THE EFFECT OF SYNAPTIC DEPRESSION ON MODEL INHIBITORY NETWORKS


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ABSTRACT. Networks of inhibitory interneurons in the cortex generate synchronous rhythmic oscillations which are believed to critically control brain output. The temporal course of the inhibitory postsynaptic potentials is known to affect this synchronous activity in a variety of ways, in particular its stability and frequency. Here we investigate theoretically the effects of frequency-dependent synaptic inhibition on network dynamics. We show how this short-term synaptic plasticity in the form of synaptic depression confers stimulus-sensitivity on the network, and creates transition regimes between synchronous and asynchronous oscillatory patterns in which bursting patterns and bistability occurs. In this manner, inhibitory networks can add further dimensions to the control of the dynamical patterns produced by the brain.

1 Introduction. It has been several decades since rhythmic, electrical brain activities have been recorded at the scalp in the form of an electroencephalogram (EEG). These activities result from interactions occurring at multiple brain networks that consist of organized assemblies of neurons, and their observation indicates a significant degree of coherence between large populations of neurons. Furthermore, these macroscopic brain rhythms can be quantified and related to behavioural states via their frequency band [33]. However, it remains to be determined how these oscillations arise.
There are two major types of neurons in the brain: principal, excitatory cells and GABAergic, inhibitory cells or interneurons. Together with input fibers and a modulatory system, they form networks that produce the electrical signals recorded in EEGs [32]. It is known that inhibitory cells play key roles in shaping the output of the excitatory neuronal populations and thus in generating brain rhythms [5], [9], [23], [45]. Although the inhibitory cells represent a small fraction of brain cells (about 10-20%), they have extensive axon arbors and are thus able to exert strong and distributed inhibition onto excitatory cells. In this way, they can provide precise temporal structure by phase locking the firing of multiple pyramidal cells via synchronously depressing their activities [5].

The presence of short-term synaptic plasticity (or the fact that synaptic transmission is not mediated by static processes of fixed strength) between neurons in several brain regions has been known for some time and is well-established (e.g., [12], [14], [28], [19], [39]). In recent times, short-term synaptic plasticity has been shown to play essential roles in the normal functioning of the synapse during sensory and motor programs [10], [11], [15], [26], [38], [46]. There are many details to consider in trying to understand the specific ways in which synaptic plasticity might be manifest. For example, synaptic depression, a form of short-term plasticity, can be due to a depletion of synaptic vesicles and/or a desensitization of postsynaptic receptors [17]. However, recent phenomenological models [2], [36] have been able to capture the essence of synaptic transmission between pairs of neurons. In particular, the frequency dependence of the synapse, or the fact that the amount of depression and facilitation seen in the postsynaptic response depends on the particular frequency or pattern of the presynaptic stimulus, has been modelled. These phenomenological models have provided insight into how such dynamic synapses might contribute functionally to neural coding and sensory-motor programs (e.g., [2], [6], [24], [34], [36]).

In this paper we investigate the effects of synaptic depression on the dynamics of inhibitory networks using single self-inhibited and two-cell physiologically-based inhibitory network models. We use both simulations and a heuristic-analytical approach to examine the network dynamics.

2 Model descriptions. We consider a single-compartment model of interneurons that has been formulated recently to replicate salient properties of hippocampal interneurons [43]. We use self-inhibitory
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single-cell networks (as a representative of a synchronously firing population) and two-cell mildly heterogeneous networks.

2.1 Interneuron model. The interneuron model below \cite{8,43} was developed by these authors to investigate the stability of synchronous oscillations under mild heterogeneity in the external drive, $I_{\text{app}}$. From here on we refer to the equations given below (which use a Hodgkin-Huxley formalism \cite{16}) as the White model.

\begin{equation}
C \frac{dV_i}{dt} = I_{\text{app}} - g_{\text{Na}}m_{\infty}^3h(V_i - V_{\text{Na}}) - g_{\text{K}}n^4(V_i - V_{\text{K}}) - g_{\text{L}}(V_i - V_L) - I_s
\end{equation}

where $C$ is the capacitance, $V_i$ is the membrane voltage of cell $i$, $g_{\text{Na}}$, $g_{\text{K}}$, $g_{\text{L}}$ are the maximal conductances of sodium (Na), potassium (K) and leak (L) currents respectively, $n$ is the activation of the K current, $h$ is the inactivation of the Na current ($m$, the activation of the Na current is assumed to be significantly faster than the K activation so that its steady state value $m_{\infty}$ is used), $m_{\infty}$, $n_{\infty}$, $h_{\infty}$ are the steady-state values, $\tau_h$, $\tau_n$ are the time constants for the Na inactivation and K activation respectively, and $I_s$ is the synaptic current (described below).
FIGURE 1: (A) Firing frequency ($f$ in Hz) versus external drive ($I_{\text{app}}$ in μA/cm$^2$) for the White model. (B) Schematic of the synaptic depression model.

