Exponential decay characteristics of the stochastic integer multiple neural firing patterns

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Abstract Integer multiple neural firing patterns exhibit multi-peaks in inter-spike interval (ISI) histogram (ISIH) and exponential decay in amplitude of peaks, which results from their stochastic mechanisms. But in previous experimental observation that the decay in ISIH frequently shows obvious bias from exponential law. This paper studied three typical cases of the decay, by transforming ISI series of the firing to discrete binary chain and calculating the probabilities or frequencies of symbols over the whole chain. The first case is the exponential decay without bias. An example of this case was discovered on hippocampal CA1 pyramidal neuron stimulated by external signal. Probability calculation shows that this decay without bias results from a stochastic renewal process, in which the successive spikes are independent. The second case is the exponential decay with a higher first peak, while the third case is that with a lower first peak. An example of the second case was discovered in experiment on a neural pacemaker. Simulation and calculation of the second and third cases indicate that the dependency in successive spikes of the firing leads to the bias seen in decay of ISIH peaks. The quantitative expression of the decay slope of three cases of firing patterns, as well as the excitatory effect

in the second case of firing pattern and the inhibitory effect in the third case of firing pattern are identified. The results clearly reveal the mechanism of the exponential decay in ISIH peaks of a number of important neural firing patterns and provide new understanding for typical bias from the exponential decay law.

Keywords Neural firing pattern · Interspike interval histogram · Integer multiple characteristic · Exponential decay · Stochastic process

Introduction

Many previous studies observed integer multiple neural firing patterns, in both spontaneous and induced activities. The noise-induced integer multiple firing patterns are closely associated with stochastic resonance (SR, an optimal cooperation in nonlinear systems stimulated by external periodic signal and noise) in the nervous system. The integer multiple firing patterns exhibit multi-peaks in their inter-spike interval (ISI) histogram (ISIH). Peaks in the ISIH locate at integer multiples of a basic ISI and the peak amplitudes decay approximately exponentially with respect to the sequential number of the peaks. The exponential decay in ISIH peaks is commonly used as an indicative characteristic of the stochastic integer multiple firing. To interpret the integer multiple firing discovered in the biological experiment (Rose et al. 1967; Siegel 1990), Longtin et al. (1991, 1994) introduced SR into neuroscience. Various studies about SR in the nervous system have demonstrated that noise can be helpful in detection of external weak signals in noisy environments (Douglass et al. 1993; Petracchi et al. 1995; Wiesenfeld and Moss 1995; Gammaitoni et al. 1998). At the level of single neuron, integer

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multiple firing were numerically simulated in neuronal models driven by both external periodic forcing and noise, and experimentally observed in sensory nerves stimulated by periodic signals (Siegel 1990; Longtin et al. 1991, 1994; Chialvo et al. 1993; Wiesenfeld and Moss 1995; Gam-maitoni et al. 1998).

Spontaneous integer multiple firing patterns were also discovered in the experiments on temperature sensory nerve (Braun et al. 1994), on rat dorsal root ganglion (Xing et al. 2001), and on an experimental neural pacemaker (Gu et al. 2001; Sun et al. 2005; Yang et al. 2009). They were simulated in stochastic neuronal model without external signal (Gu et al. 2001; Yang et al. 2004, 2009). The spontaneous firing pattern was suggested to be stochastic firing patterns related to autonomous stochastic resonance or coherence resonance (CR), i.e. SR without external signal (Pikovsky and Kurth 1997; Longtin 1997; Gu et al. 2001, 2002; Yang et al. 2009). It implied that the spontaneous integer multiple firing might play important roles via CR mechanism. Such spontaneous integer multiple firing patterns appear between period 1 firing and rest condition. The multi-peaks in the ISIH locate at approximately integer multiple to a basic ISI, whose value nearly equals to the ISI of the neighboring period 1 firing. The peak amplitudes always exhibit approximately exponential decay with respect to the increase of ISI.

Both spontaneous and stimulated integer multiple neural firing patterns exhibit exponential decay in their ISIH peaks, indicating their stochastic mechanisms. But the previous experimentally observed and theoretically simulated decay patterns in ISIH frequently show obvious bias from the exponential law (Longtin et al. 1994). Bias is frequently observed in the amplitude of the first peak. For example, in our recent studies on the experimental neural pacemaker, most of the spontaneous integer multiple firing lying between period 1 firing and rest condition exhibited a higher first peak in ISIH. In order to reveal the bias from the exponential decay law, we particularly studied three typical cases of the exponential decay in ISIH peaks. The first case is the exponential decay without bias. The second case is the exponential decay with a higher first peak and the third case is that with a lower first peak.

The rest of the present paper is organized as follows. In “[Experimental method and results](#)”, we introduced two experimental models and the corresponding integer multiple firing patterns recorded from these models. One of the patterns exhibits exponential decay without bias and the other shows a higher first peak in ISIH. In “[Numerical simulation results of the firing patterns](#)” we simulated the firing pattern characterized by exponential decay without bias and that with a lower first peak in ISIH using stochastic FitzHugh-Nagumo (FHN) model, and firing pattern with a higher first peak in ISIH by stochastic Chay model. In

“[Hypothesis of the formation of three cases of exponential decay in ISIH](#)” we proposed a hypothesis that lead to three cases of exponential decay characteristics. By probability calculation to discrete binary chain transformed from the firing, we analyzed the independency between two successive spikes to reveal the formation of exponential decay without bias in ISIH, the dependency being as an excitatory effect between successive spikes to identify the formation of the higher first peak, and the dependency being as inhibitory effect between two successive spikes to reveal the lower first peak in ISIH. “[Test the hypothesis using binary chain of the simulation firing patterns](#)” provided the test to the hypothesis using the firing patterns simulated in “[Numerical simulation results of the firing patterns](#)”. In “[Test the hypothesis using the experimental firing pattern](#)” we tested the hypothesis with the experimental firing patterns discovered in “[Experimental method and results](#)” and the last section was the discussion and conclusion.

Experimental method and results

Firing pattern characterized by exponential decay without bias in ISIH

Experimental method

Sprague-Dawley (SD) rats (10–19 day-old) were anesthetized with urethane. The brain were rapidly removed and placed in ice-cold dissecting artificial cerebrospinal fluid (ACSF). Then 300 μm -thick coronal slices were prepared using vibratome (NatureGene Corp, USA) and placed in a holding chamber of incubating ACSF and kept at room temperature for at least 1 h before being transferred to an immersion chamber for recordings.

For whole cell patch clamp, slices were transferred to a recording chamber mounted on upright microscope DM-LFSA (Leica, Germany) perfused with ACSF (room temperature). Recordings were made from hippocampal CA1 pyramidal neurons visually identified by infrared DIC-video microscopy using a high performance vidicon camera DAGE-MTI (Dage-MTI of Michigan City, Inc., USA). The resistance of microelectrode was 3–5 M Ω . All recordings from CA1 pyramidal cells were obtained using a Digidata 1440A interface connected to an AXON700B amplifier (Axon Ins., USA). Data were acquired, processed and analyzed using the Pclamp 10 software (Axon Ins., USA), respectively.

