Stimulus features underlying reduced tremor suppression with temporally patterned deep brain stimulation

Abbreviated Title: Tremor changes during temporally patterned DBS

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Abstract

Deep brain stimulation (DBS) provides dramatic tremor relief when delivered at high stimulation frequencies (≥100 Hz), but its mechanisms of action are not well understood. Previous studies indicate that high frequency stimulation is less effective when the stimulation train is temporally irregular. The purpose of this study was to determine the specific characteristics of temporally irregular stimulus trains that reduce their effectiveness: long pauses; bursts; or irregularity, *per se*. We isolated these characteristics in stimulus trains and conducted intraoperative measurements of postural tremor in eight volunteers. Tremor varied significantly across stimulus conditions (*p*<0.015), and stimulus trains with *pauses* were significantly less effective than stimulus trains without *pauses* (*p*<0.002). There were no significant differences in tremor between trains with or without bursts, or between trains that were irregular or periodic. Thus, the decreased effectiveness of temporally irregular DBS trains is due to long *pauses* in the stimulus trains, not the degree of temporal irregularity alone. We also conducted computer simulations of neuronal responses to the experimental stimulus trains using a biophysical model of the thalamic network. Trains that suppressed tremor in volunteers also suppressed fluctuations in thalamic transmembrane potential at the frequency associated with cerebellar burst-driver inputs. Clinical and computational findings indicate that DBS suppresses tremor by masking burst-driver inputs to the thalamus, and that *pauses* in stimulation prevent such masking. While stimulation of other anatomical targets may provide tremor suppression, we propose that the most relevant neuronal targets for effective tremor suppression are the afferent cerebellar fibers that terminate in the thalamus.
Keywords: Computational model; Movement disorders; Thalamus; Cerebellum.
Abbreviations: CER, cerebellar model elements; CTX, cortical model elements; DBS, deep brain stimulation; ET, essential tremor; IPF, instantaneous pulse frequency; IPG, implantable pulse generator; IPI, interpulse interval; ISI, interspike interval; MS, multiple sclerosis; PD, Parkinson’s disease; PLSD, protected least significant difference; PSD, power spectral density; RN, reticular nucleus model elements; STN, subthalamic nucleus; TC, thalamocortical relay neuron; TIN, thalamic interneuron model elements; Vim, ventral intermediate nucleus of the thalamus; $V_m$, transmembrane potential.
Deep brain stimulation (DBS) is an established therapy for the treatment of movement disorders, including essential tremor (ET) and Parkinson’s disease (PD). Although the clinical benefits of DBS are well documented, fundamental questions remain about the mechanisms of action. A hallmark of the effects of DBS on motor symptoms is the effect of stimulation frequency (Birdno and Grill 2008). Maximum reductions in symptoms are typically observed only when the frequency of stimulation is greater than 90 Hz, and lower frequencies are ineffective or may exacerbate symptoms (Benabid et al. 1991; Kuncel et al. 2006; Ushe et al. 2004). The similarity of the clinical effects of ablative lesions and DBS (Vitek 2002) and the frequency dependent effects of DBS gave rise to the hypothesis – termed the informational lesion – that effective DBS masks the intrinsic pattern of neural activity in the stimulated nucleus and replaces it with constant rate firing time locked to the stimulus (Grill et al. 2004). Consistent with this hypothesis, stimulation with temporally random patterns, which did not regularize neural firing, was not effective in suppressing tremor by thalamic DBS in ET (Birdno et al. 2008) or in treating bradykinesia by subthalamic nucleus DBS in PD (Dorval et al. 2010). These results revealed that simply high-rate stimulation was not sufficient for symptom reduction, but it was not clear which characteristic(s) of temporally irregular DBS trains reduced their effectiveness. In the present study, we conducted measurements in human subjects with tremor and computer simulations in a model of thalamic DBS to determine the characteristic(s) of irregular stimulation trains rendered them ineffective.
We used specific temporal patterns of stimulation to quantify the relative contributions of three characteristics to the loss of efficacy with high rate irregular stimulation: pauses, bursts, and irregularity, per se. The first hypothesis \((H_{\text{Pause}})\) was that pauses (long interpulse intervals, IPIs) in stimulation enabled pathological activity to propagate through the thalamus. The source of the activity could be either physiological (i.e., intrinsic pathological activity returned during pauses in stimulus trains) or stimulus-generated (e.g., long periods of hyperpolarization during stimulation deinactivated membrane conductances to enable rebound bursts during pauses).

The second hypothesis \((H_{\text{Burst}})\) was that brief bursts of high-rate stimulation drove burst-like activity in the thalamus. The presence of thalamic bursts is correlated with the symptoms of movement disorders, and irregular trains with short bursts of high-frequency stimulus pulses may disrupt the fidelity of thalamic throughput (Rubin and Terman 2004). The third hypothesis \((H_{\text{Ir}})\) was that the irregularity of the stimulus train, per se, corrupted the effectiveness of the stimulus train. Even if irregular DBS is able to override intrinsic pathological patterns of activity, it does not drive regular firing patterns, and thus is clinically ineffective.

Both experimental and computational results from this study indicate that the decreased effectiveness of irregular DBS trains is due to pauses between stimulus pulses, and that temporally irregular DBS can indeed suppress tremor effectively if there are no long pauses. Further, our findings indicate that the mechanism by which DBS suppresses tremor is by masking burst driver inputs to the thalamus from the cerebellum. Importantly, these findings provide a mechanistic basis for correlative clinical studies, which indicate that the most effective electrode location for tremor suppression is near cerebellar fibers that terminate in the thalamus (Coenen et al. 2011; Hamel et al. 2007; Herzog et al. 2007; Jimenez et al. 2000; Kitagawa et al.
2005; Struppler et al. 1978), and recent preclinical studies suggesting that activation of
presynaptic axons in the STN was necessary and sufficient to alleviate bradykinesia in a rodent
model of PD (Gradinaru et al. 2009). While stimulation of other anatomical targets may provide
tremor suppression, we propose that the most relevant neuronal targets for effective tremor
suppression are the afferent cerebellar fibers that terminate in the thalamus.

**Materials and Methods**

**Ethical Approval**

Subjects participated on a volunteer basis with written informed consent, and the study
protocol was approved by the Institutional Review Boards at Duke University and Emory
University.

**Human subjects and stimulation delivery**

We conducted experiments on eight subjects with tremor (seven ET, one multiple
sclerosis) that was responsive to DBS of the ventral intermediate (Vim) nucleus of the thalamus
and who were having their implantable pulse generator(s) (IPG) surgically replaced due to
depleted batteries. Demographic characteristics and stimulation settings for each subject are
shown in Table 1. Some subjects reported transient paresthesias for some stimulation settings,
but there were no adverse events and no incidents of infection.

Irregular trains of stimulation cannot be delivered using the clinical IPG (Soletra Model
7426 or Kinetra Model 7428, Medtronic Inc., Minneapolis, MN, USA); therefore, we used an
external stimulator that was connected to the implanted DBS lead extension via a custom sterile
extension cable at the time of IPG replacement. Stimuli were delivered with an isolated
stimulator (bp isolator, FHC Inc., Bowdoinham, ME, USA) and pulses were controlled by a high-speed digital-to-analog converter via LabView software (National Instruments, Austin, TX, USA). The regulated voltage stimulation waveform was an asymmetric, charge-balanced, biphasic pulse with a large-amplitude short-duration primary phase followed by a low-amplitude long-duration recharge phase, similar to that used in the IPG. The amplitude of the recharge phase was 10% of the primary phase amplitude and the duration of the recharge phase was 10 times the primary phase duration. Pulse width (PW) and stimulus amplitude were set to clinically programmed values (Table 1), and charge densities were below the manufacturer’s recommended limit of 30 μC/cm²/phase (using conservative estimate that impedance = 500 Ω).

In two cases where clinical settings included the IPG case as the anode the electrode configuration was changed such that the contact farthest from the cathode(s) was selected as the anode (Table 1).

Intraoperative measurements of tremor

We measured tremor in the contralateral limb during unilateral stimulation with six different temporal patterns of stimulation and with stimulation off (controls) in single intraoperative sessions with each subject. Stimulation patterns were presented in a randomized block design, and the subject was blinded to the experimental condition. In each of three trial blocks, each of the seven experimental conditions was presented for one minute in randomized order. Each trial began with one minute of stimulation off, with baseline tremor measured for 20 s beginning ~30 s into these intervals, and ~30 s after each condition was initiated experimental tremor was measured for 20 s (Fig. 1A).
Tremor was measured using an accelerometer (Crossbow CXL04LP3; 5V/4g sensitivity, San Jose, CA, USA) taped to the dorsum of the hand. The amplitude of tremor recorded by an accelerometer correlates well with clinical tremor rating scales (Elble et al. 2006). To obtain a single quantitative measure of tremor for each trial, we first calculated the power spectral density for each of the three acceleration signals (AX, AY, and AZ, Fig. 1B) using the psd function (power spectral density, Welch’s averaged periodogram, Hanning window, FFT length = 5,000) in MATLAB (Mathworks Inc., Natick, Massachusetts, USA). Next, we integrated each spectrum from 2-20 Hz to get PX, PY, and PZ. Finally, we summed PX, PY, and PZ, and took the log of the sum to get a single metric of tremor. The frequency range of 2-20 Hz was chosen to include the primary and several harmonics of the tremor and to exclude steady state acceleration due to gravity.

Temporal patterns of stimulation

The patterns of stimulation were designed to isolate the characteristic(s) that may render irregular stimulus trains ineffective at suppressing tremor: pauses, bursts, and irregularity, per se. The stimulus trains included three irregular patterns with large entropies (~5.2-5.6 bits/pulse, Fig. 2A-C), two periodic patterns with low-entropy (< 1 bit/pulse) that consisted of constant rate pulses interrupted by either long pauses (Fig. 2D) or short bursts of pulses at twice the base frequency (Fig. 2E), and regular stimulation at 185 Hz. All stimulus trains had a geometric mean of 185 Hz.

The stimulus train distributions were created using entropy as the measure of irregularity and were computed in log-space. Stimulus train types were constructed in log-space because distributions in log-space have the same shape (e.g., uniform) and entropy
regardless of whether the distribution is constructed with respect to frequencies or interpulse intervals (IPIs). This is because the nonlinear relationship between frequency and IPI, 
\[ Freq = \frac{1}{IPI} \], becomes a linear relationship in log-space:
\[ \log(Freq) = \log(1) - \log(IPI) = -\log(IPI) \].