The fixed parameters are

$$g_{\text{Na}} = 30 \text{ mS/cm}^2 \quad g_K = 20 \text{ mS/cm}^2 \quad g_L = 0.1 \text{ mS/cm}^2$$

$$V_{\text{Na}} = 45 \text{ mV} \quad V_K = -80 \text{ mV} \quad V_L = -60 \text{ mV} \quad C = 1 \mu\text{F/cm}^2,$$

where $I_{\text{app}}$ is the applied current or external drive and is varied in our simulations. Figure 1(A) shows how the frequency of the individual neuron changes with $I_{\text{app}}$ in this model. We also used the interneuron model developed by [40], and obtained similar results (not shown here).

2.2 Synaptic depression model. The inhibitory synaptic current $I_s$ has the form $I_s = gS(V - V_s)$, where $V_s$ is the synaptic reversal potential, taken as $-75 \text{ mV}$, $g$ is the maximal synaptic conductance and $S$ is the synaptic gating variable. To incorporate synaptic depression in the network we use the model developed in [20], [22], [36]. From here on, this synaptic current model (as given below) will be referred to as the T-M model.

$$\frac{dS}{dt} = U_{\text{SE}}F(V_j)R - \frac{S}{\tau_s} \tag{2}$$

$$\frac{dR}{dt} = \frac{1 - S - R}{\tau_D} - U_{\text{SE}}F(V_j)R \tag{3}$$
where \( V_j \) is the voltage of the presynaptic neuron. The synaptic kinetic function \( F \) is given by

\[
F(V_j) = \frac{1}{1 + \exp(-V_j)}
\]

as used in [43]. Without more explicit notation such as \( S_{2-1} \), the expressions \( S_1, R_1, U_{SE,1} \) and \( \tau_{D,1} \) refer to the kinetic variables and parameters of the synapse that terminates on neuron 1, while \( S_2, R_2, U_{SE,2} \) and \( \tau_{D,2} \) refer to the synapse terminating on neuron 2. Implicit in the above scheme is an activation rate constant \( \alpha \) that is chosen to be equal to 1, as in [43]. As illustrated in Figure 1(B) (for a single self-inhibited network), the variable \( R \) represents the synaptic resource in its recovered state, and \( S \) is the synaptic gating variable, termed the active or effective synaptic resource by Markram and Tsodyks. \( U_{SE} \) stands for utilization of synaptic efficacy and is taken as a parameter here (for its treatment as a continuous variable in the case of synaptic facilitation see e.g. [37]). \( U_{SE} \) can be interpreted as the neurotransmitter release probability, if synaptic depression is a presynaptic process.

\( 1/\tau_s \) is the rate of postsynaptic decay, while \( 1/\tau_D \) is the rate of recovery from synaptic depression. For \( \tau_D \approx 0 \), \( R \) instantaneously equates \( 1 - S \), once the second term on the righthand side of equation (3) vanishes after the passing of the presynaptic spike-peak. In this case equations (2), (3) effectively reduce to the standard equation for synaptic kinetics used in [43]:

\[
\frac{dS}{dt} = U_{SE} F(V_j)(1 - S) - \frac{S}{\tau_s}.
\]

Accordingly, \( \tau_D \approx 0 \) represents the non-depressing synapse.

Table 1 displays kinetic parameters for inhibitory and depressing GABA\(_A\) synapses previously used in inhibitory models and found experimentally at GABAergic synapses. (Note: For the [14] experimental data, we have only included F2 type (i.e., depressing) synapse numbers which these authors found to be the main type and are the ones relevant here. Also, two subtypes of GABAergic synapses—GABA\(_A\),fast and GABA\(_A\),slow—have been identified in electrophysiological studies on the hippocampus [27]). We explore similar parameter values for \( I_{app}, g \) and \( \tau_s \) to those used by [43] to allow comparison.

3 Results. Previous modelling work by Kopell and colleagues [8], [7], [43] has shown that the frequency at which inhibitory networks synchronize depends in distinct ways on intrinsic and synaptic time constants. To summarize this and other works [42], [40], [44]:

1) The network can synchronize if the time constant of postsynaptic
Inhibitory decay, $\tau_s$, exceeds the intrinsic oscillatory period of the individual neuron;

2) The synchrony is stable with respect to (mildly) heterogeneous intrinsic oscillatory periods up to a maximal network period $T$, if $T$ scales linearly with $\tau_s$;

3) The synchrony can hold in a $\gamma$ frequency ($\approx 40 \text{ Hz}$, associated with high cognitive processing) realm with heterogeneity; at low frequencies the temporal dispersion of individual spikes due to input heterogeneity tends to break up any existing synchrony;

4) Regimes can be identified that are predictive of the amount of coherent activity in a heterogeneous network: the “tonic” regime, in which inhibition is weak relative to the excitatory drive to the cells, and the “phasic” regime where $T$ scales linearly with $\tau_s$ and where inhibition can overcome excitation and lead to suppression of activity.

