Intracortical augmenting responses in networks of reduced compartmental models of tufted layer 5 cells

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Abstract: Augmenting responses (AR) are characteristic recruitment phenomena that can be generated in target neural populations by repetitive intracortical or thalamic stimulation and that may facilitate activity transmission from thalamic nuclei to the cortex or between cortical areas. Experimental evidence suggests a role for cortical layer 5 in initiating at least one form of augmentation. We present a three-compartment model of tufted layer 5 cells (TL5) which faithfully reproduces a wide range of dynamics in these neurons that previously has been achieved only partially and in much more complex models. Using this model, the simplest network exhibiting AR was a single pair of TL5 and inhibitory (IN5) neurons. Intracellularly, AR initiation was controlled by low-threshold Ca$^{2+}$ current ($I_T$) which promoted TL5 rebound-firing, while AR strength was dictated by inward-rectifying current ($I_h$) which regulated TL5 multiple-spike firing and also prevented excessive firing under high-amplitude stimuli. Synaptically, AR was significantly more salient under concurrent stimulus delivery to superficial and deep dendritic zones of TL5 cell than under conventional single-zone stimuli. Moreover, slow GABA$_B$-mediated inhibition in TL5 cells controlled AR strength and frequency range. Finally, a network model of two cortical populations interacting across functional hierarchy showed that intracortical AR occurred prominently upon exciting superficial cortical layers either directly or via intrinsic connections, with AR frequency dictated by connection strength and background activity. Overall, the investigation supports a central role for TL5-IN5 skeleton network in low-frequency cortical dynamics in vivo, particularly across functional hierarchies, and presents neuronal models that facilitate accurate large-scale simulations.

Keywords: neocortex; short term plasticity; voltage dependent conductance; gain; layer 5 pyramidal cell; compartmental model.
INTRODUCTION

Augmenting responses (AR) are the transient increases in cortical neuronal depolarization and activity under repetitive stimulation (Purpura 1964a,b) either directly or elsewhere and are thought to be important in synaptic facilitation and particularly neuronal recruitment because they provide a resonance-like behavior in the targeted neuronal population. Augmentation has been reported to occur selectively in vivo within specific stimulus frequency bands in the alpha ~10 Hz (Steriade et al. 1998), possibly wider ~3–15 Hz frequency range (Timofeev et al. 2002; Chrochet et al. 2006). Oscillations at these frequencies are thought to play a role in long term potentiation (Werk et al. 2005) and depression in sensorimotor cortex of rats (Werk et al. 2006). While considered earlier to be of a mainly thalamic origin (Morison and Dempsey 1943), it became clear that augmenting responses (AR) can be generated cortically (Morin and Steriade 1981, Castro Alamancos and Connors 1996a,b) as well as thalamically (Steriade et al. 1998, Gernier et al. 1998) because AR could occur after thalamic lesioning by stimulating the white matter of callosally-projecting fibers (Nunez et al. 1993).

While the mechanisms underlying augmentation in the thalamus have been well studied and modeled earlier (Steriade et al. 1998; Bazhenov et al. 1998a,b), augmentation generated within the cortex itself has remained less obvious. Suggested mechanisms for intracortical AR include NMDA facilitation coupled with GABA depression (Metherate and Ashe 1994), short term synaptic depression in cortical neurons (Timofeev et al. 2002), or intrinsic properties of layer 5 pyramidal cells (Castro-Alamancos and Connors 1996a). A proposed interplay between excitatory and inhibitory short term synaptic depression in initiating a particular form of AR was studied in a network model in (Howueling et al. 2001). An earlier preliminary model by the authors using two compartment models of layer 5 cells suggested an important role of intrinsic oscillatory properties of these cells in AR (Karameh et al. 2006), but principally because of the comparatively simple models used for TL5 cells, it stopped short of detailing...
the key properties that generate this phenomenon within neural networks. The current work presents a detailed simulation model that provides greater clarity regarding the contribution of various cortical mechanisms to AR as well as the conditions under which it is propagated between cortical areas. Based on this model, we support the impression that AR initiation and prominence depend on intrinsic membrane properties as well as local inhibition and excitatory input topography of layer 5 pyramidal neurons. We suggest how these elements interact to affect augmentation features such as strength and frequency range and provide testable predictions in realistic networks.

Large layer 5 pyramidal cells of the neocortex have been studied extensively and their anatomy, neurophysiology, connectivity and electric dynamics are probably among the best understood of the neuronal populations in the neocortex, mainly due to their large size and ease of manipulation. While the cell bodies of these tufted layer 5 (TL5) neurons (Markram 1997) lie in lower layer 5, their dendritic arborizations extend across all layers and their apical tufts reach the cortical surface layer 1. In addition to having access to the local populations of these laminae, TL5 cells are contacted by corticocortical inputs as well as thalamic inputs from nonspecific (second order or higher order) thalamic nuclei in the superficial layer and specific (first order of lower order) thalamic inputs in the middle layers of the cortex (Cauller et al. 1998; Mountcastle 1998; Zhu and Zhu 2004).

A review of the salient properties of TL5 cells and their interaction network has been presented in an earlier study (Karameh et al. 2006). Importantly, the firing properties of TL5 cells are dependent upon intrinsic ionic currents as well as the afferent input spatial topology. First, large layer 5 pyramidal neurons possess a high gain amplification property under minimal input excitatory states, such as during sleep (Sanchez-Vives and McCormick 2000). This amplification is due both to intrinsic characteristics of layer 5 cells, mainly low threshold Ca\(^{2+}\) currents \(I_T\) (Thomson and Deuchars 1997; Chen et al. 1996; Sayer et al. 1990; de la Pena
and Geigo-Barrientos 1996; Wang and Goldman-Rakic 2004) as well as to network properties of reduced inhibitory gain control in at least one subpopulation of TL5 cells (Schubert et al. 2001, 2006; Hefiti and Smith 2000). Intrinsic oscillations within 7–10 Hz have been demonstrated experimentally (Spain et al. 1991) and simulated in simple models (Jones et al. 2000; Karameh et al. 2006).

Second, TL5 cells possess a dynamic firing switch that determines whether single spikes (regularly spiking mode) or bursts of 2–4 spikes (bursting mode) are produced. This switch is governed by the input synaptic patterns to three distinct dendritic regions (i) the apical tuft (zone A), (ii) the central dendrites (zone C) and (iii) the basal dendrites (zone B). While electrically distant, these compartments have active generation mechanisms (possibly $\text{Ca}^{2+}$, Williams and Stuart 1999; Larkum et al. 1999a,b; Schwindt and Crill 1999) which amplify synaptic inputs under in vivo conditions to greatly change the cell firing dynamics (Larkum et al. 2004; Nettleton and Spain 2000). In addition, TL5 firing patterns and the zone A-zone B interaction is controlled by intrinsic currents (inward current $I_h$, Burger et al. 2001, 2003), as well as neuromodulating currents (Wang and McCormick 1993).

Finally, TL5 cells form a strong network of intralaminar and interlaminar connections (Bannister 2005; Schubert et al. 2001; Markram et al. 1997) which could extend from 100 µm (cortical column) to around 1–3 mm (local cortical assembly, Karameh et al. 2006).

While detailed multicompartmental models of TL5 cells are available (Rhodes and Gray 1994; Rhodes and Llinas 2001), their complexity can quickly render parameter value determination for large network simulations impractical. In addition, new important data on the in vivo dynamic properties of these cells have since become available including those regarding apical dendritic amplification of firing (Larkum et al. 2004) and the effect of inward $I_h$ currents in decoupling synaptic input zones (Burger et al. 2003). Finally, it is of independent scientific interest to determine the minimal complexity model sufficient to capture physiological phenomena. This identifies those neurophysiological mechanisms
that are of greatest functional significance for generating such phenomena. Accordingly, the current investigation attempts to reproduce the cortical contribution to the augmenting response using three compartment models of TL5 neurons that incorporate both newly identified and previously known properties of these cells.

The developed TL5 cell model was used to study the conditions that lead to emergence of augmenting responses in networks of excitatory and inhibitory neurons in layer 5 of the cortex. It is shown that repetitive cortical stimulation can induce a stereotypical AR at the simplest level of a single neuronal pair consisting of one TL5 cell coupled with a local inhibitory cell (IN5). Based on a series of simulations, the salient neurophysiological mechanisms to control AR were found to be the following. First, at the intracellular ionic current level, it is demonstrated that the low-threshold calcium current $I_{\text{Ca}}$ is critical for AR initiation because it underlies rebound firing in TL5 cell starting from a hyperpolarized state, and as such has a similar role to the $I_{\text{Ca}}$ currents observed in thalamocortical cells under thalamically-generated AR (Bazhenov et al. 1998a). More interestingly, the simulations suggest that the inward rectifying current $I_{\text{h}}$ in different dendritic zones plays a dual role in AR generation and over-excitability protection in TL5 cells: it both prevents AR occurrence under inadequate stimulation patterns as well as limits AR strength and cellular firing under excessively large stimulation inputs. Second, at the synaptic topography level, AR is shown to be affected by the dendritic location of a stimulus. That is, an input stimulus arriving to both the apical dendritic and basal dendritic zones of a model TL5 cell facilitate a much more prominent augmentation in this cell than an input stimulating the basal dendritic zone alone even if the earlier occurs at considerably smaller stimulus strengths. Finally, it is suggested that AR is controlled by slow inhibition arriving from the local IN5 neuron to the TL5 cell. The effectiveness of slow inhibition is mainly derived from its ability to produce prolonged hyperpolarization of membrane voltages that in turn allow for $I_{\text{Ca}}$ currents to de-inactivate causing
rebound firing in TL5 cells and initiating an augmenting response. While slow inhibition could in principle be provided by slow GABA-A type synapses, the model suggests that GABA-B type synapses provide a more natural augmentation at a wider range of stimulus frequencies (3-12 Hz), mainly due to the sub-linear increase in GABA-B associated hyperpolarization with increasing stimulus frequency. In addition, the model suggests that enhanced recruitment of fast- and slow-inhibition onto TL5 cells lead to complementary roles: slow GABA-B mediated inhibition can lead to stronger augmentation at increasingly wider frequency ranges (3-16 Hz) while fast GABA-A mediated inhibition can limit the augmentation strength and the range of stimulus frequencies under which it occurs (8-10 Hz).

Because augmentation has been demonstrated experimentally to occur between distant cortical sites (Nunez et al. 1993), we next asked the question of how augmentation can be transferred within cortical tissue itself. This was simulated using two simple interacting networks of excitatory and inhibitory layer 5 cells that represent two cortical areas interconnected across levels of cortical functional hierarchy (feedforward/feedback connections or higher-order and lower-order areas, Felleman and Van Essen, 1991; Medalla and Barbas 2006). In particular, we studied the conditions under which stimulating the higher-order area can cause AR in both areas and we examined the dependence of the simulated AR features (strength and frequency ranges) on various model parameters such as connection topology and background activity. Principally, the model suggests that AR is achieved over a wide frequency range (3-12 Hz) whenever the apical dendrites of TL5 cells in both upper and lower areas, which lie in the superficial cortical layers, are properly depolarized. That is, an augmenting response similar to that observed experimentally requires that the feedback connections into superficial layers be intact or that the external stimulus has proper access to those layers. A loss of such input is seen to limit AR to only low frequency range (< 10 Hz) as well as reduce augmentation strength (spikes/stimulus shock). Another
key finding of the model asserts that increasing the background activity to \textit{in vivo} levels can increase the gain of apical dendrites and render superficial layer inputs (such as those from higher-order or attention centers) even more potent in controlling both the ability to augment at high frequencies (11-14 Hz) as well as the strength of the ensuing augmentation, particularly at low (3-8 Hz) stimulation frequencies.

Finally, the implications and predictions of the simulated AR and its relationship to other forms of AR are discussed. In particular, there are likely to be important differences between AR generated in fully-connected cortical networks \textit{in vivo} and those in isolated cortical slices.

\textbf{METHODS}

\textbf{TL5 cell model}

A number of models for cortical layer 5 pyramidal neurons have been developed ranging in complexity from single compartments representing simple action potential firing (Jones et al. 2001) to tens of compartments representing detailed dendritic geometries and ionic concentrations (Rhodes and Gray 1996, Rhodes and Llinas 2001). Here, we attempt to summarize the critical features of TL5 neurons in three compartments: apical dendritic (zone A), proximal or central dendritic (zone C) and basal dendritic-somatic segments (zone B) as seen in Figure 1A, 1B. We test the possibility that the basal dendrites and soma may collapsed into a single compartment because of their physical closeness and low inter-segment resistance.

Accordingly, this model utilized a three compartment configuration with Hodgkin Huxley ionic channel kinetics. The apical dendritic compartment has the following voltage equation:
The voltage of the proximal dendritic (coupling) compartment is governed by

\[
\frac{dV_d}{dt} = A_d C \left[ g_{L,d} (E_{L,d} - V_d) + I_{\text{ionic}} \right] + I_{\text{syn}} + g_{pd} (V_p - V_d)
\]  

(1)

and the voltage of the somatic compartment

\[
\frac{dV_p}{dt} = A_p C \left[ g_{L,p} (E_{L,p} - V_p) + I_{\text{ionic}} \right] + I_{\text{syn}} + g_{ps} (V_s - V_p) + g_{ps} (V_s - V_p)
\]  

(2)

where the per unit area Capacitance of all compartments is \( C = 1 \mu\text{F/cm}^2 \), leakage conductances are \( g_{L,d} = 0.12 \text{mS/cm}^2 \), \( g_{L,p} = 0.08 \text{mS/cm}^2 \), and \( g_{L,s} = 0.05 \text{mS/cm}^2 \), and the leakage potentials are \( E_{L,d} = -73 \text{mV} \), \( E_{L,p} = -74 \text{mV} \), and \( E_{L,s} = -75 \text{mV} \).

The coupling conductances between different compartments are \( g_{pd} = g_{ps} = 0.12 \text{mS} \). \( I_{\text{syn}} \) are the different synaptic currents and will be described later. The somatic area was \( 4.35 \times 10^{-4} \text{cm}^2 \), the proximal area \( A_p = 10^{-4} \text{cm}^2 \), and apical dendritic compartment \( A_d = 2.9 \times 10^{-4} \text{cm} \) which are within range of reported experimental data. The different ionic currents \( I \) are either voltage dependent and have the standard Hodgkin Huxley description as

\[
I_i = g_i m^z h^y (E_i - V)
\]  

(4)

or are calcium-dependent and have the form

\[
I_i = g_i m^z h^y f ([Ca]) (E_i - V)
\]  

(5)

The variables \( m \) and \( h \) are activation and inactivation variables that vary according to

\[
\frac{dz}{dt} = \phi_z \left[ \frac{z - z}{\tau_z} \right]
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\[ z_{\infty} = \frac{\alpha_z}{\alpha_z + \beta_z}, \text{ and } \tau_z = \frac{1}{\alpha_z + \beta_z}. \]  

The temperature factor \( \Phi_z \) is chosen to adjust variables from slice experiments (~24° C) to body temperature (36-37° C, \( \Phi_z = 2.72 \) where needed). The dynamics of activation and inactivation of various ionic currents utilized are described in Tables 1 and 2.

**Figure 1**

The ionic currents in different compartments are as shown in Figure 1A. The data for the existence and densities of different channels are collected from various experiments and modeling sources as follows.

*Table 1, Table 2, Table 3*

1. **Fast Sodium current** \( I_{\text{Na}} \), and **delayed rectifier potassium current** \( I_{\text{Kdr}} \). The channel kinetics of both currents were taken from (Destexhe et al. 2001 – that were in turn were based on Traub et al. 1991). The channel densities in the soma were chosen such that a single action potential reaches about 37 mV and has rising and falling slopes of +400 mV/s and -130 mV/s (comparable to Rhodes and Llinas 1994). Sodium channel densities in the proximal and distal compartments were chosen to initiate BAC firing and \( \text{Ca}^{2+} \)-Na action potential complex (Larkum and Sakmann 2001) in the distal compartment, respectively. No \( I_{\text{Kdr}} \) was added to the distal compartment as these were not detected in layer 5 experiments, but rather fast \( I_{\text{A}} \) like currents (Korngreen et al. 2000; Bekkers 2000), discussed below.

2. **High threshold Calcium current** \( I_{\text{Ca}} \). Experiments have shown that \( \text{Ca}^{2+} \) action potentials (AP) play an integral role in initiating bursting in layer 5 cells (Larkum et al. 1999a,b; Larkum et al. 2001). Activation kinetics were taken from (Rhodes and Llinas 2001). In addition, a more accurate depiction of the calcium current using the Goldman-Hodgkin-Katz model was utilized as in (Migliore et al. 1995; Jaffe et al. 1994). Channel
densities were chosen to initiate a Ca\(^{2+}\) AP that reaches a peak of around 5 mV during a burst and is of duration 20–30 msec (Larkum et al. 2001).

3. **Hyperpolarization activated cation current \(I_h\).** The abundance of this current in dendritic processes and its role in controlling somato-dendritic interaction has been well demonstrated in experiments (Burger et al. 2001, 2003). The channel kinetics for dendritic compartments were thus taken from the aforementioned experiments and have a high density especially in the distal compartment and account for its depolarization. While \(I_h\) has not been well studied in the soma, experiments clearly show a voltage sag when these cells are hyperpolarized (CastroAlamancos and Connors 1996a; Williams and Stuart 1999). The kinetics of somatic \(I_h\) were taken from earlier work (Bazhenov et al. 1998a) with the activation time constant sped up to account for the fast hyperpolarizing sag observed in the above experiments.

4. **Low threshold Calcium current \(I_T\).** The hyperpolarization activated rebound response of layer 5 cells have been demonstrated in several experiments (Castro-Alamancos and Connors 1996a, Silva et al. 1991; Williams and Stuart 1999), in sensorimotor cortex of rats (Sayer et al. 1990) and cats (Kitagawa et al. 2004), in the guinea pig medial frontal cortex (de La Pena and Geijo-Barrientos 1996, 2000), and in the prefrontal cortical neurons in ferrets where it contributes to cell bursting (Wang and Goldman-Rakic 2004). The channel kinetics and densities were adopted from earlier models of regularly firing layer 5 cells (Jones et al. 2000; Destexhe et al. 2001).

5. **Calcium activated K current \(I_{KCa}\) and calcium dependent after hyperpolarizing current \(I_{AHP}\).** These currents are especially important in dendritic compartments to terminate Calcium action potentials and their kinetics
were taken from the model by Rhodes and Llinas (Rhodes and Llinas 2001). Channel densities were however lower than those reported in Rhodes and Llinas model as $I_{Ca}$ was rectifying (Goldman-Hodgkin-Katz) and is thus of much smaller amplitude at high membrane potentials (near 0 mV) when compared with the ohmic current model (Koch 1999).

6. **Slow inactivating voltage-dependent $K$ current $I_{KS}$**. These channels were studied in layer 5 cells and their kinetics were taken from Korngreen et al. (Korngreen et al. 1999) and sped up to account for temperature difference (experiments were done at 22-25 degrees, and thus $\Phi_z = 2.72$). We included those only in the distal dendritic compartment at densities reported in (Korngreen et al. 2000; Tsay et al. 2002).

7. **Fast inactivating $K$ current $I_A$**. The existence of this current has been reported in layer 5 cells by Korngreen and Bekkers (Korngreen et al. 2000; Bekkers et al. 2000). Channel kinetics were taken from Rhodes and Llinas (Rhodes and Llinas 2001) and were based on (Bekkers 2000). While different experiments point to different channel densities in the dendrites (0.2 to 4mS/cm², we chose an intermediate value of 0.5-2mS/cm².

