1/f FLUCTUATIONS IN BIOLOGICAL SYSTEMS

Toshimitsu Musha
Teikyo Heisei University and
Brain Functions Laboratory, Inc.
KSP Bldg.E211, Sakado, Takatsu, Kawasaki, JAPAN 213
E-mail: musha@st.rim.or.jp
Mitsuaki Yamamoto
Laboratory of Neurophysiology and Bioinformatics
Graduate School of Information Science, Tohoku University

Abstract

1/f fluctuations are ubiquitous in nature. Especially the electric conductivity of electric conductors in general, whatever they may be, is subject to *1/f* fluctuations. When an electric current passes through an electric conductor, voltage drop across it shows this type of fluctuation as noise. The highly stabilized quartz clock and the atomic clock have the same type of fluctuations in the time they show [1]. The loss part of dielectric constant also shows *1/f* fluctuations[2]. the time standard also has The interdisciplinary symposium has been organized every two years since 1977 because its physical mechanism is a keen interest of physicists as well as of engineers The mechanism of this noise or fluctuation has been a keen interest of engineers and physicists but no theory has been proposed which is widely accepted. by hence any electric devices have *1/f* noise in voltage and current. On the other hand, *1/f* fluctuations have been found in biological systems. It seems that this type of fluctuation plays a crucial role in maintaining life in biological body. The present author makes a review of different types of *1/f* fluctuations which have been observed in various levels of biological body. The present review is a modification of the review which was made at Conference on Noise in Physical Systems and *1/f* Fluctuations in Palanga, Lithuania, 1995.

Introduction

The *1/f* fluctuation is widely observed in nature, specially in electric conductors which gives rise to *1/f* voltage fluctuations in electric devices. *1/f* fluctuations in biology was first observed by Verveen and his colleagues. They applied low frequency stimulation on a nerve axon and found that the occurrence of action potentials was random. They thought it was attributed to noise in the membrane potential, and measured the voltage noise of frog node of Ranvier which are small cylindrical surfaces of active nerve membrane in myelinated nerve fibers. The first measurement of the membrane *1/f* noise was done by Verveen and Derksen near the resting potential[3], and the review was given at the *1/f* symposium in 1977[4]. After that time various findings were made about biological rhythm fluctuations which are subject to *1/f* fluctuations.

Noise is usually regarded as unwanted fluctuations which mask signals we want to get. People are trying to eliminate noise to see something behind the noise. When we look at Nature with an open mind we always see noise or fluctuations. Values of biological parameters are always fluctuating in time. This is quite natural because otherwise the biological body would not be alive. Therefore, fluctuation is particularly important for living bodies, and sometimes fluctuation of biological rhythm is manifesting *vitality*.

The biological rhythm is represented as a point process, and the power spectral density (psd) of a point process depends on the model to which the Fourier transform or FFT is applied. When the biological rhythm is almost periodic, small deviations from a complete periodicity are regarded as sampled fluctuations at equal time intervals and the ordinary FFT is applied on it. In case the rhythm is remote from complete periodicity the psd depends on the model to which FFT is applied. In very low Fourier frequencies the psd is insensitive to the model. Our interest is what kind of biological rhythm phenomena is subject to *1/f* fluctuations and what its mechanism is. Examples of biological *1/f* fluctuations in various levels are considered below.

The Cellular Level #1: Self-Discharge of Neurons

African snail has giant neurons as large as 0.2 mm, and some of them are making almost regular self-discharges; sequences of action potential im-

(0-7803-4262-3/97/$10.00 (C) 1997 IEEE)

pulses control motion of the snail body. Neurons, which are called TAN (tonically autoactive neurons) make spontaneous discharges, and the discharge interval is slightly fluctuating from discharge to discharge. One of the giant neurons was disconnected from the body of a snail and immersed in physiological saline water which was electrically grounded. A glass micropipette was inserted into the cell body and the membrane potential was recorded. It is 70~80 mV lower than the outside, and an ion current inflow increases the membrane potential until it reaches a threshold value, where it rises sharply and comes back to the resting potential, generating a spike potential. The psd of interval fluctuations is plotted in Fig.1[5]. The relation of discharge interval fluctuations to membrane potential fluctuations was investigated by computer simulation which is described below.

