

Dynamics of Parkinsonian tremor during deep brain stimulation

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The mechanism by which chronic, high frequency, electrical deep brain stimulation (HF-DBS) suppresses tremor in Parkinson's disease is unknown. Rest tremor in subjects with Parkinson's disease receiving HF-DBS was recorded continuously throughout switching the deep brain stimulator on (at an effective frequency) and off. These data suggest that the stimulation induces a qualitative change in the dynamics, called a Hopf bifurcation, so that the stable oscillations are destabilized. We hypothesize that the periodic stimulation modifies a parameter affecting the oscillation in a time dependent way and thereby induces a Hopf bifurcation. We explore this hypothesis using a schematic network model of an oscillator interacting with periodic stimulation. The mechanism of time-dependent change of a control parameter in the model captures two aspects of the dynamics observed in the data: (1) a gradual increase in tremor amplitude when the stimulation is switched off and a gradual decrease in tremor amplitude when the stimulation is switched on and (2) a time delay in the onset and offset of the oscillations. This mechanism is consistent with these rest tremor transition data and with the idea that HF-DBS acts via the gradual change of a network property. © 2001 American Institute of Physics. [DOI: 10.1063/1.1408257]

Chronic, high frequency, electrical deep brain stimulation can suppress tremor in Parkinson's disease. This surgical technique involves implanting an electrode into subcortical structures in the brain for long-term stimulation. The mechanism by which deep brain stimulation suppresses tremor is unknown, but might involve a gradual change in network properties controlling the generation of tremor. We hypothesize that high frequency deep brain stimulation induces a qualitative change in the dynamics so that the stable oscillations are destabilized as a parameter affecting the oscillation is modified. One possible qualitative change in the dynamics, which we explore with a schematic network model, is a supercritical Hopf bifurcation. With the model, we are able to make definite predictions concerning the time course of the onset and suppression of the tremor. This work should be helpful in identifying the time scale of effect of high frequency deep brain stimulation on Parkinsonian tremor.

I. INTRODUCTION

Parkinson's disease is a serious neurological disorder with a broad spectrum of symptoms. One of the most obvious and disabling symptoms is a large amplitude, low frequency $\approx 4-6$ Hz tremor.^{1,2} One way to treat this tremor is to introduce an electrode deep into a patient's brain and to deliver stimuli at frequencies of greater than 100 Hz.^{3,4} When this procedure is successful, the abnormal tremor is abolished. Consequently, high frequency deep brain stimulation is developing into an important therapeutic option for treatment of intractable Parkinsonian tremor. The development of high frequency stimulation as a means to control Parkinsonian tremor arose initially from surgical procedures in which destruction (lesioning) of certain regions of the brain led to greatly reduced tremor. Subsequently, it was observed that rapid electrical stimulation of the same regions could lead to a profound reduction of the symptoms. Thus, the development of high frequency deep brain stimulation has been largely empirical, rather than based on a theoretical foundation.

The origin of Parkinsonian tremor is not well understood. Although most models for Parkinsonian tremor assume an oscillation in complex networks that are modeled by differential equations,⁵⁻¹¹ there is not general agreement

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about the detailed structure of the network or the abnormalities that lead to Parkinsonian tremor. Excellent reviews of the neural correlates of Parkinsonian tremor are in Lenz *et al.*,¹² and McAuley and Marsden.¹³

A variety of different hypotheses have been advanced to explain the effects of high frequency deep brain stimulation on Parkinsonian tremor. Assuming that Parkinsonian tremor is associated with abnormal oscillations in some region of the brain, high frequency stimulation might act simply to block or interfere with the transmission of oscillatory activity to the motor neurons.¹⁴ With this hypothesis, the abnormal oscillations would still be present in brain structures but would no longer lead to observed tremor. Another hypothesis is that Parkinsonian tremor is associated with an abnormal synchronization of many independent oscillators, but that deep brain stimulation acts to desynchronize these oscillators.^{10,11} Yet another hypothesis is that high frequency stimulation acts via reversible inhibition of the target function, thus mimicking the effects of lesioning the target structure.⁴ Other hypotheses, that have not been considered before in the context of controlling Parkinsonian tremor, but which are well known in other contexts seem *a priori* equally plausible. For example, high frequency deep brain stimulation might act to entrain the abnormal oscillator in a 1:0 rhythm¹⁵ so that the oscillator is effectively arrested as a consequence of repetitive phase resetting as happens in simple models of cardiac cells or other oscillators.¹⁶ Finally, high frequency deep brain stimulation might lead to a change in system parameters, and this in turn would lead to a Hopf bifurcation in the dynamics¹⁷ so that the abnormal limit cycle associated with the tremor would be destabilized. This change in system parameters could be related to a gradual change in network properties generating the tremor.¹⁸ Under the Hopf bifurcation hypothesis, the periodic oscillations associated with the tremor would no longer be present in any of the brain structures.

