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Data-driven Digital Healthcare:

Developing Effective Digital Biomarkers for Parkinson's Disease

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Overview

- cloudUPDRS certified Class I Medical Device for clinical use
- Rate PD motor symptoms as precisely as an experienced clinician
- Extends and adapts Part III of the standard UPDRS protocol
- Unsupervised use at home
  - Employs accelerometer for tremor and gait measurements
  - Employs touch-screen for tapping measurements
  - No clinical or technical supervision during testing: bespoke user journey
- Data analytics

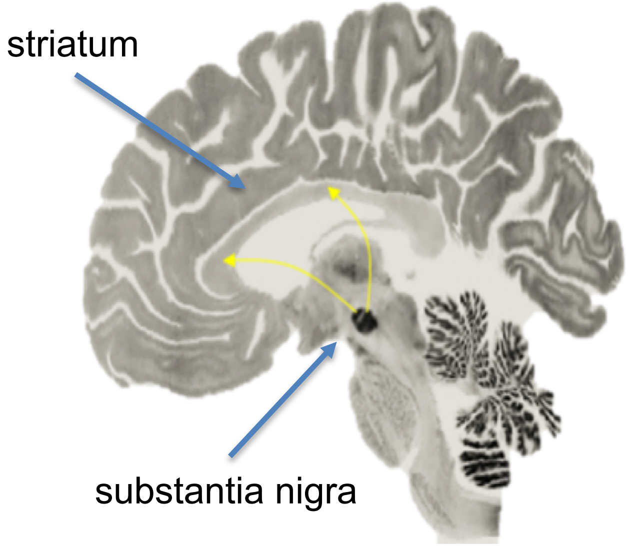
Challenges

1. Ensure unsupervised test is carried out correctly
2. Reduce testing time
3. Capture symptom variability
4. Identify high quality signal segments

People with Parkinson's

Parkinson's Disease (PD)

- No cure
- Managed mainly by replacing dopamine
- Motor symptoms
  - tremor, rigidity, slowness of movement (bradykinesia), freezing of gait, stiffness, shaking, falls
- Non-motor symptoms
  - bladder, memory, sleep, addictive behaviour, fatigue, pain, hallucinations



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Symptoms of Parkinson’s Disease

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Disease Progression

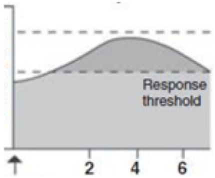
Impairment

Prodromal	Early	Moderate	Complex
Sleep disorder Loss of smell Constipation Depression	Slowness Stiffness Shaking Urgency	Anxiety Low blood pressure Dyskinesias Impulsivity Freezing	Brittle ON/OFF's Cognitive impairment Pain Hallucinations

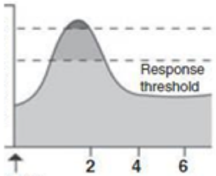
Time (years)

Levodopa response

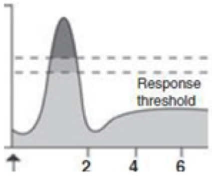
Early:



Moderate:



Complex:



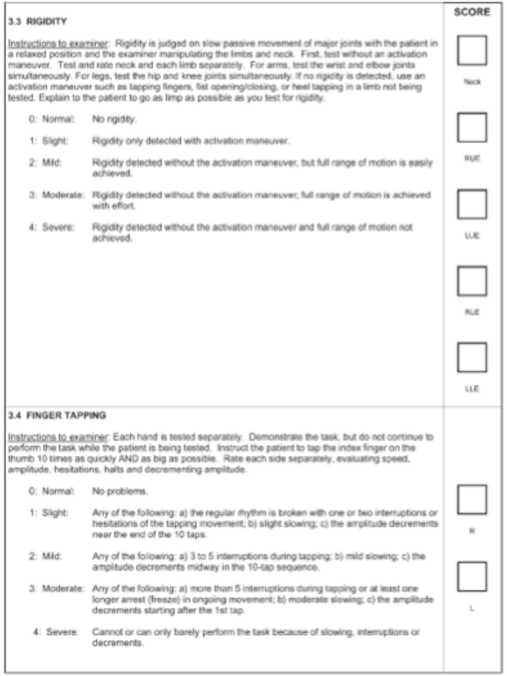
Treatments

Prodromal	Early	Moderate	Complex
?	Levodopa MAOI Agonists	COMT Agonists	Deep brain stimulation Apomorphine Duodopa

UNIFIED PARKINSON'S DISEASE RATING SCALE

- Standard clinical protocol for assessing PD
- Part III clinical assessment of motor symptoms
- Known issues:
  - time intensive
  - inter-rater variability
  - not sensitive
- Used formally
  - Drug trials
  - Consideration of advanced therapies
- Used informally as part of clinical assessment (once or twice per year) of disease progression

- Can we replace with an app?



