Neuronal Multistability Induced by Delay

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Abstract. Feedback circuits are important for understanding the emergence of patterns of neural activity. In this contribution we study how a delayed circuit representing a recurrent synaptic connection interferes with neuronal nonlinear dynamics. The neuron is modeled using a Hodgkin-Huxley type model in which the firing pattern depends on subthreshold oscillations, and the feedback is included as a time delayed linear term in the membrane voltage equation. In the regime of subthreshold oscillations the feedback amplifies the oscillation amplitude, inducing threshold crossings and firing activity that is self regularized by the delay. We also study a small neuron ensemble globally coupled through the delayed mean field. We find that the firing pattern is controlled by the delay. Depending on the delay, either all neurons fire spikes, or they all exhibit subthreshold activity, or the ensemble divides into clusters, with some neurons displaying subthreshold activity while others fire spikes.

1 Introduction

Time-delayed feedback mechanisms are relevant in many biological systems. Excitable gene regulatory circuits [1], human balance [2,3], and eye movements [4,5] are just a few examples. Many feedback loops have been proposed to explain patterns of neural activity. A well known recurrent circuit is in the hippocampal CA3 region, that is known to be involved in associative memory recall [6,7]. A neuron might experience recurrent excitatory or inhibitory feedback though an auto-synapse, and/or though a circuit of synaptic connections involving other neurons. Since recurrent connections require the propagation of action potentials along the synaptic path, finite signal transmission velocity, and processing time in synapses lead to a broad spectrum of conduction and synaptic delay times, ranging from few to several hundreds of milliseconds. Since neural spike frequencies can exceed 10 Hz, these delays times can be much longer than the characteristic inter-spike interval.

Within the framework of neuron rate-equation models, a recurrent feedback circuit has been studied by adding to the membrane potential equation a term proportional to the potential at an earlier time, $\eta V(t-\tau)$ [8]. Here η is the synaptic strength and τ is the delay time, that is the sum of conduction and synaptic delays. While this is a very simplified approach, it has been successful for understanding characteristic delayed feedback-induced phenomena, such as multi-stability [9,10].

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Early experiments on the response of a single neuron in a recurrent excitatory loop were performed by Diez-Martinez and Segundo [11], who studied a pacemaker neuron in the crayfish stretch receptor organ. By having each spike trigger electronically a brief stretch after a certain delay, they showed that with increasing delay the discharge patterns transformed from periodic spikes to trains of spikes separated by silent intervals. Pakdaman et al. [12] interpreted this behavior as due to neuronal adaptation mechanisms, that decreased sensitivity along successive firings. By studying models of various levels of complexity (an integrate and fire, a leaky integrator and a rate-equation model including membrane conductances), with and without adaptation to repeated stimuli, Pakdaman and coworkers found that models including adaptation predicted a dynamics that was similar to that observed experimentally in the crayfish receptor, exhibiting tonic firings for short delays, and multiplets or bursts for longer delays. The influence of noise on a single neuron with a delayed recurrent synaptic connection was analyzed by Vibert et al. [13]. The noise-induced inter-spike interval irregularity was found to decrease when the delay increased above the natural firing period: for short delays noise irregularizes the firing period, while for long delays, the neuron fires with a mean period equal to the delay, as observed without noise.

Recently, interest on delayed feedback circuitry has focused on its influence on neural "spontaneous" or self synchronous activity. Spontaneous synchrony is known to be part of consciousness and perception processes in the brain [14], but also of diseases such as epilepsy. Rosenblum and Pikovsky [15] proposed the use linear delayed feedback to control synchrony in ensembles of globally coupled neurons. It was shown that by variations of the delay time of the coupling, neural synchrony can be either enhanced or suppressed [16,17]. Popovych et al. [18] extended this method to the case of nonlinear delayed feedback, that is, linear delayed feedback nonlinearly combined with the instantaneous signal, showing that nonlinear feedback cannot reinforce synchronization, which can be relevant for applications requiring robust de-synchronization.

