Neural coding with spikes and bursts: characterizing neurons and networks with noisy input
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Chapter 5

Reliability

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Abstract

The reliability of the output of a neuron is an important issue in the context of the type of coding a neuron does. Many measures have been proposed to quantify this reliability and precision. In this paper, we investigated how the reliability of a thalamocortical relay (TCR) cell changes if it goes from a bursting to a spiking regime, using two of these measures: the coincidence factor [71], [78] and the Hunter and Milton measure [64]. We injected a frozen Gaussian noise current into the soma of the TCR neuron next to a DC current to put the neuron in different firing regimes (bursting or tonic spiking). We show that the reliability of the output of the TCR cell increases with depolarization. In a Morris-Lecar model [101], [126] we show that reliability measures we used are dependent on the shape of the input-output curve of the neuron. Therefore, in assessing changes in the reliability of a neuron, one should distinguish between changes due to a different position on the input-output curve and changes due to other causes. By correcting for the input-output curve, we show that the experimentally measured increase in reliability for single spikes can be expected from the neurons input-output relation. However, bursts are less reliable than expected in hyperpolarized states, which is probably due to slow adaptation.
5.1 Introduction

Neurons code their information in spike trains, well-timed series of action potentials. The details of the neuronal code are still a matter of intense debate. Spike trains are quite reliable and the information could be coded in the spike rate, in the precise timing of spikes or in both. The discussion (for an overview, see [143]) 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 fly’s visual system can produce very reliable spike trains in response to fluctuating input, as opposed to unreliable spike trains in response to constant stimuli. Two notions in this discussion are very important: ‘reliability’ and ‘precision’ [143]. The first one quantifies whether a spike occurs at about the same time of each repetition of the stimulus, the second should quantifies their how precise the timing is reproduced. Many ways have been proposed to quantify these concepts, of which the some are based on the spike-time histogram (for example [84], [93], [143]), cross-correlations or binning (coincidence factor [78]), while others are binless and defined as a function of the inter-spike interval (ISI-distance [83]) or independent of any time scale (SPIKE-distance [82]). Which one is the most appropriate might depend on the data and the precise definition of the research question [107]. Very recently, a new set of measures have been proposed [102], but are not included here.

There are several factors that can influence the reliability of the output of a neuron. Intrinsic properties of the neuron can influence its reliability: Gutkin and Ermentrout [51] showed that the coefficient of variation of output spike trains of a type 1 neuron (‘integrator’, Hodgkin classification [57]) is much higher than that of a type 2 neuron (‘resonator’). Schreiber et al. [130] showed that a higher slow potassium peak conductance and faster potassium kinetics promote spike timing reliability. Secondly, the characteristics of the input to a neuron can influence the reliability of the response: the frequency content of the input can influence the precision [52], [64]. Similarly, the background activity can have a major influence: Bernander et al. [10] showed that in a high-conductance state $\tau_m$ and the length constant decrease, resulting in a change in integrating properties of the cell. Prescott et al. [116], [117] showed that a high-conductance state together with a current like $I_M$ can shift a neuron from type 1 to type 2 with a corresponding change in reliability. Rudolph and Destexhe [129] showed that synaptic background activity can result in a more reliable and faster response. Finally, the nature of the stimulus also plays an important role. Looking at directly injected current, such as Mainen and Sejnowski [94] did, gives a much lower trial to trial variability than looking at for instance the response to visual stimuli such as in the experiments in [20].

Thalamocortical relay cells (TCR cells) can fire bursts as a rebound after hyperpolarization, due to the inactivation of the low-threshold the T-type calcium current [70]. When hyperpolarized, TCR neurons are in a bursting regime. If the neuron is depolarized, it goes smoothly from a bursting to a spiking regime, with a mixed regime in between, where the TCR neuron fires both spikes and bursts. In this work, we investigated whether the precision and robustness of spikes and bursts changes when the neuron
goes from a bursting to a spiking regime. This means that we need measures in which we can assess the precision in time of the various events. The measure also needs to be 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. Finally, we need a bounded similarity measure. For the experimental results we tested several reliability measures, such as the coincidence factor [71], [78], the Schreiber et al. [131] measure, the Hunter and Milton [64] measure, and normalized or angular versions of the Victor and Purpura [152], [153] metric and the van Rossum [148] metric. However, since all measures gave essentially the same results, we decided to use only two for this paper: the coincidence factor [71], [78] for single spikes, bursts and events (single spikes and bursts), because it is corrected for the amount of coincidences one would find for comparing random spike trains. However, this measure is not defined for multiple spikes in a bin and therefore inappropriate for use when one considers also the spikes within a burst. In this case we will use the Hunter-Milton measure [64].

To answer the question how the reliability and precision of spikes and bursts changes when going from a bursting to a spiking regime, we used a combined experimental and modelling approach. We performed current clamp experiments in slices to measure the changes in reliability and precision with the regime change. Next, we investigated what could cause these changes in reliability in a model. We used the Morris-Lecar model [101], [126] as implemented by Prescott et al. [115], [117]. This is a simple, tractable model that can still capture the most important characteristics of firing and go from a ‘type 1’ to a ‘type 2’ state. This model enabled us to investigate how the reliability depends on the mean input-output curve. Finally, to we address the more complex behaviour of a TCR neuron, we also included a T-current, an h-current and an AHP-like current.

5.2 Methods

5.2.1 Experiments

Electrophysiological experiments were performed using brain slices from wistar rats (postnatal days 12 – 16) anesthetized with isoflurane and killed by decapitation. 300 μm-thick coronal slices containing thalamic nuclei were cut at the level of the hippocampus with a vibroslicer (Leica VT1000S) in ice-cold slicing solution containing in mM: Choline chloride (120), KCl (3.5), CaCl₂ (0.5), MgSO₄ (6), NaH₂PO₄ (1.25), NaHCO₃ (25), glucose (25), continuously bubbled with 95%O₂−5%CO₂ (pH=7.4). Slices were incubated at 32°C for 1 h in ACSF containing (in mM): NaCl (120), KCl (3.5), CaCl₂ (2.5), MgSO₄ (1.3), NaH₂PO₄ (1.25), NaHCO₃ (25), glucose (25), continuously bubbled with 95%O₂−5%CO₂ (pH=7.4). Experiments were approved by the animal welfare committee of the University of Amsterdam. During recording, slices were kept submerged at room temperature (20 – 22°C) and were continuously superfused with ACSF. Patch pipettes were pulled from borosilicate glass and had a resistance of 2 – 3 MO when filled with internal solution containing (in mM): K-gluconate (130), KCl (10), EGTA (5), HEPES (10), Mg-ATP (4), Na-GTP (0.4) pH=7.3. Current-clamp recordings were made using an EPC9 patch-
clamp amplifier controlled by PULSE software (HEKA Electronic GmbH, Germany) and an in-house software (“Neuron”) running under Matlab (MathWorks, Natick, MA, USA). Signals were filtered at 5 – 10 kHz and sampled at 10 – 20 kHz. Membrane potentials were corrected for a 10 mV liquid junction potential. We used a slow feedback system that monitored controlled background current injection to guarantee that current-clamp measurements always started at the specified membrane voltage.

5.2.2 Model equations

The model we used is the Morris-Lecar model [101], [126] as implemented by Prescott et al. [115], [117], with an added T-current [128], h-current [67] or adaptation current [115]. Its differential equations are given in appendix A.3. This model was implemented in Bard Ermentrout’s XPP with an Euler method with a time step 0.1 ms.

In assessing the reliability, two parameters were varied: \( \beta_y \) and \( I_{dc} \). The first shifts the potassium activation curve \( y_\infty \) towards higher values, thereby changing the bifurcation type with which the resting state loses stability. This will make the neuron ‘type1’, ‘type2’ or ‘type 3’ excitable [115]. \( I_{dc} \) determines the average membrane potential (which will be denoted at ‘membrane states’ \(-80\text{mV}, -70\text{mV}, -60\text{mV} \) and \(-50\text{mV}\)). The bifurcation diagrams of the models we used are shown in figures 5.1 and 5.8. We chose the \( \beta_y \) as: \( \beta_y = \{-25, -20, -15, -10, 0\} \text{mV} \). Even though at \( \beta_y = -25 \) the system is at steady state for all constant input currents, this does not mean that the system is not excitable. A perturbation can still evoke a single spike, but a stable spiking state does not exist (‘type 3 excitability’, [115]). However, even with the noisy current the neuron was too quiet to perform analysis on (figure 5.5), so it will not be used any further. The T-current is only activated with a step from a hyperpolarized to a depolarized state and not at steady-state, so the addition of this current hardly changes the bifurcation diagrams (figure 5.8). We chose the magnitude of this current (\( g_T \)) in such a way that the neuron could burst at \( V_{\text{hold}} = -80 \text{mV} \), which resulted in \( g_T = 20 \). Unless stated otherwise, parameters are the same as in the Morris-Lecar model without any added ion channels.

We compared at the implementation of the h-current in many different published modelling studies [30], [39], [45], [48], [67], [97], [111], [112], [124], [128], [141], [150], [149]. Even though many of these studies claim to have been based on [92], they use very different parameters in their models. For instance the reversal potential ranges from 1mV [67] to \(-10\text{mV} \) [30], [39], [111] and \(-30\text{mV} \) [45], [97], [112], [144]. For the time-constant, many different values have been reported [39], [90], [92], probably due to the different temperatures the experiments were done at (33°C for [92], 21°C for [39], ‘room temperature’ for [90]). We decided to use parameters that came closest to [92] in the model of [67]. We could not make this h-current too large, or it would abolish all activity in hyperpolarized states. We chose \( g_h = 1.5 \). Figure 5.1 shows the changes in the bifurcation diagrams due to the addition of the h-current in grey. The subthreshold \( I_{dc} - V_m \) is less steep with than without the h-current. Therefore, the amplitude \( A \) of the frozen noise current to evoke the same membrane potential fluctuations. This is also true for the current injected to keep the neuron around the desired membrane potential \( I_{dc} \). We used \( A = 20 \) and
\(\sigma_{\text{dcnoise}} = 10\) and \(\sigma_\xi = 0.4\).

