Prediction of individual progression rate in Parkinson’s disease using clinical measures and biomechanical measures of gait and postural stability

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Background: Parkinson’s Disease

- Parkinson’s Disease (PD) is a devastating neurodegenerative disease characterized by resting tremor, limb stiffness, and bradykinesia
- Second most common neurodegenerative disorder
- Current treatments (such as dopaminergic drugs) alleviate symptoms are not cures
Background: Problem

- There is no clinically accepted method to predict individual progression rate.
Goal of this work

- A model that can predict individual progression rate and accurately identify fast progressors.

- This would allow:
  - Informing patient decision making and patient management
  - Expedite the identification of a disease modifying therapy
    - Drug trials are expensive
      - Average total cost of developing a new drug is between $2 to $3 billion\(^1\).

- Identifying fast progressors can enrich trial selection and enabling accurate identification of effective disease modifying candidate drugs within the duration of a clinical trial (typically 2 years)

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Data: Subjects

- **160 PD subjects** from the NIH-NINDS funded Parkinson’s Disease Biomarkers Program (PDBP)
  - Followed longitudinally for 2 years at UTSW by Dr. Richard B. Dewey Jr.
  - Disease severity measured by the Movement Disorder Society revision of the Unified Parkinson’s Disease Rating Scale (MDS-UPDRS)

Age histogram

- 117 male
- 90 female
MDS-UPDRS is a four-part assessment of PD severity conducted by a trained examiner

Part III: Motor Examination
- 18 sections
- e.g. Speech, facial expression, gait
- Scale of 0 (normal) to 4 (severe)

Conducted when patients on-medication

To eliminate rater as a confound, one rater was used throughout the study

3 targets are predicted in this research:
1. 2 years MDS-UPDRS Part III
2. 2 years – Baseline MDS-UPDRS Part III
3. 2 years – Baseline MDS-UPDRS Part III
Data: Features

- Previous literature has found gait and postural stability characteristics to be associated with current risk\(^1\), progression\(^2\), and diagnosis\(^3\).

Fig. 2. Plots of the sway path in anteroposterior and mediolateral directions in a control subject (A) and two PD subjects with clinically normal balance (B, C).


Data: Features

- Biomechanical gait and postural stability measures
  - Six movement sensors (accelerometer, gyroscope, and magnetometer)
  - APDM Mobility Lab using Opals® sensors
  - Conducted when patient is on-medication
  - 2 mobility tasks:
    - instrumented Timed-Up-and-Go (iTUG) test
      - Subjects stand up, walk 6m, turn 180°, walk back to chair and sit down.
    - instrumented Sway (iSway) test
      - Subjects stand still with hands across their chests and feet positioned a set distance apart

https://www.apdm.com/mobility/
Data: Features

- iTUG video: https://www.apdm.com/mobility/
Data: Features

- Clinical and demographic features
  - Age
  - Gender
  - Baseline MDS-UPDRS Part III scores
  - Levodopa Equivalent Daily Dose (LEDD)
  - Montreal Cognitive Assessment (MOCA) score
**Methods: Feature Set combinations**

<table>
<thead>
<tr>
<th>Feature Set</th>
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<tbody>
<tr>
<td>Baseline iTUG &amp; iSway (148)</td>
</tr>
<tr>
<td>6mo-Baseline iTUG &amp; iSway (148)</td>
</tr>
<tr>
<td>Asymmetric Baseline iTUG &amp; iSway (22)</td>
</tr>
<tr>
<td>Asymmetric 6mo-Baseline iTUG &amp; iSway (22)</td>
</tr>
<tr>
<td>Clinical measures (40)</td>
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\[
1 - \frac{\text{Left measure}}{\text{Right measure}}
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Methods: Partitioning, Modeling, and Feature Importance

- **Partitioning:**
  - Nested K-fold cross validation with 3 inner and 3 outer folds

- **Optimization:**
  - XGBoost and Feed Forward Neural Network (NNs) models used
  - Hyperparameter optimization and model selection on inner folds using random search
  - Random search of hyperparameter space ensures unbiased model tuning largely independent of ML experience
  - Performance evaluated using $R^2$ score on held-out partitions

- **Feature Importance:**
  - Feature permutation importance analysis
  - Each feature randomly permuted 100 times and decrease in performance measured
Results on test set: Clinical measures have most predictive power

- Biomechanical measures alone were also able to explain a substantial 21% of variance.
- First study to show biomechanical measures have prognostic value for future severity.

- Comparable to 41% performance achieved by Latourelle et al. (2017) on validation set
- Our model also achieved a PPV of 71% in identifying fast progressors
Results: Baseline MDS-UPDRS III scores most important

- **Important clinical measures:**
  - Upper extremity, hand, neck, and total MDS-UPDRS III scores rank highest in feature importance
Results: 6mo-Baseline gait features also important

- **Important biomechanical measures:**
  - 6mo-Baseline Gait measures rank highest
Strengths, Limitations and Future work

- **Strengths**
  - This is a comparatively large (160 subjects) study performed with rigorous nested cross-validation.

- **Limitations: Single dataset:**
  - Replication on independent dataset would further confirm findings

- **Future work: learn to construct biomechanical features from raw sensor data:**
  - iTUG and iSway measures were constructed from the sensor data using the APDM Mobility Lab software
  - These pre-engineered features may lose some information that could be used by the predictive models
  - Future studies on analyzing the raw sensor data may further boost predictive power
Conclusions

- **Potential to enrich clinical trials:**
  - Our best predictive model achieves a 71% PPV in identifying fast progressors on held out test data not used in training or validation.
  - This can be used to expedite clinical trials to more rapidly identify a disease modifying drug

- **Predictive power of biomechanical measures:**
  - This is the first study to show the predictive power of biomechanical measures using machine learning
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