Are Rigidity and Tremor Two Sides of the Same Coin in Parkinson's Disease?

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Abstract: In this research, we evaluate the inter-relation of tremor and rigidity in order to find whether they are the two sides of the same coin in Parkinson's disease (PD). We include the agonist and antagonist skeletal muscle models as well as the peripheral (spinal and long loop reflexes) and central (basal ganglia and cortex) mechanisms and try to present a complete model of PD. All of our simulation is developed in SIMULINK, MATLAB 7. For simulating the muscle dynamics, we used the mechanical model of Hill. Input of the model is from CNS and the output is angular movement. The agonist and antagonist muscles are used simultaneously to simulate the tremor and its relation to the rigidity. Our abstract model of Basal ganglia is able to simulate the physiological tremor. Voluntary co-contraction of muscles increases the tremor, which is physiologically plausible. The model is also able to produce The PD rest tremor. Our results showed that increased supplementary motor area output increases the rigidity. Finally our model indicated that Rigidity worsens the tremor and vice versa. We suggest that the treatment of these two abnormal motor behaviors must be fulfilled simultaneously. It seems that curing one of these two symptoms without decreasing the other is not realistic. It is worth noting that experimental studies are needed to validate this computational model.

Keywords: Parkinson's disease; Tremor; Rigidity; Mathematical model; Long loop reflex.

1. Introduction:
Parkinson's disease (PD) is one of the most prevalent neural diseases, in which a part of basal ganglia called substantia nigra (SN) is destroyed seriously and dopamine level is reduced. The essential symptoms of PD are rigidity, rest tremor with a frequency of 4 to 6 Hz, bradykinesia, and postural instability [1].

There are two hypotheses about the origin of tremor: (1) involvement of central mechanisms [2,3]. This hypothesis assumes a central origin for the tremor, which may be thalamic cells, basal ganglia, or cerebellum; (2) peripheral feedback mechanisms. This hypothesis claims that an unstable hyper-excitable long-loop reflex arc is responsible for PD tremor [4].

Since the tremor is a main sign of PD and is easily measured, it is assumed to be the output in most mathematical models of PD. As PD is related with a loss of the neurotransmitter dopamine, Edward et al. supposed a neural network model and weakened the connections between the network units [5]. Although this is an abstract model obtained from physiological information, it has included both central and peripheral loops. Terman et al. have developed a cell-level model of the external segment of globus pallidus and the subthalamic nucleus, and their interactions [6]. They proposed that conductance-based cellular models are required to capture the dynamic activity of these structures and that reciprocal connection between the external globus pallidus and the subthalamic nucleus, along with lateral
inhibition within the external globus pallidus and input from the striatum, could generate the oscillations seen in tremor of PD. In one of the last studies, Haeri et al. have modeled the physiological and pathological behavior of basal ganglia mathematically, assuming the output of the model to be the velocity of hand tremor [7].

In contrast to the mechanism of tremor, which is still a matter of debate, the mechanism of rigidity is widely accepted to be due to the hyperactivity of a long-loop reflex. Those who believe in the peripheral hypothesis of tremor suppose that tremor and rigidity have common mechanisms [8]; however, the relationship between rigidity and tremor has been studied in few experimental studies. For example, few experimental studies have evaluated the relation between rigidity and tremor using the duration of F-wave, which is an index for excitability of long loop reflex pathway. Naito et al. reported that excitability of the spinal motor neurons was enhanced in rigid Parkinsonian patients [9]. Although it seemed reasonable to assume that the main underlying cause of rigidity is an excessive supraspinal drive to the spinal motor neurons, they observed no evidence for contribution of these mechanisms in tremor. However, Milanov reported that the F wave duration was prolonged both in Parkinsonian tremor and in Parkinsonian rigidity [10].

The only mathematical model describing both rigidity and tremor is presented by Le Cavorzin et al [11]. They explored the involvement of spinal circuits in the generation of parkinsonian rigidity and related motor dysfunctions. The combination of a low reflex gain and a decreased reflex threshold simulated appropriately the experimental rigidity data. These findings are consistent with studies reporting increased spinal interneuron excitability and proprioception deficits in PD. Moreover, as the threshold parameter was much lowered, their model generated typical features of parkinsonian resting tremor, endorsing the hypothesis of participation of a spinal oscillator in this disorder. Although the possible role of spinal circuits in PD motor abnormalities was simulated carefully in Le Cavorzin's study, but he could not support this idea by perfect empirical evidences. In addition, they did not study the effect of rigidity on the tremor and vice versa. Moreover, the involvement of central mechanisms and periodic input from basal ganglia were not included.

In this research, we evaluate the inter-relation of tremor and rigidity in order to find whether they are the two sides of the same coin in PD. We include the agonist and antagonist skeletal muscle models as well as the peripheral (spinal and long loop reflexes) and central (basal ganglia and cortex) mechanisms and try to present a complete model of PD.