### 5.2.3 Stimulus

In the current clamp measurements the membrane potential was adjusted by a feedback system so that it stabilized to a desired value \((-80\text{mV}, -70\text{mV}, -60\text{mV} \text{ and } -50\text{mV})\) until the actual measurement was started. From then on the value was fixed and the same fluctuating input (frozen noise) was continuously injected into the soma of the TCR neuron for every repetition of the experiment. The current injection and the spikes and bursts it evoked implied that the actual mean membrane voltage was different from the initial one. This could have been corrected, but we preferred the bias over adding a difficult to control low-frequency component. Wherever relevant we have indicated the measured voltage in the figures, but for reasons of clarity we will indicate the different states as \((-80\text{mV}, -70\text{mV}, -60\text{mV} \text{ and } -50\text{mV}). The input consisted of Gaussian noise: an input trace was generated one time using a time series of Gaussian random numbers and was filtered with an exponential filter of \(\tau = 10 \text{ ms}\) and had a standard deviation \(\sigma = 100\text{ pA}\). We used three repetitions of 300 s. of 3 or 4 membrane states \((-80\text{mV}, -70\text{mV}, -60\text{mV} \text{ and } -50\text{mV})\).

The models were activated by current traces that were identical to the ones used in the experiments, scaled to an amplitude \(A\) that induced the same voltage fluctuations as observed in the experiments \((11\text{ mV})\). Also, the DC-component was adjusted so that the average subthreshold membrane potential was comparable to those in the experiments. Since the model is deterministic, an extra noise source is needed to assess the sensitivity of the neuron to small changes in the input. Therefore, for comparisons between the model and the experiments we added trial-to-trial variability by adding for every trial a DC component, drawn from a Gaussian distribution with a mean of \(\mu = 0\text{ pA}\) and a standard deviation of \(\sigma_{\text{dcnoise}} = 0.5A\) and white noise with a mean of \(\mu = 0\) and a standard deviation \(\sigma_\xi = 0.02A\). These standard deviations were based on comparing our experimental traces.

### 5.2.4 Spike train construction and segmentation

Action potentials were defined as a sharp peak of the membrane potential soon after a certain threshold had been crossed. The value of this threshold was optimized per trace (varied between \(-23\) and \(0 \text{ mV}\)) to accommodate small variations in spike shape. In data generated by simulations we could set the threshold at \(0 \text{ mV}\). The qualification of spikes as single spikes or part of a burst was decided based on whether the previous and following inter-spike interval were shorter than 30 ms (see also [165]), or than 10 ms for the Morris-Lecar models that included a T-current. We will classify every spike in a spike train as either a single spike, a first spike of a burst (‘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’ and ‘single spikes’). Considering all spikes will be the ‘all spikes’ case.
5.2. Methods

Figure 5.1: Bifurcation diagram and steady-state $I - V$ curves for the Morris-Lecar model. Top: bifurcation diagram of the Morris-Lecar model [101], [126] as implemented by Prescott et al. [115], [117] as a function of the input current $I_{dc}$ and parameter $\beta_y$. Solid lines: Hopf bifurcations, dashed lines: saddle-node bifurcations. Bottom: $I_{dc} - V_m$ curves for different values of $\beta_y$. Thick solid lines: stable fixed points, thin solid lines: unstable fixed points, thick dashed lines: maximum and minimum values of stable limit cycles, thin dashed lines: maximum and minimum of unstable limit cycles, squares: saddle-node bifurcation points (on or off a limit cycle, or of limit cycles), diamonds: Hopf bifurcation points (sub- or supercritical). Changes due to the addition of the h-current are denoted in grey.
Chapter 5. Reliability

5.2.5 Reliability measures

A spike train \( s_i \) with \( N_i \) spikes is defined as:
\[
s_i(t) = t_{i1}, t_{i2}, ..., t_{iN_i} = \sum_{m=1}^{N_i} \delta(t - t_{im})
\] (5.1)

where \( \delta(t) \) is the delta-function. The spike coincidence factor (\( \Gamma \)) quantifies the resemblance of two spike trains \( s_1(t) \) and \( s_2(t) \) \[71\] \[78\], based on the binning of the spike train in \( K = \frac{T}{p} \) bins of binwidth or precision \( p \). The coincidence factor is corrected for the expected number of coincidences \( \langle N_{coinc} \rangle \) of spike train \( s_1 \) with a Poissonian spike train with the same rate \( \nu_2 \) as spike train \( s_2 \). \( \Gamma \) is 1 for identical spike trains, 0 if all coincidences are accidental and negative values for anti-correlated spike trains. It is defined as
\[
\Gamma = \frac{N_{coinc} - \langle N_{coinc} \rangle}{\frac{1}{2}(N_1 + N_2)}
\] (5.2)
in which
\[
\langle N_{coinc} \rangle = 2f_2pN_1 = \frac{2N_1N_2}{K} = 2f_1f_2pT
\]

Finally, \( \Gamma \) is normalized by
\[
N = 1 - 2f_2p = 1 - 2 \frac{N_2p}{T}
\]
so it is bound by 1. Note that the coincidence factor between two spike trains is not symmetric. Therefore, we will use \( f_2 = \max(f_1, f_2) \) (see supplementary materials [5.5]), which does make it symmetric. It is also not positive. Therefore it is neither a metric nor an angular measure. Most often the coincidence factor will saturate at a value below one, which can be seen as the reliability. The time constant with which it reaches this value (for instance as defined by a fit to an exponential function) can be seen as the precision. If one of the spike trains has no spikes, both \( N_{coinc} \) and \( \langle N_{coinc} \rangle \) are equal to zero, and so is \( \Gamma \).

Hunter and Milton \[64\] define their reliability measure between two spike trains \( s_1(t) \) and \( s_2(t) \) as
\[
R_{HM} = \frac{1}{2}(\langle r_{12} \rangle + \langle r_{21} \rangle)
\] (5.3)
where
\[
\langle r_{ij} \rangle = \frac{1}{N_i} \sum_{k=1}^{N_i} \exp(-\frac{\Delta t_k}{\tau_{HM}})
\]
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 bound between 1 (two identical spike trains) and 0 (\( -\frac{\Delta t_k}{\tau_{HM}} \rightarrow \infty \)). Parameter \( \tau_{HM} \) plays a similar role as the precision \( p \) and determines the timescale for coincident spikes. For large time constants (\( \tau \rightarrow \infty \)), the reliability reaches 1. The reliability can also be defined as a function of the precision \( \sigma_S \), where the precision is defined as the value at which the reliability is 0.5 (see
5.3. Results

5.3.1 Reliability and precision in thalamocortical relay cells

On depolarization, thalamocortical relay (TCR) neurons go from a bursting to a spiking regime. To assess the reliability of bursts and spikes in different regimes of TCR neurons, in-vitro patched in rat thalamic brain slices, frozen noise superimposed on a DC current was injected into the soma in current clamp. The DC component defined the membrane state, as explained in the methods (section 5.2.3). The coincidence factor \([71, 78]\) was calculated as a function of the precision for the output spike trains at the same membrane state in the same cell (figure 5.2). It was 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 membrane state there were three spike trains, and therefore three coincidence factor traces. The coincidence factor for events at depolarized membrane potentials is high, and saturates at low precisions, indicating that the timing of events is more precise at depolarized potentials (figure 5.2). This means that the timing of events is more precise in the spiking regime than in the bursting regime. At hyperpolarized potentials the coincidence factor 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 with depolarization.

The coincidence factor is not defined for multiple spikes per bin and cannot be used to compare spike trains including all spikes of trains that contain bursts (where follower spikes often fall within the same bin). Therefore we also used the Hunter and Milton measure (\([64]\), see section 5.2.5) measure to compare the spike trains (figure 5.3). Essentially the same results are seen: on depolarization the neuron becomes more reliable, and in hyperpolarized states bursts are more reliable than single spikes. Including all spikes gives a very similar result as the ‘events’-traces. In conclusion, we observed that TCR neurons change their reliability as a function of the membrane state they are in.

5.3.2 Reliability and precision in a minimal model

We have observed in the experiments that the precision and robustness of the single spikes and bursts a TCR neuron fires change their reliability and robustness when the neuron goes from a bursting to a spiking regime. To investigate what causes these changes in reliability we used a model, the Morris-Lecar model \([101, 126]\) as implemented by Prescott et al. \([115, 117]\). We needed a simplified model like this, so one can easily distinguish different aspects of the firing properties of the neuron. Firstly, we investigated the influence of the bifurcation with which the stable resting state loses stability on the
Figure 5.2: The reliability of the output of a TCR neuron increases with depolarization. Coincidence factor $\Gamma$ \cite{28, 21} as a function of the precision or time bin $p$ (equation (5.2)), 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: Events. Middle: single spikes. Right: bursts.

Figure 5.3: The Hunter and Milton measure for the same spike trains as in figure 5.2. Reliability measure $R_{HM}$ proposed by \cite{64} as a function of $\tau_{HM}$ (equation (5.3)), 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.
reliability. According to the Hodgkin classification \[57\]) a neuron can be either ‘type 1’, ‘type 2’ or ‘type 3’. Type 1 neurons are characterized by a continuous \(f - I\) curve for constant inputs \(I\), and their stable resting state loses stability through a saddle-node on an invariant cycle bifurcation \[126\], \[67\], \[115\]. Type 2 neurons are characterized by a discontinuous \(f - I\) curve for constant inputs (but not for fluctuating inputs, see figure \[5.5\]), and their stable resting state loses stability through a Hopf bifurcation \[126\], \[67\], \[115\]. Type 3 neurons do not spike repetitively, but only once or a few times after the onset of a continuous stimulus. In the Morris-Lecar model the stable resting state can lose stability through either a Hopf bifurcation or through a saddle-node bifurcation, depending on the value of a parameter \(\beta_y\) (equations \(A.10\) and \(A.12\), figure \[5.1\]). This parameter shifts the nullcline of the potassium activation towards higher voltage values. To see how the bifurcation type influences the reliability of the spike trains, we investigated the relation between the reliability and \(\beta_y\). However, the response of a TCR neuron is much more complex than that of a Morris-Lecar model. Therefore, we tested the influence of different currents: we added a T-type calcium current as implemented by Rubin and Terman \[128\], a h-current as implemented by Izhikevich \[67\] and a ‘calcium-activated potassium-like’ current (which we will call ‘AHP’-like current) as implemented by Prescott et al. \[115\] (equations in section \[5.2.2\]).