Firing pattern

When external periodic current (the period is 200 ms) was applied, a number of resting CA1 pyramidal neurons in

Fig. 1 Firing pattern generated in CA1 neuron of hippocampal slice. **a** Spike train. **b** ISI series. **c** ISIH. The line is the regress line for peak amplitude $y(k)$ and corresponding ISI $x(k)$ of k -th peak. **d** Autocorrelation coefficient of ISI series. Insert figure is the enlargement when lag is between 0 and 9

hippocampal slice could be driven to generate integer multiple firing, as shown in Fig. 1a. The spikes located nearly at the maximum of the external signal. The ISI values were approximately integer multiple to the external period and the ISI series exhibited multiple layers correspondingly, as shown in Fig. 1b. The ISIH exhibited multiple discrete peaks located at integer multiple of the external period, as shown in Fig. 1c. The peak amplitudes exhibited exponential decay in all peaks in ISIH. There were 1941 spikes generated in 5,000 periods of external signal.

Expediently, the peak in ISIH whose sequential number is k is called as k -th peak. The k -th peak amplitude in ISIH is regard as $y(k)$ and the corresponding ISI as $x(k)$. Application the least square regress method to $y(k)$ and $x(k)$ yields that $\log y(k) = 2.794 - 0.0087 x(k)$ with a correlation coefficient being -0.97 , as shown in Fig. 1c. It shows that all peaks in ISIH decayed exponentially.

Renewal characteristic

The autocorrelation function is always employed to identify the renewal or non-renewal characteristics for an ISI series of neural firing pattern ($ISI_1, ISI_2, \dots, ISI_N$) in previous studies (Chacron et al. 2000, 2001a, b), used in this paper and shown as follows

$$\rho[i] = \frac{\sum_{j=1}^{N-i} (ISI_j - \overline{ISI})(ISI_{i+j} - \overline{ISI})}{\sum_{k=1}^N (ISI_k - \overline{ISI})^2} \quad (1)$$

where $\overline{ISI} = 1/N \sum_{i=1}^N ISI_i$ is the mean of the time series, and i is an integer and the lag ($i = 0, 1, 2, \dots, N-1$). In general, for a stochastic renewal process, the autocorrelation coefficient $\rho[i]$ is zero for non-zero lag i , implying that the time series is independent. For a stochastic non-renewal process, $\rho[i]$ is non-zero for at least one i except $i = 0$, implying that there exists some correlation within the time series. In this paper, autocorrelation coefficients of ISI series and the corresponding binary chains are calculated.

For the integer multiple firing observed in CA1 pyramidal cell, the autocorrelation coefficient is zero at non-zero lag, as shown in Fig. 1d, implying the ISI series is independent and is a renewal process. Figure 1d is the enlargement when lag is between 0 and 9. In the following section, only enlargement of figures when the lag is small is provided.

Firing pattern characterized by exponential decay with a higher first peak in ISIH

Experimental method

The experimental neural pacemaker was formed at the injured site of rat sciatic nerve subjected to chronic ligation. Surgical operation was performed using adult male SD rats (200–300 g). After a survival time of 8–12 days, the previously injured site was exposed and was perfused continuously with 34°C Krebs's solution. The spontaneous spike train of a single unit of individual fibers ending at the injured site was recorded with a PowerLab system (Australia) with a sampling frequency being 10.0 kHz. The time interval between the maximal values of the successive spikes was recorded seriatim as ISI series. The experimental protocol was described in detail in our previous studies (Gu et al. 2001, 2002, 2003a, b, 2004).

Firing pattern

In this experiment, spontaneous integer multiple firing was recorded. When extracellular calcium concentration (Gu et al. 2001) was adjusted from 1.2 to 5 mmol/L, period 1 firing can be changed into spontaneous integer multiple firing whose spike trains was shown in Fig. 2a. The

Fig. 2 Firing pattern discovered in the experimental neural pacemaker. **a** Spike trains. The spikes often appear continuously. **b** ISIH. The line is the regress line for peak amplitude $y(k)$ and corresponding ISI $x(k)$ of k -th peak. **c** Autocorrelation coefficient of ISI series

spontaneous integer multiple firing exhibited multi-peaks in ISIH (Gu et al. 2001) (Fig. 2b). The first peak in ISIH of this typical experimental result is markedly higher than expected by exponential estimation, as shown in Fig. 2b. Application of the least square regress method to $y(k)$ and $x(k)$ yields that $\log y(k) = 3.206 - 0.0061 x(k)$ with a correlation coefficient being -0.94 . The correlation coefficient is much less because the higher first peak deviated from the regress line.

Non-renewal characteristic

The autocorrelation coefficient of the ISI series is -0.10 when the lag is 1, and is nearly zero when the lag is bigger than 1, as shown in Fig. 2c (lag is between 0 and 15). It shows that the firing pattern exhibits non-renewal characteristic and there exists dependency within ISI series.

Numerical simulation results of the firing patterns

Firing pattern characterized by exponential decay without bias in ISIH

FitzHugh-Nagumo model

The integer multiple firing patterns induced by both noise and external signal via SR can be simulated near a Hopf bifurcation point in the FHN model (Moss et al. 1993;

Wiesenfield and Moss 1995) and other models including Chay model. To be compared to previous studies (Moss et al. 1993; Wiesenfield and Moss 1995), FHN model is employed in this paper when we simulate the integer multiple firing induced by both external signal and noise. The FHN model (Baltanás and Casado 1998) is shown as follows:

$$\varepsilon \frac{dv}{dt} = v(v - v_0)(1 - v) - u + I + A \cos \omega t + \xi(t) \quad (2)$$

$$\frac{du}{dt} = v - u - a_0 \quad (3)$$

where t is the time. v is the fast voltage variable of membrane potential. u is the slow recovery variable. I is the background current. $A \cos \omega t$ is the external periodic signal. $\xi(t)$ is a Gaussian white noise (reflecting the fluctuation in real neuronal system). The noise possesses statistical properties as $\langle \xi(t) \rangle = 0$ and $\langle \xi(t) \xi(t') \rangle = 2D\delta(t - t')$, where D is the noise density. $\delta(\cdot)$ is the Dirac δ -function.

The FHN model is dimensionless and the parameters are $\varepsilon = 0.001$, $v_0 = 0.5$ and $a_0 = 0.15$.

FHN models were solved by Mannella numerical integrate method (Mannella and Palleschi 1989) with integration time step being 0.0001. An action potential is said to occur when the voltage crosses a value of 0.8 from below.

