Effects of Dynamic Synapses on Noise-Delayed Response Latency of a Single Neuron

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Noise-delayed decay (NDD) phenomenon emerges when the first-spike latency of a periodically forced stochastic neuron exhibits a maximum for a particular range of noise intensity. Here, we investigate the latency response dynamics of a single Hodgkin-Huxley neuron that is subject to both a suprathreshold periodic stimulus and a background activity arriving through dynamic synapses. We study the first spike latency response as a function of the presynaptic firing rate $f$. This constitutes a more realistic scenario than previous works, since $f$ provides a suitable biophysically realistic parameter to control the level of activity in actual neural systems. We first report on the emergence of classical NDD behavior as a function of $f$ for the limit of static synapses. Secondly, we show that when short-term depression and facilitation mechanisms are included at synapses, different NDD features can be found due to the their modulatory effect on synaptic current fluctuations. For example a new intriguing double NDD (DNDD) behavior occurs for different sets of relevant synaptic parameters. Moreover, depending on the balance between synaptic depression and synaptic facilitation, single NDD or DNDD can prevails, in such a way that synaptic facilitation favors the emergence of DNDD whereas synaptic depression favors the existence of single NDD. This is the first time it has been reported the existence of DNDD effect in response latency dynamics of a neuron.

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I. INTRODUCTION

Despite the efforts made over the last decades to clarify the functions of actual neural systems, one of the most important questions not yet addressed is to understand how neural coding naturally occurs. Although the coding mechanism used by the neurons is still unclear, it is widely assumed that information coding is based on action potentials (APs) or spikes. In the context of spike based communication, a potential coding mechanism is that, under strong temporal constraints, neurons may perform information processing with only one spike using first-spike latency as an information carrier \[1, 2\]. First-spike latency coding has been found as a meaningful strategy because it provides a fast as well as an energy efficient environment for information processing in actual neural systems. In fact, numerous experimental works conducted in peripheral and central neurons have demonstrated that first spike latency duration carries a greater amount of information about the received stimulus features than subsequent spikes \[2, 9\].

Beside these experimental findings, theoretical and computational studies have also been performed to investigate the influence of different biophysical mechanisms shaping first-spike latency response of neurons. In this context, Pankratova et al. \[10, 11\] theoretically investigated the impact of noise – which is ubiquitous in whole nervous system – on latency dynamics of a single neuron that is subject to a suprathreshold periodic input current. They reported that for a range of periodic forcing frequency near the boundaries of suprathreshold spiking regime, there exists a resonance-like behavior of the mean latency depending on noise intensity. More precisely, as noise increases, mean response latency first dramatically increases, then reaches some maximum, and finally decreases to a value lower than the one in noise-free condition. The authors called this non-monotonic noise dependence of mean latency “Noise Delayed Decay (NDD)”. This phenomenon indicates that latency coding is not a convenient strategy to encode signals near the spiking threshold because it implies, first, a delay in external signal detection and, second, a very low temporal spiking precision for a particular intensity of noise. In \[12, 13\], NDD was also investigated on the level of network, and it was reported that NDD effect on latency response can be controlled via network activity. However, these studies \[10, 14\] do not motivate, from a biophysical point of view, the source of the noise and it was incorporated artificially by adding an external additive stochastic input current. Therefore, these works can not give a biophysical explanation for the emergence of NDD. Recently, more realistic assumptions have been considered to characterize the noise, including ion channel noise \[13\] - which allows to relate intrinsic dynamics of a neuron with NDD – and synaptic background activity – that allows to relate unreliability of spike transmission with NDD \[15\].

In the present study, we investigate NDD phenomenon in a more realistic scenario considering dynamic synapses. In fact, modeling synapses as static connections (with fixed conductance) does not reveal the possible influence of some biophysical processes on NDD. It is well-known, for instance, that synapses exhibit a high variability with a diverse origin during information transmission, such as stochastic release of neurotransmitters, variations in chemical concentration through synapses and spatial heterogeneity of synaptic response over dendrite tree \[16\]. The collective effect of all these factors might result in synaptic conductance fluctuations at short time scales. It is known, e.g., that synapses in different cortical areas can have varied forms of plasticity, being either in only a specific form, or showing a mixture of several forms \[17, 19\]. For instance, postsynaptic response can be depressed or facilitated during high presynaptic activity. Synaptic depression is induced due to the fact that available neurotransmitter concentration at synaptic buttons needs some time to recover after each release event originated by arrival of presynaptic APs. If APs arrive at high frequency, the release probability of neurotransmitters for subsequent APs will decrease, and therefore postsynaptic response will be decreased or depressed. On the other hand, synaptic facilitation is a consequence of residual cytosolic calcium – that remains inside the synaptic buttons after the arrival of the first APs – which favors the release of more neurotransmitter vesicles for the next arriving AP \[20\]. Such increase in neurotransmitters causes a potentiation of the postsynaptic response or synaptic facilitation. Short-term depression (STD) and short-term facilitation (STF) mechanisms have been reported to be relevant for various brain functions, i.e. cortical gain control \[21\], information storage in neural networks \[22, 24\], coincidence detection of signals \[23, 26\], synchrony and selective attention \[27, 28\], and perform new computations in diverse neural systems \[29\].