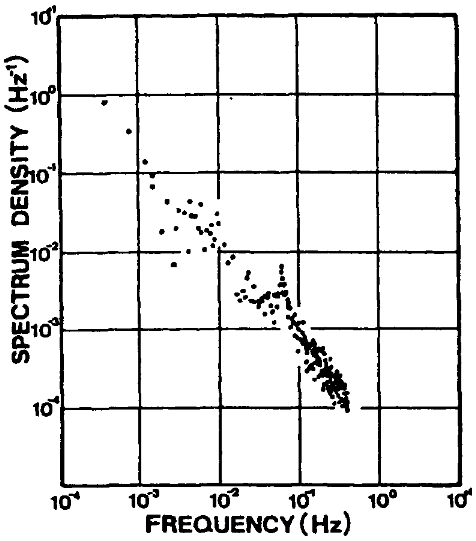

Fig.1 Psd of spike interval fluctuations of an *African snail.*

The Cellular Level #2: Computer Simulation of Neuronal Self-Discharges

The membrane potential increases as a result of ion current inflow; when it reaches a threshold level, it fires and the potential returns to the resting potential. We have examined three cases where fluctuation is in (1) the membrane potential rise, and (2) the threshold level, as shown in Fig.2. The psd in (1) has the same frequency dependence as that of the time derivative of the membrane potential, which is proportional to fluctuations of ion current inflow. Therefore, if ion currents have $1/f$ fluctuations, the observed psd is derived; this happens when the conductance of the membrane is subject to $1/f$ fluctuations. This situation is quite probable judging from the fact that electric conductance of electric conductors in general has $1/f$ fluctuations. In (2) the discharge interval fluctuation has the same frequency

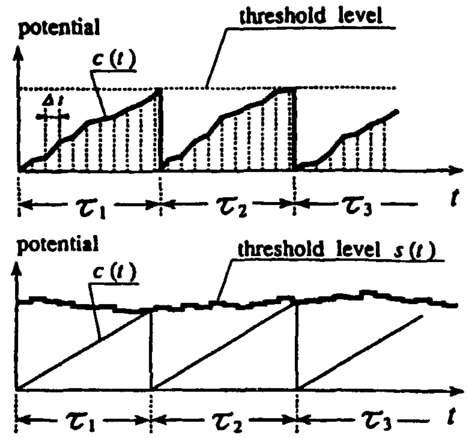

Fig.2 Two models of membrane potential fluctuations in the computer simulation.

dependence as the threshold fluctuation. The membrane potential depends on difference of ion concentrations inside and outside of the membrane; if local ion concentration is making $1/f$ fluctuations, (2) can explain the observation. If ion inflow and threshold have psd of $1/f$ type, the discharge interval also has $1/f$ fluctuations.

The Cellular Level #3: Chick Embryo

Yamauchi et al.[6] made a very interesting observation about R-R interval fluctuations of ECG of a chick embryo. In the initial stage of incubation, the heart rate fluctuations were random. In the last 3-4 days of incubation, it became of $1/f$ type over a frequency range of 0.01-0.1 Hz. This fact suggests that establishment of $1/f$ fluctuations of the heart rate is related to development of the nervous control system.

The Cellular Level #4: Brain Neurons

Action potential impulses in the brain of a cat were measured with microelectrodes inserted in brain neurons. During REM sleep $1/f^n$-type of fluctuations of action potential modulation were observed from 0.01 to 1 Hz where n ranged from 0.5 to 1.5 in several groups of neurons as the mesencephalic reticular formation, the ventrobasal complex of the thalamus, the primary somatosensory area of the cerebral cortex, the hippocampal pyramidal and θ neurons[7],[8],[9]. These neuronal activity shows random fluctuations during the slow wave sleep. The psd strongly depends on the state of consciousness. Typical examples are shown in Fig.3[10].

