MINIREVIEW

Randomness of Spontaneous Activity and Information Transfer in Neurons

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Summary

The analysis of information coding in neurons requires methods that measure different properties of neuronal signals. In this paper we review the recently proposed measure of randomness and compare it to the coefficient of variation, which is the frequently employed measure of variability of spiking neuronal activity. We focus on the problem of the spontaneous activity of neurons, and we hypothetize that under defined conditions, spontaneous activity is more random than evoked activity. This hypothesis is supported by contrasting variability and randomness obtained from experimental recordings of olfactory receptor neurons in rats.

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Information coding by spiking neuronal activity

One of the most fundamental problems in neuroscience is the problem of neuronal coding, i.e., the way information is represented in neuronal signals (Perkel and Bullock 1968, Softky 1995, Strong *et al.* 1998). Generally, neurons communicate via chemical and electrical synapses, in a process known as synaptic transmission. The crucial event that triggers synaptic transmission is the action potential (spike), a pulse of electrical discharge that travels along an axon's excitable membrane. Individual spikes in a spike train are usually well separated, and their shapes and durations for a given neuron are very similar. Therefore, it is presumed that the form of the action potential is not important in information transmission, and the whole spike train is described as a series of all-or-none point events in time (Gerstner and Kistler 2002, Nicholls *et al.* 2001). Since the lengths of the interspike intervals (ISIs) between two successive spikes in a spike train often vary, apparently randomly both within and across trials (Gerstner and Kistler 2002, Shadlen and Newsome 1998, Stein *et al.* 2005), statistical methods and methods of probability theory and stochastic point processes have been widely applied in the description and analysis of neuronal firing (Cox and Lewis 1966, Kass *et al.* 2005, Moore *et al.* 1966, Tuckwell 1988).

Two standard hypotheses, not mutually exclusive, of information coding by spike trains are usually considered (Perkel and Bullock 1968, Gerstner and Kistler 2002):

1) In the rate coding scheme, information sent along the axon is encoded by the number of spikes per observation time window (the firing rate) (Adrian 1928). In most sensory systems, the firing rate increases, generally non-linearly, with increasing stimulus intensity (Kandel *et al.* 1991). Any information possibly encoded in the temporal structure of the spike train is ignored. Consequently, rate coding is inefficient but highly robust with respect to the ISI ‚noise' (Stein *et al.* 2005). The temporal structure of ISIs, however, has also been proven to represent an informative part of the neuronal signal

(Gerstner and Kistler 2002, Shadlen and Newsome 1994, Stein *et al.* 2005), leading to the idea of temporal coding.

2) Temporal codes employ those features of the spiking activity that cannot be described by the firing rate. For example, time to the first spike after stimulus onset, characteristics based on the second and higher statistical moments of the ISI probability distribution, or precisely timed groups of spikes (temporal patterns) are candidates for temporal codes (Buracas and Albright 1999, Gerstner and Kistler 2002, Rieke *et al.* 1997). For an overview of temporal coding see Perkel and Bullock (1968), a more recent discussion can be found in Abeles (1994), Rieke *et al.* (1997), Shadlen and Newsome (1994), Stein *et al.* (2005), Theunissen and Miller (1995).

While the description of neuronal activity from the rate coding point of view is relatively straightforward (Lansky *et al.* 2004), temporal coding allows an infinite number of alternatives. Spike trains with equal firing rates may turn out to be different under various measures of their temporal structure. In order to describe and analyze the way information is represented in spike trains (Perkel and Bullock 1968, Softky 1995, Strong *et al.* 1998), particularly under the temporal coding paradigm, methods to compare different spike trains are needed (Bhumbra *et al.* 2004, Buracas and Albright 1999, Nemenman *et al.* 2004, Paninski 2003, Rieke *et al.* 1997, Victor and Purpura 1997). Here we restrict our attention to two concepts which, unfortunately, can be easily confused but, as will be seen, are entirely different: the concept of randomness versus of variability of spiking activity.