Our results in the present work reveal that dynamic synapses with STD and STF mechanisms might give rise to emergence of rich NDD features in response latency of a single neuron. We find, e.g., pure depressing synapses, with low levels of depression, induce a new intriguing double NDD (DNDD) behavior which collapses into a single NDD as the level of depression increases. This is the first time it has been reported the existence of DNDD behavior as a function of a biophysically realistic parameter controlling the level of activity in a neural medium. We also show that NDD effect can be attenuated or even completely eliminated from the latency response of a neuron when the level of depression is very high. On the other hand, in the presence of STF mechanism competing with STD and depending on the balance between these two mechanisms, both single NDD or DNDD can emerge, in such a way that synaptic facilitation favors the emergence of DNDD whereas synaptic depression favors the existence of single NDD. We finally clarify the underlying mechanism that gives rise to NDD and DNDD behavior in terms of the non-monotonic dependence of synaptic current fluctuations on presynaptic activity due to the presence of dynamic synapses.
II. MODELS AND METHODS

A schematic illustration of the system under study is depicted in Fig. 1. This consists of a postsynaptic neuron which is driven by a suprathreshold periodic stimulus and subject to an uncorrelated presynaptic activity from a finite number of excitatory and inhibitory neurons.

Figure 1. (Color online) Schematic illustration of the considered system. The postsynaptic neuron is subject to a suprathreshold periodic current and a noisy background activity resulting from random arrival of excitatory and inhibitory presynaptic spikes. Our aim here is to investigate how the dynamic properties of these synapses can influence latency response of the postsynaptic neuron.

The time evolution of membrane potential of the postsynaptic neuron is modeled based on the Hodgkin-Huxley (H-H) equations as follows [30]:

\[
C_m \frac{dV_m}{dt} = -G_{Na}m^3h(V_m - E_{Na}) - G_Kn^4(V_m - E_K) - G_L(V_m - E_L) + I_{stim} + I_{syn}
\]

where \(V_m\) is the membrane potential, \(C_m = 1 \mu F/cm^2\) is the membrane capacity per unit area. The constants \(G_{Na} = 120 mS/cm^2\), \(G_K = 36 mS/cm^2\) and \(G_L = 0.3 mS/cm^2\) are maximum conductance for sodium, potassium and leakage channels, respectively. \(E_{Na} = 115 mV\), \(E_K = -12 mV\) and \(E_L = 10.6 mV\) denote the corresponding sodium, potassium and leak current reversal potentials. The gating variables \(m\), \(h\) and \(n\) that govern activation and inactivation of sodium channels and activation of potassium channels, respectively, and obey the following differential equations [30]:

\[
d\gamma = \alpha_\gamma(V_m)(1 - \gamma) - \beta_\gamma(V_m)\gamma
\]

where \(\alpha_\gamma\) and \(\beta_\gamma\) (\(\gamma = m, n, h\)) are experimentally determined voltage dependent rate functions for the gating variable \(\gamma\) and can be found in [11]. In Eq. (1), \(I_{stim}\) is the suprathreshold periodic current stimulus, \(I_{stim}(t) = A_0 \sin(2\pi f_st t)\) where \(A_0\) and \(f_s\) stand, respectively, for the amplitude and frequency of this signal. Here “suprathreshold” refers to an input level that produces tonic spiking activity. Finally, \(I_{syn}\) represents the total synaptic current generated by \(N = 1000\) presynaptic excitatory and inhibitory neurons where excitatory to inhibitory ratio is taken as \(N_e : N_i = 4 : 1\), a choice that preserves the similar ratio found in the mammalian cortex [31]. Each presynaptic neuron is considered as an independent Poisson spike train generator with the same presynaptic firing rate \(f_s\).

Synaptic connections between presynaptic and postsynaptic neurons are modeled according to Tsodyks and Markram dynamical synapse equations [32]. Although short-term synaptic plasticity is widely considered to be valid for excitatory synapses, recent experimental studies have shown that inhibitory synapses also display this type of plasticity behavior [33-36]. Thus, in our study, it is reasonable to assume that Tsodyks and Markram equations can also be used to model inhibitory synapses, as previously considered in [32, 37]. The model assumes that an AP can be transmitted by a finite amount of neurotransmitter resources. That is, each presynaptic AP at a given synapse \(i\) activates a fraction of neurotransmitters with probability \(u_i(t)\) (release probability), which then quickly inactivates (as a fast synapse) during a characteristic time constant \(\tau_{in} = 3 ms\) [32, 38]. After a recovery period \(\tau_{rec}\), resources are reloaded and the synapse \(i\) returns to its initial state. This process is governed by the following equations [32]:

\[
\frac{d u_i}{dt} = \alpha_i u_i (1 - u_i) - \beta_i u_i
\]
\[
\frac{dx_i(t)}{dt} = \frac{z_i(t)}{\tau_{rec}} - u_i(t)x_i(t)\delta(t - t_{spk}^i) \tag{3}
\]
\[
\frac{dy_i(t)}{dt} = -y_i(t) + u_i(t)x_i(t)\delta(t - t_{spk}^i) \tag{4}
\]
\[
\frac{dz_i(t)}{dt} = \frac{y_i(t)}{\tau_{in}} - \frac{z_i(t)}{\tau_{rec}} \tag{5}
\]

where \(x_i, y_i, z_i\) are the fraction of neurotransmitters in a recovered, active and inactive state, respectively. Delta functions in equations take into account that an AP arrives to the synapse at \(t = t_{spk}^i\). The model described by Eqs. (3–5) satisfactorily explains STD mechanism in cortical neurons for relatively large values of \(\tau_{rec}\) and assuming \(u_i(t) = U\), which represents a constant neurotransmitter release probability after arrival of an AP [32, 38]. On the other hand, STF mechanism can be introduced by assuming that \(u_i(t)\) is not fixed but is increased by a certain amount due to the influx of calcium ions through voltage sensitive ion channels into the presynaptic neuron when an AP arrives. The corresponding dynamic equation for \(u_i(t)\) is given by [32]:
\[
\frac{du_i(t)}{dt} = \frac{U - u_i(t)}{\tau_{fac}} + U[1 - u_i(t)]\delta(t - t_{spk}^i) \tag{6}
\]

