

Understanding of physiological neural firing patterns through dynamical bifurcation machineries

Minghao Yang^{a,b}, Shucheng An^a, Huaguang Gu^b, Zhiqiang Liu^{a,b} and Wei Ren^{a,b}

^aLaboratory for Physiology and Biophysics of Excitation, College of Life Science, Shaanxi Normal University, Xian, Shaanxi, China and ^bInstitute of Space Medico-Engineering, Beijing, China

Correspondence and requests for reprints to Shucheng An, Laboratory for Physiology and Biophysics of Excitation, College of Life Science, Shaanxi Normal University, Xian, Shaanxi, 710062, China

Fax: + 86 29 85303736; e-mail: shuchengan@snnu.edu.cn

Sponsorship: This work was supported by the NNSF of China under Grant Nos. 30300107 and I0432010.

Received 16 April 2006; accepted 27 April 2006

The characteristics of baroreceptor firing patterns were recognized in experiment, and their dynamics revealed in theoretical analysis. During blood pressure elevation, baroreceptors gradually exhibited bursting, continuous firing, and paradoxical bursting patterns. The bursting was generated through the repeated bifurcations between rest and spiking, the continuous firing was maintained without bifurcation, and the paradoxical bursting was generated through the bifurcations between spiking and

depolarization block. Thus, the change of blood pressure spans two bifurcations and such results imply a new way for baroreceptors to encode blood pressure information. Various firing patterns were generated from the evolution of the baroreceptor system on different parts of the system's bifurcation scenario with respect to parameter I , the excitative current modulated by blood pressure. *NeuroReport* 17:995–999 © 2006 Lippincott Williams & Wilkins.

Keywords: baroreceptor, bifurcation, blood pressure, neural firing patterns

Introduction

The input signals to a neuron are integrated and reflected in its output firing trains. Through such processes, the time-dependent variations of the signal are encoded in the change of the firing patterns. In physiological context, the neuronal firing patterns are complex. A deep understanding of the complexity requires an approach that integrates physiology of excitation and nonlinear dynamics of cellular electrical oscillation, investigating the detailed biophysics of repetitive firing, and thus the temporal characteristics of the firing patterns [1].

In recent years, research into neural excitability from a nonlinear dynamics perspective has achieved rapid progress. The underlying bifurcation mechanisms of classical excitability types [2] were revealed [3], the temporal patterns of repetitive firing were rigorously defined with help of mathematical concepts of oscillations, and the transitions between different firing patterns were elucidated by dynamical bifurcation scenarios [4–7]. Most of the previous studies focused on the fundamental bifurcation mechanisms of the generation of excitation and the transition of firing patterns. In such studies, the neuronal systems are usually isolated and the control parameters unidirectionally and stepwise adjusted. The strong points of those researches are their concise understanding of the basic principles. In our previous work, the complete transition

scenarios from polarized resting to firing, between various firing patterns, and from firing to a depolarized ion block were extensively studied in both experiments and mathematical analysis [8–12]. We proposed that the bifurcation structure of a neuron with respect to its physiological parameters provides a fundamental theoretical framework for the understanding of the encoding mechanism of the neuron. With such a framework of firing pattern transition, the temporal changes of the relevant parameters will force the neuron to evolve on the bifurcation structure to experience dynamical bifurcations, and thus to exhibit complex firing behaviors. Through such dynamical bifurcation machineries, the characteristics of the temporal variation of the parameters are then represented in the change of firing patterns.

In the process of ongoing physiological activities, the physiological parameters are changing dynamically. Time-dependent change of the parameter induces more complex firing patterns than previously defined. The validity of the previous nonlinear dynamical research into neural firing patterns should be further examined. In the present paper, we briefly report the results of a further application of nonlinear dynamics to the firing patterns generated by baroreceptors working in physiological context. The results support the proposed ideas and provide new insights into the complex ongoing activities of baroreceptors.

Methods

Recording of unit firing of depressor nerve and blood pressure

Blood pressure changes repeatedly in each heartbeat period and in reflexive regulations. Pressure changes cause deformation of vessel wall and generator potential variations in the nerve terminals. Then the spikes repetitively initiated at the initial zone of the axon and thus the various firing trains are formed [13]. The temporal pattern of the firing trains encodes the time-dependent characteristics of the blood pressure variations. In the present study, blood pressure changes, as an input signal to baroreceptors, and depressor fiber unit firing, as a neural output, were simultaneously observed to study the temporal relations between the two. The generation of the neural firing patterns was then examined in the light of previously established ideas [8–12].

