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Progressive AI using multi-modality **differential diagnosis** for **individualized intervention** in the treatment of Parkinson's disease

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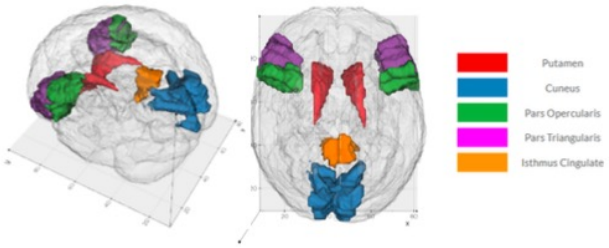
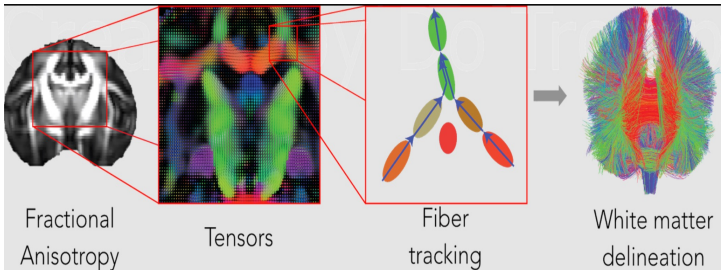
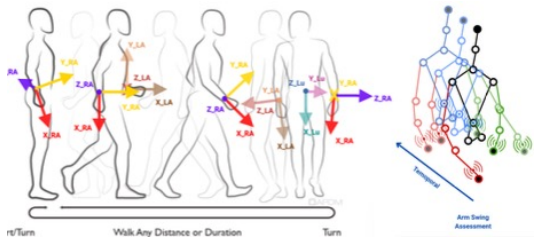






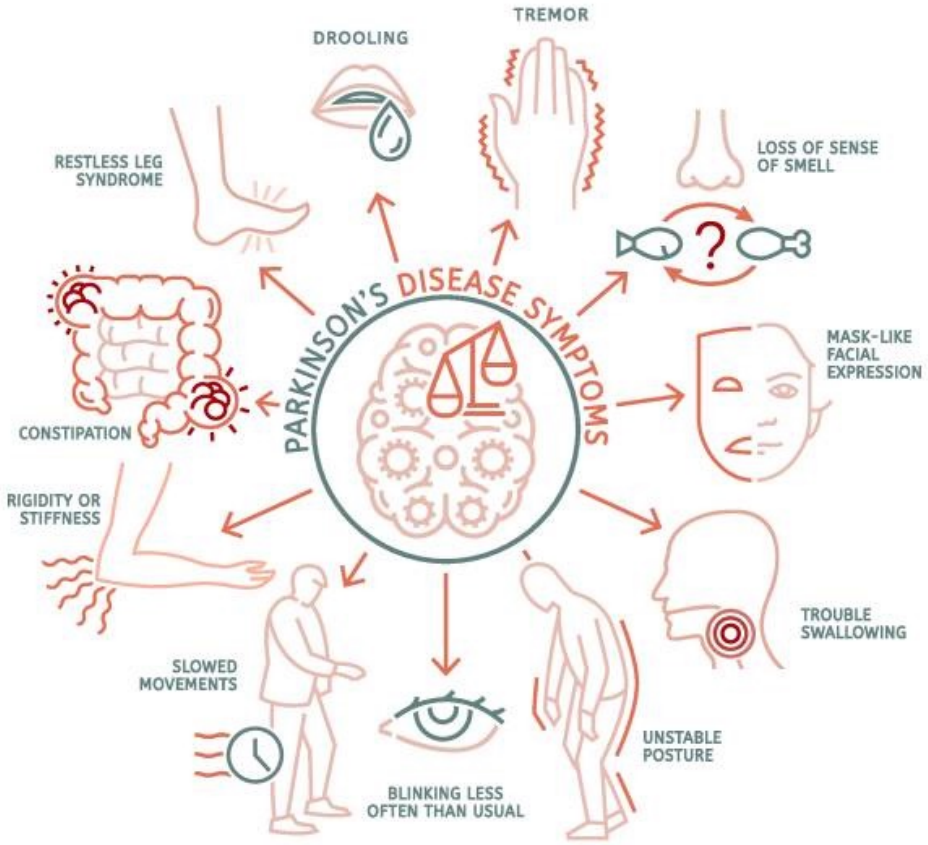
What is Parkinson's Disease (PD) ?

PD is a **multisystem α-synucleinopathy** (group of *neurological disorders*) driven by intertwined *protein-handling*, *mitochondrial*, *inflammatory* and *network factors—not just dopamine alone.*

Who all are Affected?

Here are some **rough** estimates (people *living with* Parkinson's disease):

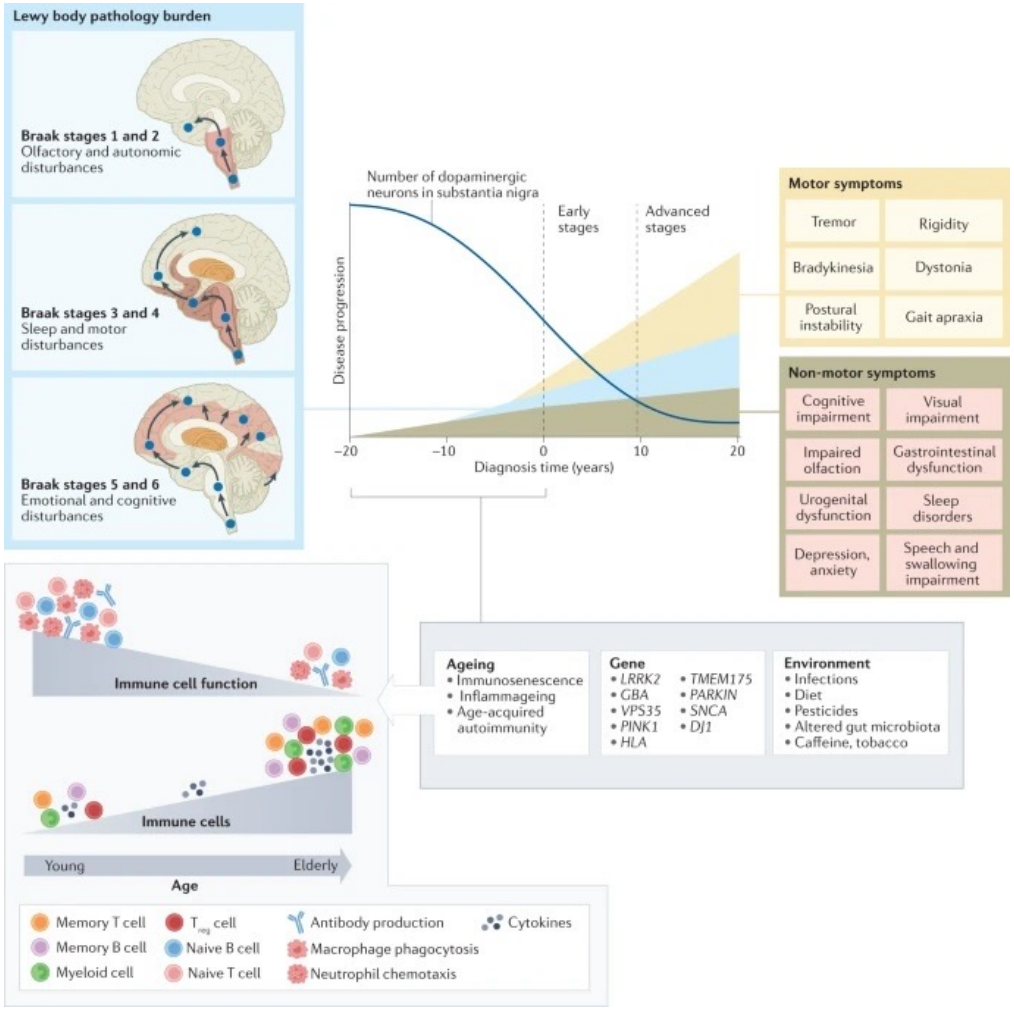
- **United States:** ≈ **1.1 million** people. (Parkinson's Foundation statistics page.) Parkinson's Foundation
- **India:** ≈ **771,000** people in **2019** (95% uncertainty interval: 635,000–919,000), from the India State-Level Disease Burden Initiative (Lancet Global Health). PMC
- **Worldwide:** ≈ **11.77 million** people in **2021**, based on Global Burden of Disease 2021 analyses. PMC



Current therapies are mostly symptomatic; no drug has definitively slowed progression in Phase 3 trials yet.

Parkinson disease (PD) affects multiple systems, and patients commonly present with accompanying non-motor symptoms, which often start in the prodromal phase.

Prodromal PD is supported by the Braak theory (blue box), in which *Lewy body* pathologies begin in the *periphery and olfactory bulb* and advance to the *brainstem* and towards *higher brain centers* following a predictable caudal-rostral pattern



When neuronal dysfunction begins, a combination of factors, from an ageing immune system, genes and environment, can create the **perfect storm** *to enable the development and progression of PD pathogenesis*

Tansey, M.G., Wallings, R.L., Houser, M.C. *et al.* Inflammation and immune dysfunction in Parkinson disease. *Nat Rev Immunol* **22**, 657–673 (2022).

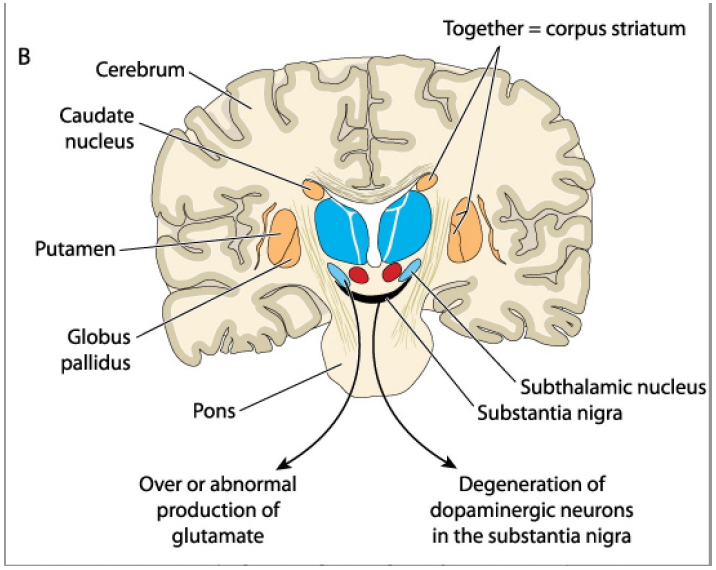
Core NeuroBiology (what causes PD at the Neuronal Cellular/Circuit level) -1

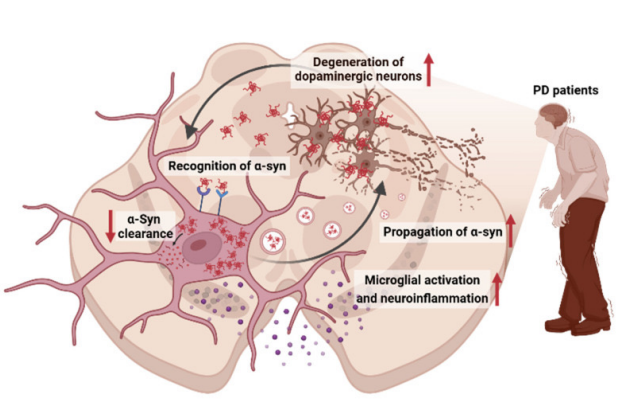
A. Misfolded α-synuclein and Lewy pathology.

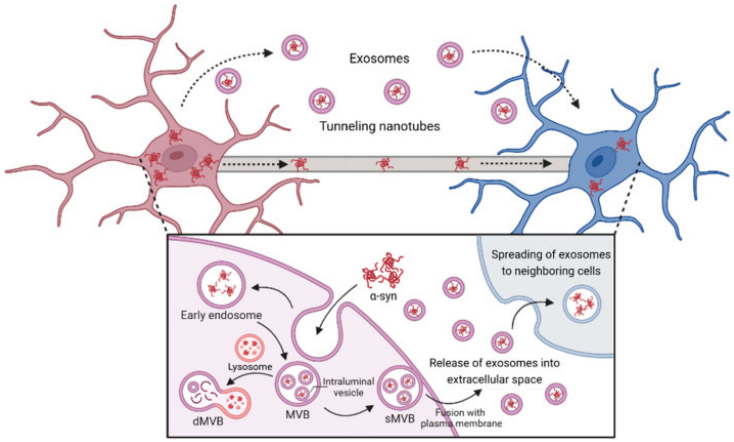
In most PD, **α-synuclein misfolds, aggregates** (Lewy bodies/neurites), and *appears to spread along connected neural networks*; this process activates microglia and other immune pathways that may further damage neurons. PMCNature

B. Failed cellular housekeeping (lysosome–autophagy) and mitochondria.

Defects in lysosomal enzymes/trafficking (e.g., GBA1) and **mitochondrial quality control** (e.g., PINK1/PRKN) *impair protein clearance* and *energy production*, *stressing dopamine neurons* in the substantia nigra. (These mechanisms are major themes across modern PD genetics and pathology reviews.) Nature



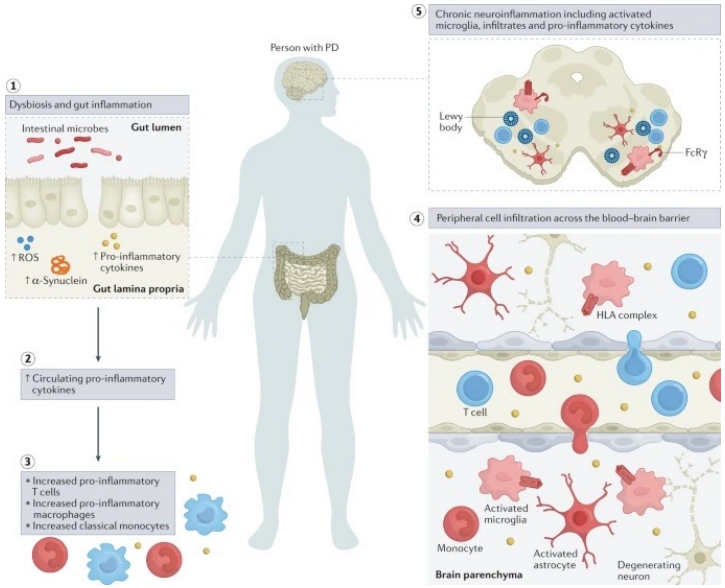


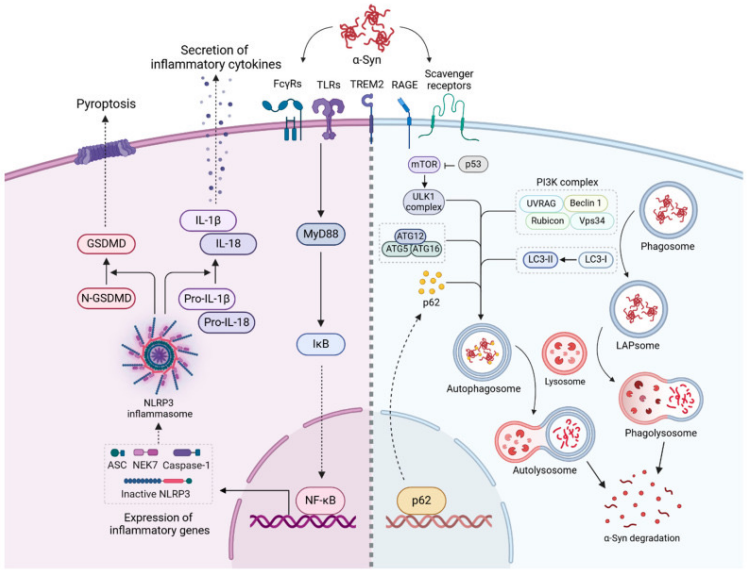


Core NeuroBiology (what causes PD at the Neuronal Cellular/Circuit level) – 2

C. **Neuroinflammation (innate + adaptive).**
Aggregated **α**-syn *can activate microglia*; T-cells recognizing **α**-syn–derived peptides have been detected in PD, suggesting maladaptive immune responses may contribute to progression.