With the aim of providing further insight into the influence of a recurrent connection in a single neuron, and global delayed coupling in a neuron ensemble, we study a small neuron ensemble composed by a few neurons that are globally coupled through their delayed mean field, and compare their activity with that of a single neuron that has a recurrent delayed synaptic connection. We show that, as for the single neuron, the firing pattern of the ensemble is controlled not only by the coupling strength but also by the delay time. Depending on the delay, either all neurons fire spikes, or they all exhibit subthreshold activity, or the ensemble divides into clusters, with some neurons displaying subthreshold activity while others fire spikes.

This paper is organized as follows. Section II presents the single neuron model and the coupling scheme of the neuron ensemble. Section III presents results of the numerical simulations, where the control parameter is the delay time and the dynamics of a single neuron with a recurrent connection is compared with that of a globally coupled neuron ensemble. Section IV presents a summary and the conclusions.

2 Model

To simulate the firing activity of a single neuron we use a model proposed by Braun et al. [19] that was developed on the basis of experimental data from shark electroreceptors [20] and mammalian cold receptors [21]. The model is a flexible neuronal pattern generator that produces different types of firing patterns, that are of relevance also in cortical neurons [22]. The temporal sequence of spikes indicates that the activity of these neurons depends on *subthreshold oscillations* of the membrane potential. In electro-receptors and in the upper temperature range of cold receptors there is an irregular sequence of spikes which, however, shows a multi-modal inter-spike interval distribution that suggest the existence of subthreshold oscillations which operate below but near the spike-triggering threshold. In this situation it essentially depends on noise whether a spike is triggered or not but the subthreshold oscillation period is still reflected in the basic rhythm of the discharge. External stimuli can alter the frequency and/or the amplitude of the oscillations, thus inducing pronounced changes of the neuron firing pattern. In contrast, in the low temperature range of cold receptors, irregular single spikes can be recorded, whose histogram of inter-spike intervals do not have a distinct modal structure but seems to reflect pacemaker activity under random fluctuations.

The model proposed by Braun et al. has been studied by several authors. As a function of the temperature different *deterministic* firing patterns have been identified [23], including coexistence of spikes and subthreshold oscillations (spikes with skippings), tonic spiking and bursting patterns. This rich dynamic behavior is due to the interplay of two sets of de- and re- polarizing ionic conductances that are responsible for spike generation and slow-wave potentials [24]. The influence of noise was studied by Feudel et al. [25], who showed that the model predictions are in good agreement with data of electro-physiological experiments with the caudal photoreceptor of the crayfish. Neiman et al. [26] demonstrated experimentally that electroreceptor cells in the paddlefish contain an intrinsic oscillator that can be synchronized with an external signal, and simulations based on Braun et al. model with a periodic external stimulus yield good agreement with the observations. Noise induced synchronization [27] and anticipated synchronization [28] have also been demonstrated. The effect of delayed recurrent feedback was analyzed by Sainz-Trapaga et al. [29], who showed that the feedback can modify the amplitude of the subthreshold oscillations in a way such that they operate slightly above threshold, therefore leading to feedback-induced spikes.

The rate equation for the potential voltage across the membrane, V, is [19]:

$$C_M \dot{V} = -I_{Na} - I_K - i_{sd} - I_{sr} - I_l + \eta V(t-\tau), \tag{1}$$

where C_M is the capacitance, I_{Na} and I_K are fast sodium and potassium currents, I_{sd} and I_{sr} are additional slow currents. These four currents depend on the temperature T as described in [19]. I_l is a passive leak current. Further details and definitions of the other quantities can be found in [19]. The last term in the

r.h.s. of Eq. (1) accounts for the recurrent synaptic connection. $V(t-\tau)$ is the membrane potential at the earlier time, $t-\tau$, η is the synaptic strength and τ the delay time. Because we are interested in feedback-induced patterns, we do not include any noise source in the equations, and consider parameters such that the neuron, without feedback, displays only subthreshold oscillations.