2. Method:

Our model contains two parts: (1) the agonist and antagonist muscles and their feedback to the spinal cord; (2) the peripheral and central neural parts. The cortex and basal ganglia, which send and receive signals to and from muscles, comprises the central neural part and the long loop reflex, comprises the peripheral part. All of our simulation is developed in SIMULINK, MATLAB 7.

2.1. Muscle model

For simulating the muscle dynamics, we used the mechanical model of Hill, containing two springs representing the passive behavior of the tendon and the muscle connective tissue, a length-dependent force generator, and a damper that relates the
muscle force to the velocity (Fig. 1) [12].

Fig. 1 Hill mechanical model of skeletal muscle. A: length-dependent force generator, b: damper, KPE and KSE: parallel and serial elasticity, respectively [12].

In order to implement the Hill model, we used Mains and Soechting formulas, which were introduced for the muscles of arm [13]. Our designed model in SIMULINK is shown in Fig.2.

Fig. 2 The designed model and the related transform functions. k: muscle stiffness, B: viscous damping, J: inertia of the forearm about the elbow joint, b: Spinal control on the muscle, Td :delay of Spindle, t: time constant and h: a constant value.

Input of the model is from CNS and the output is angular movement, theta. The model contains the spinal cord, the effect of spinal cord on the muscle, and a feedback from the muscle spindle to the spinal cord, which includes a delay (lower right box in Fig. 2).

According to physiological data, when the agonist muscle is activated by the CNS, the antagonist muscle is in rest and vice versa, because of a feedback mechanism (Fig.3). Therefore, we need to joint an antagonist muscle model with an agonist one, as shown in Fig. 4.

Fig.3. The feedback mechanism of alpha motor neurons for agonist and antagonist muscles [1].

Fig.4 The schema of the model, including agonist and antagonist muscles. Theta: angular displacement.

We simulate this behavior with two gains in the spinal cord: gaf and ganf. When the agonist muscle is excited, the gaf is 1 and ganf is 0 and when the antagonist muscle is excited, the ganf is 1 and the gaf is 0.

2.2. Peripheral and Central neural model
For modeling the peripheral neural part, a long loop was considered, which begins from muscle spindle, goes to the dorsal horn of the spinal cord, then enters the central part of the model and finally returns to alpha motor neurons and the muscle. The central part itself includes supplementary motor area (SMA), motor cortex, and basal ganglia (Fig.5). Thalamus was not included for the purpose of simplicity.
The schema of the model is shown in Fig.6.

2.2.1. Cortex subsystem:

Cortex has inputs from basal ganglia and SMA. We assume two parameters, $g_a$ and $g_{an}$, that present the amount of cortex command to muscles. $g_a$ is the gain for agonist muscle and equals 1 when it is activated and 0 when inactive. Moreover, $g_{an}$ is for antagonist muscle and equals -1 when activated and 0 when inactive. In order to indicate the alternating commands of cortex, a time delay is used in the model (Fig.7).

In normal subjects, the input of SMA to cortex inhibits the cortex command on muscles, but in PD, it induces an increase in the cortex command [14]. This behavior is modeled by putting the input of SMA to cortex below 1 in normal subjects and higher than 1 in PD, and multiplying this input by the motor command.

The motor command represents the cortex command and is supposed to be a constant value. The basal ganglia send a sinusoidal signal, which differs in amplitude and frequency between the normal and PD persons (see Fig. 7).

2.2.2. Basal ganglia subsystem:

Tremor can be subdivided into physiological and pathological tremors. Physiological tremor is a low-amplitude oscillation that, with suitable recording techniques, can be demonstrated in almost all normal subjects [7]. The frequency of this tremor is in the range of 8-12 Hz, which is twice that of PD tremor.

We assume a sinusoidal nature for the basal ganglia:

$$g = \sin \omega t$$

$$\omega = 2\pi f$$

With the Laplace Transform:

$$G(s) = \frac{\omega}{s^2 + \omega^2} = \frac{2\pi f}{s^2 + (2\pi f)^2}$$

In which, $f$ (frequency) is related to the level of dopamine neurotransmitter. When $f$ is 5Hz, basal ganglia are in PD state and are simulated as:

$$f = 5Hz \Rightarrow \omega = 10\pi = 31$$

$$G(s) = \frac{31}{s^2 + (31)^2} = \frac{31}{s^2 + 966}$$

In addition, when $f$ becomes twice (2f) the normal person is modeled:

$$f = 10Hz \Rightarrow \omega = 20\pi = 63$$

$$G(s) = \frac{63}{s^2 + (63)^2} = \frac{63}{s^2 + 3944}$$

The input of basal ganglia comes from the cortex and its output is into the
cortex. In addition, the source in the model represents the origin of tremor in the PD and is supposed to be a constant value, which is increased by progress of the PD (Fig.8). The output of this source is zero in normal humans.