D. **Ion/calcium and oxidative stress vulnerabilities.**
Nigral dopamine neurons are autonomous pacemakers with high calcium flux and metabolic demand;
hypotheses that blocking L-type channels would slow PD were **not** confirmed in a large Phase 3 trial (**isradipine**).

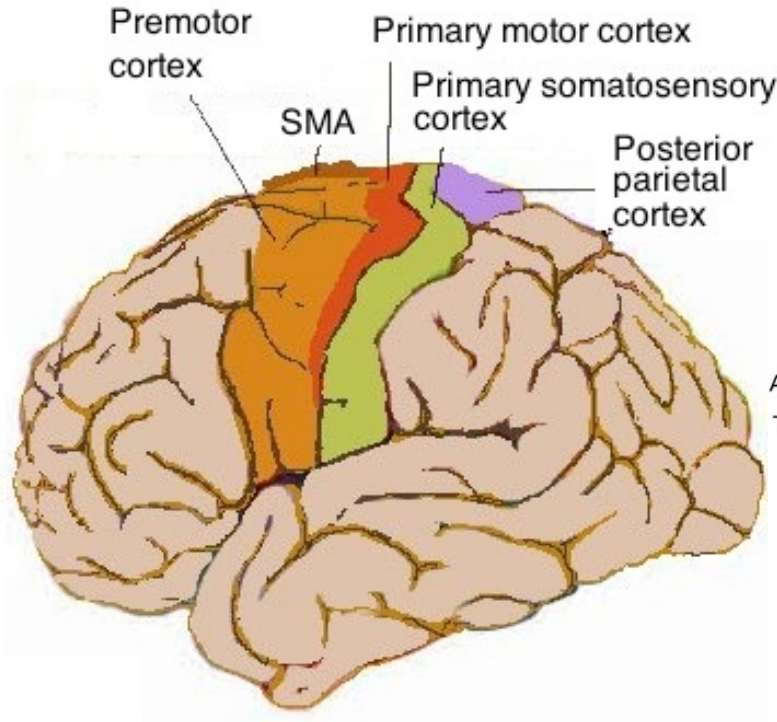


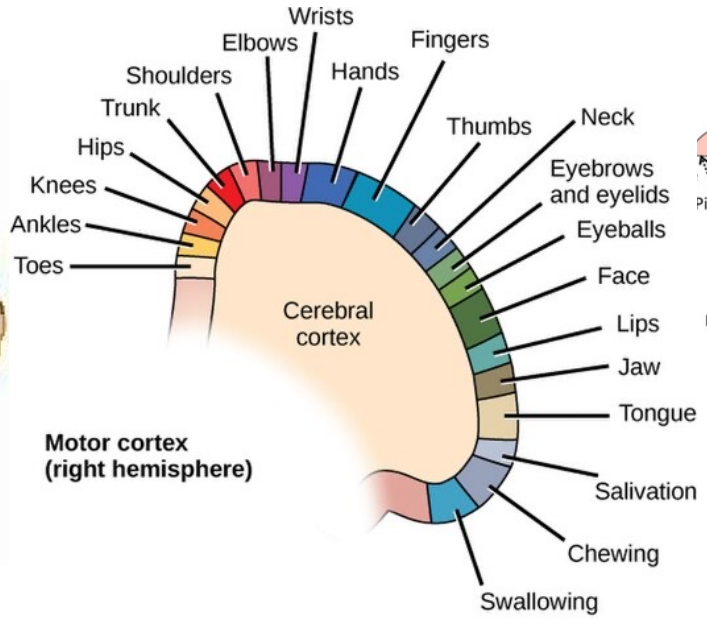


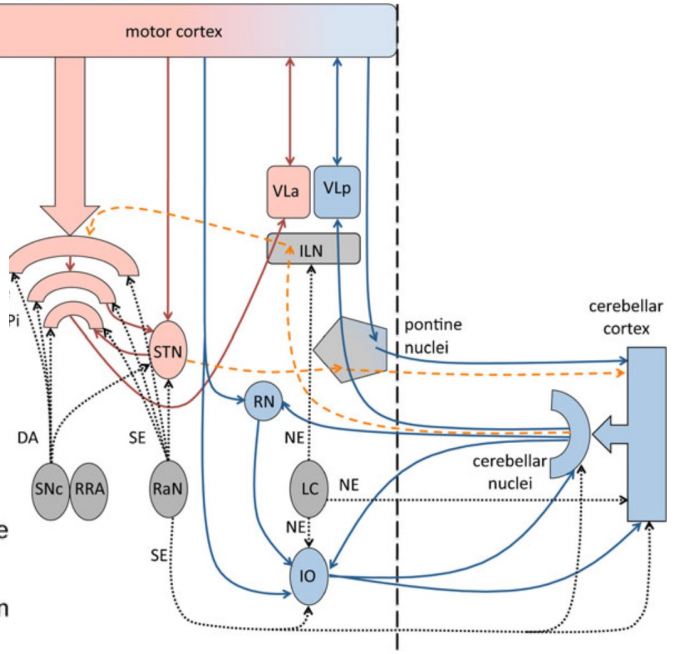
Core NeuroBiology (what causes PD at the Neuronal Cellular/Circuit level) - 3

E. **Network/circuit changes beyond dopamine.**

Motor symptoms reflect both **nigrostriatal** dopamine loss and changes in **cerebello-thalamo-cortical** and **cholinergic** systems (the latter especially for **gait/posture and cognition**). PMCPubMed







Typical Interventions to Neuro-Biological Manifestations - 1

A. Nigrostriatal dopamine deficit → Bradykinesia/Rigidity/Tremor

- *First-line dopaminergic options (early PD, motor symptoms):*
  . **Levodopa/carbidopa** (immediate or extended-release), **dopamine agonists**, **MAO-B inhibitors** (rasagiline, selegiline; **safinamide** if already on levodopa and having OFF time).
  • **Rytary®** (extended-release levodopa/carbidopa) — FDA-approved to smooth motor control.
  • **Safinamide (Xadago®)** — add-on to levodopa to increase "ON" time;

- *Continuous dopaminergic delivery (advanced PD):*
  Enteral carbidopa/levodopa gel (**Duopa®**) via PEG-J tube; **continuous subcutaneous levodopa/carbidopa** (**Vyalev™**, 2024); **continuous apomorphine infusion** (**Onapgo™**, 2025).

- *Circuit-targeting procedures:*

Deep Brain Stimulation (DBS) of STN/GPi for motor fluctuations/tremor (established standard).

MR-guided Focused Ultrasound (FUS) for ablation—initially unilateral, **bilateral staged FUS** gained FDA clearance in **July 2025** (select centers; staged months apart) and can reduce tremor/dyskinesia in advanced PD.

Typical Interventions to Neuro-Biological Manifestations - 2

B. *Tremor circuits (cerebello-thalamo-cortical) → medication-refractory tremor*

- **Try:** optimization of levodopa; limited role for **anticholinergics** in younger patients due to cognitive side effects.
- **Escalate: DBS** (VIM thalamus or STN)

C. *Dyskinesia (glutamatergic overactivity + pulsatile dopamine)*

- **Amantadine** (especially **extended-release Gocovri®**) reduces levodopa-induced dyskinesia. Dose cautiously for hallucinations, insomnia, livedo reticularis.
- **Adjust dopaminergics** (fractionate levodopa, lower agonists)

D. *Gait/postural instability, falls (cholinergic & diffuse network involvement)*

- **Rehab/exercise is foundational** (gait/balance training, amplitude-based therapy, Tai Chi); high-quality reviews and Cochrane note clinically meaningful benefits in motor function and balance.
- **Medications** offer limited benefit; **DBS** helps freezing less reliably;

Are the Interventions optimally Individualized to each patient based on manifestations?

Clinical Q/A with Dr. Conor Fearon (MD, Phd, Neurologist at Mater Misericordiae University Hospital, Dublin, Ireland)

Which Parkinson's symptoms do you prioritize or weigh most heavily during patient assessments, especially those not fully captured by standard PD scales?

So the simple answer to this is that the Parkinson's symptoms I prioritize in a clinic visit is the ones which bother the patient the most at that time.

However, a better answer to your question is getting at something else, for most people I'm generally on the look out for the
(1) **emergence of motor fluctuations (wearing off and/or dyskinesia), the emergence of gait impairment and falls**., and the
(ii) **emergence of cognitive impairment**.

Which Tests (e.g. MDS-UPDRS, QUIP, MoCA, DATSCAN, MRI) do you find most reliable or meaningful in everyday clinical practice, and why?

Good question, so this really depends on the answer to question 1 above. It depends on what I am trying to do.

Firstly, **MRI and DaTscan are useful** at the diagnostic stage. Though research based biomarkers are emerging, they are still not used routinely in clinical practice).

In routine clinical practice in a busy clinic, the only scales I really use regularly are MDS-UPDRS and MoCA. The other scales (of which there are many) are predominantly used in research studies to quantify those features which we ask about in a more qualitative way in clinic (e.g. autonomic features, impulsive/compulsive behaviours, suicidality, non-motor symptoms).

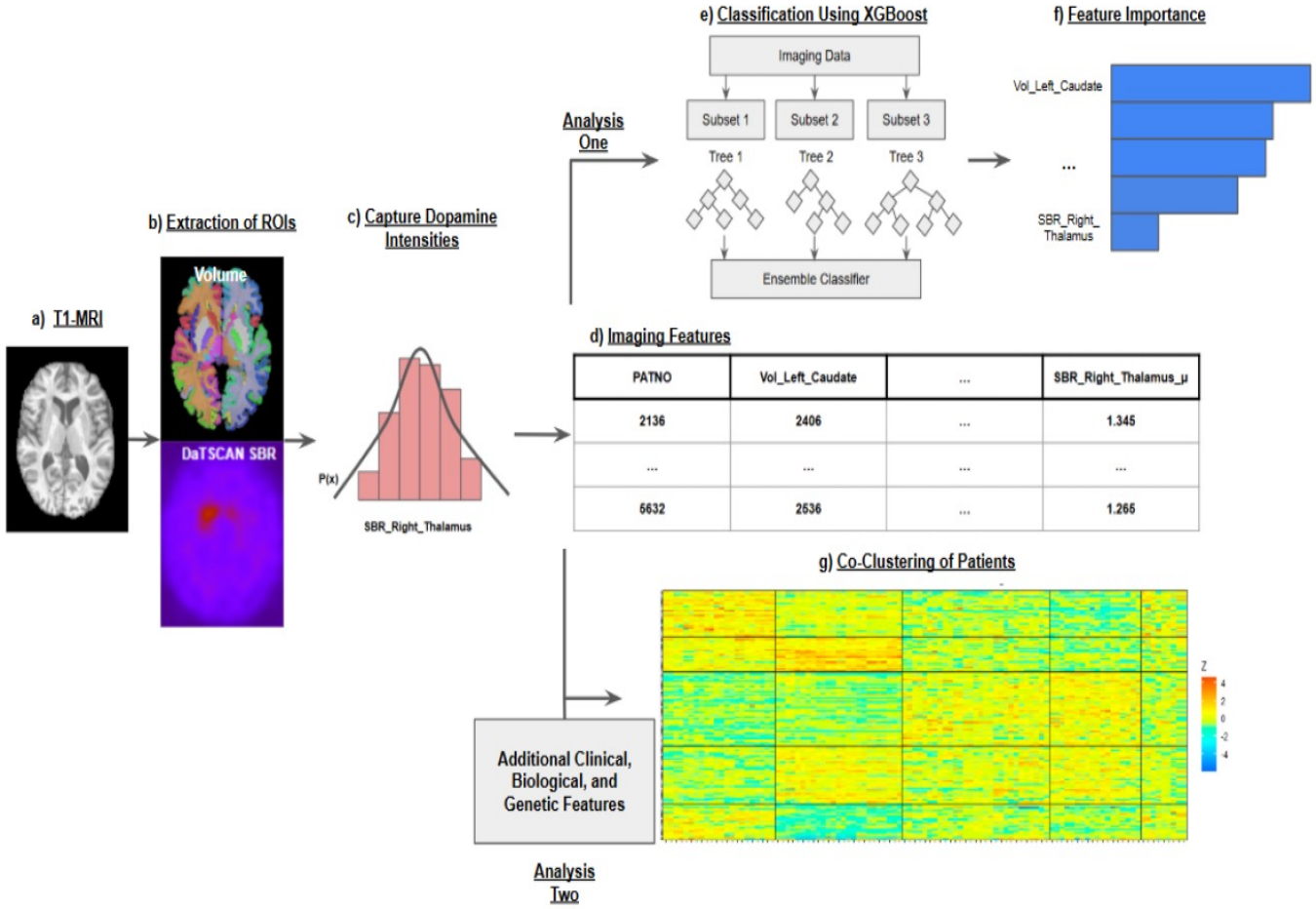
So how can AI/ML help the Patient ?

A **progressive** (continually active)
AI Decision Making Agent
that robustly filters multi-modal patient data
to **differentially diagnose,**
and to optimally guide **individualized intervention**
in the treatment of Parkinson's disease

Progressive AI : Continually Active Decision Making Processes Balancing Risk and Reward

Robust Correlative and Causal Integration of Multi-modal DaT and DTI with Genetic, Clinical, Biological and Gait/Arm Swing Signal Filtered Data

Reinforcement Learning with Stochastic Policy Optimization on Hamiltonian Manifolds



C. Bajaj, C., Nguyen, M. *"Physics-Informed Neural Networks via Stochastic Hamiltonian Dynamics Learning*. In: Arai, K. (eds) Intelligent Systems and Applications. IntelliSys 2024.LNNS, Springer

M. Nguyen, C.Bajaj *"A Differential and Pointwise Control Approach to Reinforcement Learning" ArxiV 2404.15167v3, 2025*

So what data is available to today's AI Progressive Agent ?

Data Modality / Source	Description
Clinical assessments	**MDS-UPDRS-III, UPSIT (olfactory), Sleep (Epworth, REM), QUIP, SCOPA-AUT Cognitive tests (Hopkins Verbal, Benton exam, MOCA) , history, medications**
Imaging	**DaTSCAN, structural MRI, DTI, DKI, NODDI**
Laboratory & Genetic	**CSF lab measures, DNA, genetic data**
Biospecimens	**Serum, plasma, urine, CSF, skin biopsies**
Remote assessments	**Olfactory testing, genetic via Remote protocol**
Online self-reports	**Portions of MDS-UPDRS collected via web-based app**
Telephone follow-ups	Additional clinical follow-up via phone consultations

PPMI (Parkinson's Progression Markers Initiative) database

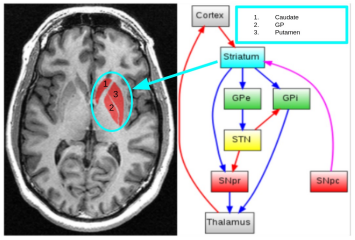
So what data is available to today's AI Progressive Agent ?