where \(\tau_{fac}\) is the time duration of transition from open to close state of calcium channel gates [32]. It is worth noting that large values of \(\tau_{rec}\) and \(\tau_{fac}\) are associated to stronger synaptic depression and facilitation at the synapse, respectively. More precisely, large \(\tau_{rec}\) implies that neurotransmitter concentration \(x(t)\) in ready-releasable pool takes more time to recover its maximum value after the release event induced by an AP. Thus, if another AP arrives at certain posterior time \(t_{spk}^i\), the amount of released neurotransmitters, that is \(u_i(t_{spk}^i)x_i(t_{spk}^i)\), will be lower and therefore the postsynaptic response for the second AP too. This depressing effect will be stronger for larger \(\tau_{rec}\) and higher presynaptic firing frequency. On the other hand, large \(\tau_{fac}\) in Eq. (6) implies that, assuming an initial low value of the release probability \(u_i(t)\), it will take a large time to grow until the value \(U\) indicating that the facilitation effect (increase of the release probability) will take place during a large period of time. Finally, for a given value of \(\tau_{rec}\), a large value of \(U\) induces a strong depletion of the available resources for a given AP, and therefore a decrease of the postsynaptic response for subsequent APs, particularly at high presynaptic frequency. In the case of facilitating synapses, for a given value of \(\tau_{fac}\), a larger value for \(U\) produces a stronger increase in the release probability after each AP so it induces a strong and fast facilitation for high-frequency presynaptic activity. Within this model, the postsynaptic current generated at a synapse \(i\) is taken to be proportional to the fraction of neurotransmitters in the active state, namely \(I_i(t) = A y_i(t)\). Here, \(A\) is the maximum synaptic current which can be generated at the synapse only by activating all resources.

Based on the description of the dynamic synapse model on the level of single synapse in Eqs. (3–6), we can now generalize the total synaptic current generated by excitatory and inhibitory presynaptic neurons as follows:
\[
I_{syn}(t) = \sum_{p=1}^{N_p} A y_p(t) - K \sum_{q=1}^{N_i} A y_q(t) \tag{7}
\]

where \(K\) is the relative strength between inhibitory and excitatory connections, and \(-KA\) as a whole stands for maximum inhibitory synaptic current per synapse. Here, we assume \(K = 4\) within the physiological range of balanced state of cortical neurons [31].

To evaluate the emergence of NDD phenomenon in response latency dynamics of the postsynaptic neuron, we define latency to the first spike as the time when an AP first crosses with a positive slope a detection threshold, taken here equal to 20 mV, relative to start of the stimulus (see Fig. 1). Then, we compute mean latency of an ensemble of first spikes by averaging over \(r\) realizations:
\[
\text{Mean Latency} = \langle t \rangle = \frac{1}{r} \sum_{i=1}^{r} t_i \tag{8}
\]

where \(t_i\) is the appearance time of the first spike for \(i\)th realization. We also consider standard deviations of latencies, or temporal jitter, as follows:
\[
\text{Jitter} = \sqrt{\langle t^2 \rangle - \langle t \rangle^2} \tag{9}
\]
where $\langle f^2 \rangle$ represents the mean squared latency. The results presented in the next sections are obtained over $r = 5000$ independent runs for each set of parameter values to warrant appropriate statistical accuracy with respect to the stochastic fluctuations in background activity. Numerical integration of the whole system equations are performed using standard fourth order Runge-Kutta algorithm with a step size of $10 \mu s$.

### III. RESULTS

#### A. Emergence of NDD behavior with dynamic synapses

In this section, we have systematically analyzed the emergence of NDD in a H-H neuron which is subject to both a suprathreshold periodic signal and a noisy synaptic background activity arising from a balanced population of excitatory and inhibitory neurons. In previous works on NDD [10, 11, 14], it has been illustrated that for a given value of periodic signal amplitude $A_0$, a H-H neuron operates in a suprathreshold regime only for a range of signal frequencies $f_s$. In these works, it has also been demonstrated that NDD effect only emerges near the lower and upper limits of such frequency regions. As an example, we consider here the case of $A_0 = 4 \mu A/cm^2$ that implies a frequency range $f_s \in [16 : 149] Hz$ for suprathreshold regime (see Fig. 1 in [11]). To investigate NDD phenomenon, we also fix the stimulus frequency to $f_s = 20 Hz$ which is just above the lower limit of the suprathreshold frequency region. Here, it is worth noting that similar qualitative results can be obtained if one considers a signal frequency near the upper limit of considered $f_s$ region.

First, we have investigated the influence of short-term synaptic depression (varying $\tau_{rec}$) on the emergence of NDD phenomenon by measuring latency response statistics of the postsynaptic neuron as a function of presynaptic firing rate $f$, which is considered here as global control parameter to scale the intensity of background activity. Since we assume that postsynaptic neuron receives inputs through purely depressing synapses, we set $\tau_{fac} = 0$ to block the facilitation mechanism in the model. In Fig. 2, mean latency and jitter are plotted versus $f$ for several values of $\tau_{rec}$ including the case of *static* or non-depressed synapses ($\tau_{rec} = 0$). Our results show that mean latency and jitter exhibit a non-monotonic behavior, i. e. NDD phenomenon, as a function of $f$, both for static and dynamic synapses with relatively large values of $\tau_{rec}$ (see Panels A and B in Fig. 2).