Adult male New Zealand rabbit, weighing 2–2.5 kg, was anesthetized with urethane intravenously, 1 g/kg, and additional doses were given in the course of the experiment if required. The trachea was cannulated. Arterial blood pressure was recorded with a cannula pressure transducer connected to an ML221 amplifier from arteria carotis. The depressor nerve, about 2 cm long, was isolated and marinated in an oil pool. A thin bundle of depressor fibers was separated, and its afferent firing trains were induced by means of a fine platinum electrode with a nearby reference and connected to a bioelectrical amplifier. Blood pressure and spike trains of individual fibers were recorded simultaneously with a Powerlab system (ASInstruments, Sydney, Australia) with a sampling frequency of 10.0 kHz and monitored to make sure that the recording was of a single unit during the experiment. The time intervals between the maximal values of the successive spikes were recorded seriatim as interspike interval series [8]. The overall blood pressure level was elevated by intravenous administration of norepinephrine (NE) after at least 20 min stable observation as control, and the recovery process after the effect of NE was also observed.

The physiological problem and its theoretical expression

Increase of blood pressure activates the stretch-sensitive cation channels and causes an influx current at the initial zone of the aortic arch baroreceptor. Such a depolarizing current is a reflection of blood pressure. We defined variable I as an expression of the influx current. The initial zone and spike generating axon was expressed by the classical Hodgkin–Huxley (HH) equations. Compared with the time scale of an action potential, the varying of blood pressure as well as variable I were much slower. Combining slow subsystem I with fast HH subsystem [14], the above experimentally studied physiological process could be expressed by means of the following equations. Such a simplification considered none of reflexive regulations but was sufficient for the analysis of the basic dynamics of the firing pattern in the present study.

The Hodgkin–Huxley model combined with I

The HH model combined with I was composed of four nonlinear coupled equations as follows:

$$\frac{dV}{dt} = (g_{Na}m^3h(V_{Na} - V) + g_K(V_K - V)n^4 + g_L(V_L - V) + I) \times M, \quad (1)$$

$$\frac{dn}{dt} = (\alpha_n(V)(1 - n) - \beta_n(V)n) \times M, \quad (2)$$

$$\frac{dm}{dt} = (\alpha_m(V)(1 - m) - \beta_m(V)m) \times M, \quad (3)$$

$$\frac{dh}{dt} = (\alpha_h(V)(1 - h) - \beta_h(V)h) \times M, \quad (4)$$

where V is the membrane potential, m and h are two gating variables for sodium ionic channel and n is the gating variable for potassium ionic channel. The constants g_{Na} , g_K , and g_L are maximal conductances for sodium ionic channel, potassium ionic channel, and leakage channel. V_{Na} , V_K , V_L are the corresponding reversal potentials. The parameters and expressions in the HH model were as follows: $\alpha_n = 0.01(V + 10)/(e^{0.1V+1} - 1)$, $\alpha_m = 0.1(25 + V)/(e^{0.1V+2.5} - 1)$, $\alpha_h = 0.007e^{V/20}$, $\beta_n = 0.125e^{V/80}$, $\beta_m = 4e^{V/18}$, $\beta_h = 1/(e^{0.1V+3} - 1)$, $V_{Na} = 120.0$, $V_K = -120.0$, $V_L = 10.59999$, $g_L = 0.3$, $g_{Na} = 120.0$, $g_K = 25.0$. $M = 1110$ is the revised parameter. The introduction of M to the HH model modified the mean firing frequency closer to that of the experiment. The unit of membrane potential was mV.

I is the influx current modulated by blood pressure. In our theoretical simulation of the firing patterns, I was simply transformed from the experimentally recorded data of blood pressure, normalized by adding a constant relevant to the overall blood pressure level as required.

The HH model was integrated with the time step 10^{-5} s using the fourth order Runge–Kutta method.

Results

Experimental results

Experiment procedure was completed in 12 animals, including control recording, NE-induced blood pressure elevation, and recovery. Among them, in three cases the recordings of firing were intermixed by recruited units during the action of NE; in the other nine cases unit recordings of depressor nerve in the course of blood pressure changes were successfully obtained. Thus, we discuss only nine such cases and investigate three typical firing patterns as follows.