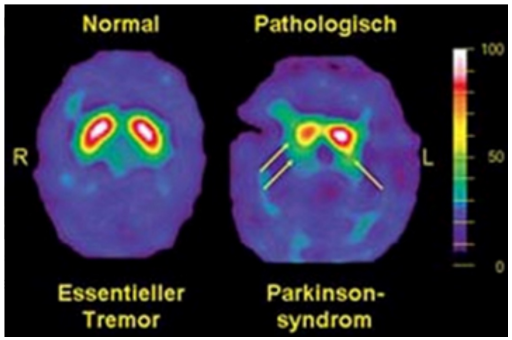
Data Modality	Data Type / Tests Collected
Smartphone & Wearable Sensors	**Accelerometry, gyroscope, touchscreen, microphone; tests include walking, tremor, daily tasks**
Levodopa Response Wearable Study	**Accelerometer + smartphone; in-lab motor tasks + home monitoring over 4 days**
Handwriting Samples	**Kinematic and pressure data during scripted writing tasks (spirals, words, sentences)**
Keyboard Dynamics	**Keystroke hold times during natural computer use**
Genomics (WGS)	**Whole-genome sequencing from large PD cohorts**
Transcriptomics (RNA-seq)	**Gene expression data for molecular profiling**
Clinical / Phenotypic Assessments	**Standard clinical test scores, demographics, motor and non-motor evaluations**

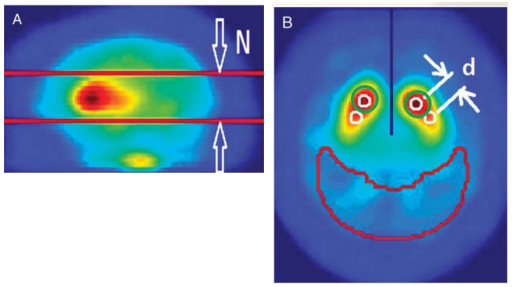
synapse.org Databases for Parkinsons Research

What are DaT Image Scans and how does it help with PD ?

Dopamine Transporter (DaT) Imaging using **DaT-SPECT or DaT-MRI** provides critical biomarkers for Parkinson's Disease (PD) by assessing **dopaminergic neuron loss**.
When combined with other **PPMI data** (DTI, clinical scores, genetic markers, CSF biomarkers), it can lead to **better diagnosis, progression tracking, and personalized treatment plans**.







Key Biomarkers from DaT-MRI for PD Treatment

1. DaT Binding Ratio (SBR - Specific Binding Ratio)

Measures **dopamine transporter (DAT) density** in the striatum. **Lower SBR in the putamen and caudate nucleus is a hallmark of PD.**

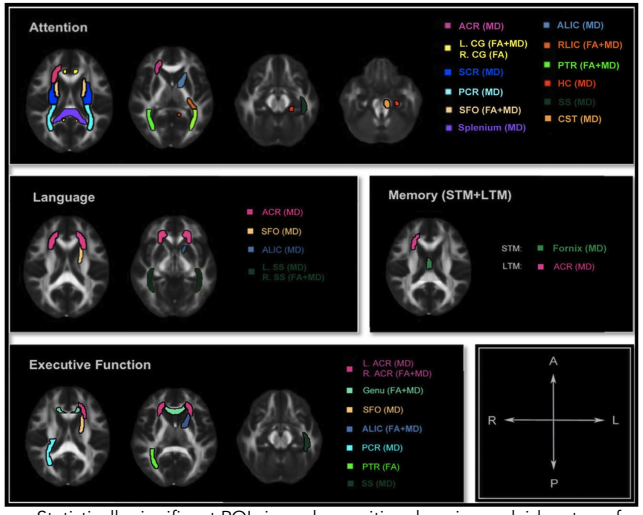
2. Striatal Asymmetry Index (SAI)
Measures the asymmetry between **left and right striatum**.
Higher asymmetry → **Earlier PD detection**.

3. Putamen/Caudate LoUptake Ratio
In PD, the **putamen is affected earlier** than the caudate.
A **low putamen/caudate ratio** correlates with motor impairment severity.

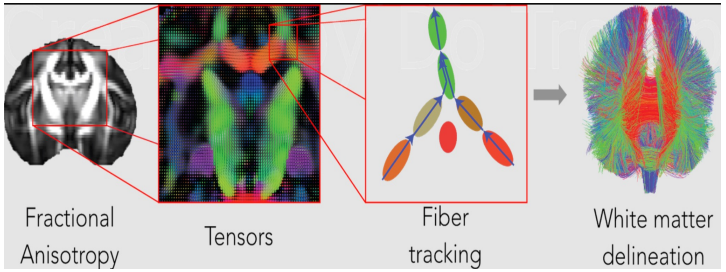
4. Progression Markers
Annual DaT loss rate (~5-10%) can predict disease progression.
Faster loss in the **posterior putamen** correlates with rapid motor decline.

Why DTI matters !

- **PD progression is highly variable**: Some patients experience rapid cognitive decline and *early dementia*, while others show slow, *primarily motor symptom progression*. [3]
- **Advanced MRI, especially diffusion imaging, reveals these individual differences**: Imaging of white-matter microstructure (such as DTI) detects early and subtle brain changes linked to both motor and cognitive decline. [4][2][1]

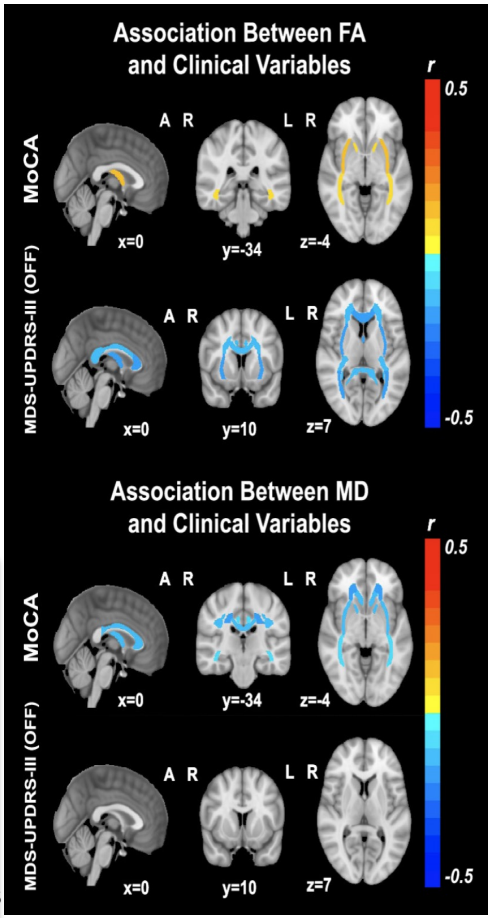


Statistically significant ROIs in each cognitive domain overlaid on top of a standard brain in axial view [1]



Diffusion Tensor Imaging (DTI)

- **Imaging biomarkers correlate with symptom severity and can predict who will decline faster**: DTI metrics not only track disease stage, but can also help identify patients at highest risk for rapid deterioration. [3][2]
- **Without definitive clinical predictors, neuroimaging is essential**: MRI biomarkers are critical for patient stratification, monitoring progression, and personalizing interventions addressing the urgent need for objective tools in this heterogeneous disease. [4]



Associations between DTI measures and MoCA and MDS-UPDRS-III [3]

[1] Zheng, Zhong, et al. "DTI correlates of distinct cognitive impairments in Parkinson's disease." Human brain mapping 35.4 (2014): 1325-1333
[2] Atkinson-Clement C, Pinto S, Eusebio A, Coulon O. Diffusion tensor imaging in Parkinson's disease: Review and meta-analysis. Neuroimage Clin. 2017 Jul 15;16:98-110. doi: 10.1016/j.nicl.2017.07.011. PMID: 28765809; PMCID: PMC5527156.
[3] Owens-Walton, Conor, et al. "A worldwide study of white matter microstructural alterations in people living with Parkinson's disease." npj Parkinson's Disease 10.1 (2024): 151.
[4] Taylor, Kirsten I., et al. "Progressive decline in gray and white matter integrity in de novo Parkinson's disease: an analysis of longitudinal Parkinson progression markers initiative diffusion tensor imaging data." Frontiers in aging neuroscience 10 (2018): 318.

Progressive AI Pipeline - II : Multi-Modal Imaging (Brain Region Specificity)

Region	DTI trend	Clinical link
Substantia Nigra	↓FA, ↑MD	Motor dysfunction
Corpus Callosum	↓FA, ↑MD	Risk of falls
Corticospinal Tract	↓FA	Bradykinesia & rigidity
Frontal White Matter	↓FA, ↑MD	Executive dysfunction
Thalamic Radiation	Altered FA/MD	Sensory–motor integration
Cerebellar Peduncles	↓FA, ↑MD	Gait & balance issues

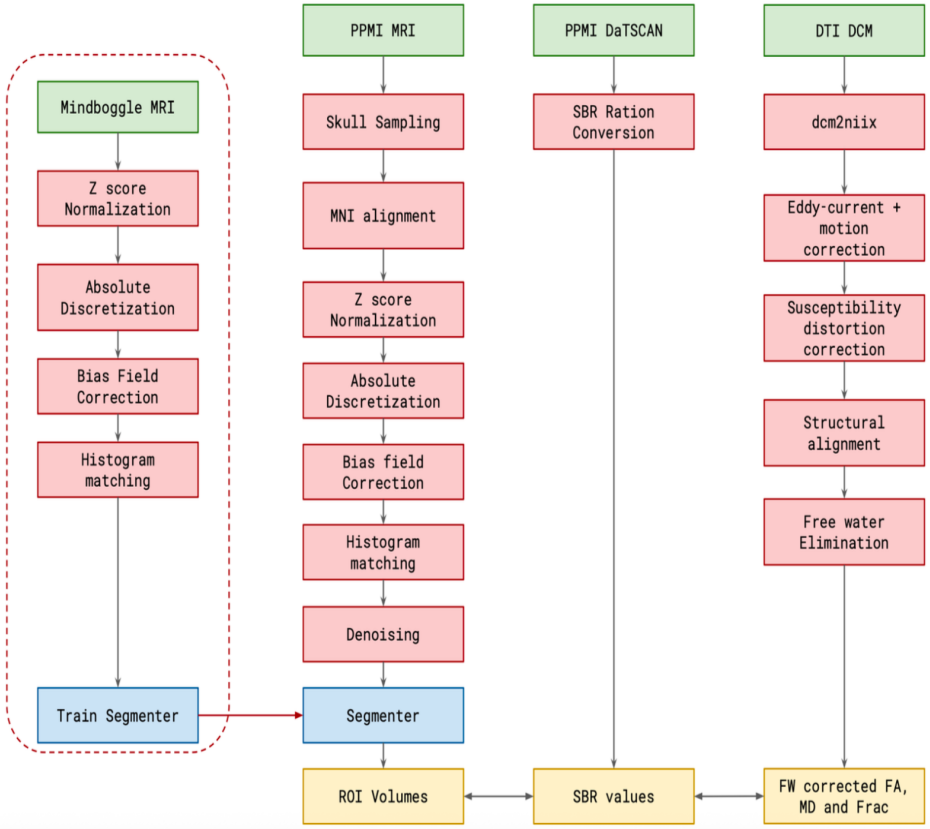
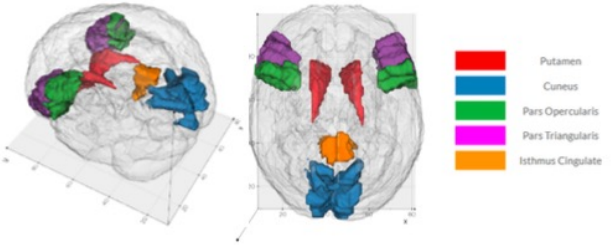
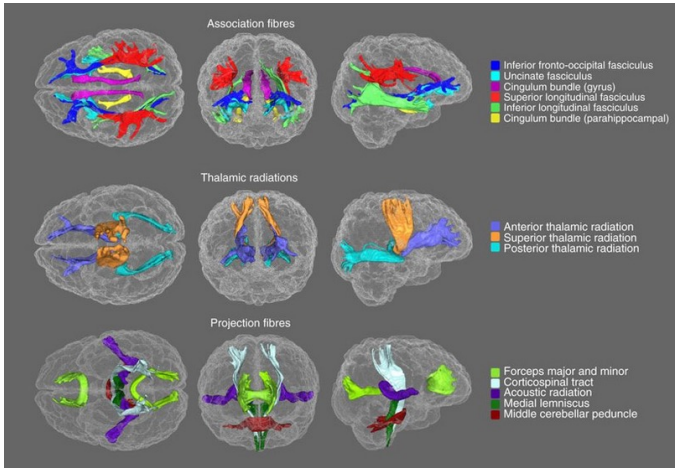


Fig. 1: Multimodal Feature extraction pipeline





Major white matter tracts

Progressive AI - III : Robust Variational Bayesian Co-Clustering

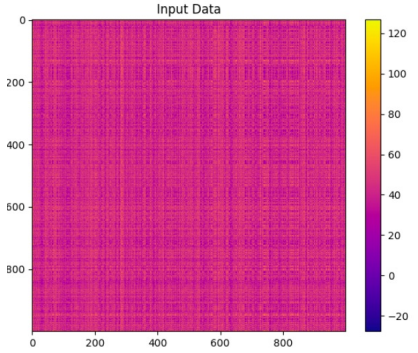
Discrete Variables and Their Partitions

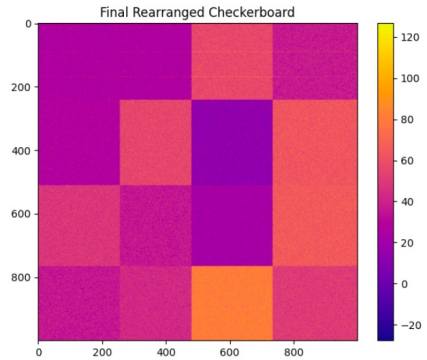
- Let X_r be a discrete random variable taking values in $\{\mathbf{x}_1, \ldots, \mathbf{x}_n\}$.
- Let X_c be a discrete random variable taking values in $\{\mathbf{y}_1, \ldots, \mathbf{y}_d\}$.
- The joint distribution on the original data is $p(X_r, X_c)$.

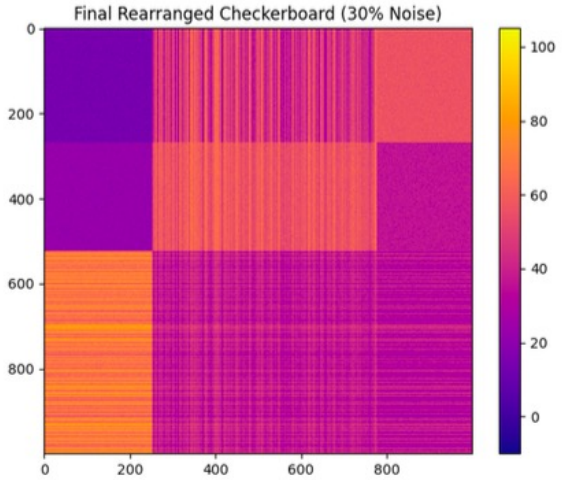
We define two new random variables $\hat{X}_r = C_r(X_r)$ and $\hat{X}_c = C_c(X_c)$ taking values in

$$\hat{X}_r \in \{\hat{\mathbf{x}}_1, \ldots, \hat{\mathbf{x}}_g\}, \quad \hat{X}_c \in \{\hat{\mathbf{y}}_1, \ldots, \hat{\mathbf{y}}_m\}.$$

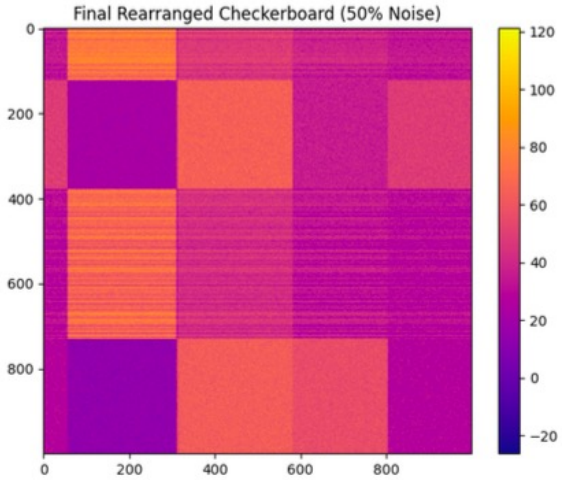
The induced distribution $p(\hat{X}_r, \hat{X}_c)$ characterizes the co-clusters.



