Neural coding with spikes and bursts: characterizing neurons and networks with noisy input

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Citation for published version (APA):
Zeldenrust, F. (2012). Neural coding with spikes and bursts: characterizing neurons and networks with noisy input Amsterdam: Wohrmann Print Service
Appendix D. Reliability measures

D.1 Introduction

The reproducibility of spike trains, and the related question whether the spike rate or the precise timing of spikes is how information is coded in the brain, is an ongoing discussion (for an overview, see [143]) that started amongst others with the work of Mainen and Sejnowski [93] and de Ruyter van Steveninck et al. [29], who showed that neurons in rat neocortical slices and motion-sensitive neurons in the flys visual system can produce very reliable spike trains in response to fluctuating input. In this context, it is important to distinguish the notions of ‘reliability’ and ‘precision’ [143]: the first should quantify whether a spike occurs or not on the same time of each repetition of the stimulus, the second should quantify their jitter. Many ways have been to quantify these concepts, of which the some are based on the spike-time histogram (for example [93], [143], [84]), cross-correlations or binning [78], while others are binless and defined as a function of the inter-spike interval [83] or independent of any time scale [82]. Which one is the most appropriate might depend on the data and the precise definition of the research question [107].

In this thesis, we wanted to know whether the precision and robustness of the single spikes and bursts a thalamocortical relay (TCR) neuron fires change their reliability and robustness when the neuron goes from a bursting to a spiking regime. This means that we need measures that depend on the time scale, so we can assess the precision in time of the various events, but that are independent of the amount of events, so the precision and robustness of single spikes and bursts can be evaluated and compared between regimes without being obscured by the fact that there are more bursts in the bursting regime and more single spikes in the spiking regime. This also means that we will need a bounded similarity measure.

In this chapter, several similarity measures will be discussed and compared. For clarity, we will use the following definition of a spike train \( s_i \) with \( N_i \) spikes:

\[
s_i(t) = t_{i1}, t_{i2}, ..., t_{IN_i} = \sum_{m=1}^{N_i} \delta(t - t_{im})
\]

where \( \delta(t) \) is the delta-function. We will classify every spike in a spike train as either a single spike, a first spike of a burst or a follower spike in a burst, based on the inter-spike interval. Events will be defined as the first two of these classes (‘bursts’ or ‘single spikes’), and we will ignore the follower spikes in bursts, assuming that there is not much extra information in these [122].

Recently, a very interesting paper by Naud et al. [102] came to out attention, in which they review most of the similarity measures discussed here and argue against the pairwise comparison against spike trains, since this comparison would have a bias proportional to the sum of the intrinsic variability of the spike trains. However, this should not be a problem in the following section, since we are not trying to fit a model to the results by maximizing the similarity, but just comparing conditions of the same neuron.
D.2 Similarity measures

D.2.1 Coincidence Factor

The spike coincidence factor is a measure of how much two spike trains $s_1(t)$ and $s_2(t)$ are alike [71] [78], based on the binning of the spike train in $K = \frac{T}{p}$ bins of binwidth $p$. The coincidence factor is corrected for the expected amount of coincidences $\langle N_{\text{coinc}} \rangle$ of spike train $s_1$ with a Poissonian spike-train with the same rate $\nu_2$ as spike train $s_2$. It gives a measure of 1 for identical spike trains, 0 if all coincidences are accidental and negative values for anti-correlated spike trains. It is defined as

$$\Gamma_{12} = \frac{N_{\text{coinc}} - \langle N_{\text{coinc}} \rangle}{\frac{1}{2}(N_1 + N_2)}$$  \hspace{1cm} (D.1)

in which

$$\langle N_{\text{coinc}} \rangle = 2\nu_2 p N_1 = \frac{2N_1 N_2}{K}$$

Finally, $\Gamma$ is normalized by

$$N = 1 - 2\nu_2 p = 1 - \frac{N_2}{K}$$

so it is bounded by 1. Note that the coincidence factor is not symmetric nor positive, therefore it is neither a metric nor an angular measure. Therefore, we will normalize by

$$N = 1 - 2 \max(\nu_1, \nu_2) p = 1 - \frac{\max(N_1, N_2)}{K}$$

which will make it symmetric, but still not positive. Moreover, it is the only measure we will consider that uses binning. It is only defined as long as each bin contains at most one event. Finally, it will in general saturate at a value below one, which can be seen as the reliability. The rate at which it reaches this value (for instance as defined by a fit to an exponential function) can be seen as the precision.