8. **Muscarinic current $I_M$**. This current was included in the soma and dendrites to produce firing adaptation (observed in Pare et al. 1998; Destexhe et al. 1999). Kinetics and densities were taken from Destexhe (Destexhe et al. 2001).

9. The dynamics of intracellular calcium concentration $[Ca]$ for all compartments are given by a simple first order pump

\[
\frac{d[Ca]}{dt} = -AI_{Ca} + \left[Ca\right]_\infty - [Ca] \tau_{Ca}
\]  
(6)

Where $[Ca]_\infty$ is the equilibrium $Ca^{2+}$ concentration $[Ca]_\infty = 0.05\muM$. For the somatic compartment, the constants $A = 30$ and $\tau_{Ca} = 80$ msec are chosen
such that a single action potential will create an $\text{Ca}^{2+}$ influx of 0.25 µM (Helmchen et al. 1996). Similarly for the proximal dendritic zone, $A = 12$, $\tau_{\text{ca}} = 50$ msec. For the apical dendritic compartment, $A = 3.36$, $\tau_{\text{ca}} = 30$ msec, and $[\text{Ca}]_o = 2$ mM (for maximum increase of $\text{Ca}^{2+}$ Concentrations of around 0.3µM after a $\text{Ca}^{2+}$ action potential as given in (Larkum et al. 1999b).

The distribution of various ionic conductances along the three compartments is shown in Table 3.

**Simulated TL5 cell firing dynamics**

The TL5 cell model demonstrates several firing properties reported in the literature.

1. The cell responds with a single action potential in response to somatic depolarization, as would be delivered by excitatory inputs from cortical layers 4,5 (Larkum et al. 1999a). This is shown in Figure 2A. At sufficient distal dendritic depolarization (an EPSP-like threshold current injection of a maximum 2.8nA as in (Larkum et al. 1999a), a $\text{Ca}^{2+}$ AP is initiated in the distal dendritic compartment, which in turn causes a full burst event of 2–3 spikes in the soma (Fig. 2B). Critically, in the presence of a back-propagating somatic action potential (BAC firing), the threshold for $\text{Ca}^{2+}$ distal dendritic AP is reduced dramatically (to around 0.5 nA). This threshold reduction occurs if the time between somatic and dendritic injections is within 10-15 msec, as reported experimentally (Fig. 2C). The membrane voltage in the three cellular compartments is shown in Figure 2D. It is seen that the proximal compartment provides a pathway between somatic and distal compartments with an intermediate voltage response. This compartment is important in controlling bursting due to the abundance of hyperpolarization activated current $I_h$ (as seen below).
Figure 2

2. The cell model replicates the rebound firing in TL5 cells as reported by (Castro-Alamancos and Connors 1996a). This is shown in Figure 3A. When the cell membrane potential is brought to sufficiently negative levels, hyperpolarization-activated cation current $I_h$ is active which produces observed experimental current sags at these negative voltage levels. Upon release from hyperpolarization, low threshold Calcium current $I_T$ is activated allowing the cell to rebound and possibly fire 1−2 action potentials (but not a full burst which is expected upon distal dendritic depolarization) and is potentially controlled by hyperpolarization-activated current $I_h$ below.

Figure 3

3. According to the recent results by (Burger et al. 2001, 2003) the hyperpolarization activated current $I_h$ acts to separate the somatic and distal dendritic compartments so that burst firing will only occur when a coincident activation of both of the latter compartments occurs. Accordingly, these experiments show that blockage of this current $I_h$ in the dendrites will remove this separation and allow burst-firing to occur. This effect is replicated in the current model and is shown in Figure 3B. In particular, when the $I_h$ current is blocked in the proximal dendritic compartment, the rebound firing of TL5 cell is able to cause the somatic action potential to fully propagate into the distal compartment causing a $Ca^{2+}$AP there, which subsequently propagates forward and induces a somatic burst.

4. The model is able to reproduce the increase in the response gain associated with dendritic current injection under *in vivo* like conditions as reported by Larkum and coworkers (Larkum et al. 2004). The simulated TL5 model results are shown in Figure 4A (compare with Figure 1C of Larkum et
The cell model was simulated under the same stimulation conditions reported experimentally. In particular (Tuckwell 1988), an in vivo-like noisy current was generated with a mean ($\mu_{dc}$), standard deviation ($\sigma$) and correlation length $\tau$ according to the following equation

$$I(t + dt) = I(t) + \frac{\mu_{dc} - I(t)}{\tau} dt + \sigma G_i \sqrt{\frac{2dt}{\tau}}$$

(7)

where $I(t)$ is the injected current and $G_i$ is a random number taken each time step from a Gaussian distribution with mean 0 and standard deviation of value 1.

**Figure 4**

With a somatic injection alone, a mean current to rate transfer gain of slope 41.01 AP/s/nA was produced (line fit $41.014I_s - 14.252$, Fig. 4A, filled circles, n=5 runs.). With distal dendritic current injection $I_d$ alone, an increased mean gain of 65.7 is produced (line fit $65.66I_d - 56.4$, Fig. 4A open circles). In addition, and in the presence of a constant dendritic injection of $I_d = 0.75$ nA, the mean gain associated with somatic injection is increased to 56 AP/s/nA (line $56.06I_s + 9.53$, Fig. 4A, squares). These values fall within experimental range and provide a verification of the nature of apical and basal dendritic zone interactions.

5. Finally, the model qualitatively replicates the burst firing behavior observed with increasing dendritic depolarization. This is shown in Fig. 4B. At low dendritic current injection that is sufficient to evoke Ca$^{2+}$ AP, repetitive burst firing can be induced at low frequency. As this current is increased, the rate of burst-firing is increased up to 12-14 Hz. With further current increase, a switch to regular firing occurs due to inactivation of high threshold calcium current $I_{Ca}$. This behavior is in agreement with the experimental recording by Schwindt and Crill (Schwindt and Crill 1999, cf. Figure 1).
Augmenting response models

Functional and anatomical evidence

The current work is based on the cortical AR as reported by (Castro-Alamancos and Connors 1996a). Here, repetitive stimulation of the Ventrolateral (VL) thalamic nucleus produced augmentation in the rat sensorimotor cortex where the cortical response increased in amplitude for few stimulus cycles and was stable thereafter.

At the cellular level, the above experiments showed that a single thalamic stimulus created a characteristic intracellular response: a fast EPSP followed by a strong hyperpolarizing and long-lasting IPSP (400-500 msec) in cortical layer 5 pyramidal cells (see Figure 1 in that reference). If subsequent thalamic stimuli were delivered during the hyperpolarizing phase within 100-200 msec, layer 5 cells displayed an increased firing from 1 spike to 2-3 spikes within few cycles. In addition, in vivo dendritic recordings around the depth of layer 3 (cf. Figure 4 in same reference) showed that large depolarizations occurred with subsequent stimuli and followed the initial firing in layer 5. Finally, somatic recordings in some layer 5 cells showed similar dynamics to the TL5 cells modeled here: burst firing in response to depolarizing currents and rebound depolarization following an injected hyperpolarizing current. Such cellular level observations will be replicated by the single TL5-IN5 pair in the Results section.

At the network level, experimental evidence suggests that the ability of electrical stimulation to elicit AR within an area of cortex depends critically on the particular afferent fiber systems that become activated. A set of thalamic stimulation experiments (Castro-Alamancos and Connors 1996b) showed that stimulation of the VL, but not the VPL thalamic nucleus, produced cortical augmentation. Importantly, VL thalamocortical connections target mainly layer 5 and layer 1 of the cortex and thus follow higher order, nonspecific thalamic, intralaminar or
matrix nuclei projection patterns. On the other hand, VPL connections target the middle cortical layers 3,4 and thus follow the lower order, specific thalamic or core nuclei projection patterns (see reviews in Sherman and Guillery 1998; Guillery and Sherman 2002 and references therein). Thus, the relative efficacy of VL stimulation in augmenting activity within the sensorimotor cortex is seen to be generally consistent with its probable effectiveness in activating simultaneously zones A and B of cortical TL5 neurons as described above.

In regard to intracortical communication, we note that there are well recognized, distinct topologies of inter-areal excitatory connections that likely have relevance to cortico-cortical AR. In particular, two trans-hierarchical connectivity patterns are similar to those of thalamocortical connections. A cortical area closer to the sensory input (lower order in the functional hierarchy) sends feedforward or ascending projections in a focused manner (cortical column scale~ 0.1 mm) to the middle layers (layers 3,4) of another cortical area further along the sensory processing stream (higher in the hierarchy). In turn, higher order areas typically sends feedback or descending projections to lower order areas in a more diffuse manner (several cortical columns ~ 0.3-1 mm) avoiding middle layers and targeting superficial and deep layers (layers 1 and 5) there. This characteristic architecture is reviewed in (Fellman and Van Essen 1991; Mountcastle 1998) and has been revealed by various other experiments (in somatosensory cortex: Cauller et al. 1998, in visual cortex: Nowak et al. 1997, Domenici et al. 1995; reviews in Thomson and Lamy 2007, Bannister 2005, Callaway 1998; in frontal areas: Medalla and Barbas 2006). Recent evidence indicates further that the feedforward-feedback (or ascending-descending) projection patterns can also be seen in primates between frontal and associational areas and can be predicted by the distinct densities of neurons in target and origin areas Medalla and Barbas 2006) as well as by synaptic morphologies (Germuska et al. 2006).
Accordingly, the core of our model’s inter-areal AR network (Fig. 1C) is a minimal canonical circuit wherein monosynaptic connections between TL5 cells of two hierarchically related areas are assumed (see Supporting Material section for more details). The model does not exclude the possibility that transfer of excitation between TL5 populations in different areas could in fact occur via disynaptic connections using intermediate neural populations of either area. For example, with feedforward (ascending) connections targeting the middle layers of Ctx-H, it is possible that the activity of TL5\textsubscript{L} neurons arriving to layer 4 in Ctx-H is either transmitted directly to TL5 neurons (Manns et al. 2004, as assumed here) or is alternately transferred first to layer 3 pyramidal cells (L3) in Ctx-H and then projected down to TL5\textsubscript{H} cells via the strong descending pathway from L3 to TL5 (Thomson and Bannister 1998; review in Schubert et al. 2007). In the latter case, the assumed inter-areal delays (between Ctx-H and Ctx-L) will increase but do not change the overall AR behavior because this phenomenon, first, is principally dependent on the dynamics of local TL5-IN5 circuits and, second, occurs at a much slower time scale (75-300 msec) compared with synaptic delays incurred (2-6 msec). Example simulations on additional inter-areal delays due to intermediate populations as well as evidence on direct/disynaptic connections are given in Supplementary Material section.

**Interneuron IN5: evidence on firing behavior and model**

The dynamics of a network of TL5 neurons are modulated strongly by local inhibitory interneurons in cortical layer 5 (IN5). In this study, the latter were taken to be the ubiquitous local fast spiking (FS) inhibitory neurons that are found in layer 5 (Schubert et al. 2000; Spain et al. 1991; Castro Alamancos and Connors 1996a). IN5 neurons were modeled as single compartments of fast spiking cells with Hodgkin-Huxley dynamics as given earlier by (Wang and Buszaki 1996) and given in the Supplementary Material section. In the model, IN5 are assumed to produce clusters of high-frequency (burst-like)
spikes upon stimulation. The exact nature of these cells is not emphasized in the current model. It is only required that these cells are able to produce GABA-B slow inhibition in TL5 cells shortly after stimulus arrival (Castro-Alamancos and Connors 1996a; Thomson and Destexhe 1999; Benardo 1994) which, in turn, implies that these cells likely produce high-frequency multiple spikes upon stimulation. Specifically, Thomson and Destexhe 1999 showed that slow GABA-B inhibition, which occurred in one-in-five monosynaptic connections they studied in layer 5 in rat S1, was properly activated only by high-frequency (bursting) presynaptic spiking activity and not by single-spike presynaptic firing. Anatomically, evidence suggests that such bursting interneurons could be nested basket cells (NBC, see Makram et al. 2004; Thomson et al. 1996). Functionally, evidence shows that fast spiking (FS) cells can fire bursts of 2-3 action potentials at 40-300 Hz due to spontaneous EPSPs (Zhu and Connors 1999). Importantly, the latter experiments show that single whisker stimulation, when causing a suprathreshold EPSP in FS cells, often triggers a brief burst of two to three action potentials (Figure 6B in Zhu and Connors 1999). Accordingly, and to produce the characteristic slow IPSP observed in AR experiments (Castro-Alamancos and Connors 1996a), the current model assumes that external inputs of the feedback type (accessing superficial and middle layers) are able to directly trigger multiple spikes in IN5 neurons. Another (remote) possibility for the origin of slow inhibition is the activation of GABA-B receptors by GABA spillover (Scanziani 2000), which implies that IN5 neurons actually represent the synchronous activity of many interneurons possibly interconnected by electrical synapses (Beierlein et al. 2000) and connected by facilitating synapses to TL5 cells (Angulo et al. 2002). The current model does not adopt this GABA spillover hypothesis, however, primarily due to the work of Thomson and Destexhe which shows that spillover need not necessarily occur to account for GABA-B responses, but rather that high frequency presynaptic interneuron activity is sufficient (Thomson and Destexhe 1999).
TL5-IN5 pair model

The model of TL5-IN5 interaction is shown in Figure 1B. In general, an input stimulus contacts the TL5 cell at the apical dendritic zone A with strength $g_d$ and the basal dendritic zone B with strength $g_{stim}$. Simulating the action of intracortical fiber bundles activated by exogenous electrical stimulation, a delivered stimulus is assumed to target the TL5 cell with an AMPA excitatory synapse of strength $(g_{stim}, g_d)$ and the associated inhibitory cell IN5 with an AMPA synapse of strength $g_{stim,i}$ (Bazhenov et al. 1998a). Note that no NMDA synapses were included here since the AR phenomenon was shown to exist when these receptors are blocked (Ketamine anesthesia).

A stimulus train arrives with varying frequencies, referred to in terms of the inter-stimulus interval (ISI) that is denoted by $T_p$ seconds. TL5 and IN5 are reciprocally connected with AMPA connection $g_{ei}$ to IN5 and both fast GABA-A $g_{ie,a}$ and slow GABA-B $g_{ie,b}$ connection to TL5 (Castro-Alamancos 2004; Schubert et al. 2001, 2006).

All connections were represented as fraction from a maximal conductance density given by $g_{ampa,max} = 100$ nS, $g_{gaba-a,max} = 100$ nS and $g_{gaba-b,max} = 60$ nS. We refer to this fraction as the per unit value (p.u.) of a conductance $g_s$; that is,

$$g_s \text{ (actual value)} = g_s \text{ (per unit value)} \times g_{s,\text{max}} \text{ (maximal value)}.$$

Two area network model

The full two area AR network is modeled as a network of eight TL5-IN5 pairs that is simulated as two groups of neurons in two distinct areas Ctx-H and Ctx-L (Fig. 1C). The two areas are assumed to belong to different levels within a hierarchical sensory system. In particular, Ctx-H is considered to be higher in the hierarchy (further away from the sensory input), and Ctx-L lower (e.g. Areas 18 and 17,
respectively in the visual cortex; Nowak et al. 1997). Within a single area, connections are reciprocal, symmetric and form a first order chain with circular boundary conditions. That is, the $j^{th}$ cell $TL5_j$ cell makes AMPA synaptic connections to its associated interneuron $IN5_j$ (strength $g_{ei}$), and to its first neighboring pairs, $TL5_{j-1}$, $TL5_{j+1}$ (strength $g_{ee}$), and $IN5_{j-1}$, $IN5_{j+1}$ (strength $g_{ei1}$). Similarly $IN5_j$ contacts $TL5_j$ with strength $g_{ie,a}$ (GABA-A) and $g_{ie,b}$ (GABA-B). It also contacts neighboring $TL5$ cells $TL5_{j-1}$, $TL5_{j+1}$ with strengths $g_{ie1,a}$ and $g_{ie1,b}$.

Corticocortical connections between the two areas are as follows (Fig. 1C): the $j^{th}$ $TL5$ cell in Ctx-L, denoted as $TL5_{j,L}$ forms AMPA excitatory connections with all the $TL5$ cells in Ctx-H $TL5_{k,H}$ at the basal zone B of these cells (strength $g_{LH,s}$) and the associated interneuron (strength $g_{LH,i}$). Feedback connections from $TL5$ cells in area Ctx-H to area Ctx-L are initiated in $TL5_{k,H}$ and contact all $TL5$ cells in area Ctx-L, $TL5_{j,L}$, at the basal zone B (strength $g_{HL,s}$) and at the apical zone A ($g_{HL,d}$). It also contacts the interneuron $IN5_{j,L}$ with strength $g_{HL,i}$. All corticocortical excitatory connections varied in strength by ($\pm15\%$) from nominal value. All connections were varied as fraction (per unit p.u.) from a maximal connection given by $g_{ampa,max} = 100 \text{nS}$, $g_{gaba-a,max} = 100\text{nS}$ and $g_{gaba-b,max} = 75\text{nS}$. Synaptic delays of 1 msec were added for local connections and 1.5 msec for corticocortical connections. Simulations were not sensitive to the exact values of such delays, given the time scale of the phenomenon under consideration.

Connection strengths: Unless otherwise mentioned, various synaptic and stimulus connection strengths for the eight cell model used are as shown in Table 4 (in per unit values). Individual changes of some parameters to simulate different scenarios were conducted and will be indicated then.

In vivo currents: To simulate in vivo conditions while varying the membrane potential of $TL5$ cells, all these cells were subjected to random in vivo like current (Tuckwell 1988 see below in results) with a nominal value for the mean of $\mu_{dc} = 0.2\text{nA}$ (baseline) and variance of 0.05 nA (see equation 7). This leads to membrane potential fluctuations with a mean of around -65 mV.
Synaptic connection models

Fast excitatory AMPA and fast inhibitory GABA-A synaptic currents follow the dynamics modeled in (Bazhenov et al. 1998a). In particular, each current is given by

$$I_{syn} = \left[ o \right] g_{syn} (E_{syn} - V)$$  \hspace{1cm} (8)

Where $[o]$ is the fraction of the open channels whose dynamics follow an exponential decay according to

$$\frac{d [o]}{dt} = a (1 - [o]) [T] - b [o]$$  \hspace{1cm} (9)

$$[T] = A \theta(t_0 + t_{max} - t) \theta(t - t_0)$$

where $\theta(x)$ is the Heaviside function and $t_0$ is the time of receptor activation. The model parameters were chosen to follow the synaptic traces produced in (Bazhenov et al. 1998a). In particular, $t_{max} = 10^{-4}$ sec, and $A=10^3$; the reversal potentials were $E_{AMPA} = 0$ mV and $E_{GABA-A} = -75$ mV. The constants $a$, $b$ were chosen as $a=0.29$ sec and $b=0.18$ sec for AMPA synapses, and $a=6.5$ sec and $b=0.16$ sec for GABA-A synapses.

Slow inhibition GABA-B currents were modeled after Destexhe (Destexhe et al. 1998) using a two states model:

$$I_{gaba-b} = g_{gaba-b} (E_k - V)$$

$$g_{gaba-b} = g_{gaba-b, max} \frac{4}{s^4 + K_d}$$

$$\frac{dr}{dt} = K_1 (1 - r) [T] - r_{gaba-b} r$$  \hspace{1cm} (10)

$$\frac{ds}{dt} = K_2 r - K_3 s$$

According to this model $g_{gaba-b}$ maximally activates with high frequency (burst-
like) inputs. Here, $E_k = -95 \text{ mV}$, $K_d = 100 \mu \text{M}$ and $K_1 = 9 \times 10^4 \text{ M}^{-1} \text{s}^{-1}$. GABA-B inhibition is maximally effective in layer 5 when TL5 cells are firing in the bursting mode. For all simulations, $\tau_{\text{gaba-b}} = 1.2$, $K_2 = 180$, $K_3 = 34$, giving a rise time constant of $\approx 60 \text{ msec}$ and a decay time constant of $\approx 300 \text{ msec}$ (as in Destexhe et al. 1998; Destexhe et al. 2001).