Figure 2. (Color online) The influence of short term synaptic depression on first-spike latency response statistics of a H-H neuron. Figure depicts the behavior of mean latency (left panels) and jitter (right panels) against presynaptic firing frequency $f$ for several values of $\tau_{rec}$. NDD behavior emerges for depressed ($\tau_{rec} > 0$) and non-depressed ($\tau_{rec} = 0$) synapses. This unwanted effect appearing for a wide range of $f$ can disappear for relatively large levels of depression as seen in panels A and B. On the other hand, panels C and D illustrate, respectively, the dependence of statistics for small values of $\tau_{rec}$. When the depression is lowered, interestingly, a double NDD behavior emerges. Other synaptic parameters were $A = 0.6 \mu A$, $U = 0.1$, $\tau_{fac} = 0$. 

A. Emergence of NDD behavior with dynamic synapses

B. On the other hand, panels C and D illustrate, respectively, the dependence of statistics for small values of $\tau_{rec}$.
In addition to the classical NDD, Fig. 2 also depicts intriguing effect of synaptic depression on NDD curves. That is how synaptic depression can modulate the shape, amplitude and width of the NDD curves. For instance, a double resonance like regime seems to emerge for the mean latency and jitter in considered $f$ domain for relatively low levels of synaptic depression $\tau_{rec} < 100 \text{ ms}$ (see Panels C and D in Fig. 2). To the best of our knowledge, this is the first time such intriguing “double NDD” (DNDD) effect has been described. DNDD behavior is more evident for very low $\tau_{rec}$ and results in a single NDD curve when $\tau_{rec}$ approaches to a value of 100 ms. On the other hand, for $\tau_{rec} \approx 100 \text{ ms}$, the resulting merged single NDD curve presents the maximum possible amplitude, as in the classical NDD behavior for static synapses, but with a very large width in $f$ domain compared with the static synapse case. This implies, therefore, a poor first spike latency coding efficiency for this range of depression. Finally, for $\tau_{rec} > 100 \text{ ms}$, mean latency and jitter start to decrease in amplitude and width as the level of depression increases, which might provide a relevant mechanism to increase the first spike latency coding efficiency by increasing the level of depression at synapses. In others words, since the existence of NDD implies a delay in signal detection by a given neuron, a decrease of NDD effect (as the level of depression increases) implies a better response of the neuron to signal detection. Moreover, since the jitter also decreases for large $\tau_{rec}$, then spike precision in response to a given external stimulus increases [39, 41].

![Figure 3](image-url)

Figure 3. (Color online) The impact of synaptic facilitation on first-spike latency statistics. Mean latency and jitter are respectively shown in panels A and B as a function of $f$ when STF and STD mechanisms are both present at synapses. As seen in the figure, facilitation favors the emergence of DNDD behavior. Release probability at rest and neurotransmitter recovery time constant were set to $U = 0.2$ and $\tau_{rec} = 100 \text{ ms}$, respectively. Other synaptic parameters were as in Fig. 2.

Synapses in the brain can present – in addition to synaptic depression – synaptic facilitation mechanism that induces an enhancement of postsynaptic response at short time scales [32, 38]. During synaptic transmission, a complex interplay between these two mechanisms can occur, a fact that can have strong implications on first spike latency in response to given stimulus. We investigated this important issue in our system and the results are depicted in Fig. 3. This figure shows latency statistics as a function of $f$ for different levels of facilitation, controlled by $\tau_{fac}$, at a given value of depression $\tau_{rec} = 100 \text{ ms}$. The main finding here is that synaptic facilitation induces a decrease (reaching a minimum) in mean latency and jitter for a given range of $f$, which is similar to the case of only depressed synapses with low $\tau_{rec}$, and that gives rise to emergence of facilitation induced DNDD. Moreover, such DNDD effect occurs for most values of $\tau_{rec}$ that one can consider as it is illustrated in Fig. 4. As seen in the figure, facilitation tends to favor the DNDD for the levels of depression considered in our analysis. However, figure also shows that, for
a given value of facilitation, DNDD effect becomes less evident by enlarging the level of depression in the system (as in the case of pure depressing synapses).

On the other hand, assuming $\tau_{in} \ll \tau_{rec}, \tau_{fac}$, it has been shown that release probability at rest, i.e. $U$, is a relevant parameter that can critically control the level of synaptic depression in the presence of facilitation, a fact that can induce different intriguing computational implications [24, 26, 29, 43–45]). In this context, another important issue concerning our study here is to investigate the impact of $U$ on the emergence and behavior of NDD as a function of $f$ when synapses present different types of short-term synaptic plasticity. Our analysis is depicted in Fig. 5 for depressing and facilitating synapses. When only STD mechanism is present at synapses with a depression level of $U$ for very small values of $\tau$ (see Panels A and B). On the other hand, for facilitating synapses, we observe similar influence of $U$ on NDD behavior, but interestingly, NDD effect is always present regardless of $U$ (see Panels C and D). Moreover, contrary to the behavior of DNDD curves induced by $\tau_{rec}$ or $\tau_{fac}$ where the second peak is modulated (see Fig. 2 and 3), $U$ has more importance on modulating the first peak of DNDD curves.