Variability and randomness

Clasically, the coefficient of variation of ISIs, C_V (the ratio of the standard deviation of ISIs to the mean ISI), is routinely used to characterize the variability of neuronal firing under steady-state conditions. Information coding by ISI variability, as a sub-type of temporal coding, is often reported in the literature: see Burns and Pritchard (1964), Fenton *et al.* (2002), Perkel and Bullock (1968), Ratliff *et al.* (1968) and many others. Furthermore, C_V is a dimensionless quantity, and spike trains with different mean ISIs can be compared meaningfully (Softky and Koch 1993). Thus, employing C_V allows one to separate the rate and temporal (variability) coding contributions.

In a series of recent papers (Kostal and Lansky 2006b, 2007, Kostal *et al.* 2007a) we have proposed an information-theoretic (Cover and Thomas 1991) measure of spiking randomness, η (Kostal and Lansky 2006a). In the simplest case of renewal spiking activity (ISIs are realizations of independent and identically distributed random variables) described by the ISI probability density function $f(t)$ (often representd by ISI histograms), η is defined as

$$\eta = -\int_0^\infty f(t)\ln f(t)dt - \ln E(T), \qquad (1)$$

where $E(T)$ is the mean ISI (integration range in (1) depends on the range of ISIs). The measure η can also be defined for non-renewal spiking activity (see Kostal and Lansky (2006a), Kostal *et al.* (2007a) for details).