D.2.2 Schreiber et al.

Schreiber et al. [131] define their reliability measure $R_S$ as

$$R_S = \frac{f_S(t) \cdot g_S(t)}{\|f_S(t)\| \|g_S(t)\|}$$  \hspace{1cm} (D.2)

In which $f_S(t), g_S(t)$ are convolutions of a spike-train with an Gaussian kernel:

$$f_S(t) = s(t) \ast h_S(t)$$

$$h_S(t) = \exp(-\frac{t^2}{\sigma_S^2})$$

Parameter $\sigma$ determines the smoothing of the spike trains, or, put differently gives a time constant for coincident spikes, i.e. a ‘precision’. For large $\sigma_S$ $R_S$ always approaches 1, so it does not saturate. Therefore, one can define the reliability only as a function of the precision $\sigma_S$, and the precision is defined as the value at which the reliability is 0.5 [143].

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D.2.3 Hunter and Milton

Hunter and Milton \[64\] define their reliability between two spike-trains \(s_1(t)\) and \(s_2(t)\) as

\[
R_{HM} = \frac{1}{2} (\langle r_{12} \rangle + \langle r_{21} \rangle) \tag{D.3}
\]

where

\[
\langle r_{ij} \rangle = \frac{1}{N_i} \sum_{k=1}^{N_i} \exp\left(-\frac{\Delta t_k}{\tau_{HM}}\right)
\]

and \(\Delta t_k\) is the absolute value of the difference between spike time \(t_k\) in spike-train \(s_i\) and the nearest neighbour spike time in spike train \(s_j\). This measure is bounded between 0 (two exactly the same spike trains) and 1 (\(\Delta t \rightarrow \infty\)). Parameter \(\tau_{HM}\) plays a similar role as \(\sigma\) for \(R_S\) and determines the timescale for coincident spikes. For big time constants (\(\tau \rightarrow \infty\)), the reliability reaches 1, and the reliability and precision can be defined as in Schreiber et al.’s case.

D.3 Metrics

Victor and Purpura \[152\], \[153\] and van Rossum \[148\] (or the generalization defined by Houghton \[61\]) define a metric distance for spike trains. Naturally, this distance depends on the amount of spikes in a spike train. However, since we are looking at the reliability and precision of spike trains, we want to use a measure that does not strongly depends on the amount of spikes in the spike train, but on weather the spikes that occur do so at the same time, and with how much jitter. Therefore, the metric itself is not appropriate to compare the reliability and precision of spike trains in different regimes, where due to the transition from bursting into spiking the amount of spikes in a spike train may vary strongly. However, we will show in this section that we can define a reliability or correlation measure based on these metrics, analogous to Tiesinga et al. \[143\] and Schreiber et al. \[131\].

D.3.1 van Rossum

van Rossum \[148\] defines a metric

\[
d_{vR}^2 = \frac{1}{\tau_{vR}} \int_0^\infty [f_{vR}(t) - g_{vR}(t)]^2 dt \tag{D.4}
\]

In which \(f_{vR}(t), g_{vR}(t)\) are convolutions of a spike train with an exponential kernel:

\[
f_{vR}(t) = s(t) * h_{vR}(t)
\]

\[
h_{vR}(t) = \exp\left(-\frac{t}{\tau_{vR}}\right)
\]

The parameter \(\tau_{vR}\) plays a similar role as the time constants defined before.
D.3.2 Victor-Purpura