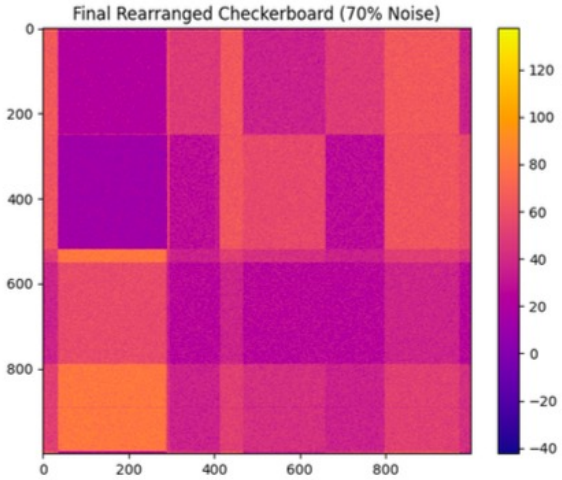




(a) Co-clustering with 30% noise level.



(b) Co-clustering with 50% noise level.



(c) Co-clustering with 70% noise level.

Robust Variational Bayesian Co-Clustering

- **Joint Clustering of Clinical & Imaging Features:** Simultaneously discovers coherent patient subtypes and joint feature clusters from mixed clinical and imaging data.
- **Bayesian Latent Space Modeling:** Embeds subjects and features into a Bayesian latent space using Gaussian mixture priors for robust, noise-tolerant clustering.
- **Mutual-Information Alignment:** Enforces concordance between imaging and clinical clusters via mutual-information cross-loss ensuring biological and clinical interpretability.
- **Handles High-Dimensional, Noisy Data:** Suppresses noise and prevents overfitting with KL-regularization, doubly re-parameterized gradients, and compositional loss reducing pathways.

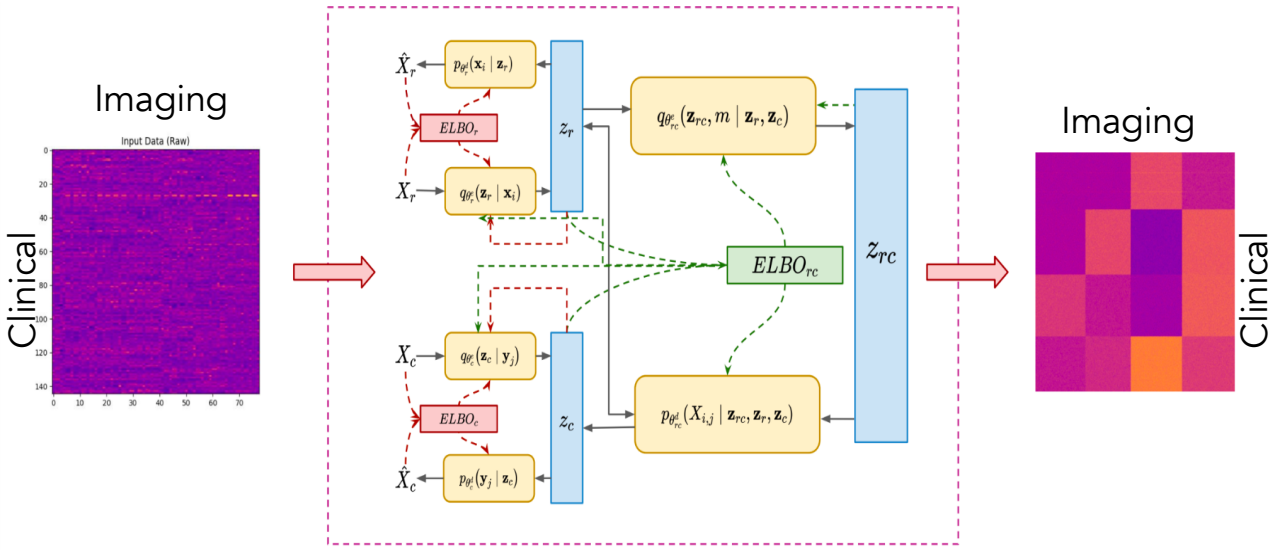


Fig. 2: The multi-modal feature-extraction pipeline produces a pre-processed data matrix, which is then passed to our Scalable Bayesian Co-clustering framework. The framework reorganizes the matrix into a checkerboard pattern, revealing coherent, clustered patient groups.

Scalable Robust Bayesian Co-Clustering with Compositional ELBOs, A. Vinod, C. Bajaj arXiv:2504.04079v2 , 2025

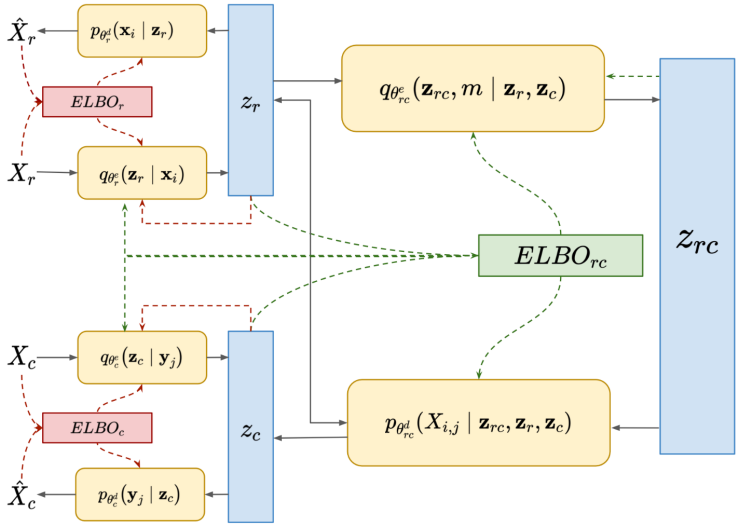
Progressive AI - IV : Co-Clustering with Compositional ELBOs

$$\mathcal{L}_{\text{ELBO}}^{(\text{row})}(\mathbf{x}_i) = \mathbb{E}_{q(\mathbf{z},\, c|\mathbf{x}_i)}\Big[\log p(\mathbf{x}_i \mid \mathbf{z}) \;+\; \log p(\mathbf{z} \mid c) \;+\; \log p(c) \;-\; \log q(\mathbf{z} \mid \mathbf{x}_i) \;-\; \log q(c \mid \mathbf{x}_i)\Big]$$

$$= \underbrace{\mathbb{E}_{q(\mathbf{z}|\mathbf{x}_i)}\big[\log p(\mathbf{x}_i \mid \mathbf{z})\big]}_{\text{reconstruction term}} - D_{\text{KL}}\Big(q(\mathbf{z}, c \mid \mathbf{x}_i) \;\|\; p(\mathbf{z}, c)\Big).$$

$$J_1^{(\text{total})} = \underbrace{\lambda_1 \|\theta_r\|^2}_{\text{(regularizer)}} + \underbrace{\lambda_2 \sum_{i=1}^{n}\Big(-\mathcal{L}_{\text{ELBO}}^{(\text{row})}(\mathbf{x}_i)\Big)}_{\text{VAE negative-ELBO on rows}} + \underbrace{\lambda_3 \sum_{\text{batches}}\Big(-c(\mathbf{x}, \mathbf{z})\Big)}_{\text{contrastive InfoNCE term}}$$

$$J_2^{(\text{total})} = \underbrace{\lambda_4 \|\theta_c\|^2}_{\text{(regularizer)}} + \underbrace{\lambda_5 \sum_{j=1}^{d}\Big(-\mathcal{L}_{\text{ELBO}}^{(\text{col})}(\mathbf{y}_j)\Big)}_{\text{negative-ELBO on columns}} + \underbrace{\lambda_6 \sum_{\text{batches}}\Big(-c(\mathbf{y}, \mathbf{z})\Big)}_{\text{contrastive loss term}}$$



$$J_{\text{total}} = \underbrace{\lambda_1 \|\theta_r\|^2 + \lambda_2 \sum_{i=1}^{n}\Big[-\mathcal{L}_{\text{ELBO}}^{(\text{row})}(\mathbf{x}_i)\Big] + \lambda_3 \sum_{\text{batches}}\Big[-c(\mathbf{x}, \mathbf{z})\Big]}_{\text{row side (Instance-Side Loss)}}$$

$$+ \underbrace{\lambda_4 \|\theta_c\|^2 + \lambda_5 \sum_{j=1}^{d}\Big[-\mathcal{L}_{\text{ELBO}}^{(\text{col})}(\mathbf{y}_j)\Big] + \lambda_6 \sum_{\text{batches}}\Big[-c(\mathbf{y}, \mathbf{z})\Big]}_{\text{column side (Feature-Side Loss)}}$$

$$+ \underbrace{\lambda_7 \sum_{i=1}^{n}\sum_{j=1}^{d}\Big[-\mathcal{L}_{\text{ELBO}}^{(\text{joint})}(X_{i,j})\Big] + \lambda_8 \sum_{\text{batches}}\Big[-c_{\text{joint}}(X_{i,j}, \mathbf{z}_{rc})\Big]}_{\text{joint side (Joint Space)}}$$

$$+ \underbrace{\lambda_9 \Big(1 - \tfrac{I(\hat{X};\hat{Y})}{I(X;Y)}\Big)}_{\text{cross-loss (Cross-Loss } J_3)}.$$

Figure 2: Variational Latent Co Clustering architecture.

Some Differential Diagnostic Takeaways from Clinical, DaT, DTI

Three Distinct Patient Subtypes Identified

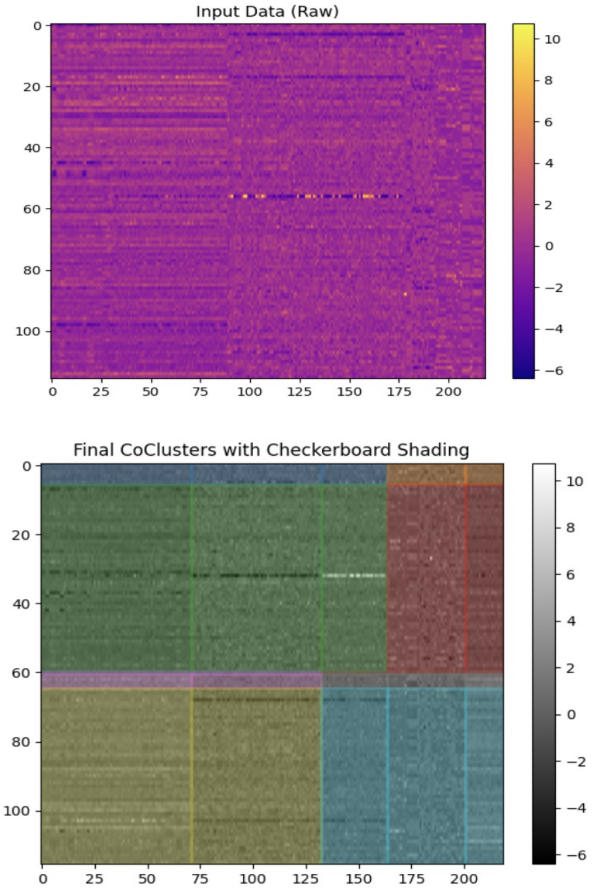
- **Mild:** Near-normal cognition (MoCA ≈ 28.5), minimal motor symptoms (UPDRS-III ≈ 10)
- **Moderate:** Intermediate impairment (MoCA ≈ 25, UPDRS-III ≈ 20)
- **Severe**: Pronounced cognitive decline (MoCA ≈ 22), severe motor dysfunction (UPDRS-III ≈ 30)

Imaging Metrics Mirror Clinical Severity

- **Thalamic Mean Diffusivity Asymmetry:** Rises from 0.02 (mild) to 0.10 (severe)
- **Caudate FA Asymmetry:** Drops from -0.01 (mild) to -0.06 (severe)
- **Minimal Overlap Between Subtypes:** Subtypes show clear, non-overlapping ranges in both clinical and imaging features

Superior Clustering & Prediction

- SRVCC framework **outperforms spectral bi-clustering, and deep clustering baselines** in both clustering purity and severity-prediction error.



(b) Final Co-clusters detected

Incorporating PD Patient Gait/Arm Swing Test Data

The gait /arm swing data of patients were calculated using wireless *APDM Opal IMU* sensors on the lumbar spine and both wrists and feet while performing standardized tasks,

- **Sway Tests (Eyes Open/ Closed):** Center of mass stability while standing.
- **Timed Up and Go (TUG):** Stand-walk-turn-sit tasks to assess mobility and balance.
- **Usual Walk:** One minute walk at preferred pace
- **Dual Task Walk:** One-minute walk while performing serial subtractions.