The current study was motivated by the wish to develop a better understanding of potential mechanisms of the effects of deep brain stimulation on Parkinsonian tremor by studying the tremor dynamics that occur during the onset and offset of high frequency deep brain stimulation in subjects with Parkinsonian tremor.

In Sec. II, we describe the effects on rest tremor in the index finger observed during high frequency deep brain stimulation in subjects with Parkinson's disease. These data suggest that a Hopf bifurcation may be underlying the transitions induced by deep brain stimulation. In Sec. III, we present a theoretical analysis of some dynamical aspects of the Hopf bifurcation from a very general perspective. To illustrate these results, in Sec. IV we show a highly simplified oscillating network model in which oscillations are destabilized during a periodic perturbation.

II. CLINICAL DATA

Rest tremor velocity was recorded using a low-intensity velocity laser¹⁹ in four subjects with Parkinson's disease receiving chronic, high frequency, deep brain stimulation. These data were recorded at a sampling rate of 100 Hz from

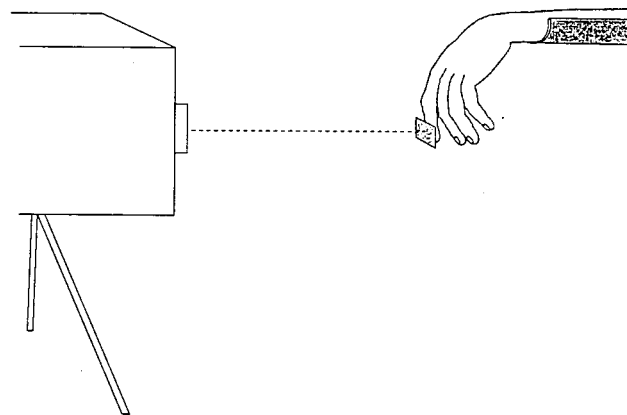


FIG. 1. Velocity laser recording of rest tremor.

the subject's index finger in a resting position continuously throughout switching the deep brain stimulation on (at an effective frequency) and off. These four subjects with high amplitude tremor were part of a study examining the qualitative effect of high frequency stimulation on rest tremor in Parkinson's disease: the comparison of separate recordings (i.e., not transitions) of the subjects' tremor with effective stimulation and without stimulation is presented elsewhere.²⁰

Figure 1 shows a schematic representation of the laser (Bruel and Kjaer, Naerum, Denmark), which is a safe (Class II) helium-neon laser, placed at about 30 cm from the finger tip during rest tremor recording. The laser beam is split with one part directed at the finger and the other, called the reference, directed at a rotating disk inside the laser. Back scattered light from the rotating disk determines the sign of the velocity signal: a positive velocity when the finger extends and negative when the finger flexes. Tremor in the finger is detected and converted to a calibrated voltage output that is proportional to finger velocity. The raw data were collected using the MacLab data acquisition system (V 3.5.6/S, AD Instruments Pty Ltd., Castle Hill Australia) and exported to Matlab (V 5.2, The Mathworks Inc.) for plotting. The data were converted from volts to meters/second and a three-point median filter was applied to interpolate across artifacts in the data created by the rotation of the laser wheel.

The amplitude and pulse duration of the deep brain stimulation were constant in a particular subject, but varied between subjects, since the parameters are determined clinically to optimize tremor suppression and to minimize undesirable effects for each individual. In general, the stimulation voltage amplitude was approximately 3 volts, the pulse width was approximately 90 μ s, and an effective frequency was >100 Hz. In the data recordings presented here, the effect of switching the stimulation on (at an effective frequency) and off was explored. Table I summarizes the stimulation parameters for each subject.

In the tremor velocity data, there is a delay on the order of several seconds from the time the deep brain stimulator is switched on at an effective frequency to the suppression of oscillations. Figure 2 contains four partial time series of the off-to-effective transition in rest tremor velocity data from four different subjects, with at least one example for each of the three stimulation targets in the deep brain: subthalamic

TABLE I. Stimulation parameters for the four subjects with Parkinson's disease receiving high frequency deep brain stimulation.

| Subject | Full subject identifier ^a | Effective frequency (Hz) | Pulse duration (μ s) | Pulse intensity (V) | Stimulation mode ^b | Contact polarity ^c |
|---------|--------------------------------------|--------------------------|---------------------------|---------------------|-------------------------------|-------------------------------|
| A | 08STN | 135 | 90 | 2.8 | cont. | ---· |
| B | 04Vim | 185 | 90 | 5.3 | cont. | ·--- |
| C | 02GPi | 160 | 120 | 3.7 | cycl. | ·---· |
| D | 07STN | 185 | 90 | 2.4 | cycl. | ·---· |

^aFinal three letters indicate the stimulation target: subthalamic nucleus (STN), internal globus pallidus (GPi) or ventrointermediate nucleus of the thalamus (Vim).

