

A measure of local variation of inter-spike intervals

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Abstract

It has been revealed in our recent study that cortical neurons are categorized into distinct types, according to a new measure of the local variation of inter-spike intervals, L_V . In this paper, we obtain values of the local variation L_V and a conventional coefficient of variation C_V for a variety of model point processes. While the value of C_V undergoes large changes by rate fluctuation of the point processes, the value of L_V does not undergo large changes by rate fluctuation, and is principally determined by the form of intrinsic interval distribution of the original model point process.

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1. Introduction

A purpose of neurophysiological study is to discover systematic changes in neuronal activity correlated to the animal's behavior. The site that contains a number of neurons that exhibit significant changes in activity in some particular behavioral context is regarded as the functional area. Though such a phenomenological understanding is interesting by itself, it is desirable to grasp the neuronal activity in the context of causal relation between anatomical circuitry and physiological function. For the purpose of obtaining such information with regard to circuitry, the information that identifies the type and location of the neuron would be useful.

Recorded data have some aspects useful for obtaining such information. It is conceived that a typical firing rate of an interneuron is higher than that of a pyramidal neuron (Ranck, 1973; Buzsaki et al., 1983). It is also conceived that there is a significant difference between the action potential waveforms of interneurons and pyramidal neurons (Csicsvari et al., 1998; Constantinidis et al., 2002; Takahashi et al., 2003).

In addition to those cues that distinguish between pyramidal neurons and interneurons, we have suggested that an analysis of the sequence of inter-spike intervals (ISIs) helps to classify the pyramidal neurons into distinct groups. In our previous study, we characterized the spike sequences with the estimated values of the coefficient of variation, C_V , the skewness coefficient, and the correlation coefficient of consecutive intervals, and found that their distributions depend strongly on the recording site (Shinomoto et al., 2002a,b). In a more recent study, we introduced a measure of local variation of inter-spike intervals,

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L_V , which characterizes the spiking randomness, and found that a distribution of L_V values for neurons in the medial frontal cortex is distinctly bimodal (Shinomoto et al., 2003). Two groups of neurons classified according to the values of L_V were found to exhibit different responses to the same stimulus. This fact suggests that neurons in the same area can be classified into different groups possessing unique spiking characteristics and corresponding functional properties.

In the present paper, we obtain values of the local variation L_V and the coefficient of variation C_V for a variety of mathematical point processes. First, we examine the doubly stochastic Poisson process to see how the values of L_V and C_V undergo changes by the rate fluctuation of the Poisson process. It is found that for the doubly stochastic Poisson process, the value of the local variation L_V stays near unity even if the rate fluctuation is comparable to the mean rate, while the value of the coefficient of variation C_V largely deviates from unity according to such rate fluctuation. Second, we obtain the range of the values of L_V and C_V for the Ornstein–Uhlenbeck process, which represents the conditions that the leaky integrate-and-fire neuron is subjected to independent inputs of many other neurons. Third, the values of L_V and C_V are obtained for the gamma process analytically, and for the rate modulated gamma process numerically. It is also confirmed that for the rate modulated gamma process, the value of L_V does not undergo large changes according to the rate fluctuation, but are mainly determined by the form of intrinsic ISI distribution parameterized by the order of a gamma distribution, while the value of C_V undergoes large changes by the rate fluctuation.

2. C_V and L_V

From a sequence of consecutive inter-spike intervals, $\{T_1, T_2, \dots, T_n\}$, we first estimate the coefficient of variation (see Cox and Lewis, 1966). An asymptotically unbiased estimator, which gives a theoretical value of the coefficient of variation in the limit of $n \rightarrow \infty$ could be

$$C_V = \frac{\Delta T}{\bar{T}}, \quad (1)$$

where ΔT is the sample standard deviation and $\bar{T} = 1/n \sum_{i=1}^n T_i$ is the sample mean interval. Throughout

this paper, we will refer to the above estimator as C_V . For a series of intervals, which are independently exponentially distributed, the C_V is expected to take a value 1 in the limit of $n \rightarrow \infty$. For a regular spike sequence in which T_i is constant, the C_V takes a value 0.

