A slow axon antidromic blockade hypothesis for tremor reduction via Deep Brain Stimulation

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***Abstract*—Parkinsonian and essential tremor can often be effectively treated by deep brain stimulation. We propose a novel explanation for the mechanism by which this technique ameliorates tremor: a reduction of the effective delay in the relevant motor control loops, via preferential antidromic blockade of slow axons. This theory accounts for several previously difficult-to-explain phenomena, and makes a variety of novel predictions.**

I. Hypothesis

Although in widespread clinical use, the precise mechanism by which Deep Brain Stimulation (DBS, periodic high frequency pulses stimulating nuclei in the pathways associated with motor control) achieves symptomatic relief from tremor remains unclear. The high therapeutic pulse frequencies of DBS, and the fact that low level DBS reduces tremor amplitude while increasing tremor frequency, are both difficult to account for with current theories. The blockade theory [1]–[4] holds that antidromic axonal activation due to DBS effectively blocks orthodromic transmission. Our novel *slow axon antidromic blockade* (SAAB) hypothesis is a variant of this: we hypothesize that axonal connections with large transmission times, i.e., slow axons, are preferentially blocked by the mechanism shown in Fig. 1. The result of this, combined with gain adaptation, is a reduction of the mean delay in the motor control loop, which in turn serves to stabilize the feedback system, thus ameliorating tremor.

II. Results

The SAAB hypothesis is plausible only if it numerically matches the DBS stimulation frequencies observed to ameliorate tremor. To calculate the effective stimulation frequency predicted by the theory, we estimate the spread of axonal propagation delays in motor pathways from published data, rescaled according to brain size [6] (see Section IV). The resultant delay distribution is commensurate with that found from STN (the subthalamic nucleus) to motor cortex in humans [7] and rats [4], and from thalamus to motor cortex in mice [3], [8]. These data allow us to identify the most probable mean delay in humans.

To estimate the shape of the distribution of delays, we use experimental data on axonal diameter distributions (ADD) in the splenium [5] and calculate a path length to match the above delays (Fig. 2a), assuming that the mean spike rate of an axon is not correlated with its diameter. (These distributions could be tested more directly in humans by observing ADDs and pathway lengths in postmortem brains, or perhaps in vivo by diffusion-weighted MRI [8]. However, the predictions of the SAAB hypothesis are quite robust to changes in the delay distribution. Similarly, although we assume that spike rate and axon diameter are uncorrelated, a positive correlation, which seems plausible, would only amplify the proposed effect and would not significantly alter the numerical results.)

The quantitative relationship between axonal diameter and propagation velocity in mylenated axons is linear [5]: as axonal diameter decreases, conduction velocity also decreases, making a collision between an antidromic blockading spike and an orthodromic signal more probable. This probability depends on the DBS frequency (Eq. 2) and the delay (Fig. 2b). The net effect of this velocity-selective blockade (Fig. 2c) is a truncation of the neural response in the usual DBS tremor ameliorating targets (TATs). The average propagation time in the motor control loop would be correspondingly reduced.

Gain adaptation is ubiquitous in the brain [9], so we can be fairly confident that it takes place in the motor control loop. Our calculations assume that gain adaptation keeps the integrated impulse response of the control system roughly constant, despite selective partial blockade. The result of this process appears in Fig. 2d. Note that the mean and spread of the propagation delay is highly dependent on the frequency of stimulation. Under high frequency stimulation, the mean delay is always less than 5 ms.