^bcont. = Continuous stimulation, cycl. = Cyclic stimulation (e.g., 1 minute on, 1 second off).

^cPolarity of stimulation for contact points in quadripolar electrode (– negative, · not stimulated).

nucleus (STN), internal globus pallidus (GPi), and the ventrointermediate nucleus of the thalamus (Vim). The choice of target for the implanted stimulating electrode depends on the symptoms of the subject at the clinical level. High frequency stimulation of any of the three currently used targets alleviates tremor, whereas rigidity and akinesia are improved under stimulation of GPi or STN.⁴

Similarly, when the deep brain stimulation at an effective frequency is switched off, the data show a delay in the onset of tremor, which also varies between subjects. Figure 3 shows the partial time series of the effective-to-off transition corresponding to the four subjects in Fig. 2. In all subjects, we see a gradual increase in the amplitude of the tremor.

The data show striking effects in which there is a delay in onset/suppression of the tremor, and second, there is gradual increase or decrease in the amplitude of the oscillations. These observations are consistent with the hypothesis

that the stimulation induces a Hopf bifurcation in the dynamics. In the next section we develop certain basic properties of the Hopf bifurcation.

III. THE HOPF BIFURCATION

In this discussion, μ is a bifurcation parameter that changes over time. We assume that there is a stable limit oscillation existing for $\mu > \mu_c$ and a stable fixed point for $\mu < \mu_c$. In the typical situation, when μ increases through the value μ_c , an oscillation of growing amplitude is induced, and similarly, when μ decreases through the value μ_c the oscillation dies out. In this scenario, which is called the supercritical Hopf bifurcation, there is no hysteresis.¹⁷

In order to model the effects of the stimulation in a schematic way, we assume that each stimulus induces release of an amount δ of a substance z that subsequently decays with a time constant t_c and that this substance induces a change in the bifurcation parameter. Recent studies have indicated that during brain stimulation, there is a buildup of

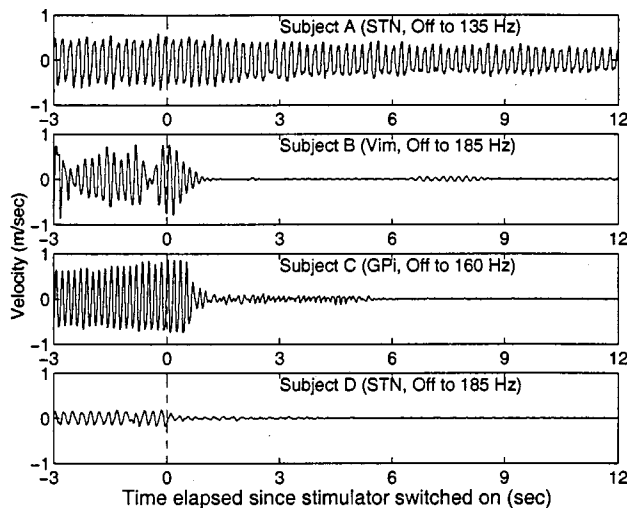


FIG. 2. Stimulation off-to-effective transitions: 15 seconds of Parkinsonian rest tremor finger velocity (in meters/second) of four different subjects during which deep brain stimulation at an effective frequency is switched on at the vertical dashed line. In the brackets following the subject identifier, we indicate the target of the deep brain stimulation, which is either the subthalamic nucleus (STN), the internal globus pallidus (GPi) or the ventrointermediate nucleus of the thalamus (Vim), as well as the frequency of effective stimulation in Hz. For subject A, although the 12 seconds shown of effective stimulation was not sufficiently long to suppress the tremor, the corresponding trace of effective-to-off transitions in Fig. 3 begins with a clearly suppressed tremor.