Data streamed by the accelerometer, the gyroscope and the magnetometer as **level 1** data:

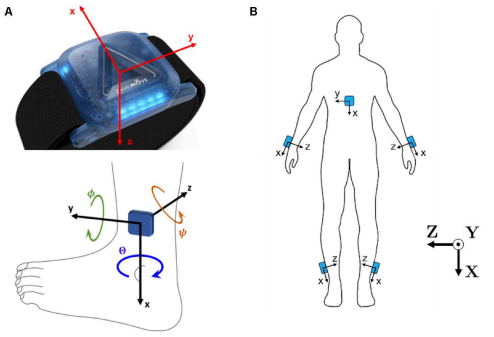


Fig 1: OPAL Sensors

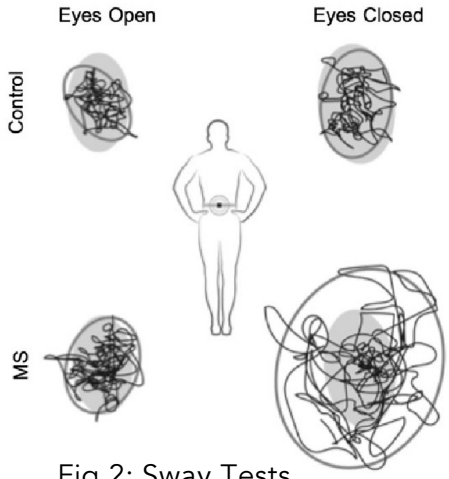


Fig 2: Sway Tests

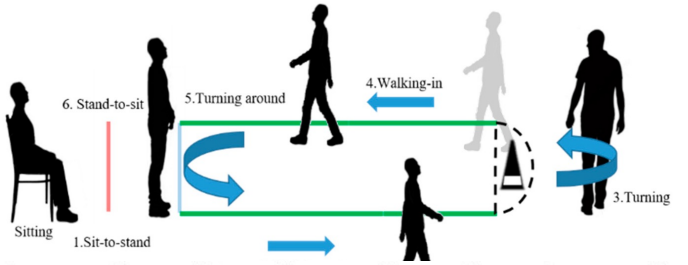


Fig 3: TUG Task

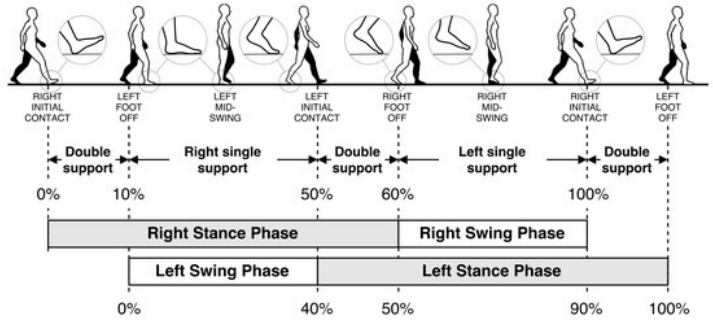


Fig 4: Walk Task

Patient Gait/Arm Swing Test Databases

Gait /Arm Swing Data	**BeatPD_Gait_Datasets**	a data challenge focused on using wearable sensor data collected from smartphones and smart watches to predict Parkinson's disease severity.	Accelerometer (x,y,z) Gyroscope (x,y,z)
	Synapse_Wear-Gait_PD	Wearable sensor and clinical data from Parkinson's patients and healthy controls for gait analysis and monitoring.	Accelerometer (x,y,z) Gyroscope (x,y,z)
	Bioclite_Restricted_Arm_Swing_Data	This dataset contains triaxial accelerometer and gyroscope data from 24 subjects performing gait activities with a smartwatch, including walking trials under varying arm-load conditions (0, 2, and 4 kg).	Accelerometer (x,y,z) Gyroscope (x,y,z)
	Mendeley_Gait_assessment_in_Parkinson_Disease	Biomechanical and IMU data from 34 Parkinson's patients and 8 healthy controls in a clinical gait and arm movement study.	Accelerometer (x,y,z) Gyroscope (x,y,z)
	PPMI_Gait_Data_selected	Binary and ordinal labels of key Parkinsonian motor symptoms across **longitudinal** visits for modeling, subtyping, and progression analysis.	Level 2 Features

Multilevel Mapping: Gait to PD

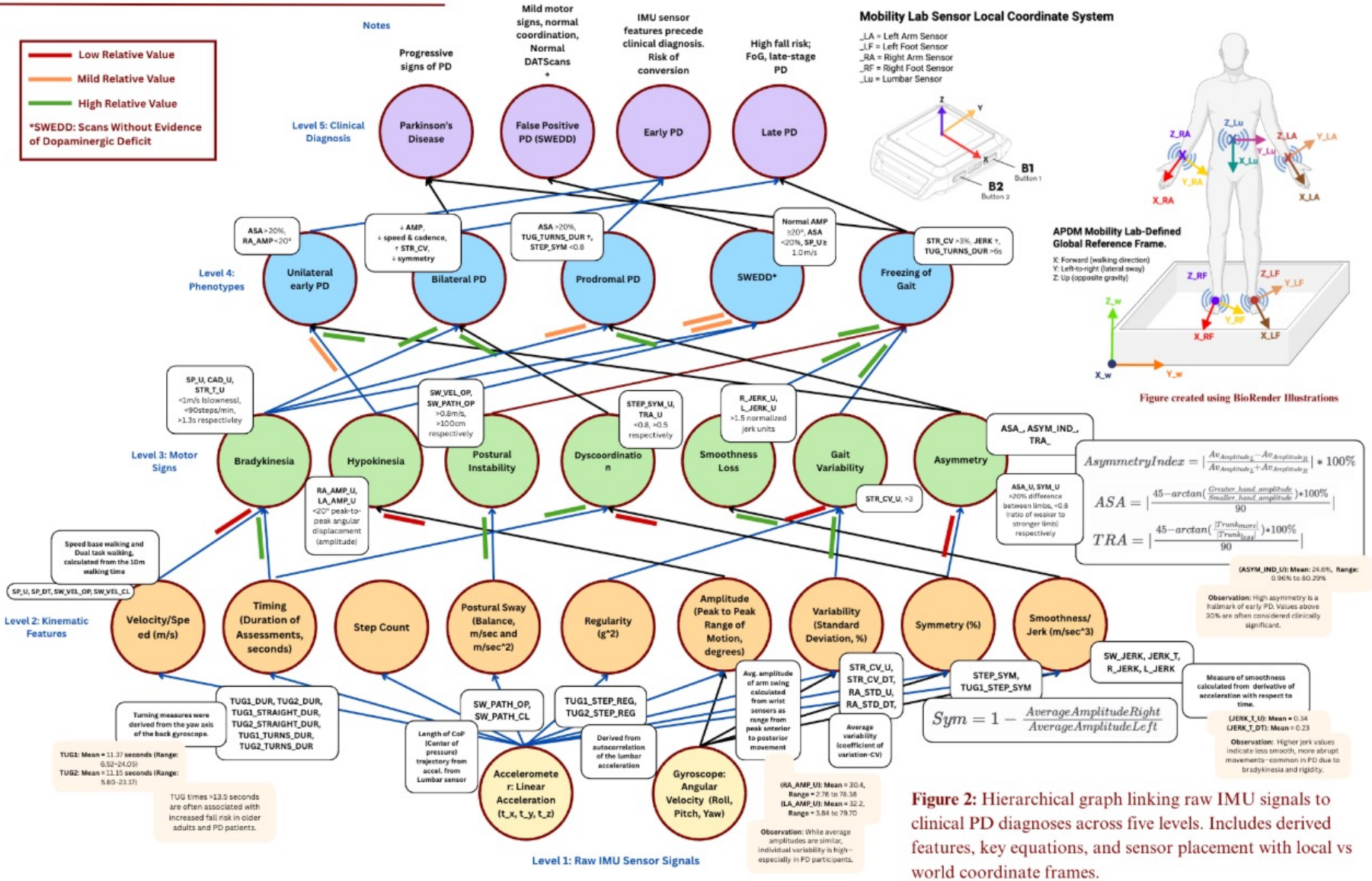


Figure 2: Hierarchical graph linking raw IMU signals to clinical PD diagnoses across five levels. Includes derived features, key equations, and sensor placement with local vs world coordinate frames.

Robust MIMO Transformations from Level 1 from Level 2 Time Series (Stochastic Processes) — Motion Code

Level 2 Feature	Computation from Level 1 Feature
Amplitude	Peak-to-peak angular range from wrist and trunk sensors using Euler angles
Velocity / Speed	Speed from 10m walk; cadence from step count per minute
Timing	Time from TUG; stride time from vertical acceleration
Variability	Standard deviation and coefficient of variation of amplitude and stride time
Symmetry	Ratios and asymmetry indices from bilateral sensors
Smoothness / Jerk	Time derivative of acceleration
Regularity	Autocorrelation of vertical acceleration
Postural Sway (Balance)	Derived from accelerometer data from lumbar sensor during 30 second stance
Step Count	Counted from vertical acceleration peaks

Prior Work: algorithms given in [1] and [2]…however not robust to very noisy data.

[1] Warmerdam, E., Romijnders, R., Welzel, J., Hansen, C., Schmidt, G., & Maetzler, W. (2020). Quantification of Arm Swing during Walking in Healthy Adults and Parkinson's Disease Patients: Wearable Sensor-Based Algorithm Development and Validation. *Sensors*, *20*(20), 5963. https://doi.org/10.3390/s20205963

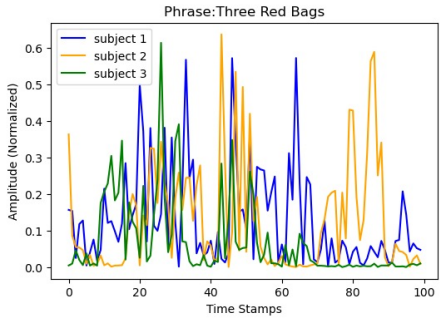
[2] Luis Pastor Sánchez-Fernández, Luis Alejandro Sánchez-Pérez, Juan Manuel Martínez-Hernández, Computer model for gait assessments in Parkinson's patients using a fuzzy inference model and inertial sensors, Artificial Intelligence in Medicine, Volume 160, 2025, 103059, ISSN 0933-3657, https://doi.org/10.1016/j.artmed.2024.103059. (https://www.sciencedirect.com/science/article/pii/S0933365724003014)

Robust MIMO Transformations from Level 2 from Level 3 Time Series (Stochastic Processes) - Motion Code

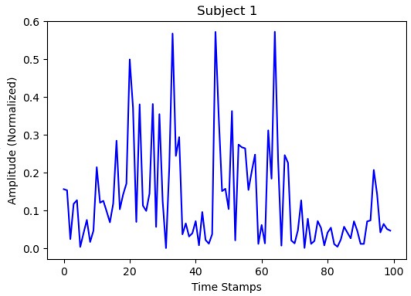
Level 3 Feature	Level 2 Features
Bradykinesia. (Slowness of Movement)	Speed of Gait<1m/s; Cadence<90 steps/min; Stride time < 1.3 sec [1]
Hypokinesia (Reductio of Amplitude)	Right and Left Arm amplitude <20° peak to peak angular displacement [2]
Asymmetry (Noticeable difference in severity of symptoms (tremor, rigidity, between left and right	ASA_U>20% difference between limbs; SYM_U<0.8(ratio of weaker to stronger limb) [3]
Dyscoordination (inability to execute movements smoothly efficiently)	STEP_SYM_U<0.8; TRA_U>0.5 [4]
Smoothness Loss	R_JERK_U,L_JERK_U>1.5 normalized jerk units [5]
Gait Variability	STR_CV_U>3 coefficient of variation, STEP_REG_U<0.7 autocorrelation [6]
Postural instability	SW_VEL_OP >0.8m/s ; SW_PATH_OP > 100 cm during 30 second stance [7]

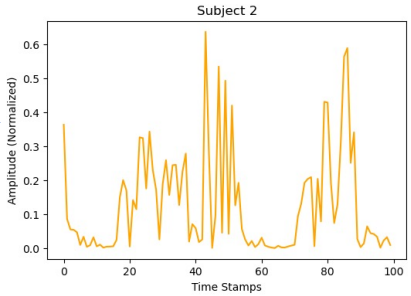
[1] Washabaugh et al. 2017: https://pubmed.ncbi.nlm.nih.gov/28433867/
[2] Warmerdam et al. 2020: https://www.mdpi.com/1424-8220/20/20/5963
[3] Lewek et al. 2009: https://e-learning.kku.ac.th/file.php/2024/current_topics/Arm_swing_in_PD.pdf
[4] Roemmich et al. 2012: https://pmc.ncbi.nlm.nih.gov/articles/PMC3552037/
[5] Kuhner et al. 2020: https://pmc.ncbi.nlm.nih.gov/articles/PMC7020741/
[6] Washabaugh et al. 2017: https://pubmed.ncbi.nlm.nih.gov/28433867/
[7] Horak 2006: https://pubmed.ncbi.nlm.nih.gov/16926210/

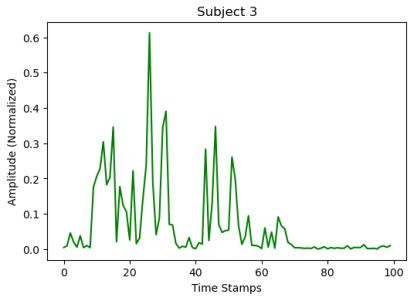
Robust Filtered Separation of a Mixture of Multi-Channel Noisy Time Series



Motion Code

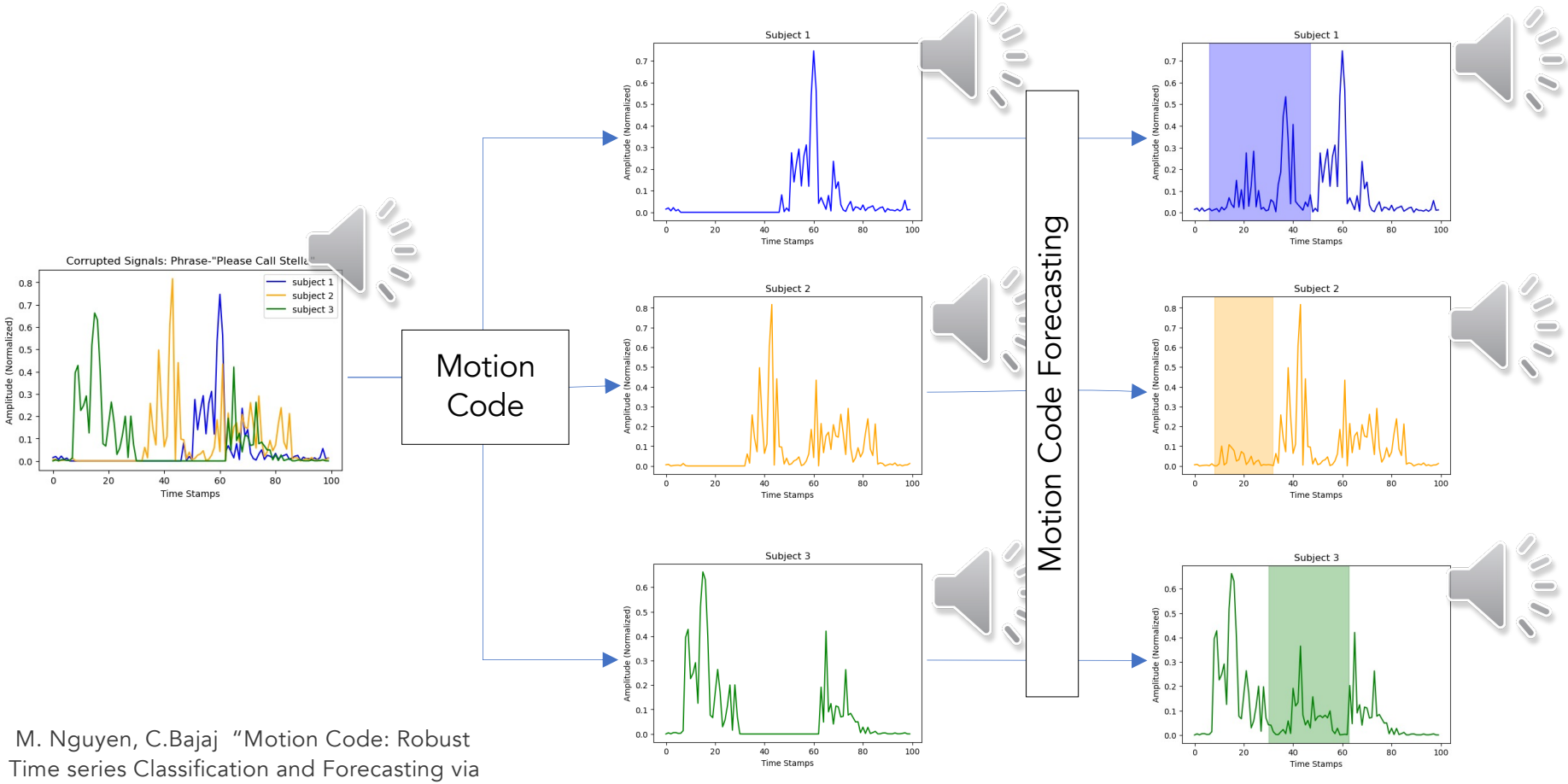






M. Nguyen, C.Bajaj "Motion Code: Robust Time series Classification and Forecasting via Sparse Variational Multi-Stochastic Processes Learning,"
arXiv:2402.14081, 2024

Robust Filtered Separation and Imputation of a Mixture of Multi-Channel Noisy Time Series



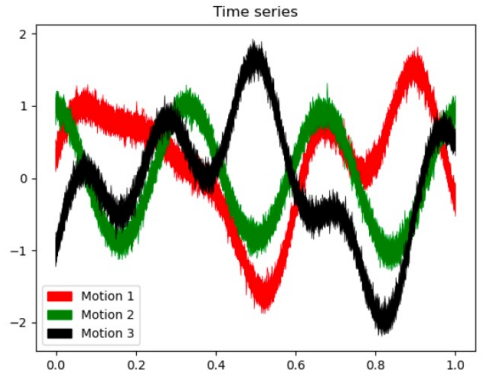
M. Nguyen, C.Bajaj "Motion Code: Robust Time series Classification and Forecasting via Sparse Variational Multi-Stochastic Processes Learning,"
arXiv:2402.14081, 2024

RobustTime Series Multi-Input Multi-Output (MIMO) Encoder

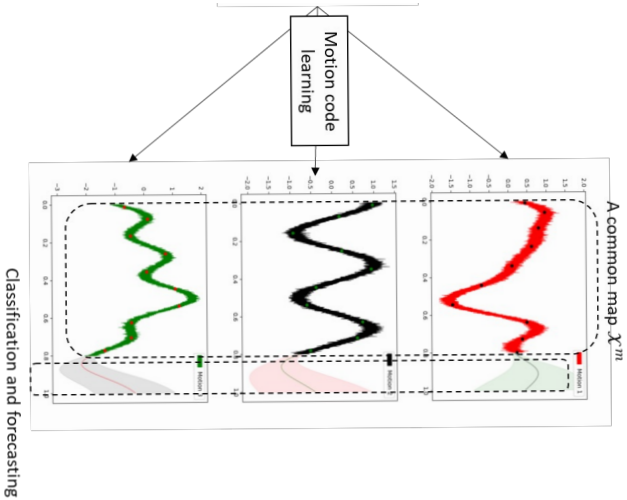
1. Input:
   - Given a collection of stochastic processes $\{S_t^k\}_{k=1}^L$.
   - For each stochastic process S_t^k, there are B_k (independent) time series sample $\{y_j^k\}_{j=1}^{B_k}$.
   - Each time series sample y_j^k is an observation data for S^k and contain a number of data points.