Large time delays are well know to have a destabilising influence upon negative feedback loops, often leading to sustained oscillation. Reducing the time delay in the motor pathway improves the stability properties of the motor control loop, with a tendency to dampen or eliminate oscillation. To illustrate this idea, a computational model of control of the hand was constructed using physiologically meaningful coefficients and structure (see Section IV). Simulation results (Fig. 5) confirm that SAAB reduces tremor amplitude and increases frequency at rates observed in patients [10]. Note that a non-delay-preferential blockade would only decrease

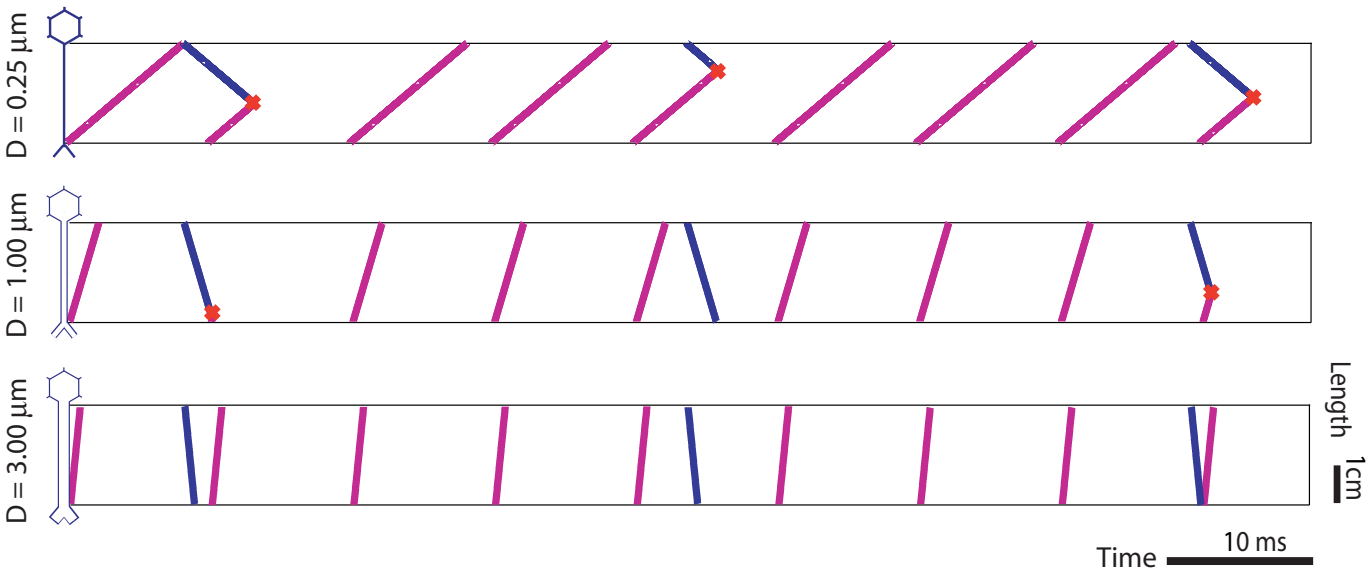


Fig. 1. **DBS antidromic blockade is less effective for axons with greater diameter.** Interaction is shown between orthodromic beta spikes and an antidromic DBS pulse train in axons of different diameters. Beta somatic spikes at 29 Hz are shown in blue traveling orthodromically (downward), while antidromic spikes due to high frequency DBS at 103 Hz are shown in violet. Velocities, distances, and pulse frequencies are in the physiologically and clinically appropriate ranges for the relevant pathways. The differing diameters result in differing conduction velocities (top to bottom: 3.3 m/s, 13.4 m/s, and 40.1 m/s) which results in a higher proportion of spikes clearing the axon without interference in larger-diameter axons.

the gain of the control loop, thus reducing tremor amplitude but maintaining or reducing tremor frequency [11]. In addition, SAAB in the model was only effective at frequencies much higher than the usual neural activity, and was robust across a broad range of stimulation frequencies, in a fashion quantitatively consistent with clinical observations.

