Criticality in the Relaxation Phase of a Spontaneously Contracting Atria Isolated from a Frog's Heart

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We investigate the spontaneous contraction generated by the atria of a frog's heart isolated in a physiological solution. In the relaxation phase, the recorded time series for two different sampling rates possesses an intermittent component similar to the dynamics of the order parameter's fluctuations of a thermal critical system belonging to the mean field universality class. This behavior is not visible through conventional analysis in the frequency space due to the presence of Brownian noise dominating the corresponding power spectrum.

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In heart electrophysiology, almost all parameters related to the heartbeat have become the target of studies using a variety of statistical and mathematical tools, since heart rate is easy to monitor using a noninvasive method, the electrocardiograph [1,2]. The obvious target is to improve diagnostic methods of heart problems [3]. However, studies on the force generated by the contraction of the human cardiac muscles are limited. These studies require data directly obtained from the human heart, which is difficult to achieve using invasive methods. However, in the study of the physiological properties of the contraction of the heart a variety of in vitro preparations have been developed using isolated heart tissue from different animals [4–8]. The main advantage of the amphibian heart is that the isolated atria can maintain their spontaneous contraction bathed in running oxygenated physiological solution for hours (under special conditions, for days), while measurements of the force of the contraction and the cardiac electrical activity can be made as an indication of the vitality of the tissue. Isolated atria of rats, mice, and frogs have been extensively used to assess the effects of a variety of chemical compounds by monitoring their contractions. However, it is likely that, in the above experiments, minor changes in the force of atria contraction (not detectable by the standard measurements on amplitude and frequency) associated with "hidden" parameters of the analogue signal could be significant for the assessment of the action of drugs on the physiological properties of the heart. Thus, in this study, first the constant in amplitude force of the spontaneously contracting atria of the frog's heart isolated in saline was recorded for hours, and second, the relaxation phase of each contraction was analyzed using a recently introduced method for detecting critical fluctuations and their dynamics in a time series [9]. Of primary interest in our analysis is the signal produced from the fluctuations in the relaxation intervals of the process which possesses a profile characteristic for colored noise. These intervals show a suitable defined (see discussion below) stationarity, compared with the corresponding nonstationary behavior of the entire time series, which is a necessary condition in order to apply our method of analysis. Traces of intermittent dynamics are found in these parts of the recorded signal. These dynamics are in close analogy with the dynamics observed in the time series of a Metropolis [10] random walk for the 3D Ising model at the critical temperature. As stated in [9], the presence of intermittent dynamics in experimentally observed (or simulated) time series is consistent with the occurrence of fluctuations at all time scales, which are therefore characterized as critical, organized in a self-similar way. Our work is closely related to recently detected signatures of criticality in cardiac tissues [1] and further supports these findings obtained through different methodology.

In [11] we have shown that the fluctuations ϕ of the order parameter that corresponds to successive configurations of a critical system at equilibrium obey a dynamical law of type I intermittency which can be described in terms of a $1-d$ nonlinear map. The invariant density $\rho(\phi)$ of such a map is characterized by a plateau which decays in a superexponential way (see Fig. (1) of [9]). The exact dynamics at the critical point can be determined analytically for a large class of critical systems introducing the so-called critical map (CM) [11]. For small values of ϕ, this map can be approximated as

$$\phi_{n+1} = \phi_n + u\phi_n^z + \epsilon_n, \quad (1)$$

where ϕ_n is defined as $\phi_n = |\bar{\psi} - \psi_n|/\Delta\psi$. Here $\bar{\psi}$ is the marginal unstable fixed point and $\Delta\psi$ is a suitable scale ensuring $0 \leq \phi < 1$. For thermal systems the exponent z is connected with the isothermal critical exponent δ

through $z = \delta + 1$, determining the universality class to which the critical phenomenon belongs. The shift parameter ϵ_n is a random variable related to the nonuniversal stochastic part of the dynamics of the critical fluctuations. The plateau region of the invariant density $\rho(\Phi)$ corresponds to the laminar region of the CM where fully correlated dynamics take place. The laminar region ends when the second (nonlinear) term in Eq. (1) becomes relevant. However, this property cannot be easily expressed in a strictly quantitative criterion, and therefore the exact value of the end of the laminar region, in general, has to be determined through our analysis. Based on the above description of the critical fluctuations, one can develop an algorithm permitting the extraction of the critical sector—if any—in a measured time series. The key observation in this approach is the fact that the distribution of the laminar intervals of the above mentioned intermittent map (1) in the limit $\epsilon_n \to 0$ is given by the power law [12]:

$$P(l) \sim l^{-p_l}; \qquad p_l = \frac{z}{z-1}. \tag{2}$$

Inversely now, the existence of such a power law as in Eq. (2), accompanied by a plateau form of the corresponding density, is a signature of underlying correlated dynamics analogous to the critical behavior. Indeed, it is straightforward to show that if the time series is dominated by a random process, then the corresponding distribution of the lengths of the laminar intervals should be exponential. In fact in this case, if the probability to be in the plateau region is q, then the corresponding distribution $\tilde{P}(l)$ should be $\tilde{P}(l) = Ce^{-l\log(1/q)}$, with $C =$ const. As mentioned in [9], it is possible in the framework of universality, characteristic for critical phenomena, to give meaning to the exponent z beyond the thermal phase transitions.