We next obtain a value of the local variation of inter-spike intervals, introduced by Shinomoto et al. (2003), defined as

$$L_V = \frac{1}{n-1} \sum_{i=1}^{n-1} \frac{3(T_i - T_{i+1})^2}{(T_i + T_{i+1})^2} \quad (2)$$

Here, the summand is proportional to the square of the individual terms of $C_{V2} = 2|T_1 - T_2|/|T_1 + T_2|$, which was introduced by Holt et al. (1996) for the purpose of comparing the temporal ISI randomness of neurons in vitro and in vivo. The factor 3 is taken here so that for a series of intervals, which are independently exponentially distributed, the L_V is expected to take a value 1. For a regular spike sequence in which T_i is constant, the L_V takes a value 0.

In this way, both the C_V and L_V are designed to stand at 1 for a sufficiently long Poisson (random) series of events, in which event intervals are independently exponentially distributed, and both stand at 0 for a sequence of regular intervals, in which event intervals are identical. The C_V detects a global variability of a whole ISI sequence, and is sensitive to the firing rate fluctuation, which may take place in natural conditions. On the other hand, the L_V detects the local stepwise variability of ISIs, and has been shown to robustly extract the firing characteristics intrinsic to individual neurons, even for the cases in which the spike rate is modulated.

Histograms of the C_V and L_V values obtained for the spike sequences recorded from neurons in the medial frontal cortex of a monkey performing a waiting period task (Shima et al., 2001) are plotted in Fig. 1. It is observed that the C_V distribution has a long tail extending to the right and possesses only a single peak, but the L_V distribution is compact, and possesses two distinct peaks. Here, the coefficients C_V and L_V were computed for a sequence of $n = 100$ ISIs, and the number of such ISI sequences was $N = 3506$. Though, it is generally true that a histogram bears spurious multimodality for too small bin size, we have confirmed that the present bimodality of the L_V distribution is not such a spurious one, but quite robust against the change of the bin size. In addition, the number of bins in Fig. 1 is roughly in

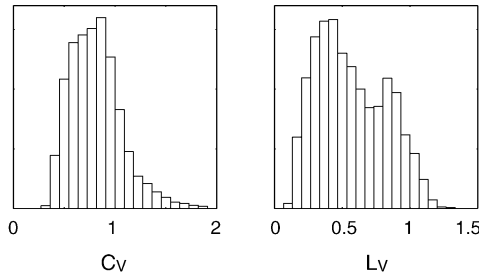


Fig. 1. Histograms of the values of C_V and L_V computed for the spike sequences recorded from neurons in the medial frontal cortex of a monkey (by courtesy of Keisetsu Shima and Jun Tanji).

accordance with Scott's rule, $\sim N^{1/3}$, with which the deviation of a sample histogram from the underlying distribution is minimized (Scott, 1992). According to this bimodal distributions of L_V values, we classified the neurons into two types; neurons that generate irregular spike sequences of large L_V values, and neurons that generate quasi-regular spike sequences of small L_V values. Those two groups of neurons were found to exhibit different responses to external stimuli (Shinomoto et al., 2003).

3. Values of C_V and L_V for model point processes

As has been shown in the preceding section, with L_V we were capable of categorizing neurons into two groups, while with C_V we were not. In order to have a grasp of the characteristics of these measures, we wish to obtain their values for a variety of mathematical point processes.

3.1. Doubly stochastic Poisson process

In the Poisson process, point events take place randomly in time with a certain fixed rate λ . In this process, the inter-event intervals t appear as independently chosen values from an exponential probability distribution,

$$p(t) = \lambda e^{-\lambda t}, \quad t \geq 0. \quad (3)$$

The expectation values of the two measures C_V and L_V for this independent and identical distribution of t are readily calculated as $C_V = 1$ (in the limit $n \rightarrow \infty$) and $L_V = 1$.