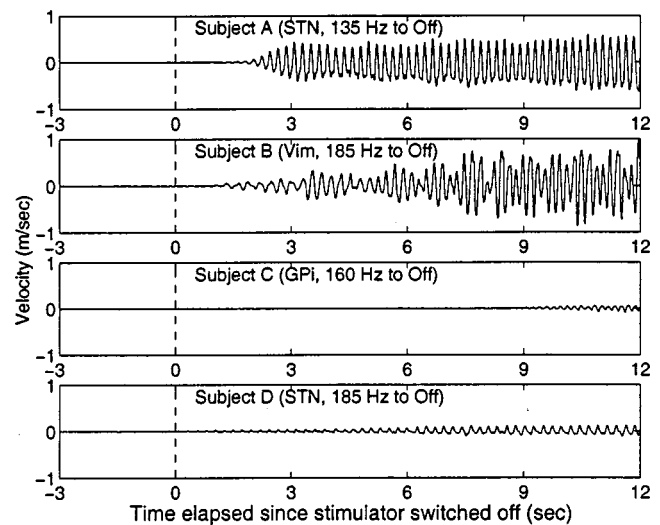


FIG. 3. Stimulation effective-to-off transitions: 15 seconds of Parkinsonian rest tremor finger velocity (in meters/second) of four different subjects during which deep brain stimulation at an effective frequency is switched off at the vertical dashed line. In the brackets following the subject identifier, we indicate the target of the deep brain stimulation, which is either the subthalamic nucleus (STN), the internal globus pallidus (GPi) or the ventrointermediate nucleus of the thalamus (Vim), as well as the frequency of effective stimulation in Hz.

neurotransmitters.^{21,22} We call δ the magnitude of the amount released per stimulus, τ the period of the stimulation, so that the frequency f of the stimulation is $f=1/\tau$. Without stimulation, z decays to 0 with the same time constant t_c .

At $t=0$ we assume that the value of μ is $\mu_0 > \mu_c$. We assume that as time proceeds

$$\mu(t) = \mu_0 - z(t), \tag{1}$$

so that eventually, μ might decrease to be less than μ_c .

The periodic stimulation leads to a time-dependent increase of $z(t)$. We call z_0 the initial value of z just before stimulation commences with a pulse which we will call the "0th" pulse. Given the period of the stimulation pulses τ , then just before the first pulse, we have $z_1 = (z_0 + \delta)e^{-\tau/t_c}$, and just before the second pulse, we have $z_2 = (z_1 + \delta)e^{-\tau/t_c}$. Continuing in this way, for the expression of z just before the n th pulse, a geometric series emerges which, when summed, simplifies the expression to

$$z_n = z_0 e^{-n\tau/t_c} + \frac{\delta(e^{-n\tau/t_c} - 1)}{1 - e^{-\tau/t_c}}. \tag{2}$$

From this it follows that as $t \rightarrow \infty$, the asymptotic value of $z(t)$ is given by

$$z_\infty = \frac{\delta}{e^{\tau/t_c} - 1}.$$

In order to determine how μ depends on time during stimulation, we assume that $z_0 = 0$, and substitute Eq. (2) into Eq. (1) to obtain

$$\mu(t) = \mu_0 - \frac{\delta(e^{-t/t_c} - 1)}{1 - e^{-\tau/t_c}}. \tag{3}$$

Here, we have used the fact that during stimulation, $t = n\tau$.

We now scale parameters by dividing by μ_0 and define $\bar{\mu}(t) = \mu(t)/\mu_0$, $\bar{\mu}_c = \mu_c/\mu_0$, and $\bar{\delta} = \delta/\mu_0$. Scaling Eq. (3), we have

$$\bar{\mu}(t) = 1 - \frac{\bar{\delta}(e^{-t/t_c} - 1)}{1 - e^{-\tau/t_c}}.$$

Thus, in the limit $t \rightarrow \infty$ we find

$$\bar{\mu}_\infty = 1 + \frac{\bar{\delta}}{1 - e^{-\tau/t_c}}.$$

Let us now put this back into the context of the deep brain stimulation. In deep brain stimulation, one can vary the frequency of the stimulator as well as the amplitude of the stimulator. We assume that changing the amplitude of the stimulation is equivalent to increasing the value δ released with each stimulus. If $\bar{\mu}_\infty < \bar{\mu}_c$, then the stimulation will eventually lead to a suppression of the tremor. The length of time, t_{\min} , until $\bar{\mu}(t)$ reaches its critical value $\bar{\mu}_c$ can be computed from the expressions above and sets a lower bound on the length of time until suppression occurs. Assuming initial values μ_0 and $z(0) = 0$, we find

$$t_{\min} = t_c \ln \frac{1 - \bar{\mu}_\infty}{\bar{\mu}_c - \bar{\mu}_\infty}. \tag{4}$$

Assuming that the frequency and amplitude of the stimulation are adjusted so that they are just on the boundary so that $\bar{\mu}_\infty = \bar{\mu}_c$, we find