The method for the analysis of the critical fluctuations can be applied in signals, which have been recorded in real time, provided these signals (or segments of them) display the necessary stationary behavior. In the present study, the signal will be the force generated by the spontaneous contraction of the isolated atria of the frog's heart. The method used for the measurements of the force is described in detail elsewhere [8]. We have analyzed two signals which differ significantly in the sampling rate: (i) a time series of 6 sec duration recorded at the scan rate of 20 kHz (120 000 points) and (ii) a time series of 40 sec at 1.5 kHz (60 000 points). In Fig. 1 we present the spontaneous contractions of the frog's atria as a function of time for the two samples. The respective histograms $N(V_f)$ are shown on the right side of each plot. The width of the bin used in these histograms is the minimum one in order to avoid discontinuities and coincides with the resolution in the voltage values $(0.005V)$. For both cases of scanning rate, the voltage distribution has the characteristics of the CM invariant density; namely, it has a plateau which decays sharply.

As a next step, one produces for each of these signals a time series which includes only the fluctuations appearing in the relaxation intervals between the cardiac pulses. The resulting time series is called in the following relaxation time series (RTS). For the high scanning rate, the RTS possesses 68 902 data points, while for the low rate (1.5 kHz) the corresponding points are 43 114. The main part of these points lies within the plateau region of the histograms shown in Fig. 1. The stationarity of RTS can

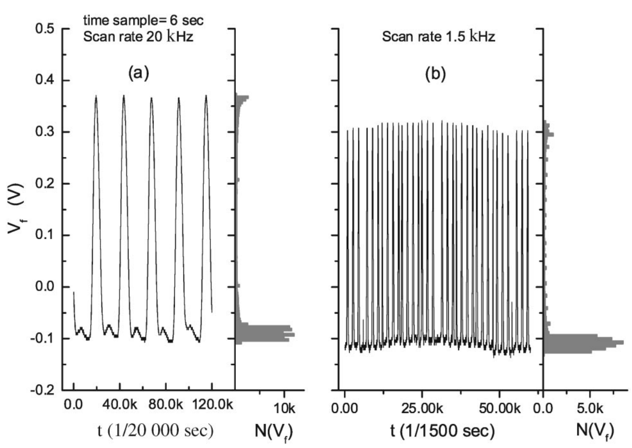

FIG. 1. The electric signal produced by the isometric tension transducer during the spontaneous contraction of the atria of the frog's heart for two different scanning rates: (a) 20 kHz and (b) 1.5 kHz (calibration: $0.4V = 200$ mg). The histogram on the right side of each plot clearly shows the plateau structure as well as the sharp decay according to the description in the text.

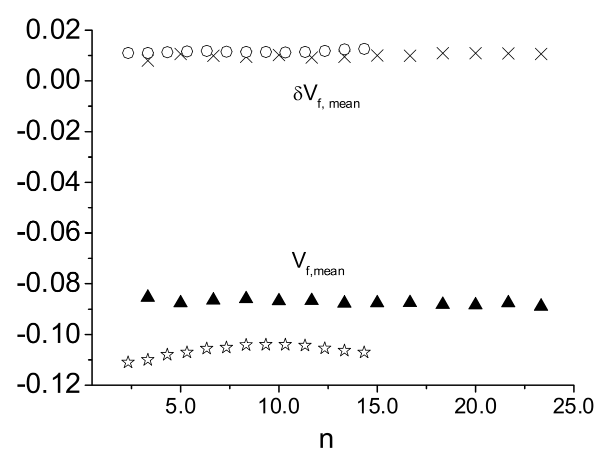

FIG. 2. The cumulative mean value (solid triangles: 20 kHz; open stars: 1.5 kHz) as well as the standard deviation (crosses: 20 kHz; open circles: 1.5 kHz) for increasing number of points used in the averaging of both analyzed RTS. One unit corresponds to 3000 points.

