

SHAPE AND PROGRESSION MODELING AND ANALYSIS IN PARKINSON'S DISEASE THROUGH MULTI-MODAL DATA ANALYSIS

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by

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To my family

Certificate

This is to certify that the thesis titled “**Shape and Progression Modelling and Analysis in Parkinson’s Disease Through Multi-modal Data Analysis**” being submitted by **Noopur Anil Bhalchandra** to the Department of Electrical Engineering, Indian Institute of Technology, Delhi, for the award of the degree of **Doctor of Philosophy**, is a record of bona-fide research work carried out by her under our guidance and supervision. In our opinion, the thesis has reached the standards fulfilling the requirements of the regulations relating to the degree.

The results contained in this thesis have not been submitted to any other university or institute for the award of any degree or diploma.

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Abstract

The diagnosis of Parkinson’s disease (PD) at early stages is crucial for management and treatment to be worthwhile. It is a difficult problem, since the early signs and symptoms are subtle for discrimination, and often fuzzy. Further, the golden standard for current clinical diagnosis of PD is anchored to classic symptoms, which appear in a patient when dopaminergic neuronal degeneration has reached 60%. Furthermore, various non-motor symptoms accompany these classic motor symptoms, with some of them appearing years before the cardinal signs do. Further complications arise due to overlapping symptoms from other disorders. The only sure-shot clinical diagnosis is possible during autopsy, which necessitates other reliable diagnosing mechanisms. In this thesis, we propose new features and methodologies to recognize early PD and to model their progression. The first two parts are based on shape-based features; the third involves detection of ‘probable PD’ cases using patient questionnaires, while the fourth is a statistical modeling of striatal degeneration.

Shape Characterization Using SPECT Based Radial and Gradient Features. We identify easy-to-compute features which characterize striatal shape. We combine these with striatal binding ratios, both sets of features identified from SPECT scans. We propose a scheme which employs feature selection to reduce redundancy and pick the most relevant features to be used for performing Early PD-vs-Normal and Early PD-vs-SWEDD classification, using machine learning tools. The radial and gradient features proposed are simple and computationally light, and they show high accuracy for both Early PD-vs-Normal and Early PD-vs-SWEDD.

Shape Based Features Derived from Parametric Eigenspace. This framework presents a stable and accurate representation of striatal shape and size change, using a parametric eigenspace. These features are then integrated with striatal binding ratios to perform Early PD-vs-Normal and Early PD-vs-SWEDD classification. The features used in this scheme are

obtained from active contours and are affine invariant and further, are mapped to an eigenspace to obtain a completely decorrelated feature set. The performance measures of the classifiers are appreciably high and should aid clinicians in early detection of the disease.

The Prodromal Phase as a Possible Indicator for Detection of Early PD. A model capable of identifying ‘probable PD’ cases is suggested. PD has its clinical diagnosis dependent on the presence of clinical features such as bradykinesia, tremor, rigidity, or postural instability. There is evidence of neuropathological, clinical and imaging features, in evincing the onset of PD pathology, preceding its manifestation. This PD latent phase is of particular importance for neuroprotective or disease altering therapies. This chapter proposes a computer aided detection framework for classifying prodromal and healthy normals. The features include MDS-UPDRS part 1 and 2 evaluations, combined with Epworth Sleepiness Scale (ESS) values and Rapid Eye Movement (REM) sleep Behaviour Disorder (RBD) screening questionnaire values. Support Vector Machine (SVM), Linear Discriminant Analysis (LDA), RUSBoost and Logistic Regression are employed for the classification stage. Encouraging results with these features can reliably assist medical community and provide better management of the disease.

Striatal Shape Change Modeling Over Temporal Data of PD Patients. This scheme proposes a temporal model of the striatal shape change in time, over three stages of PD. These prognostic models aid in designing clinical trials and in research for disease management. This study involves longitudinal SPECT data of subjects acquired from the PPMI. The dataset consists of SPECT scans taken at 3-time intervals: screening-stage 1, 12 months after screening-stage 2 and at 24 months after screening-stage 3. The shape changes of striata are analyzed in shape space and modeled with a closed form equation for both striata. Further, the discernment between different stages has been carried out using nearest neighbor classifiers. The accuracy obtained is appreciable considering there is a large overlap between stage 2 and stage 3 (as the rate of change reduces with time).