Hypotheses to be tested by model simulation

In light of the elemental neuronal physiology embodied in the models described above, several hypotheses regarding the network physiology of AR appear to be reasonable:

H1: Augmenting responses in TL5-IN5 networks are considerably facilitated by stimulation patterns that target both the superficial and deep layers of the cortex (layers 1 and 5), thus promoting interaction between zone A and zone B of TL5 cells. Under this hypothesis, it may be expected that a stimulus delivered to zone B produces less AR (spikes/stimulus shock) than a stimulus delivered bilaminarly to both zones A and B.

H2: Augmenting responses emerge in TL5-IN5 network as a rebound firing in TL5 neurons due to activation of low threshold calcium current $I_T$. Under this hypothesis, it may be expected that reducing the ionic channel density will lead to the cessation of AR in TL5 neurons.

H3: Augmenting responses are closely controlled by the hyperpolarization activated current $I_h$ principally because of its suppression of the reinforcing excitatory interaction between dendritic zones A and B in TL5 neurons. Under this hypothesis, it may be expected that an increase in ionic channel density of $I_h$ will reduce AR.
H4: Augmenting responses in TL5-IN5 network are dependent on slow GABA-B mediated inhibition of TL5 cells that allows prolonged hyperpolarization of TL5 soma. Under this hypothesis, it may be expected that both AR initiation and strength are controlled by levels of GABA-B inhibitory currents produced in TL5 cells.

**Questions to be answered by model simulation**

Certain potentially interesting quantitative features of AR are not predicted by the elemental neuronal physiology in an obvious way. These are summarized as questions to be addressed by network model simulations:

Q1: How do changes in ionic channel kinetics affect augmentation? Does slower activation/inactivation of I_T and activation of I_h in TL5 model cell modify the nature of the resultant augmentation, and how?

Q2: Can excessive increases in the input stimuli applied to a TL5 cell soma overcome the AR-suppressing effect of the inward current I_h on this cell?

Q3: What are the main roles of fast and slow inhibitory synaptic currents in AR? IN5 neurons have a strong modulatory effect on TL5 neurons. Thus it would be expected that these neurons affect the character of AR. In particular, how sensitive is the obtained augmentation to changes in the recruitment of IN5 neurons, the strength of fast and slow inhibition in TL5 cells and the decay time of GABA-B current?

Q4: Can the slow inhibition necessary for AR be mediated by other than GABA-B receptors? Since experimental evidence shows that some slow inhibitory events recorded in cortical pyramidal cells are mediated by a slow type of GABA-A receptors (Sceniak and MacIver 2008), could AR be equally well produced by these receptors?
Q5: Since AR depends on bilaminar input to cortical TL5 networks (hypothesis H1), can augmentation be produced in cortico-cortical networks which obey hierarchical connections? If so, how sensitive is the observed AR to details of connection topology and underlying background activity?

Q6: What are the factors that affect the frequency range over which AR can be elicited?

RESULTS

Augmenting response in a single TL5-IN5 pair

A simple interaction protocol between a TL5 cell and an associated inhibitory interneuron can produce the basic augmentation phenomenon (Karameh et al. 2006, see also Methods section). In particular, a regular train of electric current pulse stimulus delivered to both cells ($g_{stim,T}$, $g_{stim,i}$, Fig. 5A) with an inter-stimulus interval (ISI) given by $T_p=0.1$ sec (or 10 Hz) is able to produce a series of fast EPSP-slow EPSP sequences that give way to multiple TL5 spikes within a few stimulus shocks as shown in Figure 5B and qualitatively replicates the main experimental results on cortical AR (Castro-Alamancos and Connors 1996a). For the simulations presented hereafter, AR is considered to occur in a TL5 cell only if this cell produces two or more spikes with each and every subsequent arrival of the stimulus. This definition is particularly important to emphasize entrainment of the cell with each stimulus shock, particularly for AR occurring at high alpha-range frequencies (> 10 Hz) as will be seen later.

The model’s mechanism of augmentation underlying Figs. 5B, 5C can be explained as follows: with the initial stimulus delivered at time $t_0$ seconds, the TL5 cell produces a single spike while IN5 produces three or more spikes. This burst-like activity in IN5 is particularly effective in activating GABA-B synapses on TL5 basal dendritic compartment and produces a long lasting hyperpolarization (see...
methods section for evidence on the ability of IN5 to produce multiple spikes). With the second stimulus arrival \((t_0 + 0.1\) seconds later), more GABA-B activity is produced by the IN5 neuron, which now fires both due to the stimulus and the TL5 activity, pushing the TL5 cell further into hyperpolarized voltage levels. With the third stimulus arrival at \((t_0 + 0.2)\) sec, the TL5 membrane potential is sufficiently hyperpolarized such that it is able to produce a rebound response upon receiving excitation. Whether this rebound response results in a single spike (hence no AR) or in multiple spikes (AR) depends on the pattern in which the stimulus is delivered to TL5, as follows.

**Figure 5**

First, in the case when \(g_{\text{stim},T}\) is divided across both basal (B) and apical (A) dendritic zones \((g_{\text{stim},T} = g_{\text{stim}} + g_d = 5.5, g_{\text{stim}} = 5, g_d = 0.5; g_{\text{stim},i} = 5\) \(\mu\text{u}\)), the apical input produces sufficient dendritic depolarization which coincides with the backpropagating rebound response (first somatic spike) to produce a \(\text{Ca}^{2+}\) AP in the dendrite and a somatic burst of 2-3 action potentials (Fig. 5B,C top traces).

Second, in the case when \(g_{\text{stim},T}\) is delivered only to the basal dendritic zone B and even at stronger amplitudes \((g_{\text{stim}} = g_{\text{stim},T} = 7\) \(\mu\text{u}, g_d = 0; g_{\text{stim},i} = 7\) \(\mu\text{u}\)), the rebound response is not able to invade the dendritic zone to produce \(\text{Ca}^{2+}\) AP (Fig. 5C, dashed line), and hence only single spikes are produced in TL5 with no augmentation demonstrated (Fig. 5B, 5C bottom traces).

We next tested whether the existence of input to apical dendritic zone A is necessary for AR. Here, the AR was quantified for a wider range of stimulus strengths to zone B when zone A was not excited. In a baseline reference case of simultaneous zone A, zone B excitation \((g_{\text{stim}} = 6 = g_{\text{stim},i}, g_d = 0.4\) \(\mu\text{u}\)), augmentation (bursting) is produced after 4 input shocks (6 spikes, dash-dot line, Fig. 5D) and is prominent after 13 input shocks (24 spikes, dashed line Fig. 5D). We subsequently removed the apical input \((g_d = 0)\) and increased zone B input relative strength from 1 to 1.8 fold (across 11 trials, starting from \(g_{\text{stim}} = 6.4 = g_{\text{stim},i}, g_d = 0\)). The amount of
augmentation was measured in terms of the total number of TL5 neuronal spikes that occurred after 4 and after 13 shocks. It is noted that, when only zone B received input, no AR was achieved after 4 shocks (empty squares Fig. 5D), and AR only started after 15% increase from 6.4 after 13 shocks (filled squares Fig. 5D). It was only when $g_{\text{stim}}$ was increased by 1.8 fold ($g_{\text{stim}} = 11.5 \text{ p.u.}$) that AR equivalent to the reference case occurred. Hence, it is apparent that while basal inputs could in principle produce augmentation at excessively high stimulus strengths, apical dendritic inputs introduce a gain that is very effective in producing AR at well below the stimulus strength levels required if only the basal input is stimulated alone.

Figure 6

Role of intrinsic currents in AR:

1) Low threshold calcium current $I_T$:

- **Presence of $I_T$ is critical for AR initiation**: Since rebound response following hyperpolarization is principally a resultant of the activation of low threshold calcium current $I_T$, we predicted that reducing the associated ionic conductance $g_T$ will lead to the cessation of AR, and therefore studied the effect of changing its maximal conductance on the ability of the cell to produce AR. This is shown in Figure 6A. Here, we varied the stimulus strength to basal zone of TL5 cell ($g_{\text{stim}}$) while keeping the inhibition strength and apical input strength constant ($g_{\text{stim,i}} = 3 \text{ p.u.}$, $g_d = 0.4 \text{ p.u.}$). We also varied the maximal conductance ($g_T$) of $I_T$, starting from the reference value chosen to provide rebound depolarization levels similar to that seen in experiments (Table 3). Indeed, it is noted that, for > 20% reduction in the value of the maximal conductance $g_T$ in the proximal and somatic
compartment, the cell was unable to produce a rebound response at the original stimulus strength $g_{\text{stim}} = 6$ p.u. Similarly, at a 60% reduction in $g_T$, a significant increase in stimulus strength (at least $g_{\text{stim}} = 14$ p.u.) was required to induce rebound activity. In both cases, however, no augmentation occurred (number spikes produced = number of stimulus shocks, contour line 13 in Fig. 6A). Any reasonable augmentation resulted only when the $I_T$ ionic channel density is at least 90% of its reference or baseline value. Conversely a 25% increase in $g_T$ leads to around 1.5 fold increase in augmentation. Thus, it is apparent that AR requires a minimal threshold for $I_T$ ionic channel density below which little or no rebound (hence minimal augmentation) can occur. Beyond this threshold, TL5 produce increasingly strong rebound response and hence more prominent augmentation.

- **Slower $I_T$ inactivation kinetics increase AR frequency range:** We studied the effect of varying the inactivation/activation time constants of the $I_T$ current on the ensuing AR and the frequency range over which it occurs. Simulations showed that as the inactivation variable $h$ of the associated conductance approached its steady state value more slowly (that is, $\tau_h$ is increased in table 2 by a constant factor, see Supplementary Material, Figure S1), the TL5 cell is able to produce more spikes per stimulus cycle as well as produce AR at increasingly lower frequencies (Fig. 6B). These two effects can be explained as follows: First, and following a rebound response, $I_T$ inactivates with a time constant $\tau_h$. Hence, as $\tau_h$ increases, this current inactivates more slowly, which results in larger inward currents during the current stimulus shock and, therefore, leads to more spikes. Second, the increase in the time constant causes larger $I_T$ current residuals after a particular stimulus shock which last for increasingly longer time intervals thus allowing AR at longer and longer inter-stimulus intervals (lower frequencies). As for the activation variable $m$, its time constant $\tau_m$ is normally very small (order of 1ms, here activation was
assumed instantaneous as per Destexhe 2001). Still, it was shown that slower activation does not affect the frequency range of AR but, rather, it increases the number of spikes per stimulus shock (see Supplementary Material, Figure S2).

Figure 7

2) Inward current $I_h$:

- **Presence of $I_h$ controls both AR initiation and strength:** As seen in the TL5 model earlier (Fig. 3B), the hyperpolarization-activated current $I_h$ plays an important role in isolating the basal and apical zones, and hence could have a significant effect on the occurrence of bursting and augmentation. We studied the role of $I_h$ maximal conductance in the TL5 soma $g_{h,soma}$ and proximal dendritic $g_{h,prox}$ compartments on AR, as shown in Figure 7. Here we simulated the variation of AR for $g_{h,prox} \in [0.3] \text{ mS/cm}^2$ and $g_{h,som} \in [0.0.2] \text{ mS/cm}^2$ over three stimulus intensities ($g_{stim} = 5, 7, 9$ p.u.; $g_{stim,i}, g_d$ held constant). It is seen (Fig. 7A, left) that for low intensity $g_{stim} = 5$ p.u., the somatic $I_h$ maximal conductance $g_{h,som}$ principally controls the production of augmentation, regardless of the value of the proximal $I_h$ conductance $g_{h,prox}$ (larger $g_{h,som}$ reduces number of spikes). The proximal conductance $g_{h,prox}$, on the other hand, influences the number of spikes following each stimulus shock. The role of the proximal compartment becomes more apparent for moderate stimulus intensities ($g_{stim} = 7$ p.u.) where, while the cell can produce at least 1 spike/stimulus shock, the number of spikes (strength of AR) decreases with increasing $g_{h,prox}$ (Fig. 7A, middle).

- ** Presence of $I_h$ limits AR with excessively large stimulus shocks:** While lower $I_h$ maximal conductances in TL5 proximal and somatic compartments generally
allow larger AR with increasing strength of stimuli, a rather surprising firing behavior occurs for the intermediate values of these conductances used in the baseline AR model. It is seen in Figure 7A that in the parametric region \((g_{h,\text{som}} \in [0.1, 0.2] \text{ and } g_{h,\text{prox}} \in [0, 2])\), the cell produces less AR at \(g_{\text{stim}} = 9\) p.u. than at the lower intensity \(g_{\text{stim}} = 7\) p.u. That is, the presence of \(I_h\) current is apparently acting as a spike-rate limiter as stimulus intensities become larger. This apparently paradoxical phenomenon is investigated thoroughly in the Supplementary Material section and summarized briefly here. Consider TL5 cell firing and \(I_h\) intensities under two stimulus levels while the maximal conductance levels \((g_{h,\text{som}}, g_{h,\text{prox}})\) are kept fixed. As seen in Figure 7B1, the cell is able to produce bursts (AR) at a low stimulus intensity \(g_{\text{stim}} = 6\) p.u. (red trace) but not at the higher intensity \(g_{\text{stim}} = 9\) p.u. (blue trace). Note that this is not due to any change in inhibition because \(g_{\text{stim},i}(\text{IN5 activity})\) is kept constant. Examining the inward current \(I_h\) (Fig. 7B2, 7B3), one sees that the level of \(I_h\) after the first spike is larger for \(g_{\text{stim}} = 6\) p.u. than that for \(g_{\text{stim}} = 9\) p.u. (asterisk in Fig. 7B3). Figure 7C shows the spike-aligned inward current \(I_h\) with increasing stimulus strength. One again notes a decrease in this inward current with increasing \(g_{\text{stim}}\) (asterisk, Fig. 7C1); however, the total ionic conductance of \(I_h\) is in fact smaller for \(g_{\text{stim}} = 6\) p.u. than for \(g_{\text{stim}} = 10\) and 20 p.u. (asterisk, spike-aligned plots in Fig. 7C2). Large depolarizations associated with larger \(g_{\text{stim}}\) will bring the membrane potential closer to the reversal potential of the \(I_h\) current, thus making \(I_h\) small. Furthermore, fast depolarization associated with larger \(g_{\text{stim}}\) will result in reduced post-spike time intervals over which \(I_h\) can decrease due to deactivation, effectively keeping the total ionic conductance of \(I_h\) large (see Supplementary Materials section for detailed investigation, Figs. S4, S5). Accordingly, larger stimulus levels lead to smaller \(I_h\) currents (and hence less inward depolarizing currents) as well as larger post-spike ionic conductances (and hence more membrane shunting effects), both of which prevent the
generation of additional spikes and the occurrence of augmentation.

- **Slower $I_h$ activation kinetics increase AR strength at high frequencies.** With $I_h$ being a non-inactivating current, we only study the effect of varying its activation time constant $\tau_m$ on the features of AR in the TL5-IN5 pair model. As $\tau_m$ increases, it is expected that $I_h$ would activate more slowly because its activation variable would respond more sluggishly to changes in the membrane voltage. This is verified by simulations that show that, starting from a resting membrane potential in TL5, increasing values of $\tau_m$ result in smaller total ionic conductance of $I_h$, particularly at shorter inter-stimulus intervals. The total effect of slower $I_h$ activation is, therefore, to reduce the effect of $I_h$ in decoupling apical and basal dendritic zones and to produce more spikes/stimulus cycle at high stimulus frequencies (> 12 Hz - see Supplementary Material for details).

3) **Other ionic currents:**

We also studied the effect of the fast inactivating K+ current $I_A$ and the muscarinic current $I_M$ on AR. It turns out that both currents affect the input stimulus strength at which augmentation occurs mainly by controlling the threshold for initiation of Ca$^{2+}$ action potential generation in the apical compartment. These currents, however, do not affect the frequency range of AR or the number of spikes/stimulus shock (See supplementary material for details).

**Role and nature of inhibition in AR:**

1) **Inhibition modifies AR frequency range and strength:**

Because augmentation was principally initiated after a prolonged period of hyperpolarization, we tested the ability of the TL5-IN5 to produce AR over a range of input stimulus frequencies (3-16 Hz) as the slow and fast inhibitory influences of
the IN5 interneuron on TL5 cell were varied. For this purpose, we modified the
strength of the GABA-B and GABA-A synaptic conductances \( g_{\text{gaba-b,max}}, g_{\text{gaba-a,max}} \) respectively. We also modified the proportion of the external stimulus delivered to
the interneuron IN5 (synaptic conductance \( g_{\text{stim,i}} \) in Fig. 5A) relative to that
delivered to the pyramidal cell TL5 (synaptic conductance \( g_{\text{stim}} \)). We refer to the
fraction as the recruitment ratio \( r_c = g_{\text{stim,i}}/ g_{\text{stim}} \).

In the following simulations, we report the stimulus frequency range (in Hz) over
which AR occurs as well as the strength of AR achieved (total number of spikes)
after \( n=12 \) stimulus shocks. Since inhibition in the model network occurs only at
the basal zone, the strength of the apical input stimulus to TL5 is kept constant (\( g_d =0.4 \) p.u.) while the basal stimulus strength \( g_{\text{stim}} \) is varied with fixed \( r_c \). Accordingly,
IN5 input strength was varied proportionally as \( g_{\text{stim,i}} = r_c g_{\text{stim}} \).

Figure 8A shows AR in a baseline case (\( g_{\text{gaba-b,max}} = 60 \) nS; \( g_{\text{gaba-a,max}} =80 \) nS,
recruitment ratio \( r_c=0.25 \)). The range of \( g_{\text{stim}} \) tested is chosen so that the TL5-IN5
pair exhibit augmentation varying between minimal and maximal strength (range
\( g_{\text{stim}}=5-11 \) p.u). As seen in Figure 8A, low stimulus strengths (\( g_{\text{stim}} = 6-7 \) p.u.) can
result in prominent AR (contour line of 24 spikes) in the range of 6-12 Hz. As the
stimulus strength is increased, augmentation at higher frequencies (up to 14 Hz,
\( g_{\text{stim}} =9-10 \) p.u.) as well as at lower frequencies (down to 4 Hz, \( g_{\text{stim}} =10+ \) p.u.) can
be attained.

**Figure 8**

- **Wider AR-frequency range is achieved with larger GABA-B conductances:**
  Several changes can be noted when GABA-B conductance is increased
twofold (Fig. 8B, \( g_{\text{gaba-b,max}}=120\text{ nS} \)). First, augmentation is generally more
prominent for a given stimulus strength (contour lines are shifted
downwards in Fig. 8B vs. Fig. 8A). Second, the range of AR frequencies
achieved at low stimulus strengths is wider (\(g_{\text{stim}} = 6-7\) p.u., 4-14Hz in Fig. 8B vs. 6-12 Hz in Fig. 8A) and does increase even more (3-16 Hz) at the highest stimulus strengths tested (\(g_{\text{stim}} = 10+\) p.u.). Third, a shift in the peak AR occurs towards lower frequencies (e.g. compare contour lines 20-30 at 4-6 Hz in Fig. 8B with same lines at 6-8 Hz in Fig. 8A). A similar conclusion can be reached if the recruitment ratio \(r_c\) is doubled (Fig. 8C, 8D) or if the GABA-A maximal conductance is changed (Fig. 8E, 8F). The above changes occur due to the stronger hyperpolarization achieved with increased \(g_{\text{gaba-b, max}}\) values which, by allowing a larger de-inactivation of current \(I_T\) and a larger inward current \(I_h\), produce stronger rebound responses in TL5 for a given stimulus strength. Consequently, the TL5 cell model is able to track higher frequencies (12-16 Hz) as well as produce more spikes at lower frequencies (3-6 Hz).

