Spike statistics of stochastic homoclinic neuron models in the bistable region

Jan-Hendrik Schleimer  Janina Hesse  Susanne Schreiber
Institute for Theoretical Biology, Humboldt-Universität zu Berlin

Abstract: Neurons typically show two distinct dynamical regimes: Resting state, corresponding to a stable fixpoint, are often observed for low average input. Higher input commonly result in tonic spiking, which corresponds to a stable limit cycle. Some neurons, however, show an additional intermediate, bistable regime, with coexistence of resting-state fixpoint and limit-cycle spiking. In this article, a bistable neuron with spike onset at a saddle-homoclinic orbit bifurcation is investigated. In the bistable region, noise can switch between rest and spiking, and thus increase the variability of the spike train compared to neurons with only one stable attractor. This has consequences for spike-time coding as it effectively increases the output entropy of neuronal ensembles. Here, the spiking statistics is derived for homoclinic conductance-based neuron models. Switching between rest and spiking is mainly determined along the downstroke of the action potential, a dynamical feature lacking in common neuron models with reset dynamics. Nonetheless similar derivations can be applied to quadratic integrate-and-fire models. The derived interspike interval distribution is shown to be unimodal, which warrants the future use of meanfield approaches to networks of bistable neurons.

1 Introduction

Spike trains recorded from nerve cells vary in their degree of regularity. Some emit tonic pulses like Purkinje cells, other show very irregular spike trains, such as “stuttering cells” or the “irregular spiking cells”\(^1\)\(^-\)\(^5\). The spike patterns emitted by a neuron are influenced by the synaptic and intrinsic fluctuations in conjunction with the neuron’s intrinsic dynamics. Thus, two major sources of irregularity are conceivable: Some irregular neurons are simply subject to strong fluctuations, caused by intrinsic ion-channel noise or by synaptic bombardment, which increase their interspike interval (ISI) variability\(^6\). For others, the deterministic dynamics close to the spike onset bifurcation shows a coexistence of a stable resting-state fixpoint and limit-cycle spiking. This leads to increased variability even at moderate noise levels, for an exemplary voltage trace see Fig. 1(a). The goal of this article is to characterise the spiking statistics of the bistability that arises at a saddle-homoclinic-orbit (HOM) bifurcation, see phase plot in Fig. 1(b), a universal element of the fundamental bifurcation structure of conductance-based neurons\(^7\)\(^,\)\(^8\).

The ubiquitous irregularity of action-potential (AP) firing in nerve cells has been noted early on\(^9\). In some cases noise has been deemed a mayor obstacle for reliable responses\(^10\), while other cases have conversely highlighted its beneficent involvement in creating fast or information-optimal responses\(^11\). Indeed, nervous systems may well have in store both: cases where irregularity is facilitating neuronal function\(^12\), and other cases where it is detrimental. While the functional debate is still on, the phenomenology of irregular spiking has not been completely characterised, let alone its mechanisms quantitatively understood. Therefore in the following, stochastic properties of irregular spiking are derived for neurons near a HOM bifurcation, which show coexistence of rest and spiking behaviour (bistability).

Conductance-based neuron models with spike generation at a HOM bifurcation show a region of bistability between rest and spiking. The bistability leads to a hysteresis in the firing-rate versus input curve, see Fig. 1(c): Ramping up the input current, the neuron stays at rest until the resting state loses stability at \(I_{sn}\). Conversely, when ramping down the input current, the neuron remains spiking until the limit cycle disappears at \(I_{hom}\). Bistability is observed for inputs \(I\) with \(I_{hom} < I < I_{sn}\). Within the bistable region, noise can switch the dynamics between rest and spiking. This jumping between at-
Fig. 1: Bistability in homoclinic neurons. (a) Voltage trace of a homoclinic neuron (with gating time constant of $\tau_n = 0.16$ ms) driven with $I = 4.4 \mu A/cm^2$ plus noise with $\sigma = 24 mV/\sqrt{s}$. (b) Phase plots (gating variable versus voltage) of neurons in different dynamical regimes. (c) Bistability of rest and spiking leads to hysteresis in the frequency-input curve. Within the bistable region, noise can switch between rest and spiking. (d) The codimension-two SNL bifurcation is common to all class-1 excitable neurons. It acts as a gate to the bistable, homoclinic spiking regime (shaded area). $\tau_n$ is the time scale of the gating variable.

The here considered HOM bifurcation occurs in generic conductance-based neuron models for a range of parameters. Starting with a model showing the common saddle-node on invariant cycle (SNIC) bifurcation at spike onset, a decrease of the separation of timescales between voltage and gating kinetics switches the spike onset to a HOM bifurcation, see Fig. 1(d). The switch in spike onset bifurcation happens at the codimension-two saddle-node loop (SNL) bifurcation, which can be induced by many fundamental parameters in neuronal systems ranging from leak conductance, capacitance and temperature changes, to modifications of extracellular potassium concentration. As illustrated here, the SNL bifurcation functions for neurons with SNIC onset bifurcation as a gate to a bistable region. Besides HOM neurons, bistability between rest and spiking also occurs in neurons that undergo a subcritical Hopf bifurcation, followed by a fold of limit cycles at their firing onset (sometimes called Bautin bifurcation), which has previously been explored numerically. The spike statistics for SNIC neurons (upper part of the bifurcation diagram in Fig. 1(d)) is well characterised both for the excitable dynamics, i.e., $I < I_{sn}$ (fluctuation driven), and the limit cycle dynamics, where $I > I_{sn}$ (mean driven). The statistics in the bistable region of HOM neurons, however, is less studied and will be explored in this study. The derivation of the associated interspike interval statistics fills a gap of knowledge and provides the means to differentiate alternative underlying bifurcation mechanisms. This might be particularly interesting when relating single-cell dynamics to the up- and down-states observed at network level. Previously, up- and downstates on the single-cell level were modeled by a bistability of two fixpoints in the membrane voltage. The here considered setting is different, with a bistability between a fixpoint of the membrane voltage (the resting state), and the limit cycle (spiking dynamics).

In systems with high stochasticity, such as neurons, as alternative to the observation of hysteresis, bistability can be identified based on here derived quantities, the interspike interval statistics and the switching probability between the two attractors. As both measures can be estimated from recordings of biological neuron, they can be used to differentiate neurons in which the irregularity is solely due to noise from those in which the irregularity is enhanced by a bistability of the intrinsic dynamics. The here considered setting is different, with a bistability between a fixpoint of the membrane voltage (the resting state), and the limit cycle (spiking dynamics).
structures using spike statistics.

Sec. 2 introduces the model for which in Sec. 3 the interspike interval density is derived. To this end, the stochastic trajectories are projected onto the unstable manifold of the saddle, see Sec. 3.1. In this coordinate system both the statistics of intermittent silence, burst-firing and switching between these regimes are calculated in Sec. 3.5, 3.4 and 3.2, respectively.

2 Conductance-based neuron model with homoclinic bistability

In the bistable regime, transitions between two stable attractors can be induced by noise fluctuations. The associated transition probability between the two attractors as well as the resulting spike statistics is derived in the following for a generic class of conductance-based neuron models with additive noise and spike onset at a HOM bifurcation. The analysis focuses on HOM neurons that are close to the SNL bifurcation, which allows for useful assumptions as introduced later.

