

Basal ganglio-thalamo-cortico-spino-muscular model of Parkinson's disease bradykinesia

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Abstract Bradykinesia is the cardinal symptom of Parkinson's disease (PD) related to slowness of movement. The causes of PD bradykinesia are not known largely, because there are multiple brain areas and pathways involved from the neuronal degeneration site (dopamine (DA) neurons in substantia nigra pars compacta (SNc) and ventral tegmental area (VTA)) to the muscles. A neurocomputational model of basal ganglio-thalamo-cortico-spino-muscular dynamics with dopamine of PD bradykinesia is presented as a unified theoretical framework capable of producing a wealth of neuronal, electromyographic and behavioral movement empirical findings reported in parkinsonian human and animal brain studies. The model attempts to uncover how information is processed in the affected brain areas, what role does DA play, and what are the biophysical mechanisms giving rise to the observed slowness of movement in PD bradykinesia.

Keywords: Parkinson's disease, slowness of movement, bradykinesia, akinesia, computer model, dopamine, basal ganglia, motor cortex, spinal cord, triphasic pattern of muscle activation

Introduction

Bradykinesia is the hallmark and most disabling symptom of PD. Early in the disease, the most notable manifestation of bradykinesia is difficulty with walking, speaking, or getting into and out of chairs (Gibbert FB, 1986). Individuals fail to swing an arm during walking, or lack facial expression (Gibbert FB, 1986; Abbs JH et al., 1987; Weiner WJ et al., 1989). Later in life, bradykinesia affects all movements and, at its worst, results in a complete inability to move. Patients require intense concentration to overcome the apparent inertia of the limbs that exists for the simplest motor tasks. Movement initiation is particularly impaired

when unnatural or novel movements are attempted (Connor NP and Abbs JH, 1991), or when combining several movements concurrently (Benecke R et al., 1986; Lazarus JC et al., 1992).

The causes of bradykinesia are not known, in part because there are multiple pathways from the sites of neuronal degeneration to the muscles. Figure 1 shows three of the most important pathways: (1) the pathway from SNc and VTA to the striatum and from the striatum to the substantia nigra pars reticulata (SNr) and the globus pallidus internal segment (GPe) and from there to the thalamus and the frontal cortex, (2) the pathway from SNc and VTA to the striatum and from the striatum to the SNr and the GPe and from there to the brainstem, and (3) the pathway from the SNc/VTA to cortical areas such as the supplementary motor area (SMA), the parietal cortex, and the primary motor cortex (M1), and from there to the spinal cord.

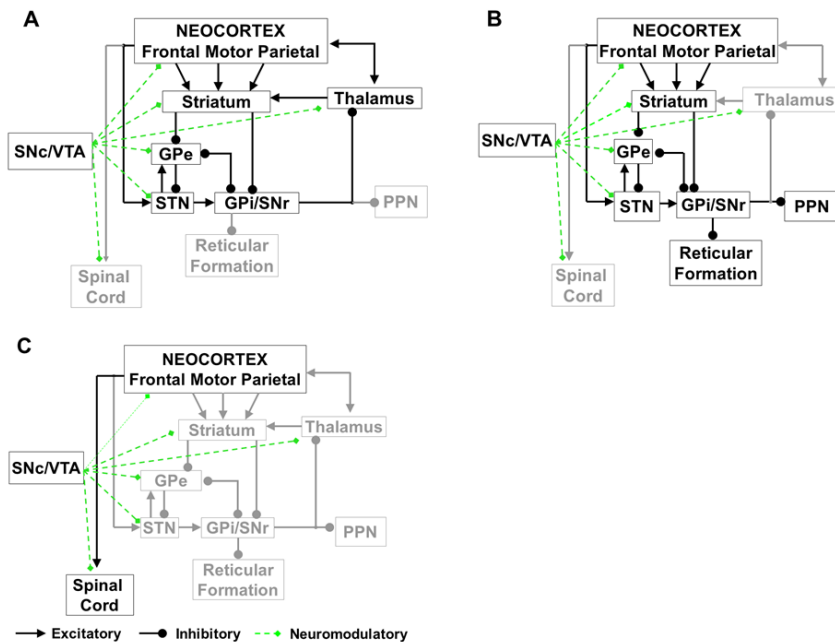


Fig. 1. Brain circuits implicated in PD bradykinesia.

One of the popular views is that cortical motor centers are inadequately activated by excitatory circuits passing through the basal ganglia (BG) (Albin et al., 1989). As a result, inadequate facilitation is provided to motor neuron pools and hence movements are small and weak (Albin RL et al., 1989). The implication of this view is that cells in the cortex and spinal cord are functionally normal. This paper will show otherwise.