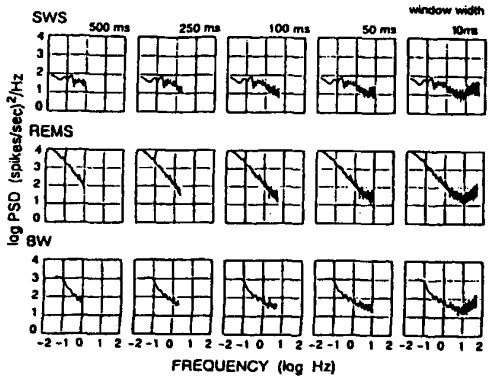

Fig. 3 Psd of a single neuronal activities of the mesencephalic reticular formation of a cat during sleep-wake cycle.

The Cellular Level #5: Axon

The axon is a strongly nonlinear transmission line of electric signals which allows conduction of action potential impulses. The conduction speed of an action potential impulse is influenced by the other impulses, and hence modulation of action potential impulses, which carries biological information, is distorted during the conduction. With a giant axon of squid Musha et al.[11] found that the modulation reaches a stable state after traveling a short distance, where the modulation has a $1/f$ spectrum. A giant axon was removed from a body of squid and laid in a chamber filled with sea water. An electrode was inserted into the axon from one end and current impulse was applied between the electrode and sea water to induce an action potential impulse. The effective length of the axon was 4 cm. Initially random impulses were launched at one end of the axon and detected at the other end. After a traveling over 4 cm the impulse waveforms were recorded, and the waveform was given to the input end of the axon to induce action potentials. Psd's after such repetitions were evaluated and the result is shown in Fig.4. Traces from the bottom refer to impulse sequences of original, after a first travel, second travel, etc. After a single travel the modulation has already acquired $1/f^n$-like spectrum where $n = 1 \sim 1.5$; repetition did not alter the modulation after that. It then follows that both generation(self-discharges) and transmission of biological signals are subject to $1/f$-like fluctuations.

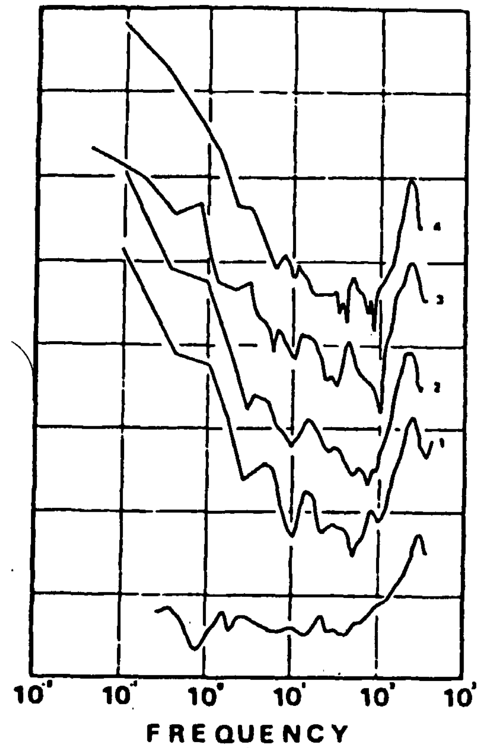

Fig.4 Psd of action potential impulses for repeated conduction from the bottom to the top.

The Organ Level #1:
Hear Rate and Blood Pressure

The initial finding of $1/f$ fluctuations in the organ level was reported by Musha and his student Kobayashi[12]. In 1982 they reported that R-R interval fluctuations of ECG had $1/f$ spectrum in a frequency range from 1×10^{-4} to 2×10^{-2} Hz over 10 hours as shown in Fig.5. Saul et al.[13] confirmed this discovery with 24-hour ambulatory records over a frequency range from 10^{-5} to 10^{-1} Hz although the reliability of the frequency dependence (spectral exponent) is not high below 10^{-4} Hz. Recently 24-hour heart rate variability (HRV) was observed by Castiglioni et al.[14] in which a significant difference in the mean HRV spectral exponent n was noticed between young and old subjects. Subjects below 40 years old had $n = 1.05$ whereas subjects over 60 years old had $n = 1.27$ for $10^{-4}\sim10^{-2}$ Hz where the heart rates are more correlated to each other. Yamamoto and Hughson[15] showed that the spectral exponent for 10^{-2} through 1 Hz was steepened to 2 by parasympathetic blockade but not influenced by sympathetic blockade. Moreover, sympathetic blockade led to flattening of the spectrum below 10^{-2} Hz. During the REM sleep the spectrum is close to the $1/f$ type similar to the result in Fig.3., and it is almost flat in the slow-wave sleep or nREM sleep[16].