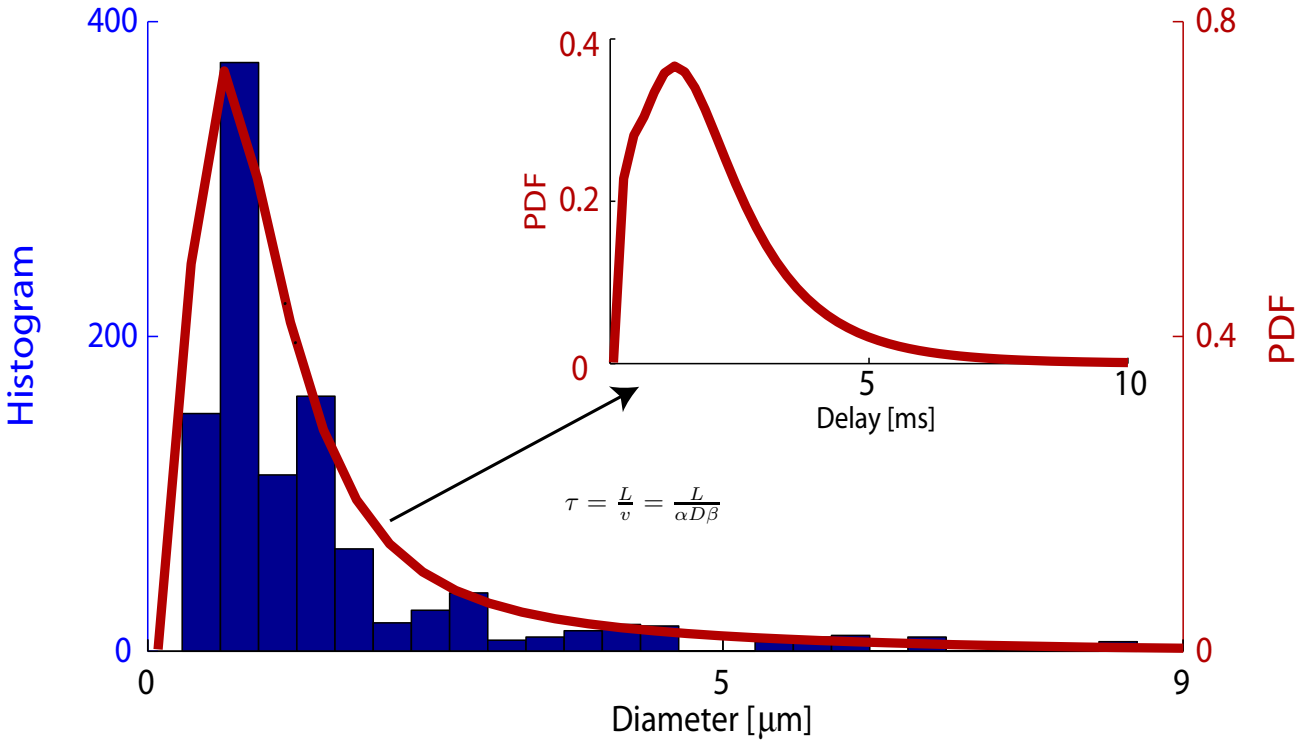
III. Discussion

The SAAB hypothesis relies on the DBS effect over axonal cortical projections to the TAT. This explains experimental results using optogenetic methods to systematically drive or inhibit an array of distinct Parkinsonian circuit elements in freely moving Parkinsonian model rodents, which show therapeutic effects within the STN resulting from direct selective stimulation of afferent axons projecting to this region [2]. The SAAB hypothesis is also compatible with findings that stimulation of the spinal chord can suppress Parkinsonian tremor [12]. These results have two noteworthy features: (a) the frequency of stimulation is more than double that in usual TATs (300 Hz); and (b) the electrode is located in the sensory fibers of the spinal cord and not in a nucleus of the basal ganglia. First, some of the spinal cord sensory fibers go to the cortex passing through the brainstem. These axons share common segments with the axons connecting the thalamus and the cortex [13]. Second, since the stimulation frequency is between two and three times higher than that usual in conventional TATs, the shared pathway should be between two and three times shorter than the thalamus-cortex pathway. Both of these predictions are testable.