SCORE

3.3 RIGIDITY

Instructions to examiner: Rigidity is judged on slow passive movement of major joints with the patient in a relaxed position and the examiner manipulating the limbs and neck. First, test without an activation maneuver. Test and rate neck and each limb separately. For arms, test the wrist and elbow joints simultaneously. For legs, test the hip and knee joints simultaneously. If no rigidity is detected, use an activation maneuver such as tapping fingers, fist opening/closing, or heel tapping in a limb not being tested. Explain to the patient to go as limp as possible as you test for rigidity.

0: Normal: No rigidity.

1: Slight: Rigidity only detected with activation maneuver.

2: Mild: Rigidity detected without the activation maneuver, but full range of motion is easily achieved.

3: Moderate: Rigidity detected without the activation maneuver; full range of motion is achieved with effort.

4: Severe: Rigidity detected without the activation maneuver and full range of motion not achieved.

Neck / RUE / LUE / RLE / LLE

3.4 FINGER TAPPING

Instructions to examiner: Each hand is tested separately. Demonstrate the task, but do not continue to perform the task while the patient is being tested. Instruct the patient to tap the index finger on the thumb 10 times as quickly AND as big as possible. Rate each side separately, evaluating speed, amplitude, hesitations, halts and decrementing amplitude.

0: Normal: No problems.

1: Slight: Any of the following: a) the regular rhythm is broken with one or two interruptions or hesitations of the tapping movement; b) slight slowing; c) the amplitude decrements near the end of the 10 taps.

2: Mild: Any of the following: a) 3 to 5 interruptions during tapping; b) mild slowing; c) the amplitude decrements midway in the 10-tap sequence.

3: Moderate: Any of the following: a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement; b) moderate slowing; c) the amplitude decrements starting after the 1st tap.

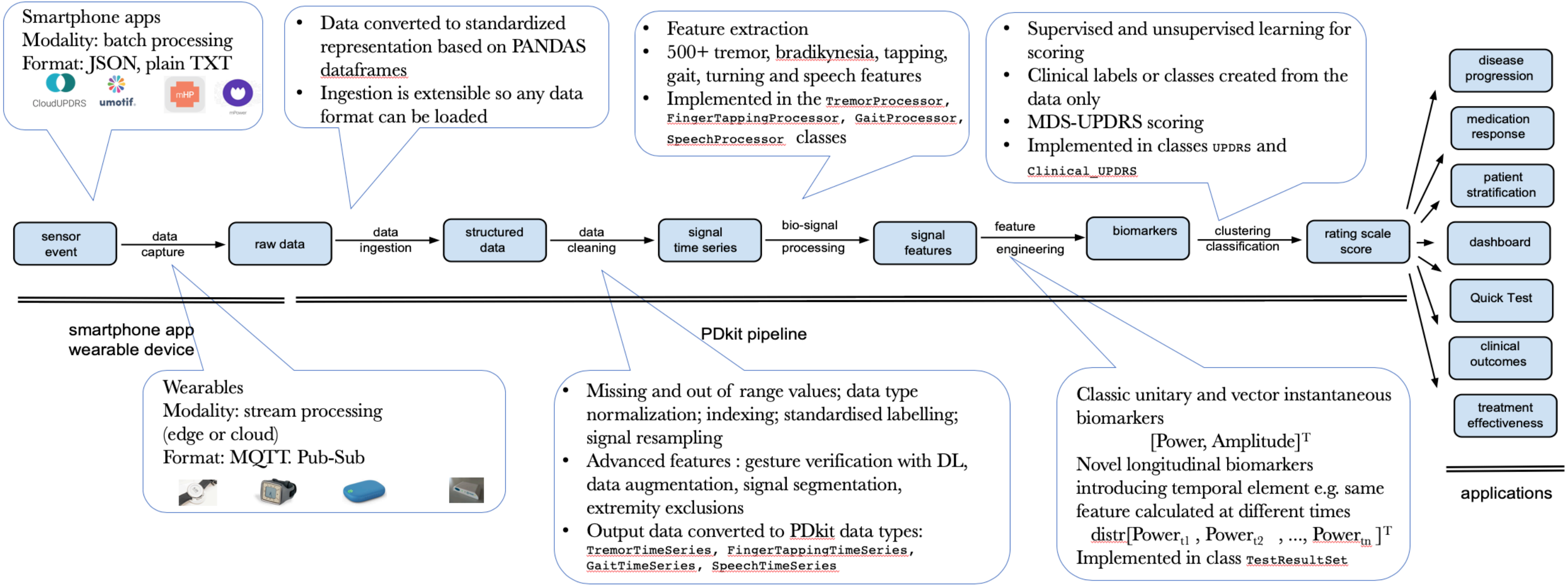
4: Severe: Cannot or can only barely perform the task because of slowing, interruptions or decrements.

