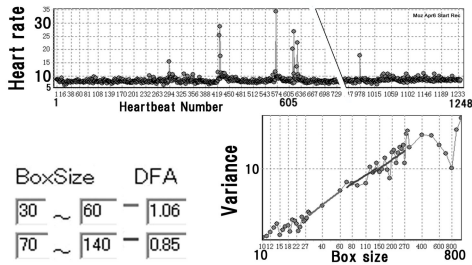


Figure 3. Mitten crab DFA. The same crab shown in Figs. 2. But the recording was immediately after the specimen was captured. The approximate scaling exponent was not low but about 1.0 (cf., Fig. 2). The crab's heart seemed to be normal on the first day of the experiment.

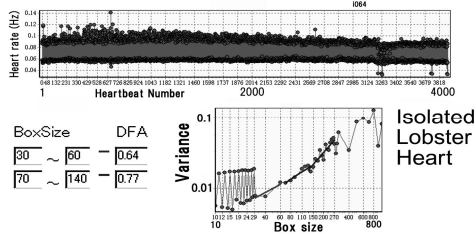


Figure 4. Isolated heart of a spiny lobster, *Panulirus japonicus*. Alternans appeared here all the way down from the first beat to 4,000th beat. The scaling exponent was found to be low.

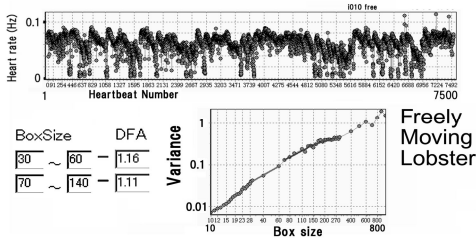


Figure 5. The DFA of an intact heart of a spiny lobster, *Panulirus japonicus*. No alternans appeared. The heart rate (shown in Hz) frequently dropped down, so-called bradycardia. This is the well known type of heartbeats in normal crabs and lobsters, first described by Wilkens et al. [19]. The present DFA revealed that the scaling exponent is normal (nearly equal to 1.0) when the lobster is healthy and freely moving in the tank.

After model experiments, we proceeded to study the human heartbeat. The finger pulse of a volunteer was tested (Figs. 6 and 7). Similar to the models, human alternans exhibited a low exponent (Fig. 7). This subject, a 65 years old female, is physically weak, and she cannot walk a long distance. However, she talked with an energetic attitude. She was at first nervous because of us (we did not realize it and even she herself didn't notice it), but finally she got accustomed to our finger pulse testing task and then she was relaxed. Hours later, we were surprised to note that her alternans decreased in numbers. The heart reflects the mind. We observed that alternans is coupled with the psychological condition. This is evidence that an impulse discharge frequency of the autonomic nervous system changes the condition of the heart.

It is known that healthy human hearts exhibit a scaling exponent of 1.0 [11]. The present analysis revealed the same results (data not shown, from age 9 to 82, 33 subjects). So, the exponent 1.0 is the sign of "healthy heart in healthy body." In the future, health checkups may use this diagnostic idea.

It is not known what exponents the sick human hearts show. As aforementioned, a human alternans heart exhibits a low scaling exponent (Figs. 6 and 7). It still remains to be investigated, because there may be other types of a diseased heart. In crab hearts we have already found out that a sudden-death heart exhibited a high exponent and a dying heart exhibited a gradual decay of exponent [20]. Here we tested our DFA computation on diseased human hearts.

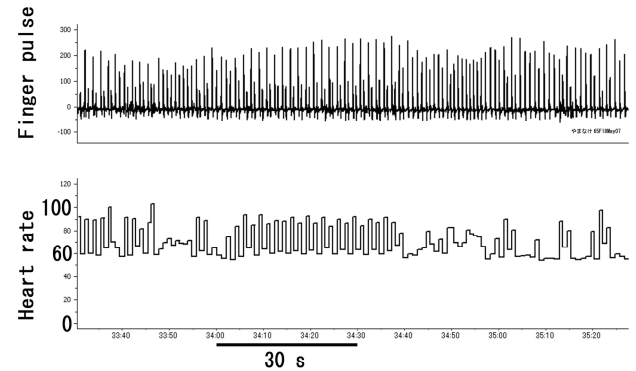


Figure 6. Human alternans. A woman, who volunteered, age 65. Upper trace, recording of finger pulses. Lower trace, heart rate. Both amplitudes alternans and intervals alternans can be seen.