The present analysis considers an n-dimensional conductance-based neuron model with one voltage dimension, the membrane voltage \( v \), and a set of \( n-1 \) ion channel gates \( a_i \). The dynamics of the state vector \( x = [v, a_1, ..., a_{n-1}]^\top \in \mathbb{R}^n \) is given by

\[
\dot{x} = F(x) + D(x)\xi(t). \tag{1}
\]

The additive noise \( D(x)\xi \) originates from a diffusion approximation of either synaptic or intrinsic noise sources. The voltage dynamics follows a current-balance equation \( F_0(x) = (I - I_{\text{ion}}(x))/C_m \), with membrane capacitance \( C_m \), and the gates have first order kinetics, see also Appendix, Sec. 8.1 for model details.

The analysis assumes that the model shows a HOM bifurcation at spike onset. Under some nonrestrictive assumptions, conductance-based neuron models can be turned into this regime\(^7 \). In HOM neurons, the limit cycle (corresponding to tonic firing) arises at \( I = I_{\text{hom}} \) from a homoclinic orbit to the saddle, and at \( I = I_{\text{sn}} > I_{\text{hom}} \), saddle and stable node (corresponding to the neuron’s resting state) collide in a saddle-node bifurcation. For inputs in between, with \( I_{\text{hom}} < I < I_{\text{sn}} \), the stable node and the limit cycle coexist as two stable attractors, see Fig. 1. The state space is divided into the basin of attraction of the fixpoint and the limit cycle by a separatrix (Fig. 2).

The analysis furthermore assumes that the noise strength is chosen small enough such that the spike shape is in first order not affected (the typical small noise approximation). With this, jumping between spiking and resting state is only possible close to the separatrix. While the separatrix is non-local, the following analysis shows that salient properties of its stochastic transition are given by the linearized dynamics around saddle and stable node.

The linearised dynamics around fixpoints are given by the Jacobian of Eq. 1, \( J(x) = \frac{\partial F(x)}{\partial x} \), which has \( n \) eigenvalues \( \lambda_0, ..., \lambda_{n-1} \). For neuronal models forgoing a HOM onset bifurcation, the Jacobian at the saddle has one simple, positive, real eigenvalue corresponding to the unstable direction, denoted by \( \lambda_0 \in \mathbb{R} \). The other eigenvalues correspond to stable directions, such that

\[
\lambda_0 > 0 > \lambda_1 \geq ... \geq \lambda_{n-1}. \tag{2}
\]

The associated orthonormal left and right eigenvectors are denoted by \( l_k \) and \( r_k \), respectively, with \( l_j \cdot r_k = \delta_{jk} \), see Fig. 3(a). An analytical expression of \( l_0 \) and \( r_0 \) is given in the Appendix, in Sec. 8.2 for the saddle-node fixpoint, and in Sec. 8.3 for the saddle fixpoint.

The statistical properties of the bistable dynamical regime are not yet sufficiently characterised and will be explored in subsequent sections.

3 Inter-spike interval

The following analysis considers the spike train of a HOM neuron in the bistable region, with \( I_{\text{hom}} < I < I_{\text{sn}} \), subjected to white noise sufficiently strong to induce jumps between the two basins of attraction, e.g., Fig. 1(a). Between two consecutive spikes, the dynamics can either remain in the basin of attraction of the limit cycle, or it can visit the basin of attraction of the fixpoint before eventually returning to the limit cycle. On average, visiting the fixpoint will induce longer interspike intervals, because the escape from the resting state requires time in addition to the duration of the limit cycle.

Because the driving stochastic process is white, the process of subsequently occurring interspike intervals is renewal, as will be argued in Sec. 3.2. The total interspike interval density is then a mixture of
trajectories that remain on the limit cycle, and such trajectories with intermittent visits to the fixpoint. The interspike interval distributions of these two possibilities are denoted as

(i) the probability \( p_{lc}(t) \) that an interspike interval results from a trajectory staying exclusively on the limit cycle dynamics, and

(ii) the probability \( p_{fp}(t) \) that an interspike interval is composed of some time spent near the resting state in addition to the time required for the limit-cycle spike following the escape of the fixpoint.

The total interspike interval density is a mixture of both kinds of trajectories,

\[
p_{isi}(t) = (1 - \nu) p_{lc}(t) + \nu p_{fp}(t),
\]

where the factor \( 1 - \nu \) determines the proportion of intervals for which the dynamics resides entirely on the limit cycle side of the separatrix, while \( \nu \) is the proportion of intervals that include time spend on the fixpoint side of the separatrix.

In the following, \( \nu \) is called the mixing factor or splitting probability. For increasing values of \( \nu \), visits to the fixpoint are increasingly likely. In spike trains, this is visible as a larger proportion of long interspike intervals. Under the impression of high variability or ratio of long and short interspike intervals, observed spike trains are sometimes termed as stochastically bursting, stuttering, missing spikes or just irregularly spiking in the experimental literature\(^2,4,5\).

In the following, the “ingredients” to approximate the interspike interval density in Eq. 3 are provided. The mixing factor \( \nu \) is derived in Sec. 3.2, and the probabilities \( p_{lc}(t) \) and \( p_{fp}(t) \) in Secs. 3.4 and 3.5, respectively. To this aim, the system is first transformed into a coordinate system that naturally facilitates the analysis (Sec. 3.1).

### 3.1 Projecting crossings of the separatrix on a double-well problem

The observation that most crossings of the separatrix happen along the downstroke of the action potential permits in the following to project the crossings of the separatrix onto a one-dimensional problem. More specifically, the high-dimensional problem of stochastic transitions through the \((n-1)\)-dimensional separatrix is reduced to a one-dimensional double-well escape problem of which the occupancy statistics are known\(^17\).

The separatrix between rest and spiking corresponds to the stable manifold of the saddle fixpoint. At the saddle, the tangent space of the separatrix is

\[
T = \left\{ \sum_{k=1}^{N-1} \alpha_k r_k : \alpha_k \in \mathbb{R} \right\}.
\]

The orthogonal complement is given by the left eigenvector \( l_0 \in T^\perp \), see Fig. 3(a) for a two-dimensional example.

For spike onset at \( I = I_{hom} \), the separatrix overlaps with the homoclinic orbit, as both align per definition with the stable manifold of the saddle. For \( I > I_{hom} \), the limit cycle detaches from the saddle. The separatrix follows the limit cycle, until it eventually diverges, see Fig. 2. Along the spike downstroke, both the limit cycle and the separatrix remain parallel to the tangent space \( T \) for a significant part of the loop, for details see Appendix, Sec. 8.5. Most relevant crossings of the separatrix happen in this region of the state space because
(i) due to the slow dynamics in the state space around the saddle, the limit cycle trajectory spends most of the time close to the saddle fixpoint, and

(ii) the distance between limit cycle and separatrix is minimal along the spike downstroke, allowing even weak noise deviations to switch the dynamics between rest and spiking.

In principle, multiple crossings back and forth across the separatrix are possible, but the final decision is taken when closing in on the saddle. In the vicinity of the saddle, trajectories on the limit cycle side of the tangent space \( T \) will follow limit cycle dynamics, while trajectories on the other side of the tangent space \( T \) will visit the stable fixpoint. The decision on which side of the separatrix a sample path is at a particular time can thus be read from a projection onto \( l_0 \in T^\perp \),

\[
y(t) = l_0 \cdot (x(t) - x_s),
\]

where, for simplicity, the dynamics is centred to the saddle at \( x_s \), such that the saddle is in the projected coordinates located at \( y_s = l_0 \cdot x_s = 0 \). The position of the stable node is \( y_s = l_0 \cdot (x_n - x_s) \), see Fig. 3(a). In the following, the convention is used that \( y > 0 \) corresponds to the limit-cycle side, while \( y < 0 \) implies the fixpoint side, corresponding to the rest.