Second, common measures used to compute the degree of irregularity in events drawn from a distribution include the coefficient of variation and the entropy of the distribution. The coefficient of variation is simple, but is ineffective in describing the variability of multimodal distributions (Holt et al. 1996). On the other hand, the entropy of a distribution provides an estimate on the maximum degree of irregularity present in the distribution, and can be generalized to any type of distribution (Darbin et al. 2006; Dorval et al. 2008).

The first high-entropy train (Uniform, Fig. 2A) had instantaneous pulse frequencies (IPFs) drawn from a log-uniform distribution with a minimum at 90 Hz and a maximum at ~380 Hz. The Uniform train was highly irregular, but contained no pauses or bursts (i.e., there were no IPIs outside of the established therapeutic frequency range of 90 - 380 Hz). The second high-entropy train (Unipeak, Fig. 2B) had IPFs also drawn from a log-uniform distribution, but with wider frequency limits such that pauses (IPIs > 20 ms) arrived at a rate of 5.4 Hz (i.e., at least as fast as the dominant tremor frequency). The Unipeak distribution had a sharp peak at 185 Hz to ensure that the entropies of the Unipeak and Uniform distributions were equal. The third high-entropy train (Bimodal, Fig. 2C) had IPFs drawn from two log-uniform distributions and contained many pauses and bursts.
The first low-entropy periodic train (Absence, Fig. 2D) contained long pauses that came at a rate of 4.4 Hz, consistent with the predominant frequency of tremor in ET subjects (Deuschl et al. 1998). The second periodic train (Presence, Fig. 2E) contained brief increases in stimulus rate intended to drive bursting in thalamic neurons. These bursts of stimulus pulses occurred at 4.4 Hz (Deuschl et al. 1998) and lasted 52.57 ms, consistent with the burst duration observed in ET (Hua and Lenz 2005).

Computational model

We implemented and validated a biophysically-based computational model of a thalamic neuronal network to simulate the responses of neurons in the ventral intermediate (Vim) nucleus of the thalamus to DBS. The model of each of 50 TC neurons was taken from our previous work, and is an anatomically and electrically accurate representation of mammalian TC neurons that reproduces a wide range of experimental electrophysiology (McIntyre et al. 2004). Presynaptic axons were modeled using a double cable representation of mammalian axons, which we previously developed and validated (McIntyre et al. 2002). Subsequently, each element that was added to the model was based on biological data (Detailed Model Description in Appendix), and the integrated network model was thoroughly validated against available data from brain slices, animals, and humans (Model Validation in Appendix). We used the model to calculate the combined effects of the intrinsic synaptic inputs and DBS on TC neurons. Thus, the responses of each TC neuron depended on a combination of the intrinsic synaptic inputs, changes in the intrinsic synaptic activity evoked by stimulation of the input axons, and the direct effects of stimulation on the TC neuron.
The fundamental unit of the model (Fig. 3) consisted of a TC neuron and four terminating axons carrying inputs from cerebellum (CER), cortex (CTX), reticular nucleus (RN), and local thalamic interneurons (TIN) (Darian-Smith et al. 1996; Tasker and Kiss 1995), and was replicated 50 times to simulate the response of a distributed population of neurons. Each input had an intrinsic pattern of activity, and the inputs were distributed across the compartments of the TC neuron based on reconstruction of synaptic inputs to cat ventral thalamic neurons (Sato et al. 1997). The intrinsic activity of CTX inputs was a 20 Hz Poisson train of spikes (Descheenes and Hu 1990), while the intrinsic activity of CER inputs was based on the burst activity recorded in the harmaline model of tremor in the cat (de Montigny and Lamarre 1973). The rate of harmaline burst activity was decreased from ~10 Hz to 5.8 Hz (11 interspike intervals (ISIs) at 7.0 ms, followed by one ISI at 95 ms) so that the burst frequency of the model TC neurons was consistent with the predominant burst frequency of Vim neurons in humans with ET (Hua and Lenz 2005). The intrinsic activity of inhibitory RN inputs resulted from synaptic excitation of RN by CTX and synaptic excitation of RN via feedback from the TC output (Ando et al. 1995; Steriade et al. 1997), while the intrinsic activity of inhibitory TIN inputs resulted from synaptic excitation of TIN by CTX and CER (Ando et al. 1995).

Model geometry and extracellular stimulation

The Vim thalamus was modeled as an oblique prism with a rectangular base and parallelogram-shaped joining faces, and the center of the cell body of each model TC neuron plus its input axons were positioned within this volume by generating uniformly distributed random coordinates (Fig. 3B). The bases of the prism had a lateral width of 4.0 mm in the
coronal plane and a width of 3.5 mm in the horizontal plane, and the perpendicular distance
between bases was 10 mm (Benabid et al. 1998; Mobin et al. 1999). The TC axons were oriented
along a straight trajectory from the center of the inferior base of Vim thalamus to the hand area
of primary motor cortex, the orientation of CTX axons was inversely symmetric to the TC axons,
the CER axons were oriented 30° posterior to the coronal plane, and the RN and TIN axons
extended directly in the lateral-medial and medial-lateral directions, respectively (Fig. 3C, 3D).
These orientations were selected so that the output of the TC neurons were pointed directly
toward the hand representations of the primary motor cortex (Hlustik et al. 2001). The length of
TIN axons was half that of other axons to account for the fact that these local axons originate
much closer to the TC neuron of interest.

The extracellular voltages produced by DBS were calculated using a finite element
model representation of a Medtronic DBS lead (Model 3387, Minneapolis, MN). The zero
contact of the DBS electrode was positioned at the center of the oblique prism representing the
Vim, and the electrode was angled 30° anterior to the coronal plane (Fig. 3C,D) (Mobin et al.
1999). The tissue was modeled as an isotropic homogeneous medium with conductivity \( \sigma = 0.2 \)
S/m, and the conductivities of the metal electrode contacts and the insulating material between
contacts were 1e7 and 1e-10 S/m, respectively (Wei and Grill 2005). The voltages in the modeled
tissue volume were computed using COMSOL Multiphysics 3.4 (COMSOL, Burlington, MA)
with ~55k tetrahedral elements, and this was sufficient density as doubling the number of
elements changed the potentials by < 6.0% (mean ± s.d. = 1.8 ± 1%). The modeled tissue volume
extended throughout a 8000 cm³ cube centered on the origin, and this volume was sufficiently
large because doubling the length of each side of the cube changed the potentials by < 6.5%
All simulations were performed with the zero contact of the lead as the cathode, and the outside faces of the cube were set to ground to approximate using the implantable pulse generator (IPG) as the return electrode. The boundary condition on the surface of the zero contact was constant voltage, while continuity of current density normal to the surface was imposed for the remaining components of the lead. Voltages outside each compartment of each model TC neuron and each presynaptic axon were calculated using quadratic interpolation of the voltages at the grid points of the finite element mesh.

Simulation Methods

The model neurons were implemented in NEURON 6.1 (Hines and Carnevale 1997), and the transmembrane potential in response to DBS was obtained by backward Euler implicit integration with a time step of 0.01 ms. The population of neurons was simulated for 14 s: 2 s before stimulation, 10 s during DBS, and 2 s after stimulation. The temporal patterns of stimulation applied in the model were the same as those used in the human subjects. Quantitative measures derived from simulation results were analyzed over the period between 2 s and 12 s, even for stimulation off conditions. The stimulation amplitude was set to 7.5 V, and this amplitude directly activated 32 of the 50 TC neurons in the absence of other inputs. The high stimulation voltage, relative to the clinical values, is a reflection of the relatively low density of (50) modeled neurons that were distributed throughout the volume of the Vim (Fig. 3B). This amplitude was chosen to activate a sufficient number of neurons, as changes in tremor suppression with changes in voltage are very strongly correlated with changes in the proportion of activated neurons with changes in voltage (Kuncel et al. 2007). Similarly, in the
present model, stimulation-induced changes in neuronal activity were strongly dependent on stimulation voltage (Figure A.5, panels A and C), and these changes saturated above 7.5 V.

Data analysis and statistics

Tremor during experimental conditions was analyzed as \( \log_{10} \) of the tremor power. Measurements made in different blocks within the same subject were considered replicates and the log-transformed tremor measurements were averaged to get a single measure for each experimental condition within each subject. Measurements from trials in incomplete blocks were included to provide the best estimate of the mean for each stimulus condition.

**Stimulus train entropy**

The average entropy of the stimulus train distributions was computed as (Dorval 2008):

\[
H = - \sum_{i=1}^{351} p(\log(IPF_i)) \log_2 \left[ (\log(IPF_i)) \right]
\]

where interpulse frequency (IPF) is the inverse of IPI and \( p(\log(IPF_i)) \) represents the proportion of the total IPFs that are within bin \( i \), where bins range from ~0.6 – 14,000 Hz in 351 bins evenly distributed in log space (bin width = 0.0125 log Hz).

** Spike train entropy**

The average entropy for the interspike interval (ISI) distributions of model neuron spike trains was computed as:

\[
H = - \sum_{i=1}^{10000} p(ISI_i) \log_2 \left[ p(ISI_i) \right]
\]

where \( p(ISI) \) represents the proportion of the total ISIs that are within bin \( i \), where bins range from 1 ms - 10 s in increments of 1 ms.
A second estimate for the average entropy of model neuron spike train ISI distributions was computed to provide an estimate of spike train entropy that should be equivalent to the entropy of the stimulus train if the model neuron spike train followed the stimulus pulses perfectly. This estimate for spike train entropy was computed as:

$$H = -\sum_{i=1}^{351} p(\log(ISI_i)) \log_2 \left[ \log(ISI_i) \right]$$

where the ISIs of the model neurons were log-transformed and binned in the same fashion as the IPFs in the stimulus train entropy calculation (ISIs binned between ~0.6 – 14,000 ms, with the bin width = 0.0125 log ms).