Victor and Purpura \[152 \] and \[152 \] define a metric based on ‘how much it costs’ to transform one spike train into the other. They define three elementary operations with associated costs:

1. moving a spike over a distance $\Delta t$ costs $q \Delta t$
2. adding a spike costs 1
3. deleting a spike costs 1

Next, they define the distance $d_{VP}$ as the minimum costs to transform one spike train into the other. The inverse of the parameter $q$ plays a similar role as the time constants defined before, therefore most figures will have $1/q$ instead of $q$ when needed. MATLAB code for the implementation of this metric can be found on http://www-users.med.cornell.edu/~jdvicto/spkdm.html and in the Spike Train Analysis Toolkit, a neuroinformatics resource funded by the NIH’s Human Brain Project.

D.3.3 From metric to similarity measure

Angular measure

For a metric $d$ on a vector space with vectors $x$ and $y$ and Euclidean geometry, such as the van Rossum metric \[148 \], one can use the following relations for vectors:

$$\|x - y\|^2 = \|x\|^2 + \|y\|^2 - 2x \cdot y$$  \hspace{1cm} (D.5)

$$\cos \theta = \frac{x \cdot y}{\|x\| \|y\|}$$ \hspace{1cm} (D.6)

to define

$$\cos \theta = \frac{\|x\|^2 + \|y\|^2 - \|x - y\|^2}{2\|x\| \|y\|}$$
$$= \frac{d(x, 0)^2 + d(y, 0)^2 - d(x, y)^2}{2d(x, 0)d(y, 0)}$$ \hspace{1cm} (D.7)

We can define such a reliability measure $R_{vR}$ for the van Rossum metric \[148 \]:

$$R_{vR} = \frac{\int_0^\infty f_{vR}(t)g_{vR}(t)dt}{\sqrt{\int_0^\infty f_{vR}^2(t)dt} \sqrt{\int_0^\infty g_{vR}^2(t)dt}}$$ \hspace{1cm} (D.8)

The functions $f(t), g(t)$ are vectors in the Euclidean function space. Since the vectors defined by the convolution contain only positive elements, the angle between two vectors will always be smaller than 90°, which results in $0 \leq R_{vR} \leq 1$, like Schreiber et al.’s measure $R_S$ \[131 \]. The reliability and precision can be defined accordingly.
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The metric space Victor and Purpura \[152\], \[153\] define their spike-trains in, is not a vector space, and an inner product cannot easily be defined: the notion of ‘addition of vectors’ is hard to imagine in the case of coincident spikes and especially ‘multiplication by a scalar’ does not seem to have a meaning in this space. But, if we denote the ‘length’ of a spike train by the amount of spikes it contains:

\[d(s, 0) = N_s\]

we can define a reliability measure similar to the cosine of the angle between vectors:

\[R_{VP} = \frac{1}{2} \frac{N_i^2 + N_j^2 - d_{VP}(s_i, s_j)^2}{N_i N_j}\]  \hspace{1cm} (D.9)

This measure has the following properties

- since the metric depends on the parameter \(q\) with units 1/time, so does the reliability measure. In both the metric and the reliability measure \(2/q\) denotes the temporal resolution.

- since the distance between two spike trains is always positive and only zero if the spike trains are exactly the same \((N_i = N_j = N)\)

\[0 \leq d_{VP}(s_i, s_j) \]

\[R_{VP} \leq \frac{1}{2} \frac{2N^2 - 0}{N^2} = 1\]

- since the distance between two spike trains can never be bigger than the sum of the number of spikes in the two trains, we have:

\[d_{VP}(s_i, s_j) \leq N_i + N_j \]

\[R_{VP} \geq \frac{1}{2} \frac{N_i^2 + N_j^2 - N_i^2 - N_j^2 - 2N_i N_j}{N_i N_j} = -1\]

So the measure is bounded between +1 and −1 like the coincidence factor, and not between 0 and 1 like \(R_{vR}\) and \(R_S\).