### 3.1 Single-cell networks: A heuristic-analytical approach.

Chow and colleagues [8] showed that inhibitory network behaviour could be analytically understood in single self-inhibited cells via a frequency control equation (FCE). They derived this equation from an integrate-&-fire model, adapted to the White model, thus preserving the physiological character of the period $T$ as a function of intrinsic and synaptic parameters. We modify the FCE by making the synaptic conductance, $g$, a function of $T$ and $\tau_D$ and use the modified FCE as a tool to analyze

<table>
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<tr>
<th>MODEL</th>
<th>$\alpha$</th>
<th>$U_{SE}$</th>
<th>$g$</th>
<th>$\tau_D$</th>
<th>$\tau_s = 1/\beta$</th>
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<tbody>
<tr>
<td>[8]</td>
<td>1 ms$^{-1}$</td>
<td>1</td>
<td>0.2 mS/cm$^2$</td>
<td>$\simeq$ 0 ms</td>
<td>5–50 ms</td>
</tr>
<tr>
<td>[43]</td>
<td>12 ms$^{-1}$</td>
<td>1</td>
<td>0.1 mS/cm$^2$</td>
<td>$\simeq$ 0 ms</td>
<td>0–30 ms</td>
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<table>
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<tr>
<th>EXPERIMENT</th>
<th>$\alpha$</th>
<th>$U_{SE}$</th>
<th>$g$</th>
<th>$\tau_D$</th>
<th>$\tau_s = 1/\beta$</th>
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<tr>
<td>[20]</td>
<td>0.1–0.95</td>
<td>–</td>
<td>200–800 ms</td>
<td>$\approx$ 10 ms</td>
<td></td>
</tr>
<tr>
<td>[14]</td>
<td>1 ms$^{-1}$</td>
<td>0.25</td>
<td>0.49</td>
<td>706</td>
<td>8.3</td>
</tr>
<tr>
<td>[30]</td>
<td>$\pm 0.13$</td>
<td>$\pm 0.41 \mu \text{S}$</td>
<td>$\pm 405 \text{ ms}$</td>
<td>$\pm 2.2 \text{ ms}$</td>
<td></td>
</tr>
<tr>
<td>[4]</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>$\approx 10–50 \text{ ms}$</td>
</tr>
<tr>
<td>[18]</td>
<td>–</td>
<td>–</td>
<td>0.63 sec</td>
<td>$\approx 2 \text{ ms}$</td>
<td></td>
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### TABLE 1: Model and Experimental Synaptic Parameters.
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the frequency control of the self-inhibitory network with a depressing synapse.

Assume that the self-inhibitory unit periodically. In this equilibrium state the accumulated postsynaptic current at a depressing synapse is constant over successive interspike intervals. We use the FCE, equation (29) of [8],

\[ \tilde{I}_{\text{app}}(1 - \exp(-\tilde{T})) - 1 = \tilde{g}(\tilde{T}) \frac{\tilde{\tau}_s}{\tilde{\tau}_s - 1} (\exp(-\tilde{T}/\tilde{\tau}_s) - \exp(-\tilde{T})) \]

and modify it with an expression for the rate-dependent amplitude of the asymptotic postsynaptic current developed by Abbott and colleagues [2], [25]:

\[ \tilde{g}(\tilde{T}) = \tilde{g}_0 \frac{1 - \exp(-\tilde{T}/\tilde{\tau}_D)}{1 - d \exp(-\tilde{T}/\tilde{\tau}_D)} . \]

In the above equations \( \tilde{I}_{\text{app}}, \tilde{g}, \tilde{\tau}_s, \tilde{\tau}_D \) and \( \tilde{T} \)—the firing period of the neuron—are rescaled parameters to fit an integrate-&-fire model of the physiological neuron. We use symbols with tilde’s to denote the scaled parameters and symbols without tilde’s to represent the White model physiological parameters (i.e., no scaling), to avoid confusion when referring to the analytical or numerical computations in this paper. (Note: In [8] their symbols with tilde’s refer to the unscaled parameters (i.e., physiological model parameters).) \( g_0 \) stands for the maximal synaptic conductance. - \( d \in [0, 1] \) modulates the extent to which the recovery rate of a depressing synapse \( \tau_D \) influences the FCE (no influence for \( d = 1 \), maximal influence for \( d = 0 \)).

If we assume that \( \tilde{\tau}_D \gg \tilde{T} \) and \( d = 0 \), then we can approximate the above two equations to obtain a modified FCE (mFCE):

\[ \tilde{I}_{\text{app}}(1 - \exp(-\tilde{T})) - 1 = \tilde{g}_0 \frac{\tilde{\tau}_s}{\tilde{\tau}_s - 1} \frac{\tilde{T}}{\tilde{\tau}_D} (\exp(-\tilde{T}/\tilde{\tau}_s) - \exp(-\tilde{T})) . \]