R / L

Expressed use intentions

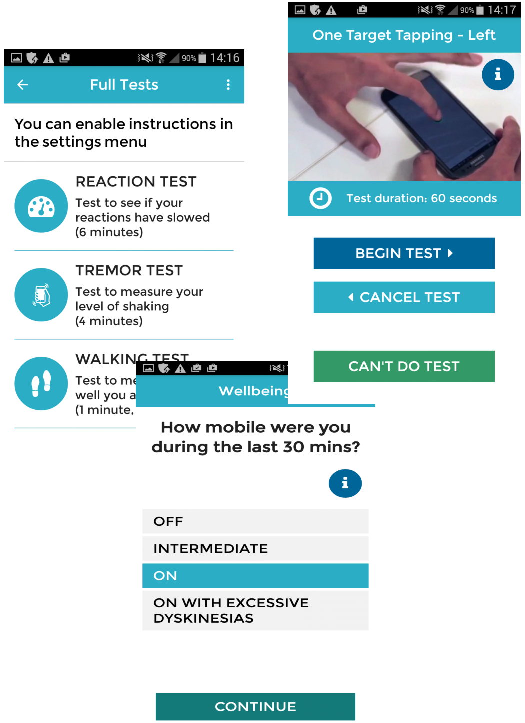
- Quantitative and qualitative methods
  - survey and audience panels
- Majority of PD patients would use app (86%)
  - Most would prefer the test to last less than 5 minutes per assessment (64%)
  - Some would accept up to 10 minutes (27%)
- Main motivation: Need to understand their condition
- No expressed privacy concerns