Morris-Lecar model

To investigate the effect of the type of excitability (‘type 1’, ‘type 2’) on the reliability, we used the Morris-Lecar model \[101\], \[126\] as implemented by Prescott et al. \[115\], \[117\]. The frozen noise was identical to the one used in the experiments. The amplitude of the frozen noise was chosen at \(A = 15\), so the standard deviation of the dc-current added to each trace was \(\sigma_{\text{dcnoise}} = 7.5\) and the standard deviation of the extra white noise was \(\sigma_\xi = 0.3\) (see Methods). We varied \(\beta_y\) to make the neuron ‘type1’ or ‘type2’ excitable \[115\] \(\beta_y = \{-20, -15, -10, 0\}\) mV (see section \[5.2.2\]). Different states were realized by a current injection that brought the membrane under rest to \(-80\) mV, \(-70\) mV, \(-60\) mV and \(-50\) mV as before. Obviously, the Morris-Lecar neuron does not burst, therefore we only look at the Hunter and Milton \[64\] measure \(R_{HM}\) for all spikes. To make a fair comparison with the experiments, we calculated \(R_{HM}\) for five groups of three spike trains for each membrane state, as if there were five ‘cells’ with three measurements per membrane state.

In figure \[5.4\] the Hunter and Milton measure \(R_{HM}\) for \(\beta_y = -20, -15, -10\) and 0 is plotted, at \(\tau_{HM} = 10\). Note that there is not a clear relation between \(R_{HM}\) and either \(\beta_y\) or the membrane state. So what predicts the reliability of this model? The reliability is calculated in a pairwise comparison between spike trains. Each of these spike trains has a mean frequency \(f\), which is the total amount of spikes divided by the total time. We define

\[
C_{V_f} = \frac{\Delta f}{\langle f \rangle} = \frac{|f_1 - f_2|}{\frac{1}{2}(f_1 + f_2)} \tag{5.4}
\]
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Figure 5.4: Reliability of the Morris-Lecar model as a function of $C_{V_f}$. Hunter and Milton measure $R_{HM}$ at $\tau_{HM} = 10$ ms as a function of $C_{V_f} = \frac{\Delta f}{\langle f \rangle}$, for different membrane states (circles: $-80$ mV, squares: $-70$ mV, triangles: $-60$ mV, diamonds: $-50$ mV). Black line: fitted curve (equation 5.5). Note that the reliability has a strong relation with $C_{V_f}$, and not with either $\beta_y$ or the membrane state.

There is a strong relation between $C_{V_f}$ and the reliability (figure 5.4). In supplementary materials 5.5, we derive the relation between the expected reliability and $C_{V_f}$:

$$R_{HM}(C_{V_f}) = \frac{1}{1 + kC_{V_f}} \quad (5.5)$$

where $k$ is a parameter that depends on the time constant $\tau_{HM}$.

The reliability shows a strong relation with $C_{V_f}$ (figure 5.4). Therefore, we can predict the reliability for the simulations: if one knows the output frequency as a function of the DC input current ('input vs frequency curve' $f(I_{dc})$), one can calculate the reliability between two repetitions of the simulation/experiment with mean input currents $I_{dc1}$ and $I_{dc2}$. In the supplementary materials we show that a neuron with a steeper input vs frequency curve is mostly less reliable. We conclude that since the relation between the reliability and $C_{V_f}$ does not change with $\beta_y$, changes in reliability are caused by changes in the output frequency distribution, for instance a different position on the input vs frequency curve, a different shape of the input vs frequency curve or other changes in the distribution of the output frequencies. Only if the relation between the reliability and $C_{V_f}$ changes over conditions (parameter $k$ for the Hunter and Milton measure), then there is an intrinsic change in the neurons reliability.

We assumed that the output frequency was a composition of the relation between the
average input current $I_{dc}$ and the resulting average membrane potential $\mu V_m$ and the relation between $\mu V_m$ and the output frequency:

$$f(I_{dc}) = f(\mu V_m(I_{dc}))$$

In the Morris-Lecar model the relation between $\mu V_m$ and $I_{dc}$ was fitted by a quadratic function, the relation between $\mu V_m$ and the output frequency by a power function (figure 5.5). The reliability of the Morris-Lecar-neuron can be largely predicted by these fits (5.9, top left). The increasing input vs frequency curve causes the reliability to increase with depolarization. The relation between $C_{V_f}$ and the Hunter and Milton measure does not only stay constant between average membrane states, it also hardly changes between models with different values of $\beta_y$ (figure 5.4). This means that changes in reliability between models with different values of $\beta_y$ can be attributed to differences in the input vs frequency curves. With increasing $\beta_y$ the input vs frequency curve becomes steeper in this noisy state (figure 5.5), which would make the reliability somewhat lower (see supplementary materials).
Figure 5.6: Reliability of the Morris-Lecar model with added T-current and T-current and AHP-like current. Top: Hunter and Milton measure $R_{HM}$ at $\tau_{HM} = 10$ ms as a function of $C_{V_f}$ for all spikes, for the Morris-Lecar model with added T-current (black) and added T-current and AHP-like current (grey). Bottom: coincidence factor $\Gamma$ at $p = 10$ ms as a function of $C_{V_f}$ for bursts. Note that the reliability is reduced by the addition of the AHP-like current in the top figures, but not in the bottom ones.
5.3. Results

Morris-Lecar model with T-type calcium current

In the previous section we found that the reliability of the Morris-Lecar neuron can be predicted by the shape of the input vs frequency curve. However, this simplified neuron can not burst. To investigate the effect of bursting and the relative reliability of bursts and spikes, we added a T-type calcium current (as implemented by [128], see section 5.2.2). Because the T-current inactivates, it will only add a transient and not a steady state component. The addition hardly changes the bifurcation diagrams (figure 5.1), but it has a large effect on the input vs frequency curve (figure 5.5), because now the neuron can become active hyperpolarized states.

In all the models including a T-current, the relation between $\mu V_m$ and $I_{dc}$ was fitted by a sigmoid, the membrane $\mu V_m - f$ curve by a polynomial. In figure 5.6, the Hunter and Milton measure $R_{HM}$ for $\beta_y = -20, -15, -10$ and 0 for all spikes is plotted. The curves as plotted in figure 5.4 still seem to exist, but now as an upper limit: some values of the reliability are lower than one would expect. Apparently, the addition of the T-current reduced the reliability of this neuron. But this is compensated by the fact that $C_{V_f}$ is lower due to the changed input vs frequency curve (see figure 5.5). To assess the reliability of bursts, the coincidence factor $\Gamma$ was used. In the supplementary materials it is shown that the coincidence factor depends linearly on $C_{V_f}$, which one can see in figure 5.6.

Another important change can be seen in figure 5.7. In this figure both the instantaneous $I - V$ curve and the average $I_{dc} - \mu V_m$ relation are plotted. Traditionally, in patch clamp experiments using inputs consisting of step protocols, one uses two types of $I - V$ curve: the steady-state and the instantaneous $I - V$ curve. However, in a noisy regime, the neuron is never in steady-state. Parallel to these two types of $I - V$ curve and following Badel et al. [5], we define two types of $I - V$ curves in the noisy regime: the average $I - V$ curve $\mu V_m(I_{dc})$ and the instantaneous $I - V$ curve $V_m(\mu I)_{\text{inst}}$. The instantaneous $I - V$ curve is constructed by binning the membrane potential in bins of 1 mV, and calculating the mean input current in each bin. The point where the instantaneous $I - V$ curve becomes vertical is the spike threshold: the membrane potential depolarizes without extra input current. Whereas the instantaneous $I - V$ curves (see supplementary materials 5.5) basically overlap for the Morris-Lecar model, the addition of the T-current causes the spike-threshold to shift to more hyperpolarized values for hyperpolarized states and to depolarized values for depolarized states. So the threshold is not longer fixed, but regime-dependent.

Morris-Lecar model with T-type calcium current and more

In the previous section we looked at the effects of the T-type calcium current that makes the Morris-Lecar model burst. Here we investigate the effects of two more currents that play an important role in the firing properties of TC relay neurons. We added the currents on top of the T-current.

\[ I_m(t) = I_{in}(t) - C_m \frac{dV_m}{dt} \]  

1Note that Badel et al. use the membrane current $I_m(t) = I_{in}(t) - C_m \frac{dV_m}{dt}$ in their $I - V$ curve, whereas we use the input current $I_{in}(t)$.

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Figure 5.7: Average and instantaneous $I - V$ curves for the four models. Average (black dots and fitted solid line, $\mu_{V_m}(I_{dc})$) and instantaneous (dotted line, $V_m(\mu_I)_{\text{inst}}$) $I - V$ curves for the Morris-Lecar model with different added ion channels at $\beta_y = -10$. The four instantaneous $I - V$ curves are the instantaneous $I - V$ curves at membrane states of $-80, -70, -60$ and $-50$ mV respectively. Note that in the Morris-Lecar model the instantaneous $I - V$ curves overlap. The addition of the T-current shifts the threshold in the hyperpolarized direction. The addition of the h-current causes that the subthreshold region of the instantaneous $I - V$ do not overlap.
5.3. Results

**h-current** We added an h-current as implemented by [67], that opens around $-82 \text{ mV}$. The main effect of the h-current is subthreshold (figure 5.1 in grey), next to an almost negligible effect on the limit cycles. The subthreshold average $I-V$ curve $\mu_{I_{\text{dc}}}(I_{\text{dc}})$ is less steep than that of the model without h-current (figure 5.7). The instantaneous $I-V$ curve does now shows regime dependence in the threshold-region and in the subthreshold region (the curves are shifted towards lower mean input for hyperpolarized states and towards higher mean inputs for depolarized states).