The paper's view is that disruptions of the BG output and of the SNc's DA input to frontal and parietal cortices and spinal cord are responsible for delayed movement initiation. Elimination of DA modulation from the SNc disrupts, via several pathways, the build-up of the pattern of movement-related responses in the primary motor and parietal cortex, and results in a loss of directional specificity of reciprocal and bidirectional cells in the motor cortex as well as in a reduction in their activities and their rates of change. These changes result in delays in recruiting the appropriate level of muscle force sufficiently fast and in an inappropriate scaling of the dynamic muscle force to the movement parameters. A repetitive triphasic pattern of muscle activation is sometimes needed to complete the movement. All of these result in an increase of mean reaction time and a slowness of movement (i.e. bradykinesia).

Empirical signatures of PD bradykinesia

PD bradykinesia has been linked with the degeneration of DA neurons in SNc and VTA. Bradykinesia manifests only when 80–90 % of DA neurons die. All motor cortical and subcortical areas are innervated by SNc and VTA DA neurons (Williams and Goldman-Rakic 1998; Bjorklund and Lindvall 1984; Gerfen et al. 1990). The degeneration of DA neurons leads to a number of changes relevant to bradykinesia in the neuronal, electromyographic (EMG), and movement parameters reported in parkinsonian human and animal brains:

- Reduction of peak neuronal activity and rate of development of neuronal discharge in the primary motor cortex and premotor area (Gross et al. 1983; Watts and Mandir 1992).
- Abnormal oscillatory GP (external and internal) neuronal responses (Tremblay et al. 1989).
- Disinhibition of reciprocally tuned cells (Doudet et al. 1990). Reciprocally tuned cells are cells that discharge maximally in one movement direction but pause their activities in the opposite direction.
- Significant increase in mean duration of neuronal discharge in motor cortex preceding and following onset of movement (Gross et al. 1983; Doudet et al. 1990; Benazzouz et al. 1992).
- Multiple triphasic patterns of muscle activation (Hallett and Khoshbin 1980; Doudet et al. 1990). Triphasic pattern of muscle activation is a characteristic electromyographic (EMG) pattern characterized by alternating bursts of agonist and antagonist muscles. The first agonist burst provides the impulsive force for the movement, whereas the antagonist activity provides the braking force to halt the limb. Sometimes a second agonist burst is needed to bring the limb to the final position. In PD patients, multiple such patterns are observed in order for the subjects to complete the movement.

- Reduction in the rate of development and peak amplitude of the first agonist burst of EMG activity (Godaux et al. 1992; Corcos et al. 1996; Hallett and Khoshbin 1980; Doudet et al. 1990; Watts and Mandir 1992; Berardelli et al. 1986).
- Co-contraction of muscle activation (Benazzouz et al. 1992). In PD patients, the alternating agonist-antagonist-agonist muscle activation is disrupted resulting in the coactivation of opponent muscle groups.
- Increases in electromechanical delay time (time between the onset of modification of agonist EMG activity and the onset of movement) (Benazzouz et al. 1992; Doudet et al. 1985, 1990).
- Asymmetric increase in acceleration (time from movement onset to peak velocity) and deceleration (time from peak velocity till end of movement) times of a movement.
- Decrease in the peak value of the velocity trace (Godaux et al. 1992; Camarata et al. 1992; Weiss et al. 1996; Benazzouz et al. 1992; Doudet et al. 1985, 1990; Rand et al. 2000).
- Significant increases in movement time (Rand et al. 2000; Weiss et al. 1996; Doudet et al. 1985, 1990; Watts and Mandir 1992; Benazzouz et al. 1992).

Basal ganglio-thalamo-cortico-spino-muscular model of PD bradykinesia

Figure 2 depicts the basal ganglio-thalamo-cortico-spinomuscular model with dopamine of PD bradykinesia dynamics. The mathematical formalism of the model has been detailed in (Cutsuridis, 2006a, 2011; Cutsuridis and Perantonis, 2006). The model is composed of three modules coupled together: (1) the basal ganglio-thalamic module, (2) the cortical module, and (3) the spinomuscular module. All modules and their components are modulated by DA. The basal ganglio-thalamic module generates a scalable voluntary GO signal that gates volitional-sensitive velocity motor commands in the cortical module, which activate the lower spinal centers in the spino-muscular module. In the cortical module an arm movement difference vector (DV) is computed in cortical parietal area 5 from a comparison of a target position vector (TPV) with a representation of the current position called perceived position vector (PPV). The DV signal then projects to area 4 (primary motor cortex), where a desired velocity vector (DVV) and a non-specific co-contractive signal (P) (Humphrey and Reed, 1983) are formed. The DVV and P signals correspond to two partly independent neuronal systems within the motor cortex. DVV represents the activity of reciprocal neurons (Doudet et al., 1990), and is organized for the reciprocal activation of antagonist muscles. P represents the activity of bidirectional neurons (i.e. neurons whose activity decreases or increases for both directions of movement (Doudet et al., 1990)), and is organized

for the co-contraction of antagonist muscles. Whereas the reciprocal pattern of muscle activation serves to move the joint from an initial to a final position, the