Let \( I_{\text{app}}, g, \tau_s, \tau_D \) and \( T \) denote the parameters and period using the White model, equation (1), i.e., the unscaled model physiological parameters. Then the rescaling scheme (as done in [8]) for the approximation by the FCE reads

\[ \tilde{I}_{\text{app}} = \frac{I_{\text{app}} + I_r}{I_T} \tilde{g}_0 = \frac{g_0}{g_T} . \]

\[ \tilde{\tau}_s = \frac{\tau_s}{\tau_m} \tilde{\tau}_D = \frac{\tau_D}{\tau_m} \tilde{T} = \frac{T}{\tau_m} . \]
To study the impact of synaptic depression on frequency control in the mFCE, equation (6), we choose parameter values $I_r = 2$, $I_T = 1.5$, $\tau_m = 12$, $g_T = 0.1$ in the rescaling scheme above. These values are similar to those selected in Figures 2A–C of [8]. Here, the mFCE serves an illustrative and heuristic purpose—to get a first idea of the impact of synaptic depression on frequency control in the inhibitory network. Therefore, only a qualitative correspondence to the periods obtained using the White model should be expected. Choosing $I_{\text{app}} = 1 \mu A / \text{cm}^2$, $g_0 = 1 \text{ mS / cm}^2$, and neglecting the term $\tilde{r}/\tilde{r} = 1$ for simplicity, we obtain:

\begin{align}
    r(\tilde{T}) &= 10 \cdot \frac{\tilde{T}}{\tilde{r}_D} \cdot (\exp(-\tilde{T}/\tilde{r}_s) - \exp(-\tilde{D})) \\
    l(\tilde{T}) &= 1 - 2 \exp(-\tilde{T})
\end{align}

as the right- and left-hand side of equation (6), respectively. The intersection point of $l(\cdot)$ and $r(\cdot)$ is the period given by the mFCE.

3.2 Single self-inhibitory network exhibits two regimes. We now make use of the framework developed above. The solutions of $\tilde{T}$ derived from the mFCE, equation (6), imply that synaptic depression imposes a transition in the dependency of the firing period on the synaptic decay time constant. Figure 2 shows the period, $\tilde{T}$, versus the synaptic decay time constant, $\tilde{r}_s$. Upon introducing and increasing the synaptic depression time constant, $\tilde{r}_D$, the linear ("phasic") relation splits up into an almost constant domain and a linear domain; for large values of $\tilde{r}_D$, the relationship is almost constant ("tonic") over the whole range of $\tilde{r}_s$. "Phasic" and "tonic" are used here to keep consistent with the terminology introduced by [43]. Note that the mFCE predicts the existence of a bistable regime (for $\tilde{r}_D = 15$ in Figure 2), in which two solutions coexist, one of which is sensitive with respect to changes in $\tilde{r}_s$, whereas the other one is not. This is illustrated later using the White model.

This division of regimes can be explained by considering that the effect of an increase in $\tau_s$ on the period $T$ is twofold: Let $R$ be the synaptic reservoir variable averaged over the period $T$ and choose $\tau'_s > \tau_s$. If, in a first step, $T_1$ denotes the period associated with $\tau'_s$ and $R$, we clearly have $T_1 > T$ by prolonged inhibition. The time $T_1 - T$ permits the synapse to recover more from depression, leading to a reservoir variable $R_1 > R$. This, in turn, enhances the inhibition beyond the effect implied by $\tau'_s > \tau_s$ alone: If $T_2$ denotes the period resulting from both effects of an increase in $\tau_s$, we obtain: $T_2 > T_1 > T$. In this relation, the right-hand inequality represents the prolonged inhibition,
FIGURE 2: Period ($\tilde{T}$) versus synaptic decay time constant ($\tilde{\tau}_s$) relationship with changing synaptic depression (in rescaled parameters) according to equations (9) and (10). The solutions $\tilde{T}$, as dependent on $\tilde{\tau}_s$, are shown for three different values of $\tilde{\tau}_D$, as indicated: For $\tilde{\tau}_D = 10$ ($\tau_D \approx 100\text{ ms}$) the $\tilde{\tau}_s - \tilde{T}$ relation changes from being almost constant to a linear dependency upon increasing $\tilde{\tau}_s$. For $\tilde{\tau}_D = 15$ ($\tau_D \approx 200\text{ ms}$), the intersection points of $r(\cdot)$ and $l(\cdot)$ lie on an S-shaped curve. For $\tilde{\tau}_D = 40$ ($\tau_D \approx 500\text{ ms}$), the period is independent of $\tilde{\tau}_s$ over the physiological range ($\tau_s < 70\text{ ms}$).
while the left-hand inequality represents the recruitment of inhibition. In the almost constant (“tonic”) domain both effects $T \rightarrow T_1$ and $T_1 \rightarrow T_2$ are negligible. At moderate values of $\tau_s$, however, the synapse recovers sufficiently so as to make the effect of any further increases in $\tau_s$ being felt by the postsynaptic neuron: $T$ becomes sensitive to $\tau_s$ and the $\tau_s/T$-relation enters the linear (“phasic”) domain.

3.3 Sensitivity profiles change with synaptic depression. The sensitivity of a model neuron with respect to the applied current is usually represented by the stimulus-frequency diagram. Model neurons are classified as either Type I or Type II, depending on whether the periodic activity starts with zero (saddle-node bifurcation) or positive (Hopf bifurcation) frequency upon increasing the external stimulus, $I_{app}$, beyond the threshold of action potential initiation [30]. The White model used here is of Type I. To capture adaptation and accommodation, the functional corollaries of synaptic depression, we use the *stimulus-elasticity of the frequency* ($f$), which we simply term the elasticity, defined as:

$$\text{Elas}(f, I_{app}) = \frac{df}{dI_{app}} \cdot \frac{I_{app}}{f}.$$  

In other words, maximal elasticity values imply that the largest frequency response is obtained for a minimal stimulus change. The elasticity is closely related to variables used in psychophysical descriptions of perceptual adaptation, such as the Weber-Fechner law and this significance has been noted [2].