Finally, decreasing the strength of GABA-B inhibition to low values will prevent the TL5 cell from producing AR altogether (not shown). In this case, the cell will either continue firing single AP (in the case of a low stimulus) or start burst-firing with the very first shock (in the case of a strong stimulus).

**Sharper tuning of AR-frequency range is achieved with larger inhibitory recruitment and is mediated by GABA-A conductances:** In the next figures (Fig.8C-F), the recruitment ratio \(r_c\) was increased from 25% to 50%; that is, interneuron IN5 now receives 50% of the stimulus received by the associated TL5 neuron. The increased recruitment caused IN5 to fire more vigorously with each delivered stimulus shock. This allowed GABA-B synapses to saturate faster and caused GABA-A synapses to exert stronger immediate inhibition to TL5 cells. The resultant AR curves are shown in Figure 8C and 8D for the two cases of \(g_{\text{gaba-b, max}} = 60\) nS and 120 nS, respectively. In comparing with corresponding curves under lower recruitment ratio \(r_c=0.25\) (Figs. 8A and 8B), the following changes are noted.
First, more spikes/stimulus shock are now achievable at high stimulus strengths and particularly for low AR frequencies (e.g. compare 4-6 Hz AR for $g_{\text{stim}}=9$ p.u, in Fig. 8C with same in Fig. 8A). Second, and more importantly, the AR frequency range is much narrower for intermediate stimulus strengths ($g_{\text{stim}}=5-7$ p.u). In particular, the AR frequency range for a stimulus of strength $g_{\text{stim}}=6$ p.u. is reduced from 6-12 Hz for $r_c=0.25$ (Fig. 8A) to 8-10 Hz for $r_c=0.5$ (asterisk, Fig. 8C). A similar effect is evident for larger GABA-B conductances (compare for $g_{\text{stim}}=6$ p.u., 6-12 Hz in Fig. 8B with 6-8 Hz in Fig. 8D). Therefore, unless the delivered input stimulus strength was very high, increased inhibitory recruitment leads to a significantly sharper tuning in the AR frequency curve.

We next investigated the mechanism behind the enhanced tuning in AR frequency curve. Recall that, since IN5 inhibits TL5 cell via both GABA-B and GABA-A synapses, both slow and fast inhibition might play a role in this frequency tuning. It is clear from Figures 8C and 8D, however, that a two-fold change in GABA-B conductance does not alter the tuning effect significantly. On the other hand, reducing GABA-A conductance from 80nS to 50 nS (63 % decrease) leads to a significant reduction in the tuning effect as seen in Figures 8E and 8F (e.g. for $g_{\text{stim}}=6$ p.u., double asterisk in Fig. 8E, AR range =6-12 Hz vs. 8-10 Hz in Fig. 8C). This suggests that fast inhibition (GABA-A conductance) is primarily responsible for the tuning effect, mainly due to vigorous firing in IN5 and correspondingly excessive inhibition of the TL5 firing with each stimulus shock.

2) GABA-B inhibition is more likely to account for AR than slow GABA-A inhibition.

Figure 9

The above simulations assumed throughout that slow inhibition observed
experimentally and modeled here was mediated by GABA-B synaptic conductances. Recent experiments, particularly in the hippocampus (Banks et al. 2002) but also in the neocortex (Sceniak and Maclver 2008) have raised the possibility that some neurogliaform cells can provide slow GABA-A type inhibition to pyramidal cells (Szabadics et al. 2007; but see Discussion section for plausibility). We therefore tested the possibility that the prolonged hyperpolarizing event generated in TL5 cells during augmentation is generated by GABA-A,slow type synapses rather than GABA-B synapses. For this simulation, we assumed that the IN5 interneuron provide a GABA-A,slow type synapse to TL5 cell where a GABA-A,slow event had a rise time of 13 msec and a decay time of 80 msec which is comparable with reported ranges (Banks et al. 2002). The results comparing GABA-A,slow with GABA-B induced augmentation are shown in Figure 9. A primary difference between the two AR scenarios is the firing dynamics of IN5 interneurons. In particular, an interneuron IN5 providing a GABA-B synapse is required to produce burst-like multiple spikes (Fig. 9C) so that these metabotropic receptors are properly activated (Destexhe et al. 1998). An interneuron IN5 providing GABA-A,slow synapse, on the other hand, need not fire multiple spikes per stimulus (Fig. 9D) for the synapse to be activated (Szabadics et al. 2007). For adequate comparison, the strength of inhibition under both GABA-B and GABA-A,slow scenarios was adjusted so that TL5 cell reaches same levels of hyperpolarization subsequent to single input shocks, and thus have the same chances to rebound during the next stimulus cycle and produce AR. The resulting AR is shown in Figure 9A. It is noted that GABA-A,slow mediated augmentation produces fewer spikes per stimulus shock and, more importantly, that this AR occurs at a much narrower stimulus frequency range than GABA-B mediated augmentation, particularly for higher frequencies (> 10 Hz) where virtually no AR was achieved under the GABA-A,slow scenario. This distinction can be understood by looking into the total effective inhibitory conductance as the stimulation frequency is increased. In particular, simulations showed that GABA-A,slow maximal conductance continues to increase with increase in stimulation
frequency (or the inter-stimulus periods decreases, Fig. 9B). On the other hand, the GABA-B maximal conductance exhibits a sublinear increase with stimulation frequency, effectively saturating at higher frequencies and allowing a stable level of AR to take hold. This sublinear increase is a hallmark of GABA-B synapses as suggested by (Thomson and Destexhe 1999; Butovas et al. 2003) and our simulations therefore suggest that does play an instrumental role in high frequency AR (10-14 Hz) range.

We finally tested the robustness of AR characteristics to variations in the decay time of GABA-B synaptic current. By reducing the decay time constant of GABA-B synapses by around 55% (from around 300 msec as given by the Destexhe et al. 1998 model to 137 msec), we noted the main effect was to reduce the cell ability to augment at lower frequencies (4-6 Hz) while AR properties at higher frequencies (>7 Hz) are essentially maintained (see Supplementary material and Fig. S6 for details). Hence, it is suggested that the reported AR characteristics within the alpha range 7-12 Hz (such as the one reported by Castro-Alamancos and Connors 1996a), commonly the relevant range as it corresponds to spindle oscillations (Werk et al. 2005, 2006, Khazipov et al. 2004), is not particularly sensitive to the exact value of GABA-B receptor decay time.

**Augmenting response in a two area network**

We next probed the various conditions under which intracortical AR can be generated in corticocortical networks by stimulation within the cortex itself (experiments of Morin and Steriade 1981, Nunez et al. 1993). The network model in Figure 1C was used to predict the dynamics of augmentation generated between interacting groups of neurons lying in two hierarchical areas Ctx-H and Ctx-L (cf. functional and anatomical background in the Methods section). The input stimuli to this network were delivered only to the upper area Ctx-H which then transferred excitation to the lower area Ctx-L in a descending or feedback manner (see Fig. 10A). The following simulations show that augmentation can indeed be
easily formed in both areas. We studied the sensitivity of this augmentation to the inter-areal synaptic connection pattern, the input stimulation pattern and frequency range, and the level background activity in the network.

**Hierarchical connections produce prominent AR**

In this reference scenario, the stimulus delivered to Ctx-H area targets both the apical dendritic zone A and the basal dendritic zone B of TL5 cells in this area \( (g_{stim,s}=5\ \text{p.u.}) \). In turn, Ctx-H is connected to the lower region Ctx-L in a feedback manner, that is, both zones A and B in TL5 cells of the lower area Ctx-L are activated \( (g_{HL,s}=1.4\ \text{p.u.},\ g_{HL,d}=0.14\ \text{p.u.}) \). Connections to the inhibitory neurons IN5 in both areas are kept constant throughout \( (g_{stim,i}=0.4\ \text{p.u.},\ g_{HL,i}=0.8\ \text{p.u.},\ g_{LH,i}=0.2\ \text{p.u.}) \).

*Figure 10*

An example firing diagram of TL5 neurons in both areas under a stimulus frequency of 12.5 Hz (inter-stimulus interval \( T_p=0.08\ \text{sec} \)) is shown in Figure 10B1. Here, augmentation is initiated in the lower area Ctx-L after 3–4 stimulus shocks and is then *transferred* to Ctx-H. After 5 stimulus shocks, TL5 cells in both Ctx-H and Ctx-L are producing 2–3 spikes per input shock. In this case, augmentation in Ctx-L occurs earliest because the local interneurons in this area IN5\(_L\) are strongly activated by the long-range descending (feedback) input from TL5\(_H\) which cause prolonged GABA-B inhibition in the associated pyramidal cells TL5\(_L\). The functional necessity for this hyperpolarization in producing AR was demonstrated earlier in the single IN5-TL5 pair scenario. Once pyramidal cells TL5\(_L\) in Ctx-L begin burst-firing (augmentation started), ascending (feedforward) connections from TL5\(_L\) cells transfer increased excitation to the upper area Ctx-H where it causes more activation of Ctx-H interneurons IN5\(_H\) and TL5\(_H\) neurons. With IN5\(_H\) then sufficiently activated (to produce multiple spikes per stimulus shock), GABA-B inhibitory
synapses are activated in the TL5 cells of Ctx-H area (TL5_H) and produce increased hyperpolarization in these cells. TL5_H cells will hence proceed to produce a rebound depolarization and burst firing with the subsequent stimulus cycles, leading to augmentation in the upper area Ctx-H. Note that with this stimulation scenario, the transfer of augmentation from Ctx-L to Ctx-H follows the sequence of increased activation of local IN5 interneurons. In particular, IN5 interneurons in area Ctx-L were vigorously activated by long-range inputs from the higher area Ctx-H since these obey the feedback topology of connection. On the other hand, IN5_H interneurons in area Ctx-H, while moderately activated by local connections to TL5_H cells, increased their activation considerably after augmentation in area Ctx-L commenced.  Note that the simulation depicted in Figure 10B1 is one representative run under random in vivo-like currents (see Methods section); therefore, an averaged AR behavior over multiple simulation runs is needed. Figure 10C (open symbols) shows the dependence of this behavior on stimulus frequency from Tp=0.08 sec (12.5 Hz) to Tp=0.24 sec (4.2 Hz). At each stimulus frequency, five runs of 9 shocks were simulated and the total neuronal spike counts from each run were averaged across runs for both TL5_L (open circles) and TL5_H (open squares). It is seen that AR in all the cells generally follows the frequency range tested with a maximum of 21 spikes after 9 shocks which occurs around mid-alpha frequency (Tp=0.1 sec, 10 Hz).

AR is maximal when Zone A is active in both Ctx-L and Ctx-H

- Zone A input in Ctx-L removed: We next examined whether the absence of the feedback topology (connection from TL5_H to zone A of TL5_L) modifies the augmenting response characteristics observed in the reference case (above). To do so, we set g_{HL,d} = 0, and increased zone B connection to TL5_L by the equivalent total strength, that is, set g_{HL,s} = g_{HL,s} (reference) + g_{HL,d} (reference) = 1.4 + 0.1 = 1.54 p.u. (while keeping all other parameters fixed). The result is shown
in Figure 10B2 for 12.5 Hz input frequency (Tp=0.08sec). Comparing this simulation with the reference run in Figure 10B1, it is noted here that TL5L cells start augmenting later than when the apical input exists (6 cycles vs. 4 cycles) and occurs simultaneously with augmentation in TL5H. Importantly, augmentation in TL5L is not able to follow the stimulus frequency but rather it may skip beats, a feature that was not observed in experimental data (Nunez et al. 1993; Castro-Alamancos and Connors 1996a). Finally, AR over different stimulus frequencies is shown in Figure 10C (filled markers). It is noted here that (1) augmentation occurs over a considerably narrower band of input frequencies (around Tp =0.1-0.2sec, 5-10 Hz), and (2) augmentation is weaker than the reference case, that is, fewer spikes are produced in both areas Ctx-H and Ctx-L over the whole frequency range tested.

Zone A input in Ctx-H removed: Since apical input to TL5H was produced by external stimuli, we asked tested whether a stimulus applied only to the deep layers (basal inputs of TL5H) was sufficient to produce AR in the interconnected Ctx-H, Ctx-L network. Figure 11A shows AR first, when zone A input to TL5H are simply removed without compensation for its loss (Fig. 11A2) and, second, when zone B inputs are increased to afford the same net excitation to TL5H (Fig 11A3).

In the first case, we set gstim,d = 0 while keeping gstim,s fixed. This corresponds to the higher area Ctx-H being driven by the stimulus in a purely feedforward manner. It is noted here (Fig. 11 A2) that the ability of Ctx-L to augment at high frequencies (12.5 Hz, Tp=0.08 sec) is reduced compared with the reference case (Fig. 11A1). Importantly, beat skipping occurs in the lower area with no-or-single spikes occurring on alternate stimulus shocks and thus does not exhibit known appearance, or satisfy our definition of AR.

In the second case, we set gstim,d = 0 while compensating for its loss by setting
the basal stimulus $g_{\text{stim,s}} = g_{\text{stim,s}(\text{reference})} + g_{\text{stim,d}(\text{reference})} = 5.4 \text{ p.u.}$ As seen in Fig. 11A3, AR at high frequencies (12.5 Hz $T_p=0.08 \text{ sec}$) is improved although occasional beat skips still occur. Finally, the effect of increased zone B stimulation is plotted over a wider stimulus frequency range in Figure 11A4. It is noted here that some reduction in the total number of spikes occurs, especially in the upper area at low frequencies (Fig. 11A4, closed squares, 25% reduction at 4.1 Hz) compared to the reference case (open squares).

In summary, removing the stimulus from superficial layers of higher area Ctx-H (zone A of TL5H) leads to a reduction in the AR strength (spikes/stimulus cycle) accompanied with a lack of tracking (beat skipping) at high stimulus frequencies, an effect which is not compensated for by increasing the deep layer (zone B) stimulus alone.

**AR is reduced in a non-hierarchical topology**

In all of the above cases, it was apparent that apical inputs to TL5H and TL5L have a main effect in facilitating augmentation. We therefore tested whether AR can in fact occur in a purely feedforward circuit (zone A inactive in both areas). Again, simulations show that, even with excitation loss compensated for (set $g_{\text{stim,s}} = 5.4$, $g_{21,s} = 1.54$, $g_{21,d} = g_{\text{stim,d}} = 0$), augmentation at high frequencies is not possible, with single spikes occurring at alternate stimulus cycles (Fig. 11B2). In addition, a stimulus frequency sweep shows that a significant reduction in augmentation at low frequencies (filled markers $T_p>0.18 \text{ sec}$, Fig. 11B3, 45% reduction at 5 Hz) occurs compared to the reference case (open markers).
Role of Zone A is amplified with increased background activity:

We finally aimed to study the effect of changing the level of spontaneous activity associated with the action of neuromodulators as well as increase in synaptic bombardment onto TL5 cells due to an increased overall network activity (Steriade et al. 2001). To simulate this effect, the resting membrane potential of TL5 cells was varied by changing the mean of in vivo like current µdc injected into these cells (see Methods section). A summary of the simulation results is shown in Figure 12 which plots firing in TL5L (averaged over 5 runs of 9 shocks using all TL5L cells) over a range of input frequencies. Simulations were performed for the two cases of reference and reduced connection strengths into the apical zone A in Ctx-L (apical gHL,d =0.14 p.u., 0.07 p.u., respectively). It is noted that no augmentation occurred for negative injected current µdc = -0.2 nA (Fig. 12A, 12B); instead, TL5 cells rebound and burst-fired at the first stimulus shock as their corresponding membranes potentials were already hyperpolarized prior to stimulation (dashed lines- triangles). Two further interesting results can be noted. First, as the injected current is increased (µdc ~0 nA to 0.6 nA), the cells’ ability to augment at low frequencies is decreased (especially evident for weak apical inputs gHL,d =0.07 p.u., Fig. 12A). That is, it appears that increased background activity in a cortical region limits the ability of cells in that region to augment at low frequencies unless the apical zone is strongly driven by the stimulating system. Second, high frequency augmentation (Tp<0.1 sec) was possible for µdc = 0 under both normal and reduced gHL,d. However, as the background activity is increased (µdc >0), HF augmentation was possible only under normal gHL,d but not under reduced gHL,d (for example, compare AR µdc=+0.4 nA in Fig. 12A, 12B). That is, simulations suggest that increased background activity limits augmentation at high and especially low frequencies unless the cortical region of interest is properly driven by the stimulation input at its superficial layers (zone A).
To analyze this change in AR recruitment further, we tested the change in firing gain associated with increasing apical strength vis a vis increasing injected current (comparing the curves in Figs, 12A and 12B). This change is quantified using the ratio of the total number of spikes produced by the stimulus again for weak and reference apical input cases.

$$G_{apical} = \frac{\text{Total average No of spikes \left( g_{HL,d} = 0.14 \right)}}{\text{Total average No of spikes \left( g_{HL,d} = 0.07 \right)}}$$ (11)

for different stimulus frequencies (Figure 12C). The gain is minimal ($G_{apical} = 1-1.2$) for no or negative injected current means ($\mu_{dc} = -0.2 \text{ nA}, \ 0.0 \text{nA}$). However, as the membrane potential is increased by virtue of increased background activity, the gain is increased, particularly in the low-alpha/upper-delta frequency range ($T_p = 0.12-0.15 \text{ sec}, 6-8 \text{ Hz}$), to reach 2.1 fold. The larger value of apical gain in this frequency range (Fig. 12C) can indicate an analog nature of apical efficacy at relatively low frequencies under in vivo conditions. That is, as the background activity increases, apical inputs can more closely control and dictate the strength of AR initiated. At higher frequencies ($T_p = 0.08 \text{ sec}, 12.5 \text{ Hz}$), however, the apical input has an all-or-none role in initiating augmentation with less effect of background activity on this role. In summary, it is therefore apparent that the apical input is well positioned to control augmentation strength in the normal depolarized states, and is less effective as the cell becomes more hyperpolarized, as will be discussed later.
DISCUSSION

This study developed a tractable model for investigating basic physiology of augmenting responses (AR) in cortical neuronal networks. The core of the model is a new three compartment model of tufted layer 5 (TL5) neurons. These are connected with model layer 5 inhibitory neurons (IN5) and then aggregated to form a skeleton network of TL5-IN5 modules that is particularly suitable for analyzing AR. The propagation of AR within the cortex represents a fundamental component of inter-areal transmission of excitation. We find that the model reproduces a large range of experimental results and makes a number of testable predictions regarding AR.

**New three compartment TL5 model**

The presented three compartment model of TL5 cells captures most of the dynamic firing features known about large layer 5 pyramidal neurons and arguably retains a significant simplicity with respect to a complete representation the complex dynamical interactions that occur between the basal, apical and proximal dendritic zones in these cells. The conductance coupling and ionic current distributions among different compartments were adjusted to produce several physically recorded waveforms in these distinct regions of TL5 cells, including the magnitude and duration of single somatic Na$^+$ action potentials, dendritic Ca$^{2+}$ action potentials, and the somato-apical dendritic backpropagating potential.