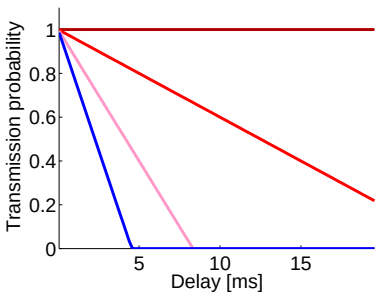
As discussed above, the SAAB hypothesis is unique in that it naturally accounts for a variety of observed phenomena, including the pulse frequency range effective in DBS and the clinical effect of slightly sub-therapeutic DBS stimulation frequencies. We will proceed to explore a variety of testable novel predictions made by this hypothesis. It is possible to measure the ADDs [8] and pathway lengths to test the following predictions. (a) Bundles of axons traveling from the cortex to the TATs should have similar delay distributions, i.e., similar relationship between the length and the diameter and even with the degree of myelination. (b) Where there are substantial differences in the minimum effective DBS frequency, there should also be differences in the delay distribution of the stimulated pathway. If this observation is confirmed, pre-clinical studies could estimate the optimal stimulation frequency, or even other DBS locations, prior to DBS electrode implantation. (c) If a patient has a narrower delay distribution, DBS is less likely to be effective.

We hypothesize that DBS reshapes the impulse response of the involved cortical-basal pathway. This distribution of delays, and its modulation by DBS, could be directly measured by transcranial magnetic stimulation in concert with the implanted electrode. Such modulation might also be measured by short-term cross-correlations between time-domain recordings of activity in cortex and TATs. The motor control loop impulse response can be directly measured by mechanical perturbation of a load during a motor control task, allowing any modulation of the impulse response during DBS to be observed.

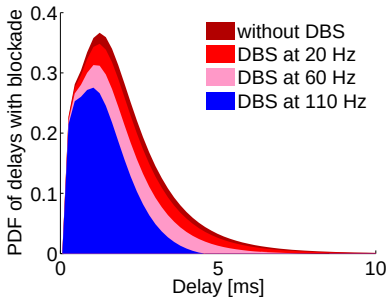
We have presented crisp predictions, which would serve as fingerprints of a slow axon antidromic blockade. It is important to note that the SAAB hypothesis does not imply that no other mechanism can ameliorate tremor, nor does it imply that SAAB is the only mechanism by which DBS ameliorates tremor. In a more speculative vein (a) other pathological



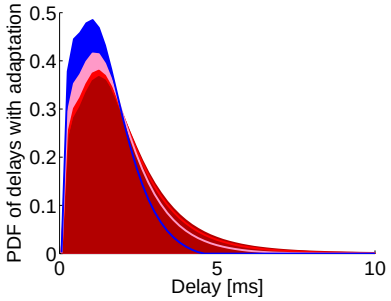
(a) Axonal diameter distribution in the human splenium [5] and the corresponding distribution of axonal delays.



(b) Transmission probability of a random orthodromic spike as a function of axonal delay, at antidromic blocking frequencies of 0, 20, 60 and 110 Hz. The blockade is complete when the axonal delay exceeds one-half of the interval between antidromic spikes.



(c) Distribution of axonal delays, as modulated by DBS at 0, 20, 60 and 110 Hz. Higher frequency DBS dramatically shortens the distribution of delays.



(d) Distribution of axonal delays, as modulated by DBS at 0, 20, 60 and 110 Hz, with gain adaptation operating to preserve the area under the curve.

Fig. 2. The effect of DBS at various frequencies on the cortex-TAT pathway.

oscillatory motor behaviour, such as stuttering, might also be ameliorated by a selective blockade of slow axons in the involved pathways, and (b) other conditions for which treatment by DBS has enjoyed success, such as depression [14], might involve SAAB.

IV. Supplementary Information

A. Tremor Ameliorating Targets

There are two main targets for tremor amelioration in the cortical-basal ganglia-thalamo-cortical loop, referred to as tremor ameliorating targets (TATs): the subthalamic nucleus (STN) and the thalamus. Fig. 3 illustrates their connections inside that loop and marks those cortical projections that can be blocked by antidromic activation. It should be noted that other projections can be also blocked antidromically although they are not depicted in the figure. The importance of cortical projections was proved in experimental results [2] where the stimulation of axonal bundles connecting the cortex and STN produced similar beneficial effects to simulating the STN itself in Parkinsonian rat models. This work plus the importance of the cortex in commanding tremor related pathways (cortical-basal ganglia-thalamo-cortical and cerebello-thalamo-cortical) support the hypothesis that connections between the cortex and TATs are of key importance in understanding tremor amelioration by DBS.

