Kinematic Modeling in Parkinson's Disease

Alexander Hui*
Department of Bioengineering
University of California, San Diego
La Jolla, CA 92093
alexhui@ucsd.edu

Abstract

Parkinson's disease is a slowly progressing neurological disorder that affects motor function, resulting in bradykinesia, resting tremor, rigidity, and postural instability. The symptoms are associated with a loss of dopaminergic neurons in the brain, and a loss of dopamine is considered the primary defect in Parkinson's disease. Recently, models of Parkinson's disease have been constructed, including one that focuses on bradykinesia in Parkinson's disease. Here, the full model with 26 equations is analyzed with principal component analysis for the purposes of dimensionality reduction. The results of principal component analysis and results of several simulations are presented, which appear to show rigidity, another characteristic of Parkinson's disease.

1 Introduction

1.1 Parkinson's Disease Background

Parkinson's disease (PD) is a neurodegenerative disease characterized by motor dysfunction[1]. Clinical manifestations of PD may include bradykinesia (slowness of movement), resting tremor, rigidity, gait abnormalities, and postural instability. Of these clinical symptoms, bradykinesia, resting tremor, rigidity, and postural instability are considered the four cardinal symptoms. Resting tremor is a tremor that occurs when the limb is at rest, and diminishes upon movement. Rigidity is thought to be associated with an increase in muscle tone. Postural instability poses balance difficulties for patients and may lead to falls and injury. Bradykinesia refers to slowness of movement as well as in its initiation and planning. Bradykinesia can progress to a severely debilitating akinesia, or a complete inability for voluntary movement.

The symptoms of PD are thought to arise from a decrease in stimulatory signals from the basal ganglia to the motor cortex. PD is often considered a disease in which there is a loss of dopamine. This line of thought is supported by some current treatment approaches in PD. L-dopa is one of the most widely used treatments for PD, and works by being transformed into dopamine in dopaminergic neurons. Dopamine agonists have also been developed, and are fairly effective in treatment of PD. For more advanced PD, an alternative treatment option includes deep brain stimulation, which was approved by the FDA as a treatment for PD in 2002. Although the exact cause of PD is unknown, and diagnosis is clinical, careful studies show that PD involves alterations in neural circuits in the basal ganglia regulating movement. Degeneration of dopamine neurons is observed in the substantia nigra pars compacta and in the striatum.

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1.2 Mathematical Models of Parkinson's Disease

In recent years, several mathematical models of PD have been formulated. Mostly recently, neural network model of PD bradykinesia was published by Cutsuridis and Perantonis in 2006[2]. The model focuses on the bradykinesia aspects of PD, which is one of the most characteristic clinical manifestations of PD. The model is a multimodular model including basal ganglia, cortex, and spino-musculo-skeletal modules. The model builds and extends on previous models of PD and incorporates the effects of dopamine at several sites in the network, including parameters for the modulatory effect of dopamine at several areas[3]. The model is able to simulate some of the experimentally observed movement and neuronal measurements in PD patients. Effects of dopamine depletion at several sites can then be tested to lend insight into PD disease processes.

1.3 Model Reduction

The Cutsuridis model is a system of 26 differential equations. Multiple techniques exist for dimension reduction, including principal component analysis, Fisher's linear discriminant, multidimensional scaling, and independent component analysis. Principal component analysis is the most commonly used dimension reduction technique, and we use this technique here to reduce the dimensions of the model by projecting to a lower dimensional space.

2 Methods

2.1 Implementation

All simulations were performed on a 2.5 GHz Intel Core 2 Duo Mac with MATLAB R2009b. The original Cutsuridis model was downloaded from ModelDB[4] and the model equations were implemented in MATLAB. Differential equations were solved with the built-in MATLAB differential equation solver ODE45. Simulations were performed with normal parameters, and then with basal ganglia output decreased, and with both basal ganglia output and dopamine modulatory effects in the cortex (D1-D4 in the model) reduced.

2.2 Model Reduction by Principal Component Analysis

Model reduction was attempted by implementing principal component analysis. Data from the full model simulations were first collected. For each dimension (26 in total), the mean was calculated:

$$\mu = \frac{1}{N}\Sigma_{i=1}^{N} x_i \tag{1}$$

The covariance of the mean-adjusted matrix of data (3025 x 26), with the dimensions along columns and the observations along rows, was calculated in MATLAB with the $cov(matrix)$ command.