$$\bar{\delta} = (1 - \bar{\mu}_c)(e^{1/f t_c} - 1). \tag{5}$$

Note that t_c sets the time scale for the lower bound of the delay from the stimulation onset to the suppression of tremor and for most values of the parameters t_{\min} will be of the same order of magnitude as t_c . However, this is not necessarily always true. In order to appreciate this assume $1 \gg \epsilon > 0$, and recall we have assumed $1 > \bar{\mu}_c > \bar{\mu}_\infty$. In Eq. (4), if $\bar{\mu}_c - \bar{\mu}_\infty = \epsilon$ and $1 \gg \bar{\mu}_\infty$, then $t_{\min} \gg t_c$. This corresponds to the situation in which the stimulation parameters lie just beyond the borders at which control is effective. In carrying out the procedures, the neurologist tries to find stimulation parameters that are most effective, and do not lie on the boundary. On the other hand, if $1 - \bar{\mu}_c = \epsilon$ and $1 \gg \bar{\mu}_\infty$, then $t_{\min} \ll t_c$. In this case, the baseline value, μ_0 , of the bifurcation parameter lies just marginally in the oscillatory region. In the scenario of the supercritical Hopf bifurcation, this parameter range would be associated with low amplitude oscillations, and it would not be likely that the subject would be receiving deep brain stimulation for tremor control. Thus, we believe it likely that the t_c for the decay of the putative substance that builds up in this scenario, is roughly of the order of the time until suppression of tremor during high frequency deep brain stimulation.

Equation (5) indicates that if the minimal stimulation amplitude is plotted as a function of the minimum frequency to obtain tremor suppression, the boundary will be a monotonically decreasing function. However, we expect that the refractory period of neurons would prevent activation at too rapid a stimulation rate. Consequently, the stimulation amplitude needed to affect control of tremor would not decrease to zero as indicated in Eq. (5), but rather would saturate at some constant positive value. Thus, the general form of the boundary separating effective and ineffective stimulation is similar to the clinical results.³ We consider these general results in the context of a definite network model for oscillations in the next section.

IV. A NETWORK MODEL FOR SUPPRESSION OF TREMOR

To illustrate the properties of the Hopf bifurcation in a concrete example, we present a mathematical model of a network with negative feedback²³ to illustrate how an oscillating system interacts with periodic stimulation. Although a number of different network models have been proposed for Parkinsonian tremor, the current model is not based on known anatomy or physiology but is simply meant to illustrate one way that the Hopf bifurcation might arise in a network context.

We consider the three-unit network model

$$\frac{dy_1}{dt} = f_I(y_3) - y_1, \quad \frac{dy_i}{dt} = f_E(y_{i-1}) - y_i, \quad i = 2, 3. \tag{6}$$

This network exhibits feedback inhibition, in which y_1 excites y_2 , y_2 excites y_3 , and y_3 inhibits y_1 .²³ Here, $f_I(y)$ and $f_E(y)$ are inhibitory and excitatory response functions respectively. Typically, response functions are sigmoidal, and are monotonically decreasing for inhibition and monotonically increasing for excitation. For our illustration, we use Hill functions, which are sigmoidal in form, to represent the response of the units

$$f_I(y) = \frac{\theta^g}{y^g + \theta^g}, \quad f_E(y) = \frac{y^g}{y^g + \theta^g}, \quad \theta = 0.5, \quad (7)$$

where the exponent g controls the slope (gain) of the response and where we have set the units' threshold, θ , to $\theta = 0.5$.

Our three-unit model involves a negative feedback system without time delay and thus, the Hopf bifurcation would be induced by an increase in gain. This network is a special case of an n -unit feedback inhibition network²³ which can display oscillations provided that $n \geq 3$. The dynamics of systems of this type are a network effect, meaning that the units will not oscillate independently. The network in Eqs. (6) and (7) exhibits a Hopf bifurcation at $g = \mu_c = 4$: for $g < \mu_c = 4$, the solution has a stable fixed point, whereas for $g > \mu_c = 4$, it has a stable limit cycle.

Given an initial value, y_0 , and the value of the exponent g , we solve the system of three ordinary differential equations in Eqs. (6) and (7) for y using a fourth-order Runge–Kutta integration scheme with a step-size of $\Delta t = 0.01$. For the simulations, we use 10 000 time steps so that the time interval in the arbitrary time units of the model corresponds to 5 seconds. We include additive noise to the system, of the form $dy/dt = f(y; g, \theta) + \xi$, where $\xi(t) = 0.02 * (\text{normally distributed random number})$, to counterbalance rounding errors in the time-stepping routine. Here, we assume that the sources of noise are independent of the precise state of the system.

As in Sec. III, we model deep brain stimulation as a periodic train of short pulsatile stimuli in which each stimulus pulse releases δ every τ time units, and this in turn leads to a decrease in g , the gain of the units' response in Eq. (7). Specifically, we let $g(t)$ be of the form

$$g(t) = g_0 - z(t), \quad \frac{dz}{dt} = -\frac{1}{t_c} z,$$

where $z(t)$ expresses the deviation due to stimulation of the response, g , from its baseline value, g_0 , without stimulation. We assume that $g_0 > \mu_c = 4$ so that without stimulation the network resides in its oscillatory state.

To describe our results, we refer to the response g (or g_0) and the time constant t_c as network parameters, which are inherent properties of the network. Also, we refer to δ and τ as stimulation parameters, which are the stimulation pulse amplitude and stimulation period, respectively.