- in the limit of \(q = 0\) there is no cost in shifting a spike in time, so the costs are only associated with the difference in the number of spikes in the train \[153\]. The distance \(d_{VP}(s_i, s_j)\) is the difference in the number of spikes in the train and we find

\[d_{VP}(s_i, s_j) = N_i - N_j \]

\[R_{VP} = \frac{1}{2} \frac{N_i^2 + N_j^2 - N_i^2 - N_j^2 + 2N_i N_j}{N_i N_j} = 1\]

So the measure indeed does not detect differences in spike count alone.
D.3. Metrics

Figure D.1: The dependence of the reliability $R_{VP}$ measure based on the Victor-Purpura metric \[152, 153\] on the amount of coincident spikes $N_c$, in the case $q \to \infty$. If $q$ is finite, the metric distance will be smaller, so the measure will be closer to one.

- in the limit of very large $q$ ($q \to \infty$), every different timing of a spike is ‘a different spike’ \[153\]. If there is an amount of $N_c$ perfect coincident spikes we find:

$$d(s_i, s_j) = N_i + N_j - 2N_c$$

$$R_{VP} = \frac{1}{2} \frac{N_i^2 + N_j^2 - N_i^2 - N_j^2 - 4N_c^2 - 2N_iN_j + 4N_c(N_i + N_j)}{N_iN_j}$$

$$= \frac{2N_c}{N_iN_j}(N_i + N_j - N_c) - 1$$

which results in

- if $N_c = 0$, $R_{VP} = -1$
- if $N_c = N_i = N_j$, $R_{VP} = 1$
- if $N_c = N_i \neq N_j$, $R_{VP} = 1$
- if we take $N_i = N_j = 1$ and $0 \leq N_c \leq 1$, so we look at the dependence of the measure on the fraction of all spikes that are coincident, we find $R_{VP} = 2N_c(2-2N_c) - 1$ which is depicted in figure [D.1]. The measure depends smoothly and monotonically on the amount of coincident spikes. If $q$ is finite, the metric distance will be smaller, so the measure will be closer to one.

One could argue that by transforming the Victor-Purpura metric and the van Rossum metric into these reliability measures, we have simply redefined the Schreiber et al. measure with a different kernel. Indeed, this is what Paiva et al. show in their paper \[107\]. They argue that to distinguish between spike trains on the basis of synchrony (coincidence), the Schreiber measure performs better than the van Rossum and the Victor-Purpura distances, irrelative of which kernel was used, due to the normalization by the number of spikes.
Normalized measure

As an alternative, we can also look for ways to normalize the metrics by the amount of spikes. The Victor-Purpura metric for instance is bounded by the amount of spikes in the two spike trains, as was noted in the previous section. By defining

\[ M_{VP} = 1 - \frac{d_{VP}}{N_i + N_j} \]  

(D.10)

one obtains another measure that is bounded between 0 and 1. For large time windows

\[ \lim_{q \to 0} M_{VP} = 1 - \frac{|N_i - N_j|}{N_i + N_j} \]

which means that for large time windows the measure is only determined by the difference in the amount of spikes. In this limit this is a good reliability measure (indeed, the reliability can never get better than the weighed difference in the amount of spikes: a difference in the amount of spikes means there will always be unreliable events!). For small time windows we find

\[ \lim_{q \to \infty} M_{VP} = 1 - \frac{N_i + N_j - 2N_c}{N_i + N_j} = \frac{2N_c}{N_i + N_j} \]

which reaches 1 if the number of coincident spikes \( N_c \) is close to the average amount of spikes, and 0 if there are no coincident spikes. A similar argument holds if we define for the van Rossum metric (see ref [148]):

\[ M_{vR} = 1 - \frac{d_{vR}}{\sqrt{\frac{1}{2}(N_i + N_j)}} \]  

(D.11)

which results in

\[ \lim_{\tau_{vR} \to 0} M_{vR} = 1 - \frac{1}{\sqrt{\frac{1}{2}(N_i + N_j)}} \sqrt{\frac{1}{2}(N_i + N_j)} = 0 \]

and

\[ \lim_{\tau_{vR} \to \infty} M_{vR} = 1 - \frac{|N_i + N_j|}{\sqrt{(N_i + N_j)}} \]

Again, for large time windows the reliability is determined by the difference in the amount of spikes and can only vanish if this number is relatively small.