In deterministic FHN model, $I_c \approx 0.1100$ is a Hopf bifurcation point. When I is smaller or bigger than I_c , the behavior is a stable focus corresponding to rest or period 1 firing, respectively. The ISI of the period 1 firing near $I > I_c$ changes slowly with respect to I . The maximal ISI is about 0.94 when $I = 0.1101$. With respect to the increase of I , ISI decreases slowly to 0.577 when $I = 0.2$.

Firing pattern

In this subsection, $\omega = 1.5$, $I = 0.095$, $A = 0.01$. When $\omega = 1.5$, the period of the external signal T is 4.19, longer than the intrinsic period of FHN model (0.94). When $I = 0.095$, no firing pattern is generated in the deterministic FHN model.

When noise with density $D = 0.0001$ is introduced, integer multiple firing pattern is reproduced, as shown in Fig. 3a. In this example, a spike appears in 68,292 signal periods and subthreshold oscillations appear in the remaining 35,709 signal periods. Under the influence of noise, the spike is generated randomly, located nearly at the time of the maximal value of the external signal. Peaks in ISIH locate approximately at the integer multiples of the external period, as shown in Fig. 3b, and the peak amplitudes decrease exponentially. Using the least square method, the relationship between $x(k)$ and the logarithm of $y(k)$ is obtained as $\log y(k) = 4.37 - 0.09x(k)$ with a correlation coefficient being -0.99 , showing a close exponential relationship between

Fig. 3 Firing pattern simulated in stochastic FHN model stimulated by external cosine signal ($I = 0.095$, $A = 0.01$, $\omega = 1.5$, $D = 0.0001$). **a** Spike train. **b** ISIH. The line is the regress line for peak amplitude $y(k)$ and corresponding ISI $x(k)$ of k -th peak. **c** Autocorrelation coefficient of ISI series

peak amplitudes and the corresponding ISI values, as shown in Fig. 3b.

Renewal characteristics

The autocorrelation coefficient of the ISI series is zero when the lag is non-zero, showing a non-renewal and independent characteristic, as shown in Fig. 3c.

Firing pattern characterized by exponential decay with a lower first peak in ISIH

Parameter configurations of FHN model

In this subsection, the parameter configurations are $\omega = 6.1$, $A = 0.01$, $I = 0.05$ and $D = 0.0001$. The period of external signal is $T = 1.03$.

Firing pattern

The integer multiple firing is simulated in this condition and the spike train is shown in Fig. 4a. The exponential decay can be seen in ISIH, as shown in Fig. 4b. Different to the firing pattern simulated in “Firing pattern characterized by exponential decay without bias in ISIH”, the first peak in ISIH becomes much shorter. Except the lower first peak

Fig. 4 Firing pattern simulated in stochastic FHN model stimulated by external cosine signal ($I = 0.05$, $\omega = 6.1$, $A = 0.01$, $D = 0.0001$). **a** Spike train. **b** ISIH. **c** Autocorrelation coefficient of ISI series

corresponding to the period of the external signal, other peaks exponentially decay.

Non-renewal characteristics

The autocorrelation coefficient of the ISI series is -0.12 when the lag is 1, showing a non-renewal characteristic and dependency within ISI series.

Inhibitory effect in two successive periods of the external signal

To further identify the dynamics of this firing pattern, the behavior of the FHN model stimulated by only periodic signal ($\omega = 6.1$, $A = 0.01$) without noise is simulated, as shown in Fig. 5. When time is less than 100, the behavior under the influence of only periodic signal is a periodic subthreshold oscillation. When time is near 100, an action potential is evoked by a suitable extra perturbation. After the action potential, the maximal value of the subthreshold oscillation corresponding to the first period of the external signal becomes much shorter, as shown by an arrow in Fig. 5b, and recovers to normal value in the second period of the external signal, as shown in Fig. 5b. The results show that the behavior does not necessarily have enough time to recover in a period of external signal after a spike when the system is driven by a periodic signal with a short period. A spike can impose influence to the behavior in the following cycle. There exists inhibitory effect within two successive periods.

The influence of a spike on the following cycle can be seen in the trajectory of V and $I + A \cos \omega t$, as shown in Fig. 5c. The direction of the trajectory is anticlockwise and

Fig. 5 **a** Spike trans of deterministic FHN model stimulated by only external periodic signal, perturbed by a suitable perturbation that can induce an action potential at time near 100. **b** Enlargement of (b). **c** The trajectory of V and $I + A \cos \omega t$ corresponding to (a). **d** The trajectory of V and $I + A \cos \omega t$ in stochastic FHN model. The critical points are B and G, where the system alternates to two different ways. Namely, the alternations are BCAB or BDEFG and GCAB or GHEFG, respectively

the turning points are labeled by capital letters such as ‘A’, ‘B’, and so on. The trajectory of the subthreshold oscillation under the influence of only external signal is the circle from A to C via B firstly and then return to A. The point B

is a critical phase, whose amplitude is less than the maximal value of the subthreshold oscillation, near which a suitable perturbation can evoke an action potential. The trajectory of the action potential induced by the perturbation is from B to D firstly and then decreased to E via C, to F. The trajectory from F to G firstly and then to C, to A, is corresponding to the behavior of the unrecovered subthreshold oscillation following the action potential. And then, the subthreshold oscillation recovers to normal subthreshold oscillation whose trajectory is from A to C via B firstly and then return to A. The trajectory shows that the voltage of the unrecovered subthreshold oscillation is much less than that of the normal ones when the external stimulation $I + A \cos \omega t$ is same, as shown in Fig. 5c, implying that a spike can impose inhibitory effect in the next period following the spike.

The inhibitory effect can also be seen from the trajectories of the integer multiple firing corresponding to Fig. 4a, as shown in Fig. 5d. The trajectories are similar to that of the Fig. 5c. B and G are two critical phase. The trajectories passing through these two points can turn to right to form a spike, or turn up-left to form a cycle of subthreshold oscillation. The spikes can be evoked easily near B than near G, because the value of V at G is relatively smaller than that at B. The maximal value near G is the amplitude of the unrecovered subthreshold oscillation after an action potential, therefore the system is less likely to generate a spike in the following external forcing cycle to a spike. The results show that a spike can result in an inhibitory effect on the generation of a spike in the following cycle. In other words, the inhibitory effects is considered as dependency between two successive spikes generated in two continuous external periods.

In the present study, it should be noted that the behavior in the period following the inhibited period can fully recover. It shows that the inhibitory effect only exists within two successive spikes or periods.