We compare the dynamics of a neuron with feedback, with that of N neurons globally coupled through their delayed mean field. The rate-equation for the membrane potential of the ith neuron of the ensemble, V_i, is:

$$C_M \dot{V}_i = -I_{Na,i} - I_{K,i} - I_{sd,i} - I_{sr,i} - I_{l,i} + \eta V_T(t-\tau), \tag{2}$$

where $V_T(t-\tau) = (1/N)\sum_{i=1}^{N} V_i(t-\tau)$ is the delayed mean field and the other variables have the same meaning as in Eq.(1). This coupling scheme resembles that studied by Rosenblum and Pikovsky [15], but in [15] the neuron ensemble ($N = 2000$ Hindmarsh-Rose neurons in the regime of chaotic bursting) was coupled by two terms, one proportional to the instantaneous mean field, and the other, proportional to the delayed mean field. The authors found that, for certain parameters, the delayed mean field destroyed the synchrony among the neurons induced by the instantaneous coupling, without affecting the oscillations of individual neurons. With the aim of providing further insight into the effect of delayed coupling, here we consider a small neuron ensemble that is coupled only through its delayed mean field.

3 Results

The parameters used in the simulations are such that the neurons, in the absence of feedback or coupling, display subthreshold oscillations of period $T_0 \sim 130$ ms (the temperature parameter is set to 35^0C, and other parameters are as in [19]). To integrate Eq. (1) [Eq.(2)] it is necessary to specify the initial value of the potential V [V_i with $i = 1, N$] on the time interval $[-\tau, 0]$. It is known that the neuron exhibits multistability as different initial conditions lead, after a transient time, to different stable firing patterns [9,10]. Here the initial conditions are such that the neuron is oscillating in its natural cycle when the feedback begins to act (i.e., the feedback starts when the neuron is at a random phase of the cycle). For the neuron ensemble, the initial conditions are such that the neurons oscillate independently one of another (i.e., they are at random, different phases of the cycle) when the coupling starts.

We begin by considering a single neuron with self-feedback. Due to the excitable nature of the dynamics it can be expected that even weak feedback strengths can be a strong perturbation to the neuron subthreshold oscillations. The feedback can amplify the amplitude of the oscillations, inducing threshold-crossings and giving rise to firing activity that can be self-regularized by the delay time. This is indeed observed in Fig. 1, that depicts the amplitude, $A = \max(V) - \min(V)$, and the frequency of the neuronal oscillations vs. the delay for fixed synaptic strength. When η is positive, Fig. 1(a), the oscillation amplitude is diminished, with respect to the natural oscillation amplitude, for

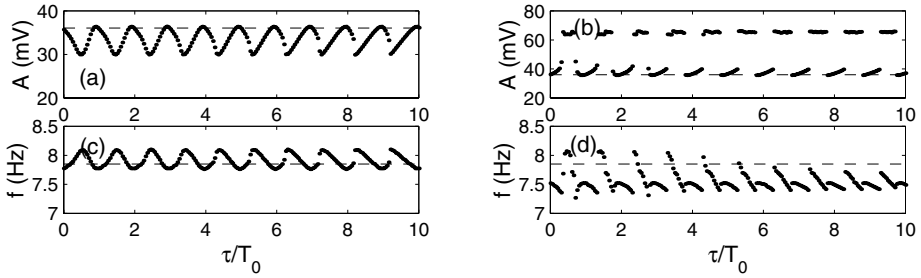

Fig. 1. (a), (b) Amplitude of the neuron oscillations vs. the delay time, normalized to the subthreshold oscillation period, T_0, for feedback strength $\eta = 0.001$ (a) and $\eta = -0.001$ (b). The dashed line indicates the amplitude of the natural subthreshold oscillations (in the absence of feedback). (c), (d) Frequency of the oscillations vs. the normalized delay time for $\eta = 0.001$ (c) and $\eta = -0.001$ (d). The dashed line indicates the frequency of the natural oscillations.