Type 1 firing pattern in experiment

Before NE administration, all the nine units fired in a firing-quiescence pattern with blood pressure varying approximately between 80 and 130 mmHg in each heartbeat period. The fibers fired as blood pressure increased and ceased firing in the course of blood pressure decrease (Fig. 1a). This kind of bursting pattern was recognized as type 1 pattern.

Type 2 and type 3 firing pattern in experiment

As blood pressure was elevated by NE to about 130–170 mmHg in each heartbeat period, two units increased their bursting length but still ceased firing apparently in each heartbeat period corresponding to decreased blood

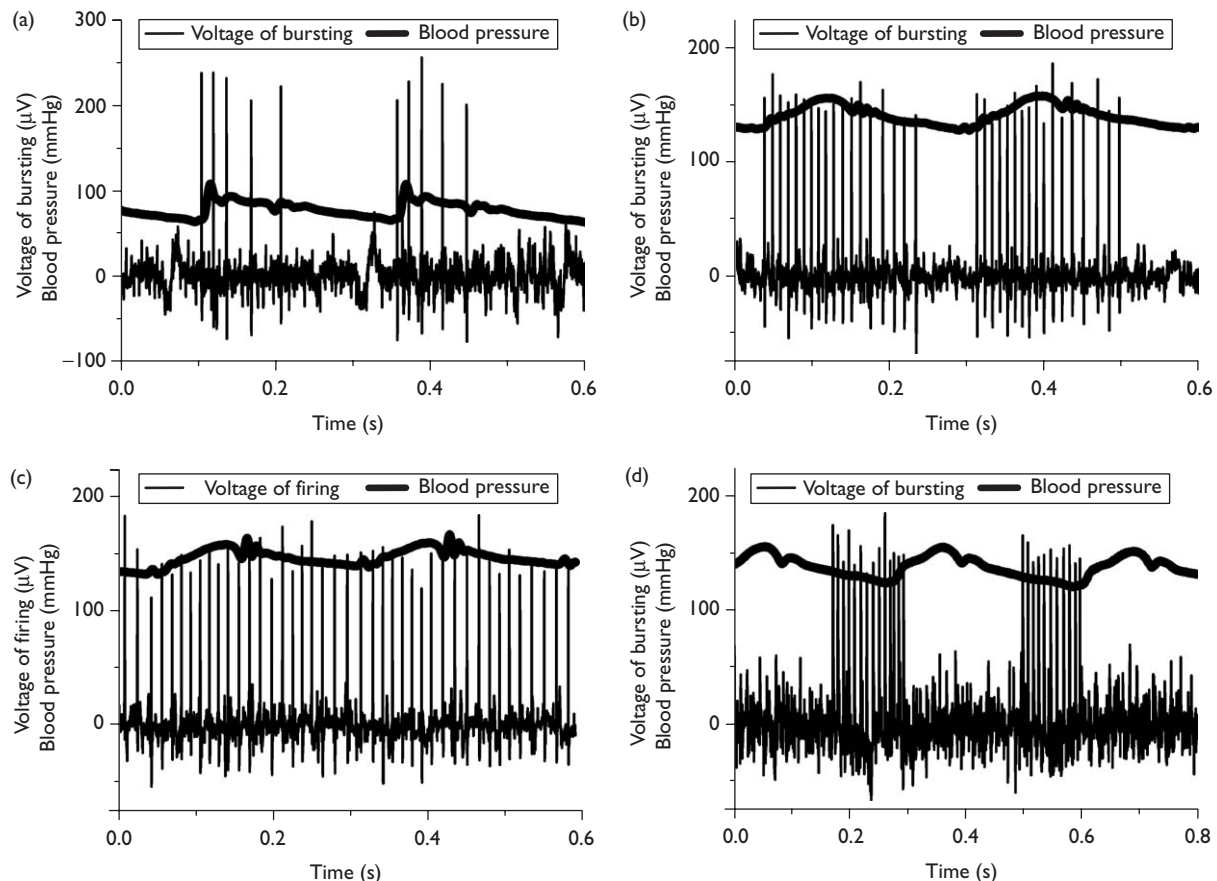


Fig. 1 Unit recording and blood pressure of the three different firing patterns. (a) Type 1 pattern in control condition. (b) Type 1 pattern under action of norepinephrine (NE). The duration of burst became longer and quiescence became shorter. (c) Type 2 pattern under action of NE. (d) Type 3 pattern under action of NE.

pressure (Fig. 1b), five units fired continuously without apparent quiescence and their firing was recognized as type 2 pattern (Fig. 1c), and the remaining two units experienced type 2 pattern during the administration of NE and reached a paradoxical bursting pattern (Fig. 1d). In the paradoxical bursting, the depressor fibers fired correspondingly with the decrease and ceased firing with the increase of blood pressure in each heartbeat period. We recognized this unexpected bursting as type 3 pattern.