We now use our mFCE described above to investigate the stimulus-sensitivity of the frequency. We choose $I_r = 0.7$ (in the rescaling scheme, other parameters the same) and rewrite equation (6) as:

$$\frac{I_{app} + 0.7}{1.5} \cdot (1 - \exp(-T))$$

$$- 10 \cdot \frac{T}{\tau_D} \cdot (\exp(-\frac{T}{\tau_D}) - \exp(-T)) - 1 \equiv 0.$$  

(12)

Here all parameters except $I_{app}$ are rescaled parameters of the mFCE (equation (6)). It is easy to see that $\frac{df}{dI_{app}} \frac{I_{app}}{f} = -\frac{dT}{dI_{app}} \frac{I_{app}}{T}$ holds for $f = 1000/T$. Using the implicit function theorem we obtain:

$$\text{Elas}(f, I_{app}) = \frac{2I_{app} \left(1 - \exp(-T)\right)}{3T \left(\exp(-T) \left(\frac{2I_{app} + 0.7}{2} + \frac{I_{app}}{1 - 0.7} \right) + \exp(-\frac{T}{\tau_D}) \cdot 10 \cdot \frac{T}{\tau_D} \cdot (\frac{T}{\tau_D} - 1)\right)},$$
Elasticity tells us about the profile of sensitivity of a particular system (in our case, inhibitory networks) over a range of incoming stimuli. Using our mFCE we can investigate the dependence of the elasticity profile on $\tau_D$. The time constant $\tau_D$ can be thought of as a phenomenological control parameter for synaptic depression: The higher the time constant, the lower the steady-state postsynaptic current. Using equation (3.3), we illustrate in Figure 3 what the mFCE predicts for the dependence of the sensitivity on $\tau_D$. It can be seen that $\tau_D$ “allocates” the maximally sensitive response of the neuron to different regions of the external current. For low $\tau_D$ ($\approx$ modest synaptic depression) the sensitivity peaks at high values of $I_{\text{app}}$—in this range equation (12) determines a solution of about $T = 2$. In the employed rescaling scheme this corresponds to a frequency of approximately 40 Hz. For higher $\tau_D$, e.g., for a doubling of $\tau_D$ (meaning more synaptic depression), the sensitivity peaks at lower value of $I_{\text{app}}$. At this peak solutions of about $T \approx 2.7$, which correspond to a period of $\approx 30$ Hz after rescaling are obtained.

3.4 Synaptic depression confers network stimulus-sensitivity.

Let us now return to the White model to examine the effect of synaptic depression. For any given exterior current $I_{\text{app}}$ above firing threshold the frequency of the self-inhibitory neuron is reduced as compared with the free neuron (Figure 4(A)). Note that self-inhibition changes the concave stimulus-frequency ($I_{\text{app}} - f$) relation into a nearly linear one. If synaptic depression is now included in the synapse, a range of convexity is introduced into the stimulus-frequency relation (Figure 4(A) ii)–iv). This is because at low input currents and low frequencies the inhibitory synapse recovers completely between two subsequent spikes, and a large time constant $\tau_s$ prevents incremental increases in $I_{\text{app}}$ from being felt by the neuron. At higher values of the applied current $I_{\text{app}}$ further increases enhance the frequency as a result of two effects:

1) the higher excitatory drive due to $I_{\text{app}}$;

2) the reduction of the self-inhibition induced by any individual spike in a train due to synaptic depression—that is, the inhibitory synaptic impact flattens out at an asymptotic value.

The neuron enters the convex realm in the $I_{\text{app}} - f$ curve, as decreases in $I_s$ sufficient to release the neuron from inhibition are transferred from the tail of the inhibitory current’s decay curve to its steeper parts by synaptic depression. Thus, synaptic depression endows the self-inhibitory neuron with a high stimulus elasticity (as defined by equation (11)).
FIGURE 3: Stimulus-sensitivity changes with synaptic depression. Using a heuristic-analytic approach, the elasticity, $\text{Elas}(f, I_{\text{app}})$, is determined for two different synaptic depression time constants. $\tau_s = 2$ ($\tau_s \approx 25\text{ ms}$) and $\tau_D = 10$ or 20 ($\tau_D \approx 120$ or 250 ms, respectively).
FIGURE 4: Transition domains in the self-inhibitory unit using the White model. (A) Firing frequency ($f$ in $Hz$) versus injected current ($I_{app}$ in $\mu A/cm^2$). i) without synaptic depression; free: without inhibition ($g = 0 mS/cm^2$); with self-inhibition: $g = 1 mS/cm^2$, $U_{SE} = 0.5$; $\tau_s = 10 ms$ and $\tau_D = 50 ms$. ii--iv) with self-inhibition and synaptic depression for $g = 1 mS/cm^2$ and $U_{SE} = 0.5$ and parameter values for $\tau_s$ and $\tau_D$ in ms as indicated. (B) Transition domains for variations in synaptic decay ($\tau_s$) and depression ($\tau_D$) time constants in the self-inhibitory unit. Changes in the period, $T$, are plotted versus the synaptic time constants (both in ms). Notice the presence of almost constant and linear domains as predicted using a heuristic-analytical approach (see Figure 2). Other parameters are $I_{app} = 2 \mu A/cm^2$, $g = 1 mS/cm^2$, $U_{SE} = 0.5$. 