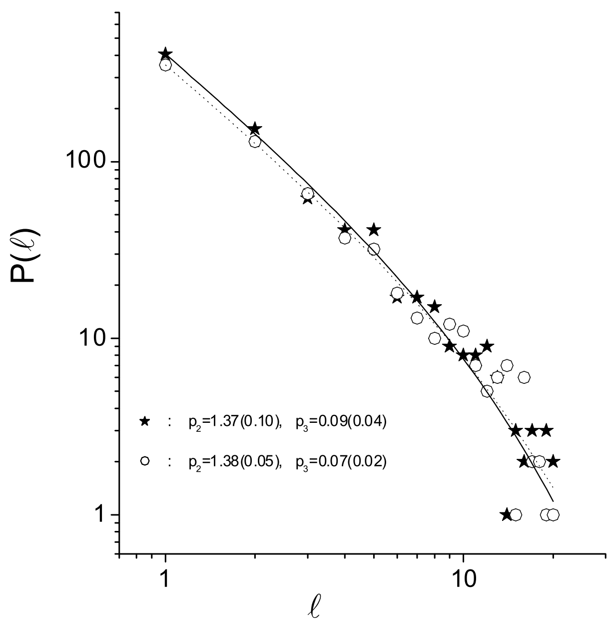

FIG. 3. The unnormalized distribution $P(l)$ of the laminar intervals as described in the text. The solid stars correspond to the 20 kHz RTS ($\psi_l = -0.0765V$), while the open circles correspond to the 1.5 kHz case ($\psi_l = -0.0955V$).

be checked by estimating the mean value and the standard deviation in the cumulative sense: starting from an initial set, we add at each step a number of data points (of the order of a few thousands), and we estimate the mean value and the standard deviation for the enlarged dataset. We find, as shown in Fig. 2, a good stationary behavior. However, it must be noted that in the 1.5 kHz RTS the time duration of the corresponding signal is much longer than in the case of 20 kHz, and therefore the appearance of a very slow oscillation of the mean value is not surprising. The horizontal axis in Fig. 2 is the number of points used in the averaging procedure.

In the following, we will look for nontrivial dynamics in the obtained RTS using the method developed in [9]. Each RTS can be divided into two phases. One phase consists of values within the plateau region (laminar phase [9]), while the other phase is the complementary set of values. We produce the distribution $P(l)$, where l is the laminar interval, i.e., the stay time within the laminar region. The kth laminar interval l_k is determined by counting the number of successive ψ_i (ψ_i are the values of voltage), fulfiling the condition $\psi_o \leq \psi_i \leq \psi_l$ $i = k + 1, \ldots, k + l$. There, ψ_o, ψ_l are the bounds of the plateau region. The value of ψ_o is practically the origin of the corresponding plateau. In the present case of analysis, the end of laminar region ψ_l is, within the uncertainty of the bin size, obvious. For the 20 kHz RTS we find $\psi_o = -0.1015V$ and $\psi_l = -0.0765V$, while for the 1.5 kHz RTS the respective values are $\psi_o = -0.1155V$ and $\psi_l = -0.0955V$. For a given value of ψ_l, we estimate the exponents p_2, p_3 using the fitting function $P(l) = p_1 l^{-p_2} e^{-p_3 l}$ as shown in Fig. 3. The estimations are accomplished on the total RTS. It is interesting to consider the dependence of p_2, p_3 on the value of ψ_l. The results of such an analysis are summarized in Table I.

For both analyzed RTS (20 kHz and 1.5 kHz) we have found that the minimum value of p_3 is very close to zero. When p_3 takes its minimum value, p_2 becomes maximal: $p_2 \approx 1.38$. In particular, for the 20 kHz case p_3 (p_2) becomes minimum (maximum) at $\psi_l \approx -0.0765$, while for the case 1.5 kHz the extremum occurs at $\psi_l = -0.0955$. For these values of ψ_l, the distribution $P(l)$ is closest to a power law. Because of the small values of p_3, the fitting function is close to the one given in Eq. (2), and therefore the exponent p_2 is approximately equal to p_l, a new critical exponent proposed in [9]. Note that this exponent ought to have, in the framework of thermal critical phenomena, a value always greater than 1, due

TABLE I. The values of p_2, p_3 for different ψ_l values in the neighborhood of the end of the laminar region for the two analyzed time series.