Eigenvectors and eigenvalues of the covariance matrix were then calculated and ordered by magnitude such that:

$\lambda_1 \geq \lambda_2 \geq \lambda_3 ... \geq \lambda_{26}$

The eigenvalues were then analyzed to determine the feasibility of data reduction. The eigenvalue λ measures the variation in the direction of eigenvector e. Eigenvalues λ that are negligible are discarded in order to reduce dimensionality in the model.

The data are then projected onto the selected eigenvectors that are retained.

A measure of the proportion of data covered by the first M eigenvalues can be determined as:

$$\frac{\Sigma_{i=1}^{M}\lambda_i}{\Sigma_{i=1}^{N}\lambda_i} \tag{2}$$

3 Results

3.1 Simulations

To confirm correct implementation of the model in MATLAB, model simulations were compared to published model figures from Cutsuridis et al., to verify that they could be replicated in MATLAB. The plots of the bradykinesia model are shown in Figure 1 and Figure 2. Figure 2 shows a delay in movement initiation, and lower velocity upon movement, for the PD case compared to the normal case, reflecting experimental observations in patients. Figures 1 and 2 are similar or identical to figures in Cutsuridis' original paper and verify that the model was implemented correctly in MATLAB.

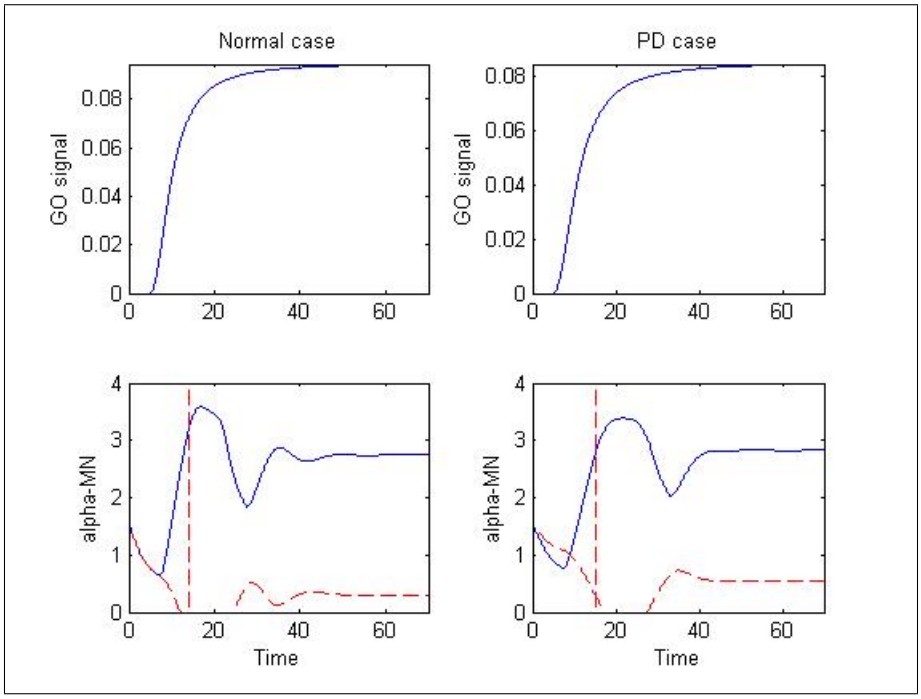

Figure 1: Globus pallidus output signal and alpha-motor neuron activity in normal and PD.

To test the effects of dopamine depletion on model dynamics, I then performed two simulations. Basal ganglia output was decreased, and then basal ganglia output was decreased in combination with a decrease in parameters representing dopamine modulatory effect. The most interesting model output from these two simulations are shown in Figure 3. Figure three shows force plots under normal conditions and parameters, under reduced basal ganglia output, and finally, under combined reduced basal ganglia output and reduced dopamine modulatory effects. Of note, force increases for the combined reduced basal ganglia output and reduced dopamine modulatory effects condition.

3.1.1 Model Reduction

Principal component analysis was used to attempt dimensionality reduction in the model, as described in the methods section. The eigenvalues calculated are shown in Figure 4.