**Statistics**

Experimental and computational data were analyzed using repeated measures analysis of variance (ANOVA), with log-transformed tremor power for each experimental condition as the repeated measure in each subject. Repeated measures for the model neuron activity were the quantitative measures computed for the spike trains or transmembrane potential. Statistical models were implemented in StatView 5.0 for Mac OS X (SAS Institute Inc., Cary, NC, USA). Fisher’s protected least significant difference (PLSD) tests were used to make post hoc comparisons across experimental conditions. Paired t-tests were used to assess the effects of pauses, bursts and irregularity, per se, in data that were pooled across stimulus conditions. The residuals of the log-transformed tremor and model quantitative measurements were normally-distributed (visual inspection of residual normality (QQ) plot). Statistical significance was defined at $\alpha = 0.05$. 
Results

Tremor responses to patterns of stimulation

We conducted intraoperative measurements of tremor during six different temporal patterns of thalamic DBS and during DBS off in eight subjects with DBS-responsive tremor (Fig. 4A). Consistent with previous studies, Regular 185 Hz DBS reduced tremor as compared to stimulation off \( (p < 0.05, \text{ post hoc Fisher’s PLSD}) \). Although all stimulation trains had the same mean frequency, tremor reduction varied across stimulation patterns (repeated measures ANOVA, \( F_{6,7} = 3.138, p < 0.015 \)). As compared to tremor with stimulation off, tremor was suppressed significantly during DBS with Regular 185 Hz, Uniform, Unipeak, and Presence trains, \( (p < 0.05, \text{ post hoc Fisher’s PLSD}) \), but not during DBS with Bimodal or Absence trains \( (p > 0.05, \text{ post hoc Fisher’s PLSD}) \).

We pooled data across stimulation trains that shared common characteristics to determine the contributions of pauses, bursts, or irregularity to the reduced efficacy of irregular DBS (Fig. 4B). To assess the effects of pauses, we pooled measurements made during Unipeak, Bimodal, and Absence DBS into a “Pause” group, and measurements made during Regular, Uniform, and Presence DBS into a “No pause” group (Fig. 4B (i)). Similarly, to assess the effects of bursts, we pooled measurements made during Unipeak, Bimodal, and Presence DBS into a “Burst” group, and measurements made during Regular, Uniform, and Absence DBS into a “No burst” group (Fig. 4B (ii)). Finally, to assess the effects of irregularity, we pooled measurements made during Unipeak, Bimodal, and Uniform DBS into an “Irregular” group, and measurements made during Regular, Presence, and Absence DBS into a “Periodic” group (Fig. 4B (iii)). Tremor during DBS with temporal patterns containing pauses was significantly larger than tremor...
during DBS with patterns containing no pauses ($p < 0.002$, paired t-test), and the median tremor power during DBS with patterns containing pauses was $1.60 - 3.46$ times (95% confidence interval) the median tremor power during DBS with patterns without pauses. There was not a significant difference between tremor during DBS temporal patterns containing bursts as compared to tremor during DBS without bursts ($p = 0.24$), and median tremor power during DBS with bursts was $0.71 - 3.16$ times the tremor power during DBS without bursts. Nor was there a significant difference between tremor measurements made during irregular DBS trains as compared to periodic DBS trains ($p = 0.35$), and median tremor power during irregular DBS was $0.58 - 3.87$ times tremor power during periodic DBS.

Subject responders were classified as having a change in tremor $\geq 30\%$ between conditions (NCT00196911 2007). Seven out of eight subjects experienced tremor suppression $> 30\%$ during Regular 185 Hz DBS as compared to DBS off, and six of eight subjects experienced tremor suppression of at least 80% as compared to DBS off. Tremor in subject G was not reduced by DBS during the experiment, and this may be due to propofol given to this subject who was unable to tolerate the surgery to access the IPG using only local anesthetic (Anderson et al. 1994).

Responders were also classified by comparing tremor suppression during Regular 185 Hz DBS to tremor suppression during stimulation with trains containing pauses, bursts, or irregularity, per se. Tremor in 7/8 subjects was suppressed at least 30% more during DBS with no pauses than during DBS with pauses, tremor in only 4/8 subjects was suppressed by 30% more during DBS with no bursts than during DBS with bursts, and tremor in only 4/8 subjects was suppressed by at least 30% more during periodic than during irregular DBS. When considering
only the trains that contained pauses, regular DBS suppressed tremor at least 30% more than Bimodal, Absence, and Unipeak DBS in 6/8, 5/8, and 6/8 subjects, respectively. Further, the least effective stimulus train in each subject was a train that contained pauses. Bimodal trains performed worst in subjects F and H; Unipeak trains performed worst in subjects A, E, and G; and Absence trains performed worst in subjects B, C, and D.

We analyzed the frequency components of tremor across the different temporal patterns of DBS. The median frequency of tremor power between 2 - 20 Hz for DBS off was 4.17 ± 0.32 Hz (mean ± s.e.m., range 3.3 – 6.2 Hz). The median frequency of the tremor power varied non-systematically across conditions, and there were no significant differences (repeated measures ANOVA, p = 0.59).

Finally, we analyzed the data for carryover effects and correlations between tremor during stimulation and during the periods between stimulation, and found that correlations were insignificant and non-systematic (Supplementary note b).

Model responses to patterns of stimulation

We used a validated model of the local Vim thalamic network to simulate the response of thalamic neurons to DBS with the same temporal patterns of stimulation used in the clinical experiments. Fig. 5 illustrates responses of a single model TC neuron across stimulation conditions, including somatic and axonal transmembrane potentials, as well as rasters showing the times of action potentials in CER, CTX, RN, and TIN terminals, the times of the inputs to CER, the Poisson inputs to CTX, and the DBS stimulation pulses. With stimulation off (Fig. 5A), the TC neuron exhibited phasic bursting activity similar to that observed in human subjects with ET (Hua and Lenz 2005). The CER axon followed faithfully the phasic, harmaline-
generated burst inputs, while the CTX axon followed faithfully the Poisson inputs. The TIN axon transmitted faithfully the combined inputs from CER and CTX, while the RN axon relayed the inputs from CTX and the TC neuron.

During Regular DBS (Fig. 5B), the presynaptic axons and the axon of the TC neuron followed the stimulus train and fired regularly at high rates due to stimulation evoked action potentials in the axons (Baldissera et al. 1972), while the cell body of the TC neuron was silenced due to synaptic inhibition arising from stimulation of the TIN and RN axons (McIntyre et al. 2004). During DBS with temporal patterns that did not contain pauses (Uniform Fig. 5C, Presence Fig. 5G), the input axons and TC axon continued to follow closely the stimulus train, and the soma remained inhibited and silent. Conversely, during stimulation with trains containing pauses (Fig. 5D-F), the TC soma responded with spikes or bursts. Specifically, during stimulation with Bimodal and Unipeak trains, the soma responded with rebound spikes at times when there were simultaneous pauses in both the DBS train and CER input (i.e., burst activity from cerebellum). Similarly, during DBS with the Absence pattern, somatic bursts occurred during simultaneous pauses in stimulation and the CER input. Thus, the temporal patterns of DBS that were effective in suppressing tremor overrode the burst driver (harmaline-generated input from CER), while the temporal patterns of DBS that were ineffective (those with pauses) allowed the burst driver input to generate rebound events in the TC neuron.

The responses of 10 representative TC neurons (from the population of 50) to the same temporal patterns of stimulation used in the clinical experiments are shown in Fig. 6. The strengths of GABAergic conductances were varied across the population to produce regular-spiking, random-spiking, and bursting neurons in the proportions observed in humans with ET:
~50 % bursting, ~30 % regular-spiking, and ~20 % random-spiking (Molnar et al. 2005) (see Detailed Model Description in Appendix), and the model population included 15 regular-spiking TC neurons, 10 random-spiking neurons, and 25 bursting neurons. The times of axonal action potentials for three regular-spiking, two random-spiking, and five bursting model neurons are illustrated in Fig. 6.

The responses across neurons to Regular DBS were somewhat heterogeneous; however, the responses within each neuron were quite regular. From the population of 50 model neurons, 19 neurons responded with axonal action potentials that were phase-locked to the 185 Hz DBS (Fig. 6B, rows 2, 5, and 9), 5 neurons responded with axonal spikes at integer multiples of stimulus pulses (every 5th – 8th pulse) (Fig. 6B, rows 3 and 10), and 14 neurons were silenced due to activation of the TIN and RN presynaptic axons and subsequent synaptic inhibition (Fig. 6B, rows 7 and 8). The remaining 12 cells fired intermittently without a consistent pattern (Fig. 6B, rows 1, 4, and 6). The patterns of model neuron firing in response to Uniform, Unipeak, and Bimodal DBS were noticeably more irregular than the responses to Regular DBS. The rastergrams indicate more neuronal bursts during the Bimodal and Absence trains, where the bursts during the Bimodal train were brief and frequent, and the bursts during the Absence trains occurred during the long pauses in the stimulus train.

Quantitative measures of TC neuron firing during stimulation

We quantified the responses of model TC neurons to DBS using the average entropy of ISI distributions (Fig. 7A), the average entropy of log-transformed ISI distributions (Fig. 7B),
and the fraction of power in the somatic transmembrane voltage ($V_m$) within 1 Hz of the burst-driver frequency ($5.8 \pm 1\) Hz) (Fig. 8).

The average firing pattern entropy is correlated with the effectiveness of DBS in treating the motor symptoms of PD (Dorval et al. 2008), and is a valid measure of temporal irregularity that does not require normal distributions of ISIs. The average entropy of model neuron ISI distributions was well correlated with the mean log-transformed tremor power across stimulus conditions ($R^2 = 0.78$) (Fig. 7A). The trends of ISI entropies followed closely those of tremor with one exception: Absence DBS was slightly, but not significantly, less effective than Unipeak DBS in suppressing tremor (Fig. 4A), but ISI entropies were significantly higher during Unipeak DBS than during Absence DBS (Fig. 7A).

The average entropy of the log-transformed ISI distributions was a measure of entropy that should be equivalent to the average entropy of the stimulus train log-transformed IPIs if the model neuron spike trains followed faithfully the stimulus train (Fig. 7B). The median entropy of the log-transformed ISI distributions was approximately equal to the entropy of the stimulus train log-transformed IPIs across conditions, with one important exception (Fig. 7C). The median log-transformed ISI entropy for the Absence train was much higher than the log-transformed IPI entropy of the stimulus train (2.9 bits/spike as compared to 0.18 bits/pulse), i.e., the low-entropy stimulus train that contained pauses generated high-entropy neural activity. The entropy of the log-transformed ISI distributions was also correlated with tremor responses across experimental conditions ($R^2 = 0.59$, Fig. 7B).