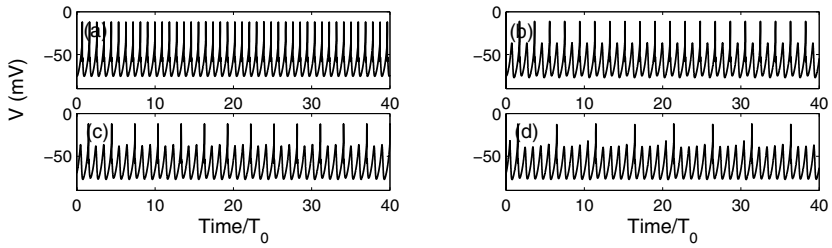

Fig. 2. Oscillatory waveforms for increasing values of the delay time and negative feedback strength, $\eta = -0.001$. $\tau/T_0 = 2.4$ (a), 2.5 (b), 2.65 (c) and 2.7 (d).

all delay values, but there is a non-monotonic relationship of the amplitude with the delay: the oscillation amplitude is maximum (minimum) for $\tau \sim nT_0$ [$\tau \sim (n + 1/2)T_0$] with n integer. When η is negative, Fig. 1(b), the oscillation amplitude is enhanced with respect to the natural amplitude, and the neuron fires spikes; however, the feedback is not strong enough to induce firings for all delay values; there are feedback-induced spikes only in "windows" of the delay centered at $\tau \sim (n+1/2)T_0$ with n integer. The frequency of the neuronal oscillations [Figs. 1(c), 1(d)] is also modified by the feedback: for delays longer than a few oscillation periods, the frequency decreases with τ in a piece-wise linear way, increasing abruptly at certain delay values.

In the windows of delay values where feedback-induced spikes occur, the firing pattern is governed by the value of the delay: at the beginning of the window the firings are frequent [tonic spikes are displayed in Fig. 2(a)], they become increasingly sporadic as the delay increases [spikes with skippings are displayed in Figs. 2(b)-2(d)], until they disappear at the end of the window. The process repeats itself in the next window, that is separated by an interval $\sim T_0$.

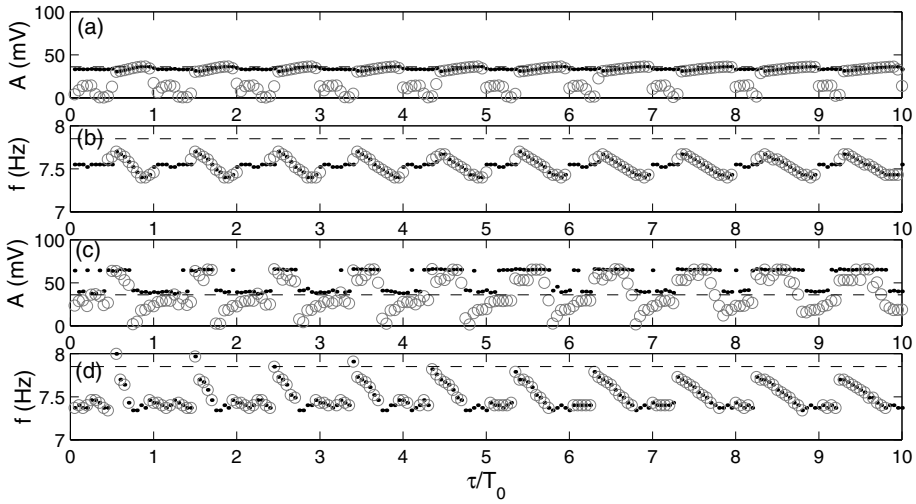

Fig. 3. Amplitude (a), (c) and frequency (b), (d) of the mean field oscillations (gray circles) vs. τ/T_0, for $\eta = 0.001$ (a), (b); and $\eta = -0.001$ (c),(d). The black dots display the amplitude and the frequency of one neuron of the ensemble. The dashed lines indicate the amplitude and frequency of the natural oscillations.

Next, we consider the ensemble of N neurons under the influence of delayed global coupling. we present results for $N = 5$ neurons, but similar patterns are observed for other values of N.