We demonstrate that by using these simple shape- and size-based features in conjunction with suitable machine learning tools, it is possible to identify early PD with reasonably high degree of accuracy.

सारांश

पार्किन्सन रोग (Parkinson's Disease: PD) का प्रारम्भिक स्थिति में ही निदान, इसके प्रबन्धन और उपचार के लिए महत्वपूर्ण है। यह कार्य अत्यंत कठिन भी है क्योंकि इसके संकेत और लक्षण अत्यंत सूक्ष्म / दबे हुए होते हैं। पार्किन्सन रोग (PD) का वर्तमान निदान उसके परम्परागत लक्षणों से किया जाता है, जो मरीज में तब प्रतीत होते हैं, जब नसों का डोपमीन संबंधित अधःपतन (Dopamine deficiency) ६० प्रतिशत पहुँच जाता है। इसके इलावा, परम्परागत आन्दोलन लक्षण (motor symptoms) के साथ विभिन्न गैर आन्दोलन लक्षण (non-motor symptoms) आते हैं, जो परम्परागत लक्षणों से अनेक वर्ष पूर्व उत्पन्न होते हैं। इसके लक्षणों का अन्य रोगों के साथ अतिव्यापन के कारण निदान में अधिक जटिलता आती है। नैदानिक विश्लेषण का पुष्टिकरण केवल मरणोपरान्त (*post mortem*) ही सम्भव है, अतः अन्य विश्वसनीय निदान प्रणालियों की आवश्यकता है। इस प्रबन्ध (thesis) में पार्किन्सन रोग के प्रारम्भिक दौर (Early PD) की पहचान के लिए नई विशेषताओं एवं पद्धतियों का, और पार्किन्सन रोग (PD) के अग्रसर होने की विधि के सिद्धान्त का प्रस्ताव हुआ है।

अर्धव्यास (radial) और ढाल सम्बन्धी (gradient) विशेषताओं के माध्यम से आकार का चरित्रांकन

इस पद्धति में स्पेक्ट (SPECT) आधारित स्ट्राइएटल बंधनकारक अनुपात (Striatal Binding Ratio) के साथ स्ट्राइएटम (striatum) के आकृति का परिवर्तन दर्शाने वाले विशेषताओं का उपयोग किया गया है। विशेषता चयन (feature selection) के माध्यम से अतिरिक्त घटाकर उन विशेषताओं का उपयोग किया गया है, जो मशीन अधिगम (Machine Learning) प्रविधियों के प्रयोग से प्रारम्भिक पार्किन्सन रोग और सामान्य (Early PD-vs-Normal), और प्रारम्भिक पार्किन्सन रोग और स्वेड (Early PD-vs-SWEDD) वर्गीकरणों (classification) में सक्षम हैं। अर्धव्यास (radial) और ढाल सम्बन्धी (gradient) सरल और अल्प विशेषताएँ ऊपलिखित वर्गीकरणों (classification) में उच्च सटीकता प्रदान करते हैं।

मापदण्डकृत आइगनस्पेस (Parametric Eigenspace) से प्राप्त आकृति आधारित विशेषताओं के माध्यम से प्रारम्भिक पार्किन्सन रोग (Early PD) की जाँच

यह रूपरेखा मापदण्डकृत आइगनस्पेस (Parametric Eigenspace) से स्ट्राइएटम (Striatum) के आकार और परिमाण परिवर्तन का स्थिर और सटीक निरूपण प्रस्तुत करता है। इन विशेषताओं का स्ट्राइएटल बंधनकारक अनुपात (Striatal Binding Ratio) के साथ एकाकीकरण का, प्रारम्भिक पार्किन्सन रोग और सामान्य (Early PD-vs-Normal), और प्रारम्भिक पार्किन्सन रोग और स्वेड (Early PD-vs-SWEDD) वर्गीकरणों (classification) में हम उपयोग करते हैं। ये विशेषताएँ सक्रिय समोच्च रेखा (Active Contour) से प्राप्त करते हैं, और ये एफ़ाइन अपरिवर्तनीय (Affine Invariant) भी हैं। इनका आइगनस्पेस (eigenspace) में प्रतिचित्रण एक असहसम्बन्धित विशेषताओं (decorrelated feature set) की रचना करता है। इन वर्गीकरणों (classification) का प्रदर्शन अत्यन्त उत्साहजनक है, पार्किन्सन रोग (PD) के शुरुआती/प्रारम्भिक दौर में ही जाँच में चिकित्सकों के लिये सहायक होगा।