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FIGURE 5: Elasticity in the self-inhibitory unit using the White model. (A) Dependence of the elasticity profile on $\tau_D$ (ms). The y-axis shows $I_{app}$ on a logarithmic scale, where the increment $d\ln(I_{app}) := \frac{d\ln(I_{app})}{dI_{app}}$ is fixed at 0.25, i.e. each point represents an increase in $I_{app}$ by 25% of the preceding value. $I_{app}$ begins at the bifurcation value of spike initiation, which is set to 1 in determining the increments $I_{app}^{(k+1)} - I_{app}^k$ logarithmically. Elas$(f, I_{app})$ is approximated by $4 \cdot \frac{f(I_{app}^{(k+1)}) - f(I_{app}^k)}{f(I_{app}^k)}$, where $I_{app}^k$ adopts the values $-0.62, -0.37, -0.06, 0.33, 0.82, 1.43, 2.19, 3.14, 4.33 \mu A/cm^2$ successively for $k = 0 \ldots 8$ and $I_{app}^0 = 5.82 \mu A/cm^2$. Other parameters are $g = 1 \text{ mS/cm}^2$, $\tau_s = 50 \text{ ms}$, $U_{SE} = 0.5$. (B) Dependence of the elasticity profile on $\tau_s$ (ms). $I_{app}$ is increased as in (A). Other parameters are $g = 1 \text{ mS/cm}^2$, $\tau_D = 200 \text{ ms}$ and $U_{SE} = 0.5$. 
Figure 4(B) displays the dependence of the firing period $T$ on both synaptic time constants, $\tau_s$ and $\tau_D$, in our model simulations. Without synaptic depression, i.e. for $\tau_D \approx 0$, the $\tau_s - T$ relationship is linear. Upon introducing synaptic depression into the model, i.e. choosing $\tau_D$ equal to several hundred msec, the relation splits up into two separate domains of almost constant and linear relationships as predicted using a heuristic-analytic approach (see above). In essence, the reason for these different domains is due to the twofold effect described earlier. For example, a smaller $\tau_D$ allows a larger $R$ to develop in the given time which in turn allows a larger inhibitory current to be produced and to be able to affect network period (i.e., a linear $\tau_s - T$ relationship for lower $\tau_D$ values).

The elasticity of the neuron with a depressing self-inhibitory synapse is shown in the sensitivity profiles over a range of $\tau_s$ and $\tau_D$ values (in Figures 5(A) and (B)). The peak in the back of the figure is due to a threshold phenomenon for the type-I neuron. The simulations indicate that with synaptic depression, i.e. for $\tau_D > 0$, a second peak emerges in the $\text{Elas}(f, I_{\text{app}})$ profiles. In Figure 5(A), we see that for low values of $\tau_D$ this peak is located at high values of $I_{\text{app}}$ and vice versa, as indicated using the heuristic-analytical approach (see Figure 3). For fixed $\tau_D$, Figure 5(B) shows that an increase in $\tau_s$ allocates the elasticity peak to regions of higher $I_{\text{app}}$. The elasticity peaks reflect the changing shapes of the $I_{\text{app}} - f$ curve in Figure 4(A). Consider a fixed intrinsic frequency, as set by $I_{\text{app}}$ in our model. Then we see that a transition from an almost constant to a linear $\tau_s - T$ relationship occurs, as synaptic depression is introduced into the model. Specifically, Figure 4(B) shows that the threshold value in $\tau_s$, beyond which the period $T$ depends linearly on $\tau_s$, varies with the time constant $\tau_D$. The latter determines the duration and thus the severity of synaptic depression. If $\tau_s$ is held fixed and $I_{\text{app}}$ allowed to vary, the $I_{\text{app}} - f$ curve assumes an S-like shape producing an elasticity peak for intermediate $I_{\text{app}}$ values. As Figures 4(A) (iii), (iv) and 5(A) show, this elasticity peak shifts to lower values of $I_{\text{app}}$ for higher synaptic depression, because the domain of frequency over which synaptic depression weakens inhibition is reached earlier with higher values of $\tau_D$. A similar reasoning explains the rightward shift of the elasticity for higher values of $\tau_s$ which is displayed in Figures 4(A) (ii), (iii) and 5(B). These results clearly demonstrate that synaptic depression endows the neuron with a higher overall sensitivity that can be fine-regulated or allocated to different stimuli realms by a proper choice of temporal kinetic parameters.
3.5 Linking to two-cell heterogeneous networks. [43] previously showed that consideration of the single self-inhibited unit is predictive of the stability of synchronous oscillations in mildly heterogeneous networks (defined as $\leq \approx 5\%$ intrinsic frequency differences). Simulations of two-cell mutually inhibitory networks with mild heterogeneity indicates that predictive information from the single cell network is still possible, but in a different way.