With stimulation off, the burst activity arising from CER inputs generated bursting activity in TC neurons at 5.8 Hz—the burst-driver frequency (Fig. 5A). The presence of
fluctuations in somatic $V_m$ that were in the range of $5.8 \pm 1.0$ Hz (i.e., the burst-driver band) was computed as the proportion of the total $V_m$ power spectrum. This measure of the degree to which the burst driver was represented in the output of the model neuron responses exhibited a very strong correlation with tremor across different temporal patterns of DBS ($R^2 = 0.81$, Fig. 8A). The primary difference between this measure and tremor was the stimulation off condition, and when this point was not included the correlation increased to $R^2 = 0.91$ (Fig. 8A, right inset).

Similarly, we quantified oscillations in the firing rates of TC axons within the burst-driver band by computing smoothed firing rate histograms for each axonal spike train (Gaussian smoothing window, $\sigma = 50$ ms) and then calculating the cross-correlation between the smoothed firing rate of a neuron during a given stimulus condition and the smoothed firing rate of the same neuron during stimulation off. The mean power of these cross-correlations within the burst-driver band ($5.8 \pm 1$ Hz) is illustrated in Fig. 8B across all 50 model neurons. Trends in the mean power in the axonal spike rate cross-correlations also paralleled trends in mean tremor power across stimulus conditions ($R^2 = 0.59$, Fig. 8B, inset), with the most power in the burst-driver band observed during stimulation with trains containing pauses.

As with the tremor measurements (see Fig. 4B), we pooled model data across stimulation trains that shared common characteristics to determine the contributions of pauses, bursts, or irregularity, per se, to the fraction of $V_m$ power in the burst-driver band. We computed the difference between the power in the burst-driver band for each neuron during stimulation with a given characteristic (pauses, bursts, or irregularity) and without a given characteristic (no pauses, no bursts, periodic). The difference between the power with/without pauses was significantly larger than the difference between the power with/without bursts or with/without
irregularity \((p < 0.0001, \text{Fisher's PLSD after significant repeated measures ANOVA})\) (Fig. 8C). Thus, the trends in the fraction of somatic \(V_m\) power in the burst driver band during stimulation with/without pauses, bursts, and irregularity paralleled remarkably well the trends we observed in tremor across the same stimulus characteristics (Fig. 4B).

Collectively, these results suggested that the mechanism by which DBS suppresses tremor is by masking burst driver inputs to the thalamus from the cerebellum. Therefore, we implemented an additional version of the network model of thalamic DBS to determine the efficacy of stimulating selectively the cerebellar fiber inputs to the Vim thalamus. In this version of the model, we eliminated the effects of extracellular stimulation on all neuronal elements, and replaced regular 185 Hz extracellular stimulation with 185 Hz intracellular stimulation of only the cerebellar afferent terminals (CER). The burst-driver fluctuations in somatic \(V_m\) during stimulation of cerebellar afferents was nearly identical to the burst-driver fluctuations in somatic \(V_m\) observed during extracellular Vim DBS \((p = 0.89, T_{49} = 0.14, \text{paired t-test})\) (Fig. 9).

**Discussion**

We conducted measurements in human subjects with tremor and Vim thalamic DBS and simulations in a computational model of thalamic DBS to identify the characteristics of irregular stimulus trains that rendered them ineffective: pauses; bursts; or irregularity, *per se*. Trains with pauses were the least effective at suppressing tremor, and when tremor responses were pooled across Pause/No pause, Burst/No burst, and Irregularity/Periodic groups, tremor was significantly different between groups only in the Pause/No pause grouping. Further, our results indicate that the mechanism by which DBS suppresses tremor was by masking burst
driver inputs to the thalamus from the cerebellum. Importantly, these findings provide a
mechanistic basis for correlative clinical studies, which indicate that the most effective electrode
locations for tremor suppression are near cerebellar fibers that terminate in the thalamus

Previous studies demonstrated that DBS with temporally random stimulation patterns,
even when delivered at a high average frequency, was not effective at treating tremor or
(Birdno et al. 2008) or bradykinesia (Dorval et al. 2010), and we evaluated three potential
hypotheses for the decreased effectiveness of irregular DBS: H_{Pause}, H_{Burst}, and H_{IR}. We tested
hypothesis H_{IR} by comparing the relative effectiveness of the Uniform, Bimodal and Absence
trains, all of which had high entropy (i.e., were highly irregular). The Uniform train was
effective, but the Bimodal and Absence trains were not, and therefore, we rejected H_{IR}. We tested
H_{Burst} by comparing the effectiveness of the Absence and Presence trains. The Presence train, which
contained burst-like patterns of pulses, suppressed tremor significantly as compared to
stimulation off, while the Absence train did not; therefore, we rejected H_{Burst}. We concluded that
the ineffectiveness of the Absence and Bimodal trains was due to pauses in the trains enabling
pathological activity to propagate through the thalamus (H_{Pause}), and the least effective train in
all subjects was one that contained pauses.

Results from simulations in the validated biophysical model of thalamic DBS provided a
mechanistic basis for the conclusion that the ineffectiveness of the irregular stimulus trains was
due to pauses. When pauses in the stimulus train coincided with pauses in the input from CER,
the thalamic neurons were prone to burst (Fig. 5F). The fraction of power in TC somatic V_m and
in the TC axon spike train within the burst-driver band (5.8 Hz ± 1 Hz) correlated well with tremor across stimulation patterns (Fig. 8). Thus, to be effective, DBS must mask or override the input from the cerebellum (i.e., the pathological burst driver). Further, stimulation that is temporally irregular, provided that it effectively overrides this driver (e.g., Uniform train), can also suppress tremor.

Correlative clinical data indicate the importance of activating the cerebellar inputs for effective tremor suppression (Coenen et al. 2011; Hamel et al. 2007; Herzog et al. 2007; Jimenez et al. 2000; Kitagawa et al. 2005; Struppler et al. 1978), and the present results provide a mechanistic basis for this clinical observation. DBS in the subthalamic area—comprised of the zona incerta and prelemniscal radiation—suppressed postural and intention tremor more effectively than DBS in Vim thalamus proper (Herzog et al. 2007). The optimal lead location for tremor suppression was 1.5 ± 2 mm ventral to the mid-commissural point—a location the authors concluded was in the subthalamic area (Hamel et al. 2007). Additionally, in vitro experiments demonstrated that high frequency stimulation of afferent neuronal fibers suppressed mimicked-tremor EPSP responses in thalamic neurons, providing further support for the role of afferent fibers in suppressing tremor (Anderson et al. 2006). Most recently, diffusion tensor imaging revealed that the most effective contact of a DBS electrode was not only in the subthalamic area, but also directly adjacent to the cerebellothalamic tract (Coenen et al. 2011). These results are consistent with our conclusion that effective thalamic DBS stimulates CER inputs, thereby masking the burst driver activity.

The effects of thalamic DBS on motor evoked potentials support our finding that thalamic DBS activates the cerebellothalamocortical pathway (Molnar et al. 2004; Pinto et al.
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2003), however, activation of corticothalamic afferents might also contribute to the reduction in
tremor by thalamic DBS in ET. Thalamic DBS facilitated the cerebellothalamocortical pathway,
indicating activation of this pathway during therapeutic DBS (Molnar et al. 2004). Pinto and
colleagues concluded that thalamic DBS does not work by inhibiting an overactive
cerebellothalamocortical pathway, and their findings were “consistent with an oscillating
source feeding into the cerebellum (Ugawa et al. 1997), and the inferior olive has been
implicated in this role (Deuschl and Bergman 2002)” (Pinto et al. 2003). Further, the hypothesis
that cortical afferents to the thalamus are the primary target of therapeutic thalamic DBS
contradicts the findings that stimulation of the subthalamic area is more beneficial than
stimulation in the thalamus proper (Hamel et al. 2007; Herzog et al. 2007). Finally, a very recent
clinical study implicated transient changes in pallidal input to the cortical/cerebellar/thalamic
loop in Parkinsonian resting tremor (Helmich et al. 2011). Specifically, they found that activity
in the cerebellothalamic pathway correlated well with tremor amplitude, and concluded that
resting tremor in PD is produced by the cerebellothalamic circuit.

Although the present results are restricted to thalamic DBS to treat tremor, previous
findings suggests that pauses also corrupt the effectiveness of subthalamic (STN) DBS in
Parkinson’s disease. DBS of the STN in a healthy monkey with a stimulation pattern containing
pauses and bursts disrupted motor performance, while stimulation with the same IPIs shuffled
to eliminate the presence of pauses and bursts did not disrupt motor performance (Ma and
Wichmann 2004). In human subjects with PD, movement times were shorter (i.e., better effect)
during continuous STN DBS than when DBS was cycled on and off for either 0.1 or 0.5 s,
although all patterns had the same average rate (Montgomery 2005). This finding is consistent
with our conclusion that pauses (off cycles in their experiments) disrupt the effectiveness of
stimulation. Finally, computational (Babadi 2005) and experimental (Person and Perkel 2005)
results also indicate that pauses between spikes in trains of thalamic input led to burst
responses in thalamus.

The range of stimuli that can be generated with the clinically-implanted IPG is limited,
and we used an innovative setting to make these measurements—during surgery to replace the
IPG—which allowed us to establish a direct connection to implanted DBS leads under stable
conditions (i.e., months to years after the original implant, with stable lead function). In contrast
to investigations conducted using externalized leads between the implant of the DBS lead and
subsequent implantation of the IPG (Birdno et al. 2007), this approach eliminated the
confounding effects of focal acute brain edema (i.e., microlesion) caused by the insertion of the
lead. However, the intraoperative setting imposed several experimental limitations.

The duration of DBS prior to assessment of tremor and the interval between trials were
short, but longer trials would result in the experiment becoming too long to conduct during an
operative procedure. Similarly short trial lengths have been used in studies of parameter settings
(Kuncel et al. 2006; Moro et al. 2002; O'Suilleabhain et al. 2003), and the effects of short stimulus
trials were mitigated partially by the fact that tremor reduction following onset of DBS occurs
“within a few seconds” (Beuter and Titcombe 2003). Further, the potential impact of the short
trial length was minimized by randomizing the trial order and by making comparisons of
tremor relative to baseline. The amount of baseline tremor was variable across subjects.
However, repeated measures ANOVA models allowed each subject to act as their own control,
thus increasing the statistical power to reveal significant effects on tremor across experimental conditions.