![Fig.8 Basal Ganglia subsystem. G(s): transform function of basal ganglia.](image)

**2.2.3. SMA subsystem:**
SMA has an inhibitory role in normal person. However, for the PD person, this inhibitory effect is decreased, and hence excitability of long-loop reflex increased.

The SMA model is designed to change the amount of the motor command by changing the long-loop reflex excitability. The nonlinear function of SMA is shown in Fig.9. The model contains three components; absolute function, saturation function, and the gain. The SMA output can be augmented by changing the gain. The amount of saturation function is 0.5 to 1 in normal persons and between 1 and 2 in PD.

![Fig.9 SMA Subsystem, which includes absolute function, saturation function, gain, and a bias.](image)

**2.3. The complete model**
The complete model used in this study is depicted in Fig. 10. It is obtained by joining the compartments of Fig. 4 and Fig. 6.

![Fig.10. Complete SIMULINIK model, used in our study.](image)

The ‘b_a’ and ‘b_an’ are similar to the gain ‘b’ of Fig.2.

Suppose that the person is sitting and the arm remains in a fixed horizontal position, whereas the forearm is allowed to move only in the vertical plane. Angular displacement is supposed to be the output of the system.

The nominal parameter values used for muscle modeling are $J=0.1 \text{ kgm}^2$, $k=50 \text{ Nm}$, $B=2 \text{ Nms}$, $\tau_d=0.02 \text{ s}$, $\tau=1/300 \text{ s}$, $\eta=5$, and $\beta=100$. These values are consistent with the average physiological quantities found in normal adults.

The oscillatory changes of theta will be considered as tremor in our study.

Choosing simultaneously the $g_a=1$ and $g_an=-1$ is equivalent to co-contraction, which can be interpreted as rigidity of the muscle. The greater the motor command, the greater the amount of rigidity. Motor command itself is increased with increment of SMA output. Therefore, we can suggest that the amount of SMA output in co-contraction state is an indicator of the degree of rigidity.

**3. Results:**

Fig.11 (a) shows the result, when only the agonist muscle is excited in a normal person. Exciting only the antagonist muscle has the result depicted in Fig.11 (b). Both the curves show the physiological tremor with 10Hz frequency.
The co-contraction of the muscles in PD causes a tremor, which has larger amplitude than when only one muscle is excited (Fig. 15). In this case, we have supposed that the person is in rest and we change the gain in the SMA, but the amount of source for basal ganglia, which is equivalent to the state of disease, is not changed in our model (see Fig. 8).

Increasing the gain of SMA in the previous condition increases the amplitude of the tremor (Fig. 16).

Finally, in order to evaluate the effect of tremor on rigidity, we increased the amount of source (the signal from basal ganglia in Fig. 8). This change increased the SMA output, which is equivalent to increased co-contraction and rigidity. In this case, we did not change the gain of SMA, but by
increasing the tremor the output of SMA is augmented.

4. Discussion:

The agonist and antagonist muscles were used in our model simultaneously to simulate the tremor and its relation to the rigidity, because the motor cortex gives alternating commands to the agonistic and antagonistic muscles, resulting in the typical alternating pattern of the parkinsonian resting tremor [15].

The output of our model is theta, which is in coordination with the velocity of tremor, presented in [16] as the output in their study.

Our model includes the long loop reflex and spinal reflex, peripheral mechanisms that are involved in tremor [4]. The central mechanism, i.e. the involvement of basal ganglia in tremor, is also included in the model.

Our abstract model of Basal ganglia is able to simulate the physiological tremor (see Fig.11). Voluntary co-contraction of muscles increases the tremor (see Fig. 12), which is physiologically plausible.

Our model is also able to produce The PD rest tremor (see Figs. 15 and 16). Figures 13 and 14 indicate that during activity, tremor is also present in PD.

Because the long loop reflex is supposed to be the main mechanism of rigidity, our model can evaluate truly the rigidity. It is claimed in experimental studies that SMA normally inhibits the motor cortex. However, this loop would be less inhibitory in PD [14]. Hayashi et al has indicated in an experimental study that the rigidity increases by increasing the feedback gain [17]. In accordance with these studies, our results showed that increased SMA output increases the rigidity.

Our model maneuvers on tremor and rigidity by two parameters: (1) the amount of SMA output that results from increasing the gain in it. (2) the amount of source (see Fig. 8) in basal ganglia that can increase the tremor. With changing these two parameters in PD, we explored the effect of tremor on rigidity and vice versa at rest.

The tremor and rigidity are two signs of PD, which are related to each other. As our model proposes, Rigidity worsens the tremor and vice versa. The increment of both these signs during aggravation of the disease is in accordance with this finding. Therefore, we suggest that the treatment of these two abnormal motor behaviors must be fulfilled simultaneously. It seems that Curing one of these two symptoms without decreasing the other is not realistic.

We tried to include all the involved mechanisms in rigidity and tremor in the model. We hope that this model can be used in more detailed studies on PD. It is worth noting that experimental studies are needed to validate this computational model.

References:
[16] www.physionet.org