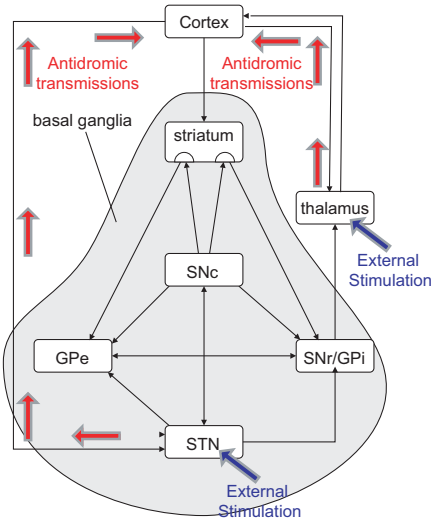


Fig. 3. Cortical-basal ganglia-thalamo-cortical loop including the Tremor Ameliorating Targets (TAT): STN and thalamus.

B. Estimation of axonal propagation delays in motor pathways

It is well-known in neurology that long myelinated axons conduct traveling spikes at different velocities, and that this velocity is proportional to the axonal diameter. For example, the following relation between propagation times and diameters is obtained from experimental data [5]:

$$\tau_i = \frac{L}{v_i} = \frac{L}{\alpha D_i + \beta} \quad \text{with} \quad \begin{array}{l} \alpha = 9.7 \times 2.15\,\mathrm{m/s/\mu m} \\ \beta = 9.7 \times 0.013\,\mathrm{m/s} \end{array} \tag{1}$$

where τ_i [ms], L [mm], v_i [m/s], and D_i [µm] are the travelling times, length, velocities, and axonal diameters, respectively, and i ranges from one to the number of fibers with different diameter. The parameters α and β describe the linear relationship found between velocity and diameter, including the correction factor for the shrinkage of the axonal diameter after fixing and embedding the tissue in paraffin.

The probability density function (PDF) of axonal diameters is obtained by rescaling observations of neural delay in other nerve bundles. Fig. 2a, was calculated from histograms of different diameters in the human midbody [5]. To obtain a smooth approximation to the PDF, we use a method implemented in MATLAB (R2009a, The MathWorks) to estimate distributions by using a normal kernel and restricting the probability to positive values [15]. Common measures of latency between TAT and the cortex are approximately 2 ms [3], [4], [7]. From this and the diameter PDF in Fig. 2a we obtain an estimate of the length of the pathway as $L = 23.79\,\mathrm{mm}$. With these data, the resulting distribution of delays can be seen in Fig. 2a.

Let us denote by λ the time between consecutive DBS pulses, the probability of transmission can be easily computed if noting that there is complete blockade when $2\tau \geq \lambda$:

$$P(\text{transmission}\,|\,\lambda,\tau) = \begin{cases} 0 & \text{when} \quad 2\tau \geq \lambda \\ 1 - \frac{2\tau}{\lambda} & \text{when} \quad 2\tau < \lambda \end{cases} \tag{2}$$

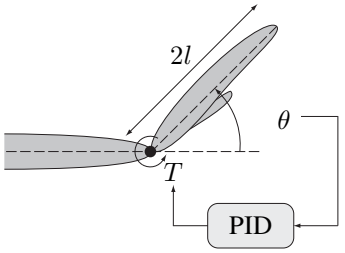


Fig. 4. A simple biomechanical model of a hand.

The relationship between delay and blockade probability (2) is illustrated in Fig. 2b for several DBS frequencies.

Finally, by multiplying the delay PDF by the transmission probability at different stimulation frequencies, the PDFs in Fig. 2c are obtained. As can be seen, it is necessary to stimulate at frequencies greater than 110 Hz to achieve significant attenuation of transmissions with delay greater than 5 ms.