In order to calculate the proportion of data covered by the first M eigenvalues, Eqn. 2 was used and the results plotted as a figure, as shown in Figure 5. The proportion of data covered by the first few eigenvalues is listed in Figure 6. The results show that the principal component covers 72.1% of the data, and retaining two eigenvectors covers 95.7% of the data.

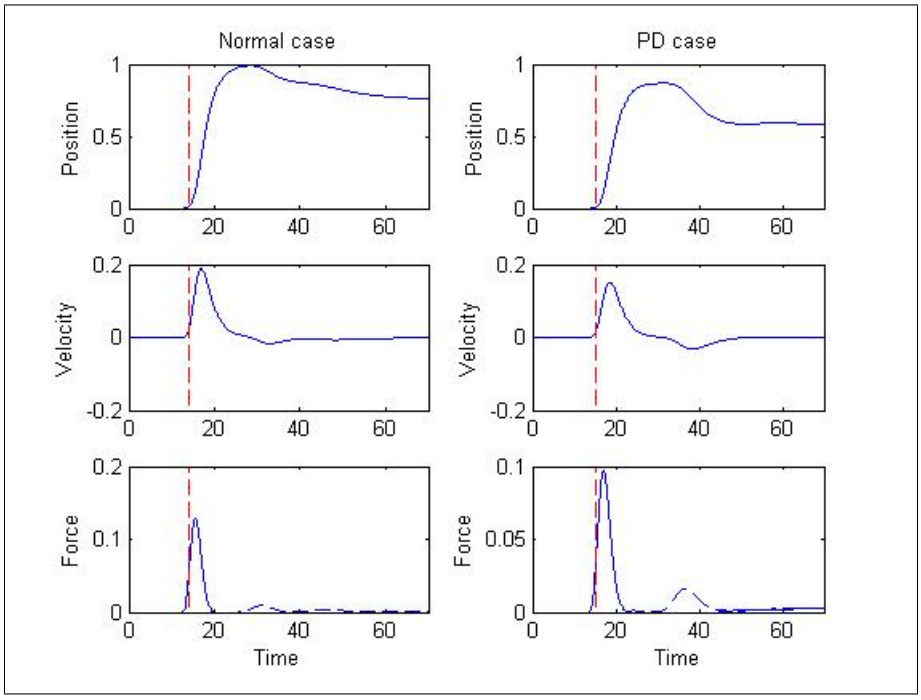

Figure 2: Position, velocity, and force in normal and PD.

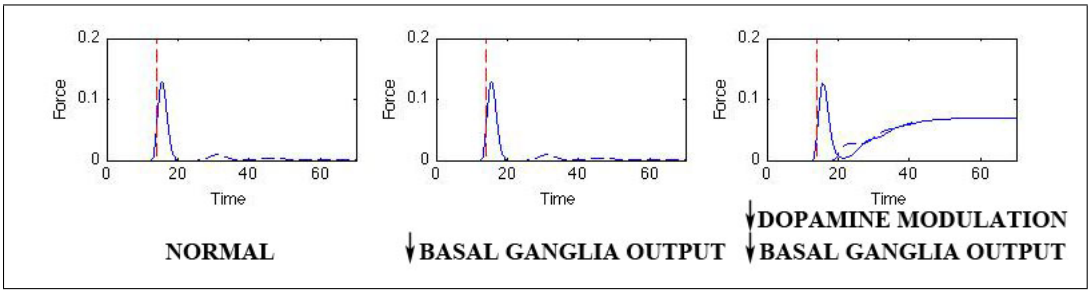

Figure 3: Force in normal, decreased basal ganglia output, and combined decreased basal ganglia output + decreased dopamine modulation conditions.