पूर्वरूप/अग्रगामी चरण (Prodromal phase) - पार्किन्सन रोग (PD) की शीघ्र जाँच के लिए संकेतक

यह भाग सम्भावित पार्किन्सन रोग (probable PD) का चरित्रांकन करता है। पार्किन्सन रोग (PD) का निदान इन लक्षणों पर निर्भर करता है: ब्रडिकेनेशिया (bradykinesia), कंपन, अकड/अनम्यता और मुद्रा अस्थिरता। नस विकृति विज्ञान (Neuropathology), नैदानिक और प्रतिमा विश्लेषण के अनुसन्धान, पार्किन्सन रोग (PD) की अभिव्यक्ति का आरम्भ स्पष्ट दर्शाता है। पार्किन्सन रोग (PD) के अव्यक्त चरण का न्यूरोप्रोटेक्टिव (neuroprotective) उपचार या बीमारी बदलने वाले उपचारों के लिए विशेष महत्व है। प्रबन्ध के इस भाग में स्वस्थ और प्रारम्भिक पार्किन्सन रोग स्थिति (Early PD) का विभेदीकरण, एक अभिकलित्र सहायता प्राप्त अनुसंधान पद्धति (Computer-Aided Detection Mechanism) के माध्यम से प्रस्तावित है। एमडिएस - युपिडिआरस (MDS-UPDRS) भाग १ और २ मूल्यांकन, एप्वरथ तन्द्रा स्तर (Epworth Sleepiness Scale), और रेम शयन व्यवहार विकार (REM Sleep Behaviour Disorder: RBD) इस पद्धति के विशेषताओं में हैं। समर्थन वेक्टर मशीन (Support Vector Machine: SVM), रैखिक विभेदक विश्लेषण (Linear Discriminant Analysis: LDA), रसबूस्ट (RUSBoost), तथा तार्किक प्रतिगमन विश्लेषण (Logistic Regression) - वर्गीकारक (classifier) के रूप में प्रयुक्त हुए हैं। इन विशेषताओं के साथ उत्साहजनक परिणाम से चिकित्सा समुदाय की सहायता हो सकती है और रोग का बेहतर प्रबन्धन हो सकता है।

पार्किन्सन रोगीओं के (PD patients') समय के साथ बदलते आँकड़ों में स्ट्राइएटम (Striatum) के आकार परिवर्तन का चरित्रांकन

इस भाग में स्ट्राइएटम (Striatum) के आकार का तीन चरणों में विकार का चरित्रांकन किया गया है।

नैदानिक परीक्षणों की रचना और प्रबन्धन के लिए अनुसंधान, दोनों के लिए ये भविष्यकल्प चरित्रांकन सहायक है। इस अध्ययन में पीपीएमई (PPMI) से प्राप्त अनुदैर्घ्य (longitudinal) स्पेक्ट (SPECT) आँकड़ों का विश्लेषण हुआ है। ये स्पेक्ट (SPECT) आँकड़े तीन अवस्थाओं में लिए गये हैं, पहले चरण में, उसके १२ महीने बाद दूसरे चरण में, तथा २४ महीने बाद तीसरे चरण में। स्ट्राइएटम (Striatum) के विकार का आकार स्पेस (Shape Space) में विश्लेषण हुआ है, और इसका चरित्रांकन बन्द रूप समीकरण (closed-form equation) में किया गया है। विभिन्न चरणों का प्रभेद नियरेस्ट नेइबर (nearest-neighbour) वर्गीकारक (classifier) से किया गया है। चरण २ और ३ के बीच का अतिव्यापन कम होने के बावजूद (समय के साथ परिवर्तन का दर कम होता है) प्राप्त सटीकता सराहनीय है।