C. Biomechanical Model

We use a basic control model to argue that reducing the effective delay of the feedback loop has two effects observed in experiments: decrease of the tremor amplitude and increase of its frequency.

As background, we first review a known result from control theory: that a communication delay in the feedback path of a control system can have a destabilizing effect [16]. Fig. 4 shows a simple biomechanical model of wrist angle under the action of torque T induced by a motor control circuit. We assume that the motor control circuit uses a generic control structure (PID, or proportional, integral plus derivative [17]) to maintain the hand in a horizontal position against gravity.

For the biomechanical model depicted in Fig. 4, the equations of motion are

$$\ddot{\theta}(t) = -\frac{g}{l}\cos\theta(t) + \frac{1}{ml^2}T(t). \tag{3}$$

where $\theta(t)$ denotes the wrist angle as a function of time, $g = 10\,\mathrm{ms}^{-2}$ is the local acceleration due to gravity, $m = 375\,\mathrm{g}$ is the mass of the hand, $l = 9\,\mathrm{cm}$ is the distance from the joint to the center of mass and $T(t)$ is the applied torque (usual hand mass and length are $m = 375 \pm 125\,\mathrm{g}$ and $l = 18 \pm 3\,\mathrm{cm}$, respectively). We assume that the torque exerted is a control force, of the form

$$\begin{aligned} T(t) = k_p \sin\theta(t-\tau) + k_d \operatorname{atan}\alpha_d\,\dot{\theta}(t-\tau) \\ + k_i\ \operatorname{atan}\alpha_i \int_{-\tau}^{t-\tau} \theta(t')\,\mathrm{d}t' \end{aligned} \tag{4}$$

where $k_p = 1.1315$, $k_d = 0.3234$, $k_i = 2.8098$ are the proportional, derivative and integral controller gains and $\tau > 0$ is a fixed delay associated with motor circuit control processing. The function atan models saturation and α_d and α_i are scaling factors.

Fig. 5 shows the behavior of the closed-loop system as a function of the delay parameter. The set up of the experiment consists of simulating how the hand muscles try to remain