Adding the h-current had hardly an effect on the reliability (not shown): it shows a similar pattern as the model without h-current (figure 5.6). The addition of the h-current makes the input vs frequency curve wider, so less steep (figure 5.5). This makes the neuron more reliable. However, the h-current will also make both $I-V$ curves wider. For a fair comparison we chose the standard deviation of the distribution of the dc input $I_{\text{dc}}$ as a fraction of the amplitude of the frozen noise input, which was chosen so that it keeps the standard deviation of the membrane potential at a desired value of 11 mV. Since the $I-V$ curves were wider, both the amplitude of the frozen noise input and the standard deviation of the distribution of the dc input were chosen larger. This balanced the increase in reliability due to the wider $I-V$ curves, so there was no net effect. Of course, when we would use the distribution of the dc input from the model without h-current, a less steep input vs frequency curve would result in a more reliable neuron, because the difference between two simulations is relatively smaller.

**adaptation** In the experiments, the neuron keeps its firing rate more or less constant over membrane states, with only a slight increase at $V_{\text{hold}} = -50 \text{ mV}$. As the burst rate decreases and the single spike rate increases, the event frequency naturally increases. For the Morris-Lecar model, the steady-state input vs frequency curve depends on the value of $\beta_y$: it is continuous for the ‘type 1’-regime ($\beta_y = 0 \text{ mV} $) and discontinuous or non-existent for the ‘type 2/3’-regime ($\beta_y < 10 \text{ mV}$). With noisy input, however, the distinction is not that clear, and the mean input vs frequency curves become much more smooth (figure 5.5). Without the T current, the neuron can hardly respond at all in hyperpolarized states. On depolarization the output frequency becomes very high, up to 80 Hz for $V_{\text{hold}} = -50 \text{ mV}$ and $\beta_y = 0$. Adding the T current makes it possible for the neuron to respond at hyperpolarized states, but it does not reduce the unrealistically high frequency in depolarized states. Adding the h-current did not solve this problem. We hypothesized that TCR neurons must have a mechanism to keep their firing frequency within limits. Candidates are potassium currents that activate at relatively depolarized membrane potentials, such as the $I_A$ and $I_{K2}$, or are activated by calcium, such as $I_{C}$ [31], [62], [95]. Following [115] we considered both cases, by using the ‘adaptation current’ from [115] (see equations 5.2.2), and using parameters $\alpha_z = 0.08$, $\beta_z = -43 \text{ mV}$, $\gamma_z = 17$ and $g_{\text{adap}} = 2$ for a $I_A$ or $I_{K2}$-like current, and $\alpha_z = 0.005$, $\beta_z = 0 \text{ mV}$, $\gamma_z = 0$ and $g_{\text{adap}} = 40$ [115] for a ‘calcium-activated potassium-like’ current. However, the $I_A$ or $I_{K2}$-like current abolished all spiking at membrane states of $-60 \text{ mV}$ and $-70 \text{ mV}$, because of its lower activation values. Therefore we will consider only the ‘calcium-activated potassium-like’ current, which we will call ‘AHP-like current’.
Chapter 5. Reliability

Figure 5.8: Bifurcation diagram and steady-state $I - V$ curves for the Morris-Lecar model with T and AHP current. Top: bifurcation diagram of the Morris-Lecar model [101], [126] as implemented by Prescott et al. [115], [117] with an added T current and AHP-like current. Solid lines: Hopf bifurcations, dashed lines: saddle-node bifurcations. Bottom: $I_{dc} - V_m$ curves for different values of $\beta_y$. Thick solid lines: stable fixed points, thin solid lines: unstable fixed points, thick dashed lines: maximum and minimum values of stable limit cycles, thin dashed lines: maximum and minimum of unstable limit cycles, squares: saddle-node bifurcation points (on or off a limit cycle, or of limit cycles), diamonds: Hopf bifurcation points (sub- or supercritical), circles: bifurcations with higher co-dimension through which the limit cycles lose stability (such as torus bifurcations of period-doubling bifurcations). Even if there are no stable limit cycles, the neuron can still spike, but the limit cycles might change shape over time.
The addition of the AHP-like current reduced the reliability (figure 5.6). The addition of the AHP-like current changes the behaviour of the neuron mostly at supra-threshold levels: at $\beta_y = -15$ and $-20$ it shows unstable limit cycles instead of stable ones (figure 5.8). This does not mean that the neuron doesn’t spike, it just means that not all limit cycles (spikes) have the exact same shape. The addition also had a threshold effect in the ‘type 1’-regime: the Hopf-bifurcation does not disappear for higher values of $\beta_y$ (compare figure 5.8 with figure 5.1), but keeps existing at slightly lower values of $I_{dc}$ than the saddle-node bifurcation, which has as a result that a true ‘type 1’-regime no longer exists. In figure 5.5 one can see that the addition of this current indeed reduces the spike-frequency. The reliability of the output is reduced for all spikes at high values of $\beta_y$ (‘type 1’ regime), but not for bursts only (figure 5.6). This can be understood intuitively: the AHP-like current only becomes active after a few spikes, so it is natural that it does not influence the generation of a burst. It has the strongest effect on the regime with the highest output frequency, so at the highest value of $\beta_y$ (see figure 5.5).

Conclusion

The Morris-Lecar model was used to investigate basic principles of the reliability and how different currents influence this. We found that in this model the reliability shows a strong relation with $C_{V_f}$ (figure 5.9). Therefore, we can predict the reliability for the simulations and experiments: if one knows the output frequency as a function of the DC input current ('input vs frequency curve' $f(I_{dc})$), one can calculate the reliability between two repetitions of the simulation/experiment with mean input currents $I_{dc1}$ and $I_{dc2}$:

$$R_{HM}(C_{V_f}) = R_{HM}(f_1, f_2) = R_{HM}(f(I_{dc1}), f(I_{dc2}))$$

We can distinguish two causes of changes in reliability with changes in parameters such as the mean input current $I_{dc}$ or $\beta_y$. Firstly, a change in reliability can be caused by a change in the shape or position on the input vs frequency curve. This means that the relation between the reliability and $C_{V_f}$ does not change. Secondly, a change in the mean input current $I_{dc}$ can cause intrinsic changes in the neuron that influence the reliability. In this case the relation between the reliability and $C_{V_f}$ does change. We can only distinguish between these two causes, if we can make predictions on how the reliability would change purely based on the input vs frequency curve. How to make these predictions will be explained in the supplementary materials. In the following figures, we will show one or more of the following predictions together with the measured values from simulations or experiments:

1. **Ideal** An ideal experiment, in which we choose two mean input currents $I_{dc}$, with a fixed distance $\Delta I = |I_{dc1} - I_{dc2}|$. We increase the mean $\frac{1}{2}(I_{dc1} + I_{dc2})$ to walk over the input vs frequency curve. In this case, we can calculate the predicted reliability analytically, based on the fit for the input vs frequency curve. This will be shown as a black line.

2. **Ideal input distribution** In the simulations, the mean input currents $I_{dc}$ were drawn from a distribution with the same standard deviation over all membrane
states. We can make an approximation of the resulting distribution of output frequencies and hence of the distribution of $C_{V_f}$. This would make it possible to calculate the distribution of reliability values. However, as shown in the supplementary materials, the distributions of $C_{V_f}$ and the reliability are very non-Gaussian and cannot be calculated analytically. Therefore, in the figures we show a random draw from a distribution of frequencies with mean and standard deviation calculated from the distribution of $I_{dc}$ and the input vs frequency curve. The resulting prediction for the reliability values is shown in the figures as open circles.

3. **realized input distribution** In the experiments, the standard deviation of the distribution of input currents $I_{dc}$ was slightly different for different membrane states. Therefore, we draw a random sample of a distribution of frequencies with a mean and standard deviation calculated from the distribution of $I_{dc}$ and the input vs frequency curve for each membrane state. The predicted reliability values based on this sample will be shown as open diamonds.

4. **$C_{V_f}$ distribution** Based on the fit of the reliability vs $C_{V_f}$ curve, one can plot the expected value of the reliability for each $C_{V_f}$ value. This will be shown as open squares.

The reliability of the Morris-Lecar model depends mostly on the input vs frequency curve, and changes in the reliability can be attributed to changes in this curve (figure 5.4). The addition of a T-current makes the neuron capable of generating bursts. It makes the spike-threshold regime-dependent (figure 5.7). The T-current makes the neuron less reliable in depolarized states, but more reliable at hyperpolarized states (figure 5.9). A telltale of the h-current is the subthreshold shift in the instantaneous $I - V$ curve (figure 5.7). It makes the input vs frequency curve less steep, which makes the neuron more reliable. An AHP-like current is hardly visible in the instantaneous or average $I - V$ curves, but strongly reduces the output frequency, and reduces the reliability of the neuron if all spikes are taken into account, but not if bursts only are taken into account.