Firing pattern characterized by exponential decay with a higher first peak in ISIH

Chay model

Spontaneous integer multiple firing pattern can be simulated near a Hopf bifurcation point in autonomous stochastic Chay model, verified to be closely relevant to those discovered in the experimental neural pacemaker (Gu et al. (2001); Yang et al. (2009)). Chay model has been verified to be a successful model to simulate complex behavior such as bifurcation scenarios, chaos and CR discovered in the experimental neural pacemakers (Gu et al. 2001, 2002, 2003a, b, 2004; Yang et al. 2009). The deterministic Chay model (Chay 1985) is as follows

$$\frac{dV}{dt} = g_i m_\infty^3 h_\infty (v_i - V) + g_{kv} (v_k - V) n^4 + g_{kc} \frac{C}{1+C} (v_k - V) + g_l (v_l - V) \quad (4)$$

$$\frac{dn}{dt} = \frac{n_\infty - n}{\tau_n} \quad (5)$$

$$\frac{dC}{dt} = \frac{\rho(m_\infty^3 h_\infty (v_c - V) - k_c C)}{\tau_c} \quad (6)$$

where, t is the time. V is the membrane potential. n is the probability of potassium channel activation. C is the dimensionless intracellular concentration of calcium ion. m_∞ and h_∞ are the probabilities of activation and inactivation of the mixed inward current channel. n_∞ is the steady state value of n . $\tau_n = \frac{1}{\lambda_n(\alpha_n + \beta_n)}$ is the relaxation time. k_c is the rate constant for efflux of the intracellular Ca^{2+} ions. τ_c is a proportionality constant. The explicit expressions for m_∞ , h_∞ , and n_∞ obey the equation $y_\infty = \frac{\alpha(y)}{\alpha(y) + \beta(y)}$, where y stands for m , h , and n , respectively. In the model, $\alpha_m = 0.1(25 + V)/(1 - e^{-0.1V-2.5})$, $\beta_m = 4e^{-(V+50)/18}$, $\alpha_h = 0.07e^{-0.05V-2.5}$, $\beta_h = 1/(1 + e^{-0.1V-2})$, $\alpha_n = 0.01(20 + V)/(1 - e^{-0.1V-2})$ and $\beta_n = 0.125e^{-(V+30)/80}$. The explicit interpretation of Chay model was given in previous studies (Chay 1985; Gu et al. 2001). v_c is the reversal potential of Ca^{2+} ion. The parameters are $v_i = 100$ mV, $v_k = -75$ mV, $v_l = -40$ mV, $g_{kc} = 10$ mS/cm², $g_{kv} = 1,700$ mS/cm², $g_i = 1,800$ mS/cm², $g_l = 7$ mS/cm², $\lambda_n = 230$, $k_c = 3.3/18$ and $\tau_c = 1/0.27$.

Adding a Gaussian white noise, $\xi(t)$, directly to the right hand of the first equation of deterministic Chay model, with the other two equations unchanged, forms the stochastic Chay model.

Chay models are solved by Mannella numerical integrate method (Mannella and Palleschi. 1989) with integration time step being 0.0001 s. An action potential is said to occur when the voltage crosses a value of -20 mV from below.

In the deterministic Chay model, $v_c \approx 486.75$ is a Hopf bifurcation point. When v_c is bigger than 486.75, the system is at a fixed point being as a stable focus, when v_c is smaller than 486.75, the system is at a period 1 limit cycle. When noise is introduced, spontaneous integer multiple firing pattern lying between period 1 firing and rest condition can be simulated (Gu et al. 2001; Yang et al. 2004, 2009).

Firing patterns in stochastic Chay model

The integer multiple firing pattern can be simulated near the Hopf bifurcation point in a large range of noise density and parameter v_c (Gu et al. 2001). Spike trains of the

integer multiple firing pattern when $v_c = 486.78$ and $D = 1.0$ is shown in Fig. 6a. Spike trains and ISIH corresponding to $v_c = 486.3$ and $D = 0.05$ simulated in stochastic Chay model is shown in Fig. 6b, c, respectively, exhibiting characteristics similar to the experimental observation. Except the first higher peak in ISIH, the amplitudes of all other peaks decrease approximately exponentially, as shown in Fig. 6c.

The autocorrelation coefficient of the ISI series is zero when the lag is non-zero, as shown in Fig. 6c. It is different to the experimental firing patterns. The cause will be interpreted in “Non-renewal characteristics and excitatory effect”

Excitatory effect in the firing pattern

For the focus near the Hopf bifurcation point ($v_c = 486.78$), its behavior of membrane voltage is a stable value in the deterministic Chay model, as shown in Fig. 7a when time is less than 2,500 s. An action potential can be induced by a suitable perturbation when time is 2,500 s. Subthreshold oscillation whose amplitude is decreased after the action potential when time is larger than 2,500 s. In other words, the amplitude of the first subthreshold oscillation after an action potential is higher than the other ones, as shown in Fig. 7a, b. Therefore, the continuous spikes appeared easily in the stochastic Chay model because a spike can impose an excitatory effect to the next subthreshold oscillation or spike following the spike. It can also be seen from the spike trains of the integer multiple firing, as shown in Fig. 7a, b. The amplitude of the first subthreshold oscillation after an action potential is higher than the other ones, as shown in Fig. 7c, d.

Hypothesis of the formation of three cases of exponential decay in ISIH

Binary chain transformed from the firing pattern

For the integer multiple firing patterns with exponential decay characteristic in ISIH simulated in FHN model, the response of the model in each external period is a spike or subthreshold oscillation. In general, the location of the spike is not the exact maximal value of the external period, leading to the dispersed distribution of ISI in each peak in ISIH. Based on this recognition, we can reduce the integer multiple firing pattern to a binary chain, ignoring the exact generation time of the spike in an external period. A binary discrete chain can be transformed according to the rules as follow, a spike in an external period is labeled as 1 and a subthreshold oscillation as 0. For example, the chain corresponding to the spike train shown in Fig. 3a is

Fig. 6 Spontaneous integer multiple firing in stochastic Chay model. **a** Spike trains ($v_c = 486.78$, $D = 1$). **b** Spike trains ($v_c = 486.3$, $D = 0.05$). The spikes often appear continuously. **c** ISIH ($v_c = 486.3$, $D = 0.05$). **d** Autocorrelation coefficient of ISI series ($v_c = 486.3$, $D = 0.05$)

0110101011. In addition, the chain can also be transformed from ISIH. If an ISI locates in the k -th peak in ISIH, its chain is a string containing $k-1$ continual 0, and ended with a 1. This method is employed in this paper to acquire the

Fig. 7 **a** Subthreshold oscillation following an action potential generated from a focus by a suitable perturbation at time 2,500 s in deterministic Chay model ($v_c = 486.78$). **b** Enlargement of **a**. **c** The enlargement of subthreshold oscillation after the fourth spike in Fig. 6a. The amplitude of the first subthreshold oscillation is higher than others. **d** The enlargement of subthreshold oscillation after the fourth spike in Fig. 6b. The amplitude of the first subthreshold oscillation is higher than others

chain for the spontaneous integer multiple firing patterns simulated in the stochastic Chay model and recorded in the experimental neural pacemaker.