The following analysis uses the minimum distance of the deterministic limit cycle dynamics to the separatrix,

\[
d_{lc} = \arg \min_{x \in \Gamma} \{ l_0 \cdot (x - x_s) \},
\]

see Fig. 3(a). Here \( \Gamma \) denotes the invariant set of the limit cycle. As mentioned above, the minimal distance is typically reached during the downstroke of the action potential, \( d_{lc} \) is the distance in \( r_0 \)-direction of the projection along \( T \) of the closest point of the limit cycle to the separatrix.

The projection aims to collapse the decision, whether or not the fixpoint is visited, into one dimension such that the theory of double-well potentials can be applied to calculate the occupancy statistics. A histogram of the projected values, \( y(t) \), from a simulation shows a bimodal distribution in Fig. 3(b). Such bimodal distributions also appear in the Brownian motion of a particle in a double-well potential. This motivates the here presented approach to reduce the properties of stochastic bursting in a high-dimensional neuron model to a double-well problem:

\[
\dot{y} = -U'(y) + \sigma \xi(t).
\]

The coefficient \( y(t) \) here results from the projection of the dynamics onto the normal direction to the separatrix, as introduced above.

Approximations for the potential \( U(y) \) and the noise strength \( \sigma \) will be discussed for the different quantities that are calculated in the following sections.

### 3.2 Splitting probability

For uncorrelated noise, the series of spike-time events is a renewal process. After each spike, during the downstroke when the trajectory is close to the separatrix, the noise in the system operates akin to a (biased) coin flip that determines if the fixpoint is visited, or if immediately another round on the limit cycle is taken. Hence, the consecutive decisions from which distribution the spike times are drawn, i.e., \( p_{lc}(t) \) or \( p_{fp}(t) \), are Bernoulli trials. Indeed, all of it is covered by calculating the splitting probability (or mixing factor) in a double-well potential.

In a double-well problem, the splitting probability depends on the curvature of the barrier and initial conditions, i.e., where the trajectory is injected in relation to the barrier peak. During the downstroke, the projected limit cycle dynamics near the separatrix is approximated by Eq. 7, where the potential in the direction of \( l_0 \) is \( U_s(y) = -\frac{\lambda_0}{2} y^2 \), and the “mixing noise” in that dimension is approximated by \( \sigma^2 = \sigma_m^2 = l_0 \cdot D_s l_0 \), with the diffusion matrix evaluated at the saddle, \( D_s = D(x_s) \).

For the initial conditions, one may assume that, after a spike, the stochastic path is near the deterministic limit cycle trajectory that is parallel to the separatrix, see Fig. 3(a). Thus, the splitting probability depends on the distance between limit cycle and separatrix, \( d_{lc} \), which will be derived in Sec. 3.3. For small \( d_{lc} \), the splitting probability can be approximated by

\[
\varpi = \frac{1}{2} \left( 1 - \text{erf} \left( \frac{d_{lc} \sqrt{\lambda_0}}{\sigma_m} \right) \right).
\]

If the injection occurs at the separatrix, which corresponds to the situation when the limit cycle is born from the homoclinic orbit at spike onset (Fig. 2), the probability of ending up on either side of the separatrix is \( 1/2 \). For increasing distance, the probability of visiting the fixpoint decays, see inset in
Fig. 4(a), such that repetitive, burst-like, limit cycle excursions become more likely.

![Graph showing limit cycle distance and mixing factor](image)

Figure 4: Comparison of theoretical prediction (lines) and numerical simulations (markers) for different gating time constants \( \tau_n = 0.155, 0.16 \) and 0.165 ms. (a) Distance between limit cycle and separatrix, \( d_{lc} \), versus input current. Inset: Mixing factor \( \varpi \) as a function of \( d_{lc} \). (b) \( 1 - \varpi \) versus input current.

### 3.3 Limit cycle distance to the separatrix

The limit cycle originates from a homoclinic orbit at \( I = I_{hom} \). As can be seen from the quadratic dynamics in the centre manifold of the saddle-node, the saddle, and thus the separatrix, moves as a square-root function of the input current. The limit cycle position is more invariant, compare Fig. 2 and the Appendix, 8.4. Using Eq. 6, the distance of the limit cycle to the saddle in the centre manifold, and thus to the separatrix, is

\[
d_{lc} = \sqrt{l_{00} \left( \sqrt{I_{sn} - I_{hom}} - \sqrt{I_{sn} - I} \right)}, \tag{9}
\]

where \( l_{00} \) is the entry of the left eigenvector \( l_0 \) that corresponds to the voltage dimension. The factor \( a \) is the curvature term of the nullclines, and can be determined by\(^{19,20}\)

\[
a = \frac{1}{2} \cdot l_0 H r_0 r_0,
\]

where \( H \) is the Hessian matrix of the deterministic dynamics.

Fig. 4(a) depicts the analytical \( d_{lc} \) from Eq. 9 and the simulated distance of the limit cycle to the separatrix as a function of the input current. For values of \( I \) away from the saddle-node, \( I_{hom} < I << I_{sn} \), the relation is rather linear. Hence, near the onset of bistability, the limit cycle distance can be approximated by

\[
d_{lc} \approx \sqrt{l_{00} \left( \frac{I_{sn} - I}{2 a C_m \sqrt{I_{sn} - I_{hom}}} \right)}. \tag{11}
\]

With these expressions for the distance \( d_{lc} \), the mixing factor \( \varpi \) can be calculated according to Eq. 8. For comparison, the mixing factor \( \varpi \) is evaluated in stochastic simulations. To this end, the relative time spend on the side of the stable fixpoint and of the limit cycle is detected by recording a spike when a voltage threshold of -10 mV is crossed from below; and recording a visit to the fixpoint when a two-dimensional threshold is crossed (crossing the voltage value of the saddle from above and the value of the \( n \)-variable 5% above the value corresponding to the node). The comparison between simulations and the analytical results can be inspected in Fig. 4(b).

Next, the probability \( p_{lc}(t) \) for staying on the limit cycle, the probability \( p_{fp}(t) \) for visiting the stable fixpoint, as well as the intra- and inter-burst statistics are calculated.

### 3.4 Intra-burst statistics

This section determines the probability \( p_{lc}(t) \) for staying on the limit cycle without visiting the fixpoint used in Eq. 3. From this, the statistics of spikes inside a “burst” is derived, \( i.e., \) a consecutive sequence of limit cycle excursions uninterrupted by a crossing of the separatrix into the attraction domain of the fixpoint.