   For example, we can have 3 stochastic processes, and the first process has 10 time series sample. The first sample has 100 data points, the second has 200 points, and the third may only have 50 points.

2. Output: Given a new time series sample y, can we do:
   - Classification: Which stochastic process y represents?
   - Forecasting: Let say y has 100 data points with equally spaced time from 0 to 1. Can we forecast the value at time 1.05 for example?



(a) Synthetic data set with 3 time series collections



M. Nguyen, C.Bajaj "Motion Code: Robust Time series Classification and Forecasting via Sparse Variational Multi-Stochastic Processes Learning,"
arXiv:2402.14081, 2024

MIMO-Variational Inference with Motion Code

Definition 3. *Suppose we are given a stochastic process* $G = \{g(t)\}_{t\geq 0}$ *and a collection of time series* $\mathcal{C} = \{y^i\}_{i=1}^B$ *consisting of* B *independent time series* y^i *sampled from* G*. Each series* $y^i = (y_t^i)_{t\in T_i}$ *consists of* $N_i = |T_i|$ *data points and is called a* ***realization*** *of* G*. Let* m *be a fixed positive integer. We define the* ***generalized evidence lower bound function*** $\mathcal{L} = \mathcal{L}(\mathcal{C}, G, S^m, \phi)$ *as a function of the data collection* $\mathcal{C}$*, the stochastic process* G*, the* m*-elements timestamps set* $S^m = \{s_1, \cdots, s_m\} \subset \mathbb{R}_+$*, and a variational distribution* ϕ *on* $\mathbb{R}^m$*:*

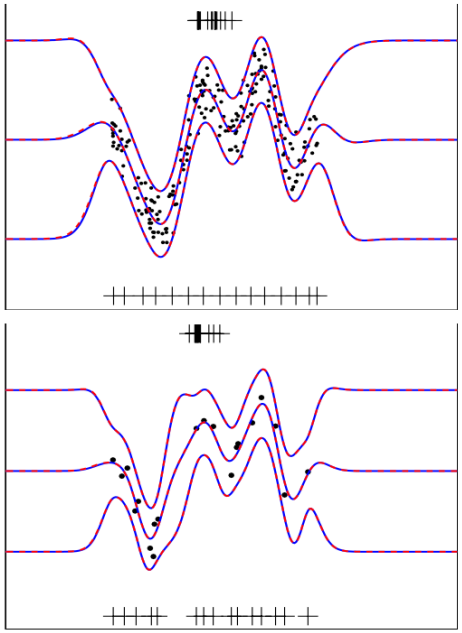
$$\mathcal{L}(\mathcal{C}, G, S^m, \phi) := \frac{1}{B}\sum_{i=1}^{B}\int p(g_{T_i}|g_{S^m})\phi(g_{S^m})\log\frac{p(y^i|g_{T_i})p(g_{S^m})}{\phi(g_{S^m})}dg_{T_i}dg_{S^m} \quad (3)$$

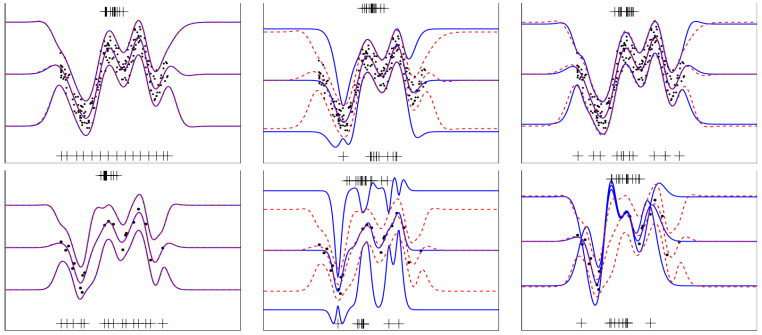
Again, the vectors g_{T_i} *and* g_{S^m} *are the signal vectors* $(g(t))_{t\in T_i} \in \mathbb{R}^{|T_i|}$ *and* $(g(t))_{t\in S^m} \in \mathbb{R}^{|S^m|}$ *on timestamps* T_i *of* y^i *and on* S^m*.*

Definition 4. *For a fixed* $m \in \mathbb{N}$*, the* m*-elements set* $(S^m)^* \subset \mathbb{R}^+$ *is said to be* ***the most informative timestamps*** *with respect to a noisy time series collection* $\mathcal{C}$ *of a stochastic process* G *if there exists a variational distribution* ϕ^* *on* $\mathbb{R}^m$ *so that:*

$$(S^m)^*, \phi^* = \arg\max_{S^m,\phi} \mathcal{L}(\mathcal{C}, G, S^m, \phi) \quad (4)$$

Also define the function $\mathcal{L}^{max}$ *such that* $\mathcal{L}^{max}(\mathcal{C}, G, S^m) := \max_\phi \mathcal{L}(\mathcal{C}, G, S^m, \phi)$*. Hence,* $(S^m)^*$ *can be found by maximizing* $\mathcal{L}^{max}$ *over all possible* S^m*.*





PD_Beat Dream Challenge

Dataset	Train	Test	Length	Description
CIS-PD 1	20	322	257-1665	Parkinson's disease sensor data focusing on understanding recovery stage
CIS-PD 2	24	429	208-1665	Parkinson's disease sensor data focusing on detecting tremor patterns

Parkinson's Disease Sensor Data: The Parkinson data are derived from the Clinician Input Study (CIS-PD) [1, 2], a 6-month project using Apple Watch devices to monitor patients during clinic visits and at home.
For two days before each clinic visit, patients reported symptoms every 30 minutes, focusing on medication state and tremor severity. The accelerometer data was segmented into 20-minute intervals.

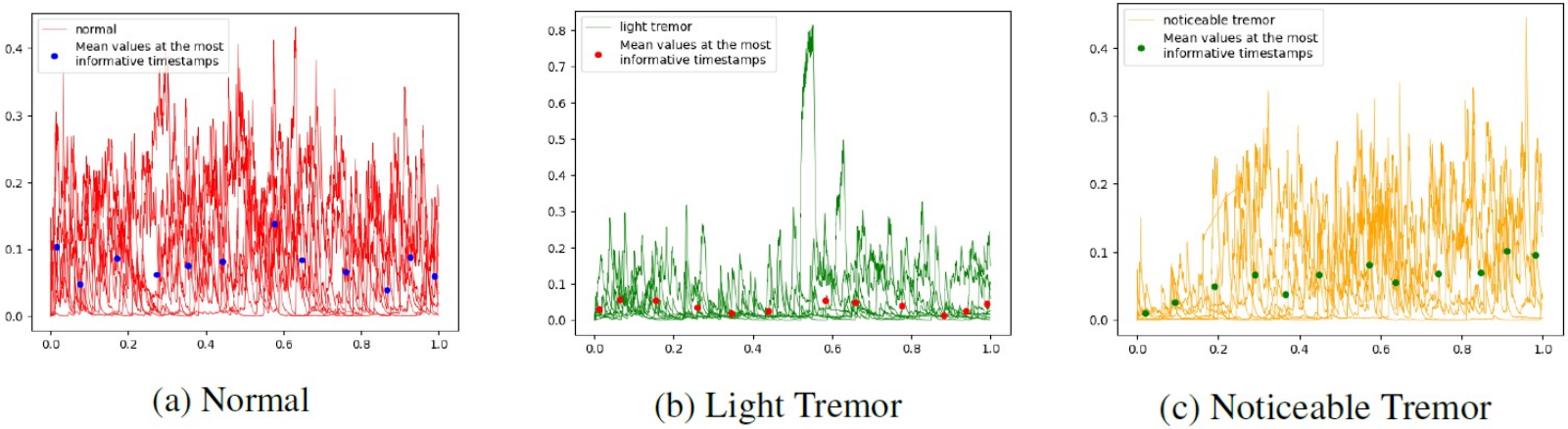
The above Parkinson data were obtained from the Biomarker & Endpoint Assessment to Track Parkinson's disease DREAM Challenge.
https://www.synapse.org/Synapse:syn20825169/wiki/600898.

During data processing, all personal identifying information (PII) has been thoroughly removed from the dataset to ensure privacy and data security.

Application of Motion Code (1/3)

The **important timestamps** of Motion Code captures a skeletal approximation of the underlying stochastic process even though the individual realizations deviates from the mean process.

Allows us to **visualize the global features of the underlying dynamics** which might not evident at first glance.



(a) Normal (b) Light Tremor (c) Noticeable Tremor

Fig1: Interpretable Features Showing Tremor Patterns And Disease Stages For Parkinson Data

Application of Motion Code (2/3)

Motion code can handle timeseries data with different/missing timestamps due to its ability to learn the underlying dynamics using important timestamps.

For Parkinson's dataset (PD), Motion Code efficiently handles out-of-sync timestamps and missing values.

PD time series of wearable sensors vary in length from 200 to 1660 points. Traditional techniques interpolate data, which causes distortion. Motion code circumvents it, thereby preserving data integrity.

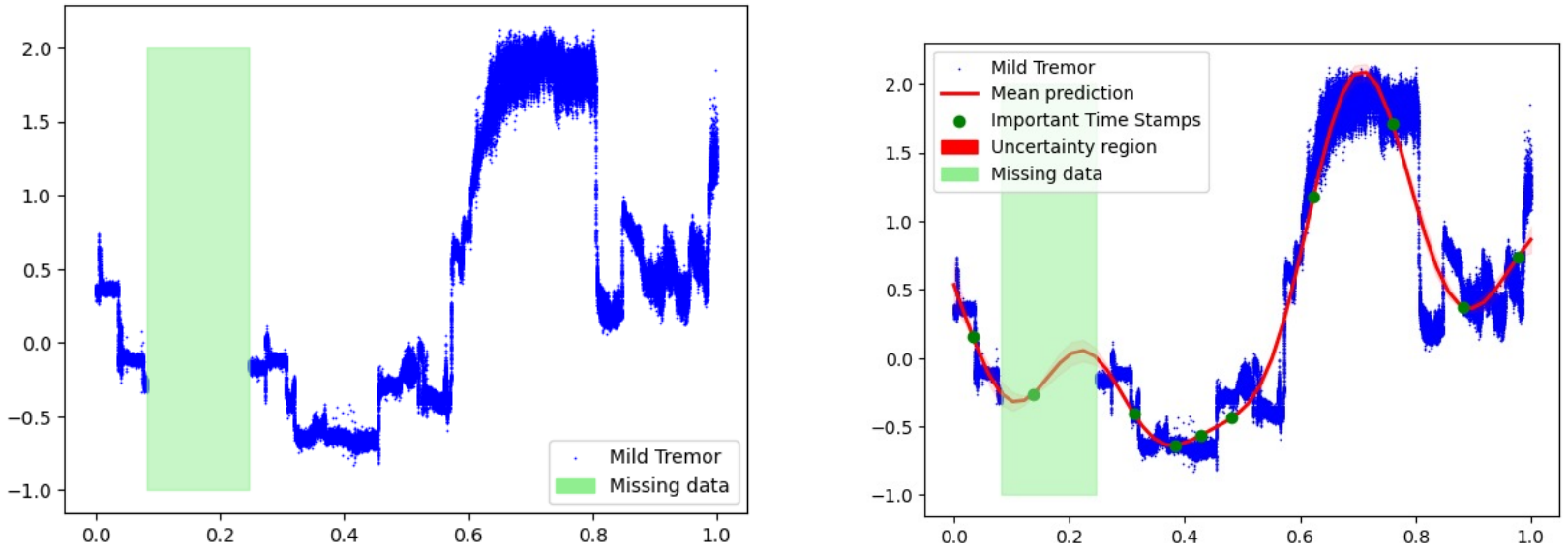
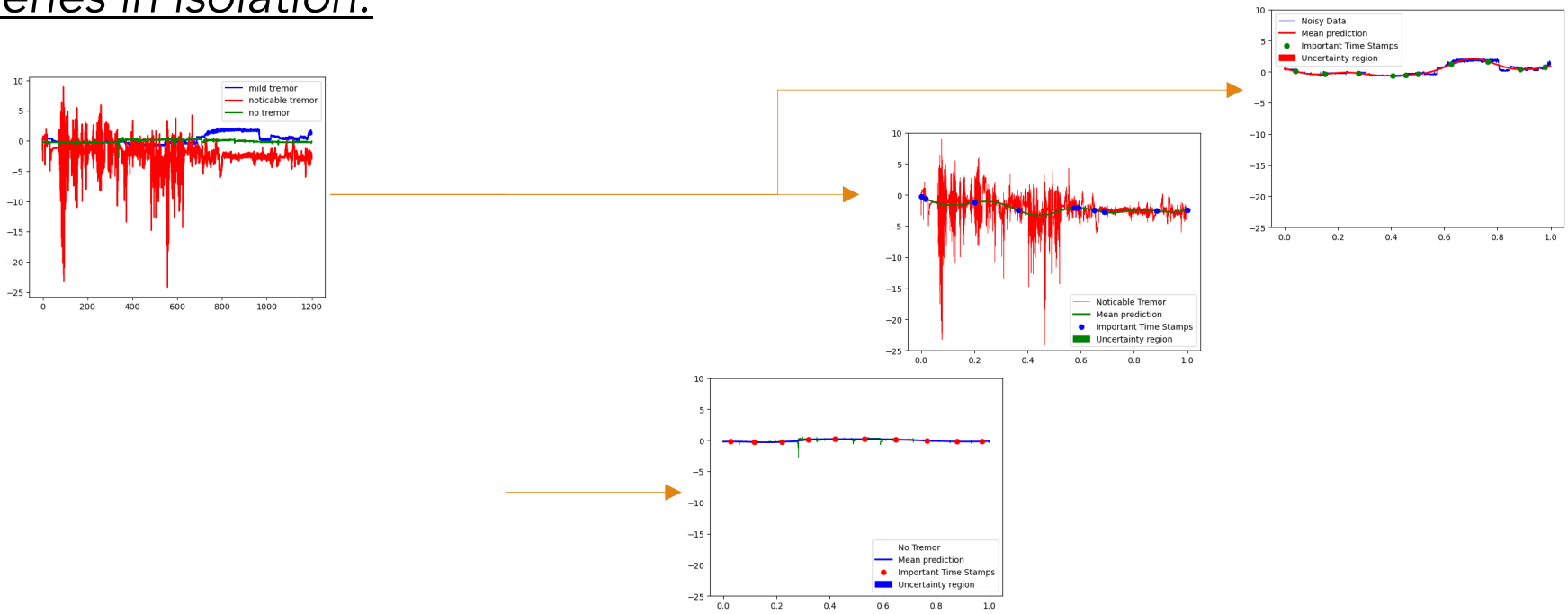