Information Processing Pipeline

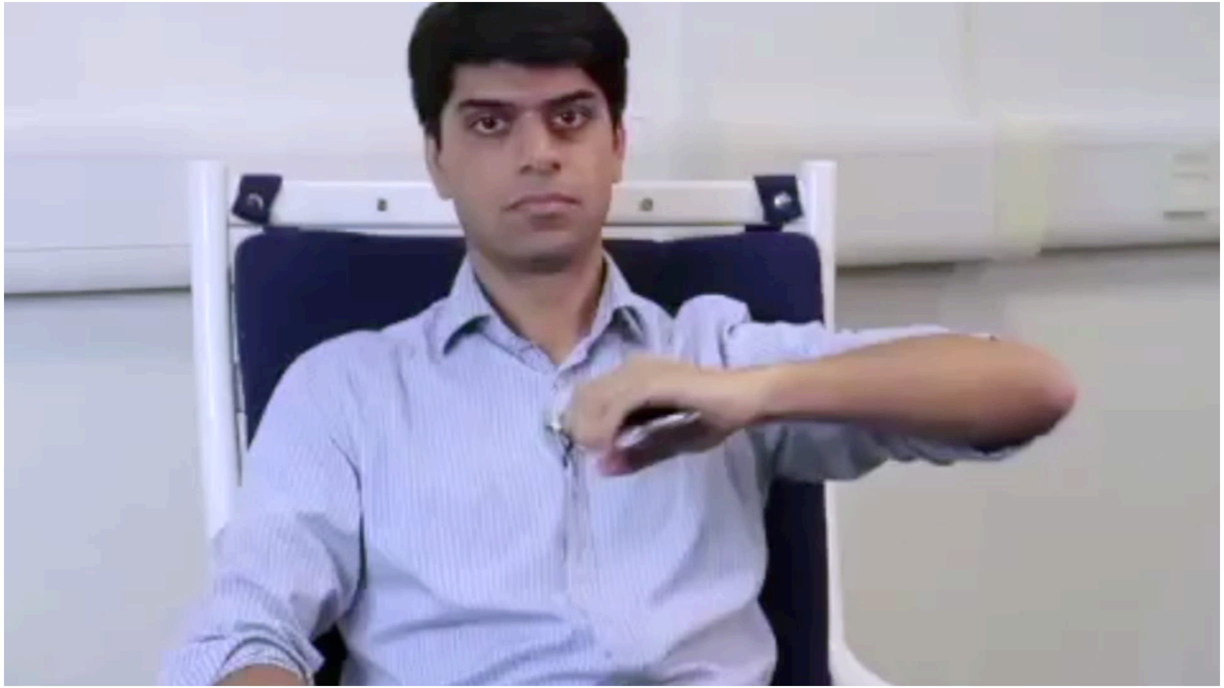


cloudUPDRS app

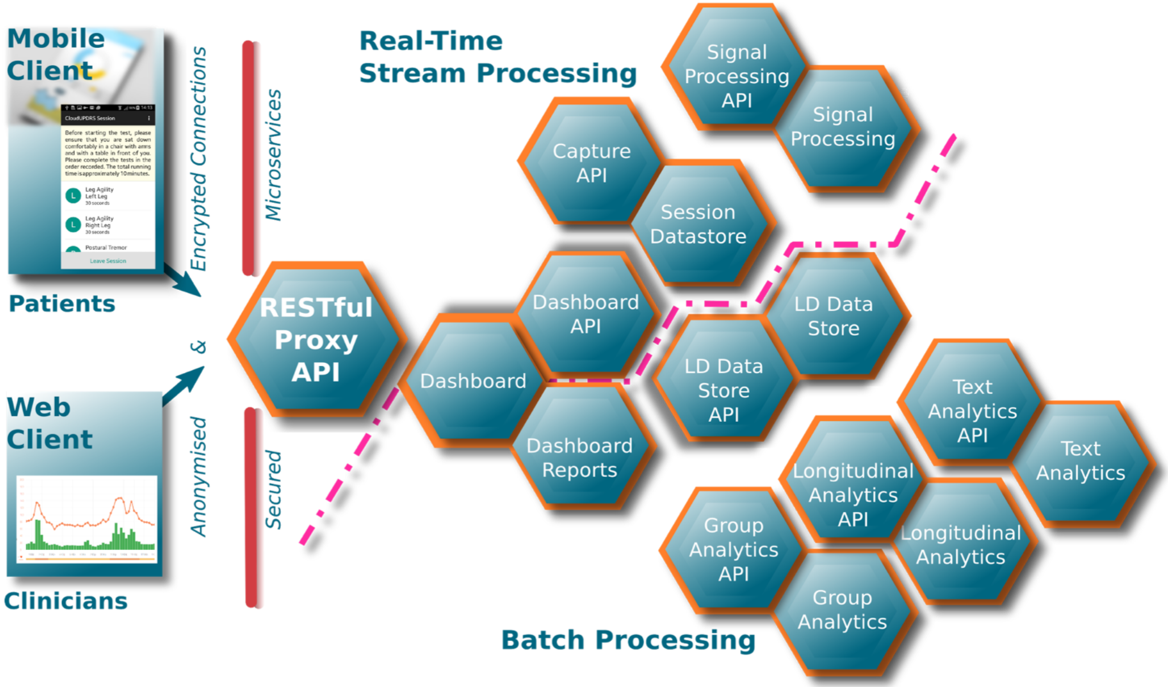
- Design objectives:
  - Sensitive to patient mobility constraints
  - Sensitive to patient cognitive impairments
- Approach:
  - Constrain user context for reliable interpretation of data
  - Encourage frequent use