It should be noted that synapses are unreliable and that the current model neglects many details in this regard. However, during electrical stimulation, there are a large number of axon terminals stimulated simultaneously, and it is reasonable to assume that the overall impact of stimulation on the receptors can be modeled by reliable transmission. Indeed, in vivo recordings in GPi during STN DBS (Hashimoto et al. 2003) and in thalamus during GPi DBS (Anderson et al. 2003) suggest that post-synaptic activity is reliably generated, even during long trains of stimulation. The synapses in the current model were not intended to represent individual cell-to-cell transmission, but rather they represent the aggregate input from one group of cells to another group of cells.

The bursts in the thalamic network model were driven by oscillations in the cerebellar afferents, premised on activity recorded in the harmaline model of essential tremor. Although the etiology of ET is not well understood (Rothwell 1998), the harmaline model is the most commonly accepted animal model of ET (de Montigny and Lamarre 1973; Deuschl and Elble 2000; Miwa 2007), and it has even been suggested that the harmaline model should be used screen pharmaceutical interventions (Martin et al. 2005). Thus, we chose to implement the model with thalamic bursts driven by harmaline-induced activity in the cerebellar afferents.

Conclusions

The decreased effectiveness of temporally irregular DBS trains is due to the pauses in the stimulus trains and not to temporal irregularity alone. Thus, temporally irregular DBS can suppress tremor effectively if there are no long pauses. The ability of DBS to control tremor was
correlated most strongly with the ability of DBS to override burst driver inputs from the
cerebellum. Both clinical and computational data support the hypothesis that the most relevant
neuronal elements to stimulate for effective tremor suppression are the afferent cerebellar fibers
that terminate in Vim thalamus, and that the mechanism by which DBS suppresses tremor is
masking cerebellar burst-driver input to the thalamus.

Disclosures

The authors declare that they have no competing financial interests.

Appendix: model development and validation

Detailed model description

This Appendix includes a detailed description of the computational model that we developed and
simulated for this study. Source code files for the model can be downloaded from the NEURON
modelDB database: http://senselab.med.yale.edu/modeldb/.

Thalamocortical relay neuron

We used computer-based models of thalamocortical relay neurons and their synaptic inputs to
simulate the response of Vim thalamus neurons to DBS. The thalamocortical relay neuron
included a cell body, 251 dendritic compartments, and a double-cable axon with 30 nodes of
Ranvier. The thalamocortical cell geometry was derived from a 3-D reconstruction of a filled
thalamocortical cell from rat (Destexhe et al. 1998), and the axon diameter was selected as
representative of those in ventrolateral thalamus (Kultas-Ilinsky et al. 2003). The resting
transmembrane potential of the TC neuron cell body was -69 mV, and the resting membrane
potential of all axons was -70 mV. Noise was introduced into the TC neuron via a somatic
current injection that followed a normal distribution ($\mu=0$, $\sigma^2 = 5$ nA). The noise current changed amplitudes every time step and resulted in fluctuations in somatic transmembrane voltage that paralleled those observed in vivo (Destexhe et al. 2001).

**Inputs to thalamocortical relay neuron**

Each input axon had an intrinsic pattern of activity subjected to modification by DBS. The cortical input (CTX) consisted of a 20 Hz Poisson train of suprathreshold pulses (Descheenes and Hu 1990; Person and Perkel 2005). Intrinsic activity of cerebellar inputs (CER) was based on the burst activity recorded in the harmaline model of tremor in the cat (de Montigny and Lamarre 1973). The rate of harmaline burst activity was decreased from ~10 Hz to 5.8 Hz (11 IPIs at 7 ms, followed by 1 IPI at 95 ms) so that the interburst frequency of the model TC neurons was consistent with the predominant interburst frequency of Vim neurons in humans with ET (Hua and Lenz 2005). Inhibitory input from reticular neurons (RN) resulted from synaptic excitation of RN from the cortical input and excitation of RN via feedback connections from the TC output (Ando et al. 1995; Steriade et al. 1997). Finally, input from thalamic interneurons (TINs) resulted from synaptic excitation of TINs by CTX and CER inputs (Ando et al. 1995).

This model configuration assumed that the harmaline-induced bursting in the CER fibers comprised the primary source of tremor-related oscillations in the thalamus. The etiology of ET is not well understood; however, “disturbance of olivocerebellar rhythmicity” is the most prominent hypothesis for the pathology underlying ET” (Deuschl and Elble 2000; Haslinger et al. 2003; Koster et al. 2002). Supporting evidence for the role of the cerebellum in ET comes from
a recent post-mortem histological study that identified a decrease in the number of Purkinje
cells in the cerebellum of subjects with ET (and without Lewy bodies) as compared to healthy
controls (Louis et al. 2007). They also saw a seven-fold increase in “torpedoes” (fusiform
swellings of Purkinje cell axons) in the same ET subjects as compared to healthy controls (Louis
et al. 2007). Additionally, an ischemic cerebellar lesion due to stroke produced ipsilateral tremor
suppression in a subject with ET, suggesting a role of the cerebellum in the development of ET
(Dupuis et al. 1989). Finally, positron-emission tomographic studies revealed bilateral increases
in olivary glucose metabolism, as well as increases in blood flow in the cerebellum, red nucleus,
and thalamus of patients with essential tremor (Boecker and Brooks 1998). Hence, the CER
fibers were assumed to be the source of tremor-related oscillations in our computational model.

Activation of input synapses on the TC neuron was evoked not only by the intrinsic
activity of the input axons, but also by the effects of stimulation on the biophysically-modeled
input axons. The input axons were modeled as having the same morphological and
conductance properties as the axon of the TC neuron, with a slight adjustment made to the
nodal slow potassium conductance from 0.07 to 0.08 S/cm². In addition, because TINs are local
cells, the TIN axons consisted of only 15 nodes of Ranvier. Hence, the responses of the TC
neuron depended on a combination of the intrinsic synaptic inputs, changes in the intrinsic
synaptic activity evoked by stimulation of the input axons, and the direct effects of stimulation
on the TC neuron.

The synaptic effects on TC neurons were modeled by applying either excitatory or
inhibitory synaptic conductances to each of the dendritic and somatic compartments of each TC
neuron, with the distribution of synapses based on electron microscopic reconstructions of
glutamatergic and GABA-ergic terminals on cat ventral thalamic neurons (Table A.1) (Sato et al. 1997).

The CER input axon drove AMPA-dominated glutamatergic synapses that were located near the soma and whose effect was large in amplitude, but brief in duration (Miyata 2007; Schwarz and Schmitz 1997). The CTX input axon drove longer-lasting, but weaker, NMDA-dominated glutamatergic synapses that were located more distally than the cerebellar synapses (Table A.1) (Jones 2007; Miyata 2007). The TIN and RN input axons both drove inhibitory GABA$\alpha$ and GABA$\beta$ synapses, with distributions concentrated closer to the cell body than the glutamatergic inputs (Table A.1) (Sato et al. 1997). The strength of GABA-ergic conductances was varied to separate TC neuron response types into the three groups identified in a human study: ~50% bursting, ~30% regular-spiking, and ~20% random-spiking (Table A.2) (Molnar et al. 2005). Other channel dynamics and conductances were constant across regular-spiking, random-spiking, and bursting TC neurons.

In addition to synapses formed by the terminating axons onto the thalamocortical relay neuron, we included 1:1 synapses at the following locations:

- cerebellar axon to thalamic interneuron axon (Ando et al. 1995)
- thalamocortical axon to reticular nucleus axon (Ando et al. 1995)
- cortical axon to thalamic interneuron axon (Ando et al. 1995)
- cortical input to reticular nucleus axon (Ando et al. 1995).

These 1:1 synapses were assumed to be reliable, with each spike in the terminating axon resulting in a postsynaptic current sufficient to produce an action potential at the proximal end of the postsynaptic axon. The terminating axons of these synapses were assumed to lie outside
the volume affected by the extracellular potentials generated by stimulation, and we implemented virtual terminating axons at these synapses (Fig. 3A, light lines, main text). These virtual terminating axons fired action potentials faithfully with the middle node of the corresponding biophysically-modeled presynaptic axons (Figure 3A, bold lines, main text), but after a time delay appropriate for conduction of the action potential down a separate branch of the axon. This allowed antidromic action potentials generated by stimulation to drive these synapses in conjunction with the intrinsic inputs to the biophysically-modeled axons (Grill et al. 2008).

The kinetic schemes and parameters of the TC neuron and input axons were implemented following the bursting TC neuron as previously reported (McIntyre et al. 2004), with to parameters detailed in Table A.3. As well, the strength of glutamatergic conductances was adjusted to approximate experimental postsynaptic potentials for AMPA- and NMDA-dominated synapses (Table A.2) (Ando et al. 1995; Miyata 2007). We also modeled the effects of putative neuromodulators released by stimulated terminals, including adenosine, histamine, acetylcholine, serotonin, and noradrenaline (McCormick 1992b; Steriade et al. 1997). The role of neuromodulators in the effects of DBS are being investigated and a recent paper highlights the influence of adenosine. Adenosine levels increased during intervals of high frequency stimulation in thalamic slices and intrathalamic infusion of adenosine suppressed tremor in the harmaline mouse model of tremor, even in the absence of stimulation (Bekar et al. 2008).

The neuromodulators activated a pertussis toxin sensitive potassium current (I\textsubscript{KG}) (McCormick and Prince 1987a; b), inhibited a non-pertussis toxin sensitive leak potassium
current ($I_{KL}$) (McCormick 1992a), and shifted the activation curve of the hyperpolarization-
activated cation current ($I_h$) (McCormick and Williamson 1991; Pape 1992).