The cell model is able to rebound from hyperpolarized state with single or multiple action potentials, depending appropriately on the strength of the ionic current $I_h$ in the proximal and distal dendritic regions which acts to decouple zones A and B of TL5 cells (Burger et al. 2003). The model also closely replicates the dramatic increase in burst firing probability in TL5 cells whenever
both apical and basal zones receive nearly synchronous inputs within a 5–20 msec 'coincidence detection' window (Larkum et al. 1999a). In addition, it produces a switch in firing from bursting to single firing under increased dendritic depolarization (Schwindt and Crill 1999). Finally, the model is able to semi quantitatively replicate the firing gain modulation associated with activation of apical dendritic zone (Larkum et al. 2004), which, to our knowledge, has not been accurately modeled before in a detailed Hodgkin-Huxley formulation, and which the current modeling effort has shown to play an instrumental role in augmentation in TL5 cells.

Therefore, it is arguable that this simplified model retains the most important features of "logical" interaction between the three TL5 compartments, as outlined experimentally in (Larkum et al. 2001). While an even simpler version of this model was devised in (Karameh et al. 2006), some non-physiological parameters were required for that model to function properly. The present model achieves greater accuracy in current and membrane voltage values, fits more experimental conditions (e.g. gain modulation, effect of $I_h$) and is based on properties that are neurophysiologically justified (e.g. including ionic current dynamics and distribution).

Other more detailed models of TL5 cells exist (Rhodes and Gray 1994; Rhodes and Llinas 2001). These include realistic geometries of the cell soma, dendrites and axons, requiring tens of compartments, which renders them computationally expensive for network simulations. In addition to reproducing basic firing behavior reported in earlier models, it was seen here that in vivo like current injections will increase the apical input efficacy reported in the detailed model by Rodes and Llinas (Rhodes and Llinas, 2001). In addition, the current model provides a new prediction that such efficacy is maximal for low frequencies stimuli (< 10 Hz) as will be discussed later (Fig. 12). Furthermore, previous models did not incorporate recent experimental data on gain modulation (Larkum et al. 2004) and $I_h$ current dynamics (Burger et al. 2003). The current model reproduces such
new details, using only three compartments without sacrificing the basic characteristic input/output dynamics of TL5 cells.

**Rebound bursting or single spike firing**

The utility of the new three compartment model is demonstrated in a simplified network model of intracortical augmenting response where the rebound response of TL5 plays seems essential. The model predicts an important role for the inward current $I_h$ in controlling whether a TL5 cell fires single spikes or bursts upon release from inhibition. Based on the experimental $I_h$ current activation dynamics reported by Burger and coworkers (Burger et al. 2003) and modeled herein, a TL5 cell is predicted to respond with single rebound spikes when released from moderate hyperpolarization. As seen in the model cell rebound response, a somatic AP is unable to invade the dendrites when this cell is suddenly released from moderate inhibition. Under the same condition, removal of $I_h$ allows a backpropagating AP to reach the distal dendritic region and generate a Ca$^{2+}$ AP there, resulting in a burst response. Accordingly, $I_h$ ionic channel density dictates whether a cell responds as an intrinsically bursting (IB) or regularly spiking (RS) cell during inhibitory rebound from moderate hyperpolarization. It is predicted here that release from excessive hyperpolarization, on the other hand, might overpower $I_h$ control, leading to cellular bursting. This could account partially for the dominance of bursting in TL5 cells observed earlier under conditions where membrane potentials are shifted towards more hyperpolarized potentials such as slow-wave sleep (Steriade et al. 1993), anesthesia (Nunez et al. 1993), and upon removal of excitatory neuromodulators in vitro (Wang and McCormick 1993).
**Intracortical augmenting responses**

Generically augmenting response (AR) refers to the increase in spike firing of cortical neurons that can be generated by steady repetitive stimulation of either the thalamus or other cortical areas. Experimentally, cortical AR has been evoked by local or thalamic stimulation in rat sensorimotor areas under Ketamine anesthesia and in slices (Castro-Alamancos and Connors 1996); the current modeling effort showed similar AR patterns by specific stimulation pattern in a minimal network of TL5-IN5 neurons in the absence of NMDA receptor activity (effect of Ketamine). Intracortical AR has also been evoked by callosal or white matter stimulation in thalamically lesioned animals (Nunez et al. 1993, Morin and Steriade 1981); again the model showed that it is possible to evoke similar AR upon stimulating a single-area within a two-area network model specifically when the corticocortical connection topography follows functional hierarchy connectivity patterns.

Accordingly, we propose that intracortical networks of interconnected TL5-IN5 neurons, when properly activated, can provide the backbone of one form of intracortical augmentation which does not contradict, but rather complements other augmentation forms reported in the literature.

**Sufficiency of TL5 modeling**

The conducted simulation at a single TL5-IN5 pair level helped in clarifying the roles of intrinsic cellular mechanisms, the nature and role of slow inhibition, and the location of excitatory stimulus delivery in AR genesis. In this regard, the three-compartment model of TL5 cells provided sufficient detail level where conditions under which AR can be generated are clearly dissected. In comparison, a single compartment model does not provide the conditional bursting activity in TL5 cells due to interaction of apical and basal dendritic zones which is the main premise of the input coincidence detection discovered nearly a decade ago (Larkum et al. 1999). Such a model therefore will not account for experiments that clearly show that apical dendritic events do occur during augmentation (Castro-Alamancos and
Connors 1996) and, importantly, that augmentation occurs upon stimulation of VL thalamus (targeting zones A and B), but not the VPL thalamus (targeting zone B only). Similarly, a two-compartment model, such as the one presented earlier by the authors (Karameh et al. 2006), while providing a gross-scale description in terms of the necessity of interaction between zones A and B of TL5 cells to produce, does not allow for accurate analysis of this phenomenon, particularly the role of hyperpolarization activated current $I_h$ in decoupling the two zones. In fact, recent evidence showed that accurate modeling of zone A-zone B interaction should necessarily include modeling the proximal dendritic compartment as a bottleneck controlling this interaction (Larkum et al. 2001) principally due to the presence of $I_h$ currents which control current follow to and from zone A (Burger et al. 2001, 2003). The current three-compartment model corroborates these findings in explaining basic AR at a detail level sufficient to provide new insights as to how zone C might act to not only control AR initiation and strength but also as to prevent excessive excitability in the network.

**TL5 cell firing behavior**

The AR network model emphasizes the importance of the interaction between TL5 neurons and their associated interneurons. The inhibitory neurons provide important hyperpolarization of the TL5 neurons during physiological operation. At the level of a single reciprocally-connected TL5-IN5 pair, AR is manifested in TL5 neurons within 3–5 shocks of a repeating stimulus delivered principally at frequencies 3–12 Hz. Here, three main cellular mechanisms are required. First, IN5 cell firing is able to produce slow hyperpolarization in a TL5 cell; second, TL5 cell is able to rebound from hyperpolarization with single spikes with subsequent stimulus pulses; and third, apically arriving input to TL5 cell is able to amplify the rebound spiking phenomenon to produce burst firing in the TL5 cell model.

The characteristic AR firing response of the TL5 neurons in the model agrees with
activity reported in somatic recordings of large layer 5 cells in (Castro-Alamancos and McCormick 1996a). A single shock resulted in early fast EPSP followed by a long-lasting IPSP, a sequence commonly reported in slices (Schubert et al. 2006, Mann and Sakmann 2004) and in vivo in rats (Garabedian et al. 2003) and cats (Baranyi et al. 1993). In the model, rebound bursting of TL5 cells resulted in large dendritic events (Ca^{2+} action potential), as has been reported by experimental recordings in Castro-Alamancos and McCormick 1996a, and required the concurrent arrival of apical inputs to TL5 cells.

Most of the AR responses described here, particularly at high levels of GABA-B inhibition, showed that TL5 cells often augment to 2 spikes at most (although three or more spikes are possible under excessive stimulation conditions). This correlates with the many experimental recordings obtained in these cells under cortical stimuli (Castro-Alamancos and McCormick 1996a, Figures 1d, 3, 5b; Nunez et al. 1993, Figure 7d; Steriade et al. 1998, Figure 9b).

**TL5-IN5 AR network connection topology:**

AR can be produced in both single TL5-IN5 pair and interconnected networks upon low-frequency delivery of simultaneous superficial and deep layer inputs, effectively binding basal and apical zones of the underlying TL5 cell population. This requirement is consistent with various experiments reporting cortical AR both at the thalamus-to-cortical and corticocortical levels. At the cellular level, activation of TL5 basal dendrites by inputs arriving in the middle and deep layers of the cortex has been reported in several experiments (Schubert et al. 2001, 2006; Mann and Sakmann 2004). Furthermore, the AR experiments by Castro-Alamancos and Connors showed clear dendritic events at the level of layer 3 that occur following firing of pyramidal cells in layer 5 (cf. Figure 3 of that reference). In addition, other experiments showed that the apical dendritic processes were actively recruited by apically-arriving (thalamic) inputs in somatosensory cortex of rats in vivo (Zhu and Zhu 2004) and were suggested to play an important role in
binding different thalamocortical streams (Llinas et al. 2002).

At the network level, AR can be initiated between two spatially separated TL5-IN5 populations that belong to different levels of a hierarchy which is consistent with several experimental observations. In intracortically-induced AR, stimulation of callosally projecting layer 5 cells, whose termini were distributed preferentially to superficial layers (1, 2) and layer 5, induced bursting-type, sustained augmentation in the target cortical area (Nunez et al. 1993). This inter-cortical area effect is similar to that attributed to bottom-up inputs from "nonspecific" or "second order" thalamic nuclei such as the Ventrolateral (VL) nucleus. Stimulation of the VL nucleus, which projects to cortical layers 1 (zone A) and 5 (zone B) but not to layer 4 (zone C) induced cortical AR which was accompanied by rebound depolarization and bursting in layer 5 cells (sensorimotor cortex of rats, Castro-Alamancos and Connors 1996a,b). Stimulation of the ventroposterior lateral (VPL) nucleus, a "specific", or "first order" thalamic nucleus that projects dominantly to middle cortical layers (3-5) failed to produce augmentation. Similarly, in early experimentation (Pupura 1964a,b), Pyramidal tract neurons (PT) produced burst-like discharges during augmentation when the VL thalamus was stimulated, but produced only single spikes when the (specific) centromedial (CM) thalamic nucleus was excited. The latter, is often referred to as (specific) neuronal recruitment and is distinguished from broader augmentation.

**Key findings and model predictions**

The TL5-IN5 AR network model was used to study relevant intrinsic ionic properties of TL5 cells as well as strength of excitation and inhibition for initiation of AR in a single TL5-IN5 pair as well as between areas. This lead to the following predictions:

a. **Role of low threshold current $I_T$:** Low threshold calcium current is predicted to be instrumental in cortical augmentation. A decrease in $I_T$ ionic channel
density (maximal $I_T$ conductance) in the soma and proximal dendritic regions in the model lead to cessation of augmentation in TL5 cells even for large increases in the stimulus magnitude (Fig. 6) while an increase in maximal $I_T$ conductance lead to rapid increase in the total number of spikes produced. This behavior is in agreement with that reported in thalamocortical (TC) cells undergoing augmentation (Bazhenov et al. 1998a). Experimental evidence further suggests that low-threshold calcium currents (LTCC), which are the main vehicle for initiating rebound response in the current modeling study, are localized in cells with the delayed inhibitory postsynaptic potentials (presumed GABA-B IPSPs) (de La Pena and Geijo-Barrientos 1996) where they promote bursting (Wang and Goldman-Rakic 2004). This model prediction of a direct involvement of LTCC in AR generation can be experimentally verified by manipulating the $I_T$ current during AR experiment (such as blockage of LTCC by application of NiCl$_2$). Finally, the model also demonstrated that while AR is rather insensitive to kinetics of the $I_T$ current in the 7-12 Hz range, slower $I_T$ inactivation kinetics will allow prominent AR to occur at considerably lower frequencies (3-5 Hz). Accordingly, a prediction of the model is that changes in $I_T$ inactivation, whether developmental within a single animal or when compared across animal species, should correspond to specific changes in the prominence of low-frequency AR phenomena in conducted experiments.

b. **Role of hyperpolarization-activated current $I_h$:** At the level of a single TL5-IN5 pair, the ability of a TL5 cell to augment is predicted to be directly related to its ability to produce bursting as an inhibitory rebound response. Therefore, it is expected that $I_h$ ionic channel density plays an important role in controlling augmentation, principally because $I_h$ acts to prevent somatically-generated back-propagating action potentials (BAP) from reaching apical zone to activate Ca$^{2+}$ action potentials there and hence somatic bursting. The model shows that, as the somatic and proximal concentrations of $I_h$ are reduced, the cell can produce AR for lower stimulus strength. Conversely, an increase in $I_h$,
particularly in the soma, is able to inactivate the bursting rebound response and thus eliminate augmentation (Fig. 7). Furthermore, the model predicts that slower $I_h$ activation kinetics reduce $I_h$ effects and hence increase AR. In addition to the decoupling role of $I_h$ suggested by earlier experiments (Burger et al. 2003), a key and novel prediction of the presented model is that, at the level of a single TL5 cell, $I_h$ current plays an excitation limiter role under conditions of excessive stimulation. Starting from a state wherein the cell is properly augmenting under somatic/apical stimuli, large increases in somatic excitation could prevent the cell from producing AR (bursting), principally due to a reduction in the driving force of the inward current $I_h$ as well as an increase in the shunting effect of its associated conductance. This role of $I_h$ correlates with experimental findings in TL5 cells in vitro that hyperpolarization of the soma is more likely to produce supralinear summation between dendritic and somatic EPSPs in these cells (Nettleton and Spain 2000). If proven experimentally, this inherent excitation limiter, acting to prevent bursts under the effect of hypersynchronous excitatory inputs to the soma, may be normally important to prevent states of runaway excitation, such as seizures. Consistent with this possibility is the fact that some classes of anticonvulsant drugs (e.g. acetazolamide) have been reported to upregulate $I_h$ (Munsch and Pape 1999, Chen et al. 2002). Future verification of the above predictions may be conducted during AR experiments by manipulating/blockade of $I_h$ (e.g. using ZD7288, Burger et al. 2001, 2003).

c. **Nature of slow inhibition:** The effect of slow inhibition on somatic regions of layer 5 neurons has been demonstrated experimentally in (Castro-Alamancos1996a,b) and discussed in (Thomson et al. 1996) and was presumed due to GABA-B receptors (Thomson and Destexhe 1999). More recently, and using multiunit recordings, (Butovas et al. 2003) showed slow inhibition to be followed by a rebound response at high intensity stimulation specifically at a depth of layer 5 in rat S1, a response that also seemed to have
an oscillatory component of about 10 Hz (cf. Fig. 5 in that reference). In the current TL5-IN5 AR model, the presence of slow inhibition was a critical element for AR generation because it provided the prolonged membrane potential hyperpolarization necessary for deinactivating \(I_T\) currents (De La Pena and Geijo-Barrientos 1996) in TL5 cells. In addition, the model shows that such inhibition is more likely to be mediated by GABA-B synapses and not by slow GABA-A receptors since the latter produces little augmentation and only at low frequencies unlike the wide frequency range observed experimentally. This model suggestion agrees with several experimental findings. First, GABA-B receptors are predominant near the somatic region of layer 5 cells as shown in rats (Eder et al. 2001; Princivalle et al. 2000) and cats (van Brederode and Spain 1995) and clear GABA-B events were recorded in layer 5 cells in rat visual cortex where they participate in plasticity (Komatsu 1996). Second, GABA-B receptors are activated either by spillover of GABA, hence requiring synchronized activity of many interneurons, or by high rate of neuronal firing. Here, interneurons firing in multiple high-frequency spikes is documented (stimulation in rats S1 cortex: Benardo et al. 1994; see also Methods section); also, synchronized activity in the interneuron network, which could lead to abundance and spillover of GABA, is commonly reported and is amplified by electrical coupling within the network (Beierlein et al. 2000). Third, and perhaps more importantly, Butovas and coworkers (Butovas et al. 2003) showed that slow inhibition under a double stimulation paradigm produces a sub-linear non-depressing response at higher frequencies where it fuses to form an almost uniform inhibitory, an observation which is characteristic of GABA-B synapses (Thomson and Destexhe 1999). Fourth, GABA-A,slow synapses were recently shown to be activated by neurogliaform cells as events that occur very infrequently (once in 90 sec) which was not the case in AR experiments. Nonetheless, the unequivocal involvement of GABA-B requires an experimental setup where augmentation ceases or is greatly reduced when GABA-B
receptors are blocked.

d. **Effect of inhibition on AR:** In the current model, slow gabaergic inhibition produces a long lasting hyperpolarization from which rebound activity in TL5 cells occurs. To reach this hyperpolarized state, either GABA-B synapses should be abundant (large maximal conductance $g_{\text{gaba-b, max}}$) and arriving from many interneurons (and thus input is distributed, $g_{\text{stim, i}}$ small) or few interneurons need to be vigorously excited during the first two stimulus cycles ($g_{\text{stim, i}}$ large). The latter possibility is supported by preliminary results showing that fast spiking interneurons (IN5) receive facilitating synapses from layer 5 pyramidal cells which could account for the possibility of vigorous activation of these interneurons by TL5 neurons (Angulo et al. 2003).

The current simulations for a single TL5-IN5 pair suggested complementary roles for slow and fast inhibition in controlling the strength of augmentation as well as the range of frequencies at which AR could occur. Slow GABA-B inhibition has the role of providing the membrane hyperpolarization levels necessary for rebound responses to occur in TL5 cells (Fig. 3A in current paper; Figure 4A in Castro-Alamancos and Connors 1996a) and thus increasingly larger $g_{\text{gaba-b, max}}$ will produce AR with more spikes/stimulus shock and at wider frequency ranges. Fast GABA-A inhibition, on the other hand, provides a tight control of the TL5 cell ability to burst-fire immediately following a stimulus arrival by way of controlling back-propagating action potentials (Larkum et al. 1999), and thus increasingly larger $g_{\text{gaba-a, max}}$ can, under strong recruitment conditions, restrict AR to fewer spikes/stimulus shock and limit the AR frequency range to a very narrow band of ~ 2 Hz.

In regard to the role of slow GABA-B mediated inhibition, it is noted that the TL5-IN5 network exhibited augmentation within 5-12 Hz range under intermediate values of GABA-B concentrations ($g_{\text{gaba-b, max}}$). This frequency range corresponds to spindle oscillations that have been reported to occur in
S1 cortex of awake rats (Wiest and Nicolelis, 2003) as well as in developing animals (Khazipov et al. 2004) where it might be related to formation of somatotopic sensorimotor maps in these animals. With increased GABA-B concentrations \( (g_{\text{gaba-b, max}}) \), large hyperpolarization events allowed the widening of AR frequency range to include low delta (3-4 Hz) and high alpha (14-16 Hz) band. At the lower end of frequencies (3-5 Hz), large hyperpolarization levels allowed the TL5 cell to respond to stimulus shocks with increasingly stronger rebound firing, and thus stronger bursting. This scenario is similar to the large delta-band oscillations that are known to occur during late stages of sleep and that were shown previously to correspond to strong hyperpolarization-strong burst firing cycles in layer 5 intrinsically bursting pyramidal cells (Steriade et al. 1993). At the higher end of frequencies (14-16 Hz), the combination of large \( g_{\text{gaba-b, max}} \) and excessively large stimulus amplitudes allowed the TL5 cells to augment (Fig. 8B) by exhibiting doublet firing (not shown). Augmentation at these frequencies was shown in the AR experiments of Castro Alamancos and Connors 1996a (cf. Figure 2A of that reference).