![Figure 5](image-url) (Color online) The influence of release probability at rest $U$ on NDD. Panels A and B illustrate, respectively, variations of mean latency and jitter as a function of $f$ for several different values of $U$ in the presence of only STD mechanism ($\tau_{rec} = 100 \text{ms}$ and $\tau_{fac} = 0 \text{ms}$). Panels C and D shows the same statistics when STD and STF mechanisms are both present at synapses ($\tau_{rec} = 100 \text{ms}$ and $\tau_{fac} = 300 \text{ms}$). Other parameters were as in Fig. 2.

### B. Mechanism of NDD and DNDD

The underlying mechanism for the emergence of NDD in our system is the following. First, let us assume that a typical H-H neuron is set at its resting state in absence of a noisy synaptic input. Let us consider then that it is subject to a sinusoidal signal which puts it in a spiking regime such that the neuron generates only an AP within the positive phase of the signal around its maximum amplitude (i.e., one AP per period of the signal). In the presence of a noisy synaptic input, however, this regime is conserved as far as the appearance of non-depolarizing noise fluctuations around the maximum signal amplitude impedes the generation of the AP in the current signal cycle. The last postpones the generation of AP to the subsequent signal cycles. That is, neuron can fire then around the maximum amplitude of second or third positive phase of the signal, skipping first signal cycle with enough noise. This is clearly shown in Fig. 6. Here the case of low presynaptic firing rate, e.g. $f = 2 \text{Hz}$, corresponds to a low noise regime at which there is not enough strong non-depolarizing fluctuations to make postsynaptic neuron to skip toward subsequent depolarizing phases. In fact, first spikes occur only in the first cycle for low $f$. When presynaptic firing rate increases, for instance, to $f = 30 \text{Hz}$, synaptic noise intensity also enlarges. In this regime, firing events of neuron depict some skipping behavior from the first signal cycle. That is, for a given set of trials, neuron fires in first cycle predominantly (blue), approximately same amount of times in second cycle (red), and only a few times in third
Figure 6. (Color online) The mechanism underlying the emergence of NDD. This figure depicts the position of the first spikes relative to the injected suprathreshold signal phase for three different values of $f$. In each panel, we superimpose 50 membrane potential traces obtained from independent realizations. For each trace, membrane potential is clamped to the resting state after appearance of first spike. Depending on the level of $f$, first spike in response to the driving signal might occur within first (blue), second (red) or even third signal cycle (green). Neurotransmitter recovery time constant was set to be $\tau_{\text{rec}} = 100 \text{ ms}$ and other synaptic parameters were as in Fig. 2. (Note that vertical scaling does not refer to the amplitude of periodic signal)

cycle (green). This fact induces an increase in mean latency and jitter (see Fig. 2). Finally, for $f = 1000 \text{ Hz}$, skipping from the first signal cycle stops and neuron fires again within the first cycle, so mean latency and jitter start to decrease (see Fig. 2). However, the mechanism behind this decreasing phase of the NDD curves is different for the case of depressed ($\tau_{\text{rec}} > 0$) and non-depressed ($\tau_{\text{rec}} = 0$) synapses. For depressed synapses (the case depicted in Fig. 6) and for large $f$, strength of the synaptic fluctuations decreases which makes the neuron to fire again in the first signal cycle near the maximum amplitude, as in the case of very low $f$. For non-depressed synapses, however, for all trials neuron fires an AP at the beginning of first signal cycle due to strong fluctuations (data not shown). Mean latency and jitter then take small values (see Fig. 2A and B) which is lower than the noiseless case (very low $f$).

On the other hand, emergence of DNDD behavior in the presence of both facilitation and depression can be explained with the same skipping mechanism. This can be seen, for instance, looking at the skipping behavior of firings depicted in Fig. 7 for $\tau_{\text{fac}} = 100 \text{ ms}$ and $\tau_{\text{rec}} = 400 \text{ ms}$. One can observe that first spikes only occur within the first signal cycle for very low and very large $f$. However, skipping behavior is maximum (which implies larger mean latency and jitter) for two distinct values of $f$, namely $f = 4 \text{ Hz}$ and $500 \text{ Hz}$. In fact, for these cases there is a significant amount

Figure 7. (Color online) The mechanism underlying the emergence of DNDD when facilitation competing with depression is present at synapses. Figure depicts skipping behavior from the first signal cycle as a function of $f$. There are two values of $f$ (around $4 \text{ Hz}$ and $500 \text{ Hz}$) at which the skipping to second and third signal cycles occurs frequently. These two points correspond to two maxima of the DNND curve. Synaptic parameter values were $\tau_{\text{fac}} = 400 \text{ ms}$ and $\tau_{\text{rec}} = 100 \text{ ms}$, and other parameters were as in Fig. 3. (Note that vertical scaling does not refer to the amplitude of periodic signal)
of generated spikes during second and third signal cycles (see red and green voltage traces in Fig. 7). On the other hand, for \( f = 30 \text{ Hz} \) – which is within these two frequencies that provide maximum skipping events – the number of cycle skipped firings starts to decrease resulting in a minimum of mean latency and jitter among the two previous maxima (see Fig. 3 and 4). Although, we consider here facilitation induced DNDD, it is worth noting that the mechanism is the same for only depression induced DNDD.