**$I_{KG}$: Potassium channel activated by GABA$\beta$ and putative neurotransmitters**

First, we included a potassium current known as $I_{KG}$, which is modulated by a pertussis toxin-
sensitive G-protein that can be activated by either GABA$\beta$, muscarinic, or A1-adenosine
receptors (McCormick 1992b). To implement this channel, we started with a GABA$\beta$ mechanism
that allowed the release of GABA to summate when multiple presynaptic action potentials
arrived within a short period of time to enhance the postsynaptic response to presynaptic
bursting (Destexhe et al. 1996; Otis et al. 1993). The kinetic scheme for the GABA$\beta$ mechanism
was taken from Destexhe et al. (Destexhe et al. 1996), and the effects of activating A1-adenosine
and muscarinic receptors was modeled by adding a new equation to the kinetic scheme for this
channel. The modified kinetic scheme was as follows:

$$\dot{R} = K_1 [C](1-R) - K_2 R$$

$$\dot{S} = K_5 M(1 - S) - K_6 S$$

$$[\dot{\mathcal{G}}] = K_3 (R + 2 \phi S) - K_4 [G],$$

where $R$ is the fraction of activated GABA$\beta$ receptor, $S$ is the fraction of activated A1 and/or
muscarinic receptor, $[G]$ is the concentration of activated G-protein, $[C]$ is the concentration of
GABA in the synaptic cleft, and $M$ represents a unitless time course of adenosine and/or
acetylcholine in the synaptic cleft. When GABA$\beta$ receptors are activated, $[C]$ changes
instantaneously from zero to 1, and then returns to zero after 0.3 ms (Destexhe et al. 1996). In a
similar fashion, when A1 and/or muscarinic receptors are activated, $M$ follows an alpha function (Fig. A.1):

$$\dot{\alpha} = -\frac{a}{\tau_1} + w$$  \hspace{1cm} (A.4) \\
$$\dot{\beta} = -\frac{b}{\tau_2} + w$$  \hspace{1cm} (A.5) \\
$$M = b - a, \hspace{1cm} (A.6)$$

where $a$ and $b$ are dummy variables used to construct the alpha function; $w = 0.0035 \text{ ms}^{-1}$ is a constant weight added to both $a$ and $b$ upon the arrival of each stimulus pulse; and $\tau_1$ and $\tau_2$ are the decay time constants associated with $a$ and $b$, respectively ($\tau_1 = 500 \text{ ms}$, $\tau_2 = 510 \text{ ms}$).

In Equations A.1 – A.3, the Ks are the kinetic rate constants for activating (odd) and deactivating (even) the receptors or G-proteins, and were set to the following values: $K_1 = 0.52 \text{ mM}^{-1}\text{ms}^{-1}$, $K_2 = 0.0013 \text{ ms}^{-1}$, $K_3 = 0.098 \text{ ms}^{-1}$, $K_4 = 0.033 \text{ ms}^{-1}$, $K_5 = 0.1 \text{ ms}^{-1}$, and $K_6 = 0.0003 \text{ ms}^{-1}$.

In Equation A.3, $\phi_i$ is a unitless constant that represents the magnitude of the response of adenosine and/or acetylcholine terminals to extracellular stimulation in the volume near the $i$-th TC neuron. The value of $\phi_i$ was set equal to the extracellular potential generated at the soma of cell $i$ during stimulation at 1V. $\phi_i$ has a theoretical maximum of 1; however, the random population used in this study had a maximum of 0.52.

Linear “leak” potassium current ($I_{KL}$) inhibited by putative neurotransmitters

Activation of muscarinic acetylcholine, $\alpha_1$ adrenergic, and/or H1 histaminergic receptors results in the suppression of a relatively linear “leak” potassium current, $I_{KL}$, leading to slow
depolarization of the TC neuron (McCormick 1992a; b). $I_{KL}$ suppression was modeled by altering the leak current in McIntyre, et al. (McIntyre et al. 2004) as follows:

$$I_{KL} = \overline{g}_{KL} m (V_m - E_k) \quad (A.7)$$

$$\dot{m} = \frac{m_{\infty} - m}{\tau_m} - \phi_i M w, \quad (A.8)$$

where $\overline{g}_{KL} = 0.00016 \text{ S/cm}^2$ is the maximal conductance of the leak current; and $m$ is a state parameter that decreases with activation of muscarinic, $\alpha_1$, and/or H1 receptors following Equation A.8. In Equation A.8, $\phi_i$ and $M$ have the same meaning and values as in Equations A.2 – A.6; $w = 0.2 \text{ ms}^{-1}$ is a constant weight added upon the arrival of each stimulus pulse; and $\tau_m = 400 \text{ ms}$ is the decay time constant of $m$. Due to the linearity of this current, a simple scaling of the maximal conductance by $m$ was sufficient to produce lasting depolarization in the soma of the TC neuron.

**Shifts in activation curve of $I_h$ driven by putative neurotransmitters**

Activation of $\beta$ adrenergic, serotonergic and H2 histaminergic receptors enhances the hyperpolarization-activated cation current $I_h$ (Steriade et al. 1997), while activation of A1 adenosine receptors inhibits $I_h$ (McCormick 1992b; Pape 1992). Enhancement and inhibition of $I_h$ are driven by rightward and leftward shifts in the activation curve of this current, respectively (McCormick and Williamson 1991; Pape 1992). $I_h$ was modeled as:

$$I_h = g_h m^3 (V_m + 43) \quad (A.9)$$

$$\tau_m = \frac{1}{e^{-14.59 - 0.086(V_m + V_{shp})} + e^{-1.87 + 0.070(V_m + V_{shp})}} \quad (A.10)$$
\[
m_\infty = \frac{1}{1 + e^{-\left(\frac{V_m + V_{\text{shift}} + 75}{5.5}\right)}}
\]  
(A.11)

\[
\dot{V}_{\text{shift}} = \frac{V_{\text{sho}} - V_{\text{shift}}}{\tau_{V_{\text{shift}}}} - \phi_i M w,
\]  
(A.12)

where \(V_{\text{shift}}\) determines the left/right shifts in the activation curve, \(g_h = 0.0015 \text{ S/cm}^2\) is the maximal conductance, and \(V_{\text{sho}} = 5 \text{ mV}\) is the baseline shift used previously (McIntyre et al. 2004). In Equation A.12, \(\phi_i\) and \(M\) have the same meaning and values as in Equations A.2 – A.6; \(w = 0.5 \text{ mV/ms}\) is a constant weight added upon the arrival of each stimulus pulse; and \(\tau_m = 400 \text{ ms}\) is the decay time constant of \(V_{\text{shift}}\).

Model validation

The computational model of Vim TC neurons and their inputs reproduced a variety of experimental results without changing biophysical parameters or ionic conductances across validation or experimental simulations.

Single cell responses to various polarizations

First, a single-cell version of the TC neuron, with no synaptic inputs, demonstrated responses to 60 ms depolarizing pulses that were similar to in vitro recordings of guinea pig thalamic slices (Jahnsen and Llinas 1984) under various levels of DC polarization (Fig. A.2A). The responses of the single-cell TC neuron to 45 ms hyperpolarizing pulses was also similar to those of the same thalamic slice neurons (Fig. A.2B) (Jahnsen and Llinas 1984). Finally, the model reproduced well the tonic bursts that occur in thalamic neurons during DC hyperpolarization (Fig. A.2C) (McCormick and Pape 1990).
More important than comparing the responses of the model to *in vitro* preparations was comparing the responses of the model to spike activity recorded in the Vim of humans with ET, and the model neuron replicated well several behaviors observed in human recordings.

We set the strength of GABA-ergic conductances to obtain three classes of TC neuron response types: regular-spiking, random-spiking, and bursting neurons (Table A.2) in the proportions observed in humans with ET (~50% bursting, ~30% regular-spiking, and ~20% random-spiking (Molnar et al. 2005)). Other channel dynamics and conductances remained constant across regular-spiking, random-spiking, and bursting TC neurons. Responses during stimulation off are shown for each of the three classes of model neurons in Fig. A.3A.

Action potential rasters from the bursting model neuron were qualitatively similar to rasters recorded from humans with ET during epochs of tremor (Fig. A.3B) (Hua and Lenz 2005). Furthermore, the mean ± s.e.m. firing rates across the population of 25 bursting, 15 regular-spiking, and 10 random-spiking neurons (23.4 ± 1.9 Hz) was very close the firing rate observed in Vim thalamus of human subjects with ET (Fig. A.3C) (Ohara et al. 2007).

We computed the mean normalized autopower spectra of the each model neuron by calculating the autocorrelation of the spike times for each neuron, then taking the power spectrum of the autocorrelation (autopower spectrum). We normalized the autopower for each neuron and then computed the mean and s.e.m. of the autopower spectra across the population of 50 model neurons. The mean normalized autopower of the model neuron spike times paralleled closely the mean normalized autopower spectra of neurons in the Vim of human subjects with ET (Fig. A.4A,B) (Hua and Lenz 2005). The length of pre-burst ISIs were also very
similar between human subjects with ET and model TC neurons (Fig. A.4C) ET (Ohara et al. 2007).

We also compared the responses of the model to the response of a low-threshold spike (LTS) bursting neuron in human thalamus in the period immediately after 200 Hz stimulation delivered for 0.5 s. The human LTS bursting neuron responded immediately after cessation of stimulation with a short epoch of burst activity, followed by a prolonged period of inhibition before a return to LTS bursting (Fig. A.4D, top) (Dostrovsky and Lozano 2002). The model replicated well the measured post-stimulus burst, inhibition, and recovery (Fig. A.4D, bottom).

Finally, we examined the responses of the model to DBS with constant IPIs (i.e., Regular DBS) at various amplitudes and frequencies (Fig. A.5). As the amplitude of stimulation increased, the ability to regularize neuronal firing and suppress fluctuations at the burst-driver frequency improved (Fig. A.5A,C). Likewise, as the frequency of stimulation increased, the ability to regularize neuronal firing and suppress fluctuations at the burst-driver frequency improved (Fig. A.5B,D).

We observed a small increase in entropy of ISIs during stimulation at very low frequencies; however, we did not observe an increase in burst-driver power during stimulation at low frequencies. This is a limitation of the model, as it departs slightly from clinical studies, which demonstrate exacerbation of tremor during stimulation at very low frequencies (Grill et al. 2004; Kuncel et al. 2007). This finding indicates that the mechanism by which low frequency stimulation exacerbates tremor is not solely due to the pauses in the low frequency stimulus train. The mechanisms of tremor exacerbation at low stimulus frequencies is not addressed in the current study, but this question warrants future examination.
References


Hamel W, Herzog J, Kopper F, Pinsker M, Weinert D, Muller D, Krack P, Deuschl G, and Mehdorn HM. Deep brain stimulation in the subthalamic area is more effective than nucleus...