The 3 typical firing patterns with exponential decay characteristic are simulated in FHN model with long period, short period and stochastic Chay model, respectively, in the “Numerical simulation results of the firing patterns” They exhibit independency, dependency being as inhibitory effect within two successive spikes and excitatory effect within two successive spike, as primarily analyzed in “Numerical simulation results of the firing patterns” Therefore, the chains transformed from the three typical firing patterns exhibit characteristics that a spike only imposes influence to the following spike in the next period or no influence to the following behavior, while a subthreshold oscillation imposes no influence to the following behavior.

For such a transformed binary chain, the total number of ISI in the k -th peak labeled as $NP(k)$ can be acquired easily by calculating the number of a string beginning with 1, followed by $k - 1$ continual 0 and ended with a 1 over the whole chain. Therefore, the relationship between $NP(k)$ and k in the chain can be acquired easily, employed to identify the relationship between peak amplitudes $y(k)$ and the corresponding ISI values $x(k)$ for the integer multiple firing.

For the convenience, the definitions or symbols used in the following section are given as follows. The total number of symbols in the chain is labeled as N . The number of symbol 1 and 0 is N_1 and N_0 , respectively. The corresponding probability is regarded as R_1 and R_0 , corresponding to the frequencies of the times of the symbol over the whole chain. $N_1 + N_0 = N$, $R_1 = N_1/N$ and $R_0 = N_0/N$, $R_1 + R_0 = 1$. The number of sequences 11, 10, 01 and 00 over the whole chain is labeled as N_{11} , N_{10} , N_{01} and N_{00} , respectively, and the corresponding probability is labeled as R_{11} , R_{10} , R_{01} and R_{00} , respectively. $N_{11} + N_{10} + N_{01} + N_{00} = N$. $R_{11} = N_{11}/(N - 1)$, $R_{10} = N_{10}/(N - 1)$, $R_{01} = N_{01}/(N - 1)$ and $R_{00} = N_{00}/(N - 1)$. where $R_{11} + R_{10} = R_1$, $R_{01} + R_{00} = R_0$. The probability from 0 to 0, 0 to 1, 1 to 0 and 1 to 1 in the chain is labeled as $P_{(0 \rightarrow 0)}$, $P_{(0 \rightarrow 1)}$, $P_{(1 \rightarrow 0)}$ and $P_{(1 \rightarrow 1)}$, respectively, and the value can be correspondingly calculated as R_{00}/R_0 , R_{01}/R_0 , R_{10}/R_1 , and R_{11}/R_1 . $P_{(0 \rightarrow 0)} + P_{(0 \rightarrow 1)} = 1$, $P_{(1 \rightarrow 0)} + P_{(1 \rightarrow 1)} = 1$.

The above mentioned binary chain in this paper can be classified into three cases as follows.

Case 1: A symbol 1 imposes no influence to the next symbol over the whole chain, whether it is 1 or 0. A symbol 0 also imposes no influence to the next symbol. The transition from 0 to 0, 0 to 1, 1 to 0 and 1 to 1 over the whole chain is independent, $P_{(1 \rightarrow 1)} = P_{(0 \rightarrow 1)}$, i.e. $R_{11}/R_1 = R_{01}/R_0$, $R_{11} = R_1^2$, $R_{10} = R_1 R_0$, $R_{01} = R_0 R_1$ and $R_{00} = R_0^2$.

Case 2: A symbol 1 can impose excitatory effect to the next symbol 1. $P_{(1 \rightarrow 1)} > P_{(0 \rightarrow 1)}$, i.e. $R_{11}/R_1 > R_{01}/R_0$.

Case 3: A symbol 1 imposes inhibitory effect to the next symbol 1. $P_{(1 \rightarrow 1)} < P_{(0 \rightarrow 1)}$, i.e. $R_{11}/R_1 < R_{01}/R_0$.

Exponential decay characteristic in the binary chain

$NP(k)$, equals to the number of a string in the chain beginning with 1, followed by $k - 1$ continual 0 and ended with a 1. Therefore the relationship between $NP(k)$ and k is:

$$NP(1) = NR_1 P_{(1 \rightarrow 1)} = NR_1 \frac{R_{11}}{R_1} = NR_{11} \quad (7)$$

$$\begin{aligned} NP(2) &= NR_1 P_{(1 \rightarrow 0)} P_{(0 \rightarrow 1)} = NR_1 \frac{R_{10}}{R_1} \frac{R_{01}}{R_0} \\ &= N \frac{R_0 R_{10} R_{01}}{R_{00}^2} \left(\frac{R_{00}}{R_0} \right)^2 \end{aligned} \quad (8)$$

$$\begin{aligned} NP(k) &= NR_1 P_{(1 \rightarrow 0)} P_{(0 \rightarrow 0)}^{k-2} P_{(0 \rightarrow 1)} \\ &= N \frac{R_0 R_{10} R_{01}}{R_{00}^2} \left(\frac{R_{00}}{R_0} \right)^k \quad (k > 2) \end{aligned} \quad (9)$$

Equations (7)–(9) can be written as

$$NP(1) = NR_{11} \quad (10)$$

$$NP(k) = N \frac{R_0 R_{10} R_{01}}{R_{00}^2} \left(\frac{R_{00}}{R_0} \right)^k \quad (k > 1) \quad (11)$$

The above calculation shows that the changes of $NP(k)$ ($k > 1$) with respect to the increase of k are decreased exponentially and can also be explicitly expressed by the probabilities of symbols in the binary chain.

Applying logarithm on Eq. (11) yields,

$$\log NP(k) = k \log \left(\frac{R_{00}}{R_0} \right) + \log \left(N \frac{R_0 R_{10} R_{01}}{R_{00}^2} \right) \quad (k > 1) \quad (12)$$

It shows that the decay slope of $\log NP(k)$ is $\log \frac{R_{00}}{R_0}$ when $k > 1$.

In the following subsection, we will study that the three cases of binary chain to reveal that the first peak (R_{11}) equals, is higher and lower than what estimated from Eq. (11) when $k = 1$, being as $\frac{R_0 R_{10} R_{01}}{R_{00}^2} \left(\frac{R_{00}}{R_0} \right)^k = \frac{R_{10} R_{01}}{R_{00}} \quad (k = 1)$.

Case 1

In this condition, $R_{11} = R_1^2$, $R_{10} = R_1 R_0$, $R_{01} = R_0 R_1$ and $R_{00} = R_0^2$. We can acquire $R_{11} = \frac{R_{10} R_{01}}{R_{00}}$.

The proof procedure is as follows,

$$R_{11} = R_1^2 \quad (13)$$

$$\frac{R_{10}R_{01}}{R_{00}} = \frac{R_1R_0R_0R_1}{R_0R_0} = R_1^2 \quad (14)$$

Therefore

$$R_{11} = \frac{R_{10}R_{01}}{R_{00}} \quad (15)$$

The relationship between $NP(k)$ and k in this condition is reduced to

$$NP(k) = N \frac{R_1^2}{R_0} R_0^k \quad (16)$$

The result shows that $NP(k)$ decrease exponentially with respect to k for all peaks. Because R_0 is less than 1, $NP(k)$ decreases exponentially with respect to the increase of k .