C. Non-monotonic frequency dependency of synaptic current fluctuations shapes NDD and DNDD curves

Cycle-skipped firings and emergence of NDD in our considered system are mainly related with the behavior of total synaptic current fluctuations with \( f \) and synapse dynamics. Because of the presence of short-term plasticity mechanisms at synapses, each individual transmitted AP in a spike train evokes different postsynaptic current (PSC) responses depending on the type of plasticity and \( f \). As an example in Fig. 8, we illustrate such difference at a single synapse where only STD mechanism is considered during synaptic transmission. At a certain level of STD (fixed value of \( \tau_{\text{rec}} \)), it is seen that the amplitude of generated PSCs in response to each AP does not change very much for small \( f \) because there is enough time between successive APs to recover neurotransmitter vesicles. However, with increase in \( f \), since presynaptic APs tend to appear more likely within the recovery time interval (\( \tau_{\text{rec}} \)), vesicles could not be fully recovered for closely time-spaced successive APs. This indicates a reduction in PSC amplitudes for those of APs. Or alternatively, for a fixed \( f \), an increase in \( \tau_{\text{rec}} \) induces attenuation of PSCs. 

Since we assume in our study that all synapses present such dynamical behavior, the resulting total synaptic current introduced into the postsynaptic neuron will present statistical features that will depend on both \( \tau_{\text{rec}} \) and \( f \) in a complex way. Moreover, we are considering a balance between excitation and inhibition, and therefore, the resulting mean synaptic current \( \mu_I \approx 0 \) and will not change when these parameters are varied. However, the magnitude of total synaptic current fluctuations, namely \( \sigma_I \), exhibits a non-monotonic behavior with \( f \) as shown in Fig. 9A for depressing synapses (see also [45] and [46] for analytical approximation of such dependency), which is more prominent when \( \tau_{\text{rec}} \) increases. That is, at low \( f \) values, there is a small number of transmitted spikes that contribute to total synaptic current. Since these spikes are temporally uncorrelated (they are Poissonian distributed) and synaptic depression is weak due to low \( f \) (there are not strong differences in the amplitude of the PSC generated by each arriving spike), it is straightforward to demonstrate that \( \sigma_I \) is proportional to \( f \) (see Fig. 9A), which then is small. As \( f \) increases up to a moderate value where STD mechanism still has not a strong effect, \( \sigma_I \) continues rising monotonically but slowly because of the appearance of some closely time-spaced spikes in presynaptic input train which can be then depressed. After this limiting point of \( f \), STD mechanism starts to decrease mean PSCs seriously that gives rise to a decrease in \( \sigma_I \) for high \( f \) because of increased number of closely time-spaced spikes. Besides, increasing the level of depression at synapses (\( \tau_{\text{rec}} \rightarrow \infty \)) modulates this trend by decreasing the peak value of \( \sigma_I \) (STD is stronger).

Behavior of \( \sigma_I \) with \( f \) for different values of \( \tau_{\text{rec}} \) can explain the shape of NDD curves. When \( \tau_{\text{rec}} = 0 \) (static
synapses), since $\sigma_I$ rises monotonically with increase in $f$ (see Fig. 9A), it can fall within an interval $(\sigma_I^{\text{min}}, \sigma_I^{\text{max}})$ for a particular range of $f$, namely $(f_{\text{min}}, f_{\text{0}})$, that induces an increase of the mean latency and jitter based on the mechanism described above in Fig. 6. Here $\sigma_I^{\text{min}}$ is by definition the minimum current fluctuation value that can start first signal cycle skipping, and $\sigma_I^{\text{0}} \approx 0.7 \text{nA}$ is the value of current fluctuations at which number of skipping events is maximum $\text{III}$. When $f$ increases further within the interval $(f_{\text{0}}, f_{\text{max}})$, $\sigma_I$ also rises passing through the interval $(\sigma_I^{\text{0}}, \sigma_I^{\text{max}})$. Here $\sigma_I^{\text{max}}$ is the level of current fluctuations that stops skipping for large $f$. Therefore, within the range $(\sigma_I^{\text{0}}, \sigma_I^{\text{max}})$, $\sigma_I$ starts to decrease the number of skipping events (probability of firings during the first signal cycle tends to increase) and creates the decay phase of NDD curve. For very large values of $f$ (that implies $\sigma_I \geq \sigma_I^{\text{max}}$), background activity suppress the suprathreshold periodic signal, and consequently mean latency gets lower values than the deterministic case because the response time is mostly determined by large synaptic current fluctuations at each trial.

On the other hand, as STD mechanism takes place at synapses, the optimal amount of synaptic current fluctuations for cycle-skipped firings can be achieved for a wide range of $f$ and $\tau_{\text{rec}}$ due to non-monotonic behavior of $\sigma_I$ with $f$. More precisely, as $f$ increases, $\sigma_I$ first exceeds the $\sigma_I^{\text{min}}$ triggering cycle-skipped firings and initiating the rising phase of the NDD. Then, it starts to decrease after reaching some maximum, which is determined by the level of depression $\tau_{\text{rec}}$ and that induces the maximum level of NDD curve. Finally, it crosses again $\sigma_I^{\text{min}}$ from above which stops cycle-skipped firings and creates the decay phase of the NDD curve. Therefore, it can be said that appearance of NDD with depressing synapses depends on $f$ range that provides the condition of $\sigma_I \geq \sigma_I^{\text{min}}$. As seen in Fig. 9A, since $f$ range providing this condition starts to shrink with increase in $\tau_{\text{rec}}$, width and maximum of NDD curves decrease for more depressed synapses indicating tendency to disappearance of NDD effect (see Fig. 2A and B).