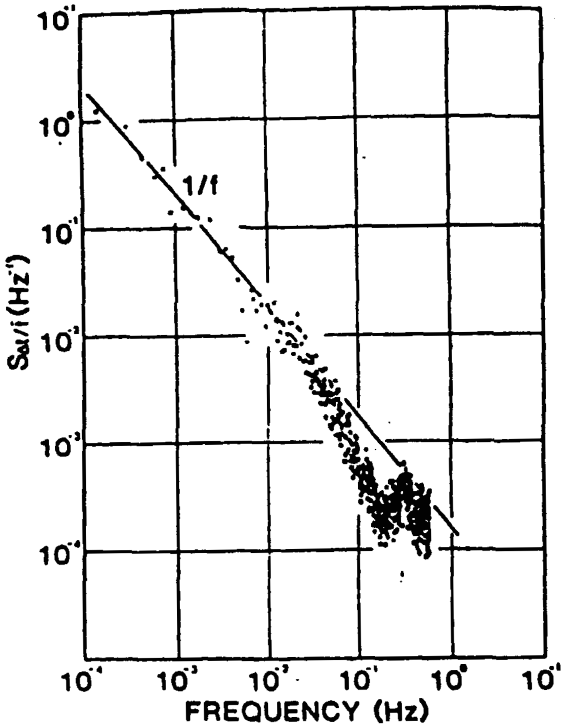

Fig.5 Heart rate fluctuations

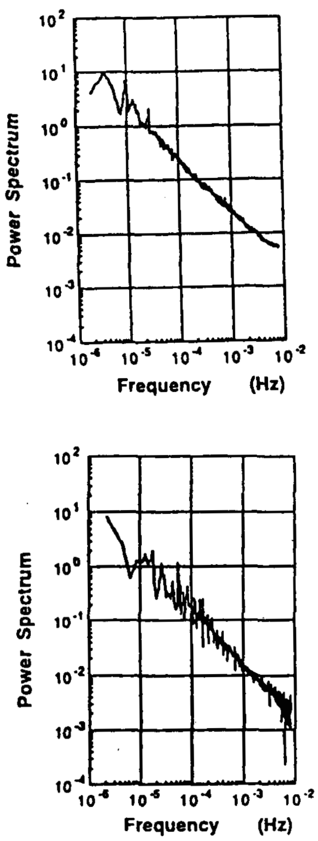

Fig.6 Heart rate fluctuations of two brain-death patients for consecutive 6 days.

According to Tamura et al.[17] the heart rate fluctuations of brain-death patients were recorded, and the psd over 6 days is plotted for one the patients. The result is shown in Fig. 6 in which the spectrum is of $1/f$ type over 10^{-6} to 10^{-2} Hz and the spectral level was lower than that of normal subjects. The heartbeat of brain-death patient is controlled by the cardiac automaticity without central nervous control and till 1/f fluctuations were observed but at lower level without control by the sympathetic and parasympathetic nervous systems.