Figure 3 displays the amplitude and the frequency of the oscillations of the mean field (black dots) vs. the delay time for fixed coupling strength. For comparison, the amplitude and the frequency of the oscillations of one of the neurons of the array are also displayed (gray circles). For both, positive and negative coupling strength, it can be observed that the mean field oscillation amplitude [Figs. 3(a), 3(c)] exhibits periodic features at delay times separated by T_0, similar to those observed in Fig. 1 for a single neuron with a recurrent connection. In windows of τ separated by T_0 the amplitude of the oscillations of the mean field decreases to close to zero, revealing that the neurons organize their activity such that they oscillate out of phase, and even in perfect antiphase, keeping the mean field nearly constant. The frequency of both, the mean field and one neuron of the array has a piece-wise linear dependence with the delay [Figs. 3(b), 3(d)]. In the regions of out of phase behavior the frequency of the individual neurons is nearly constant, equal to the natural frequency $f_0 = T_0^{-1}$, while the frequency of the mean field is nf_0 with $n \geq 2$ integer (not shown because of the scale).

For positive coupling strength all the neurons display subthreshold oscillations. The oscillations can be either in-phase, out-of-phase, or in perfect antiphase depending on the delay τ. A few examples are displayed in Fig. 4: in Fig. 4(a) the neuron oscillate inphase; in Fig. 4(b) two neurons display in-phase oscillations (i.e., they form a cluster); in Fig. 4(c) the ensemble splits into two

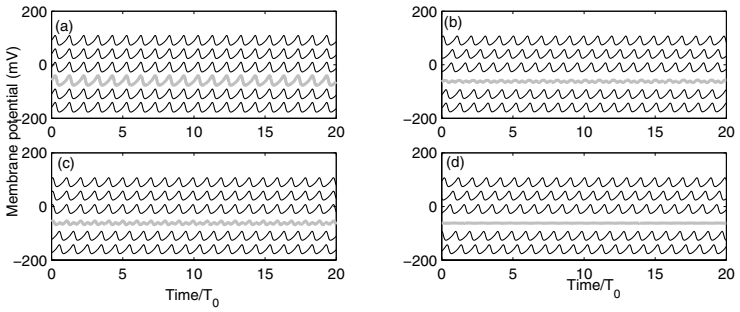

Fig. 4. Oscillatory waveforms for $\eta = 0.001$ and $\tau/T_0 = 6.9$ (a), 7.0 (b), 7.1 (c), and 7.3 (d). The black lines display the oscillation of the individual neurons (displaced vertically for clarity) and the grey lines, the collective mean field.

clusters, and the oscillations of the clusters are in antiphase, in Fig. 4(d) the five neurons display perfect antiphase behavior that leaves the mean field constant.

For negative coupling strength the ensemble displays more complex behavior: depending on τ either all the neurons fire spikes, or they all display subthreshold oscillations, or some neurons display subthreshold oscillations while others fire spikes. The neuronal oscillations can be either in-phase or out-of-phase depending on the delay. A few examples are displayed in Fig. 5: in Fig. 5(a) the neurons fire synchronized spikes; in Fig. 5(b) four neurons fire out of phase spikes, while the other displays subthreshold oscillations; in Fig. 5(c) the five neurons display perfect antiphase subthreshold behavior that leaves the mean field constant; in Fig. 5(d) the ensemble splits into two clusters, one fires synchronized spikes while the other displays subthreshold oscillations; in Fig. 5(e) the ensemble splits into two clusters that alternate their firing pattern; in Fig. 5(f) the neurons synchronize their firings again, but the pattern is different from that of Fig. 5(a).

The firing pattern varies not only with τ, but also with the initial conditions of the neurons, that is, with the positions of the neurons in the subthreshold oscillation cycle when the coupling begins to act. For most values of the delay, different initial positions lead to different firing patterns, and there is multistability of solutions with the coexistence of in-phase and out-of-phase behaviors. As an example, Figs. 6(a) and 6(b) display, for the same parameters as Figs. 5(a) and 5(b), different firing patterns, that occur with different (random) initial conditions. However, for specific values of the delay, the basins of attraction of inphase firings and out of phase subthreshold oscillations are very wide, and almost all initial conditions lead to these states. Fig. 6(c) and 6(d) display the mean field oscillation amplitude and the oscillation amplitude of one neuron of the array, respectively, for 8 random initial conditions. For τ/T_0 =5.5, 6.5 and 7.5, it is observed that all initial conditions lead to large amplitude oscillations of both, the mean field and one neuron of the array, indicating inphase firings, while for τ/T_0 =5.8, 6.8 and 7.8, almost all initial conditions lead to small amplitude oscillations, of both, the mean field and one neuron of the array, reveling out of phase subthreshold oscillations.