The previous scenario described for depressing synapses occurs for values of $\tau_{\text{rec}}$ such that maximum of current fluctuations is smaller than $\sigma_I^{\text{0}}$, that happens for $\tau_{\text{rec}} \geq 100 \text{ ms}$ and induces single NDD curves. For values of $\tau_{\text{rec}} < 100 \text{ ms}$, as we have already mentioned in Section III. A, a DNDD effect emerges. This can be explained due to the fact that maximum of $\sigma_I$ (in the $f$ domain) is larger than $\sigma_I^{\text{0}}$ for such levels of depression (see Fig. 9A). This happens since non-monotonic behavior of $\sigma_I$ occurs for very large values of $f$ in such a way that $\sigma_I$ still grows as a function of $f$, for the range of frequencies at which NDD appears, and may exceed $\sigma_I^{\text{0}}$. Then, since $\sigma_I^{\text{0}}$ corresponds to the strength of the current fluctuations at which maximum skipping behavior occurs, a larger value of $\sigma_I$ starts to stop skipping events, which creates the first NDD curve. This takes place until $\sigma_I$ reaches its maximum. When $\sigma_I$ decreases from its maximum (for larger $f$), skipping events start to increase again until $\sigma_I$ becomes smaller than $\sigma_I^{\text{0}}$. Further increase in $f$ provides $\sigma_I$ to be less than $\sigma_I^{\text{0}}$ that creates the second NDD curve due to reduced number of skipping events. The overall behavior of mean latency and jitter follow thus a DNDD curve as a function of $f$ (see Fig. 2C and D).

Emergence of DNDD behavior can be also easily understood in terms of the complex dependence of $\sigma_I$ with $f$, $\tau_{\text{rec}}$ and $\tau_{\text{fac}}$ when STF is present at synapses competing with STD (see Fig. 9B). Such dependency profile can also be found in [44] and [26] where the behavior of $\sigma_I$ qualitatively matches with our Fig. 9B. In fact for the present situation, $\sigma_I$ can be significantly larger than $\sigma_I^{\text{0}}$ (due to facilitation) for some range of intermediate values of $f$. This increase of $\sigma_I$ is due the the fact that STF cancels STD mechanism for such $f$ values – so $\sigma_I$ can be as large as in the case of static synapses – and has no effect at higher values of $f$, so $\sigma_I$ decreases due to STD mechanism. In other words, the rising phase of $\sigma_I$, when facilitation is considered, is mainly determined by STF mechanism. However, the

Figure 9. (Color online) Variation of synaptic current fluctuations with $f$ when dynamic as well as static synapses are considered. Panel A shows the dependency of $\sigma_I$ on $f$ in the presence of only STD mechanism at synapses ($\tau_{\text{rec}} = 0$). Several different values of $\tau_{\text{rec}}$ are considered including $\tau_{\text{rec}} = 0$ which characterizes the case of static synapses. In Panel B, variation of $\sigma_I$ with $f$ is illustrated when STD and STF mechanism are both present at synapses. Note that $\tau_{\text{rec}}$ is used to control competition between two mechanism where $\tau_{\text{rec}}$ is fixed to $100 \text{ ms}$. The condition $\sigma_I = \sigma_I^{\text{0}}$ marks the emergence of the two maxima on DNDD curve (see Fig. 3), whereas the maximum of $\sigma_I$ is associated to minimum between these two maxima (see main text for a more detailed explanation).
decreasing phase after a certain $f$ is due to STD mechanism. The non-monotonic dependence of $\sigma_I$ with $f$ makes it to cross the value $\sigma_I^0$ two times, one with positive and the other with negative slope, both corresponding then to maxima in mean latency and jitter. The minimum between these two maxima – which defines the DNDD curve – appears where $\sigma_I$ reaches its largest value above $\sigma_I^0$ since at this value the number of cycle skipping events is smallest within the frequency range among the two maxima of the DNDD curve. As larger is the distance above $\sigma_I^0$ to the maximum of $\sigma_I$ (e.g. increasing $\tau_{fac}$), a more deep minimum can be obtained for the DNDD curve (compare Fig. 3 and Fig. 9B). Moreover, for very large $\tau_{fac}$ and a given value of $\tau_{rec}$, this minimum of DNDD saturates and cannot be more deep as shown in Fig. 3 because the maximum of $\sigma_I$ also saturates for large $\tau_{fac}$.

### D. Sensitivity of latency on synaptic current fluctuations

As a final result of our study, we here present an interesting low-frequency behavior of mean latency and jitter when depressing synapses are present. As can be observed by comparing the latency statistics and $\sigma_I$ values, respectively, in Fig. 2 and Fig. 9A, although there is no significant variation in $\sigma_I$ for different levels of synaptic depression at low $f$, mean latency and jitter get different values. Note that this effect does not emerge when facilitation is present at synapses (see Fig. 3). To illustrate this fact, we compute the probability distribution of first spike latencies for three different values of $\tau_{rec}$ that generate almost equal strengths of $\sigma_I$ at $f = 2 \text{ Hz}$, a value at which difference in latency statistics is more obvious. As seen in Fig. 10, although amplitudes of synaptic current fluctuations $\sigma_I$ are almost same for different levels of depression, first spike latency probability distributions are quite different. For instance, for the lowest level of synaptic depression considered here, latency probability distribution has a pronounced second peak around the time for the depolarization phase of second signal cycle (see inset). Notably, such a multimodal behavior of H-H model for low noise regime was also reported in [47]. This second peak at low $f$ indicates that a small increase in $\sigma_I$ significantly increases the probability for skipping from first cycle of the stimulus. A higher probability of skipping results in an increased values of corresponding mean latency and jitter for low $\tau_{rec}$ with respect to other considered synaptic depression levels (where this second peak in probability distribution is less pronounced or even absent).