Figure 1 shows the relation between variability and randomness for two frequently employed neuronal models - the leaky and perfect integrate-and-fire models (Tuckwell 1988, Gerstner and Kistler 2002). Three simulated (Kostal and Lansky 2006b, 2006a, Kostal *et al.* 2007b) and two real spike trains (Duchamp-Viret *et al.* 2005, Kostal and Lansky 2006a) are shown alongside one another. Essentially, η measures the ,choice' of different ISI lengths that appear in the spike train and the 'freedom' in their serial ordering. A larger choice of ISIs and more freedom in their ordering results, intuitively, in a greater randomness of spiking. There exists a unique maximally random spiking activity (η=1, Fig. 1A), which is generated by the Poisson model (Tuckwell 1988, Kostal *et al.* 2007a), and there exists a unique minimally variable activity ($C_V = 0$, pacemaking neuron). Although C_V and η are similar in concept (Kostal and Lansky 2006a, Kostal *et al.* 2007a), each of these measures provides a different point of view. For example, consider a hypothetical spike train consisting only of ,long' and ,short' ISIs. In the completely random case, there is an equal probability that each ISI is either long or short, while in a less random case there is a pattern formation (i.e., ,long-short' couplings). The C_V is the same in both cases since ISI correlations do not affect the variability (Fig. 1A and E). Even if there are no correlations between successive ISIs, the spike trains may still differ in their randomness but not in variability (Fig. 1A and C). On the other hand, equal ,choice' of possible ISI lengths may be either concentrated around one particular ISI length or ,spread' in such a way that the randomness is the same, but variability differs (Fig. 1B, C and D). Generally, spike trains with $C_V < 1$ look more regular (Fig. 1D), while $C_V > 1$ is often used as a marker for bursting
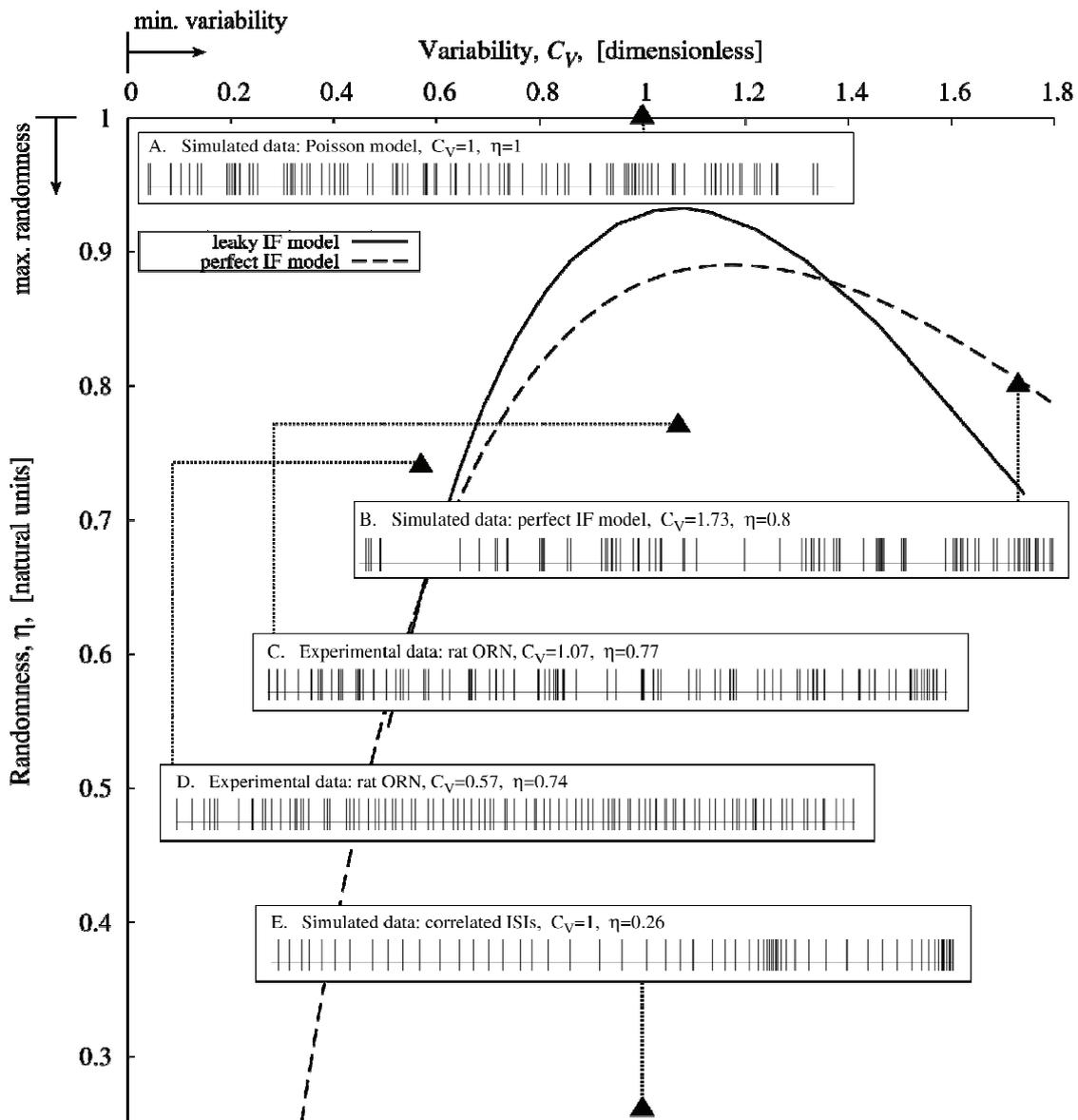
Fig. 1. Variability (C_V) and randomness (η) of simulated and experimental neuronal spiking activity. The solid and dashed curves show continuous dependence between C_V and η for a range of parameters of two standard neuronal models – the leaky and perfect integrate-and-fire models. The curves have a similar shape with maxima around $C_V = 1$, although this shape is not universal for all neuronal models (Kostal and Lansky 2006b, 2007). Five spiking activities (re-scaled to the same mean firing rate) are shown and their C_V and η are plotted (triangles). Although both C_V and η have intuitive interpretations, the samples show clearly that visual inspection of spike trains is not sufficient to quantify the degree of randomness or variability.

activity (Fig. 1B) (Duchamp-Viret *et al.* 2005, Kostal and Lansky 2006b, Tuckwell 1988). However, the quantities C_V and η are not entirely independent, e.g, there is no spiking activity with low variability and high randomness at the same time.

Finally, we note that making a strict distinction between randomness and variability avoids paradoxical results, although these two terms are often colloquially interchanged. Consider again, for example, a spike train consisting of ‚long‘ and ‚short‘ ISIs with no interval correlations. By adding ‚medium‘ length ISIs we do not increase the spiking variability, contrary to what might be

expected intuitively, but rather we decrease it. On the other hand, since the ‚choice‘ of ISIs is larger, the spiking randomness is increased. Furthermore, even if conventional analysis of two spike trains reveals no difference, the spike trains may still differ in their randomness, and the difference is detectable with a relatively limited amount of data (Kostal *et al.* 2007a).