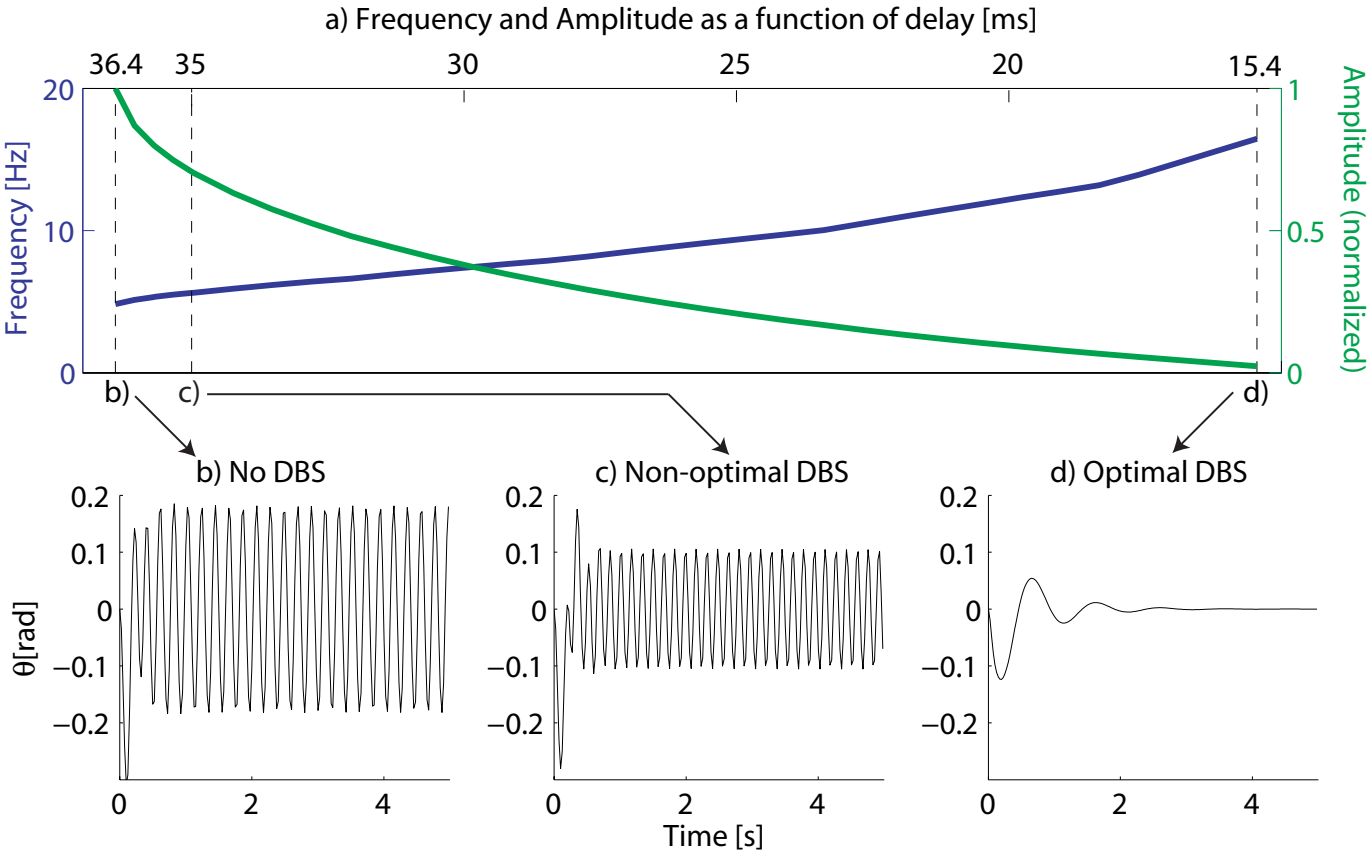


Fig. 5. Closed-loop control is used to regulate wrist angle at the horizontal position $\theta(t) = 0$ with control gains selected to reproduce the mean measured amplitude and frequency [10]. Panel (a) shows how the the frequency of the oscillation increases and the amplitude decreases when reducing the delay. Panels (b–c) show different PD tremor at different conditions: b) no DBS, c) a non-optimal DBS and d) optimal DBS (normal physiological tremor usually ranges between 6–15 Hz) [18].

in the horizontal position when the support is removed and gravity starts acting, as it has been previously carried out in several experiments [10], [19]. Firstly we calculate the controller gains given above in order to reproduce the measured mean amplitude and frequency [10] in Parkinsonian patients under a feedback delay [18]. The dynamics of this experiment are despited in Fig. 5b. When the delay is reduced to $35\,\mathrm{ms}$, the amplitude and frequency predicted by the model match those results measured in PD patients under DBS (Fig. 5c). In a third experiment, we decrease even further the delays and the model, Fig. 5d, predicts a behavior typical in normal physiologic tremor [18]

As can be seen in Fig. 5a, the model predicts that both amplitude and frequency depend upon the value of the delay parameter in a predictable manner, with a larger delay corresponding to a lower frequency and a higher amplitude respectively. This behavior is characteristic of a well-known phenomenon in the theory of dynamical system known as a (supercritical) Hopf bifurcation [20]: the same bifurcation observed in the models simulating the competition between feedback loops in the BG [21]. We note that the stable regime is finite: delays beyond a certain critical value lead to a bifurcation that renders the oscillations unstable. This phenomenon is also extremely robust to the particular details of the controller. In fact, normal physiologic tremor can be also obtained for different delays by selecting proper controller gains, but still with similar behaviour to that shown in Fig. 5a. Hence, we should stress that the lack of dopamine may not necessarily change the loop delays, but may change the gains such that pathological tremors arise. On the other hand, DBS may affect tremor by a different mechanism: reducing the control loop delays. This also agrees with the observations that drug lepadova, changing the gains between direct and indirect pathway in the BG, suppresses tremor but keeps the frequency invariant [10], [19], [22].

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