5.3.3 Experiments revisited

Based on the theoretical consideration, we can now revisit the experimental results and reinterpret them. The average $I - V$ curve was fitted by a sigmoid and the membrane $\mu V_m - f$ curve was fitted by a linear function. For all spikes (figure 5.10, top left), both the ‘ideal’ curve and the expected values based on the input distribution (‘realized input distribution’, diamonds) have a bias to high values. The open squares give a more appropriate fit, as does the reliability vs $C_{V_f}$ curve (figure 5.11). Apparently the values of $C_{V_f}$ are different from what one would expect based on the input vs frequency curve. Indeed, in figure 5.12 one can see that the values of $C_{V_f}$ are much higher than what would be expected on the bases of the input vs frequency curve, especially for hyperpolarized states. If all events are taken into account, the fit improves. For single spikes only, the reliability (figure 5.10, bottom left) is underestimated. This can be explained: especially at depolarized states the values of $C_{V_f}$ are lower than expected (figure 5.12, bottom left).
5.3. Results

Figure 5.9: Expected and simulated reliability of the models. Top: Reliability measure as a function of input. Dots: the measured values from the simulations for different membrane states (blue: -80 mV, green: -70 mV, red: -60 mV, black: -50 mV), at $\beta_y = -10$. Black line: expected reliability for an ‘ideal’ experiment (section 5.3.2). Open circles: predicted reliability of a random sample of inputs (‘input distribution’, section 5.3.2). Bottom: same as top, but for bursts.
For bursts, the mismatch is even larger: the expected values are too high in hyperpolarized states and too low at depolarized states (figure 5.10, bottom right) and the fit of the reliability vs $C_{V_f}$ curve is bad (figure 5.11, bottom right). Here the reliability vs $C_{V_f}$ curve does change with the membrane state. The relative variability in output frequency of these neurons is much higher than expected from the input-vs output frequency curve. This causes the neuron to be particularily unreliable at hyperpolarized states. In addition there is an intrinsic change in reliability with the depolarization for bursts: in hyperpolarized states the neuron is unreliable, whereas on depolarization it becomes more reliable on top of the output frequency effects. Single spikes are also very unreliable at hyperpolarized states, but this is merely due to the shape of the input vs frequency curve.

5.4 Discussion

The reliability of the output of a neuron was calculated using the coincidence factor \cite{71, 78} or the Hunter and Milton measure \cite{64}. We were able to distinguish whether changes in reliability are caused by a change in the input vs output frequency curve, or by an intrinsic factor. The calculations were applied on data from models and from recorded thalamocortical relay cells in acute slices from rats. Predicting the input vs output frequency curve in a noisy regime is not trivial, as it may be influenced by currents inactivated in a silent or steady-state regime.

In simple models, such as the Morris-Lecar model, the reliability of the output spike train can almost be completely predicted by the input vs output frequency curve. The changes in reliability caused by either changes in (mean) input or by changes in the type of bifurcation through which this neuron loses stability can be explained by changes in the input vs output frequency curve in this noisy state. This noisy state is very different from a state in which a quiescent neuron receives a single or a few step-like inputs. Making the model is more complex by adding more currents, reduces the predictability becomes less and the neuron becomes less reliable, which also holds if the analysis is restricted to a part of the output, such as single spikes or bursts.

Introducing a T-type calcium current makes the spike threshold depend on the mean of the input, i.e. on the regime the neuron is in. This is expected, since the T-type calcium current can only be activated after a period of hyperpolarization, which enhances the relevance of the short-term history of the input. The T-type calcium current also increased the variability of the reliability, resulting sometimes in a lower value if the compared output spike trains had a similar frequency. Because it also increased the output frequency of the neuron, especially at hyperpolarized membrane potentials, this effect was compensated. Other ionic currents with a strong dynamic component have similar effects on the instantaneous $I - V$ curve. An h-current made the subthreshold instantaneous $I - V$ curve also depend on the mean of the input, i.e. on the regime the neuron is in, but for our simulation protocols it did not have a large effect on reliability. This was expected, as it operates only at hyperpolarized potentials and hardly influences spiking behaviour. An adaptative current (AHP-like current) on the other hand, influenced mainly the spik-
Figure 5.10: Reliability of thalamocortical relay neurons as a function of the input current. Coincidence factor or Hunter and Milton measure as a function of the input current for five cells, for all spikes, all events (spikes and bursts), single spikes only and bursts only. Dots: measured values (blue: membrane state of $-80$ mV, green: $-70$ mV, red: $-60$ mV, black: $-50$ mV). Black line: predicted reliability for an ‘ideal’ experiment (section 5.3.2). Open diamonds: predicted reliability of a random sample of inputs (‘realized distribution’, section 5.3.2). Open squares: predicted reliability of a random sample of $C_{V_I}$ (‘$C_{V_I}$ distribution’, section 5.3.2).
Figure 5.11: Reliability as a function of $CV_f$ of thalamocortical relay cells. Coincidence factor or Hunter and Milton measure as a function of $CV_f$ for five cells, for all spikes, all events (spikes and bursts), single spikes only and bursts only. Dots: measured values (blue: membrane state of $-80$ mV, green: $-70$ mV, red: $-60$ mV, black: $-50$ mV). Black line: fit (see supplementary materials 5.5).
Figure 5.12: $C_V f$ of thalamocortical relay neurons as a function of the input current. $C_V f$ as a function of the input current for five cells, for all spikes, all events (spikes and bursts), single spikes only and bursts only. Dots: measured values (blue: membrane state of $−80$ mV, green: $−70$ mV, red: $−60$ mV, black: $−50$ mV). Open diamonds: predicted $C_V f$ of a random sample of frequencies (‘realized distribution’, section 5.3.2).
ing behaviour and not the subthreshold behaviour: it reduced the output frequency of the neuron. Since it only activated after a few spikes, it did not influence the reliability of bursts, but it reduces the overall reliability of the neuron.

Real thalamocortical relay cells become more reliable with depolarization, for spikes, events (single spikes and bursts), single spikes and bursts. For a large part, this can be explained by a high variability of the output frequency at the hyperpolarized states, more than one would expect from the average input vs frequency curve. Bursts are less reliable then predicted from the output frequency. This could be caused by fluctuations in the T-type calcium current, by fluctuations in the h-current or by any other mechanism that is mainly active at hyperpolarized membrane potentials. Consecutive traces at a hyperpolarized state slowly reduced spike and burst count, but recovered after some time. Simulations with the Morris-Lecar model where the conductance of the T-type calcium current was allowed to change over traces could showed a similar effect: the reliability increased with depolarization, because at hyperpolarized membrane potentials the output frequency was variable, but the way the reliability depended on $C_{V_f}$ was unchanged (not shown). It can be concluded from this that in the experiments some long-term effects, such as slow adaptation, a run down of T-type calcium current or changes in calcium concentration, play a role and cause extra changes in the output frequency and hence in the reliability.

Theoretical considerations showed that the distributions of the reliability might be non-Gaussian, so the mean and standard deviation might not be the best way to compare them. Naud et al. show in a recent paper [102] that there are biases concerned with pairwise comparisons and small sampling sizes. They conclude that by comparing spike trains pairwise one cannot correctly discriminate between underlying point processes, but that they are valid measures for comparing spike trains. In this paper we are not trying to find underlying statistical processes or fit a model to experimental data, but we are trying to distinguish between changes in reliability that are caused by the shape of the input vs output frequency curve and changes in reliability caused by other intrinsic factors. Both Naud et al. and this paper show that depending on the research question reliability measures without correction can be hard to interpret.

The relation between the reliability and $C_{V_f}$ shows that there is a tradeoff between reliability and sensitivity: the steeper the input vs frequency curve of a neuron, the lower its reliability will be, but the more sensitive it is to changes in the mean input. A flat input vs frequency curve can have a high reliability, but will not signal a change in the mean input in the output frequency. It might be able to show other features of the input in the timing of the output spikes. So this might be an ideal situation for a neuron that shows ‘temporal coding’ and not ‘rate coding’. On the other hand, a neuron that is a pure ‘rate coder’ might have a steeper input vs frequency curve, since the spike-to-spike reliability is less important, but the sensitivity of the output frequency to the input all the more. The steepness of the input vs frequency curve could be a telltale of the type of coding a neuron performs. TCR cells have a relatively flat mean input current vs frequency curve for all spikes, suggesting that the timing of the spikes is important. The reliability of this
neurons is high, even in a millisecond range. On the other hand, they also have a strongly increasing single spike frequency and a decreasing burst frequency, which implies that the mean of the input, i.e. the background, is coded in parallel in the burst frequency or in the spike frequency. Such a neuron could at the same time be a ‘spike coder’ and a ‘rate coder’.

5.5 Expected shape of the reliability measures

5.5.1 Frequency curve, coefficient of variation and $I - V$ curves

$C_V$ changes as a function of the input-output curve of a neuron. This relation can be estimated. If the output frequency of a neuron as a function of the DC input current is described by a function $f(I_{dc})$, and two realizations were obtained at an average input current of $I^* - \frac{1}{2} \Delta I$ and $I^* + \frac{1}{2} \Delta I$ ($\Delta I > 0$), the coefficient of variation can be approximated by

$$ C_V(I_{dc}) = \frac{\Delta f(I_{dc})}{\langle f(I_{dc}) \rangle} = 2 \frac{f(I^* + \frac{1}{2} \Delta I) - f(I^* - \frac{1}{2} \Delta I)}{f(I^* + \frac{1}{2} \Delta I) + f(I^* - \frac{1}{2} \Delta I)} $$

$$ = 2(1 - \frac{2f(I^* - \frac{1}{2} \Delta I)}{f(I^* + \frac{1}{2} \Delta I) + f(I^* - \frac{1}{2} \Delta I)}) $$

$$ = 2(1 - \frac{2}{1 + \frac{f(I^* + \frac{1}{2} \Delta I)}{f(I^* - \frac{1}{2} \Delta I)})} $$

(5.6)

for an increasing function, in which we define both $\Delta f$ and $C_V$ as their absolute values. Similarly for a decreasing function we find

$$ C_V(I_{dc}) = \frac{\Delta f(I_{dc})}{\langle f(I_{dc}) \rangle} = 2 \frac{f(I^* - \frac{1}{2} \Delta I) - f(I^* + \frac{1}{2} \Delta I)}{f(I^* + \frac{1}{2} \Delta I) + f(I^* - \frac{1}{2} \Delta I)} $$

$$ = 2(1 - \frac{2}{1 + \frac{f(I^* - \frac{1}{2} \Delta I)}{f(I^* - \frac{1}{2} \Delta I)}}} $$

(5.7)

If we now assume that $\Delta I$ is small enough for a linear approximation so

$$ f(I^* + \frac{1}{2} \Delta I) = f(I^*) + \frac{1}{2} \Delta I \frac{df(I_{dc})}{dI_{dc}} |_{I_{dc}=I^*} $$

(5.8)

we can combine equations (5.6) and (5.8) to find

$$ C_V(I^*) = \frac{\Delta I}{f(I^*)} \frac{df(I_{dc})}{dI_{dc}} |_{I_{dc}=I^*} $$

(5.9)

for an increasing function, and similarly we can combine equations (5.7) and (5.8) to find

$$ C_V(I^*) = -\frac{\Delta I}{f(I^*)} \frac{df(I_{dc})}{dI_{dc}} |_{I_{dc}=I^*} $$

(5.10)
Figure 5.13: $C_{V_f}$ for different input vs frequency functions. The coefficient of variation for the frequency $C_{V_f}$ for different increasing (left) and decreasing (right) functions $f(I)$, if one would pick two traces at $I^*-\frac{1}{2}\Delta I$ and $I^*+\frac{1}{2}\Delta I$, with $\Delta I = 1$.