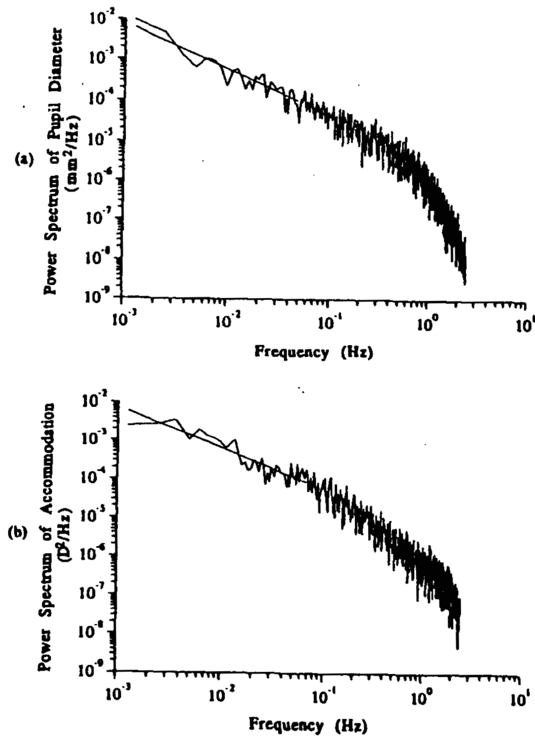

Fig.7 Fluctuations of focal accommodation (a) and pupil diameter (b).

The Organ Level #2: Pupil Diameter

The pupil diameter and focal accommodation in man vary around the optimum values even when a subject gazes at a fixed target[18],[19]. Their fluctuations under a constant illumination. Therefore, their fluctuations are partly originated from changes in autonomic nervous activity. The psd over 45 min is shown in Fig. 7[20].

The Organ Level #3: Alpha Rhythm

The alpha rhythm of EEG has a frequency range of 8~13 Hz and is observable when a subject keeps eyes closed. The potential waveform of this rhythm is close to sinusoid, but its instantaneous period is slightly fluctuating in time. The instantaneous frequency is defined as a reciprocal of adjacent up-going zero-crossing interval. Examples of the psd are shown in Fig.8. In a normal state the spectrum is very close to the $1/f$ type. When the subject feels pains the psd is flattened. The psd is very sensitive to the state of mind.

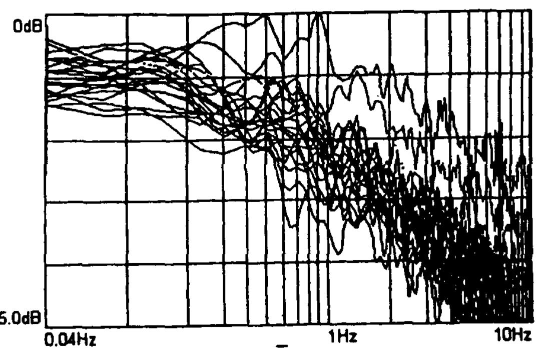

Fig.8 Fluctuations of the EEG alpha rhythm period.

The Organ Level #4:
Peripheral Blood Conductance

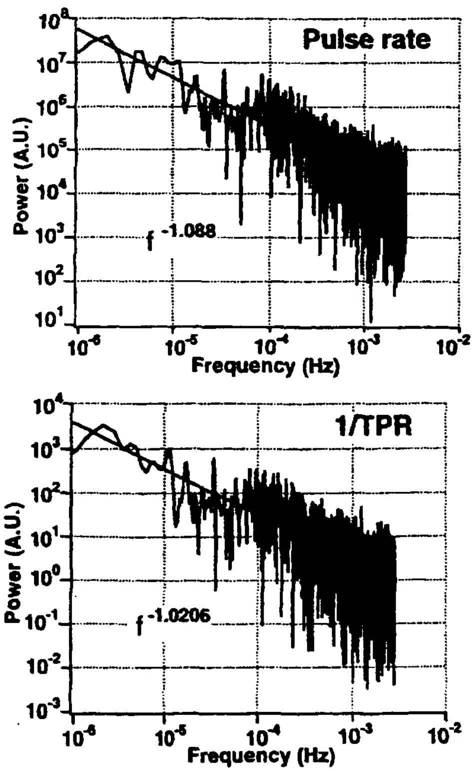

Fig.9 Psd of fluctuations in the heart rate of an artificial heart, peripheral conductance 1/TPR from 10-day data for the total artificial heart with automatic 1/R control.