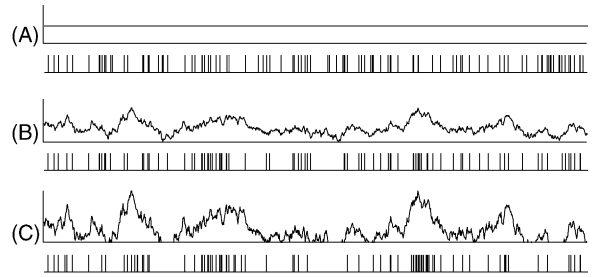


Fig. 2. Time dependent rates $\lambda(t)$ and the sample spikes derived: (A) the Poisson process of a constant rate $\lambda(t) = \lambda_0$, (B) doubly stochastic Poisson process of $\Delta/\lambda_0 = 0.5$, and (C) that of $\Delta/\lambda_0 = 1$.

Here, we obtain values of these two measures for the doubly stochastic Poisson process (see for instance Cox and Lewis, 1966), in which the spike rate of the Poisson process is temporally modulated (see Fig. 2). In particular, we consider the case that the spike rate $\lambda(t)$ is modulated according to the Ornstein–Uhlenbeck process,

$$\frac{d\lambda}{dt} = -\frac{\lambda - \lambda_0}{s} + \Delta \sqrt{\frac{2}{s}} \xi(t), \quad (4)$$

where λ_0 , Δ , and s , respectively, represent the mean rate, the amplitude of rate fluctuation, and the time scale of the rate fluctuation. $\xi(t)$ is Gaussian white noise with ensemble-averaged quantities $\langle \xi(t) \rangle = 0$ and $\langle \xi(t)\xi(t') \rangle = \delta(t-t')$. This process yields the fluctuating spike rate

$$\lambda(t) = \lambda_0 + \Delta \eta(t), \quad (5)$$

which is Gaussian and it is characterized by

$$\langle \eta(t) \rangle = 0, \quad \text{and} \quad \langle \eta(t)\eta(t') \rangle = e^{-|t-t'|/s} \quad (6)$$

In this process, we stipulate that spikes are not generated when $\lambda(t) \leq 0$, which may occur by fluctuation. It was proven that $C_V \geq 1$ for an infinite length spike sequence generated by a time dependent Poisson processes of arbitrary $\lambda(t)$ (Shinomoto and Tsubo, 2001). For the doubly stochastic Poisson process, the C_V and other coefficients are analytically tractable for the parameter range $s\Delta^2 < \lambda_0$. As we are concerned here with the wider parameter range, we performed a numerical simulation for computing values of C_V and L_V .

In our numerical simulation, a total interval of time is taken sufficiently long compared to the time scale

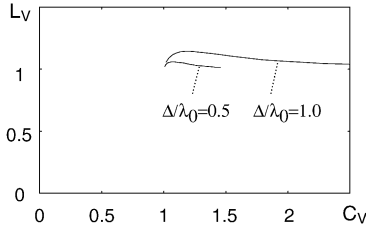


Fig. 3. Values of L_V and C_V for the spike sequences generated from the doubly stochastic Poisson process (see the text for detail). The local variation L_V does not undergo large changes even for the strong rate fluctuation Δ comparable to the mean spike rate λ_0 , while the coefficient of variation C_V undergoes large changes.

of fluctuation s to assure that the solutions are stationary, and insensitive to an initial condition, which we took $\lambda(t=0) = \lambda_0$. For each set of model parameter values, we numerically obtained 10 sequences of 100,000 ISIs, from which we compute the sample means and deviations of C_V and L_V . The mean C_V and L_V values obtained are depicted in Fig. 3. Sample standard deviations of those coefficients computed for such long sequences of ISIs are very small and are not described in the figure.