Since a frequency is always positive, the function $f(I)$, but also $f(I^*) \pm \frac{1}{2}\Delta I \frac{df}{dI}$ has to be positive, which means that $|\Delta I \frac{df(I)}{dI}| \leq 2f(I)$ and $0 \leq C_{V_f} \leq 2$. Moreover, $C_{V_f} = 2$ if and only if one of the two spike trains contains no spikes. Several examples of how $V_{V_f}$ depends on the shape of the input-output curve are shown in figure 5.13

The value of $C_{V_f}$ originates from several sources. We can estimate what part of the observed changes in $C_{V_f}$ (and later in reliability) are caused by what sources, both in models and experiments. The relation between $I_{dc}$ and the frequency depends on the relation between $I_{dc}$ and the mean membrane potential $\mu_{V_m}$:

$$f(I_{dc}) = f(\mu_{V_m}(I_{dc}))$$

(5.11)
so that

\[ f(I^* \pm \frac{1}{2}\Delta I) = f(\mu_{V_m} \cdot \mu_{V_m}(I^*)) \pm \frac{1}{2}\Delta I \frac{df(I_{dc})}{dI_{dc}}|_{I_{dc}=I^*} \]

\[ = f(\mu_{V_m} \cdot \mu_{V_m}(I^*)) \pm \frac{1}{2}\Delta I \frac{df(\mu_{V_m})}{d\mu_{V_m}}|_{\mu_{V_m}=\mu_{V_m}(I^*)} \frac{d\mu_{V_m}(I_{dc})}{dI_{dc}}|_{I_{dc}=I^*} \]

and

\[ C_{V_f}(I^*) = \frac{\Delta I}{f(\mu_{V_m} \cdot \mu_{V_m}(I^*))} \frac{df(\mu_{V_m})}{d\mu_{V_m}}|_{\mu_{V_m}=\mu_{V_m}(I^*)} \frac{d\mu_{V_m}(I_{dc})}{dI_{dc}}|_{I_{dc}=I^*} \]

Ideally, one would keep \( \Delta I_{dc} \) constant over the experiments, i.e. only the mean of the DC input is varied to put the neuron in different membrane states. In the experiments however, there are always small variations. This causes a change in output frequency; the effect is dependent on the steepness of the input-output curve. Simulations will have their limits due to finite sampling. We will denote this first factor as the ‘extra variation’ \( \Delta I_{dc,\text{extra}} \) due to experimental variation or the specific set of realizations one obtains in modelling. A second factor is caused by frequency variations. Experiments can contain various forms of non-stationary effects such as long-term adaptation, changes in calcium concentration in the cell, changes in input resistance, run down of the T-type calcium current, etc. This type of effects will in general play no role in simulations if it is not explicitly included in the model, but in experiments where cells are current clamped for a long time (over an hour) this might have a significant effect. We will call this \( \Delta f_{\text{extra}} \). Taken together this gives us

\[ C_{V_f}(I^*) = \frac{1}{f(\mu_{V_m} \cdot \mu_{V_m}(I^*))} \left( \frac{df(\mu_{V_m})}{d\mu_{V_m}}|_{\mu_{V_m}=\mu_{V_m}(I^*)} \frac{d\mu_{V_m}(I_{dc})}{dI_{dc}}|_{I_{dc}=I^*} \cdot (\Delta I_{dc,\text{const}} + \Delta I_{dc,\text{extra}} + \Delta f_{\text{extra}}(V_m, I_{dc}, ...)) \right) \]

(5.12)

This equation separates \( C_{V_f} \) in several contributing factors: we can estimate what parts are caused by changes in relative steepness in the input-output curve, what part is caused by the ‘extra’ variation in input current and what part is caused by other causes. To determine \( C_{V_f} \) we need to have an estimation of the input-output curve \( f(I_{dc}) \), so of both \( f(\mu_{V_m}) \) and \( \mu_{V_m}(I_{dc}) \). We did this separately for each model and for the experiments.

### 5.5.2 Reliability as a function of \( C_{V_f} \)

#### Coincidence factor

The spike coincidence factor \( \Gamma \) measures the coincident spikes corrected for what could be expected from a Poissonian spike trains with the same rate. In the definition, the spike count can be substituted by firing frequency:

\[ \Gamma_{12} = \frac{f_c - \langle f_c \rangle}{\frac{1}{2}(f_1 + f_2)N} \]

In which \( \langle f_c \rangle = 2f_1f_2p \) and \( p \) is the precision or binwidth. For two Poisson spike trains \( \Gamma \) is close to zero, but for two spike trains generated by the same neuron after presenting the
same stimulus, $\Gamma$ is expected to be greater than zero. We will now calculate $\Gamma$ based on the assumptions that the coincident spike frequency $f_c$ increases with the frequency of the spike trains and decreases with the difference in frequency between the spike trains $\Delta f$. Moreover, we assume that $f_c$ depends on the binsize $p$ with a saturating function $g_s(p)$, that is small for small $p$ and saturates to 1 for large $p$. In first order approximation

$$f_c = g_s(p)H(a\langle f \rangle - \frac{b}{2}\Delta f)$$

where $H(x)$ is the Heaviside step function, $a$ and $b$ are positive constants. How fast $f_c$ saturates gives information on the precision of the neuron, whereas $a$ and $b$ contain information on the reliability. The coincident spike frequency can never be higher than the lowest of the two frequencies:

$$g_s(p)(a\langle f \rangle - \frac{b}{2}\Delta f) \leq \min(f_1, f_2) = f_{\min}$$

Since

$$\langle f \rangle = \frac{1}{2}(f_{\max} + f_{\min})$$

and

$$\Delta f = f_{\max} - f_{\min}$$

we find for the coincidence factor

$$\Gamma = \frac{g_s(p)H(a\langle f \rangle - \frac{b}{2}\Delta f) - 2f_{\max}f_{\min}p}{\langle f \rangle} \cdot \frac{1}{N}$$

$$= \frac{g_s(p)H(a\langle f \rangle - \frac{b}{2}\Delta f) - 2f_{\max}p(\frac{1}{2}f_{\min} + \frac{1}{2}f_{\min} + \frac{1}{2}f_{\max} - \frac{1}{2}f_{\max})}{\langle f \rangle} \cdot \frac{1}{N}$$

$$= \left\{ \begin{array}{ll}
\frac{1}{1-2f_{2p}}(g_s(p)a - 2f_{\max}p - \frac{1}{2}\Delta f \langle gs(p)b - 2pf_{\max} \rangle) & \text{if } a - \frac{b}{2}\frac{\Delta f}{\langle f \rangle} > 0 \\
\frac{-2pf_{\max}}{1-2f_{2p}}(1 - \frac{1}{2}\frac{\Delta f}{\langle f \rangle}) & \text{else}
\end{array} \right.$$

The choice for $f_2 = f_{\max}$ or $f_2 = f_{\min}$ is nontrivial, and it is also what makes this measure asymmetric. Therefore, we will use from now on in all the calculations $f_2 = f_{\max}$, so

$$\Gamma = \left\{ \begin{array}{ll}
g_s(p)\frac{a-2f_{\max}p}{1-2pf_{\max}} - \frac{1}{2}C_{V_f}g_s(p)\frac{a-2f_{\max}p}{1-2pf_{\max}} & \text{if } a - \frac{b}{2}C_{V_f} > 0 \\
g_s(p)\frac{-2pf_{\max}}{1-2f_{2p}}(1 - \frac{1}{2}C_{V_f}) & \text{else}
\end{array} \right.$$

$$= \left\{ \begin{array}{ll}
(1 + \frac{g_s(p)a-1}{1-2pf_{\max}}) - \frac{1}{2}C_{V_f}(1 + \frac{g_s(p)b-1}{1-2pf_{\max}}) & \text{if } a - \frac{b}{2}C_{V_f} > 0 \\
(1 - \frac{1}{1-2f_{2p}})(1 - \frac{1}{2}C_{V_f}) & \text{else}
\end{array} \right.$$ (5.13)

Note that for an increasing function

$$f_{\max}(I^*) = f(I^* + \frac{1}{2}\Delta I) \approx f(I^*) + \frac{1}{2}\Delta I \frac{df(I_{dc})}{dI_{dc}}|_{I_{dc}=I^*}$$
and similarly for a decreasing function

\[ f_{\text{max}}(I^*) = f(I^* - \frac{1}{2} \Delta I) \approx f(I^*) - \frac{1}{2} \Delta I \frac{df(I_{dc})}{dI_{dc}} |_{I_{dc}=I^*} \]

If the neuron is spiking with a low enough frequency, so \(2pf_{\text{max}} \ll 1\), the expression reduces to

\[ \Gamma = \begin{cases} 
  g_s(p)(a - \frac{b}{2} C_{V_f}) & \text{if } a - \frac{b}{2} C_{V_f} > 0 \\
  O(pf_{\text{max}}) & \text{else} 
\end{cases} \quad (5.14) \]

In this approximation \(\Gamma\) depends linearly on \(C_{V_f}\) (see figure 5.14).