The immediate effect of synaptic depression consists in diminishing the inhibition and is equivalent to mapping $g$-values from the phasic realm of the unit without synaptic depression towards low, i.e., “tonic”, values for the unit with synaptic depression. Figures 6(A) and (B) can be seen to constitute a phasic relationship between $\tau_s$ and $T$ for a mildly heterogeneous two-cell network with synaptic depression. In Figure 6(C), an alternating bursting dynamical behaviour emerges, and Figure 6(D) shows one cell suppressing the other. Figure 6(E) displays the realm of synchronous activity in the mildly heterogeneous two-cell network over the same range of parameter values for $g$, $\tau_s$, $\tau_D$ and $I_{\text{app}}$ as in Figure 4(B) (where self-inhibitory network simulations were done with the White model). The linear domain (“phasic”) of the self-inhibitory unit corresponds roughly to the domain of suppression in Figure 6(E) whereas the almost constant domain (“tonic”) corresponds to synchronous activity in the two-cell network. This is surprising only on the first view: A $g$-value, whose transform under equation (5) lies in the phasic domain of the self-inhibitory unit using the White model, can be associated with synchronous activity in the two-cell network with synaptic depression (as in Figures 6(A) and (B)). The almost constant domain in Figure 4(B) is indeed indicative of a regime in which the only heterogeneity of both neurons is given by $I_{\text{app},1}$, $I_{\text{app},2}$. The linear domain in the $\tau_s/T$-relationship of the self-inhibitory unit with depression, by comparison, is a domain of added heterogeneity in that the dynamics of the inhibitory current becomes significant in the frequency control. In other words, the linear part in the $\tau_s - T$-relationship represents a domain of higher sensitivity with respect to $\tau_s$, compared to the almost-constant domain. Thus, the heterogeneity in $I_{\text{app},1}$, $I_{\text{app},2}$ is mild only with respect to a given frequency. The twofold effect of an increase in $\tau_s$, as discussed above, transfers the absolute difference $I_{\text{app},1} - I_{\text{app},2}$ towards lower activity levels of both neurons, where the same difference entails largely different relative effects on both neurons and destabilizes synchrony (when synaptic depression is present). This explains why the linear domain seen with the self-inhibitory unit corresponds approximately to a domain of suppression and the almost-constant domain to synchronous...
activity.

Therefore, the informative value of the self-inhibitory unit with synaptic depression lies in the prediction and localization of a transition domain with enhanced sensitivity, that separates domains of synchrony and suppression in the heterogeneous two-cell network with synaptic depression.

3.6 Alternating bursting and bistability with synaptic depression. The heuristic-analytic approach employed above indicates that a region of bistability can occur in our inhibitory network models with synaptic depression. Furthermore, in linking an understanding of the single self-inhibited unit with two-cell networks above (Figure 6), we find that alternating bursting patterns can occur. We now illustrate this more fully using the White model.

Heterogeneity, as modeled by $I_{\text{app},1} \approx I_{\text{app},2}$, in which we have fixed and low absolute differences $I_{\text{app},1} - I_{\text{app},2}$ is assumed. With this heterogeneity, we find that network dynamics in which one cell tonicly fires and suppresses the other (see Figure 6(D)) gives way to synchronous firing (see Figures 6(A) and (B)) at higher values of $I_{\text{app},1}$ and $I_{\text{app},2}$ since there is now a smaller difference in intrinsic frequencies. This is shown in Figure 7. We further find that the transition between synchronous firing and suppression is bistable, as illustrated in Figure 7, where ‘I’ refers to dynamical behaviour in which one cell fires and suppresses that other, ‘II’ refers to synchronous firing, and ‘III’ refers to an alternating bursting pattern (also shown in Figure 6(C)).