For trajectories that stay within the basin of attraction of the limit cycle and a sufficiently small noise amplitude, a phase reduction maps the process to a one-dimensional Brownian motion in the phase, \( \theta \), which has constant drift,

\[
\dot{\theta} = 1/\tau_{lc} + 2\tilde{D}_{lc}(t). \tag{12}
\]
Here, $\tau_c$ is the intrinsic, deterministic period of the limit cycle and $\xi(t)$ a stochastic white-noise process with effective diffusion matrix $\bar{D}_c$. The effective diffusion matrix, $\bar{D}_c$, is obtained by averaging the potentially non-stationary noise over the time scale of one interspike interval with an appropriate weighting function, $Z_0$, that quantifies how susceptible the spike time is to perturbations at a given phase $\varphi$:

$$\bar{D}_c = \int_0^1 d\varphi \, Z_0(\varphi) \cdot \mathbf{D}(\mathbf{x}_c(\varphi)) \mathbf{Z}_0(\varphi).$$  \hspace{1cm} (13)

The weighting function is the so-called phase-response curve, $Z_0(\theta) = \nabla\mathbf{b}|_{\mathbf{x}(\theta)=\mathbf{x}_c(\theta)}$, which can be determined numerically or calculated via centre-manifold reductions.\(^{20}\) Provided that channel or synaptic fluctuations act on time scales faster than the average limit cycle period, the effective phase diffusion, $\bar{D}_c$, quantifies the averaged noise per interspike interval that causes jitter in the timing of spikes. It disregards radial excursions due to noise, in particular those that would cause jumps over the separatrix into the phaseless set (where no phase is defined). Assuming the intra-burst dynamics is governed by the stochastic phase evolution in Eq. 12, the waiting-time density follows an inverse Gaussian distribution:

$$p_c(t) = \frac{\exp\left(-\frac{(t-\tau_c)^2}{\tau_c^2 D_c t}\right)}{\sqrt{\pi D_c t^3}}. \hspace{1cm} (14)$$

The mean of the distribution, $\tau_c$, is identical to the deterministic period of the limit cycle. In the case of a homoclinic neuron, it scales according to\(^{18}\)

$$\tau_c = -\frac{1}{\lambda_0} \ln\{d_c\}. \hspace{1cm} (15)$$

Here, $d_c$ is the distance of the limit cycle to the separatrix, cf. Eq. 6, expressed in terms of system parameters in Eq. 9.

### 3.5 Inter-burst statistics

This section develops the probability $p_{ib}(t)$ for interspike intervals composed of a visit to the resting state fixpoint and a limit-cycle spike used in Eq. 3. The inter-burst intervals resulting from fixpoint visits are on average longer than the intra-burst intervals derived in the last section. The corresponding interspike interval, $t_{ip}$, can be obtained by adding the time it takes for the trajectory to escape from the fixpoint, $t_e$, and the proceeding time, $t_{lc}$, for a spike excursion around the limit cycle, to obtain $t_{ip} = t_e + t_{lc}$. The escape time, $t_e$, from the resting state is described by Poisson statistics with a Kramer’s rate\(^6\). The required assumption for Kramer’s theory, \textit{i.e.}, that the dynamics be equilibrated around the resting state, though not perfectly satisfied, appears reasonable enough, given that the decay time constant of the exponential decay is correctly described by the escape rate, as previously validated by comparisons with numerical simulations.\(^6\) However, there is disagreement in the very short ISIs\(^6\). Therefore, in the present case, the escape rate is only supposed to describe the existence of the separatrix, which is then followed by the time taken for another limit-cycle spike, $t_{lc}$. If the escape and limit-cycle dynamics were to be statistically independent, the waiting time of the complete inter-burst statistics $p_{ib}(t)$ would be the convolution of the escape statistics $p_e$ and the additional time corresponding to the duration of the spike, $p_{lc}$, \textit{i.e.},

$$p_{ib}(t) = (p_e * p_c)(t) = \int_0^t p_e(t-r)p_c(r)dr. \hspace{1cm} (16)$$

Note that Eq. 16 effectively describes a Poisson neuron with a refractory period drawn from $p_c$. The assumption of statistical independence can be motivated by two observations. Firstly, due to the fast contraction of the stable directions onto the one-dimensional unstable manifold at the saddle, the trajectories that leave the stable manifold are likely to penetrate the separatrix near one point. This gives delta-like initial condition for the limit-cycle dynamics. Secondly, the noise is uncorrelated.

The interval statistics of the escape, \textit{i.e.}, the Poisson neuron with Kramer’s rate $r$, is exponential,

$$p_e(t) = e^{-t/r_c} / r_c. \hspace{1cm} (17)$$

The mean interval $\tau_c$ is given by the inverse of the Kramer’s rate\(^5\)

$$\tau_c \approx \frac{2\pi}{|\lambda_0|^2} \frac{\Delta U_{sn}/2\sigma^2}{}, \hspace{1cm} (18)$$

where $\lambda_0$ is the eigenvalue associated with the unstable manifold of the saddle. $\Delta U_{sn}$ is the potential difference between saddle and node, $\Delta U_{sn} = U_{sn}(y_s) - U_{sn}(y_n)$. The latter can be approximated
in the vicinity of the saddle-node bifurcation. Saddle and node depart from the saddle-node according to a square root function, such that locally \( y_{sn} = (y_s + y_n)/2 \). If \( y_s \) and \( y_n \) have not departed too far from \( y_{sn} \), the potential \( U \) is centrally symmetric around \( y_{sn} \) and hence has no quadratic part (i.e., the linear dynamics of saddle and node cancel in the middle). Therefore, the remaining dynamics can be captured in the following potential:

\[
U_{sn} \approx \frac{(I_{sn} - I)(y - y_{sn})}{C_m} + \frac{a(y - y_{sn})^3}{3},
\]

with the factor \( a \) from Eq. 21.

The potential difference between saddle and node is hence

\[
\Delta U_{sn} \approx (I - I_{sn})(y_n - y_s)/C_m + \frac{a}{12}(y_n - y_s)^3.
\]

Figure 5: Near spike onset, the analytical escape rate (red) fits the probability distribution of the escape duration from fixpoint to the separatrix \((\tau_n = 0.165\text{ms})\).

Using this approximation of the potential height in Eq. 18, the escape time density in Eq. 17 can be compared to the simulated neuron. The validity of the approximation can be inspected in Fig. 5 for different input currents. With this, all elements of the interspike density in Eq. 3 have been derived.

### 3.6 Burst length statistics

As argued in Sec. 3.2, the sequence of interspike intervals generated by the present bistable neuron, driven by white noise, is a renewal process, i.e., after each spike at the downstroke, the decision from which of the mixture components the interval is drawn happens irrespective of the previous intervals. Hence, no serial correlations between intervals are to be expected. Consequently, the burst length (number of consecutive limit cycle traverses before crossing the separatrix to the fixpoint) follows a geometric distribution which only depends on the splitting probability,

\[
p(k) = \varpi(1 - \varpi)^{k-1}.
\] (19)

Fig. 6 shows a comparison of numerically obtained burst-length statistics and the theory. This supports the initial assumption that the distribution of interspike intervals is indeed a renewal process.

If, for longer experimentally recorded spike trains, histograms of burst length distribution are available, the splitting probability \( \varpi \) can be inferred as the single parameter that fits \( p(k) \) to the data.

### 4 Multimodal ISI densities in bistable neurons

Neuronal bistability at a separatrix connected to the stable manifold of a saddle is not the only known bistability in single neuron dynamics. Already in Hodgkin and Huxley’s equations for the squid axon a coexistence of resting and spiking was found for

Figure 6: Burst-length statistics fitted using a geometric distribution and the splitting probability from Eq. 8.

If, for longer experimentally recorded spike trains, histograms of burst length distribution are available, the splitting probability \( \varpi \) can be inferred as the single parameter that fits \( p(k) \) to the data.
a small parameter range\textsuperscript{22}. In that case, for increasing input, a stable and an unstable limit cycle originate from a fold of limit cycle bifurcation and the unstable limit cycle subsequently terminates in a subcritical Hopf bifurcation, which also changes the stability of the fixpoint. ISI histograms estimated from numerical simulations of the squid model with noise\textsuperscript{14,15}, as well as analytical calculations with simplified resonate-and-fire type models\textsuperscript{23,24}, have suggested the presence of multimodal peaks in the ISI density. This raises the question if the kind of bistability in homoclinic neurons treated here can produce multimodal ISI densities, too, or if this hallmark can be used to differentiate between the two kinds of bistability?