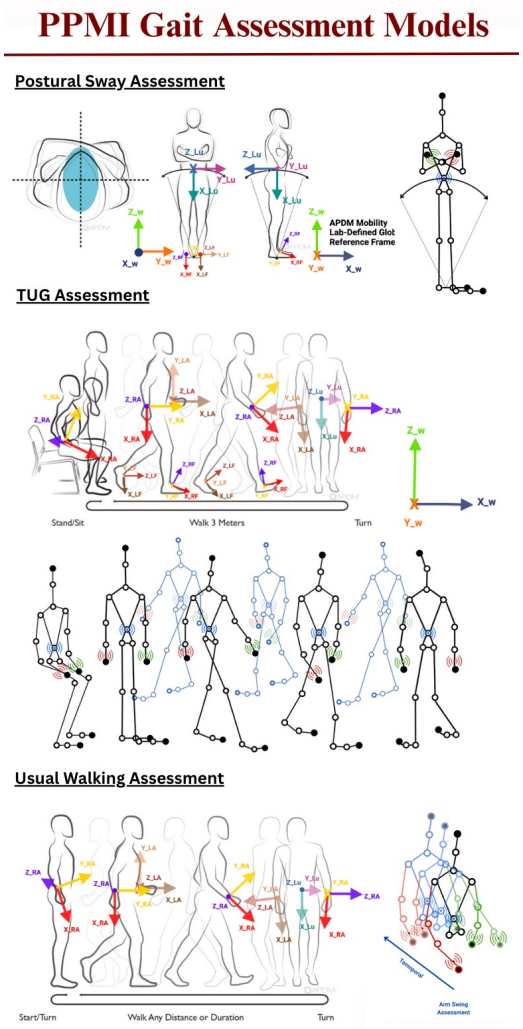
Fig2: Motion Code Handling missing data in PD smartphone accelerometer sensor data

Application of Motion Code (3/3)

Motion Code employs a *multi-stochastic process learning approach* across multiple time series, enabling it to capture relationships and patterns that might be missed by algorithms that *analyze individual series in isolation.*



Differential Diagnosis on PPMI Gait/Arm Swing data

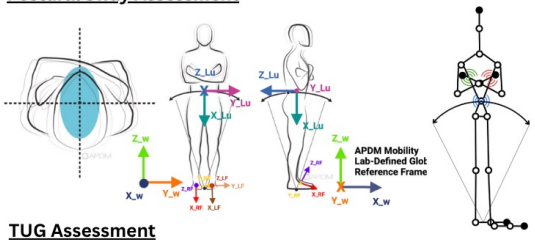


Level 3: Motion Code Classification/Quantification

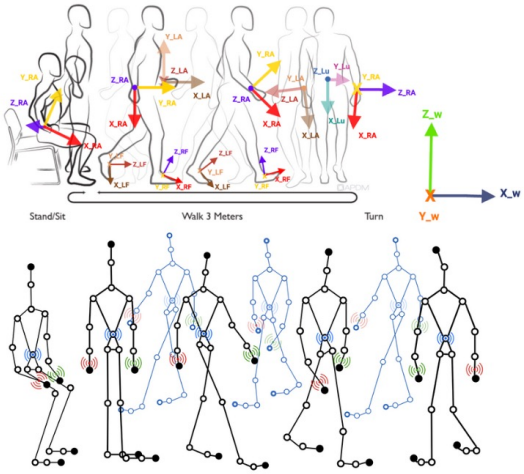
Motor Sign	Derived From Features	Typical Cutoffs / Indicators	Clinical Relevance
Bradykinesia	SP_U, SP_DT, TUG1_DUR, TUG2_DUR	**↓ speed, ↑ duration**	**Slowness** of movement
Hypokinesia	RA_AMP_, LA_AMP_, T_AMP_*	**↓ amplitude**	**Smaller range of motion**
Asymmetry	ASA_, ASYM_IND_, SYM_, STEP_SYM_, TRA_*	**↑ asymmetry indices**	Often **early sign**; **lateralized dysfunction**
Dyscoordination	STEP_SYM_, TRA_, TUG_TURNS_DUR	**↓ synchronization**	Interlimb or **postural desynchronization**
Smoothness Loss	JERK_*	**↑ jerk**	**Loss of fluidity**; may relate to **FOG**
Gait Variability	STR_CV_, STEP_REG_	**↑ Coefficient of variation, ↓ regularity**	Marker of **instability**, **fall risk**
Postural Instability	SW_VEL_, SW_PATH_, SW_FREQ_*	**↑ sway parameters**	**Reduced control** during quiet **stance**

PPMI Gait Assessment Models

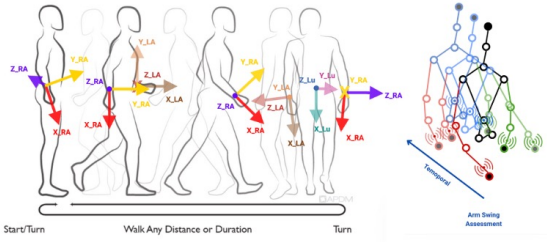
Postural Sway Assessment



TUG Assessment



Usual Walking Assessment



Level 4: Phenotypic Patterns/Profiles Sub-Typin

Phenotype	Dominant Signs	Sensor Feature Patterns	Diagnosis Risk
Unilateral Early PD	**Asymmetry, hypokinesia**	**↑ ASA, ↓ RA_AMP** or **LA_AMP, ↑ ASYM_IND**	**High likelihood of PD**
Bilateral PD	**Bradykinesia, dyscoordination**	**↓ AMP, ↓ speed, ↓ symmetry, ↑ STR_CV**	**Advanced PD**
SWEDD (Scans Without Evidence of Dopaminergic Deficit)	**Mild motor signs, normal coordination**	**Normal AMP & symmetry, mildly ↓ speed**	**No progression; false positive PD**
Prodromal PD	**Subclinical signs**	**Mild ↑ turn time, ↑ ASA, ↓ sync**	**Early indicator; risk of conversion**
Freezing of Gait	**High variability, poor turns, jerk**	**↑ TUG_TURNS_DUR, ↑ jerk, ↓ smoothness, ↑ STR_CV**	**Fall risk; late-stage PD**

Progressive AI Inference and Visualization Architecture

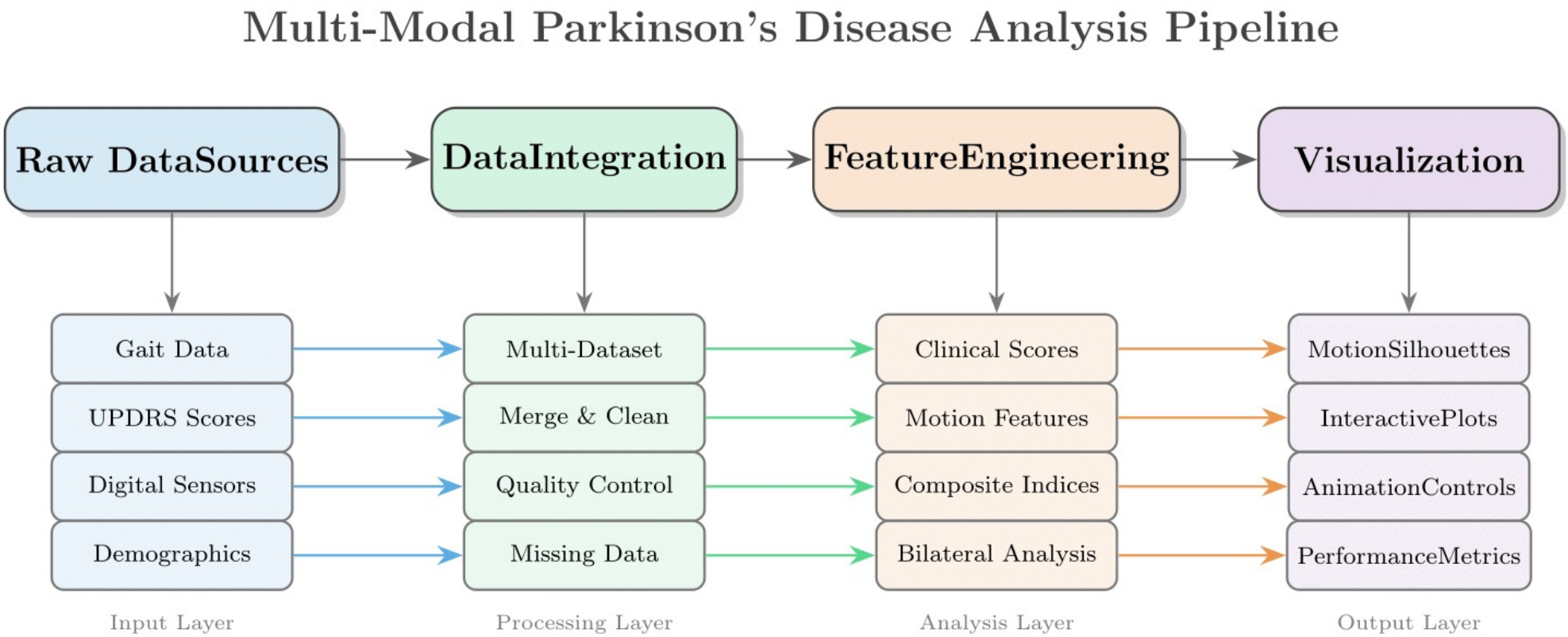


Figure 1: End-to-end pipeline architecture for multi-modal Parkinson's disease motion visualization system. The system transforms raw clinical data through integrated processing and feature engineering to produce real-time anatomically-accurate motion silhouettes and interactive analysis tools.

Select Patient: Patient 40553

Motion Test Type: Gait/Walking Test

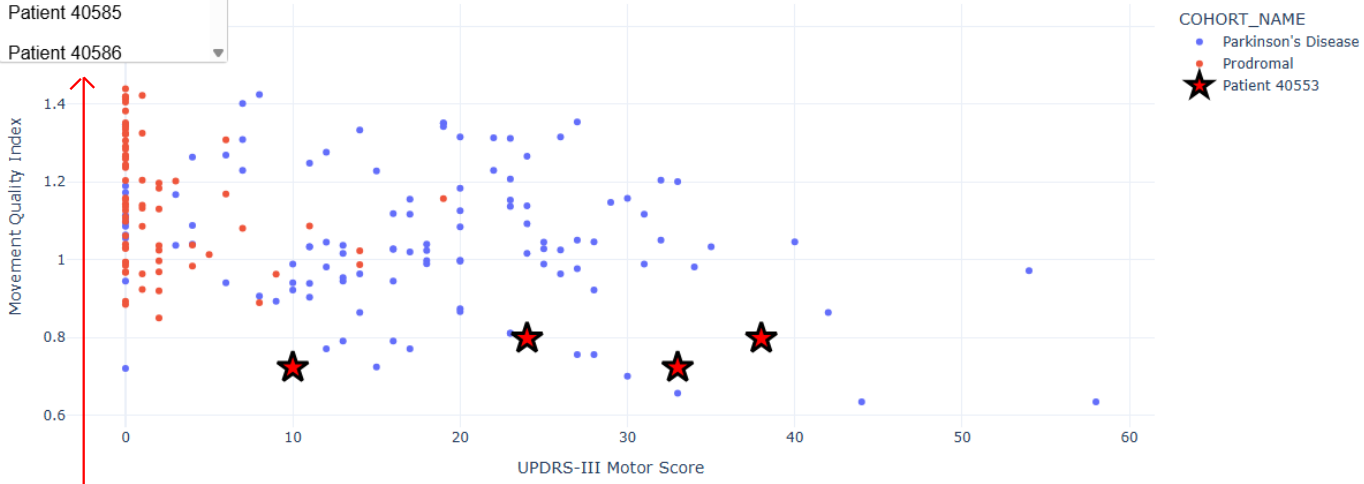
Animation Speed: 0.5x 1

X-Axis Feature: UPDRS-III Motor Score

Y-Axis Feature: Movement Quality Index

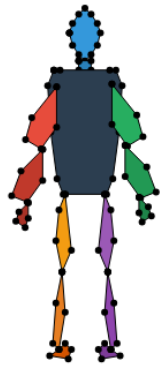
- Patient 40553
- Patient 40555
- Patient 40567
- Patient 40578
- Patient 40585
- Patient 40586

nt Quality Index vs. UPDRS-III Motor Score



Real-Time Motion Silhouette

Motion: Gait (Phase: 4.69)



0.84 m/s

27.994

Ability to choose specific patient

See how patient does on different standardized motor assessments

1. Gait/Walking Test: How a person walks
2. Tug Test: Time it takes a person to perform a sequence of actions
3. Postural Sway/Balance: Measures person's ability to maintain balance while standing still
4. Free Motion: Visualization movement patterns that don't' fit into a standardized test