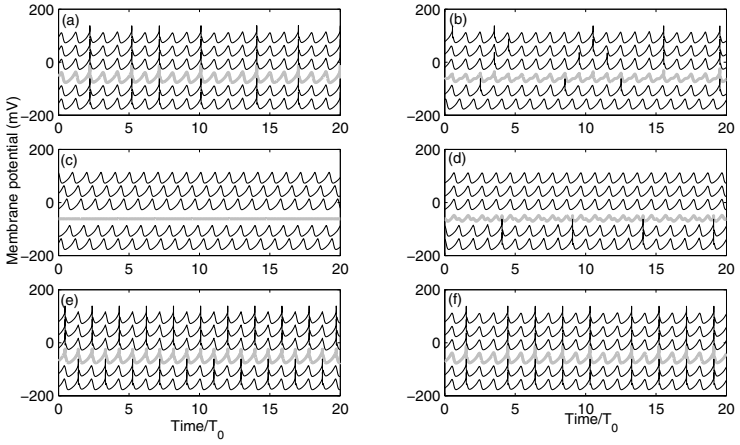

Fig. 5. Oscillatory waveforms for $\eta = -0.001$ and $\tau/T_0 = 6.6$ (a), 6.7 (b), 6.8 (c), 7.0 (d), 7.3 (e), and 7.5 (f)

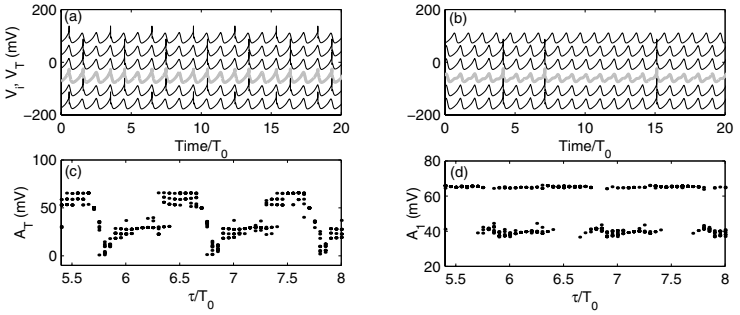

Fig. 6. (a), (b) Oscillatory waveforms for $\eta = -0.001$, $\tau/T_0 = 6.6$ (a), 6.7 (b), and initial conditions different from those of Figs. 5(a), 5(b). (c), (d) Amplitude of the oscillations of the mean field (c) and of the oscillations of one neuron of the ensemble (d) for 8 random initial conditions.

4 Summary and Conclusions

We studied the dynamics of a neuron under the influence of a delayed feedback circuit representing a recurrent synaptic connection. The neuron was modeled using a Hodgkin-Huxley type model with parameters corresponding to the subthreshold oscillation regime, and the feedback was included as a time delayed linear term in the membrane voltage equation. We found that weak positive feedback strengths reduce the amplitude of the subthreshold oscillations, while weak negative feedback strengths amplify the oscillation amplitude, inducing threshold-crossings and firing activity for certain values of the delay time, which are related to integer multiples of the subthreshold oscillation period, T_0. We also studied the firing pattern of a small ensemble of neurons globally coupled

through the delayed mean field, and found a rich variety of different behaviors, with the firing pattern controlled by the delay time of the mutual coupling. For certain intervals of the delay, related to T_0, the neurons synchronize their oscillations, either subthreshold oscillations (for positive coupling strength), or firing activity (for negative coupling strength). Outside the synchronization regions, depending on the value of the delay time, either the neurons exhibit out of phase oscillations, or the ensemble divides into clusters, with the clusters exhibiting anti-phased oscillations. As the delay is increased for a fixed coupling strength, the different regimes repeat themselves in a periodic sequence (synchronization, out of phase, cluster behavior, and synchronization) with a periodicity approximately equal to T_0. These results can be of relevance for a deeper understanding of the role played by time delays in weakly coupled neuronal ensembles.

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