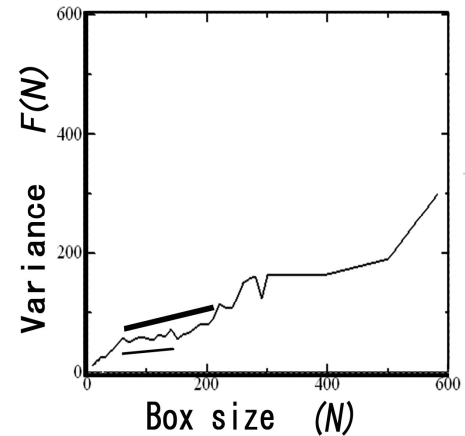


Figure 7. Result of the DFA of human alternans shown in Fig. 7. Thick and thin straight lines represent a slope obtained from a different box-size-length. The slope determines the scaling exponent. The 45-degree slope (not shown here) gives the scaling exponent 1.0 which represents that the heart is totally healthy. The two lines are obviously less steep than the 45-degree slope. This argument draws a conclusion: The alternans significantly lowers the scaling exponent.

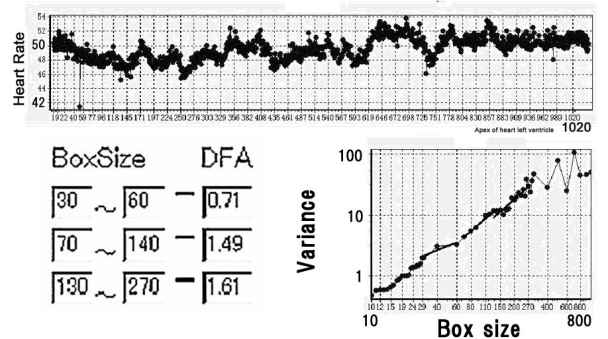


Figure 8. Ischemic heart disease. The scaling exponent is high, see Box size 70-270.

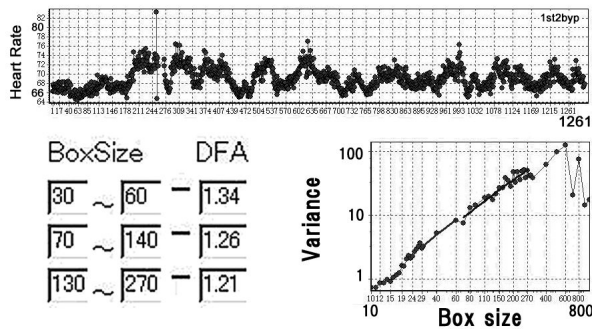


Figure 9. A bypass surgery subject. The scaling exponent is high, see Box size 30-270.

A subject (male age 60), whose heartbeats are shown in Fig. 8, once visited us and told us that he had a problem with his heart. He did not give us any other information about his heart, but challenged us and ordered: "Check my heartbeat with your machine, and tell me what is wrong with my heart." The result of the analysis is shown in Fig. 8. I replied to him: "According to our experience, I am sorry to tell you, that I diagnosed your heart and is indeed having a problem with its heartbeats. I wonder if there is a partially injured myocardium in your case, such as the ischemic heart." After listening to my opinion he explained that his heart has an implanted defibrillator, because of the damage of an apex of the heart in its left ventricle. He continued: "Please call me if your analysis machine will be commercially available in the future. I will buy it."