For our simulations, we have set the baseline value of the bifurcation parameter (i.e., the response of the units without stimulation) at $g_0 = 6.0$ so that the network is in its oscillatory state. Thus, $\bar{g} = g/6.0$. For $\bar{g} = 1$ and with no stimulation, the period of oscillation in the network model is 3.53

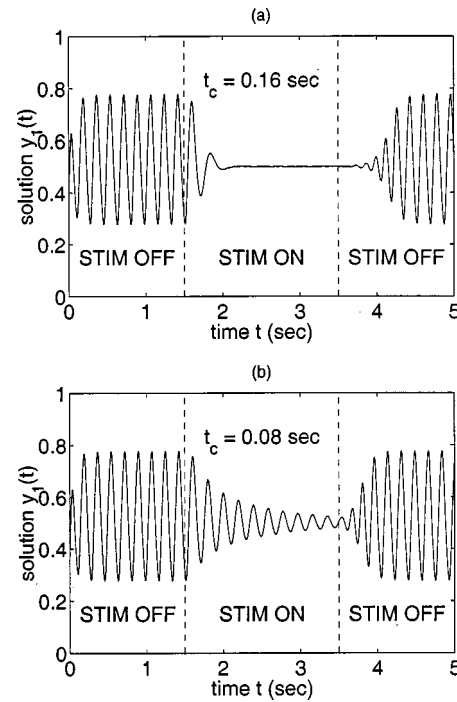


FIG. 4. Numerical simulations of the three-unit network corresponding to the periodic stimulation in Fig. 5 (frequency 125 Hz, scaled amplitude $\bar{\delta} = 1/30$) which leads to time-dependent decrease of the parameter \bar{g} (Fig. 5) and thereby induces a Hopf bifurcation in the dynamics. The solution of y_1 is shown for two values of the time constant t_c , which governs the buildup/decay of the control parameter.

in arbitrary time units. A typical period of oscillation in Parkinsonian tremor is 0.18 s, which corresponds to a tremor with frequency 5.7 Hz. Thus, in the figures, we scaled the arbitrary time of the model by a factor of 20 (arb. time units)/s so that it corresponds to the characteristic time scale of the tremor data.

Figure 4 shows the solution from unit 1 in the three-unit network in Eqs. (6) and (7) as a result of the variation of the parameter, \bar{g} , through high frequency ($f = 125$ Hz) pulsatile periodic stimulation for two values of the time constant t_c . Figure 5 illustrates how the stimulation decreases the parameter \bar{g} until it crosses $\bar{g} = \bar{\mu}_c$ and induces a Hopf bifurcation in the dynamics. The value of \bar{g} after the n th pulse is $\bar{g}_n = 1 - \bar{z}_n$, where $z_n = g_0 \bar{z}_n$ is in Eq. (2). For a smaller time constant, we observe in Fig. 4 an increased delay in suppression of the oscillations. As well, in this figure, we see the gradual decrease and increase in the amplitude of oscillation as the parameter \bar{g} is varied which are typical of oscillation transitions in a supercritical Hopf bifurcation.^{17,24} Figure 4(b) demonstrates the increase in suppression time when the stimulation parameters lie just beyond the border at which stimulation is effective [i.e., when $(\bar{\mu}_c - \bar{g}_\infty)$ is small]. The minimum time to suppression is t_{\min} given in Eq. (4), which does not include the time for decaying transients and the effect of noise added to the system.

Figure 6(a) displays the scaled steady-state gain, $\bar{g}_\infty(\tau)$, for a fixed stimulation amplitude ($\bar{\delta} = 1/60$) for three values of the time constant, t_c . From this figure, for $\tau = 0.01$ (i.e., stimulation frequency = 100 Hz) as an example, the value of t_c corresponding to the critical value of the control parameter

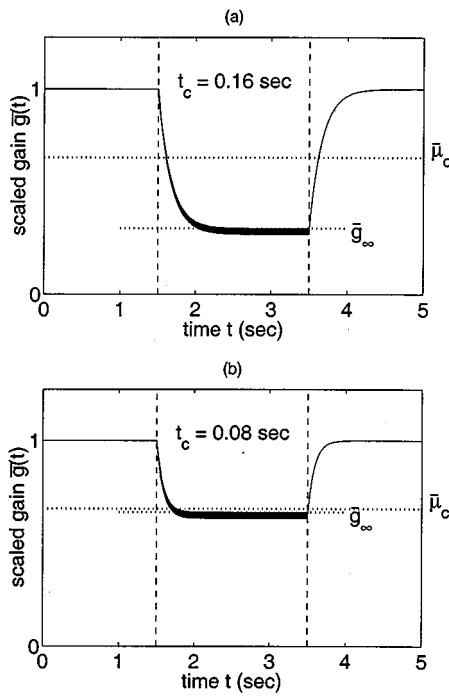


FIG. 5. Periodic stimulation leads to time-dependent decrease of gain of response, $\bar{g}(t)$, to its steady-state value \bar{g}_∞ . The critical value $\bar{\mu}_c$ defines the border below which the control is effective. The time constant of the buildup/decay of the control parameter is t_c . Stimulation parameters: frequency $f=125$ Hz, scaled amplitude $\bar{\delta}=1/30$.