To answer the question of multimodality, the modes of the components of the mixture are examined. The inverse Gaussian, $p_{\text{ic}}(t)$, has a single mode at

$$\hat{t}_{\text{ic}} = \tau_{\text{ic}} \left( \frac{1}{4} \right) \left( \frac{9 \nu_{\text{ic}}^2 D_{\text{ic}}^2}{4 \tau_{\text{ic}}^2 D_{\text{ic}}^2} - \frac{3}{2} \nu_{\text{ic}} D_{\text{ic}} \right).$$

The convolution with an exponential kernel does not produce additional peaks, and hence $p_{\text{ip}}(t)$ as defined by the convolution in Eq. 16 is unimodal, too. The derivative of $p_{\text{ip}}(t)$ is $\tau_{\text{p}} p_{\text{ip}}(t) = p_{\text{ic}}(t) - p_{\text{ip}}(t)$. If set to zero, it is found that it has a single mode $\hat{t}$ which satisfies

$$p_{\text{ip}}(\hat{t}_{\text{ip}}) = p_{\text{ip}}(\hat{t}_{\text{ip}}),$$

\textit{i.e.}, the single mode is located at the crossing of the two distributions.

The curvature of $p_{\text{ip}}$ is given by

$$p''_{\text{ip}}(t) = \frac{1}{\tau_{\text{ip}}} (p''_{\text{ic}}(t) - p''_{\text{ip}}(t)).$$

The curvature at the mode is thus given by $p''_{\text{ip}}(\hat{t}_{\text{ip}}) = p''_{\text{ic}}(\hat{t}_{\text{ip}})/\tau_{\text{ic}}$. The curvature is negative because $\hat{t}_{\text{ip}}$ corresponds to a maximum. Hence, the mode of $p_{\text{ip}}(t)$ is to be found on the declining part of $p_{\text{ic}}(t)$, \textit{i.e.}, $\bar{t}_{\text{ip}} < \hat{t}_{\text{ip}}$.

The modes of the mixture distribution are confined to lie in the interval $[\hat{t}_{\text{ic}}, \bar{t}_{\text{ip}}]$. Within this interval between both individual peaks, $(p'_{\text{ic}}(t) < 0$ and $p'_{\text{ip}}(t) > 0$, such that Eq. 21 implies the concavity of $p_{\text{ip}}(t)$. Let $\bar{t}$ denote the inflection point of the concave part of the inverse Gaussian distribution, $p_{\text{ic}}(t)$. The distribution $p_{\text{ic}}(t)$ is concave on the interval $[\bar{t}_{\text{ic}}, \bar{t}]$. Within the interval $[\bar{t}_{\text{ic}}, \min(\bar{t}, \bar{t}_{\text{ip}})]$, both distributions, $p_{\text{ic}}(t)$ and $p_{\text{ip}}(t)$, are concave, which permits no more than a single peak for the mixing distribution. If the inflection point lies beyond the mode of $p_{\text{ip}}(t)$, \textit{i.e.}, $\bar{t}_{\text{ip}} < \bar{t}$, this implies unimodality of $p_{\text{ic}}(t)$. For the other case, $\bar{t}_{\text{ip}} > \bar{t}$, this implies no more than a peak on the interval $[\bar{t}_{\text{ic}}, \bar{t}]$. For unimodality, it remains to show that the mixing distribution decays on the interval $[\bar{t}, \bar{t}_{\text{ip}}]$. Within this interval, let us assume that $\tau_{\text{c}}$ is the longest time scale in the system. According to Eq. 21, the density $p_{\text{ip}}(t)$ can be made arbitrarily flat compared to the derivative $p''_{\text{ip}}(t)$ by increasing $\tau_{\text{c}}$. This means that for sufficiently large $\tau_{\text{c}}$, $p_{\text{ic}}(t)$ is within the interval $[\bar{t}, \bar{t}_{\text{ip}}]$ dominated by the derivative $p''_{\text{ip}}(t)$, and is thus negative with no possibility for a peak.

Coming back to the question of the modality of bistable homoclinic ISI density, it can be asserted that for large $\tau_{\text{c}}$, which occur close to $J_{\text{hom}}$, and with all other assumptions used in this article, the ISI density is unimodal. This is in contrast to at least a large proportion of bistable Hopf neurons and could offer a way to distinguish these regimes.

### 5 Estimates of the splitting probability

In the presence of noise, hysteresis effects as shown in Fig. 1(c), a distinctive signature of bistability in deterministic systems, may be obscured. But can bistability still be detected from stochastic properties of the spike time series? Once bistability is established, the previous section has identified multimodality as the distinguishing fact between the bistability resulting from a saddle-homoclinic orbit bifurcation \textit{versus} a subcritical Hopf bifurcation. The splitting probability, $\varpi$, may be taken as an indicator for which region around the SNL bifurcation the neuron is in,\textit{(i)} $\varpi \approx 0 \to$ SNIC mean-driven regime
\textit{(ii)} $\varpi \approx 1 \to$ SNIC fluctuation-driven regime
\textit{(iii)} $\varpi \approx \frac{1}{2} \to$ bistable HOM neuron

In Sec. 3.6, it was surmised that for long enough spike trains, the mixing factor $\varpi$ could be estimated based on the burst length statistics in Eq. 19. One may explore how the moments of the ISI distribution are related to system parameters. The uncentred moments of the ISI distribution are obtained from its Laplace transform in Eq. 22 via

$$\nu_k = (-1)^k \frac{d^k}{ds^k} P_{\text{is}}(s) \bigg|_{s=0}.$$
Although the convolution in Eq. 16 cannot be evaluated analytically, its Laplace transform is a simple product of the transform of the inverse Gaussian distribution of the limit cycle dynamics,

\[
P_{lc}(s) = \exp \left( 1 - \sqrt{1 + 2s\sigma_{lc}^2/\tau_{lc}^2} \right)/\sigma_{lc}^2\tau_{lc}.
\]

and that of the exponential distribution, which is \(P_{lp} = \left(1 + \frac{s}{\tau_{lp}}\right)^{-1}\). Together the Laplace transform of the ISI distribution is

\[
P_{isi}(s) = \varpi P_{lc}(s) + \frac{(1 - \varpi)P_{lc}(s)}{1 + s/\tau_{c}}.
\]  

(22)

Thus, mean and variance of \(p_{isi}(t)\) are given by

\[
\mu_{isi} = \varpi\tau_{c} + \tau_{lc}
\]  

(23)

and

\[
\sigma_{isi}^2 = (2 - \varpi)\varpi\tau_{c}^2 + \tau_{lc}^3\sigma_{lc}^2.
\]  

(24)

For the high firing rates present in HOM neurons with a small saddle-homoclinic orbit, the mean escape time \(\tau_{c}\) is the longest time scale in the system and can be estimated independently by fitting a histogram of the largest ISI samples. For low noise, \(\tau_{lc}\) can be estimated as the peak of the ISI histogram. Then, using Eq. 23, the mixing factor \(\varpi\) can be estimated.

6 Discussion

Interspike-interval distributions are commonly investigated to characterise spiking behaviour in neurons. Experimentally, these distributions are easily measured by observing spike trains in response to step currents or noise injections. Theoretical distributions have been derived for several types of neuron models, in particular the Poissonian distribution for fluctuation-driven integrate-and-fire-type models or excitable conductance-based neurons\(^8\), and the inverse Gaussian distribution for mean-driven neurons with a SNIC bifurcation at spike onset\(^21,25\). Here, the interspike-interval distribution for neurons with a saddle-homoclinic orbit bifurcation at spike onset was derived for the bistable regime. These neurons show, close to spike onset, a region of bistability between resting state and spiking, and if the dynamics visits the resting state between two spikes, particularly long interspike intervals can occur.