D.4 Results

D.4.1 Reliability vs input

A noisy current with variable mean, but constant standard deviation (see chapter [5]) was injected into the soma of thalamocortical relay neurons (TCR neurons) in-vitro patched
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Figure D.2: Reliability measure $R_S$ proposed by Schreiber et al. [131] as a function of $\sigma$ (equation (D.2.2)), at different membrane states (darkest - lightest: $-80$, $-70$, $-60$ and $-50$ mV, means marked by circles). Frozen noise was injected three times per membrane state, in five different cells. Left: All spikes. Middle left: Events. Middle right: Single spikes. Right: Bursts.

in rat thalamic brain slices. In figures D.2-D.4 we plotted the results of the similarity measures we discussed in this paragraph and not in chapter 5 as a function of the precision for the output spike trains at the same membrane state in the same cell. These measures were calculated for 5 different cells at 3 or 4 different membrane states (darkest - lightest: $-80$, $-70$, $-60$ and $-50$ mV). For every cell at every initial membrane potential there were three spike trains (frozen noise). The figures show that for these experiments it does not matter which of the measures is used, because one can reach the same conclusion for all measures: the reliability for events increases with depolarization and saturates at lower precisions, indicating that the timing of events is more precise with depolarization, i.e. the timing is more precise in the spiking regime than in the bursting regime. Moreover, the figures show that at hyperpolarized states the reliability traces for bursts are much higher than for single spikes, indicating that in these regimes bursts are more reliable than single spikes, and that single spikes increase their reliability strongly on depolarization.

D.4.2 Reliability vs $\Delta f/\langle f \rangle$

In chapter 5 we showed that for the Morris-Lecar model the reliability of the output as measured by the Hunter and Milton measure depends strongly on the input vs frequency curve, on $\Delta f/\langle f \rangle$. In figures D.5 and D.6 we show the same for both Victor-Purpura measures, the Schreiber measure and both van Rossem measures 1. Because the coincidence factor is not defined for multiple spikes per bin, it cannot be used to compare

1Unlike in chapter 5 we only used the first 90 s. of each trace instead of the full 300s., for computational speed.
Figure D.3: Two different reliability measures based on the van Rossum metric \[^{148}\] as a function of $\tau_{vR}$ (equation [D.4]), at different membrane states (darkest - lightest: -80,-70,-60 and -50 mV, means marked by circles). Frozen noise was injected three times per membrane state, in five different cells. Left: All spikes. Middle left: Events. Middle right: Single spikes. Right: Bursts.
Figure D.4: Two different reliability measures based on the Victor-Purpura metric [152, 153] as a function of $2/q$ (section D.3.2), at different membrane states (darkest - lightest: -80, -70, -60 and -50 mV, means marked by circles). Frozen noise was injected three times per membrane state, in five different cells. Left: All spikes. Middle left: Events. Middle right: Single spikes. Right: Bursts.
Figure D.5: The two different normalized reliability measures as described in section D.3.3 at a precision of 10 ms, at different membrane states (circle: -80 mV, square: -70 mV, triangle: -60 mV, diamond: -50 mV) for the Morris-Lecar model. Note the strong relation between $\Delta f/\langle f \rangle$ and the reliability.
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Figure D.6: The three different normalized reliability measures as described in section D.2 and D.3.3 at a precision of 10 ms, at different membrane states (circle: -80 mV, square: -70 mV, triangle: -60 mV, diamond: -50 mV) for the Morris-Lecar model. Even though the relation is less clean, there is still a strong correlation between $\Delta f/\langle f \rangle$ and the reliability.