In regards to the role of fast GABA-A mediated inhibition, it is noted that strong recruitment of inhibitory interneurons and abundance of fast GABA-A receptors lead to the modulation of the AR frequency curve from wide (broadly tuned) to narrow (sharply tuned), which might correspond to two functional circumstances wherein TL5 cells undergo bursting. In particular, a wide resonance curve can be attained at low external stimulus strength when interneurons fire at relatively low rates and a moderate number of \( g_{\text{gaba-a}} \) receptors are active (Fig. 8A). This could occur under states of low vigilance such as delta sleep wherein presumably loose temporal coupling within large networks of neurons may be acceptable, that is, when diffuse input causes low levels of excitation in local IN5 cells which in turn fire at low rates, thus allowing TL5 cells to burst under minimal inhibitory control. Sharper resonance curves, on the other hand, are associated with stronger external stimulus, more focused recruitment of IN5
neurons and larger number of g\textsubscript{gaba-a} receptors (Fig. 8B), thus restricting the range of frequencies under which TL5 cells burst. Such a situation might be more typical of active cognitive states wherein feedforward excitatory drives (increased excitation from middle layers: Schubert et al. 2001; Jellema et al. 2004, or superficial layers: Thomson and Bannister 1998; Bannister 2005) are more focused onto inhibitory interneurons and resonances are expected to be more frequency selective and restricted to much more tightly-organized and temporally coupled neuronal networks (see, for example, receptive field tuning in barrel cortex; Bruno and Simons 2002).

Accordingly, the model predicts that augmentation frequency tuning in AR experiments will become sharper and occur at intermediate frequency ranges (8-10 Hz Fig. 8C) under \textit{in vivo} conditions as the overall excitability of the system is increased (e.g. effect of neuromodulators and increased vigilance).

e. **Role of bilaminar inputs in facilitating AR:** Earlier simulations and experimental results on individual TL5 cells highlight the firing gain associated with inputs arriving at apical dendritic zone (Larkum et al. 2004; Zhu and Zhu 2004; Llinas et al. 2002). In regard to cortical AR, the current simulations confirm that inputs arriving at superficial cortical layers and that have access to both apical zone A and basal zone B of TL5 cells are able to produce stronger responses (more spikes per input shock) than when the same strength input is applied to the deep layers and access basal dendritic regions of TL5 cells alone, and that this holds for a wide range of augmentation frequencies tested (Tp=0.08-0.3 sec, 3-12 Hz). More importantly, it is apparent that apical inputs are instrumental in achieving augmentation at relatively high frequencies (Tp=0.08 sec, 12.5 Hz), as suggested by the various stimulation scenarios presented (Figures 10, 11). That apically-arriving inputs are related to descending connections from higher order to lower order areas suggests a possible cognitive role for augmentation occurring at higher frequencies. In
particular, the two-area simulation network shows a clear effectiveness of the apical-basal connectivity in AR initiation at (10-13) Hz range as well as its strength over the whole range tested. The simulations in Figures 10 and 11 predict that AR occurs preferentially when TL5 and IN5 are excited concurrently and is more prominent under bilaminar inputs, as occurs with physiological excitatory projections, and less readily when TL5 neurons are stimulated directly in isolation as might be done experimentally. Many more simulations will be required to characterize inter-areal transmission of AR that is to be expected under various experimental conditions and in vivo. As a first step, it is clearly important to design experiments that verify AR initiation is considerably enhanced under local repeated stimulation of cortical slices in the reported frequency ranges (3-12 Hz) coupled with stimulation of cortical layer 1 of the same slices (experiments by Schlosberg et al. 2006).

f. **Gain modulation:** The change in resting membrane potential under in vivo-like injected current conditions provided a critical change in the effectiveness of gain associated with apically arriving inputs. The amount of injected current was intended to simulate the change in spontaneous activity due to neuromodulators and the increase in synaptic bombardment under waking states (Steriade et al. 2001). Under low injected current magnitudes, the cells’ ability to fire is less affected by the magnitude of apical currents and the network ability to follow middle-range frequencies (5-10 Hz) is limited (Fig. 12C). As the injected current is increased, the membrane potential of the TL5 cell becomes more depolarized, the cell firing becomes highly sensitive to the magnitude of apical inputs and augmentation in this frequency range becomes possible. Therefore, it is apparent that ability of apical inputs to control augmentation is highly dependent on the level of background activity in TL5 cells, as simulated by the amount of random input current. This agrees with earlier simulation result using detailed layer 5 cell models (Rhodes and Gray 2001) showing heightened efficacy of the apical dendritic region under in vivo-
like conditions.

g. **Factors determining AR frequency range:** The conducted simulations suggest that the range of stimulation frequencies over which augmentation occurs is affected by various intracellular factors as well as synaptic dynamics. At the intracellular level, it is predicted that slower inactivation kinetics of $I_T$ current would allow for more prominent AR particularly at lower delta range frequencies (Fig. 6B), and that slower activation kinetics of $I_h$ current increases AR abilities at higher alpha frequencies (> 12-13 Hz, supplementary material Fig. S3). At the synaptic level, it is predicted that a decrease in the decay time of GABA-B currents does not affect ability of AR initiation at high frequency but rather limits AR at the lower edge of frequencies (< 6 Hz, supplementary material Fig. S6). In terms of synaptic conductances, simulations suggest that increased GABA-B synaptic conductances generally lead to wider frequency ranges while increased GABA-A conductances, when coupled with strong inhibitory interneuron recruitment, lead to narrower or more tuned frequency ranges (Fig. 8). Finally, and with all the cellular parameters fixed, both single TL5-IN5 pair and network simulations pointed to a significant role for apically-arriving inputs in specifying AR strength (AP/shock) and the ability of TL5 cells to follow higher-alpha stimulation frequencies (Figures 10 and 11).

**Relationship to other AR forms**

The presented model proposes intrinsic properties of TL5-IN5 interaction as the principal basis of augmentation that occurs within the intracortical network and is based on earlier experiments showing a main role of layer 5 in AR initiation (Castro-Alamancos and Connors 1996a,b). This contrasts with recent experiments and modeling that attribute a form of intracortical augmentation to synaptic plasticity within a generic network of Regularly spiking pyramidal and Fast spiking inhibitory (RS/FS) neurons of the cortex and not due to intrinsic properties (Houweling et al. 2002; Timofeev et al. 2002). Several observations lead us to as-
sert that physiological intracortical augmentation requires an intact network of connections and that the augmentation observed in isolated slabs (Timofeev et al. 2002) is not fully representative of the behavior of the cortex in vivo.

First, plasticity-induced AR in isolated slabs (thalamus, modulatory, other cortical areas removed) was reported to occur only close to the stimulating electrode and decreased with distance from the stimulation site. AR obtained in intact cortex occurred at large distances (3–6 mm; Timofeev et al. 2002), or across hemispheres (Nunez et al. 1993). This suggests that some cortical mechanism other than the proposed synaptic plasticity was likely responsible for AR at such long distances. The laminar specificity of long distance connections is a well documented feature in several cortical areas at the early motor-sensory stages (Fellman and Van Essen 1991) and possibly higher cognitive areas (Medalla and Barbas 2006). In the current simulations, all stimuli to TL5 cells arrive under a specific topology to both apical and basal dendritic zones (A and B) and in specific proportions. While intermediate levels of stimuli to zone B created AR in TL5 cells when interacting with zone A inputs, high levels of zone B inputs alone caused intrinsic \( I_h \) currents to dissociate zones A and B, thus preventing AR (Fig. 7). We speculate that these large zone B inputs might be one reason why intrinsically bursting (IB) cells were seen not to augment in some experiments (Timofeev et al. 2002). [Note that the set of cells designated traditionally as strictly-bursting (IB) cells does not necessarily include all type of TL5 cells we model here, that is, ones which switch their firing behavior].

Second, our simulations require that the applied stimuli activate the local IN5 neurons creating GABA-B type response in TL5 cells, which was not obvious in cortical slabs of Timofeev and coworkers (Timofeev et al. 2002). This type of early EPSP followed by long-lasting hyperpolarization (IPSP), however, was reported in the intact cortex by the same authors (Timofeev et al. 2002, Figure 9) as well as in earlier experiments (Castro-Alamancos et al. 1996a). The model shares several properties with augmentation occurring in thalamic and thalamocortical networks.
Simulations in the thalamus point to an instrumental role for Low threshold Calcium current $I_{\text{L}}$ in two interacting populations (RE and TC) cells. Here, since the inhibitory (RE) and excitatory (TC) populations have rebound properties, initial excitatory stimulus spikes lead to a sequence of increasingly hyperpolarization and depolarization events in both cell types which subsequently augment their firing by producing multiple burst-like spikes. The switch in firing from single to multiple spikes appears to be an autonomous response occurring upon inhibitory rebound.

In the current intracortical augmentation, low threshold calcium currents $I_{\text{L}}$ are also instrumental in producing rebound response. The ability to augment (produce bursts), however, is not autonomous. Rather, it is controlled by intrinsic properties in the cell (inward current $I_{\text{h}}$ in proximal dendrites), and other inputs arriving at its apical dendritic zone. The existence of apical input appears to be instrumental for inducing AR at high frequencies (10-12 Hz). In addition, apical inputs seem to modulate the strength of augmentation at lower frequencies (3-8 Hz).

Accordingly, the detailed understanding of active dendritic zones in TL5 cells based on experimental data allows the current model to highlight more specific predictions for the conditions under which intracortical augmentation occurs. In particular, simulations point to a more active role for the apical dendrite under *in vivo* like conditions (gain modulation) and to the importance of this zone in facilitating augmentation when stimuli are applied at the upper edge of the AR frequency band (> 10 Hz). We conjecture that it is precisely this intricate active control of augmentation which could make the experimental recording of AR possible even in small cortical networks.

**Model relevance to further aspects of cortical physiology**

The current effort in modeling intracortical augmentation phenomena gains an additional relevance given the preponderance of 3-12 Hz rhythms, the involvement of layer 5 cells in plasticity and their participation in both superficial and deep circuits. First, layer 5 cells have been closely linked to long term potentiation and
depression following tetanization of callosal connection in sensorimotor areas (Chapman et al. 1998), as well as to the generation of spindle activity during periods of sleep and awake immobility (Werk et al. 2005, 2006). Although such plasticity phenomena and the ensuing spreading activity are likely to require full thalamocortical interaction (Steriade and Timofeev 2003), as well as modeling other pyramidal cell types of layer 5 (Christophe et al. 2005), the current work represents a first step effort in understanding resonance phenomena in layer 5 networks that might facilitate the production of potentiation. Second, recent work suggests that the organization principles of hierarchical networks might well extend from early sensory-motor stages to higher cognitive stages in primates (prefronto-associational areas) where a clear predictability in distinguishing between feedforward and feedback connections can be found in cellular density and synaptic morphology (Medalla and Barbas 2006; Germuska et al. 2006). Again, the fact that TL5 cells operate within multiple synaptic pathways in superficial and deep layers highlights the importance of developing layer 5 cellular models as well as understanding related dynamics such as the AR phenomenon modeled here.

**Scale limitations**

The presented model included only up to 8 TL5-IN5 pairs. Accordingly, the strength of individual synaptic connections is significantly amplified when compared to realistic networks. In this case, the model assumed that individual synapses represented the activity of many presynaptic partners. This is justifiable because AR phenomena are caused by concurrent stimulation of a large number of thalamic (or cortical) neurons that have widespread axonal connectivity patterns in the target neural population and thus cause the concurrent activation of multiple target neurons. To reduce spurious synchronization effects in the network, multiple simulations were conducted using random in vivo-like currents and their average behavior was reported. Finally, given the network scale, it was not possible to study the spatiotemporal propagation of AR activity (Bazhenov et al. 1998a,b). We
instead focused here on the main controls of AR initiation and the ability of different cortical areas to participate in and transfer augmentation at different frequencies. It appears that the intracortical AR phenomenon at hand is at least as complicated as that studied in thalamocortical systems for the aforementioned considerations regarding bursting control in TL5 cells, and the ability of the system to augment over a wide range of frequencies 3–12 Hz. Analysis of spatial propagation of these AR patterns is undoubtedly important, and could predict new constraints on how different stimulus frequencies can recruit the TL5 network. This is, however, beyond the scope of the current work and remains a topic of interest.

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Figure Legends

**Figure 1:** (A) Schematic of the simplified three compartment model of TL5 cells. (B) Schematic of a TL5-IN5 pair with connections capable of inducing augmentation. Indicated on TL5 are approximate locations of apical dendritic zone A, proximal dendritic zone C and basal dendritic zone B. Excitatory connections are given by open triangle and are of AMPA type. Inhibitory connections are filled triangles and are of GABA-A and GABA-B type. (C) Schematic of the eight cell two-area model. Shown are connections of each type of cell. Note that all connections are symmetric. Neighborhood connections are of length 1. Ctx-L to Ctx-H have characteristic ascending (feedforward) topology, Ctx-H to Ctx-L have descending (feedback) topology.

**Figure 2:** Response of TL5 cell model to current injections. (A) A somatic pulse $I_s$ injection (green trace) produced single action potential at soma compartment (blue trace) and little depolarization in dendritic compartment (red). Scale bars and colors apply to figures A, B, and C. (B) An EPSP-like injection $I_d$ to the distal dendritic compartment (light green) produced a $Ca^{2+}$ AP and an associated somatic burst. (C) Injection of $I_s$ followed by $I_d$ within after 10 msec of much lower magnitude produced a burst at the soma and a $Ca^{2+}$ AP in the dendrite. (D) Membrane voltage in the three model compartments during a burst. By injecting a current pulse to distal dendritic compartment of sufficient amplitude, $Ca^{2+}$ AP is produced (red trace). This is associated with a burst of 2-3 spikes in the soma compartment (blue trace) and backpropagating APs in the proximal dendrite (black trace).

**Figure 3:** (A) Response of TL5 cell model to increasing levels of somatic hyperpolarization (three traces shown). As an injected hyperpolarizing somatic current is removed after 300 msec, a rebound depolarization occurs, which could lead to firing.
Note the initial sag in the hyperpolarized voltage due to presence of $I_h$ (Castro-Alamancos and Connors 1996a). (B) Effect of $I_h$ on TL5 cell model response. Top: rebound depolarization, after somatically-injected hyperpolarizing current, in the unaltered cell causes regular spiking at the soma (solid trace) and small depolarization in the dendritic compartment (dashed trace). Bottom: rebound depolarization after removal of $I_h$ from the proximal compartment. Injected current to the soma is equivalent to that in above trace. Note that the regular firing at the soma can now invade the distal dendritic compartment to evoke $\text{Ca}^{2+}$ AP there (dashed) and burst firing at the soma (solid).

**Figure 4:** (A) Current to rate transfer function in TL5 cell model under somatic and/or dendritic compartment *in vivo* like current injections. The current to rate transfer functions were obtained by calculating the mean spike rate at the soma for each current step and plotting the rate against the mean current $\mu$. (i) For somatic current injections only (filled circles, Gaussian $\sigma = 0.3 \, \text{nA}$, $\tau = 3 \, \text{ms}$, $\mu_{\text{start}} = 0.02 \, \text{nA}$, $\mu_{\text{dc}} = 0.1 \, \text{nA}$, step duration $= 2 \, \text{s}$, 9 steps, mean of $n=5$ simulations), the rate was fitted with the linear threshold function $F = 41.0143I_s - 14.252$. (ii) For current injection to the distal dendritic compartment only, (open circles, $\sigma = 0.3 \, \text{nA}$, $\tau = 3 \, \text{ms}$, $\mu_{\text{start}} = 0.7 \, \text{nA}$, $\mu_{\text{dc}} = 0.05 \, \text{nA}$, step duration $= 2 \, \text{s}$, 13 steps, mean of $n=5$ simulations), the rate function was fitted with the linear threshold function $F = 65.66I_d - 56.4$. (iii) Modulation of the somatic current to rate transfer function in the presence of dendritic current. Here, a Gaussian current with constant mean ($\mu_{\text{dc}} = 0.75 \, \text{nA}$) and standard deviation ($\sigma_d = 0.3 \, \text{nA}$) was injected into distal dendritic location. The somatic current was then injected (open squares, Gaussian $\sigma = 0.3 \, \text{nA}$, $\tau = 3 \, \text{ms}$, $\mu_{\text{start}} = 0.02 \, \text{nA}$, $\mu_{\text{dc}} = 0.1 \, \text{nA}$, step duration $= 2 \, \text{s}$, 6 steps, mean of $n=5$ simulations) to give a linear fit of $F = 56.06I_s + 9.53$. (B) Model cell response to increased sustained depolarization of dendritic compartment. Top left: Low injection levels (lower trace, $I_d = 1.15 \, \text{nA}$) produced burst firing at a low repetition rate (upper trace). As dendritic current injection is increased, the rate of burst firing increases (top right: $I_d = 1.25 \, \text{nA}$, bottom left: $I_d = 1.3 \, \text{nA}$). A switch to regular firing occurs with further depolarization (bottom right, $I_d = 1.65 \, \text{nA}$).
**Figure 5:** Augmenting response is a single TL5-IN5 pair. (A) TL5-IN5 pair and associated weights, in per unit (p.u.): gaba-a: $g_{ie,a} = 0.8$ p.u., gaba-b: $g_{ie,b} = 1.0$ p.u., ampa: $g_{ei} = 2.0$ p.u., $g_{stim,i} = g_{stim}$. (B) Top trace: Somatic voltage trace in TL5 shows AR achieved when apical input is present ($g_d = 0.5$ p.u.) in addition to somatic stimulus ($g_{stim} = 5.0$ p.u.). Middle trace: no AR is achieved when apical is not present, even with a 1.5 fold increase in somatic stimulus ($g_{stim} = 7.5$ p.u.). Bottom trace: stimulus delivery times ($T_p = 0.1$ sec, 10 Hz) represented by filled up triangles. (C) Expanded view of B showing dendritic voltage (zone A, dashed lines) and somatic voltage (zone B, solid lines) in TL5 cell model. (D) Relative Synaptic strength required for augmentation (somatic baseline $g_{stim} = 6.0$ p.u.). Lines are for simultaneous zones A and B stimulation (reference case, $g_{stim} = 6.0$ p.u., $g_d = 0.4$ p.u.). Dashed lines: number of spikes after 13 shocks; dashed-dotted lines: number of spikes after 4 shocks. Squares are for zone B only stimulation ($g_d = 0.0$ p.u.). Filled markers: the number of spikes after 13 shocks; open markers: number of spikes after 4 shocks.

**Figure 6:** (A) Effect of somatic low threshold calcium current $I_T$ channel density change on AR in TL5 cell model. Shown are contour lines for the number of spikes in TL5 after the stimulus delivery of 13 shocks of strength $g_{stim}$ (in per unit). Base line for conductances in soma is $g_{T,som} = 1.15$ mS/cm$^2$ and in proximal dendrite is $g_{T,prox} = 1.60$ mS/cm$^2$. Synaptic connections strengths are the same as before except $g_{stim,i} = 3.0$ p.u.. Note that AR implies contour lines greater than 13 (> 13 spikes after 13 shocks). Dotted contour with 5 spikes: No AR. (B) Effect of varying $I_T$ inactivation kinetics on AR. Plotted are contour lines of achievable number of spikes after 13 shocks as a function of a constant multiple of the inactivation time constant of $I_T$ (fraction of $\tau_m$) and the stimulus period ($T_p$ in sec).