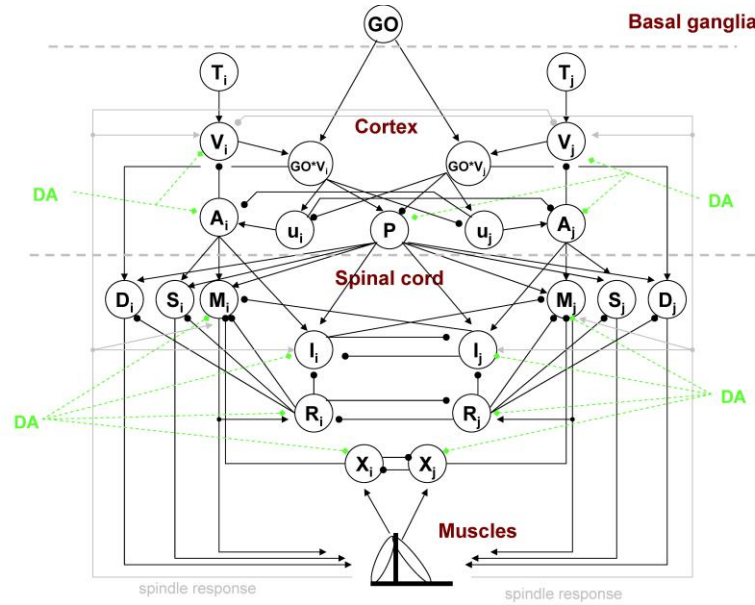


Fig. 2. Neural architecture of the dopamine modulated basal ganglio-thalamo-cortico-spino-muscular model. *Top*: basal ganglia module (GO signal representing the opening of the thalamo-cortical gate via inhibition of GPi response). *Middle*: cortical module for trajectory formation. *Bottom*: opponent-processing spino-muscular module for agonist-antagonist-agonist muscle activation. Arrow black lines, excitatory projections; solid dot black lines, inhibitory projections; diamond-dotted green lines, dopamine modulation; solid arrow gray lines, excitatory feedback pathways from muscle spindles. Solid dot gray lines: inhibitory feedback pathways from muscle spindles. GO, globus pallidus internal segment (GPi) output signal; P, bidirectional co-contractive signal; T, target position command; V, difference vector (DV) activity; u, desired velocity vector (DVV) activity; A, current perceived position vector (PPV) activity; M, alpha motoneuronal activity; R, Renshaw cell activity; X, spinal type-b inhibitory interneuronal activity; I, spinal type-a inhibitory interneuronal activity; S, static gMN activity; D, dynamic gMN activity; i and j, antagonist cell pair.

antagonist co-contraction serves to increase the apparent mechanical stiffness of the joint, thus fixing its posture or stabilizing its course of movement in the presence of external force perturbations (Humphrey and Reed, 1983; Bullock and Contreras-Vidal, 1993). The spinomuscular module is an opponent processing muscle control model of how spinal circuits afford independent voluntary control of joint stiffness and joint position. It incorporates second-order dynamics, which play a large role in realistic limb movements.

Results

The model can account for all empirical signatures of PD bradykinesia as they have been described in the previous section and reported in previous publications of the author (Cutsuridis 2006a, 2006b, 2007, 2011, 2010a, 2010b, 2013a, 2013b, 2018; Cutsuridis and Perantonis, 2006). To assist the readers of this paper, a subset of these simulation results are reported here. Reduction of DA in cortical and subcortical motor areas disrupts, via several pathways, the rate of development and peak neuronal activity of primary motor cortical cells (reciprocal and bidirection neurons) (see Figures 3 & 4 for comparison). A clear triphasic AG1-ANT1-AG2 pattern marked with *arrows* which is evident in control case PSTH of reciprocally and bidirectionally organized neurons (figure 3) disappears in the dopamine depleted case (Figure 4). The same triphasic pattern is evident in simulated control DVV cell activities (Figure 3) disappears in the DA depleted case (Figure 4).