The numerical integration of the stochastic differential equation was carried out using the Heun method (Kloeden and Platen, 1997) with the step size $dt = 0.001$. By fixing $\lambda_0 = 1$, we took the cases $\Delta = 0.5$ and 1. For each value of Δ , the time scale of rate fluctuation s was changed from 0.03 to 16. For the rapid rate fluctuation (small s), both C_V and L_V do not deviate significantly from unity, but for the slow rate fluctuation (large s), the value of C_V deviates largely from unity. It is notable that even for the case that the amplitude of rate fluctuation Δ is comparable to the mean rate λ_0 , the value of L_V still stays near unity.

3.2. The Ornstein–Uhlenbeck process

Next, we wish to obtain values of C_V and L_V for the spiking processes of the conditions that a neuron is subjected to a number of independent input signals. A neuron is often modeled simply as a leaky integrator of incoming spike signals. If the cell membrane potential exceeds a certain threshold value, a neuron fires and emits a spike, and then the potential quickly returns to a certain fixed level. This membrane dynamics can be

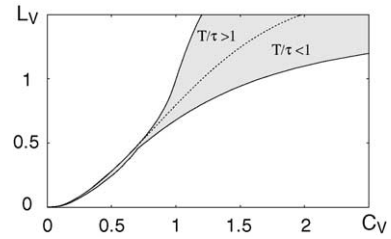


Fig. 4. The range of C_V and L_V for the spike sequences generated from the Ornstein–Uhlenbeck process. The range is divided according to whether mean inter-spike interval, T , is greater than the membrane time constant, τ , or not.

written as

$$\frac{dV}{dt} = -\frac{(V - V_r)}{\tau} + I(t),$$

if $V > V_1$, then $V \rightarrow V_0$, (7)

where V , V_r , τ , and $I(t)$ represent the cell membrane potential, the resting level, the membrane time constant, and the input, respectively. In the classical theory in which a neuron is regarded as an RC circuit, the decay time constant τ is given by the product of the membrane capacitance and the membrane resistance, and the input $I(t)$ represents the current flowing into the neuron, divided by the membrane resistance. If individual excitatory and inhibitory input currents are small in amplitude, its duration short, and if the frequency of inputs is high and temporally independent, then the total input current $I(t)$ can be regarded as the Gaussian white noise. Then the dynamics are identical to the Ornstein–Uhlenbeck process, and the ISI corresponds to the first passage time starting from V_0 and reaching V_1 .

There have been a number of theoretical studies on the first passage time of the stochastic process. The first passage time density can be given in a form of the integral “renewal equation” represented as Eq. (4.2) in Van Kampen (1992), or Eq. (9.49) in Tuckwell (1988). Solving the integral equation numerically, we obtain the range of the theoretical values of C_V and L_V , which should be obtained in the asymptotic limit $n \rightarrow \infty$ that the Ornstein–Uhlenbeck processes can cover (see Fig. 4).

3.3. Gamma process

Finally, we obtain values of C_V and L_V for the gamma process analytically, and for the rate modulated gamma process numerically.

For the Poisson ISI sequence, in which T_i and T_{i+1} are derived independently from the exponential distribution function, $p(t) = \lambda \exp(-\lambda t)$, the expectation value of the local variation is computed by

$$\int_0^\infty dt_1 \int_0^\infty dt_2 3 \frac{(t_1 - t_2)^2}{(t_1 + t_2)^2} \lambda^2 \exp(-\lambda t_1 - \lambda t_2) \quad (8)$$

This integration can be carried out with the transformation from $\{t_1, t_2\}$ to $\{x, y\} = \{\lambda(t_1 + t_2)/2, \lambda(t_1 - t_2)\}$ as

$$\int_0^\infty dx \int_{-2x}^{2x} dy 3 \frac{y^2}{(2x)^2} \exp(-2x) = 1 \quad (9)$$