There is another example analysis of a human diseased heart. A professor of Physiology at an Indonesian National University came to meet us when we visited his medical school for a lecture. He told me that he had a bypass surgery of his heart, before we started to analyze his heartbeat. Finally, we found out that he had a high exponent, way over 1.0 (not shown).

The subject shown in Fig. 9 is a case study: A man (age 65) has had a bypass operation 10 month before this measurement. One of the coronary artery had received a stent placement. Two other coronary arteries received bypass operations. This heart again exhibited a high exponent as shown in Fig. 9.

4. DISCUSSION

A real time observation of both, EKG-signal and biological condition of a specimen, is important to deduce the physiological meaning from the scaling exponent. We performed all experimentations with our own eyes in front of us, together with the on-line EKG or on-line pulse recordings. We have engaged in both, recordings and analysis, by the same scientists. We thus were able to interpret the relationship between subjects' behavior, EKG waveform and DFA exponent. This is one important point of advantage in this study.

Other important points of our present studies are that we made our own PC program, which assisted the accuracy of the peak-identification of heartbeats and then the calculation of the scaling exponent. Our DFA program shortened the period length of time-consuming analysis. We are currently developing a much simpler program for a practical use. It is a series of automated calculations, intended to be used by non-physicists who have no physical training. The program freed us from

complicated PC tasks before obtaining the result of a calculation of the scaling exponent. As a result, we will be able to handle many data, sampled from various subjects.

It is said that alternans is the harbinger of a sudden death of humans. That was true in dying models. However, alternans was also detectable in non-dying occasions of models, for example, during emotional changes (Fig. 11) [21]. This is evidence that under stressful psychological circumstances and invoke autonomic acceleratory commands, it can lead to trigger alternans in the heart. In the early to mid-1990's, a series of clinical trials demonstrated that an adrenergic blockade (which is a pharmacological blockade of the sympathetic acceleratory effects on the heart) was actually cardio-protective, particularly in post-myocardial infarction (MI) patients.

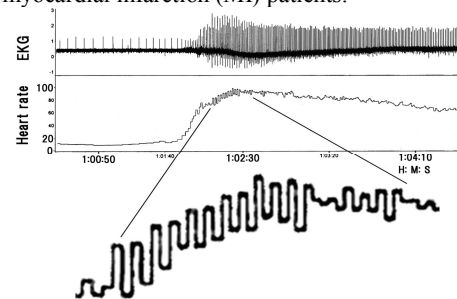


Figure 11. EKG and heart rate recordings from a freely moving crayfish, *Procambarus clarkii*. Alternans can be seen at a rising phase of a heart rate tachogram. This occurred spontaneously when the animal was in the shelter. An arousal from sleep might happen. Generally, alternans occurs at a top speed of a cardiac acceleration.

Physiological rhythms are considered to be generated by nonlinear dynamical systems [25]. There is evidence that physiological signals under healthy condition have a fractal temporal structure [26]. Free-running physiological systems are often characterized by $1/f$ -like scaling of the power spectra, $S(f)$, where f is the frequency [27]. This type of spectral density is often called the $1/f$ spectrum and such fluctuations are called $1/f$ fluctuations. The $1/f$ fluctuations were well documented in the heartbeat of normal persons [27]. After all, we noticed that a disease often leads to alterations from a normal to a pathological rhythm, and then we distinguished normal conditions from pathological conditions with our DFA program, by computing the scaling exponent for the healthy and diseased heart [28].

5. CONCLUDING REMARKS

Alternans lowers the approximate scaling exponent. An ischemic heart pushes the scaling exponent up, way over 1.0. In our present study, the DFA identified a typical diseased heart, the ischemic heart, which has a partially damaged myocardium. This might be good news in the future for persons, who might potentially have a sudden death, to prevent it! Indeed cardiac failure has a principal underlying etiology of ischemic damage from a vascular insufficiency (which is a decreased oxygen supply, particularly from coronary arteries). The life science may have profited from the ability of the DAF. The DFA provides analytical strategies, if models and human beings live on all functions under the same set of physical laws. This is still a testable hypothesis.

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