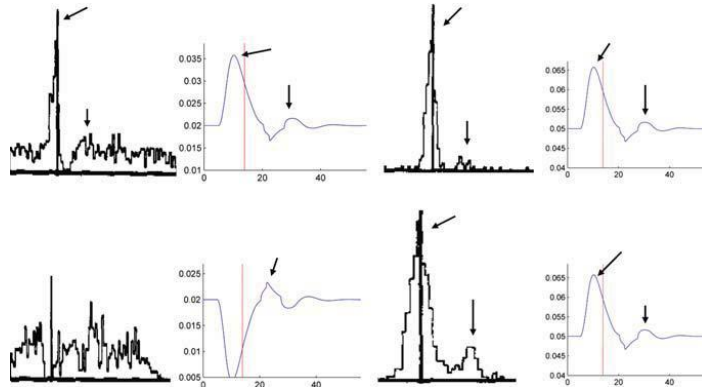


Fig. 3. Comparison of peristimulus time histograms (PSTH) of reciprocally organized neurons (column 1; reproduced with permission from Doudet et al. [23, Fig. 4A, p. 182], Copyright Springer-Verlag) in area 4, simulated area's 4 reciprocally organized phasic (DVV) cell activities (column 2), PSTH of area's 4 bidirectional neurons (column 3; reproduced with permission from [23, Fig. 4A, p. 182], Copyright Springer-Verlag) and simulated area's 4 co-contracting (P) cells activities (column 4) for a flexion (row 1) and extension (row 2) movements in normal monkey. The *vertical bars* indicate the onset of movement. Note a clear triphasic AG1-ANT1-AG2 pattern marked with *arrows* is evident in PSTH of reciprocally and bidirectionally organized neurons. The same triphasic pattern is evident in simulated DVV cell activities. The second peak in simulated activities marked with an arrow arises from the spindle feedback input to area's 5 DV activity.

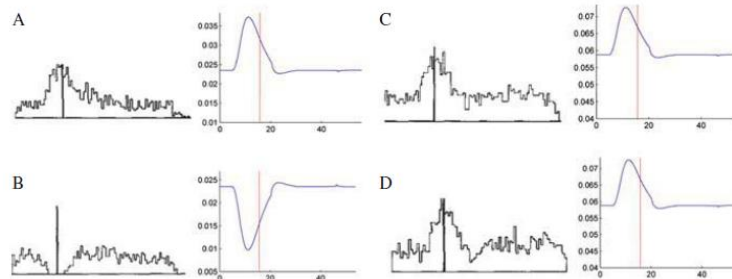


Fig. 4. Comparison of PSTH of reciprocally organized neurons (column 1; reproduced with permission from [23, Fig. 4A, p. 182], Copyright Springer-Verlag) in area 4, simulated area's 4 reciprocally organized phasic (DVV) cell activities (column 2), PSTH of area's 4 bidirectional neurons (column 3; reproduced with permission from [23], Fig. 4A, p. 182, Copyright Springer-Verlag) and simulated area's 4 co-contracting (P) cells activities (column 4) for a flexion (A and C) and extension (B and D) movements in MPTP-treated monkey. The vertical bars indicate the onset of movement. Note that the triphasic pattern is disrupted: Peak AG1 and AG2 bursts have decreased, and ANT pause is shortened.

These changes lead in delays in recruiting the appropriate level of muscle force sufficiently fast and in a reduction of the peak muscle force required to complete the movement (see Figure 5).

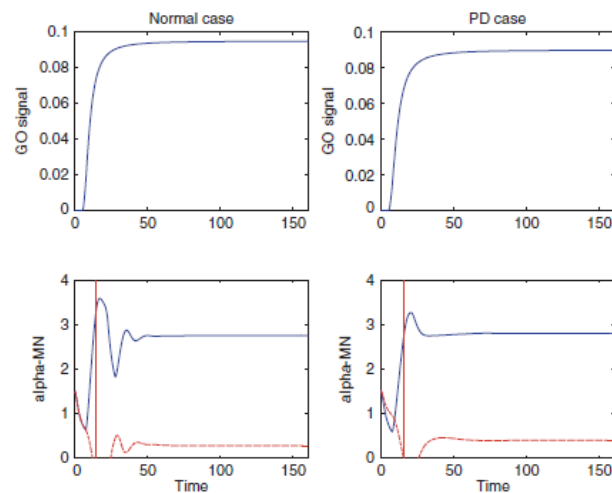


Fig. 5. Comparison of simulated GO signals (row 1) and α -MN activities (row 2) in normal (column 1) and dopamine-depleted (column 2) conditions. (Row 2) *Blue solid curve*: agonist α -MN activity; *Red-dashed curve*: antagonist α -MN activity. Note in PD (DA depleted) case, the triphasic pattern is disrupted and it is replaced by a biphasic pattern of muscle activation. Also, the peaks of agonist and antagonist bursts are decreased.