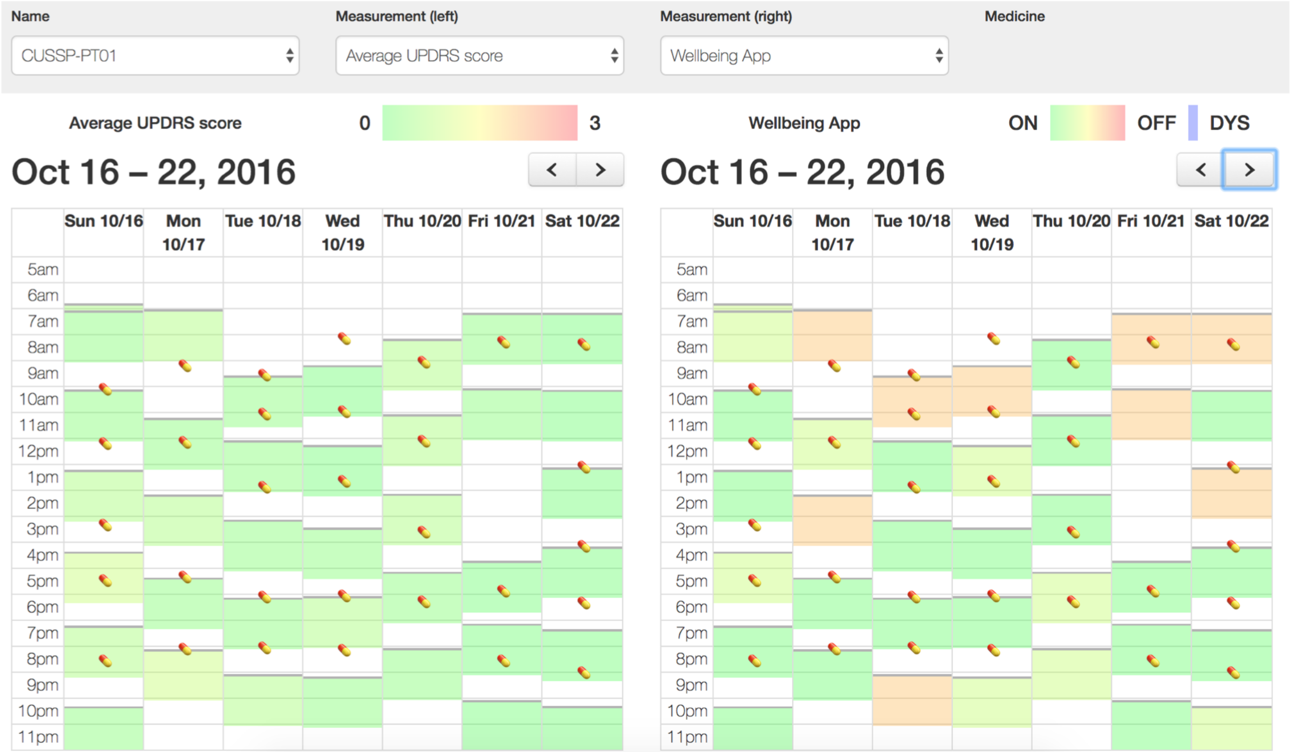
Test Movements



Architecture



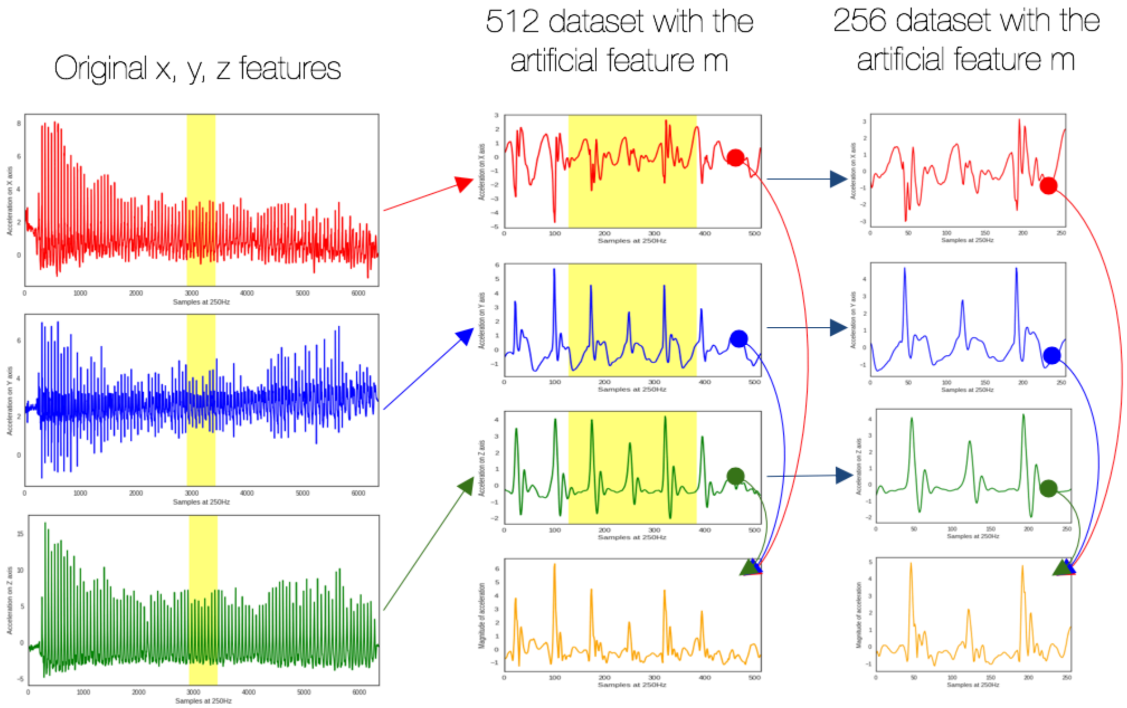
Clinical dashboard



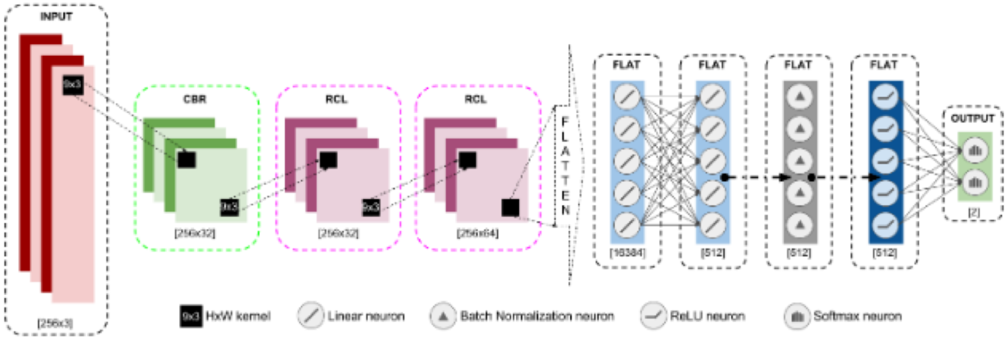
Unsupervised patient use

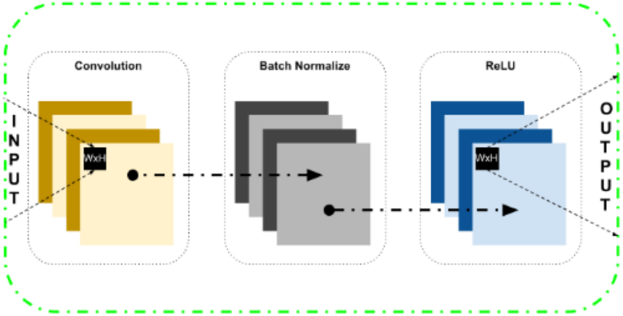
- Achieve firm user adherence to the prescribed movements
  - Accept test record only when movement executed correctly
  - Reject test when movement does not match expectations
- Use deep learning to learn movement features
- Apply offline or online (i.e. at the server on in the app)
- Use Tensorflow to learn and apply model