Can the present statistical analysis help to discern HOM, SNIC and SNL bifurcations in recordings? Fitting inverse Gaussian, exponential or the bistable ISI density derived here to recordings and comparing the model likelihood can be construed as supportive evidence for one or the other mechanism. However, for generalised inverse Gaussian distributions, it was shown that several diffusion processes can result in the same waiting time distribution, or, conversely, ISI distributions cannot be uniquely mapped to their underlying diffusion processes\(^26\). Therefore, caution is warranted not to overestimate the generality of one’s mechanistic explanation. Nonetheless, features of the ISI density, such as its skewness, have been related to underlying biophysical processes such as adaptation currents\(^25,27\). A question similar in spirit may be whether neuronal bistability is uniquely tied to the ISI distribution derived in the present article?

In terms of the underlying bifurcation structure at least one other scenario giving rise to bistability of spiking and resting has been described previously: The subcritical Hopf bifurcation in association with a fold of limit cycles (sometimes called Bautin bifurcation) – present in the equations derived for the classical squid axon – also leads to a region of bistability and hysteresis\(^22\). In combination with noise, numerical investigations\(^14,15\) indicated that the ISI distribution is multi-modal for the tested parameter combinations. At present, no parameters have been documented for which multimodality does not manifest in the ISI density. In the case of simplified resonate-and-fire models, the ISI distribution has been investigated analytically and multimodal peaks were confirmed\(^23,24\). In contrast, the present manuscript argues for the absence of multimodality in the homoclinic-type bistability and hence this difference may be exploited to distinguish both kinds of bistability.

As was argued, bistability in homoclinic neurons can lead to spike time patterns, which resemble spiking observed experimentally in neurons, such as “stuttering cells”\(^1,2\) or “irregular spiking cells”\(^3–5\). Some cells show membrane-voltage bistability in the form of distinct downstates and upstates\(^28\). The likelihood of seeing this dynamics seems to be increased during sleep and certain anesthetics. The emergence of up-/downstates is associated with altered concentration dynamics in the intra- and extracellular space. Since the required time scale separation to induce the SNL bifurcation can also be achieved by
While up- and downstates have been modeled previously as bistable fixpoints in an integrate-and-fire like model, the bistability between resting state and spiking dynamics introduced here is easily implemented in biologically more realistic conductance-based neuron model.

The emergence of bistability in neurons changes their coding properties, too. It has been noted that, in the absence of noise, rate coding in neurons close to a SNIC bifurcation is undermined by undesirable nonlinearities. More favorable for coding, bursting neurons have been shown to linearise the rate-tuning curve. Furthermore, in a network, bistability in the membrane voltage has been shown to increase the power for certain frequency bands of a population transfer function. In a similar way, the filtering associated with individual homoclinic neurons can transfer considerably higher frequencies during the spiking periods. Hence, spike-timing based codes can benefit from the high-frequency coding arising from the symmetry breaking that is induced by the switch in spike generation from SNIC to HOM at the SNL point. The option to visit the fixpoint before spiking adds to the versatile coding possibilities of these neurons when explicitly considering their bistability. An open question is if the interspike-interval distribution of the bistable neuron has favourable properties similar to the power-law interspike interval density appearing in some theories of optimal coding. The mutual information between a fast stimulus and the emitted spike train is bounded from above by the output entropy of the alphabet (i.e., the spike train entropy). The spike train entropy is increased by more diverse spike patterns arising from the stochastic bursting responses in the bistable regime, compared to the tonic response of a SNIC neuron. It remains to be shown how the conditional entropy is influenced, which also contributes to the system’s information transmission rate.

The bistability of homoclinic neurons also influences various network phenomena. Early theories of spiking network dynamics have assumed identical neurons. Some theoretical models of spiking network dynamics have allegedly shown that single neuron properties are of minor consequence to the generation of rhythms. In fact, in some network models, parameter heterogeneity is placed in specific abstract parameter like the firing threshold, where it is ineffective in altering the computational filtering properties of the individual neuron. Changing parameters that lead to the emergence of bistability with completely different onset bifurcations and spike statistics is an entirely different matter. Recent studies have shown that, if placed at specific biophysical parameters, even small heterogeneities can have massive effects on synchronisation patterns. Future analysis of balanced neural networks with a portion of neurons in the bistable region could benefit from the firing statistics derived in the present article as a basic ingredient. Such network theories often rely on simplified heuristic integrate-and-fire (IF) models. These models focus on capturing only the spike onset dynamics while relying on a reset for the spike downstroke, and have been used to investigate the influence of spike generation (and Na+ channels) on network dynamics. The quadratic IF model can be derived from the centre-manifold reduction of saddle-node bifurcations, and can with an appropriately chosen reset serve as the “normal form” of the bifurcation structure in Fig. Then again, this article shows the switching dynamics to occur outside the centre manifold dynamics during the downstroke along the strongly stable direction. Hence, the window of opportunity for jumping the separatrix is more related to the timescale of the K+ channel dynamics. Nonetheless, the quadratic IF with a positive reset and noise will produce the same ISI dynamics as derived here and can thus be taken as a simplified from in network theories of homoclinic bistable neurons.

In summary, the interspike interval distribution derived in this paper is useful on various levels. It provides an experimental check for bistability due to homoclinic spike generation, conveys information on coding properties, and forms the basis for mean-field networks with bistable dynamics. Translated to other oscillating systems, the analysis might even inform about homoclinic bistability beyond the neurosciences.

7 Acknowledgements

Funded by the German Federal Ministry of Education and Research (Grants No. 01GQ0901 and No. 01GQ1403). Authors J.-H.S. and J.H. contributed equally to this work.
The gating time constant is independent of \( v \)

The activation curves of the gates are \( \tau \)

For the saddle-node, the right eigenvectors to \( \lambda_1, \ldots, \lambda_{n-1} \) span the tangential space to the stable manifold. Due to the orthogonality of right and left eigenvectors, the normal to the tangent space of the stable manifold is given by the left eigenvector corresponding to the unstable direction, \( l_0 \).

8.3 Directions of stable and unstable manifold around the saddle

The analysis of the HOM neuron model assumes that the spike-onset lies in proximity to the SNL bifurcation, such that the saddle at \( I_{hom} \) inherits properties of the saddle-node at \( I_{sn} \). It is shown in the following for a planar model that this implies similar linearized dynamics along the unstable manifold of saddle and saddle-node. To this aim, the eigenvectors around the saddle are expressed as the eigenvectors of the saddle-node, as given in Sec. 8.2, plus a small term. The closeness of the saddle to the saddle-node is translated into two mathematical assumptions: It is assumed that \( \lambda_0 \ll 1 \) at the saddle (because \( \lambda_0 = 0 \) at the saddle-node), and it is assumed that the voltage values of saddle and saddle-node are similar, \( \Delta v = v_{saddle} - v_{sn} \ll 1 \).

The linearized dynamics around saddle or saddle-node are given by their Jacobian. The Jacobian of the saddle-node at \( \lambda_0 \), \( \lambda_1, \ldots, \lambda_{n-1} \) span the tangential space to the stable manifold. To this aim, the eigenvectors around the saddle are expressed as the eigenvectors of the saddle-node, as given in Sec. 8.2, plus a small term. The closeness of the saddle to the saddle-node is translated into two mathematical assumptions: It is assumed that \( \lambda_0 \ll 1 \) at the saddle (because \( \lambda_0 = 0 \) at the saddle-node), and it is assumed that the voltage values of saddle and saddle-node are similar, \( \Delta v = v_{saddle} - v_{sn} \ll 1 \).