Applying logarithm to Eq. (16),

$$\log NP(k) = k \log R_0 + \log \left(N \frac{R_1^2}{R_0} \right) \quad (17)$$

$\log NP(k)$ decays lineally with respect to k , and the decay slope is reduced to $\log R_0$, corresponding to the condition $R_{00} = R_0^2$.

Case 2

In this case, $P_{(1 \rightarrow 1)} > P_{(0 \rightarrow 1)}$, i.e. $R_{11}/R_1 > R_{01}/R_0$. We can acquire that $R_{11} > \frac{R_{10}R_{01}}{R_{00}}$. The proof procedure is as follows,

$$\begin{aligned} P_{(1 \rightarrow 1)} > P_{(0 \rightarrow 1)} &\Rightarrow 1 - P_{(1 \rightarrow 1)} < 1 - P_{(0 \rightarrow 1)} \\ &\Rightarrow P_{(0 \rightarrow 0)} > P_{(1 \rightarrow 0)} \Rightarrow P_{(1 \rightarrow 1)} P_{(0 \rightarrow 0)} \\ &> P_{(0 \rightarrow 1)} P_{(1 \rightarrow 0)} \\ &\Rightarrow \frac{R_{11}}{R_1} \frac{R_{00}}{R_0} > \frac{R_{01}}{R_0} \frac{R_{10}}{R_1} \Rightarrow R_{11} > \frac{R_{01}R_{10}}{R_{00}} \end{aligned} \quad (18)$$

The above calculation shows that, except a higher first peak $NP(1)$, the changes of $NP(k)$ ($k > 1$) with respect to the increase of k are decreased exponentially. The decay slope of $\log NP(k)$ is $\log \frac{R_{00}}{R_0}$ when $k > 1$.

Case 3

In this case, $P_{(1 \rightarrow 1)} < P_{(0 \rightarrow 1)}$, i.e. $R_{11}/R_1 < R_{01}/R_0$. We can acquire that $R_{11} < \frac{R_{10}R_{01}}{R_{00}}$.

Following the proof procedure of excitatory effect of Eq. (18), changing the symbol ‘>’ to ‘<’ gives the calculation of a lower R_{11} caused by the inhibitory effects.

The result shows that in this condition, except a lower $NP(1)$, the changes of $NP(k)$ ($k > 1$) with respect to the increase of k are decreased exponentially. The decay slope of $\log NP(k)$ is also $\log \left(\frac{R_{00}}{R_0} \right)$ when $k > 1$.

Test the hypothesis using binary chain of the simulation firing patterns

In this Section, we test the hypothesis of the exponential decay law proposed in “[Hypothesis of the formation of three cases of exponential decay in ISIH](#)”, using binary chains transformed from 3 typical firing patterns simulated in “[Numerical simulation results of the firing patterns](#)”.

The firing pattern characterized by exponential decay without bias

Exponential decay and decay slope

For the chain of the firing pattern characterized by exponential decay without bias, $R_0 = 0.396$. The calculated value of decay slope is $\log R_0 = \log 0.396 = -0.402$.

The least square regression of the relationship between $\log NP(k)$ and k yields

$$\log NP(k) = 5.157 - 0.405k \quad (19)$$

with a correlation coefficient being -0.995 , implying that $\log NP(k)$ and k strictly obey negative linear law. The decay slope is -0.405 , very close to what calculated with binary chain (-0.402), with a relative error being 0.75% .

Renewal characteristics

The autocorrelation coefficient of the binary chain of the simulation trial also exhibit zero value at non-zero lags, as shown in Fig. 8b, exhibiting a renewal characteristics.

The influence of noise induced dispersed distribution of ISI in each peak on exponential decay

Considering that under the influence of noise, the spikes do not exactly appear at the time corresponding to the maximum of the periodic signal, led to a stochastic distribution of ISI in each peak in ISIH. While the stochastic distribution of ISI in each peak in ISIH is ignored when the binary chain is transformed. Can the dispersed ISI distribution in each peak in ISIH change the exponential decay law between $NP(k)$ and k ? We further calculate the relationship between $NP(k)$ and $y(k)$ to identify how the exponential decay law between $NP(k)$ and k influence the exponential decay between $y(k)$ and $x(k)$. $x(k) \approx kT$ in this condition.

If $\log NP(k)$ and $\log y(k)$ obeys a linear relationship as follows

$$\log NP(k) = M \log y(k) + B \quad (20)$$

where M and B are constants, then

Fig. 8 Firing pattern simulated in stochastic FHN model stimulated by external cosine signal ($I = 0.095$, $\omega = 1.5$, $D = 0.0001$). **a** Relationship between the total number of ISI in k -th peak $NP(k)$ and k . **b** Autocorrelation coefficient of binary chain. **c** Linear relationship between $\log NP(k)$ and $\log y(k)$. Where $y(k)$ is the k -th peak amplitude in ISIH

$$\log NP(k) = M \log y(k) + B = k \log R_0 + \log \left(N \frac{R_1^2}{R_0} \right) \quad (21)$$

$$\log y(k) = \frac{\log R_0}{M} k + \frac{\log \left(N \frac{R_1^2}{R_0} \right) - B}{M} \quad (22)$$

$$\log y(k) = \frac{\log R_0}{MT} kT + \frac{\log \left(N \frac{R_1^2}{R_0} \right) - B}{M} \quad (23)$$

$$\log y(k) \approx \frac{\log R_0}{MT} x(k) + \frac{\log \left(N \frac{R_1^2}{R_0} \right) - B}{M} \quad (24)$$

We can acquire that if $\log NP(k)$ and $y(k)$ obeys linear relationship, $\log y(k)$ also decreases linearly with respect to the increase of $x(k)$. The decay slope is $\frac{\log R_0}{MT}$.

Applying this calculation to the simulation data, least square regression method to $\log NP(k)$ and $\log y(k)$ yields that $\log NP(k) = 1.08 \log y(k) + 0.43$ with a correlation coefficient being 0.998, showing that there exists a linear relationship between $\log NP(k)$ and $\log y(k)$, as shown in Fig. 8c. $M = 1.08$ and $B = 0.43$. Then $\log y(k)$ decreases with respect to the increase of $x(k)$. The decay slope is $\frac{\log R_0}{MT} = -0.088$ ($T \approx 4.19$), which is very close to the value (-0.09) directly calculated from $y(k)$ and $x(k)$ using linear regress method. If logarithm is ignored, $NP(k) = 10^{0.43} (y(k))^{1.08} \approx 2.69 y(k)$. It shows that $NP(k)$ is approximately proportional to $y(k)$.

The result shows that the dispersed distribution of ISI in each peak in ISIH caused by noise can not essentially change the exponential decay characteristics of the binary chain. Therefore the exponential decay law between $NP(k)$ and k can be hold and exhibit between $y(k)$ and $x(k)$.