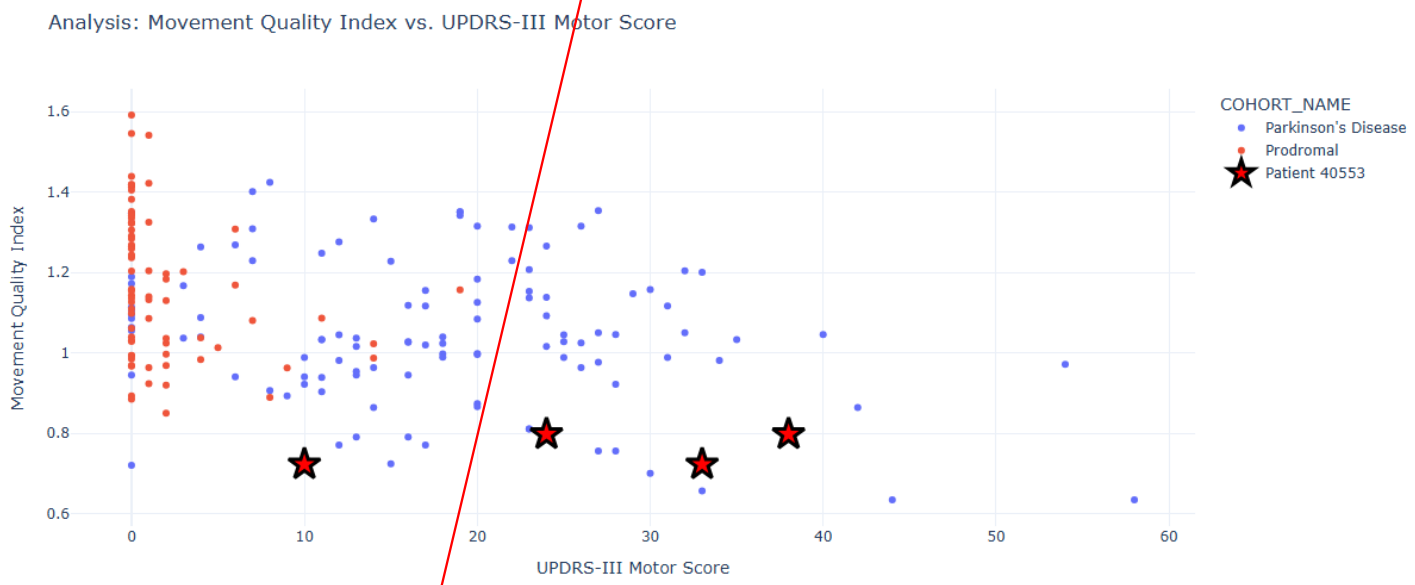
Select Patient: Patient 40553 ×

Motion Test Type: Free Motion ×

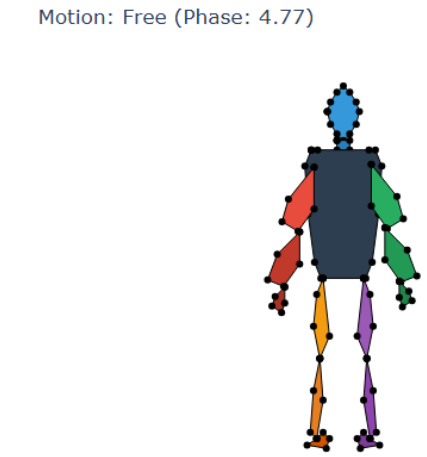
Animation Speed: 0.5x 1

X-Axis Feature: UPDRS-III Motor Score

Y-Axis Feature: Movement Quality Index



Real-Time Motion Silhouette



Control animation speed

Choose different measurements on x-axis

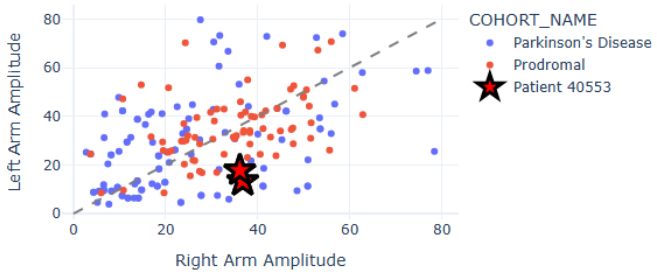
1. UPDRS-III Motor Score: Standard clinical score to rate severity of patient's motor symptoms
2. Objective Motor Impairment: Score calculated from sensor data of overall motor function
3. Gait Speed (m/s): Patient's walking speed
4. Arm Swing Asymmetry: Difference in swing between left and right arm during walking
5. Digital Sensor Response (Mean): Patient's average performance across all fine-motor tasks

Choose different measurements on y-axis

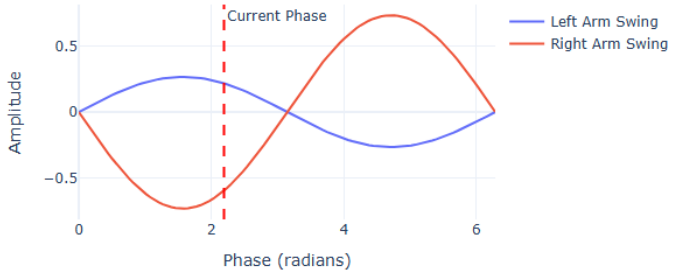
1. Movement Quality Index: Score to represent smoothness, control, and efficiency of patient's movements
2. Objective Motor Impairment: Score calculated from sensor data of overall motor function
3. Gait Speed (m/s): Patient's walking speed
4. Bilateral Coordination Score: Score measures how well the left and right sides of body work together during movements
5. Sensor-Clinical Correlation: Score to evaluate how closely the objective sensor data aligns with UPDRS score

Dynamic Motion Analysis Dashboard

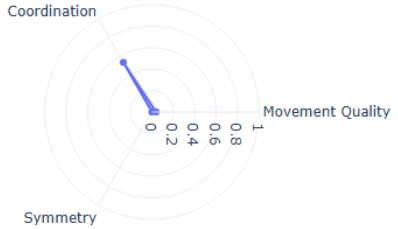
Bilateral Arm Movement Asymmetry



Gait Cycle - Patient 40553



Motion Quality - Patient 40553



Motion Animation Controls

Play | Pause | Reset | Animation playing

Measures asymmetry in arm swing

Dashed Line shows perfect symmetry

Chart visualizes one full walking cycle

X-Axis: Represents phase of gait cycle, measured in radians

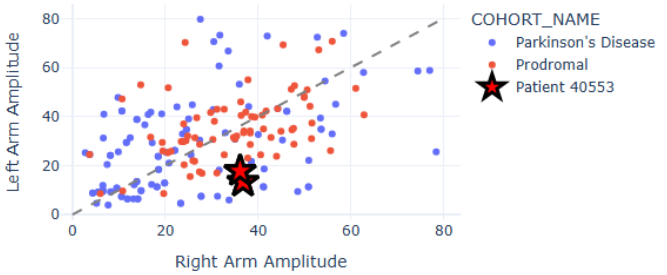
Y-Axis: Shows Amplitude, which is the forward and backward position of the arms

Visualizes three different aspects of movement:

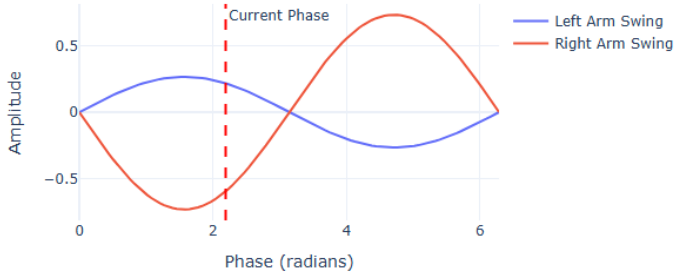
1. Coordination: How well patient's limbs move together in a synchronized way
2. Movement Quality: Represents smoothness and control of patient's movements
3. Symmetry: Measures balance between left and right sides of the body

Dynamic Motion Analysis Dashboard

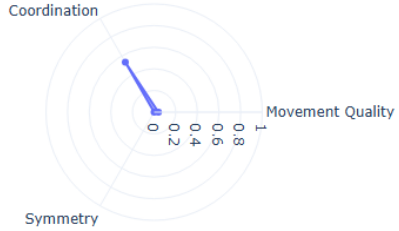
Bilateral Arm Movement Asymmetry



Gait Cycle - Patient 40553



Motion Quality - Patient 40553

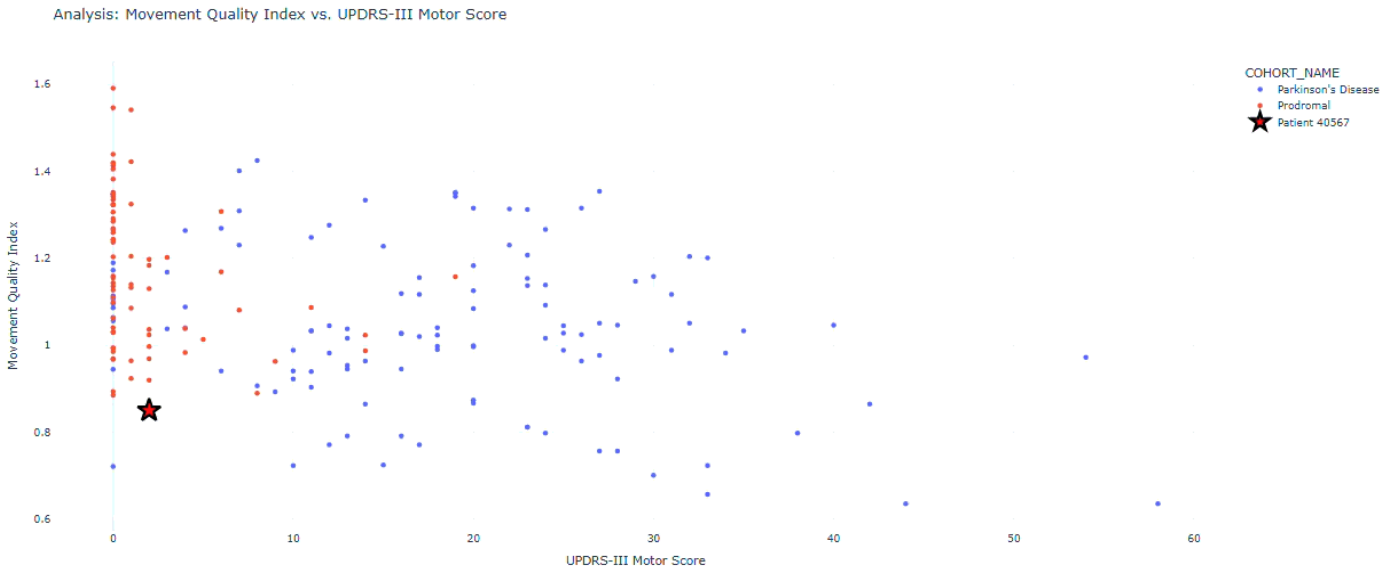


Motion Animation Controls

Play | Pause | Reset | Animation playing

Control Animations

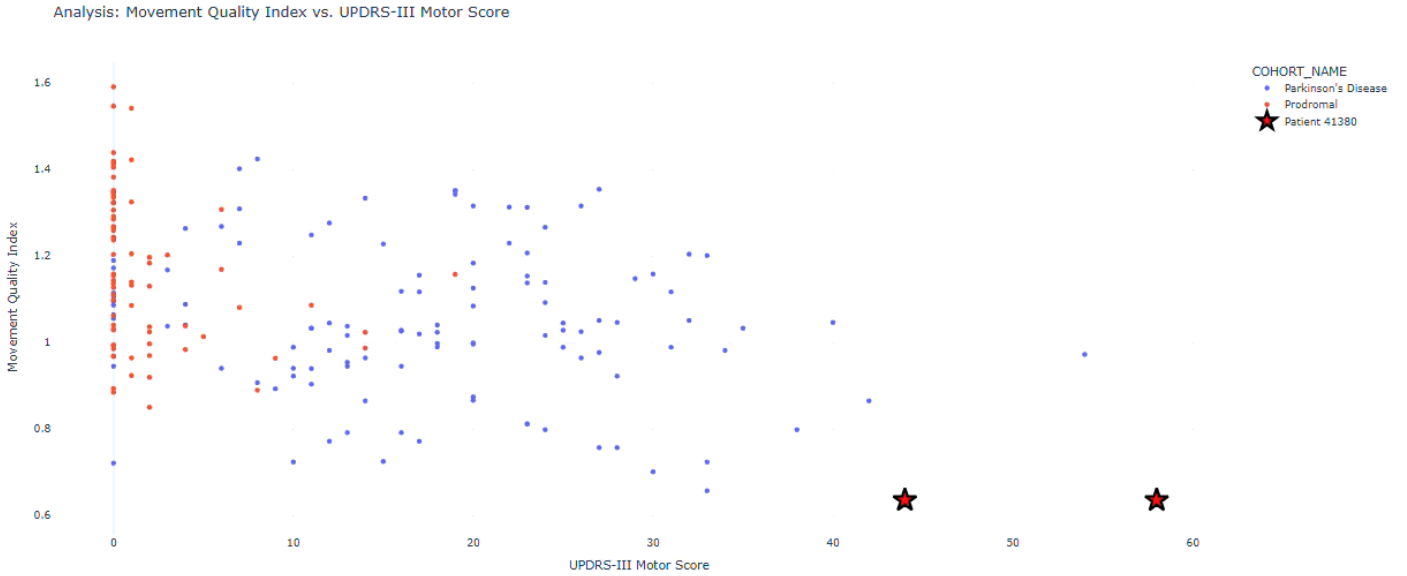
Demonstration of Patient with Low PD (2)



Gait Speed: 0.97 m/s

Arm Swing asymmetry: 23.303

Demonstration of Patient with Severe PD (44 & 58)



Gait Speed: 0.65 m/s

Arm Asymmetry: 14.734

Challenges & Way Forward

While **multi-modality differential diagnosis** and **individualized interventions** offer significant promise, several challenges remain:

I. Validation and Standardization: Validating diagnostic tools and ensuring consistent results across different research centers is crucial for widespread clinical application.

II. Data Standardization and Regulatory Hurdles: Standardizing data across diverse populations and addressing regulatory concerns regarding data usage are essential for integrating AI into clinical practice.

III. Cost and Accessibility: Some diagnostic and treatment options can be expensive and require specialized expertise, limiting accessibility for many patients.

Despite these challenges, the continued development of **Progressive AI** and advancements in understanding the multifaceted nature of Parkinson's disease hold immense potential for *revolutionizing precision individualized diagnosis and treatment.*

Acknowledgement

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Level 5: Clinical Diagnoses

Diagnosis	Clinical Criteria	Sensor Contribution	Key Differentiators
Parkinson's Disease (PD)	**Bradykinesia + tremor/rigidity + DAT deficit**	**↓ AMP, ↑ ASA, ↑ STR_CV, ↑ jerk**	**Progressive signs**; matches sensor profile
SWEDD	**Parkinsonian signs** but **normal DAT**	**Normal AMP, normal coordination**	Lack of **sensor-detectable progression**
Prodromal PD	**RBD/anosmia + mild motor changes**	**Mild ↑ turn time, mild asymmetry**	Sensor features **precede** clinical diagnosis
Healthy Control	**No motor dysfunction**	**Symmetric, stable, high amplitude + speed**	**Baseline** for comparison

Differential Diagnosis using Gait/Arm Swing Tests:

- **PD vs. Functional Parkinsonism:** Observing passive arm swing and arm swing during walking/running can help *differentiate functional Parkinsonism from PD*. In functional Parkinsonism, passive arm swing may be normal even with marked asymmetry during walking/running, while it typically remains reduced in PD.
- **PD vs. Atypical Parkinsonism:** *Arm swing asymmetry is a distinct characteristic of early PD,* while atypical parkinsonisms are usually associated with a more symmetrical pattern.
- **PD vs. Other Neurological Conditions:** Some *non-neurological conditions, like frozen shoulder syndrome*, can also cause unilaterally reduced arm swing, *necessitating a thorough evaluation for accurate diagnosis*.
- **Monitoring and Progression:** *Quantifying arm swing*, especially using wearable sensors, can monitor the r*esponse to dopaminergic medication and potentially track disease progression in PD.* Changes in arm swing, like decreased elbow amplitude, may even predict disease progression in conditions like *multiple sclerosis.*
- **Limitations:** In-clinic assessments can be subjective and may not accurately reflect daily life function. While wearable sensors offer continuous and objective data collection, accurately detecting and filtering out other arm activities during gait in free-living conditions remains a challenge.

The Knowledge of Genes implicated in Parkinsons Disease ?

SNCA—This gene, which makes the protein alpha-synuclein, was the first gene identified rolhat Lewy bodies seen in all cases of PD contain clumps of abnormal alpha-synuclein. This discovery revealed the link between hereditary and sporadic forms of the disease.

LRRK2—LRRK2 codes for a complex protein called *dardarin* that plays a role in many cellular functions, causing aggregation
of Lewy bodies.

DJ-1—This gene helps protect cells from oxidative stress, and mutations in this gene can cause rare, early-onset forms of PD.

PRKN (Parkin)—The parkin gene makes a protein that helps cells break down and recycle proteins. Mutations in this gene can cause early-onset PD.

PINK1—PINK1 codes for a protein active in mitochondria. Mutations in this gene appear to increase susceptibility to cellular stress.

GBA (glucocerebrosidase-beta)—Mutations in GBA cause *Gaucher disease*, a type of *lipid storage disorder*.