Repetitive and sometimes co-contracting patterns of muscle activation are needed to complete the movement (see Figure 6).

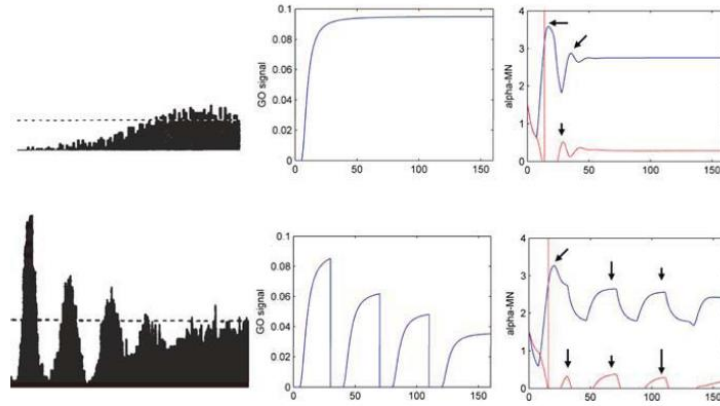


Fig. 6. Comparison of the experimental GPI PSTH (column 1), GO signals (column 2), and α -MN activities (column 3) in normal (row 1) and dopamine-depleted (row 2) conditions. (Column 3, rows 1 and 2) Blue-colored solid curve: agonist α -MN unit; Red-colored dashed curve: antagonist α -MN unit. Note in dopamine depleted case the α -MN activity is disrupted and replaced by repetitive and co-contractive agonist-antagonist bursts (row 2, column 3). (Column 1, row 1) GPI PSTH in intact monkey reproduced with permission from Tremblay et al. [49, Fig. 4, p. 6], Copyright Elsevier. (Column 1, row 2) GPI PSTH in MPTP monkey reproduced with permission from [49, Fig. 2, p. 23], Copyright Elsevier.

These disruptions result in an abnormal slowness of movement (see Figure 7).

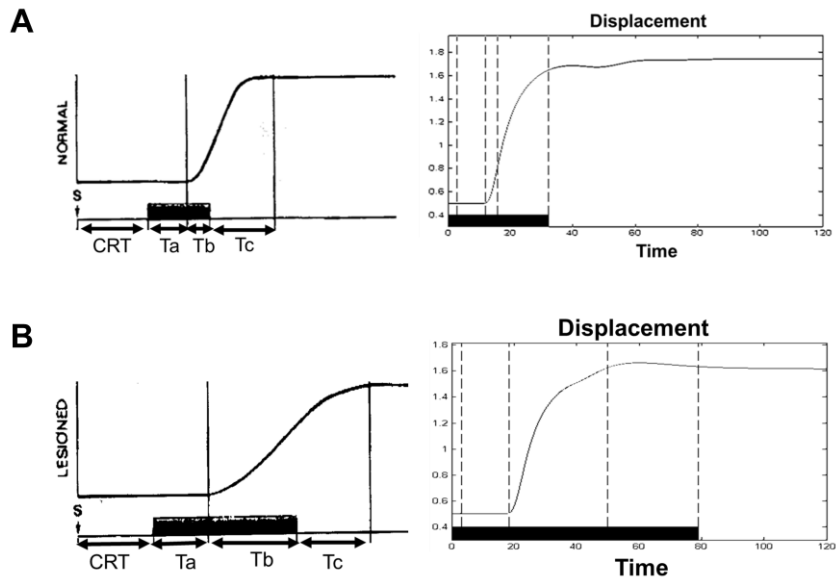


Fig. 7. Comparison of experimentally obtained (column 1; adapted from Gross et al., 1983, Fig. 5, p. 189) and simulated (column 2) forearm displacement (position) in normal (A) and Parkinson's disease (B) conditions. *Shaded area*: representation of neuronal change related to movement. In A and B: (*column 1*) the vertical bar indicates the onset of forearm displacement; *S*: auditory cue; *CRT*: mean value of cellular reaction time; *T_A*: changes of neuronal activity preceding onset of movement (OM); *T_B*: changes of neuronal activity following OM; *T_C*: changes of neuronal activity from *T_B* till movement end (ME). (*column 2*) the time interval between vertical dashed lines starting from left to right indicate CRT, T_A, T_B, and T_C, respectively.

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