In the total artificial heart, there is no fluctuation of the pulse rate when the drive condition is fixed. Abe et al.[21],[22] tried control of the pumping rate of an artificial-heart of blood pumps set outside the body of an adult female goat to be adaptive to the peripheral blood conductance. The peripheral blood conductance is estimated from the pulse rate, aortic pressure and right atrial pressure. The pulse rate was controlled to be proportional to the peripheral blood conductance. As a result, the goat acquired a life as long as 532 days. This control technique is called the 1/R control. Power spectral densities of the heart rate of an artificial heart, peripheral conductance 1/TPR are shown in Fig.9. The spectral exponent is 1.088 and 1.02 in the heart rate and 1/TPR, respectively, over 10^{-6} to 10^{-3} Hz. This artificial heart follows requirement of blood of the biological body, and as a result it is subject to $1/f$ fluctuations.

The Behavioral Level: Clapping

One of the typical behaviors of the body is clapping. Its interval fluctuations were first investigated by Musha et al.[23] A microswitch was placed on a palm and it was tapped with the other hand. Usually mean clapping interval is 1/2~1/3 s. The clapping was repeated 3,000 times; this sequence was repeated 10 time with 10 min breaks. These tasks were tried with 5 normal subjects in two different modes; one was in listening to metronome ticking and the other was without metronome ticking. The variability of interval fluctuations was almost independent of the mode, but the spectra were entirely different as shown in Fig.8.

When a subject listened to metronome ticking, the psd was almost flat or going down for lower frequencies, whereas it was proportional to $1/f^{1.2}$ ~$1/f^{1.3}$ for all the subjects we examined.

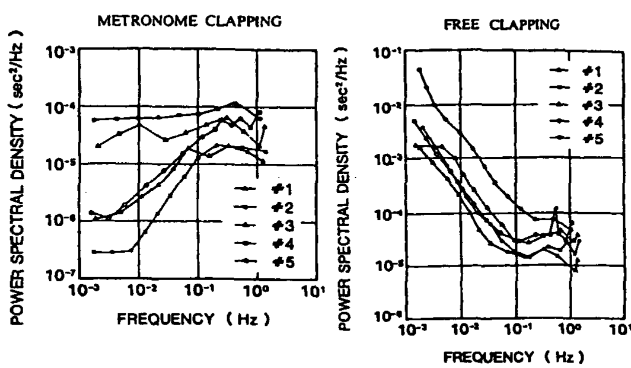

Fig.10 Clapping interval fluctuations with and without metronome ticking.

When the subject relied on a metronome ticking to keep clapping, correlation among intervals was lost. When, on the other hand, the subject was free from metronome ticking, $1/f$ When the subject relied on a metronome ticking to keep clapping, correlation among clapping biological fluctuations were observed in the clapping rhythm.

Conclusions

Judging from these observations it seems that the biological rhythm is basically subject to $1/f$ fluctuations from cellular to behavioral levels. There are three possible generation mechanisms of $1/f$-like rhythm fluctuations. Firstly, $1/f$ ionic conductance fluctuations of a cellular membrane would modulate ion current flowing into a biological cell which would modulate discharge intervals of the neuron. Secondly, a Hopfield-type of artificial neural network consisting of neurons, each of which has binary states 0 and 1 and has connections with all other neurons, show 1/f level fluctuations when random noise is given to each neuron with a proper inhibitory threshold.[24] Thirdly, we mention the clustering Poisson process in which sequences of randomly occurring point events (clusters) overlap each other. When probability of for cluster with size N is proportional to $1/N$, the clustering Poison process has $1/f$ spectrum over a certain frequency range. [25]

As regards biological phenomena, we often ask "How?" and "Why?". The question of "Why?" is still unsolved. "$1/f$ fluctuations" was first found in electronic devices, and now it is ubiquitous in nature. The physical *why* is still unsolved, but this phenomenon is very basic in physics as well as in biology.

References

[1] D. W. Allan, *Proc. Symp. on 1/f Fluctuations* (ed. T. Musha, Tokyo, 1977), pp.158-172.

[2] T. Musha, Akira Nakajima and H. Akabane, *Jpn J. Appl. Phys*. vol.27, pp.L311-L313, 1988.