We should emphasize herein that the above three recognized firing patterns are typical and can be readily discriminated, and there are still many transitional patterns that need further investigation in future.

Bifurcation structure with static I as the control parameter in Hodgkin-Huxley model

In the autonomous HH model with static I , the threshold from polarized resting to excitation could be dynamically described by a Hopf bifurcation [9,15]. The Hopf bifurcation point was at $I_{HB1}=2.7$. When $I < I_{HB1}$, the behavior of the system was polarized resting, relevant to physiological resting potential. As I was increased to $I > I_{HB1}$, the behavior became periodic spiking. When I was further increased to the other threshold, the threshold from excitation to a depolarization block, the system experienced another Hopf bifurcation from periodic firing to rest [15]. The Hopf

bifurcation point was at $I_{HB2}=124.6$. Therefore, the behavior of the system was at rest when $I < I_{HB1}$ or $I > I_{HB2}$ and was period one limit cycle spiking when $I_{HB1} < I < I_{HB2}$. The whole bifurcation scenario with respect to static I is shown in Fig. 2a. Such a bifurcation structure can be used as a guiding framework to understand the firing patterns generated by varying I .

Dynamical simulation of experimentally recognized type 1 firing patterns

In the case of the recognized type 1 firing pattern, the overall blood pressure was relatively low, and thus I varied about I_{HB1} and the system experienced dynamical bifurcations twice in each heartbeat period, from fixed point to limit cycle when I increased across I_{HB1} and from limit cycle to fixed point when I decreased across I_{HB1} (Fig. 2a, left). Such dynamics could be used as an underlying explanation of the behavior of baroreceptors that fired about the systolic pressure and ceased firing about the diastolic pressure and thus generated type 1 firing pattern (Fig. 2b and c).

Dynamical simulation of experimentally recognized type 2 and type 3 firing patterns

In the case of type 2 firing pattern, I varied between I_{HB1} and I_{HB2} (Fig. 2a, middle) and generated continuous firing with interspike interval variations (Fig. 2d). In the case of type 3