Eigenvalue		Eigenvalue		Eigenvalue	
λ_1	13.14	λ_{10}	0.001	λ_{19}	0
λ_2	4.307	λ_{11}	0.001	λ_{20}	0
λ_3	0.548	λ_{12}	0	λ_{21}	0
λ_4	0.148	λ_{13}	0	λ_{22}	0
λ_5	0.044	λ_{14}	0	λ_{23}	0
λ_6	0.021	λ_{15}	0	λ_{24}	0
λ_7	0.014	λ_{16}	0	λ_{25}	0
λ_8	0.006	λ_{17}	0	λ_{26}	0
λ_9	0.002	λ_{18}	0		

Figure 4: Eigenvalues

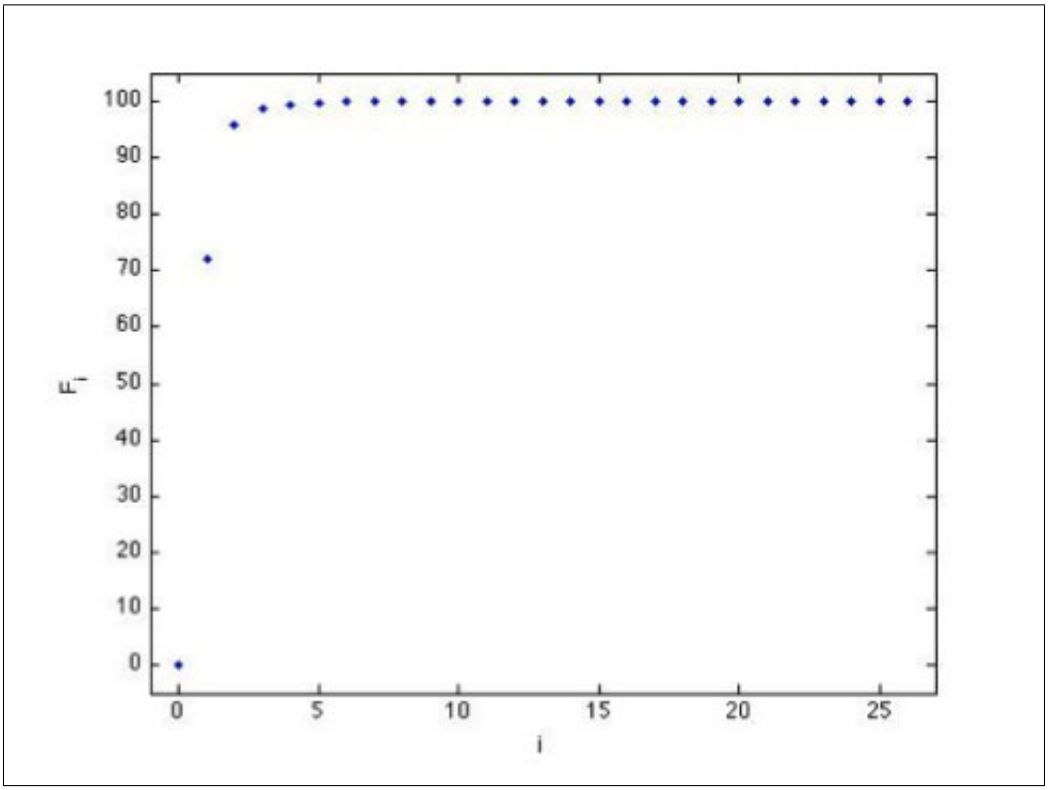

Figure 5: Proportion of data covered by the first i eigenvalues.

# of Eigenvectors	%
1	72.0692
2	95.6940
3	98.7020
4	99.5145
5	99.7582

Figure 6: Proportion of data covered by retaining the eigenvectors with the largest eigenvalues.

4 Discussion

The results from the model simulations show an interesting result. When the GO signal is reduced, compared to when the GO signal is reduced in combination with a reduction in dopamine modulatory effects in the cortex, the force of the movement in the model simulation, as seen in Figure 3, shows that force increases to a steady state non-zero value. Although the Cutsuridis model is primarily a model focused on PD bradykinesia, the simulation for the combined reduction in basal ganglia output and dopamine modulation show that the model may also be able to replicate another clinical manifestation of PD, namely, rigidity. Rigidity refers to increased muscle tone, or stiffness, in the muscles. The increased force in the plot for reduced dopamine modulation and basal ganglia output may be interpreted as an increase in rigidity.

The principal component analysis of the model shows that 72.1% of the data can be covered by the principal component, while two eigenvectors can represent 95.7% of the data. Directions in which the covariance are small may be neglected. These results show that it maybe possible for this model, with 26 dimensions in the full model, to be reduced to 2 dimensions in a reduced model. A reduced model may provide advantages in phase space analysis and provide further insight into model dynamics.

Acknowledgments

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References

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