FIGURE LEGENDS:

Figure 1. Intraoperative measurements of tremor in response to different temporal patterns of thalamic DBS.

A, Trial timeline that was followed to measure tremor suppression under experimental conditions. B, Triaxial raw accelerometer signals recorded during two tremor trials in subject F. The raw traces illustrate the acceleration magnitude in each of the three dimensions during 20 s trials with DBS off (i) and during 185 Hz regular DBS (ii). Scale bars in (ii) apply to both traces. C, Power spectral density for the acceleration trials signals shown in (B) with DBS off (i) and during 185 Hz regular DBS (ii).

Figure 2. Stimulus trains designed to test whether pauses, bursts or irregularity, per se are the causes of the ineffectiveness of temporally-irregular DBS.

A-C, High-entropy log-uniform distributions with various frequency limits. Sample stimulus trains are shown in insets above corresponding distributions. A, Uniform stimulus distribution designed with a minimum at 90 Hz and a geometric mean of 185 Hz. B, Unipeak stimulus distribution with wider frequency limits than the Uniform stimulus. C, Bimodal stimulus distribution, where the frequency limits were adjusted such that IPIs were either greater than or less than the therapeutic frequency range. D, Absence trains had a geometric mean frequency of 185 Hz and pauses of 50.7 ms that came at a rate of 4.4 Hz. E, Presence trains had a geometric mean frequency of 185 Hz and brief bursts of stimulus pulses that lasted 52.57 ms and came at a rate of 4.4 Hz.

Figure 3. Computational model of the response of thalamic neurons to DBS.

A, Schematic representation of three-dimensional cable model of a thalamocortical (TC) neuron and four terminating axons providing input to the TC neuron. Elements with bold lines were biophysically-modeled and subjected to the extracellular potentials generated by stimulation, while elements with light lines were modeled as virtual axon branches that mimicked activity in the biophysical axons with a time delay consistent with action potential propagation down an axon branch. B, Prism representation of the Vim thalamus (Benabid et al. 1998; Mobin et al. 1999) and sample 3-D locations of 50 cell bodies within the nucleus. C, Coronal view of Vim thalamus with DBS electrode drawn to scale. The orientations of the TC neuron and input axons are also shown; however, the neural elements are not drawn to scale. D, Sagittal view of Vim thalamus taken 15 mm lateral to the anterior commissure–posterior commissure (AC-PC) line, with DBS electrode drawn to scale. The orientations of the TC neuron and input axons are also shown, but these elements are not drawn to scale. The RN and TIN axons cannot be seen, because they extend directly in the lateral and medial directions, respectively. Legend in (D) also applies to (C).

Figure 4. Tremor during different temporal patterns of thalamic DBS.

A, Mean ± s.e.m. log-transformed tremor power across seven experimental conditions in all eight subjects. Significant changes in tremor were observed across stimulus condition (repeated measures ANOVA). *As compared to tremor during stimulation off, tremor was suppressed significantly during Regular 185 Hz DBS, Uniform DBS, Unipeak DBS, and Presence DBS. Tremor tended toward suppression during Bimodal and Absence DBS as compared to DBS off, but not significantly. †Tremor was suppressed more effectively with Regular DBS than with Bimodal DBS. B, Data pooled across stimulus train characteristics: no pauses versus pauses (i); no bursts versus bursts (ii); and periodic versus irregular (iii). Lines connect tremor measurements within subjects. *Stimulus trains with pauses were significantly less effective than stimulus trains without pauses (p < 0.002, paired t-test). There were no significant differences in tremor
between trains with bursts and those without bursts ($p = 0.24$), or between trains that were irregular and those that were periodic ($p = 0.35$, paired t-test).

**Figure 5. Model neuron responses to different temporal patterns of DBS.**

Responses for a single model TC neuron during stimulation off (A), Regular (B), Uniform (C), Unipeak (D), Bimodal (E), Absence (F), and Presence (G) DBS are shown. Somatic and axonal transmembrane potentials are illustrated, along with rasters showing the times of action potentials in CER, CTX, RN, and TIN terminals. The times of harmaline-generated inputs to CER (Harm), Poisson inputs to CTX (Poiss), and DBS stimulus pulses are also indicated. Traces illustrate the responses during one second of stimulation. The time scale bar in (A) applies to all traces in the figure, while the amplitude scale bar refers to only the soma and axon traces in each panel. Somatic spikes and/or bursts occurred only during periods of time when there were pauses in both the stimulus train, and the CER input to the thalamus. These events were only evident during stimulation with Unipeak, Bimodal, and Absence trains, as well as in the stimulation off condition.

**Figure 6. Responses of ten model neurons to different temporal patterns of DBS.**

The times of action potentials for 10 of 50 TC neurons are shown as rasters during stimulation off (A), as well as during Regular (B), Uniform (C), Unipeak (D), Bimodal (E), Absence (F), and Presence (G) DBS. Rasters illustrate the times of action potentials in the distal axon of each TC neuron during one second of stimulation. The top three rows in each panel are the responses of regular spiking TC neurons, the next two rows are the response of random-spiking TC neurons, and the bottom five are bursting TC neurons. The time scale bar in (A) applies to all panels. These data are intended to provide an overview of the responses of the model neurons during the different stimulus conditions.

**Figure 7. Average spike train entropies of model neurons in response to different temporal patterns of DBS.**

A, Average entropy of ISI distributions for model neuron responses across stimulation conditions. B, Average entropy of log-transformed ISI distributions for model neuron responses across stimulation conditions. The entropy for the log-transformed ISI distributions was used to provide a direct comparison with the stimulus train log-transformed IPI entropy. If the neurons responded faithfully to every stimulus pulse, the entropy would be the same for the log-ISIs and log-IPIs. Data are shown as mean ± s.e.m. Markers not containing the same letters are significantly different from one another ($p < 0.05$, post hoc comparisons with Fisher’s PLSD). Insets in panels (A) and (B) illustrate the correlation between the spike train entropies for a given condition as a function of the mean log-transformed tremor power for the same condition across eight subjects. C, Median entropy of model log-transformed ISI distributions versus the average entropy of the stimulus train log-transformed IPI distributions. Dashed line represents a 1:1 correlation. Points for all conditions except Absence DBS fell very close to the 1:1 line.

**Figure 8. Fraction of somatic $V_m$ power in the burst-driver band.**

A, Power in somatic $V_m$ in the burst-driver band (5.8 ± 1 Hz) across stimulation conditions. Data are shown as mean ± s.e.m. Markers not containing the same letters are significantly different from one another ($p < 0.05$, post hoc comparisons with Fisher’s PLSD). The two insets illustrate the fraction of somatic $V_m$ in the burst-driver band as a function of mean tremor across eight subjects. The left inset includes all experimental conditions, and the right inset includes only the conditions with stimulation on.
B, Power in the burst-driver band of the cross correlation between the smoothed axonal spike rates during a given condition and stimulation \textit{off}. Data are shown as mean ± s.e.m. Markers not containing the same letters are significantly different from one another ($p < 0.05$, post hoc comparisons with Fisher’s PLSD). The inset illustrates the correlation between the axonal spike rate cross-correlations and the mean tremor in eight subjects across conditions with stimulation \textit{on}. C, Difference between the somatic $V_m$ power in the burst-driver band for each neuron during stimulation \textit{with} a given characteristic (\textit{Power(with)}: pauses, bursts or irregularity) and the power in the burst-driver band for each neuron during stimulation \textit{without} a given characteristic (\textit{Power(without)}: no pause, no bursts, periodic), respectively.

\textbf{Figure 9. Stimulation of cerebellar terminals exclusively is effective at eliminating somatic $V_m$ burst-driver power.}

Somatic $V_m$ burst-driver power during stimulation \textit{off} and regular 185 Hz DBS (filled bars), along with somatic $V_m$ burst-driver power during stimulation \textit{off} and intracellular stimulation of cerebellar terminals only (CER only, open bars). Due to differences in the total somatic $V_m$ power between 0 – 5000 Hz during intracellular cerebellar and extracellular DBS, we compared the absolute value of power in the burst-driver band rather than the proportion of power. Data are shown as the mean ± s.e.m. across the population of 50 TC neurons.

\textbf{Figure A.1. Response of $M$ to stimulation.}

A, Time course of $M$ in response to a single stimulus pulse (arrow) follows an alpha function. B, Time course of $M$ in response to a 10 s epoch of DBS at 10 Hz and 185 Hz. In these cases, the alpha function responses to individual stimulus pulses summate temporally and stabilize at different steady state amplitudes (au = arbitrary units, unitless).

\textbf{Figure A.2. Comparison of responses of model and \textit{in vitro} TC neurons.}

A, Responses to 60 ms depolarizing pulses were similar to those recorded in \textit{in vitro} thalamic slices under various levels of DC polarization. (i) Responses from thalamic neurons recorded from guinea pig slices in a hyperpolarized cell (left), a cell at rest potential (middle), and a depolarized cell (right) (Jahnsen and Llinas 1984). (ii) Responses of model thalamic neuron to a depolarizing pulse of 0.55 nA for 60 ms at hyperpolarized (left), rest (middle), and depolarized (right) potentials. B, Model rebound responses to 45 ms hyperpolarizing pulses was similar to those of the same thalamic slice neurons. (i) Responses of \textit{in vitro} neurons (Jahnsen and Llinas 1984). (ii) Responses of the model TC neuron. C, Model responded to DC hyperpolarization with rhythmic bursting. (i) Responses of \textit{in vitro} neurons (McCormick and Pape 1990). (ii) Responses of the model TC neuron.

\textbf{Figure A.3: Comparison of thalamic model activity to data recorded in human Vim.}

A, Transmembrane potential recordings from model (i) regular-, (ii) random-, and (iii) burst-spiking neurons. B, (i) Action potential raster recorded from Vim of human with ET (Hua and Lenz 2005). (ii) Action potential raster recorded from model burst-spiking neuron. C, Firing rates in the Vim and ventral caudal (Vc) thalamus in subjects with ET (Ohara et al. 2007), along with the firing rates of the model Vim neurons (mean ± s.e.m. = 23.4 ± 1.8 Hz). The human Vc data are shown to demonstrate that the internuclear difference is much larger than the difference between the model and human Vim. Model firing rate estimates were averaged across all 50 neurons during the time period from 2 – 12 s with stimulation \textit{off}. 