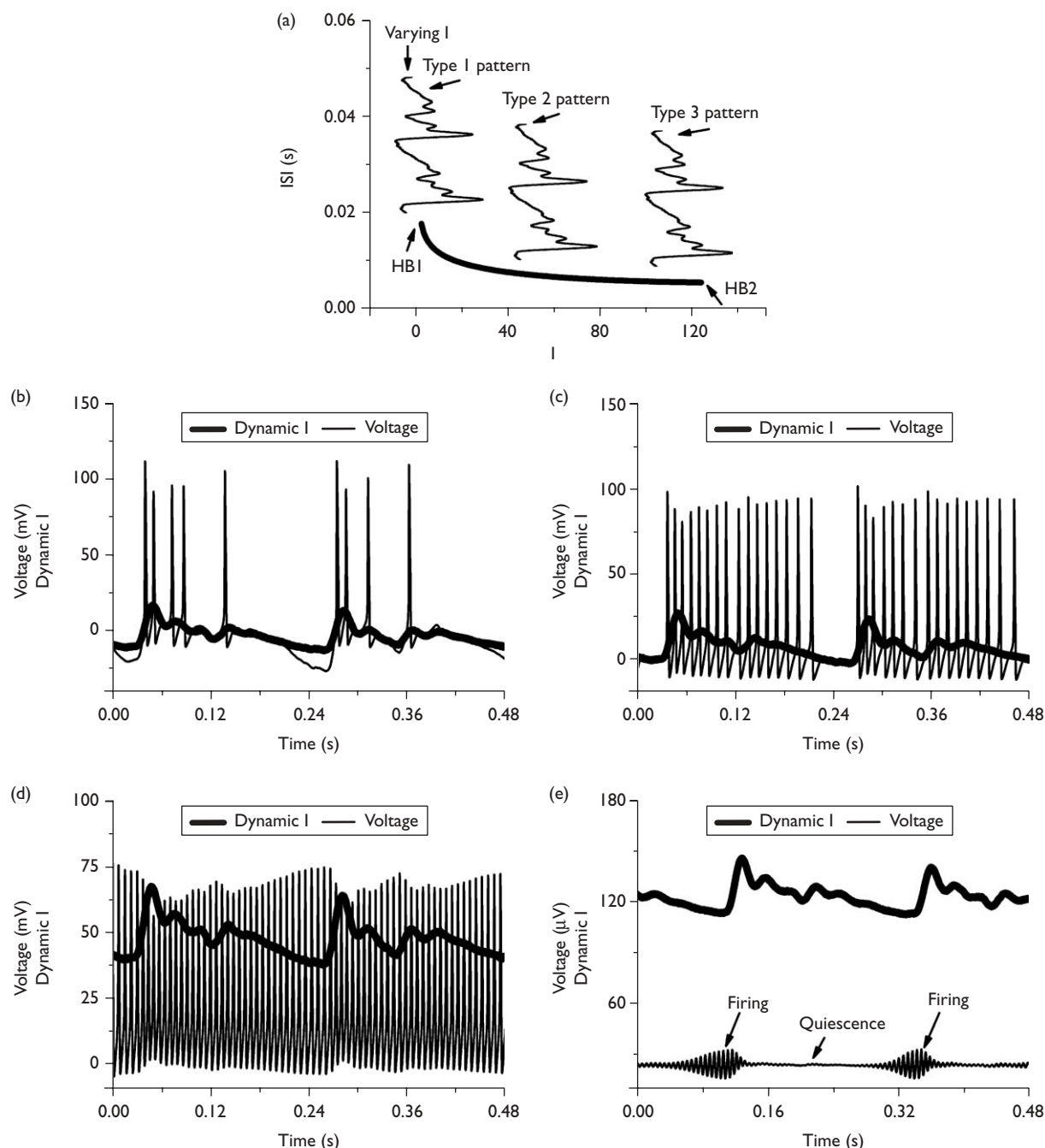


Fig. 2 (a) Schematic figure of the three types of firing patterns simulated with Hodgkin–Huxley (HH) model. The thick descendent line was the bifurcation of interspike interval (ISI) of the HH model with static I . HB_1 and HB_2 are the two Hopf bifurcation points. Dynamic I with three different average levels was shown, corresponding to type 1, 2 and 3 firing patterns, respectively. The model neuron was stimulated with the waveform shown rotated 90° , where the horizontal size represents the dynamic range of I along the x-axis. (b) Simulation of type 1 pattern with the average of dynamic I being 1.2. (c) Simulation of type 1 pattern with the average of dynamic I being 11.2. (d) Simulation of type 2 pattern with the average of dynamic I being 50.5. (e) Simulation of type 3 pattern with the average of dynamic I being 122.5. Note the membrane potential is highly depolarized at the initial segment, then all or none action potentials will be generated along the axon by the indicated membrane potential oscillation.

firing pattern, I varied about I_{HB2} and the system experienced dynamical bifurcations twice in each heartbeat period again, but from firing to rest when I increased across I_{HB2} and from rest to firing when I decreased across I_{HB2} (Fig. 2a, right). Thus, the paradoxical type 3 pattern was also formed through time-dependent bifurcation (Fig. 2e).

Discussion

Employing rabbit depressor baroreceptors under the pulsatile forcing of blood pressure as an example, the present research offered dynamic machineries for the physiological firing patterns from a perspective of nonlinear dynamical analysis. With the help of the fast-slow technique [14], we

firstly obtained the bifurcation structure of the initial zone of depressor fiber, and then defined the parameter I representing the dynamical stimulation caused by blood pressure variations. As parameter I changed, the baroreceptor system was driven to evolve on the bifurcation structure with respect to static parameter I . For a given depressor fiber and under a given blood pressure level, such an evolution could generate specific firing patterns, which represented not only the range but also the time-dependent features of the blood pressure. The three types of classification here are a brief outline, and the experimental model is a simple case. This research demonstrated the validity and power of nonlinear dynamics in the study of physiological firing patterns, guided by the previously proposed ideas [8–12].