	$\psi_l(V)$	p_2	p_3
20 kHz	−0.0815	0.91(05)	0.23(02)
	−0.0765	1.37(10)	0.09(04)
	−0.0715	0.75(06)	0.36(04)
1.5kHz	−0.1005	1.16(04)	0.105(02)
	−0.0955	1.38(05)	0.07(02)
	−0.0905	1.28(05)	0.10(02)

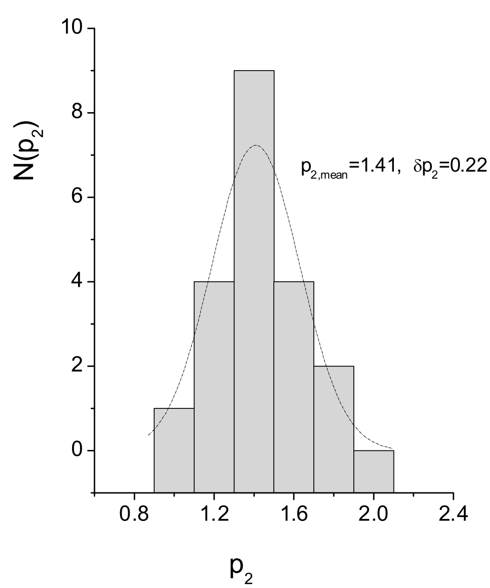

FIG. 4. The histogram of p_2 exponents obtained from 22 different data sets recorded at scanning rate 20 kHz.

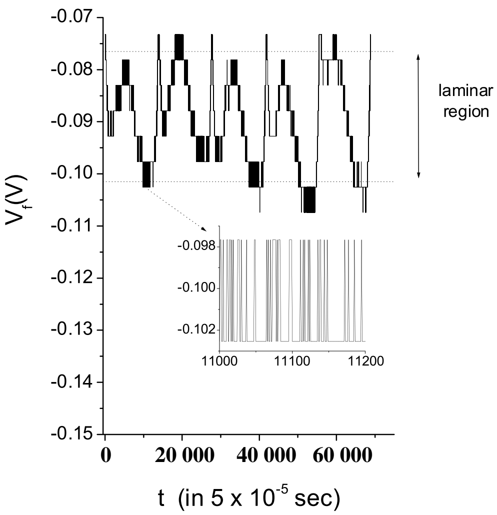

FIG. 5. The RTS time series for the 20 kHz case. The laminar region is dictated by the two dotted horizontal lines. The inset displays an example of a time window characterized by complicated dynamics as described in the text.

to the fact that the isothermal critical exponent δ is always greater than 0.

For the case of 20 kHz sampling rate, we have analyzed 22 time series which where of comparable quality or duration and correspond to different samples. The distribution of p_2 obtained this way is shown in Fig. 4. The mean value for p_2 exponent is 1.41, while the peak in the corresponding distribution is at 1.40, which is equivalent to the p_2 value of a thermal critical system with an isothermal critical exponent $\delta \approx 2.5$ (close to the mean field exponent $\delta = 3$). The corresponding distribution for p_3 is peaked at $p_{3,\max} \approx 0.07$, while all p_3 values are less than 0.2. Similar results, especially concerning the values of $p_{2,\max}$ and $p_{3,\max}$, are obtained also for the case of 1.5 kHz. It must be noticed that the critical properties of RTS cannot be revealed by a trivial power-spectrum analysis. The reason for this is the presence of Brownian noise in this time series leading to a $1/f^2$ behavior, which in the range of small frequencies dominates the $1/f^{\beta}$ ($\beta \approx 0.8$) dependence expected for the intermittent dynamics ($\delta = 2.5$ [12]) found through the above analysis. A possible way to reduce the noise is to define a symbolic dynamics for RTS by assigning the value 1 each time the corresponding RTS value lies within the plateau region or the value 0 in the opposite case. The resulting time series has per construction the same distribution of laminar intervals as RTS leading to exactly the same value for the exponents p_2, p_3. Performing the corresponding power-spectrum analysis for the RTS at 20 kHz, we obtain a $1/f^{1.28}$ dependence (for $f < 0.001$) characteristic for colored noise, indicating the presence of nontrivial dynamics in the sample. Furthermore, for this case we can further reveal the complexity of RTS by considering the dynamics within small time windows. Then we can calculate the distribution of the sizes of time subintervals within each window for which the recorded signal is constant (see Fig. 5). The form of this distribution changes drastically as we move from window to window being power law (with different exponents) or exponential occasionally. The critical intermittent dynamics observed in the RTS is an effective description of this large variety of dynamical behaviors occurring at different time scales.

Let us come to our conclusions. Using a recently introduced method suitable to reveal critical dynamics, we have found that the time series describing the relaxation intervals of a spontaneous contracting cardiac tissue possesses critical properties analogous to a thermal system at a transition point. This behavior turns out to be quite independent of the scanning rate used in the recording of the data as well as the duration of the time series. This finding indicates the critical character of the normal working heart characterized by the presence of long range correlations as well as fluctuations at many different time scales. Our work is in accordance with previous results found in heartbeat time series from the healthy human heart [1–3]. The analysis of time series originating from pathological behavior, for example, the supplying of medicines in frogs, is left for future investigations.

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