The firing pattern characterized by exponential decay with a lower first peak

Exponential decay and decay slope

For the binary chain transformed from the firing pattern characterized by exponential decay with a lower first peak characterized by exponential decay with a lower first peak in ISIH, the probabilities yield that $R_1 = 0.403$, $R_0 = 0.597$, $R_{11} = 0.064$, $R_{10} = 0.339$, $R_{01} = 0.339$ and $R_{00} = 0.258$.

$\frac{R_{11}}{R_1} = 0.159 < \frac{R_{01}}{R_0} = 0.567$, and $R_{11} = 0.064 < R_1^2 = 0.162$, showing that a spike imposes inhibitory effect on the generation of a spike in the next period. $\log R_0 = -0.224$ and $\log \frac{R_{00}}{R_0} = -0.364$.

Considering the first peak in ISIH and applying the least square regress method to $NP(k)$ and k yields that $\log NP(k) = 3.987 - 0.288 k$ with a correlation coefficient being -0.95 , as shown in Fig. 9a (dashed line). The decay slope -0.288 is quite different from $\log R_0 = -0.224$.

Ignoring the first peak and applying the least square regression method, $\log NP(k) = 4.398 - 0.360 k$ ($k > 1$) with a correlation coefficient being -0.998 , as shown in Fig. 9a (solid line), implying more confident than that obtained when $NP(1)$ is considered. The decay slope -0.360 is very close to theoretical value (-0.364), with a relative error being 1.10%.

Non-renewal characteristics and inhibitory effect

The autocorrelation coefficient of the binary chain is -0.39 when the lag is 1, as shown in Fig. 9b, showing non-renewal characteristic. The negative correlation when lag is 1 is consistent with the inhibitory effect within two successive symbols. Compared to the binary chain, the autocorrelation coefficient $\rho[1]$ (-0.12) of the ISI shown in Fig. 4c is decreased. It is caused by the dispersed distribution of ISI in each peak in ISIH.

Fig. 9 Firing pattern simulated in stochastic FHN model stimulated by external cosine signal and noise ($I = 0.05$, $\omega = 6.1$, $A = 0.01$, $D = 0.0001$). **a** Relationship between the total number of ISI in k -th peak ($NP(k)$) and k . The solid line is for other peaks exclusive the first peak. The dashed line is for all peaks. **b** Autocorrelation coefficient of binary chain

The firing pattern characterized by exponential decay with a higher first peak

Exponential decay and decay slope

For the binary chain of the firing pattern characterized by exponential decay with a higher first peak, the probabilities are $R_1 = 0.625$, $R_0 = 0.375$, $R_{11} = 0.449$, $R_{10} = 0.176$, $R_{01} = 0.176$ and $R_{00} = 0.198$.

$\frac{R_{11}}{R_1} = 0.718 > \frac{R_{01}}{R_0} = 0.469$, and $R_{11} = 0.449 > R_1^2 = 0.391$, indicating that a spike imposes an excitatory effect on its following spike. $\log R_0 = -0.426$ and $\log \frac{R_{00}}{R_0} = -0.276$.

The least square regression method to all peaks yields $\log NP(k) = 3.567 - 0.349 k$ with a correlation coefficient being -0.975 , as shown in Fig. 10a (dashed line). The decay slope is -0.349 , different from $\log R_0 = -0.426$.

If the first peak in ISIH is ignored, an equation being $\log NP(k) = 3.260 - 0.283 k$ is acquired with a correlation coefficient being -0.996 , using the least square regression method, as shown in Fig. 10a (solid line). The decay slope is -0.283 , is very close to $\log \frac{R_{00}}{R_0} = -0.276$. The relative error is 2.54%.

Non-renewal characteristics and excitatory effect

The autocorrelation coefficient of the binary chain is 0.30 when the lag is 1, as shown in Fig. 10b, indicating existence of probability dependency in the binary chain. The positive value of autocorrelation coefficient is consistent with the excitatory effect within the binary chain.

The $\rho[1]$ of ISI series shown in Fig. 6c is zero, much less than that of the binary chain. It shows that in this condition the probability dependency within the binary chain can be disturbed by stochastic component that induces the distribution of ISI in each peak in ISIH.

Fig. 10 Firing pattern simulated in stochastic Chay model). **a** Relationship between the total number of ISI in k -th peak ($NP(k)$) and k . The solid line is for other peaks exclusive the first peak. The dashed line is for all peaks. **b** Autocorrelation coefficient of binary chain

Test the hypothesis using the experimental firing pattern

Firing pattern characterized by exponential decay without bias

Exponential decay and decay slope

For the binary chain of the integer multiple firing recorded from CA1 pyramidal neuron characterized by exponential decay without bias in ISIH, the probabilities are $R_1 = 0.388$ and $R_0 = 0.612$. $\log R_0 = -0.213$.

Applying the least square regress method to $NP(k)$ and k , yields $\log NP(k) = 2.497 - 0.198 k$ with a correlation coefficient -0.983 , as shown in Fig. 11a. The decay slope is -0.198 , close to $\log R_0 = -0.213$ with a relative error 7.05%. Because there exists more influencing factors than only white noise used in theoretical model, the acquired correlation coefficient is smaller and the error is larger, respectively, than the simulated values.

Renewal characteristics

The autocorrelation coefficient of the binary chain is zero for non-zero lag, exhibiting independent and renewal characteristics, as shown in Fig. 11b.

Firing pattern characterized by exponential decay with a higher first peak

Exponential decay and decay slope

For the binary chain of the spontaneous integer multiple firing recorded from the experiment on a neural pacemaker shown in Firing pattern characterized by exponential decay with a higher first peak in ISIH, the probabilities are $R_1 = 0.671$, $R_0 = 0.329$, $R_{11} = 0.533$, $R_{10} = 0.138$, $R_{01} = 0.138$ and $R_{00} = 0.192$.

Fig. 11 Firing pattern generated in CA1 pyramidal neuron of hippocampal slice. **a** Relationship between the total number of ISI in k -th peak ($NP(k)$) and k . **b** Autocorrelation coefficient of binary chain

Fig. 12 Firing pattern discovered in the experiment on neural pacemaker. **a** Relationship between the total number of ISI in k -th peak ($NP(k)$) and k . The solid line is for other peaks exclusive of the first peak. The dashed line is for all peaks. **b** Autocorrelation coefficient of binary chain

$\frac{R_{11}}{R_1} = 0.794 > \frac{R_{01}}{R_0} = 0.419$, $R_{11} = 0.533 > R_1^2 = 0.450$, showing that a spike imposes excitatory effect on the following cycle. $\log R_0 = -0.483$ and $\log \frac{R_{00}}{R_0} = -0.234$.

Application of the least square regress method to all peaks in ISIH yields a relationship between $\log NP(k)$ and k , which is $\log NP(k) = 3.238 - 0.269 k$ with a correlation coefficient being -0.96 , as shown in Fig. 12a (dashed line). The decay slope is -0.269 , which is quite different from $\log R_0 = -0.483$.