This bistability gives rise to a frequency transition zone (FTZ) which is characterized as follows: Upon increasing $(I_{\text{app},1}, I_{\text{app},2})$, the network passes through a zone of alternating bursting dynamics before switching to synchrony (Figure 7 (i)), whereas the reversed paradigm of decreasing $(I_{\text{app},1}, I_{\text{app},2})$ values induces the network to switch directly from synchrony to suppression (Figure 7 (ii)). The FTZ is given by those pairs $(I_{\text{app},1}, I_{\text{app},2})$ for which the entries in the diagrams of Figure 7 (i) and 7 (ii) differ. The bistability is shown in the voltage versus time plots of Figure 7 (iii) where ‘b’ and ‘d’ patterns derive from the same parameter set. It is interesting to note that with synaptic depression the alternating bursting pattern occurs in the direction of increasing rather than decreasing values of the excitation parameter $I_{\text{app}}$. By this, synaptic depression endows the inhibitory network with a desynchronizing mechanism in its output, that is effective for increasing excitation levels, but it tends to conserve an already existent network synchrony with respect to decreases in the excitation level.
FIGURE 6: Two-cell network with mild heterogeneity and synaptic depression using the White model: Dependence of the synchrony and dynamics on synaptic time constants. (A)–(D): Voltage traces $V$ (in mV) vs. time (in ms) for $\tau_s = 10, 30, 50, 70$ ms respectively; (E) displays the period $T$ (in ms) of the two-cell network and the type of dynamics along the two time constants $\tau_D$(ms) and $\tau_s$(ms). Dark columns represent phase-locked synchronous firing of both neurons as in (A) and (B), shaded columns represent alternating bursting as in (C), and white columns stand for lack of synchrony or suppression as in (D). Other parameters are: $I_{\text{app},1} = 2.1 \mu\text{A/cm}^2$, $I_{\text{app},2} = 2 \mu\text{A/cm}^2$, $g = 1 \text{mS/cm}^2$, $U_{SE} = 0.5$ and $\tau_D = 300$ ms in (A)–(E).
FIGURE 7: Bistability in the two-cell network with synaptic depression. Using the White model with synaptic depression; $g = 1.5 \text{mS/cm}^2$, $U_{SE} = 0.5$, $\tau_D = 300 \text{ms}$. Throughout we set $I_{app,2} = I_{app,1} = 0.1 \mu\text{A/cm}^2$, where $I_{app,1}$ is shown on the $x$-axis and $\tau_s$ varies from 10 to 50 ms on the $y$-axis in (i)–(ii). (i) $I_{app,1}$ and $I_{app,2}$ are enhanced by $0.5 \mu\text{A/cm}^2$ every 2000 ms. (ii) $I_{app,1}$ and $I_{app,2}$ are diminished by $0.5 \mu\text{A/cm}^2$ every 2000 ms. In both cases the dynamical behaviour is recorded after transients. (iii) Voltage (mV) versus time (ms) plots of both neurons for the $I_{app}$-path shown below and indicated by $a, b, c$ and its reverse $c, d, e$ in (i) and (ii), respectively, $\tau_s = 20 \text{ms}$. Boxed regions illustrate the various patterns after transients have died away.
4 Discussion. We have investigated the impact of synaptic depression on the synchronicity and firing frequency in self-inhibited single cell and mutually inhibitory two-cell network models with mild heterogeneity. With the self-inhibited single cell network model (also representing a homogeneous network of synchronized cells), we showed that the sensitivity of the network (i.e., its elasticity as determined from the $f-I_{app}$ curve) can be understood by the two temporal determinants of the synaptic kinetics, $\tau_s$ and $\tau_D$. Specifically, as the time to recovery from synaptic depression increases, the required input stimulus to invoke maximal sensitivity decreases. We also showed that the single cell network behaviour predicts for two-cell networks the approximate location of where dynamical patterns would switch from synchronous to suppressive behaviour and where bistability with more complex dynamics, alternating bursting, could occur. In other work [13], we describe this alternating bursting pattern more fully as well as the situation of non-mild heterogeneity.

Work by [2], [36] shows that synaptic depression provides a mechanism by which a neuron can become sensitive to a wider frequency range of input afferents. In other words, depressing synapses can detect changes in presynaptic frequency over several orders of magnitude effectively due to its frequency-dependent responses. This aspect is captured in our study as the elasticity of frequency with respect to stimulus. Indeed, we would like to suggest that the observed dependence of the elasticity profile on the time constants of synaptic kinetics, $\tau_s$ and $\tau_D$, functionally “allocates” inhibitory networks with different synaptic kinetics as detectors to different excitation levels. One such inhibitory network detects a change in the excitation level of its maximal sensitivity by losing synchrony at particular frequencies, another one—with a different combination of $\tau_D, \tau_s$—does the same at a different excitation level. This elasticity or sensitivity allocation may complement the organizing principles of GABAergic interneurons in terms of frequency-dependent synaptic kinetics recently found by [14] and termed “GABA-groups”.

Temporal coherence (or synchrony) is a well-recognized brain activity that possibly contributes to neuronal coding [29]. Given the myriad of intrinsic and synaptic heterogeneities and details that brain networks have, the mechanisms of generating this coherence or synchronous firing are likely to be complex and diverse. Theoretical mechanisms determined in smaller networks can be helpful in understanding dynamical behaviours in larger networks. For example, the seminal work by [41] that used a two-cell mutually inhibitory network to show that synchrony was possible in purely inhibitory networks, given appropriate balances.
between intrinsic and synaptic properties has been invoked in larger network studies such as [35].

4.1 Closing remarks and future work. Synaptic plasticity is the basis of several modelling studies addressing learning and memory in neuronal networks [1], and there is a recognized need for stable activity. Interactions between short and long-term plasticity have been shown to be present [21], [31], [46] so that studies such as these become even more significant for an understanding of information coding in the brain. Furthermore, the observed desynchronizing effect of the burst-generating dynamics (Figures 6 and 7) deserves closer attention in a future study, focusing on the possible protective effects of inhibitory networks with synaptic depression against epileptiform activity elicited by rising excitation levels.

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