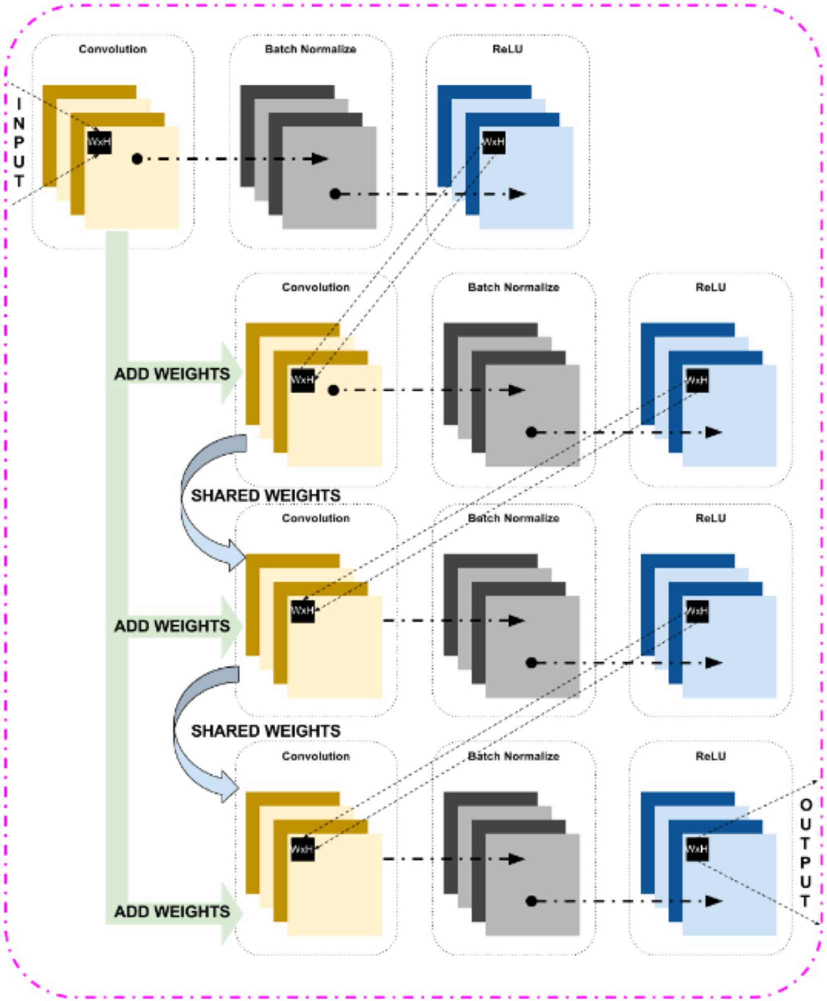
Tremor signal



Deep Learning Architecture







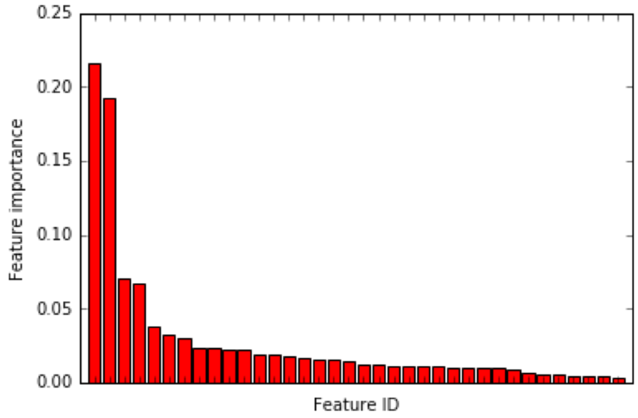
Performance using DNN

Classifiers	Accuracy	F1-score	AUC
ExtraTrees	0.73	0.79	0.83
BernoulliNB	0.73	0.79	0.83
RandomForest	0.73	0.79	0.83
GradientBoosting	0.72	0.80	0.83
Bagging	0.72	0.78	0.83
AdaBoost	0.66	0.75	0.81
GaussianNB	0.69	0.75	0.83
DMLP	0.75	0.81	0.85
RCNN	**0.78**	**0.82**	**0.87**

	TP	(%)	FN	(%)	TN	(%)	FP	(%)
ExtraTrees	141.52	93	8.98	6	13.36	17	63.14	82
BernoulliNB	146.23	**96**	4.27	**3**	6.92	8	69.58	91
RandomForest	138.39	91	12.11	8	16.19	20	60.31	79
GradientBoosting	146.02	**96**	4.48	**3**	8.12	10	68.38	89
Bagging	135.58	89	14.92	10	18.03	23	58.47	76
AdaBoost	128.0	84	22.5	15	17.34	22	59.16	77
GaussianNB	116.01	76	34.49	23	35.41	45	41.09	54
DMLP	135.73	89	15.77	10	28.19	37	49.31	63
RCNN	133.22	87	18.28	12	38.38	**50**	39.12	**50**

Quick Test

- UPDRS exhaustive search of all possible symptoms
- Each patient presents only a few
- Symptoms typically change slowly e.g. 6 months
- ~6 features are predictive of overall score
- Use ML to identify the specific tests that offer the highest inferential power
  - Observer five full tests
  - Apply standard ensemble of randomized decision tree method to rank tests according to predictive strength
  - Select top 3 tests for individualised quick test