The linearized dynamics around saddle or saddle-node are given by their Jacobian. The Jacobian of a two-dimensional system akin to the model in Sec. 8.1 is given as

\[
J = \begin{pmatrix}
\frac{\partial F_1}{\partial v} & \frac{\partial F_1}{\partial w} \\
\frac{\partial F_2}{\partial v} & \frac{\partial F_2}{\partial w}
\end{pmatrix} = \begin{pmatrix}
a & b \\
c & d
\end{pmatrix}.
\]

For a two-dimensional matrix, the eigenvalues are \( \lambda_{0/1} = 0.5(a + d \pm E) \) with \( E = \sqrt{a^2 - 2ad + 4bc + d^2} \). The right eigenvector corresponding to \( \lambda_0 \) is \( r_0 = (1, \frac{2c}{E^2 - a - d}) \), the left eigenvector is \( l_0 = (1, \frac{2b}{E^2 + a - d}) \) (equal to the right eigenvalue of the transposed matrix).

Expressing \( E \) by \( \lambda_0 \) gives \( r_0 = (1, \frac{\varepsilon}{\varepsilon^2 + \lambda_0}) \) and

Table 1: Model parameters of the sodium-potassium neuron used for the simulations.

| Parameter                  | Value         |
|----------------------------|---------------|
| Membrane capacitance       | \( C_m \) 1\mu F/cm\(^2\) |
| Leak reversal potential    | \( E_L \) -80mV |
| Sodium reversal potential  | \( E_{Na} \) 60mV |
| Potassium reversal potential| \( E_K \) -90mV |
| Maximal leak conductance   | \( g_L \) 8mS/cm\(^2\) |
| Maximal sodium cond.       | \( g_{Na} \) 20mS/cm\(^2\) |
| Maximal potassium cond.    | \( g_K \) 10mS/cm\(^2\) |
| Gating time constant       | \( \tau_n \) 0.165ms |
The simulations in Fig. 2 show that the location of the limit cycle downstroke of the homoclinic orbit attaches to the saddle, as suggested by the simulations of the limit cycle trajectory, see Fig. 2.

8.4 Limit cycle downstroke is in first order independent of the input

The simulations in Fig. 2 show that the location of the limit cycle remains surprisingly constant with an increase in input current. This can be understood by observing that for the flow on the limit cycle, the major change in velocity occurs in proximity to the saddle: The flow on the limit cycle trajectory, \( v \), is given by the velocity at each point \( (v, n) \in \Gamma \). The speed of the gating, \( \dot{n} \), is independent of \( I \). The speed of the voltage, \( \dot{v} = (I + I_{ion})/C_m \), depends on \( I \), but the influence of \( I \) is small as long as \( I << I_{ion} \). During the spike, ionic currents dominate the dynamics (Fig. 7), and \( I_{ion} \) has the same order of magnitude as \( I \) only in between two spikes, i.e., close to the saddle (green background in Fig. 7). This implies that the only significant changes in the limit cycle trajectory happen close to the saddle, as suggested by the simulations of the limit cycle trajectory, see Fig. 2.

8.5 At spike onset, the limit cycle downstroke aligns with the stable eigenvector of the saddle

The derivation in the main text assumes that the downstroke of the limit cycle follows the stable \( r_1 \) eigenvector of the saddle at spike onset. This is trivially true for the saddle-homoclinic orbit in an infinitesimal small environment of the saddle. As shown in the following, this also holds for a significant part of the dynamics along the spike downstroke.

The argument relies on the following observations. For the homoclinic orbit attached to the saddle, two points in the phase plane are known. (1.) The downstroke of the homoclinic orbit attaches to the saddle. More precisely, it enters the saddle along its stable manifold tangential to \( r_1 \) (Fig. 8, green line). (2.) At the limit cycle maximum in the phase plane, \( (v(n_{max}), n_{max}) \) with \( n_{max} = \max_t(n_{LC}(t)) \), the flow is tangential to the voltage direction, i.e., \( \dot{n} = 0 \), such that the maximum lies on the gating nullcline given by \( n_{in}(v) \) (Fig. 8). Because the limit cycle circles around the unstable node, the limit cycle maximum \( (v(n_{max}), n_{max}) \) lies above the unstable node. Because voltage and gating nullcline cross at the unstable node, the limit cycle downstroke, once it passed \( (v(n_{max}), n_{max}) \), lie above both nullcline. In consequence, the velocity along
the downstroke trajectory points in the third quadrant (i.e., to the bottom left), such that the trajectory approaches $r_1$ monotonously. As the trajectory of the limit cycle downstroke has a horizontal velocity at $(v_{\text{max}}, n_{\text{max}})$ and a velocity aligned to $r_1$ at the saddle, and approaches $r_1$ monotonically, an application of the least action principle hence allows to conclude that the trajectory of the saddle-homoclinic orbit aligns for a significant part of the limit cycle with $r_1$.

![Figure 8](image_url)

Figure 8: The downstroke of the limit cycle aligns with $r_1$ (green line). Nullclines for voltage (dark grey) and gating variable (light grey).

References

1. Gupta, A., Wang, Y., and Markram, H. (2000). Organizing Principles for a Diversity of GABAergic Interneurons and Synapses in the Neocortex. Science 287, 273–278. Available at: [http://science.sciencemag.org/content/287/5451/273](http://science.sciencemag.org/content/287/5451/273) [Accessed May 10, 2018].

2. Song, C., Xu, X.-B., He, Y., Liu, Z.-P., Wang, M., Zhang, X., Li, B.-M., and Pan, B.-X. (2013). Stuttering Interneurons Generate Fast and Robust Inhibition onto Projection Neurons with Low Capacity of Short Term Modulation in Mouse Lateral Amygdala. PLOS ONE 8, e60154. Available at: [http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0060154](http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0060154) [Accessed May 10, 2018].

3. Galarreta, M., Erdélyi, F., Szabó, G., and Hestrin, S. (2004). Electrical Coupling among Irregular-Spiking GABAergic Interneurons Expressing Cannabinoid Receptors. Journal of Neuroscience 24, 9770–9778. Available at: [http://www.jneurosci.org/content/24/44/9770](http://www.jneurosci.org/content/24/44/9770) [Accessed May 10, 2018].

4. Stiefel, K.M., Englitz, B., and Sejnowski, T.J. (2013). Origin of intrinsic irregular firing in cortical interneurons. Proceedings of the National Academy of Sciences 110, 7886–7891. Available at: [http://www.pnas.org/cgi/doi/10.1073/pnas.1305219110](http://www.pnas.org/cgi/doi/10.1073/pnas.1305219110) [Accessed April 21, 2017].

5. Mendonça, P.R., Vargas-Caballero, M., Erdélyi, F., Szabó, G., Paulsen, O., and Robinson, H.P. (2016). Stochastic and deterministic dynamics of intrinsically irregular firing in cortical inhibitory interneurons. eLife 5, e16475. Available at: [https://elifesciences.org/content/5/e16475v2](https://elifesciences.org/content/5/e16475v2) [Accessed December 2, 2016].

6. Chow, C., and White, J. (1996). Spontaneous action potentials due to channel fluctuations. Biophysical Journal 71, 3013–3021. Available at: [http://www.cell.com/biophysj/abstract/S0006-3495(96)79494-8](http://www.cell.com/biophysj/abstract/S0006-3495(96)79494-8) [Accessed August 18, 2014].