![Figure 10](image)

Figure 10. (Color online) Probability distribution of first spike latencies for three different levels of synaptic depression ($\tau_{rec} = 100, 300$ and $600 \text{ ms}$) when the presynaptic firing rate was set to $f = 2 \text{ Hz}$. Although amplitudes of synaptic current fluctuations $\sigma_I$ are almost same, probability distributions of first spike occurrence time is quite different. Inset shows enlargement of the second peak that is not clear in the main plot. Other synaptic parameters were as in Fig. 2.

### IV. CONCLUSION

In this work, we have studied first spike latency response of a H-H neuron that receives, in addition to a suprathreshold signal, a noisy current from a finite number of afferents through dynamic synapses. The noisy input current is originated from arrival of uncorrelated spikes trains in each afferent that follow a Poissonian statistics with mean firing frequency $f$. To characterize NDD phenomenon, we have computed mean latency response and its jitter as a function of this presynaptic firing rate $f$. This constitutes a more realistic scenario than traditional studies, since $f$ provides a suitable biophysically realistic parameter to control the level of activity in actual neural systems. Our work reveals that when synapses do not present activity dependent synaptic mechanisms, such as STD nor STF, classical NDD behavior is found as a function of $f$, which in this case (static synapses) is a biologically meaningful measure of noise level. However, when dynamic synapses with STD and STF are included in description of synapses, we found a
very different behavior of response latency as a function of $f$. This is due to the non-monotonic dependency of current fluctuations on $f$ and how it is modulated by the dynamic synapse parameters (i.e., $\tau_{rec}$, $\tau_{fac}$ and $U$). For instance, for the case of pure depressing synapses, we found two different behaviors: a new intriguing DNDD behavior occurs for low levels of STD. This disappears as STD level increases and single NDD emerges. In addition, we found that when STD level increases even more in this last case, NDD effect starts to disappear. This provides possible use of large STD levels as a mechanism to improve first spike latency coding. However, for intermediate values of $\tau_{rec}$ (100 – 200 ms), latency coding efficiency may be poor because one has large amplitude and width in the frequency domain of the resulting single NDD curves. On the other hand, in the presence of STF competing with STD, single NDD or DNDD can emerge depending on the balance between these two synaptic mechanisms, in such a way that STF favors the emergence of DNDD whereas STD favors the existence of single NDD. We have also demonstrated the importance of release probability at rest $U$ on NDD. When only STD mechanism is present at synapses, it is shown that NDD is not emerging for very low values of $U$, however both NDD and DNDD can emerge as it is increased. On the other hand, in the case of STF mechanism, NDD exists in response latency of the neuron regardless of $U$ and it can be transformed to DNDD as $U$ increases. Such effects of $U$ are also originated from its influence on shaping total synaptic current fluctuations as $f$ varies.

An interesting point not considered in the present work concerns the behavior of NDD in the case of unbalanced synaptic background activity. Note that in our study, the scaling factor $K$ in Eq. (7) determines the competition between excitation and inhibition. Variation of this variable would provide either an excitation or an inhibition dominated synaptic background activity. For instance, for $K < 4$, presynaptic excitatory neurons would dominate the overall synaptic background activity resulting in a positive mean synaptic current. In contrast, for $K > 4$, the sign of the mean synaptic current would be negative due to the large inhibition. For a given set of dynamic synapse model parameters, mean synaptic current for these two unbalanced situations quickly saturates to a positive (for excitation dominated) or negative (for inhibitory dominated) value in $f$ domain (more or less it is a DC current) due to the nature of dynamic synapses [15]. When $K < 4$, injection of a such depolarizing positive bias current would provide a strong stable spiking regime to the postsynaptic neuron in which influence of synaptic current fluctuations on spike timing is negligible. Therefore, we expect that NDD effect would be reduced significantly or completely removed from latency response of the postsynaptic neuron. On the other hand, in the case of inhibitory dominated background activity, a negative hyper-polarizing mean synaptic current would cause a non-spiking regime for the postsynaptic neuron because suprathreshold driving periodic signal is already very close to the subthreshold boundary. In such a non-spiking regime where the neuron exhibits subthreshold oscillations near its resting potential, occurrence of APs would be determined randomly by fluctuations of synaptic current. Therefore, one cannot mention about the NDD phenomenon in inhibitory dominated synaptic input regime due to definition of this phenomenon (resonance like dependency on noise).

The present study reports for the first time the emergence of DNDD behavior as a function of a biophysically realistic parameter controlling the level of activity in a neural medium. DNDD behavior can be useful for first spike latency coding when one is interested to encode the stimulus within a particular range of noise in the system. In fact, a minimum of mean latency among the two maxima might provide a suitable range of intermediate working frequencies at which the mean latency is near to the deterministic case. The similar behavior for the jitter as a function of $f$ (see, e.g., Fig. 3 and 4) indicates an increase in spike precision that might be useful for some specific information tasks requiring spike time reliability.

Finally, we would like to note that the results presented in this work were obtained by considering first, a balance between presynaptic excitation and inhibition resulting in a zero mean fluctuating total synaptic current and, second, a critical driving suprathreshold signal frequency range providing the postsynaptic neuron to operate closely to its spiking threshold. Under these conditions, due to the mechanism explained in Section III. B, we expect that any biological process having capacity to modulate $\sigma_I$ non-monotonically between $\sigma_{I\min}$ and $\sigma_{I\max}$ might give rise to similar NDD and DNDD effects on response latency of a postsynaptic neuron. In this context, a possible extension of our study could be investigating the influence of astrocytic gliotransmission on the emergence and behavior of NDD, since it has been shown that activation of presynaptic receptors by chemicals released by surrounding glia can regulate the mechanism of short term plasticity in an activity dependent manner (see [19]).

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