Raw Observations to Biomarkers

1. Digital biomarkers critical for precise disease progression monitoring
2. Google Scholar: 1,000+ papers on Parkinsonian tremor using accelerometers and ML in 2018-19
   - Impossible to replicate and to compare results
   - Differences in data processing and algorithm implementation
   - In most cases, insufficient details provided to replicate algorithm used
3. Common pattern emerging:
   - Machine Learning processing pipeline
   - From raw data to severity assessment (often using MDS-UPDRS scores)

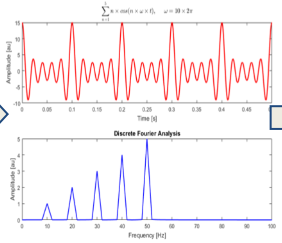
Example: Tremor processing pipeline

From raw accelerometer data to UPDRS score (0-4 scale)

Rest Tremor of the Left Hand

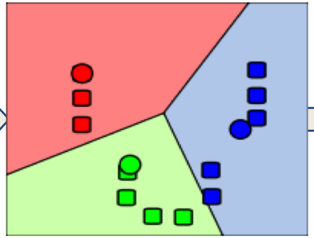
Raw data		
1.2	30.2	0.1
2.1	31.1	0.1
1.6	37.1	0.2
1.2	25.5	0.0
1.3	34.2	0.4
2.1	29.1	0.3
...	...	...

Fast Fourier Transform + Biomarker extraction



Digital biomarkers		
25.1	0.95	12.1

Clustering and Classification



UPDRS: 2

Open Source PDkit for python on github

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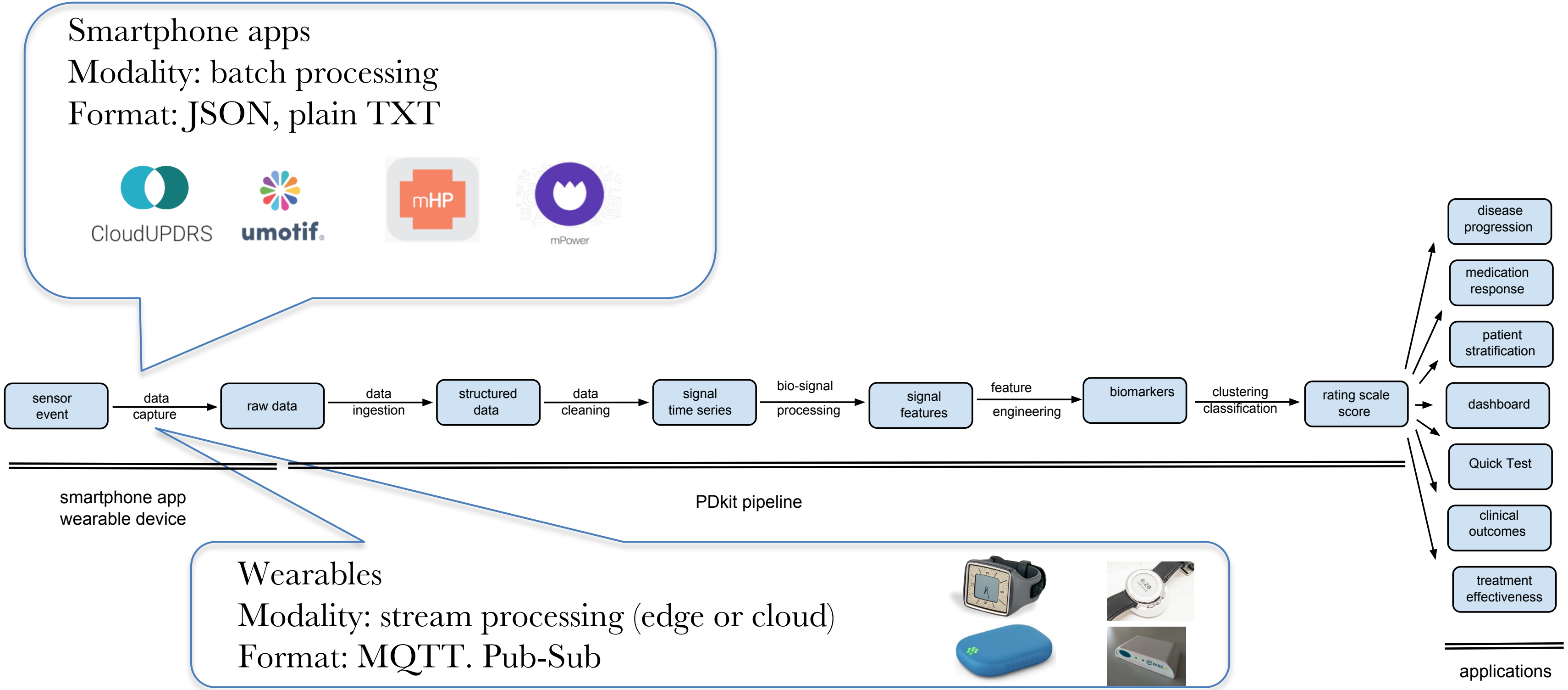
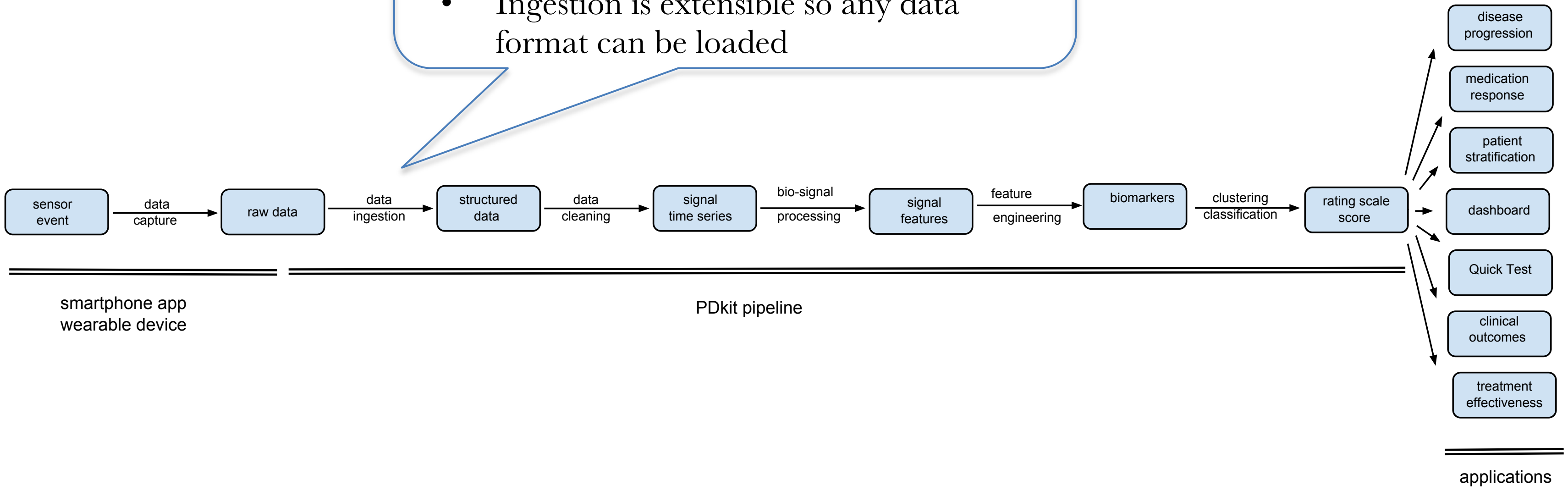
PDkit Processing Pipeline