Ignoring the first peak in ISIH and using the least square regress method, the relationship between $\log NP(k)$ and k can be acquired as $\log NP(k) = 2.905 - 0.224 k$ ($k > 1$), as shown in Fig. 12a (solid line), with a correlation coefficient being -0.986 . The decay slope is -0.224 , which is very close to the calculated value $\log \frac{R_{00}}{R_0} = -0.234$ with a relative error being 4.27%.

Non-renewal characteristics and excitatory effect

The autocorrelation coefficient of the binary chain is 0.3 when the lag is 1, as shown in Fig. 12b. The result indicates the probability dependence in the binary chain. The positive $\rho[1]$ is consistent with the excitatory effect within the binary chain. The decrease of $\rho[1]$ in ISI series shown in Fig. 2c is induced by the stochastic component that induces the dispersed distribution of ISI in each peak in ISIH.

The links to previous experimental results

The integer multiple firing pattern with exponential decay characteristic except the first lower peak whose ISI is located at the external signal, was discovered in previous experimental studies (for example, Fig. 30f, g in Gammaitoni et al. (1998)). According to the results in this paper, this firing pattern is suggested to be generated when the period of external forcing is on the order of the intrinsic period for the nervous system, awaited further experimental demonstration.

Discussion and conclusion

This paper studied three typical cases of exponential decay observed in ISIH peaks of stochastic integer multiple firing patterns. The first case is the exponential decay without bias. In experiments on rat hippocampal CA1 pyramidal neuron, we observed such an integer multiple firing pattern induced by the external stimulation. The experimentally obtained ISIH exhibits exponential decay without bias. By transforming the firing train into a discrete binary chain composed of symbol 0 (a cycle of quiescence) and 1 (a cycle of spike), we calculated the probabilities or frequencies of symbols in the binary chain and revealed that this case of exponential decay results from a stochastic renewal process. There is no dependency between the spikes within this firing pattern. And the exponential decay slope is related to the probability of symbol 0 in the binary chain. The second case is the exponential decay with a higher first peak and the third case is that with a lower first peak. An example of the second case was provided by experimentation on a neural pacemaker. Simulation and calculation of the second and the third cases indicate that the dependency in successive spikes of the firing leads to the bias seen in decay of ISIH peaks. We also transformed the original firing trains of the second and the third cases into stochastic binary chains and calculated the probabilistic of the different chains. If the binary chain is a stochastic non-renewal process and the dependency existed only within two successive symbols, the first peak in ISIH becomes a deviated value while other peaks exhibit exponential decay characteristics. The decay slope is related to not only the probability of the symbol 0 but also the joint probability of two successive symbols 00. If dependency within two successive symbol 1 is an excitatory effect, the first peak becomes higher. If the dependency within two successive symbol 1 is an inhibitory effect, the first peak in ISIH becomes lower. A simulation example of the inhibitory effect was provided and linked to the previous experimental discovery. The results of this paper clearly reveal the mechanism of the exponential decay in ISIH peaks of a number of important neural firing patterns and provide new understanding for typical bias from the exponential decay law.

Previous studies have demonstrated that the stochastic integer multiple firing patterns exhibiting exponential decay in ISIH appear in the situations of SR (Longtin et al. 1991, 1994; Wiesenfeld and Moss 1995; Chialvo et al. 1993; Gammaitoni et al. 1998) and CR phenomena (Gu et al. 2001; Braun et al. 1994; Gu et al. 2002). Such firing activities usually appear when the system is adjusted to be near to a bifurcation from resting to firing, including super-critical (Gu et al. 2001; Yang et al. 2004) and sub-critical (Yang et al. 2004) Hopf bifurcation, whose coexisting parameter region of the bistable states was very narrow

(Yang et al. 2004). There are two aspects of the effect of noise on the firing. One is that noise induces a stochastic transition between a cycle of spike and a cycle of sub-threshold oscillation. The other is that noise disperses the timing of the spikes leading to an ISI distribution in ISIH. The former stochastic effect can be reflected by a binary chain transformed from the firing and cause the exponential decay characteristic existed in the binary chain. The latter stochastic effect can not influence the exponential decay law determined by the former effect, but can influence the correlation degree within firing patterns. The noise induced firing patterns near sub-critical Hopf bifurcation with wide coexisting parameter region should be different to the integer multiple firing, awaited to be further analyzed.

The presently discussed three cases of the stochastic integer multiple firing are typical examples. If dependency between spikes is not limited within only two successive symbols, the firing pattern and its multi-modal ISIH can be more complex. For example, the firing with multi-peaks in ISIH discovered in the experiment on P-type electroreceptors of electronic fish was simulated in a leaky integrate-and-fire with dynamic threshold (LIFDT) model (Chacron et al. 2000, 2001a, 2001b). The negative correlation characterized by autocorrelation coefficient and memory in the firing train was identified to play an important role in the dynamic property of the firing train. Peak amplitude in ISIH of such firing train does not show exponential decay, but increases firstly and then decreases.

Other than the stochastic integer multiple firing patterns, a series of deterministic multi-modal firing patterns, exhibiting non-exponential decay characteristic in ISIH, have also been observed in simulations and in experiments (Wang 1994; Kaplan et al. 1996; Suzuki et al. 2000; Gong et al. 2002; Xie et al. 2006; Yang et al. 2009). For example, some deterministic firing patterns with multi-modal ISIH were discovered in experiments on giant axon stimulated by external periodic signal (Kaplan et al. 1996). The experimental observation was simulated with FHN model (Kaplan et al. 1996). In addition, deterministic firing pattern with multi-peaks in ISIH was simulated with a leaky-integrator model and experimentally observed on wind receptor cells of crick stimulated by a chaotic signal constructed from Rössler attractor (Suzuki et al. 2000), also exhibiting non-exponential decay characteristics. The diversity in ISIH distribution seen in multi-modal firing patterns, and the difference between stochastic and deterministic multi-modal firing pattern are all interesting questions to be assessed. The results and methods of this paper will be also helpful to distinguish the stochastic and deterministic multi-modal firing patterns.

In addition, multiple samples of time series are employed to perform the stochastic mechanism analysis in theoretical studies (Zhu 1992) or in some experimental

studies where multiple samples can be acquired easily. In the experiments on neural firing patterns, multiple trials corresponding to a same condition are difficult to be acquired because the changeable animal and environmental conditions or complex experimental performance. Only a long sample of the time series can be acquired (Chacron et al. 2000, 2001a, b; Gong et al. 2002; Gu et al. 2001, 2002, 2003a, b, 2004; Kaplan et al. 1996; Yang et al. 2009), thought to be a stable process, and employed to study its deterministic or stochastic mechanism. To test stochastic or deterministic mechanism using multiple samples has been seldom performed on the neural firing patterns with restrict to the realistic difficulties.

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