We can also obtain the expectation value of L_V for the gamma process in which the ISIs are derived from the gamma distribution of the order κ ,

$$p_\kappa(t) = \lambda^\kappa t^{\kappa-1} \exp(-\lambda t) / \Gamma(\kappa), \quad (10)$$

where $\Gamma(\kappa) = \int_0^\infty dt t^{\kappa-1} \exp(-t)$ is the gamma function. The expectation value can readily be obtained analytically by means of the above-mentioned transformation,

$$\langle L_V \rangle = \frac{3}{2\kappa + 1}, \quad (11)$$

where $\langle \cdot \rangle$ represents the average operation with respect to the distribution. On the other hand, the expectation value of the C_V estimator for the gamma distribution in the limit of $n \rightarrow \infty$ is (see Cox and Lewis, 1966),

$$\langle C_V \rangle = \frac{1}{\sqrt{\kappa}} \quad (12)$$

The values of C_V and L_V obtained for the gamma processes of various order κ are depicted in Fig. 5.

In addition to those analytical results, we obtain values of C_V and L_V for the rate modulated gamma processes, using a numerical simulation. The original gamma processes of the integer order $\kappa = 2, 3, 4, \dots$ corresponds to the accumulated Poisson process, in which the neuron generates spikes when the number of incoming Poisson inputs reaches κ . The generalization from the gamma process to the rate modulated gamma process can be realized by replacing the incoming Poisson inputs with the doubly stochastic Poisson inputs. It is observed from Fig. 5 that L_V stays near the value for the original gamma process of the same order κ even if

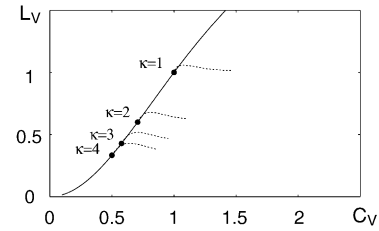


Fig. 5. C_V and L_V values for the gamma processes of various order κ are depicted as a line. Those for typical integer κ are given as closed circles. Numerical results obtained for the rate modulated gamma processes for the cases of $\Delta/\lambda_0 = 0.5$ are depicted as dotted lines.

the rate is greatly modulated, while C_V deviates largely according to the rate fluctuation.

4. Discussion

In the present paper, we have obtained values of the measure of local variation L_V and the conventional coefficient of variation C_V for typical mathematical point processes.

First, we examined the doubly stochastic Poisson process, and found that L_V stays near unity even if the amplitude of rate fluctuation is comparable to the mean rate, while C_V deviates very largely according to such rate fluctuation. Second, we examined the Ornstein–Uhlenbeck process, which represents the conditions that the leaky integrate-and-fire neuron is subjected to independent inputs of many other neurons, and obtained the possible range of those two measures for the Ornstein–Uhlenbeck process. Third, we examined the gamma process analytically, and the rate modulated gamma process numerically. We found that for the rate modulated gamma process, the L_V does not undergo large changes according to the rate fluctuation, but are mainly determined by the form of intrinsic ISI distribution parameterized by the order of a gamma distribution, while C_V undergoes large changes by the rate fluctuation.

In this way, it was confirmed that the measure of the local variation L_V is a good measure, which faithfully reflects an intrinsic spiking property even for the cases where the spike rate is largely modulated. We have seen in Fig. 1 that for the same set of the spike sequences recorded from neurons in the medial frontal cortex, the

distribution of L_V values possesses two peaks, while the distribution of C_V values possesses only a single peak. One plausible hypothesis is that each neuron is generating spikes according to an intrinsic ISI distribution, which is one of two alternative types such as quasi-regular and random, but the spike rate fluctuates in a natural condition in vivo. Such a condition can be modeled by the rate modulated gamma processes. For instance, the quasi-regular and random intrinsic distribution could be modeled by the gamma processes of the parameters $\kappa = 3\text{--}5$ and $\kappa = 1$. As we have seen above, even if the rates of those gamma processes fluctuate, the L_V values do not significantly deviate from their original values, and the distributions of the L_V values of two groups of neurons would not mix and the total distribution remains bimodal. On the other hand, the C_V values change largely according to the time scale of the rate fluctuation. If the time scales of rate fluctuation of the segmented sequences of 100 ISIs distribute widely, then their C_V values would distribute widely, and the distributions of the C_V values of two groups of neurons could mix and the total distribution may become unimodal.

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