$\bar{g} = \bar{\mu}_c$ is $t_c=0.2$ s. Figure 6(b) displays the corresponding amplitude of oscillations in the network model solution which undergoes a Hopf bifurcation when \bar{g} crosses through $\bar{\mu}_c$. In the model, there is a buildup/decay of a substance induced by the stimulation that changes on a time scale of approximately 0.2 seconds.

The simulations of our model reflect qualitatively the observations in the data. In addition to identifying a time constant governing the oscillation stability, our model accounts for the frequency dependence of effective stimulation. Figure 7 shows the curve $\bar{g} = \bar{\mu}_c$ separating the effective and ineffective stimulation regimes for different time constants and compares this with clinical data for thalamic stimulation.³ To compute this curve, we solve for $\bar{\delta}$ as a function of τ , using

$$\bar{\delta}(\tau) = \begin{cases} (1 - \bar{\mu}_c)(e^{\tau/t_c} - 1), & \tau \geq \tau_s, \\ (1 - \bar{\mu}_c)(e^{\tau_s/t_c} - 1), & \tau < \tau_s. \end{cases}$$

Here, we assume that the refractory period of neurons prevents activation at too rapid a stimulation rate (we chose τ_s corresponding to a stimulation frequency of $f_s = 180$ Hz) and thus the stimulation amplitude saturates. The units of the stimulation pulse amplitude $\bar{\delta}$ from the model were scaled to the data points: we multiplied $\bar{\delta}$ by a scale factor of $500 \approx (\text{intensity necessary to abolish tremor of one subject from Benabid et al.}^3) / (\text{stimulation pulse amplitude } \bar{\delta} \text{ for } t_c = 0.10)$ both at a frequency of 250 Hz. Although there is qualitative agreement between the shape of the curve predicted by the theory and the clinical data, we cannot deter-

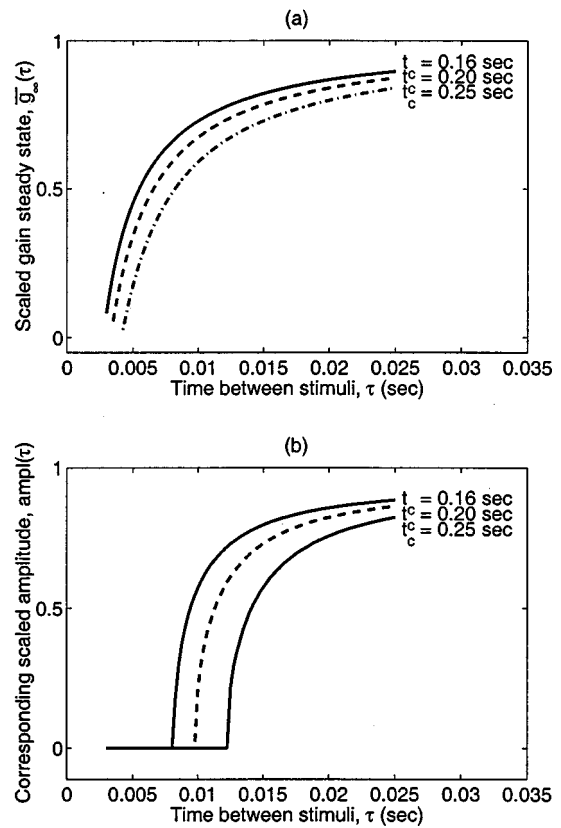


FIG. 6. (a) Scaled steady state of gain, $\bar{g}_\infty(\tau) = 1 - \bar{\delta}/(e^{\tau/t_c} - 1)$, where τ is the stimulation period in seconds. (b) The corresponding amplitude of oscillations, scaled by its maximum value. To obtain the amplitude of oscillations, we computed the standard deviation of three cycles of computed points after transients in the oscillations died away. Parameter values for both (a) and (b): scaled stimulation amplitude $\bar{\delta}=1/60$; time constant, $t_c = \{0.25, 0.2, 0.16\}$ s.

mine the value of t_c from these data. For $0 < \tau/t_c \ll 1$, $\bar{\delta}(\tau) \approx (1 - \bar{\mu}_c)\tau/t_c$, so the value of t_c depends on the scaling of $\bar{\delta}(\tau)$. More physiological information is necessary to remove the degree of freedom.