**Figure 7:** Effect of inward current $I_h$ on AR with varying stimulus intensity. Stimulus strength to Inhibitory neuron IN5 and to dendritic compartment of TL5 are kept constant ($g_{stim,i} = 3.0$ p.u., $g_d = 0.4$ p.u.). Other parameters are same as before; $g_{stim}$ is the strength of soma stimulus in per unit. (A) Effect of maximal ionic conductance $g_h$ (soma: $g_{h,som}$, proximal dendrites: $g_{h,prox}$) under different stimulus strengths (n=13 shocks, inhibition
kept constant). Note that intermediate stimulus strength gives largest range for augmentation. **(B)** Large stimulus intensity could prevent AR firing under intermediate $g_h$ concentrations ($g_{h,\text{prox}} = 0.10 \text{ mS/cm}^2$, $g_{h,\text{som}} = 0.13 \text{ mS/cm}^2$). Notation for all plots in B: Blue: $g_{\text{stim}}$ = 9.0 p.u., red: $g_{\text{stim}}$ = 6.0 p.u.. B1: somatic membrane potential. B2: corresponding somatic $I_h$ current. Section marked by horizontal bar is expanded in B3. (* is effect of reduced membrane voltage after firing first AP). **(C)** Another example on the controlling effect of $I_h$ as $g_{\text{stim}}$ is increased. Shown are the (C1) total inward current $I_h$ and (C2) the corresponding $I_h$ total ionic conductance. Legend applies to C1 and C2. Plots at asterisk: see text for explanation.

**Figure 8:** Effect of slow inhibition increase on augmentation in a single TL5-IN5 pair. Plotted are contour lines for the number of spikes in TL5 after n=12 shocks (shown only contour lines with numbers at or above 20). Titles above plots refer to the utilized variations with respect to reference values of GABA-B synaptic strength ($g_b = g_{\text{gaba-b,max}} = 60 \text{ nS}$), GABA-A synaptic strength ($g_a = g_{\text{gaba-a,max}} = 80 \text{ nS}$), and recruitment ratio ($r_c = g_{\text{stim,i}} / g_{\text{stim}} = 0.25$) for each of the plots. **(A)** At low levels of gaba-b synaptic strength of gb, TL5 cell can augment between 6-12 Hz and increase with stimulus strength. **(B)** At high levels of GABA-B synaptic strength of 2gb, TL5 cell can augment between 4 and 14 Hz. **(C)** Increasing recruitment ratio to $2r_c$ at low levels of GABA-B synaptic strength leads to reduced AR frequency range or increased frequency tuning at low stimulus strength ($g_{\text{stim}}$ = 5-7 p.u., asterisk). **(D)** AR frequency range is also restricted for increased recruitment ($2r_c$) and increased GABA-B strength (2gb). **(E, F)** The increased frequency tuning is due to GABA-A synapses. With higher recruitment ratio ($2r_c$), decreasing GABA-A synaptic strength to 0.6$g_a$ ($= 0.6g_{\text{gaba-a,max}} = 50 \text{ nS}$) will remove the increased frequency tuning observed under higher GABA-A strengths ($g_a$ in c and d) both for low GABA-B strength (E) and higher GABA-B strength (F). Throughout, apical input to TL5 is kept fixed to $gd=0.4$ p.u.

**Figure 9:** Effect of changing the nature of slow inhibition from GABA-B mediated to GABA-A,slow mediated. **(A)** Augmentation strength (number of spikes/per stimulus shock, n=12 shocks) as a function of stimulus frequency. Circles: GABA-B synapses are
used for slow inhibition (reference case); squares: GABA-A, slow synapses are used. Note the dashed line represents single spike per stimulus and thus minimum desired. (B) Maximum synaptic conductance for slow inhibition achieved after n=12 shocks for the two cases of reference GABA-B synapses (circles) and GABA-A,slow synapses (squares). Note the sublinear (saturating) nature of GABA-B synapses with increasing frequency (> 10 Hz). (C) Example of the membrane potentials of TL5 and IN5 cells when GABA-B synapses are used to create slow inhibition. Note the high frequency firing in IN5 which is necessary for GABA-B activation. Filled upward triangles: stimulus delivery time. (D) Example of membrane potentials of TL5 and IN5 cells when GABA-A,slow inhibition is used to create slow inhibition. Voltage scale bar applies to both C and D.

Figure 10: Firing characteristics in eight cell model under different synaptic connection patterns from upper area Ctx-H to lower area Ctx-L. (A) Schematic of the hierarchical connection topography between Ctx-H and Ctx-L. In all scenarios to follow, 9 shocks of the stimulus are delivered as shown to zones A and B of Ctx-H TL5 neurons (strengths \( g_{\text{stim},s} = 5.0 \text{ p.u.}, \ g_{\text{stim},d} = 0.4 \text{ p.u.} \)), and to IN5 (strength \( g_{\text{stim},i} = 0.4 \text{ p.u.} \) see table 4). (B) Firing diagram for the eight cells under a stimulus frequency of \( T_p = 0.08 \text{sec} \) (12.5 Hz) represented as triangles at bottom of plots. Dots on a single horizontal line indicate times of single spike firing of one TL5 neuron. In this and all similar traces to follow, Ctx-H cells are upper group of four traces, Ctx-L are the lower group. B1: Synaptic inputs from upper area Ctx-H to lower area Ctx-L arrive to both zones A and B in TL5 cells of area Ctx_L (\( g_{HL,s} = 1.40 \text{ p.u.}, \ g_{HL,d} = 0.14 \text{ p.u.} \)), augmentation starts after 3-4 cycles. B2: Synaptic input arriving to zone B only with equivalent total strength (\( g_{HL,s} = 1.54 \text{ p.u.}, \ g_{HL,d} = 0.00 \text{ p.u.} \)); augmentation is delayed and occurs at alternate cycles. (C) Augmentation in average number of spikes in Ctx-H, Ctx-L under different stimulus periods \( T_p \) (in seconds). In this and subsequent similar plots, each data point shown represents average number of spikes obtained after 9 shocks. Averaging is performed over 4 cells in any particular area and over 5 simulation runs with random in vivo currents applied. Circles/solid lines: number of spikes in lower area Ctx-L. Squares/dashed lines: number of spikes in upper area Ctx-H. For this scenario: Open markers (squares, circles)
are when both zones A and B of Ctx-L are active (as in B1). Filled black markers (squares, circles) are when only zone B of Ctx-L is active (as in B2). Note here that augmentation implies greater than 9 spikes over 9 input shocks.

**Figure 11:** (A) Augmentation is maximal when zone A of Ctx-H is active. Firing diagram in eight cell model under high frequency stimulus (Tp=0.08 sec, 12.5 Hz) under different input patterns to upper area Ctx-H. Notation is that used in previous figure. **A1:** Reference case (as in Figure 10B1): Both (zone B, zone A) of upper area Ctx-H are active (g\text{stim},s = 5.0 p.u., g\text{stim},d = 0.4 p.u.). **A2:** Stimulus to zone A of Ctx-H is removed (g\text{stim},s = 5.0 p.u., g\text{stim},d = 0.0 p.u.). Note missed stimulus cycles in Ctx-H and Ctx-L cells. **A3:** increasing stimulus to zone B of Ctx-H does not account for loss of corresponding zone A input (equivalent strength to zone B g\text{stim},s = 5.4 p.u., zone A g\text{stim},d = 0.0 p.u.). Connection strengths between areas and stimulus to local IN5 are kept fixed (gHL,s = 1.40 p.u., gHL,d = 0.14 p.u.). **A4:** Average number of spikes for different frequencies under loss of zone A inputs to Ctx-H. Shown are AR frequency curve in reference case (represented by Ctx-H: open circles/thin solid line; Ctx-L open squares/thin dashed line) and AR frequency curves under increased zone B, no zone A stimulus in Ctx-H (as in A3, represented by Ctx-H, filled circles/thick solid line; Ctx-L filled squares/thick dashed line). (B) Augmentation is highly reduced when zone A inputs to Ctx-H and Ctx-L are lost, even if zone B inputs are increased by equivalent strength. **B1:** Firing diagram of another simulation of the reference case at 12.5 Hz stimulus frequency (g\text{stim},s = 5.0 p.u., g\text{stim},d = 0.4 p.u., gHL,s = 1.40 p.u., gHL,d = 0.14 p.u.). **B2:** Removal of zone A in Ctx-L and Ctx-H with zone B compensated by equivalent total strength (g\text{stim},s = 5.4 p.u., g\text{stim},d = 0.0 p.u., gHL,s = 1.54 p.u., gHL,d = 0.0 p.u.) shows delayed AR initiation and beat-skipping at 12.5 Hz. **B3:** AR frequency curve for the latter case (no zone A, compensated zone B in Ctx-H and Ctx-L, represented in Ctx-H by filled circles/thick solid line, and in Ctx-L by filled squares/thick dashed line) is significantly reduced at all frequencies compared to the reference case (both zones A and B active in the two areas, represented in Ctx-H by open circles/thin solid line, and in Ctx-L by open squares/thin dashed line).

**Figure 12:** Effect of increased background activity on augmentation strength and
frequency under different feedback connection strengths from Ctx-H to Ctx-L. The value $\mu_{dc}$ in legend of plot (C) is the mean of the in vivo like current injected and applies to all plots. ($gstim, s = 5.0 \text{ p.u.}, \, gstim, d = 0.4 \text{ p.u.}, \, gHL, s = 1.40 \text{ p.u.}$ and inhibitory strengths are fixed). All Plots are averages of n=5 runs. (A and B) AR frequency curves under varying background activity for (A) low apical feedback synaptic strength ($gHL, d = 0.07 \text{ p.u.}$) and (B) increased apical feedback synaptic strength ($gHL, d = 0.14 \text{ p.u.}$). Note: dashed lines in A,B (zero or negative current) correspond to no augmentation but burst firing in TL5 at onset of stimulus.; also, asterisk in plot a at ($\mu_{dc} = +0.2 \text{ nA}$) shows beat skipping at 12.5 Hz (C) Effect of background activity on the gain associated with the zone A feedback input from Ctx-H to Ctx-L. Plotted is the ratio of the number of spikes generated under increased apical input ($g21, d = 0.14 \text{ p.u.}$) to the number of spikes under low input ($g21, d = 0.07 \text{ p.u.}$) . Plots are for fixed basal input to Ctx-L ($gHL, s = 1.40 \text{ p.u.}$) .
Table 1 - Ionic currents in TL5 cell

<table>
<thead>
<tr>
<th>Current Type</th>
<th>Formula</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fast Sodium current $I_{Na}$</td>
<td>$I_{Na} = g_{Na} m^3 h (E_{Na} - V)$</td>
</tr>
<tr>
<td></td>
<td>$\alpha_m = -320 (V + 50) / e^{-(V+50)/4.0 - 1}$</td>
</tr>
<tr>
<td></td>
<td>$\beta_m = 280 (V + 23) / e^{(V+23)/5.0 - 1}$</td>
</tr>
<tr>
<td></td>
<td>$\alpha_h = 128 e^{-(V+46)/18}$</td>
</tr>
<tr>
<td></td>
<td>$\beta_h = 4000 [1 + e^{-(V+23)/5}]$</td>
</tr>
<tr>
<td>Delayed rectifier current $I_{Kdr}$</td>
<td>$I_{Kdr} = g_{Kdr} n^4 (E_K - V)$</td>
</tr>
<tr>
<td></td>
<td>$\alpha_n = -32 (V + 48) / e^{-(V+48)/5.0 - 1}$</td>
</tr>
<tr>
<td></td>
<td>$\beta_n = 500 e^{-(V+53)/40.0}$</td>
</tr>
<tr>
<td>High threshold Ca2+ current $I_{Ca}$</td>
<td>$I_{Ca} = g_{Ca} m^2 h \left( \frac{1}{1 + [Ca]/0.5} \right) I_{GHIK}$</td>
</tr>
<tr>
<td></td>
<td>$\alpha_m = 1600 / (1 + e^{-(V-5)/13.9})$</td>
</tr>
<tr>
<td></td>
<td>$\beta_m = 20 (V + 8.9) / e^{(V+8.9)/5 - 1}$</td>
</tr>
<tr>
<td></td>
<td>$h_\infty = 1 / (1 + e^{(V+42)/8})$</td>
</tr>
<tr>
<td></td>
<td>$\tau_h = 0.2 \text{ sec}$</td>
</tr>
<tr>
<td></td>
<td>$I_{GHIK} = k_o \left[ 1 - \left[ \frac{Ca}{[Ca]_o} \right] e^\lambda \right] f(\lambda)$</td>
</tr>
<tr>
<td></td>
<td>$k_o = \frac{RT}{2F} = 25.3 \left( \frac{T + 273.15}{2 \times 293.15} \right)$</td>
</tr>
<tr>
<td></td>
<td>$\lambda = \frac{V}{k_o}$</td>
</tr>
<tr>
<td></td>
<td>$f(\lambda) = \begin{cases} \frac{\lambda}{e^{\lambda} - 1} &amp; \lambda &gt; 0 \ 1 - \lambda / 2 &amp; \text{else} \end{cases}$</td>
</tr>
<tr>
<td>Slow voltage-dependent K current $I_{Ks}$</td>
<td>$I_{Ks} = g_{Ks} m^2 \left( 0.5 h_{fast} + 0.5 h_{slow} \right) (E_{Ks} - V)$</td>
</tr>
<tr>
<td></td>
<td>$m_\infty = 1 / (1 + e^{-(V+14.3)/14.6})$</td>
</tr>
<tr>
<td></td>
<td>$\phi_m = 2.72$</td>
</tr>
<tr>
<td></td>
<td>$\tau_m = \begin{cases} 1 e^{-3} \left[ 1.25 + 13 e^{-0.026 V} \right] &amp; V &gt; -50 \text{ mV}; \ 1 e^{-3} \left[ 1.25 + 175 e^{0.026 V} \right] &amp; V \leq -50 \text{ mV} \end{cases}$</td>
</tr>
<tr>
<td></td>
<td>$h_{n,fast} = h_{n,slow} = 1 / (1 + e^{(V+54)/11})$</td>
</tr>
<tr>
<td></td>
<td>$\phi_m = 2.72$</td>
</tr>
<tr>
<td></td>
<td>$\tau_{h,fast} = 1 e^{-3} \left[ 360 + (1010 + 24 (V + 55)) e^{-\left(\frac{V+75}{48}\right)^2} \right]$</td>
</tr>
<tr>
<td></td>
<td>$\tau_{h,slow} = 1 e^{-3} \left( 4V + 3330 \right)$</td>
</tr>
<tr>
<td>Ca2+-dependent K current $I_{KCa}$</td>
<td>$I_{KCa} = g_{KCa} min \left( \frac{[Ca] - 0.05}{0.5} \right) (E_K - V)$</td>
</tr>
<tr>
<td></td>
<td>$\alpha_m = \begin{cases} 2000 e^{(V+53.5)/27} &amp; V &gt; -10 \text{ mV}; \ 52.7 e^{(V+50)/11 - (V+53.5)/27} &amp; V \leq -10 \text{ mV} \end{cases}$</td>
</tr>
<tr>
<td></td>
<td>$\beta_m = \begin{cases} 2000 e^{-(V+53.5)/27} - \alpha_m &amp; V \leq -10 \text{ mV} \end{cases}$</td>
</tr>
</tbody>
</table>
### Table 2: Ionic currents in TL5 cell –continued

<table>
<thead>
<tr>
<th>Current Type</th>
<th>Equation</th>
<th>Parameters</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ca^{2+}-dependent AHP current</strong></td>
<td>In soma: $I_{AHP} = g_{AHP} m_{\infty} \min \left( 1, \frac{[Ca] - 0.05}{0.5}, (E_K - V) \right)$</td>
<td>$m_{\infty} = \left{ \begin{array}{ll} 1 &amp; V \geq -40 mV \ \frac{1}{(V+54)/14} &amp; -54 &lt; V &lt; -40 mV \end{array} \right.$</td>
</tr>
<tr>
<td>In dendrites: $I_{AHP} = g_{AHP} m_{\infty} \min \left( 1, \frac{[Ca] - 0.05}{2}, (E_K - V) \right)$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$E_K = -90 mV$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Fast inactivating K current</strong></td>
<td>$I_A = g_A m h (E_K - V)$</td>
<td>$E_K = -90 mV$</td>
</tr>
<tr>
<td>$m_{\infty} = \frac{1}{1 + e^{-(V+17.7)/16.6}}$</td>
<td>$\tau_m = 1.25 \times 10^{-3}$</td>
<td></td>
</tr>
<tr>
<td>$h_{\infty} = \frac{1}{1 + e^{(V+7.2)/6.7}}$</td>
<td>$\tau_h = 6.3 \times 10^{-3}$ / $e^{(V+46)/5} + e^{-(V+238)/37.5}$</td>
<td>$V &gt; -63 mV$</td>
</tr>
<tr>
<td></td>
<td>$0.3 \times 10^{-3}$ / $e^{(V+46)/5} + e^{-(V+238)/37.5}$</td>
<td>$V \leq -63 mV$</td>
</tr>
<tr>
<td><strong>Muscarinic current</strong> $I_M = g_M m (E_K - V)$</td>
<td>$E_K = -90 mV$</td>
<td></td>
</tr>
<tr>
<td>$m_{\infty} = \frac{1}{1 + e^{-(V+35)/10}}$</td>
<td>$\tau_m = 1 / (3.33 e^{(V+35)/20} + e^{-(V+35)/20})$</td>
<td></td>
</tr>
<tr>
<td><strong>Low-threshold Calcium current</strong> $I_T = g_T m_{\infty}^2 h (E_{Ca} - V)$</td>
<td>$E_{Ca} = 110 mV$</td>
<td></td>
</tr>
<tr>
<td>$m_{\infty} = \frac{1}{1 + e^{-(V+57)/6.2}}$</td>
<td>$\tau_h = 1 e^{-3} \left[ 8.2 + 56.6 + 0.27 e^{(V+115.2)/5}/(1 + e^{(V+86)/3.2}) \right]$</td>
<td></td>
</tr>
<tr>
<td>$h_{\infty} = \frac{1}{1 + e^{(V+80)/4}}$</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Hyperpolarization-activated mixed cation current</strong> $I_h$</td>
<td>In soma: $I_h = g_h m_{\infty} (E_h - V)$ $E_h = -43 mV$</td>
<td>$m_{H_{\infty}} = \frac{1}{1 + e^{(V+75/5.5)}}$</td>
</tr>
<tr>
<td>In dendrites: $I_h = g_h m_{\infty} (E_h - V)$ $E_h = -47 mV$</td>
<td>$m_{H_{\infty}} = \frac{1}{1 + e^{(V+94.8)/7.8}}$</td>
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</tbody>
</table>
Table 3- Channel Densities (mS/cm²)

<table>
<thead>
<tr>
<th>Current</th>
<th>Soma</th>
<th>Proximal</th>
<th>Distal</th>
</tr>
</thead>
<tbody>
<tr>
<td>$g_{Na}$</td>
<td>20</td>
<td>4</td>
<td>2.75</td>
</tr>
<tr>
<td>$g_{Kdr}$</td>
<td>7</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>$g_{Ca}$</td>
<td>1.67</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>$g_{AHP}$</td>
<td>0.5</td>
<td>0</td>
<td>1.32</td>
</tr>
<tr>
<td>$g_{KCa}$</td>
<td>0</td>
<td>0</td>
<td>0.5</td>
</tr>
<tr>
<td>$g_{A}$</td>
<td>1</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>$g_{Ks}$</td>
<td>0</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>$g_{M}$</td>
<td>0.03</td>
<td>0</td>
<td>0.005</td>
</tr>
<tr>
<td>$g_{h}$</td>
<td>0.06</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>$g_{T}$</td>
<td>1.15</td>
<td>1.6</td>
<td>0</td>
</tr>
<tr>
<td>$g_{leak}$</td>
<td>0.05</td>
<td>0.08</td>
<td>0.12</td>
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Table 4-Connection strengths of eight cell model