The randomness of spontaneous activity

Spontaneous activity generally denotes such neuronal activity that is not related in any obvious way

to external stimulation (Gerstner and Kistler 2002, Shadlen and Newsome 1994). Such a relatively vague definition permits to denote as „spontaneous" very different conditions, often only in contrast to specifically controlled conditions, denoted as evoked activity. Spontaneous activity crucially affects information transfer, since the coding properties must be judged according to the deviation of the evoked activity from the spontaneous activity (Chacron *et al.* 2001, Chacron *et al.* 2003). Furthermore, spontaneous activity seems to be important for the establishment and maintenance of connectivity between neurons (Yu *et al.* 2004).

There is an ambiguity in the definition of spontaneous activity as provided above, because apparently „spontaneous" neuronal firing may still be affected by phenomena that are not under direct experimental control. For example, cortical neurons (or generally neurons interconnected in active networks) constantly receive signals from other neurons, and it is essentially these signals from other neurons that contribute the most to the character of the spontaneous activity. In the following we attempt to distinguish the „true" spontaneous activity that can be characterized as an intrinsic property of neurons. Such spontaneous activity may be best observed in first-order sensory neurons. Duchamp *et al.* (2005) suggested that the „spontaneous" activity of olfactory neurons in rats is modulated by the breathing frequency if the animals are allowed to breathe freely. Their experiment showed that if we wish to observe true spontaneous activity, any possible external effect must be reduced to a minimum. Does the absence of these external effects change the properties of the spontaneous activity?

From the rate coding perspective, the presence of a stimulus is clasically marked by an increased firing rate (Adrian 1928, Gerstner and Kistler 2002). Since there is a metabolic cost associated with each spike (Laughlin *et al.* 1998), it follows that true spontaneous activity should be characterized by low energy demands. Since low energy results in small spike counts, we may ask whether low energy affects the temporal structure of the spike train (temporal coding) in any way. The creation of particular spiking patterns, highly regular or modulated spiking requires energy or external stimulation, therefore we hypothetize that true spontaneous activity maximizes spiking randomness (according to the definition provided above). In other words, the Poisson model of spiking (Gerstner and Kistler 2002, Kostal and Lansky 2006b, Tuckwell 1988) should provide a good approximation (the Poisson model is idealized and lacks certain real-world features, for example the refractory phase). We note that there are sensory systems in which spontaneous activity is not random at all, for example, the electrosensory system of certain fish (Chacron *et al.* 2001, Ratnam and Nelson 2000). However, the spontaneous activity of such cells requires further mechanisms and energy to be maintained.

Chow and White (1996) analyzed the statistical properties of neuronal firing described by the classical Hodgkin-Huxley neuronal model (Hodgkin and Huxley 1952) with the inclusion of stochastic channel dynamics. It was shown that the spontaneous activity arising from channel fluctuations is well described by the Poisson model. Also, the firing of the leaky integrate-and-fire model without input current (but with stochastic fluctuations of the membrane potential) is described by the Poisson spiking model (Lansky and Sato 1999).

Statistical analysis of true spontaneous activity of first-order auditory neurons in guinea pigs (Lansky *et al.* 2006) confirmed that the Poisson model provides a good description. Duchamp-Viret *et al.* (2005) estimated variability and randomness from spontaneous activity recordings done on olfactory receptor neurons in freely breathing and tracheotomized rats. The recordings were obtained under steady-state conditions, and it was shown that in the majority of cases the firing can be considered renewal. It was demonstrated by considering the ‚amount' of randomness per time unit (Kostal and Lansky 2006a) that the activity is less variable but more random in the case of tracheotomized animals than in those freely breathing and that the Poisson model provides a good approximation. In other words, the activity observed in the case of tracheotomized animals is close to the ideal of true spontaneous activity. The result further illustrates that variability and randomness should not be used interchangeably.

Conflict of Interest
There is no conflict of interest.

Acknowledgements

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