V. DISCUSSION

In this work, we have analyzed the transitions between tremor and its control induced by high frequency deep brain stimulation in subjects with Parkinsonian tremor. The clinical data show that following onset of stimulation at stimulation parameters that are capable of effecting control, there is typically a decrease in amplitude of the tremor leading to suppression of tremor within several seconds. Similarly, upon removal of the stimulation there is a lag of several seconds following which there is a buildup of oscillations. We believe that these observations indicate that the mechanism by which high frequency stimulation suppresses tremor is by modifying a parameter so that the previously stable oscillation is now destabilized.

Although this is a natural hypothesis in the context of nonlinear dynamics, it is a bit surprising that previous hypotheses for the mechanism of high frequency deep brain stimulation on tremor control have not mentioned this possibility. Several hypotheses put forth previously relate to an inhibitory mechanism (i.e., that deep brain stimulation inhib-

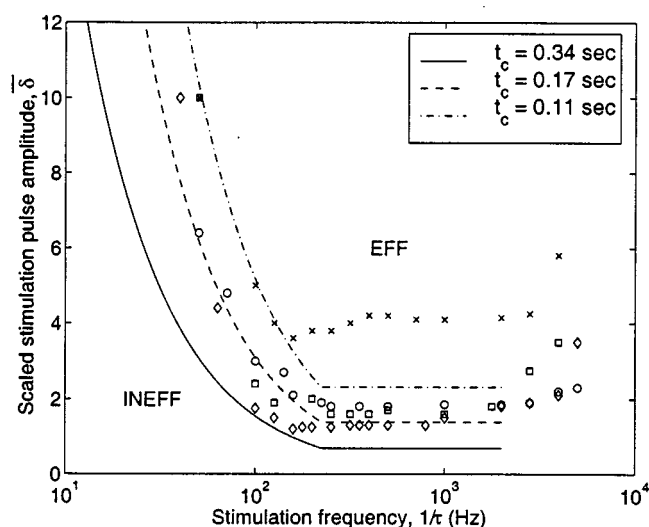


FIG. 7. The range of effective (EFF) and ineffective (INEFF) stimulation parameters in the theoretical model in the stimulation amplitude-frequency plane for three different time constants $t_c = 0.33, 0.16, 0.10$ s. The discrete points are data values from Benabid *et al.* (1991) illustrating electrical stimulation frequency versus intensity necessary to abolish tremor in four different patients receiving chronic electrical deep brain stimulation of the Vim.

its neuronal output, either by a depolarization block of STN glutamatergic neurons²⁵ or GPi GABAergic neurons²⁶ or by a habituation of thalamic relay cells²⁷). However, only a few previous studies have proposed a theoretical model to examine tremor control by deep brain stimulation.^{10,11,14} Further, in contrast to the current work, the other hypotheses of tremor control by block or interference with the transmission of oscillatory activity to the motor neurons,¹⁴ desynchronization of many independent oscillators,^{10,11} or entrainment of the tremor oscillator in a 1:0 rhythm¹⁵ do not appear to lead to the sorts of transitions that were observed in the present study.

Although the schematic three-unit model with excitatory and inhibitory connections captures the clinically observed behaviors, i.e., gradual increase and decrease in oscillation amplitude; time delay for onset and suppression of oscillations; increased time delay in suppression coupled with decreased delay in onset of oscillations (Figs. 2 and 3, Subjects A and D), similar observations could be observed in any other model that shows a Hopf bifurcation induced by stimulation as discussed in Sec. III.

In our model, we apply the periodic stimulation directly to the bifurcation parameter of the oscillatory network. By modeling stimulation in this way, the effects of each stimulation pulse can be easily reformulated to represent an increase or decrease of a parameter controlling the stability of the oscillations. For the particular type of network we use to illustrate our results, we require at least three units for the network to oscillate. However, oscillations can arise via a Hopf bifurcation in systems with fewer units: for example, by increasing the gain or time delay in a one-variable model of the human pupil light reflex.²⁸

In the context we presented, the stimulation decreases the gain in a network that eventually induces a bifurcation.

However, bifurcations could be induced by other parameter changes as well, which would depend on the particular form of the oscillating network.

What is important is the notion that the stimulation induces changes in the stability of an oscillating network and that the time scale for the observed transitions in the dynamics reflects the time scale for parameter changes induced by the stimulation. These parameter changes could be related to the release of neurotransmitters, which if released to the extent of depletion could then inactivate certain motor pathways.

The idea we have presented here does not exclude the interplay of other physiological mechanisms such as neurons switching their mode of discharge (e.g., bursting to spiking) due to depolarization via the high frequency stimulation. At this stage of our understanding, these mechanisms could be operating simultaneously. Future work needs to focus on the particular changes induced by electrical stimulation.

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