<table>
<thead>
<tr>
<th>Values in per unit of $g_{\text{ampa}, \text{max}} = 100 , nS$; $g_{\text{gaba-a, max}} = 80 , nS$; $g_{\text{gaba-b, max}} = 75 , nS$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Within one area</strong></td>
</tr>
<tr>
<td>$g_{e,e} = 0.4$, $g_{e,i} = 0.2$, $g_{e,i1} = 0.05$, $g_{i,e,a} = 1.0$, $g_{i,e,b} = 1.0$, $g_{i,e,a1} = 0.2$, $g_{i,e,b1} = 0.2$</td>
</tr>
<tr>
<td><strong>Feedback Ctx-H to Ctx-L:</strong></td>
</tr>
<tr>
<td>Pyramidal-pyramidal $TL5_H$ to $TL5_L$</td>
</tr>
<tr>
<td><em>To soma:</em> $g_{HL,s} = x$ (cell 1), 0.95x, 0.9x, 1.0x (cells 2,3,4)</td>
</tr>
<tr>
<td><em>where cell 1 is first order neighbor, cell 2 is second order, etc.</em></td>
</tr>
<tr>
<td><em>To dendrites:</em> $g_{HL,d} = y$ (uniform, cells 1–4)</td>
</tr>
<tr>
<td>Pyramidal-interneuron $TL5_H$ to $IN5_L$: $g_{HL,j} = 0.8$ (uniform, cells 1–4)</td>
</tr>
<tr>
<td><strong>Feedforward Ctx-L to Ctx-H:</strong></td>
</tr>
<tr>
<td>Pyramidal-pyramidal $TL5_L$ to $TL5_H$: $g_{LH,s} = 0.2$, $g_{LH,d} = 0$ (uniform, cells 1–4)</td>
</tr>
<tr>
<td>Pyramidal-interneuron $TL5_L$ to $IN5_H$: $g_{LH,j} = 0.2$ (uniform, cells 1–4)</td>
</tr>
<tr>
<td><strong>Stimulus to Ctx-H:</strong></td>
</tr>
<tr>
<td>Pyramidal cells $TL5_H$</td>
</tr>
<tr>
<td><em>To soma:</em> $g_{stim,s} = z$ (cell 1), 0.87z, 0.92z, 0.95z (cells 2,3,4)</td>
</tr>
<tr>
<td><em>To dendrites:</em> $g_{stim,d} = w$ (cell 1), 0.87w, 0.92w, 0.95w (cells 2,3,4)</td>
</tr>
<tr>
<td>Interneurons $IN5_H$: $g_{sim,j} = v = 0.4$ (cell 1), 0.97v, 0.92v, 0.95v (cells 2,3,4)</td>
</tr>
</tbody>
</table>
Figure 1: (A) Schematic of the simplified three compartment model of TL5 cells. (B) Schematic of a TL5-INS pair with connections capable of inducing augmentation. Indicated on TL5 are approximate locations of apical dendritic zone A, proximal dendritic zone C and basal dendritic zone B. Excitatory connections are given by open triangle and are of AMPA type. Inhibitory connections are filled triangles and are of GABA-A and GABA-B type. (C) Schematic of the eight cell two-area model. Shown are connections of each type of cell. Note that all connections are symmetric. Neighborhood connections are of length 1. Ctx-L to Ctx-H have characteristic ascending (feedforward) topology, Ctx-H to Ctx-L have descending (feedback) topology.
Figure 2: Response of TL5 cell model to current injections. (A) A somatic pulse Is injection (green trace) produced single action potential at soma compartment (blue trace) and little depolarization in dendritic compartment (red). Scale bars and colors apply to figures A, B, and C. (B) An EPSP-like injection Id to the distal dendritic compartment (light green) produced a Ca2+ AP and an associated somatic burst. (C) Injection of Is followed by Id within after 10 msec of much lower magnitude produced a burst at the soma and a Ca2+ AP in the dendrite. (D) Membrane voltage in the three model compartments during a burst. By injecting a current pulse to distal dendritic compartment of sufficient amplitude, Ca2+ AP is produced (red trace). This is associated with a burst of 2-3 spikes in the soma compartment (blue trace) and backpropagating APs in the proximal dendrite (black trace).
Figure 3: (A) Response of TL5 cell model to increasing levels of somatic hyperpolarization (three traces shown). As an injected hyperpolarizing somatic current is removed after 300 msec, a rebound depolarization occurs, which could lead to firing. Note the initial sag in the hyperpolarized voltage due to presence of Ih (Castro-Alamancos and Connors 1996a). (B) Effect of Ih on TL5 cell model response. Top: rebound depolarization, after somatically-injected hyperpolarizing current, in the unaltered cell causes regular spiking at the soma (solid trace) and small depolarization in the dendritic compartment (dashed trace). Bottom: rebound depolarization after removal of Ih from the proximal compartment. Injected current to the soma is equivalent to that in above trace. Note that the regular firing at the soma can now invade the distal dendritic compartment to evoke Ca2+ AP there (dashed) and burst firing at the soma (solid).
Figure 4: (A) Current to rate transfer function in TL5 cell model under somatic and/or dendritic compartment in vivo like current injections. The current to rate transfer functions were obtained by calculating the mean spike rate at the soma for each current step and plotting the rate against the mean current $\mu$. (i) For somatic current injections only (filled circles, Gaussian $\sigma = 0.3 \text{ nA}$, $\tau = 3 \text{ ms}$, $\mu_{\text{start}} = 0.02 \text{ nA}$, $\mu_{\text{dc}} = 0.1 \text{ nA}$, step duration $= 2 \text{ s}$, 9 steps, mean of $n=5$ simulations), the rate was fitted with the linear threshold function $F = 41.0143I_s + 14.252$. (ii) For current injection to the distal dendritic compartment only, (open circles, $\sigma = 0.3 \text{ nA}$, $\tau = 3 \text{ ms}$, $\mu_{\text{start}} = 0.7 \text{ nA}$, $\mu_{\text{dc}} = 0.05 \text{ nA}$, step duration $= 2 \text{ s}$, 13 steps, mean of $n=5$ simulations), the rate function was fitted with the linear threshold function $F = 65.66I_d + 56.4$. (iii) Modulation of the somatic current to rate transfer function in the presence of dendritic current. Here, a Gaussian current with constant mean ($\mu_{\text{ddc}} = 0.75 \text{ nA}$) and standard deviation ($\sigma_{\text{d}} = 0.3 \text{ nA}$) was injected into distal dendritic location. The somatic current was then injected (open squares, Gaussian $\sigma = 0.3 \text{ nA}$, $\tau = 3 \text{ ms}$, $\mu_{\text{start}} = 0.02 \text{ nA}$, $\mu_{\text{dc}} = 0.1 \text{ nA}$, step duration $= 2 \text{ s}$, 6 steps, mean of $n=5$ simulations) to give a linear fit of $F = 56.06I_s + 9.53$.

(B) Model cell response to increased sustained depolarization of dendritic compartment. Top left: Low injection levels (lower trace, $I_d = 1.15 \text{ nA}$) produced burst firing at a low repetition rate (upper trace). As dendritic current injection is increased, the rate of burst firing increases (top right: $I_d = 1.25 \text{ nA}$, bottom left: $I_d = 1.3 \text{ nA}$). A switch to regular firing occurs with further depolarization (bottom right, $I_d = 1.65 \text{ nA}$).

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Figure 5: Augmenting response is a single TL5-IN5 pair. (A) TL5-IN5 pair and associated weights, in per unit (p.u.): gaba-a: gie,a =0.8 p.u., gaba-b: gie,b =1.0 p.u., ampa: gei =2.0 p.u., gstim,i = gstim. (B) Top trace: Somatic voltage trace in TL5 shows AR achieved when apical input is present (gd = 0.5 p.u.) in addition to somatic stimulus (gstim = 5.0 p.u.). Middle trace: no AR is achieved when apical is not present, even with a 1.5 fold increase in somatic stimulus (gstim = 7.5 p.u.). Bottom trace: stimulus delivery times (Tp=0.1 sec, 10 Hz) represented by filled up triangles. (C) Expanded view of B showing dendritic voltage (zone A, dashed lines) and somatic voltage (zone B, solid lines) in TL5 cell model. (D) Relative Synaptic strength required for augmentation (somatic baseline gstim = 6.0 p.u.). Lines are for simultaneous zones A and B stimulation (reference case, gstim = 6.0 p.u., gd = 0.4 p.u.). Dashed lines: number of spikes after 13 shocks; dashed-dotted lines: number of spikes after 4 shocks. Squares are for zone B only stimulation (gd = 0.0 p.u.). Filled markers: the number of spikes after 13 shocks; open markers: number of spikes after 4 shocks.

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Figure 6: (A) Effect of somatic low threshold calcium current IT channel density change on AR in TL5 cell model. Shown are contour lines for the number of spikes in TL5 after the stimulus delivery of 13 shocks of strength $g_{stim}$ (in per unit). Base line for conductances in soma is $g_{T,som}=1.15$ mS/cm$^2$ and in proximal dendrite is $g_{T,prox} = 1.60$ mS/cm$^2$. Synaptic connections strengths are the same as before except $g_{stim,i} = 3.0$ p.u.. Note that AR implies contour lines greater than 13 (> 13 spikes after 13 shocks). Dotted contour with 5 spikes: No AR. (B) Effect of varying IT inactivation kinetics on AR. Plotted are contour lines of achievable number of spikes after 13 shocks as a function of a constant multiple of the inactivation time constant of IT (fraction of $\tau$) and the stimulus period (Tp in sec).
Figure 7: Effect of inward current $I_h$ on AR with varying stimulus intensity. Stimulus strength to Inhibitory neuron IN5 and to dendritic compartment of TL5 are kept constant ($g_{stim,i} = 3.0$ p.u., $g_d = 0.4$ p.u.). Other parameters are same as before; $g_{stim}$ is the strength of soma stimulus in per unit. (A) Effect of maximal ionic conductance $g_h$ (soma: $g_{h,som}$, proximal dendrites: $g_{h,prox}$) under different stimulus strengths ($n=13$ shocks, inhibition kept constant). Note that intermediate stimulus strength gives largest range for augmentation. (B) Large stimulus intensity could prevent AR firing under intermediate $g_h$ concentrations ($g_{h,prox} = 0.10$ mS/cm$^2$, $g_{h,som} = 0.13$ mS/cm$^2$). Notation for all plots in B: Blue: $g_{stim} = 9.0$ p.u., red: $g_{stim} = 6.0$ p.u.. B1: somatic membrane potential. B2: corresponding somatic $I_h$ current. Section marked by horizontal bar is expanded in B3. (* is effect of reduced membrane voltage after firing first AP). (C) Another example on the controlling effect of $I_h$ as $g_{stim}$ is increased. Shown are the (C1) total inward current $I_h$ and (C2) the corresponding $I_h$ total ionic conductance. Legend applies to C1 and C2. Plots at asterisk: see text for explanation.
Figure 8: Effect of slow inhibition increase on augmentation in a single TL5-IN5 pair. Plotted are contour lines for the number of spikes in TL5 after n=12 shocks (shown only contour lines with numbers at or above 20). Titles above plots refer to the utilized variations with respect to reference values of GABA-B synaptic strength \( g_{\text{gaba-B,max}} = 60 \, \text{nS} \), GABA-A synaptic strength \( g_{\text{gaba-A,max}} = 80 \, \text{nS} \), and recruitment ratio \( r_{\text{c}} = \frac{g_{\text{stim,i}}}{g_{\text{stim}}} = 0.25 \) for each of the plots. (A) At low levels of gaba-B synaptic strength of \( g_b \), TL5 cell can augment between 6-12 Hz and increase with stimulus strength. (B) At high levels of GABA-B synaptic strength of 2\( g_b \), TL5 cell can augment between 4 and 14 Hz. (C) Increasing recruitment ratio to 2\( r_c \) at low levels of GABA-B synaptic strength leads to reduced AR frequency range or increased frequency tuning at low stimulus strength \( g_{\text{stim}} = 5-7 \, \text{p.u.} \), asterisk). (D) AR frequency range is also restricted for increased recruitment (2\( r_c \)) and increased GABA-B strength (2\( g_b \)). (E, F) The increased frequency tuning is due to GABA-A synapses. With higher recruitment ratio (2\( r_c \)), decreasing GABA-A synaptic strength to \( 0.6 g_{\text{gaba-A,max}} = 50 \, \text{nS} \) will remove the increased frequency tuning observed under higher GABA-A strengths (ga in c and d) both for low GABA-B strength (E) and higher GABA-B strength (F). Throughout, apical input to TL5 is kept fixed to \( g_d = 0.4 \, \text{p.u.} \).
Figure 9: Effect of changing the nature of slow inhibition from GABA-B mediated to GABA-A,slow mediated. (A) Augmentation strength (number of spikes/per stimulus shock, n=12 shocks) as a function of stimulus frequency. Circles: GABA-B synapses are used for slow inhibition (reference case); squares: GABA-A, slow synapses are used. Note the dashed line represents single spike per stimulus and thus minimum desired. (B) Maximum synaptic conductance for slow inhibition achieved after n=12 shocks for the two cases of reference GABA-B synapses (circles) and GABA-A,slow synapses (squares). Note the sublinear (saturating) nature of GABA-B synapses with increasing frequency (> 10 Hz). (C) Example of the membrane potentials of TL5 and IN5 cells when GABA-B synapses are used to create slow inhibition. Note the high frequency firing in IN5 which is necessary for GABA-B activation. Filled upward triangles: stimulus delivery time. (D) Example of membrane potentials of TL5
and IN5 cells when GABA-A,slow inhibition is used to create slow inhibition. Voltage scale bar applies to both C and D.

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Figure 10: Firing characteristics in eight cell model under different synaptic connection patterns from upper area Ctx-H to lower area Ctx-L. (A) Schematic of the hierarchical connection topography between Ctx-H and Ctx-L. In all scenarios to follow, 9 shocks of the stimulus are delivered as shown to zones A and B of Ctx-H TL5 neurons (strengths \(g_{stim,s} = 5.0\) p.u., \(g_{stim,d} = 0.4\) p.u.), and to IN5 (strength \(g_{stim,i} = 0.4\) p.u. see table 4). (B) Firing diagram for the eight cells under a stimulus frequency of \(T_p = 0.08\) sec (12.5 Hz) represented as triangles at bottom of plots. Dots on a single horizontal line indicate times of single spike firing of one TL5 neuron. In this and all similar traces to follow, Ctx-H cells are upper group of four traces, Ctx-L are the lower group. B1: Synaptic inputs from upper area Ctx-H to lower area Ctx-L arrive to both zones A and B in TL5 cells of area Ctx_L (\(g_{HL,s} = 1.40\) p.u., \(g_{HL,d} = 0.14\) p.u.), augmentation starts after 3-4 cycles. B2: Synaptic input arriving to zone B only with equivalent total strength (\(g_{HL,s} = 1.54\) p.u., equivalent strength, and \(g_{HL,d} = 0.00\) p.u.); augmentation is delayed and occurs at alternate cycles. (C) Augmentation in average number of spikes in Ctx-H, Ctx-L under different stimulus periods \(T_p\) (in seconds). In this and subsequent similar plots, each data point shown represents average number of spikes obtained after 9 shocks. Averaging is performed over 4 cells in any particular area and over 5 simulation runs with random in-vivo currents applied. Circles/solid lines: number of spikes in lower area Ctx-L. Squares/dashed lines: number of spikes in upper area Ctx-H. For this
scenario: Open markers (squares, circles) are when both zones A and B of Ctx-L are active (as in B1). Filled black markers (squares, circles) are when only zone B of Ctx-L is active (as in B2). Note here that augmentation implies greater than 9 spikes over 9 input shocks.
Figure 11: (A) Augmentation is maximal when zone A of Ctx-H is active. Firing diagram in eight cell model under high frequency stimulus (Tp=0.08 sec, 12.5 Hz) under different input patterns to upper area Ctx-H. Notation is that used in previous figure. A1: Reference case (as in Figure 10B1): Both (zone B, zone A) of upper area Ctx-H are active (gstim,s =5.0 p.u., gstim,d =0.4 p.u.). A2: Stimulus to zone A of Ctx-H is removed (gstim,s =5.0 p.u., gstim,d =0.0 p.u.). Note missed stimulus cycles in CtxGH and CtxGL cells. A3: Increasing stimulus to zone B of Ctx-H does not account for loss of corresponding zone A input (equivalent strength to zone B gstim,s =5.4 p.u., zone A gstim,d =0.0 p.u.). Connection strengths between areas and stimulus to local IN5 are kept fixed (gHL,s = 1.40 p.u., gHL,d =0.14 p.u.). A4: Average number of spikes for different frequencies under loss of zone A inputs to Ctx-H. Shown are AR frequency curve in reference case (represented by Ctx-H: open circles/thin solid line; Ctx-L open squares/thin dashed line) and AR frequency curves under increased zone B, no zone A stimulus in Ctx-H (as in A3, represented by Ctx-H, filled circles/thick solid line; Ctx-L filled squares/thick dashed line). (B) Augmentation is highly reduced when zone A inputs to Ctx-H and Ctx-L are lost, even if zone B inputs are increased by equivalent strength. B1: Firing diagram of another simulation of the reference case at 12.5 Hz stimulus frequency (gstim,s =5.0 p.u., gstim,d =0.4 p.u., gHL,s = 1.40 p.u., gHL,d =0.14 p.u.). B2: Removal of zone A in...
Ctx-L and Ctx-H with zone B compensated by equivalent total strength (gstim,s =5.4 p.u.,
gstim,d =0.0 p.u., gHL,s = 1.54 p.u., gHL,d =0.0 p.u.) shows delayed AR initiation and beat-
skipping at 12.5 Hz. B3: AR frequency curve for the latter case (no zone A, compensated zone
B in Ctx-H and Ctx-L, represented in Ctx-H by filled circles/thick solid line, and in Ctx-L by
filled squares/thick dashed line) is significantly reduced at all frequencies compared to the
reference case (both zones A and B active in the two areas, represented in Ctx-H by open
circles/thin solid line, and in Ctx-L by open squares/thin dashed line).

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Figure 12: Effect of increased background activity on augmentation strength and frequency under different feedback connection strengths from Ctx-H to Ctx-L. The value $\mu_{dc}$ in legend of plot (C) is the mean of the in vivo like current injected and applies to all plots. ($g_{stim,s} = 5.0$ p.u., $g_{stim,d} = 0.4$ p.u., $g_{HL,s} = 1.40$ p.u. and inhibitory strengths are fixed). All Plots are averages of $n=5$ runs. (A and B) AR frequency curves under varying background activity for (A) low apical feedback synaptic strength ($g_{HL,d} = 0.07$ p.u.) and (B) increased apical feedback synaptic strength ($g_{HL,d} = 0.14$ p.u.). Note: dashed lines in A,B (zero or negative current) correspond to no augmentation but burst firing in TL5 at onset of stimulus.; also, asterisk in plot a at ($\mu_{dc}= +0.2$ nA) shows beat skipping at 12.5 Hz (C) Effect of background activity on the gain associated with the zone A feedback input from Ctx-H to Ctx-L. Plotted is the ratio of the number of spikes generated under increased apical input ($g_{21,d} = 0.14$ p.u.) to the number of spikes under low input ($g_{21,d} = 0.07$ p.u.) . Plots are for fixed basal input to Ctx-L ($g_{HL,s} = 1.40$ p.u.)

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