In the results, the full shape of \(g_s(p)\) is not required for an estimation at a single value of \(p\). One simply fits the \(\Gamma - C_{V_f}\)-curve to

\[ \Gamma = a^* - \frac{b^*}{c} C_{V_f} \]

where \(a^* = ag_s(p)\) and \(b^* st = \frac{b}{2}g_s(p)\), which are the starting value and slope of the curve. The full shape of \(bg_s(p)\) can be fitted if we calculate \(\Gamma\) for many different values of \(p\), like in figure 5.2. In the limit \(2pf_{\text{max}} \approx 1\), \(\Gamma\) does not depend linearly on \(C_{V_f}\). In this limit \(\Gamma\) is probably not defined, since there will be multiple spikes in each bin due to the high frequency or large binwidth. So in this regime \(\Gamma\) is not a good measure. With the results from the previous section we can now give an estimation of how the coincidence factor depends on the input vs frequency curve \(f(I)\).

**Hunter and Milton measure**  The reliability measure defined by Hunter and Milton is an adjusted expectation value of the exponent of the inter-spike interval between the two spike trains:

\[ R_{HM} \approx E(\exp(\frac{\Delta t}{\tau_{HM}})) \]

A first rough approximation for this expectation value for two Poissonian spike trains with mean rate \(f_1\) and \(f_2\) can be made by merging the spike trains. The merged spike train is a Poissonian spike train with rate \(f = (f_1 + f_2)\), and hence with an inter-spike interval distribution of

\[ P(\Delta t) = (f_1 + f_2) \exp(-(f_1 + f_2)\Delta t) \]

which results in

\[ E(\exp(\frac{\Delta t}{\tau_{HM}})) = \frac{(f_1 + f_2)\tau_{HM}}{1 + (f_1 + f_2)\tau_{HM}} \quad (5.15) \]

In this approximation, we ignored the fact that a spike belongs to either one or the other spike train, so not all inter-spike intervals are valid. For instance, if one has two spikes that follow each other shortly in spike train 1, the short ISI between these two spikes will be counted for the expectation value of the ISI of the merged spike train, but not for \(R_{HM}\).
This will make $R_{HM}$ larger than the approximation by the merged spike trains. On the other hand, we also ignored the bias towards shorter inter-spike intervals by taking the nearest neighbours in $R_{HM}$, which will make $R_{HM}$ smaller. This expectation value behaves like $R_{HM}$ in that $\lim_{f \tau_{HM} \to 0} E(\exp(\frac{\Delta t}{\tau_{HM}})) = 0$ and $\lim_{f \tau_{HM} \to \infty} E(\exp(\frac{\Delta t}{\tau_{HM}})) = 1$, so for very small $\tau_{HM}$ relative to the spike frequency the measure vanishes, and it reaches one for large $\tau_{HM}$.

When using two spike trains that originate from trials of an experiment in which we used identical inputs, we expect the spikes from the two spike trains to be much closer and hence the nearest-neighbour inter-spike intervals to be much shorter than for two Poissonian spike trains. Therefore, we expect the measure for the experimental spike trains to be higher than for the merged Poissonian spike trains, but to behave similarly as a function of $\tau_{HM}$:

$$R_{HM}(\tau_{HM}) \approx \frac{a \tau_{HM}(f_1 + f_2)}{1 + a \tau_{HM}(f_1 + f_2)}$$  \hspace{1cm} (5.16)

where the factor $a$ determines how much more alike the experimental spike trains are than two merged Poissonian spike trains: if $a > 1$, the spike trains are much more alike than merged Poissonian spike trains, $a = 1$ is what we would expect from merged Poissonian spike trains, and $a < 1$ hints at an anticorrelation.

Based on our observations, we would expect $a$ to depend on the difference in mean frequency between the two experimental spike trains:

$$a = \frac{b}{\Delta f}$$

so that it increases for a decreasing frequency difference. This results in

$$R_{HM}(\tau_{HM}) \approx \frac{\frac{b}{\Delta f} \tau_{HM} 2(f)}{1 + \frac{b}{\Delta f} \tau_{HM} 2(f)} = \frac{1}{1 + \frac{1}{\Delta f} \tau_{HM}(f)} = \frac{1}{1 + \frac{1}{2 \tau_{HM}} C_{V_f}} = \frac{1}{1 + k C_{V_f}}$$  \hspace{1cm} (5.17)

For vanishing frequency difference $\Delta f, C_{V_f} \to 0$ and $R_{HM} \to 1$. This means that two spike trains with the same frequency result in $R_{HM} = 1$. To allow for lower values, one could include an extra parameter, but in this paper we did not do this. For a maximum frequency difference $C_{V_f} \to \max(C_{V_f}) = 2$, $R_{HM} \to \frac{b \tau_{HM}}{1 + b \tau_{HM}}$ which is not equal to zero (see figure 5.14). So $R_{HM}$ will never vanish.
5.5. Expected shape of the reliability measures

In this section we calculated the expected shape of the two reliability measures given the input vs frequency relation. The reliability as defined by the two measures depends on the mean input, due to the input vs frequency curve. So a part of a change in reliability can be predicted from the the input vs frequency relation, and is not very informative. We can distinguish between a change in reliability and precision due to a change in the input vs frequency curve, and a change due to other causes plotting the reliability as a function of $C_{V_f}$, as in figure [5.4]. If a change in reliability is only caused by the input vs frequency curve, the parameters of the fit of the reliability vs $C_{V_f}$ curve do not change. If there is an intrinsic change in reliability, the curve and hence the fit changes. So by looking at the $C_{V_f}$-reliability curve, one can distinguish between a change in reliability and precision due to a change in the input vs frequency curve, and a change due to other causes. In combination with the results from the previous section we can make a prediction for the expected reliability:

$$\text{reliability } R = R(C_{V_f}) \ast C_{V_f}(I_{dc}, \Delta I_{dc, \text{const}}, \Delta I_{dc, \text{extra}})$$

5.5.3 Calculating with distributions

The previous derivations were based on comparing two spike trains. However, in our simulations as well as in our experiments, we compare multiple spike trains. This means that we present the neuron a distribution of stimuli, represented in this case by a distribution of the mean input current $I_{dc}$. This results in a distribution of reliability measure values. How do these distributions relate, based on the calculations in the previous sections?

It can be shown [108] that for a function $y = g(x)$ of a random variable $x$ with probability distribution $P_x(x)$, the probability distribution looks like

$$P_y(y) = \frac{P_x(x_1)}{|g'(x_1)|} + \cdots + \frac{P_x(x_n)}{|g'(x_n)|} + \cdots$$  

(5.18)

where $x_n$ is a root of $y = g(x)$ and $g'(x)$ is the derivative of $g$ with respect to $x$. In the binned or discretized case, the factor $\frac{1}{|g'(x)|}$ takes into account the fact that with the transformation the binwidths change, so that in order to keep $\sum_y P_y(y)\Delta y = 1$, we need to renormalize by $\frac{\Delta x}{\Delta y} \approx \frac{1}{|g'(x)|}$. This means that if we know the distribution of $C_{V_f}$, and the relation between $C_{V_f}$ and the reliability measure, we can calculate the distribution of the reliability measure. For the Hunter and Milton measure, with the help of equation (5.17) we find

$$P_{R_{HM}}(R_{HM}) = \frac{1}{kR_{HM}^2} P_{C_{V_f}}(\frac{1 - R_{HM}}{kR_{HM}})$$  

(5.19)

where $k$ is the fitted parameter. The coincidence factor as defined in equation (5.14) is not differentiable at $a - \frac{b}{2}C_{V_f} = 0$, and for $a - \frac{b}{2}C_{V_f} \leq 0$ the equation $\Gamma(C_{V_f})$ is constant. Thus, equation (5.18) only partially applies: for $0 < \Gamma < g_s(p)a$

$$P_{\Gamma}(\Gamma) = \frac{2}{bg_s(p)} P_{C_{V_f}}(\frac{2}{b}(a - \frac{\Gamma}{g_s(p)}))$$  

(5.20)
Figure 5.14: Expected reliability for different input vs frequency functions. Top: Expected shape of the coincidence factor and Hunter and Milton’s reliability measure as a function of $\mathcal{C}_V f$ and the precision (binsize $p$ for the coincidence factor, $\tau_{HM}$ for Hunter and Milton’s measure) for (if applicable) $f_1 = 4.5$ Hz, $f_2 = 5$ Hz, $p = 10$ ms. For the coincidence factor $g_s(p) = 1 - \exp\left(\frac{-p^3}{3}\right)$, $a = 0.8$, $b = 1.1$ was used. For the Hunter and Milton measure $b = 25$ was used. Bottom: Expected shape of the coincidence factor and Hunter and Milton’s reliability measure as a function of the input, for different increasing (left) and decreasing (right) functions $f(I)$, if one would pick two traces at $I^* - \frac{1}{2}\Delta I$ and $I^* + \frac{1}{2}\Delta I$, with $\Delta I = 1$. 
5.5. Expected shape of the reliability measures

At $\Gamma = 0$ there will be a discontinuity, because $P_\Gamma(\Gamma = 0)$ will be relatively high. Also, there will be a discontinuity at $\Gamma = g_s(p)a$, since $P(\Gamma > g_s(p)a) = 0$, but $P(\Gamma = g_s(p)a) \neq 0$ (see figure 5.15).