The results here are primary and schematic, more problems prompted than solved. The time-dependent bifurcation problem is one such example [16]. As the physiological parameters are always changing, time-dependent bifurcation problems are inevitable in the application of nonlinear dynamics to physiology. Such bifurcations may cause delay in pattern transition and bring more complex behaviors. The effects and significance of time-dependent bifurcation in physiology should be further addressed. Another implication is about the neurophysiological significance of the temporal pattern of the firing trains of the sensory fibers. It is still popularly accepted that firing rate is the most important index that represents the intensity of the input signal [17]. The temporal relationships that we observed in this research indicate that the firing patterns of the sensory fibers could be more informative and capable of conveyance of temporal characteristics.

Baroreceptors are believed to respond uniformly, acting like one transducer [13]. The appearance of paradoxical bursting during blood pressure elevation indicates that the physiological range of blood pressure spans the bifurcation scenario of some baroreceptors. This new finding implies the existence of a working range for single baroreceptors as well as the possibility of population encoding of blood pressure information by all baroreceptors as a whole. In the cases of other sensations like audition, the working range of single receptors is limited and the complete sensory range is formed by the collaboration in receptor populations [18]. Our results imply that baroreceptors may also have to 'collaborate' under certain blood pressure to encode the information on blood pressure. The validity of this implication should be further investigated.

Conclusion

The formation of different physiological firing patterns can be dynamically understood through bifurcation machineries.

References

1. Glass L, Mackey MC. *From clock to chaos, the rhythm of life*. Princeton: Princeton University Press; 1987.
2. Hodgkin AL. The local electric changes associated with repetitive action in a non-modulated axon. *J Physiol* 1948; **107**:165–181.
3. Izhikevich EM. Neural excitability, spiking and bursting. *Int J Bifur Chaos* 2000; **10**:1171–1266.
4. Chay TR. Chaos in a three-variable model of an excitable cell. *Physica D* 1985; **16**:233–242.
5. Chay TR, Fan YS, Lee YS. Bursting, spiking, chaos, fractals and universality in biological rhythms. *Int J Bifur Chaos* 1995; **5**:595–635.
6. Holden AV, Fan YS. From simple to complex oscillatory behaviour via intermittent chaos in the Rose-Hindmarsh model for neuronal activity. *Chaos, Solitons Fractals* 1992; **2**:349–369.
7. Fan YS, Holden AV. Bifurcations, burstings, chaos and crises in the Rose-Hindmarsh model for neuronal activity. *Chaos, Solitons Fractals* 1993; **3**:439–449.
8. Ren W, Hu SJ, Zhang BJ, Gong YF, Xu JX. Period-adding bifurcation with chaos in the interspike intervals generated by an experimental neural pacemaker. *Int J Bifur Chaos* 1997; **7**:1867–1872.
9. Li L, Gu HG, Yang MH, Liu ZQ, Ren W. A series of bifurcation scenarios in the firing transitions in an experimental neural pacemaker. *Int J Bifur Chaos* 2004; **14**:1813–1817.
10. Ren W, Gu HG, Jian Z, Lu QS, Yang MH. Different classification of UPOs in the parametrically different chaotic ISI series. *NeuroReport* 2001; **12**:2121–2124.
11. Gu HG, Yang MH, Li L, Liu ZQ, Ren W. Experimental observation of stochastic bursting caused by coherence resonance in experimental neural pacemaker. *NeuroReport* 2002; **13**:1657–1660.
12. Yang MH, Gu HG, Li L, Liu ZQ, Ren W. Characteristics of period adding bifurcation without chaos in firing pattern transitions in an experimental neural pacemaker. *NeuroReport* 2003; **14**:2153–2157.
13. Brown AM. Receptors under pressure. An update on baroreceptors. *Circ Res* 1980; **46**:1–10.
14. Rinzel J, Lee YS. Dissection of a model for neuronal parabolic bursting. *J Math Biol* 1987; **25**:653–675.
15. Gu HG, Ren W, Lu QS, Wu SG, Yang MH, Chen WJ. Integer multiple spiking in neural pacemakers without external periodic stimulation. *Phys Lett A* 2001; **285**:63–68.
16. Hua CC, Lu QS. Time-dependent bifurcation: a new method and applications. *Int J Bifur Chaos* 2001; **11**:3153–3162.
17. Kandel ER, Schwartz JH, Jessell TM. *Principle of neural science*. 4th ed. Chapter 21. New York: McGraw-Hill Companies, Inc; 2000.
18. Chatterjee M, Zwillocki JJ. Cochlear mechanisms of frequency and intensity coding. I. The place code for pitch. *Hearing Res* 1997; **111**: 65–75.