[3] A. A. Verveen and H. E. Derksen, *Kybernetik*, vol.2, 152 , 1965.

[4] R. J. van den Berg, E. Siebenga,J. de Goede, W. E. Moolenar and A. A. Verveen, *Proc. Symp. on 1/f Fluctuations* (ed. T. Musha, Tokyo, 1977), pp.97-105.

[5] T. Musha, H. Takeuchi and K. Inoue, *IEEE Trans. Biomed. Eng.*, **BME-30**, 194-197 (1983).

[6] Y. Yamauchi, T. Nakamura and G. Kawahara, *Proc. 8th Symposium on Biological and Physiological Engineering*, 71-74 (1994).

[7] M., Yamamoto, H. Nakahama, K. Shima, T. Kodama and H. Mushiake, *Brain Res.*, 366, 279-289(1986).

[8] H. Mushiake,K. Shima H. Nakahama and M. Yamamoto, *J. Neurophysiol.*, 60, 925-939(1988).

[9] T. Kodama, H. Mushiake, K/ Shima, H. Nakahama and M. Yamamoto, *Brain Res*, 487, 26-34(1989).

[10] M. Yamamoto, M. Nakao, Y. Mizutani, T. Takahashi, K. Watanabe, H. Arai and N. Sasaki, *Methods in Information in Medicine*, (E.K.Schattauer Verlagsgesellschaft mbH) , 1994, 125-128.

[11] T. Musha, Y. Kosugi, G. Matsumoto and M. Suzuki, *IEEE Trans. Biomed. Eng.*, **BME-28**, 616-623 (1981).

[12] M. Kobayashi and T. Musha, *IEEE Trans. Biomed. Eng.*, **BME-29**, 456-457(1982).

[13] J. P. Saul, et al., *Computer in Cardiology*, 1987, 419-422(1988).

[14] P. Castiglioni, A. Paratolla, G. Parati and M. D. Rienzo, *Proc. Ann. Intntl Conf.. IEEE Eng. in Med. and Biol. Sci.*, 465-466(1993).

[15] Y. Yamamoto and R. L. Hughson, *Am. J. Physiol.*, 266, R40-R49(1994).

[16] Y. Ichimaru and S. Katayama, *Proc. 11th Conf. Noise in Phys. Sys. and 1/f Fluctuations, ed. T. Musha, S. Sato and M. Yamamoto, Kyoto, Japan*, 691-695 (1991).

[17] T. Tamura, K. Nakajima and A. Tateishi, *Proc. 12th Conf. Noise in Phys. Sys. and 1/f Fluctuations, ed. P. H. Handel and A. L. Chung, St. Louis*, 693-696 (1993).

[18] L. Stark, *Neurological Control Systems: Studies in Bioengineering*, Chapt.3, Plenum Press, New York, 1968.

[19] F. W. Cambell, *J. Physiol.*, vol.145, pp.579-594, 1959.

[20] H. Ishida, S. Fukushima, K. Yana, F. Okuyama and T. Tokoro, *Proc. 11th Conf. Noise in Phys. Sys. and 1/f Fluctuations, Kyoto, Japan*, 511-514 (1991).

[21] Y. Abe, M. Yamamoto, T. Chinzei, K. Mabuchi, H. Matsuura, T. Isoyama, A. Kouno, T. Ono, K. Atsumi, I. Fijimasa and K. Imachi, *Heart Replacement-Artificial Heart* 5 (Springer-Verlag, Tokyo, 1996) pp303-306.

[22] K. Imachi, *Yuragi no Kagaku(Science of Fluctuation Phenomena)* , vol.6, ed. T. Musha, (Morikita Pub. Co.) 105-154 (1966).

[23] T. Musha, K. Katsurai and Y. Teramachi, *IEEE Trans. Biomed. Eng.*, **BME-32**, 578-582 (1985).

[24] M. Nakao, et al., *Biol Cybernetics*, **63**, 243-250 (1990).

[25] F. Brüneis, M. Nalao, Y. Mizutani, M. Yamamoto and T. Musha, *Biol. Cybernetics*, **68**, 193-198 (1993).