In a first order approximation, it can be shown [108] that for a function $g(x)$ of a (Gaussian distributed) random variable $x$ with probability distribution $P_x(x)$, mean $\mu$ and standard deviation $\sigma$, so that

$$g(x) \simeq g(\mu) + g'(\mu)(x - \mu)$$

that

$$E(g(x)) \simeq \int_{-\infty}^{\infty} (g(\mu) + g'(\mu)(x - \mu))P_x(x)dx$$

$$= g(\mu) + g'(\mu)(\int_{-\infty}^{\infty} xP_x(x)dx - \mu)$$

$$= g(\mu)$$

and

$$\sigma^2(g(x)) \simeq \int_{-\infty}^{\infty} (g(\mu) + g'(\mu)(x - \mu) - g(\mu))^2P_x(x)dx$$

$$= g'(\mu)^2 \int_{-\infty}^{\infty} (x - \mu)^2P_x(x)dx$$

$$= g'(\mu)^2 \sigma^2$$

This can also be shown as a series expansion of $g$ around $\mu$ [108]:

$$g(x) = g(\mu) + g'(\mu)(x - \mu) + g''(\mu)\frac{(x - \mu)^2}{2} + \ldots + g^(n)(\mu)\frac{(x - \mu)^n}{n!} + \ldots$$

From this it follows that in a second order approximation

$$E(g(x)) \simeq g(\mu) + g''(\mu)\frac{\sigma^2}{2}$$

These results mean, that a distribution of injected stimuli $P(I_{dc})$ results in a distribution of output frequency values with mean

$$\mu_f \simeq f(V(\mu_{I_{dc}})) + \frac{df}{d\mu_{V_m}}|_{\mu_{V_m} = \mu_{V_m}(\mu_{I_{dc}})} \frac{d\mu_{V_m}}{dI_{dc}}|_{I_{dc} = \mu_{I_{dc}}} \frac{\sigma_{I_{dc}}^2}{2}$$

and standard deviation

$$\sigma_f^2 \simeq (\frac{df}{d\mu_{V_m}}|_{\mu_{V_m} = \mu_{V_m}(\mu_{I_{dc}})} \frac{d\mu_{V_m}}{dI_{dc}}|_{I_{dc} = \mu_{I_{dc}}} \frac{\sigma_{I_{dc}}^2}{2})^2$$

(5.23)
Note that when $\mu_{V_m}(I_{dc})$ and/or $f(\mu_{V_m})$ are nonlinear, $P(f)$ will not be Gaussian. However, in the following we will use only the mean and the standard deviation and assume the distribution is (approximately) Gaussian. To look at the reliability measures the distribution over $C_{V_I}$ is needed. The step from the distribution of output frequencies to the distribution of $C_{V_I}$ is less trivial. Suppose we draw from a Gaussian distribution of frequencies $P(f)$, with mean $\mu_f$ and standard deviation $\sigma_f$, two frequencies: $f_1$ and $f_2$, and define the difference $\Delta f = |f_1 - f_2|$ and the mean $(f) = \frac{1}{2}(f_1 + f_2)$ as before. The distribution of the mean frequency $P((f))$ will be another Gaussian distribution with mean $\mu_{(f)} = \mu_f$ and standard deviation $\sigma_{(f)} = \frac{1}{2}\sqrt{2}\sigma_f$. Without the absolute value, the difference distribution $P(\Delta f)$ would also be a Gaussian distribution with mean 0 and standard deviation $\sqrt{2}\sigma_f$, but the absolute value makes the distribution to look like only its positive half, twice as high, with mean $\mu_{\Delta f} = \frac{2\sigma_f}{\sqrt{\pi}}$ and standard deviation $\sigma_{\Delta f} = \sigma_f\sqrt{\frac{2}{\pi}(\pi - 2)}$. The distribution of $C_{V_I}$ is the distribution of the ratio the variables $\Delta f$ and $(f)$. Even if both distributions were Gaussian, this ratio would not be easy to define: if the distributions were not correlated and their means would not be equal to zero, the ratio distribution would be a Cauchy distribution. With weak correlations and nonzero means a Geary and Hinkley transformation [44] [56] [55] could have been made, but this needs the coefficient of variation of $P((f))$ to be small (< 0.39), which we cannot assume. Finally, the way in which we compared traces (in groups of three, since in the experiments there were three traces per neuron per condition. To make a fair comparison, the traces of the simulations were also compared in groups of three), also makes the analytical expression for the distribution of $C_{V_I}$ nontrivial. Since we cannot calculate the distribution of $C_{V_I}$ analytically, we did a numerical simulation (figure 5.15): for every value of $\mu_f$, $\sigma_f$ and the number of samples, we draw fifteen samples from a normal distribution. The distribution over $C_{V_I}$ depends on the amount of samples. In figure 5.15 a few examples of how this distribution will look are shown for different values of $\mu_f$ and $\sigma_f$. Note that if $\mu_f \approx \sigma_f$ the distributions are slightly bimodal, whereas from $\mu_f > 3\sigma_f$ the distributions are more unimodal. A low $\mu_f$ with a high $\sigma_f$ will result in relatively many cases in which one of the two spike trains contains no spikes, which results in $C_{V_I} = 2$. Higher values of $\mu_f$, or lower values of $\sigma_f$, will have almost no cases in which one of the spike trains contains no spikes, so the peak at 2 will disappear. Figure 5.15 also shows that the mean of $C_{V_I}$ will decrease with increasing $\mu_f$ if we keep $\sigma_f$ constant, which we would expect based on figure 5.13. However, with an increasing mean input vs frequency curve, $\sigma_f$ will increase with $\mu_f$, and it is the ratio between the two (so the ratio between the value and the slope of the input vs frequency curve) that determines the shape of the distribution.

We conclude that even if $I_{dc}$ follows a Gaussian distribution, $C_{V_f}$ and the reliability will not be Gaussian. Therefore, in the paper we show a random draw from a distribution of frequencies with mean and standard deviation calculated from the distribution of $I_{dc}$ and the input vs frequency curve.

\[\text{IF a draw was negative, it was put to zero. If for a realization $C_{V_f}$ was } 0 \text{, because both frequencies vanished, this was not included in the mean distributions.}\]
5.5. Expected shape of the reliability measures

![Distributions of CVf](image)

Figure 5.15: Top: Examples of distributions of $C_{V_f}$ resulting from distributions over $f$ with different mean (left) or standard deviation (right). Like in the experiments/simulations, 15 samples are used. Bottom: artist impression of how the distributions of the reliability measure would look based on the shape of the reliability-$C_{V_f}$-curve and the shape of the distribution of $C_{V_f}$.
5.5.4 A note on the standard deviation of the membrane potential distribution

Traditionally, in patch clamp experiments, to describe a neuron, one typically uses two types of $I - V$ curve, the steady-state and the instantaneous $I - V$ curve using inputs consisting of step protocols. The same holds true for the input vs frequency ($I - f$) relation. However, in a noisy regime, the neuron is never in steady-state. Parallel to these two types of $I - V$ curve and following Badel et al.\(^3\), we define two types of $I - V$ curves in the noisy regime: the average $I - V$ curve $\mu V_m(I_{dc})$ and the instantaneous $I - V$ curve $V_m(\mu_I)_{\text{inst}}$. The first is constructed by fitting the amplitude distributions of both the input current and the membrane potential to a Gaussian distribution. Obviously, the input current distribution is a Gaussian distribution, since we constructed it this way. The membrane potential distribution, however, is not, since the membrane potential is a highly nonlinear function of the input current: it looks like a subthreshold Gaussian distribution with an extra tail representing spikes. Since the subthreshold part approximates a Gaussian, the membrane potential can be approximated by a linear function of the input for small deviations and the nonlinearity is mainly in the spikes. We exclude

\(^3\)Note that Badel et al. use the membrane current $I_m(t) = I_{in}(t) - C_m \frac{dV_m}{dt}$ in their $I - V$ curve, whereas we use the input current $I_{in}(t)$.
5.5. Expected shape of the reliability measures

these from the Gaussian fit. The instantaneous $I-V$ curve is constructed by using Badel et al.’s method [5]: we binned the membrane potential in bins of 1 mV, and looked at the mean input current in each bin. This instantaneous $(I-V)$ curve determines how a neuron responds to a change in input current from the mean, and is therefore largely responsible for the standard deviation of the membrane potential amplitude distribution (see the previous section). This means that in a first order approximation

$$\sigma_{Vm} \approx \left. \frac{dV_m(\mu_I)}{d\mu_I} \right|_{\mu_I=I_{dc}} \sigma_I$$

Indeed, in figure 5.16 one can see that the slope of the instantaneous $I-V$ curve is a good predictor for the standard deviation of the membrane potential (without spikes). However, it is always slightly too high, since the instantaneous $I-V$ curve becomes steeper with increasing input current and less so for lower input currents. This means that especially at higher mean input currents our estimate will always be slightly too high.

In figure 5.17 we show the average and instantaneous $I-V$ curves for the experiments. The instantaneous $I-V$ curves show both a changing threshold and a shift on depolarization, as in the Morris-Lecar model with a T-current and an h-current. The standard deviation of the membrane potential can be reasonably explained by the slope of the instantaneous $I-V$ curve, but is slightly too high, since the point at which we fitted (roughly where the instantaneous and the average $I-V$ curves cross) is also where they have the highest slope, which will overestimate the standard deviation of the membrane potential, as expected.

In summary, we defined two types of $I-V$ curve for the noisy regime: the instantaneous $I-V$ curve, that predicts the standard deviation of the membrane potential and other characteristics of the neuron such as the spike-threshold (see figure 5.5.4) and the average $I-V$ curve that predicts together with the frequency-membrane potential curve the normalized frequency difference $C_V$, hence the reliability.

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Figure 5.17: $I - V$ curves of thalamocortical relay cells. Average (dots and fitted line) and instantaneous $I - V$ curves, and the resulting standard deviation of the membrane potential (dots: measured values, stars: approximation by $\frac{dV_m(\mu_I)}{d\mu_I}\big|_{\mu_I=I_{dc}\sigma_I}$).