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Figure A.4. Comparison of firing patterns in model and human thalamic neurons.

A, Mean normalized autopower computed for tremor-related neurons in human thalamus during postural tremor exhibits a strong peak at ~ 5 Hz (Hua and Lenz 2005). B, Mean normalized autopower computed for the population of 50 model neurons shows a similar peak at ~ 5 Hz. Normalized autopower was averaged across all 50 neurons during the time period from 2 – 12 s with stimulation off. C, Pre-burst ISIs in the Vim and Vc thalamus in subjects with ET (Ohara et al. 2007), along with the pre-burst ISIs of the model Vim neurons. The human Vc data are shown to demonstrate that the internuclear difference is much larger than the difference between the model and human Vim. Model pre-burst ISI estimates were made by combining all averaged across the 25 bursting neurons during the same time period (mean ± s.e.m. = 173 ± 2 ms). D, Post stimulus inhibition seen after 0.5 of stimulation at 200 Hz observed in human thalamus (top) (Dostrovsky and Lozano 2002), and in the model Vim neuron (bottom). Time scale bar applies to both traces. 20 mV transmembrane potential scale bar applies only to the bottom trace, as the top trace is an extracellular recording. Thick gray bar represents stimulation on in both the human and model.

Figure A.5. Effects of stimulus amplitude and frequency on $V_m$ fluctuations at burst driver frequency.

A, Average spike train entropy across stimulus amplitudes during stimulation with Regular 185 Hz DBS. B, Average spike train entropy across stimulus frequencies during stimulation with Regular DBS at 7.5V. C, Somatic $V_m$ power in burst-driver band (5.8 ± 1 Hz) across stimulus amplitudes during stimulation with Regular 185 Hz DBS. D, Somatic $V_m$ power in burst-driver band (5.8 ± 1 Hz) across stimulus frequencies during stimulation with Regular DBS at 7.5V. Data are shown as mean ± s.e.m.
### Table 1. Demographic characteristics and stimulation settings for each subject.

<table>
<thead>
<tr>
<th>Subject</th>
<th>Age/ Sex</th>
<th>Diagnosis</th>
<th>Arm position during tremor trials</th>
<th>*Electrode contacts</th>
<th>PW (μs)</th>
<th>Amplitude (V)</th>
<th>Medications taken morning of experiment</th>
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</thead>
<tbody>
<tr>
<td>A</td>
<td>57/M</td>
<td>ET</td>
<td>Elbow extended and unsupported, holding bottle (~20 oz)</td>
<td>0’1’2⁺</td>
<td>120</td>
<td>5.0</td>
<td>ropinirole hydrochloride</td>
</tr>
<tr>
<td>B</td>
<td>31/M</td>
<td>MS</td>
<td>Elbow unsupported &amp; extended (blocks A &amp; B), elbow flexed (block C)</td>
<td>0’1’3⁺</td>
<td>120</td>
<td>5.4</td>
<td>none</td>
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<tr>
<td>C</td>
<td>78/M</td>
<td>ET</td>
<td>Elbow &amp; wrist both supported &amp; relaxed</td>
<td>0’1’2’3⁺</td>
<td>150</td>
<td>4.9</td>
<td>none</td>
</tr>
<tr>
<td>D</td>
<td>65/F</td>
<td>ET</td>
<td>Elbow flexed &amp; supported; wrist unsupported &amp; straight</td>
<td>0’1’2⁺</td>
<td>90</td>
<td>3.1</td>
<td>propranolol, midazolam for surgery</td>
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<tr>
<td>E</td>
<td>79/M</td>
<td>ET</td>
<td>Elbow flexed &amp; unsupported; wrist unsupported &amp; straight</td>
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<td>2.4</td>
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<td>F</td>
<td>82/F</td>
<td>ET</td>
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<td>ET</td>
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<td>1’2⁺</td>
<td>120</td>
<td>3.0‡</td>
<td>none</td>
</tr>
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</table>

* DBS electrodes contain four contacts, with 0 being the most distal and 3 the most proximal. C = case of IPG used as anode. Contacts programmed as anodes denoted by ‘⁺’, while contacts programmed as cathodes denoted by ‘⁻’.

†Experimental contact configurations differed from clinically-programmed configurations (clinical configurations in brackets).

‡Amplitude decreased in subject H from clinical amplitude of 3.7 V due to strong stimulus onset paresthesias in this subject.

M = male; F = female; PW = pulse width.
A. NMDA-dominated glutamatergic synapses
B. AMPA-dominated glutamatergic synapses
C. GABAergic synapses
D. Virtual excitatory 1:1 synapse (every input spike translates to a single output spike)
E. Non-modulatory excitatory synapse
A

Log-transformed tremor power

B

(i) *

(ii) (iii)
<table>
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<th>Compartments*</th>
<th>Synapse type</th>
<th>Percent of synapses in compartment of given type</th>
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<td>Primary dendritic &amp; cell body</td>
<td>GABA</td>
<td>60%</td>
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<tr>
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<td>Cortical</td>
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<tr>
<td>Secondary dendritic</td>
<td>GABA</td>
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</tr>
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<tr>
<td>Distal dendritic</td>
<td>Cortical</td>
<td>74%</td>
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*Dendritic compartments were classified as follows. Sections between the soma and first bifurcation were defined as primary dendrites, while sections between the first and second bifurcations were defined as secondary dendrites, and any sections distal to the second bifurcations were defined as distal dendrites.
<table>
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<th>Origin</th>
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<th>Regular, Random or Bursting cells</th>
<th>Conductance (nS)</th>
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<tr>
<td>Cortical</td>
<td>NMDA</td>
<td>All</td>
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<tr>
<td>Cerebellar</td>
<td>NMDA</td>
<td>All</td>
<td>0.0006</td>
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<tr>
<td>Cortical</td>
<td>AMPA</td>
<td>All</td>
<td>0.00082</td>
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<tr>
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<td>AMPA</td>
<td>All</td>
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<tr>
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<td>GABA\textsubscript{A}</td>
<td>Regular</td>
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</tr>
<tr>
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<td>GABA\textsubscript{A}</td>
<td>Regular</td>
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<tr>
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<td>Bursting</td>
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<tr>
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### Table A.3. Parameters altered from model published previously (McIntyre et al., 2004)

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<th>Parameter</th>
<th>Previous value [or equation]</th>
<th>New value [or equation]</th>
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<td>T-type Ca(^{2+})</td>
<td>(P_{CaT})</td>
<td>0.0001 cm/s</td>
<td>0.00075 cm/s *</td>
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<tr>
<td>TC soma/dendrites</td>
<td>T-type Ca(^{2+})</td>
<td>(\tau_h) for (V_m &gt; -80)</td>
<td>(9.33 + 0.333e^{-(V_m+25)/10.5})</td>
<td>(1.6147[8.91 + 0.318e^{-(V_m+25)/10.5}]) †</td>
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<td>T-type Ca(^{2+})</td>
<td>(\tau_h) for (V_m \leq -80)</td>
<td>(0.333e^{-(V_m+470)/66.6})</td>
<td>(0.318e^{-(V_m+470)/66.6})</td>
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<td>T-type Ca(^{2+})</td>
<td>(\tau_m)</td>
<td>(0.204 + \frac{0.333}{e^{-(V_m+135)/16.7} + e^{-(V_m+19.8)/18.2}})</td>
<td>(0.195 + \frac{0.318}{e^{-(V_m+135)/16.7} + e^{-(V_m+19.8)/18.2}})</td>
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<td>TC soma/dendrites</td>
<td>T-type Ca(^{2+})</td>
<td>(m_\infty)</td>
<td>(m_\infty = 1/[1 + e^{-(V_m+60)/6.2}])</td>
<td>(m_\infty = 1/[1 + e^{-(V_m+68)/6.2}]) *</td>
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<td>TC soma/dendrites</td>
<td>Leak</td>
<td>(g_{Na\text{L}})</td>
<td>0.0000095 S/cm(^2)</td>
<td>0.0000305 S/cm(^2) **</td>
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<td>TC soma/dendrites/initial segment</td>
<td>Slow K(^{+})</td>
<td>(I_{Ks})</td>
<td>(g_{Ks}m(0.4 * h1 + 0.6 * h2)(V_m - E_K))</td>
<td>(g_{Ks}m(0.6 * h1 + 0.4 * h2)(V_m - E_K)) §</td>
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<td>ALL nodes</td>
<td>Slow K(^{+})</td>
<td>(\beta_s)</td>
<td>(0.03/[1+exp((V_m+80)/-1)])</td>
<td>(0.03/[1+exp((V_m+40)/10)]) ‡</td>
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<tr>
<td>ALL nodes</td>
<td>Slow K(^{+})</td>
<td>(g_{Ks})</td>
<td>0.07 S/cm(^2)</td>
<td>0.07 S/cm(^2) TC axon, 0.08 S/cm(^2) input axons</td>
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<td>Leak</td>
<td>(g_{Lk})</td>
<td>0.005 S/cm(^2)</td>
<td>0.007 S/cm(^2) *</td>
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<tr>
<td>ALL ALL</td>
<td>All K(^{+})</td>
<td>(e_K)</td>
<td>-95 mV</td>
<td>-95 mV, ([K^{+}]_i = 106 \text{ and } [K^{+}]_o = 3 \text{ mM})</td>
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</table>

* Adjusted to facilitate tonic bursting during DC-hyperpolarization (Fig. A.2c) (McCormick and Pape, 1990) and post-stimulus inhibition (Fig. A.4d) (Dostrovsky and Lozano, 2002).

† Equation updated to ensure that \(\tau_m\) curves for \(V_m \leq -80\) mV and \(V_m > -80\) mV meet at \(V_m = -80\) mV.

§ Equation updated with correct proportions from earlier study (Huguenard and McCormick, 1992).

‡ Equation updated to correct \(\alpha_s\) and \(s_{\infty}\) curves (\(\beta_s\) were previously both monotonic in same direction).
** This was equal to the conductance used in the tonically-active version of previous model.