7. Kirst, C., Ammer, J., Felmy, F., Herz, A., and Stemmler, M. (2015). Fundamental Structure and Modulation of Neuronal Excitability: Synaptic Control of Coding, Resonance, and Network Synchronization Available at: [http://biorxiv.org/lookup/doi/10.1101/022475](http://biorxiv.org/lookup/doi/10.1101/022475) [Accessed February 19, 2016].

8. Hesse, J., Schleimer, J.-H., and Schreiber, S. (2017). Qualitative changes in phase-response curve and synchronization at the saddle-node-loop bifurcation. Physical Review E 95. Available at: [http://link.aps.org/doi/10.1103/PhysRevE.95.052203](http://link.aps.org/doi/10.1103/PhysRevE.95.052203) [Accessed May 4, 2017].

9. Adrian, E. (1928). The Basis of Sensation: The Action of the Sense Organs (Christophers).

10. Schreiber, S., Samengo, I., and Herz, A.V. (2008). Two Distinct Mechanisms Shape the Reliability of Neural Responses. Journal of Neurophysiology 101, 2239–2251. Available at: [http://jn.physiology.org/cgi/doi/10.1152/jn.90711.2008](http://jn.physiology.org/cgi/doi/10.1152/jn.90711.2008) [Accessed March 9, 2017].

11. Stemmler, M. (1996). A single spike suffices: The simplest form of stochastic resonance in model neurons. Network: Computation in Neural Systems 7, 687–716. Available at: [https://www.tandfonline.com/doi/full/10.1088/0954-898X_7_4_005](https://www.tandfonline.com/doi/full/10.1088/0954-898X_7_4_005) [Accessed September 5, 2018].

12. Ly, C., and Doiron, B. (2017). Noise-enhanced coding in phasic neuron spike trains. PLOS ONE 12, e0176963. Available at: [http://dx.plos.org/10.1371/journal.pone.0176963](http://dx.plos.org/10.1371/journal.pone.0176963) [Accessed September 5, 2018].

13. Wei, W., Wolf, F., and Wang, X.-J. (2015).
Impact of membrane bistability on dynamical response of neuronal populations. Physical Review E 92. Available at: https://link.aps.org/doi/10.1103/PhysRevE.92.032726 [Accessed July 13, 2018].

14. Tuckwell, H.C., and Jost, J. (2012). Analysis of inverse stochastic resonance and the long-term firing of Hodgkin-Huxley neurons with Gaussian white noise. Physica A: Statistical Mechanics and its Applications 391, 5311–5325. Available at: http://linkinghub.elsevier.com/retrieve/pii/S0378437112005225 [Accessed October 26, 2018].

15. Rowat, P.F., and Greenwood, P.E. (2014). The ISI distribution of the stochastic Hodgkin-Huxley neuron. Frontiers in Computational Neuroscience 8. Available at: http://journal.frontiersin.org/article/10.3389/fncom.2014.00111/abstract [Accessed July 5, 2017].

16. Lindner, B. (2004). Interspike interval statistics of neurons driven by colored noise. Physical Review E 69. Available at: http://link.aps.org/doi/10.1103/PhysRevE.69.022901 [Accessed August 11, 2014].

17. Gardiner, C.W. (2004). Handbook of stochastic methods for physics, chemistry, and the natural sciences 3rd ed. (Berlin ; New York: Springer-Verlag).

18. Izhikevich, E.M. (2007). Dynamical Systems in Neuroscience (MIT Press).

19. Ermentrout, B., and Kopell, N. (1986). Parabolic Bursting in an Excitable System Coupled with a Slow Oscillation. SIAM Journal on Applied Mathematics 46, 233–253. Available at: http://epubs.siam.org/doi/abs/10.1137/0146017 [Accessed January 23, 2017].

20. Schleimer, J.-H., and Schreiber, S. (2018). Phase-response curves of ion channel gating kinetics. Mathematical Methods in the Applied Sciences 41, 8844–8858. Available at: https://onlinelibrary.wiley.com/doi/abs/10.1002/mma.5232 [Accessed November 29, 2018].

21. Schroedinger, E. (1915). Zur Theorie der Fall- und Steigversuche an Teilchen mit Brownscher Bewegung. Physikalische Zeitschrift 16, 289–295. Available at: https://ci.nii.ac.jp/naid/10026662599/ [Accessed May 10, 2018].

22. Rush, M.E., and Rinzel, D.J. (1995). The potassium A-current, low firing rates and rebound excitation in Hodgkin-Huxley models. Bulletin of Mathematical Biology 57, 899–929. Available at: http://link.springer.com/article/10.1007/BF02458299 [Accessed April 20, 2015].
Neural Oscillator Populations. Neural Computation 16, 673–715. Available at: http://dx.doi.org/10.1162/089976604322860668 [Accessed December 3, 2014].

32. Schleimer, J.-H., and Stemmler, M. (2009). Coding of Information in Limit Cycle Oscillators. Physical Review Letters 103, 248105. Available at: http://link.aps.org/doi/10.1103/PhysRevLett.103.248105 [Accessed November 17, 2014].

33. Tsubo, Y., Isomura, Y., and Fukai, T. (2012). Power-Law Inter-Spike Interval Distributions Infer a Conditional Maximization of Entropy in Cortical Neurons. PLoS Computational Biology 8, e1002461. Available at: http://dx.plos.org/10.1371/journal.pcbi.1002461 [Accessed August 11, 2014].

34. Strong, S.P., Koberle, R., Ruyter van Steveninck, R.R. de, and Bialek, W. (1998). Entropy and Information in Neural Spike Trains. Physical Review Letters 80, 197–200. Available at: https://link.aps.org/doi/10.1103/PhysRevLett.80.197 [Accessed January 31, 2019].

35. Brunel, N., and Hakim, V. (1999). Fast global oscillations in networks of integrate-and-fire neurons with low firing rates. Neural computation 11, 1621–1671. Available at: http://ieeexplore.ieee.org/xpls/abs_all.jsp?arnumber=6790868 [Accessed June 15, 2015].

36. Amit, D.J., and Brunel, N. (1997). Dynamics of a recurrent network of spiking neurons before and following learning. Network: Computation in Neural Systems 8, 373–404. Available at: http://www.tandfonline.com/doi/abs/10.1088/0954-898X_8_4_003 [Accessed June 16, 2015].

37. Mejias, J.F., and Longtin, A. (2012). Optimal Heterogeneity for Coding in Spiking Neural Networks. Physical Review Letters 108. Available at: http://link.aps.org/doi/10.1103/PhysRevLett.108.228102 [Accessed December 7, 2016].

38. Fourcaud-Trocmé, N., Hansel, D., Vreeswijk, C. van, and Brunel, N. (2003). How Spike Generation Mechanisms Determine the Neuronal Response to Fluctuating Inputs. The Journal of Neuroscience 23, 11628–11640. Available at: http://www.jneurosci.org/content/23/37/11628 [Accessed May 5, 2015].

39. Monteforte, M., and Wolf, F. (2010). Dynamical Entropy Production in Spiking Neuron Networks in the Balanced State. Physical Review Letters 105. Available at: http://link.aps.org/doi/10.1103/PhysRevLett.105.268104 [Accessed March 11, 2016].

40. Chow, S.-N., and Lin, X.-B. (1990). Bifurcation of a homoclinic orbit with a saddle-node equilibrium. Differential and Integral Equations 3, 435–466. Available at: https://projecteuclid.org:443/euclid.die/1371571144.