हम यह सिद्ध करते हैं कि इन सरल आकार और परिमाण विशेषताओं (shape and size features) के साथ सुयोग्य मशीन लर्निंग (Machine Learning) साधनों के उपयोग से पार्किन्सन रोग के प्रारम्भिक स्थिति (Early PD) का सटीक पहचान सम्भव है।

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List of Key Abbreviations

EVestG	Electrovestibulography
[123I]FP-CIT	¹²³ I-Ioflupane Injection (DATscan)
18F-DMFP	18f-Desmethoxyfallypride
18Fdopa	Fluorodopa F-18
ALFF	Amplitude of Low Frequency Fluctuations
ANOVA	Analysis of Variance
ASAP	Advanced Sensing for Assessment in PD
CAD	Computer Aided Diagnosis
CSF	Cerebrospinal Fluid
DAT	Dopamine Transporter
DT	Dopaminergic Therapy
DTI	Diffusion Tensor Imaging
DTI-FA	Diffusion Tensor Imaging Fractional Anisotropy
EDS	Excessive Daytime Sleepiness
EEG	Electroencephalography
ELM	Extreme Learning Machine
EOG	Electrooculography
EPNN	Enhanced Probabilistic Neural Network
ESS	Epworth Sleepiness Scale
ET	Essential Tremor
fMRI	Functional Magnetic Resonance Imaging
GEE	Generalized Estimating Equations
GLM	Generalized Linear Model
GM	Grey Matter

IBZM	Iodobenzamide
IPD	Idiopathic Parkinson's Disease
IRBD	Idiopathic Random Sleep Behavior Disorder
KLt	Karhunen-Loève Transform
K-NN	K-Nearest Neighbor
KSOM	Kohonen Self-Organizing Map
LBD	Lewy Body Dementia
LDA	Linear Discriminant Analysis
LRRK2	Leucine-Rich Repeat Kinase 2
MC	Mahalanobis Classifier
MCC	Matthew's Correlation Coefficient
MDS-UPDRS	Movement Disorder Society- Unified Parkinson's Disease Rating Scale
MID	Mutual Information Difference Criterion
MIQ	Mutual Information Quotient Criterion
MMRM	Mixed Effect Modeling With Repeated Measurements
MMSE	Mini-Mental State Examination
MNI	Montreal Neurologic Institute
MoCA	Montreal Cognitive Assessment
MRI	Magnetic Resonance Imaging
mRMR	Minimum Redundancy Maximum Relevance
MSA	Multiple System Atrophy
NN	Nearest Neighbor Mean Classifier
OPF	Optimum Path Forest
PD	Parkinson's Disease
PET	Positron Emission Tomography
PLM	Periodic Leg Movement
PLS	Partial Least Squares
PNN	Probabilistic Neural Network
PPMI	Parkinson Progression Marker Initiative
PS	Parkinsonian Syndrome
PSG	Polysomnography

PSP	Progressive Supranuclear Palsy
QDA	Quadratic Discriminant Analysis
RBD	Random Sleep Behavior Disorder
RBDSQ	Rem Sleep Behavior Disorder Screening Questionnaire
RBF	Radial Basis Function
ReHO	Regional Homogeneity
RFCS	Regional Functional Connectivity Strength
ROC	Receiver Operator Curve
ROI	Regions Of Interest
RS	Reflexive Saccades
rsfMRI	Resting State FMRI
RSWA	Rapid Eye Movement Without Atonia
RUSBoost	Random Undersampling Boosting Algorithm
RVM	Relevance Vector Machine
SBR	Striatal Binding Ratio
SIFT	Scale Invariant Feature Transform
SNe	Substantia Nigra Pars Compacta
SNE	Substantia Nigra Echogenicity
SNM	Society Of Nuclear Medicine
SPECT	Single Photon Emission Computed Tomography
SPM	Statistical Parametric Mapping
SVM	Support Vector Machines
SWEDD	Sans Without Evidence Of Dopaminergic Deficit
TCUS	Transcranial B-Mode Sonography
UPDRS	Unified Parkinson's Disease Rating Scale
VAf	Voxel-As-Feature
VGRF	Vertical Ground Reaction Force
WM	White Matter