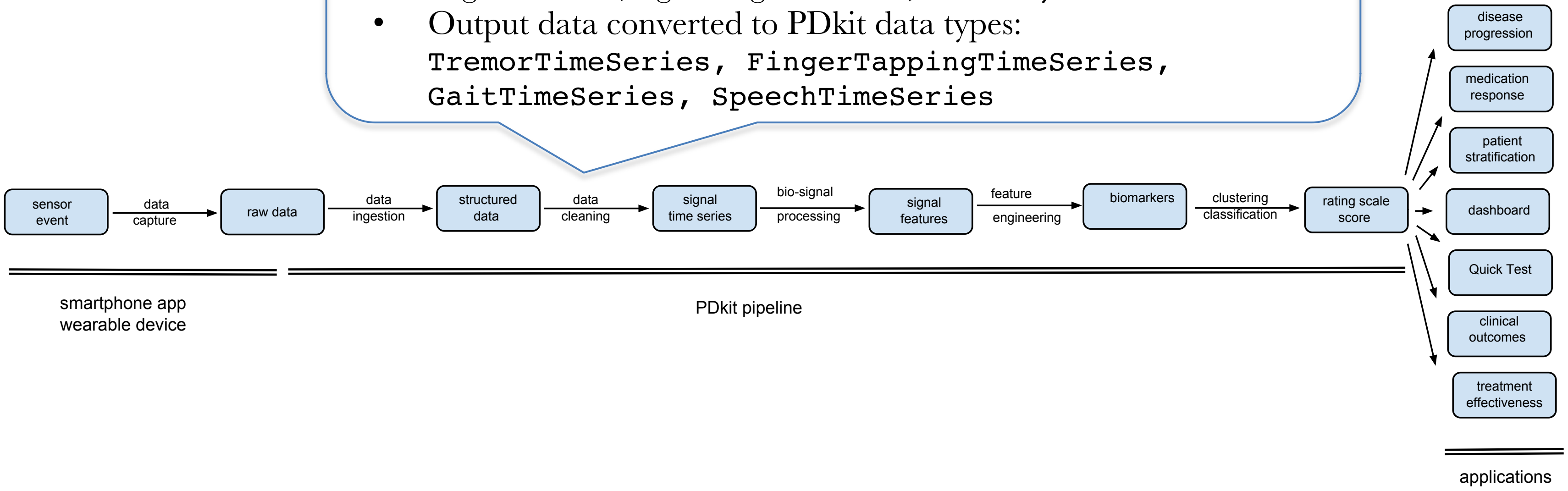
PDkit Processing Pipeline

- Data converted to standardized representation based on PANDAS dataframes
- Ingestion is extensible so any data format can be loaded



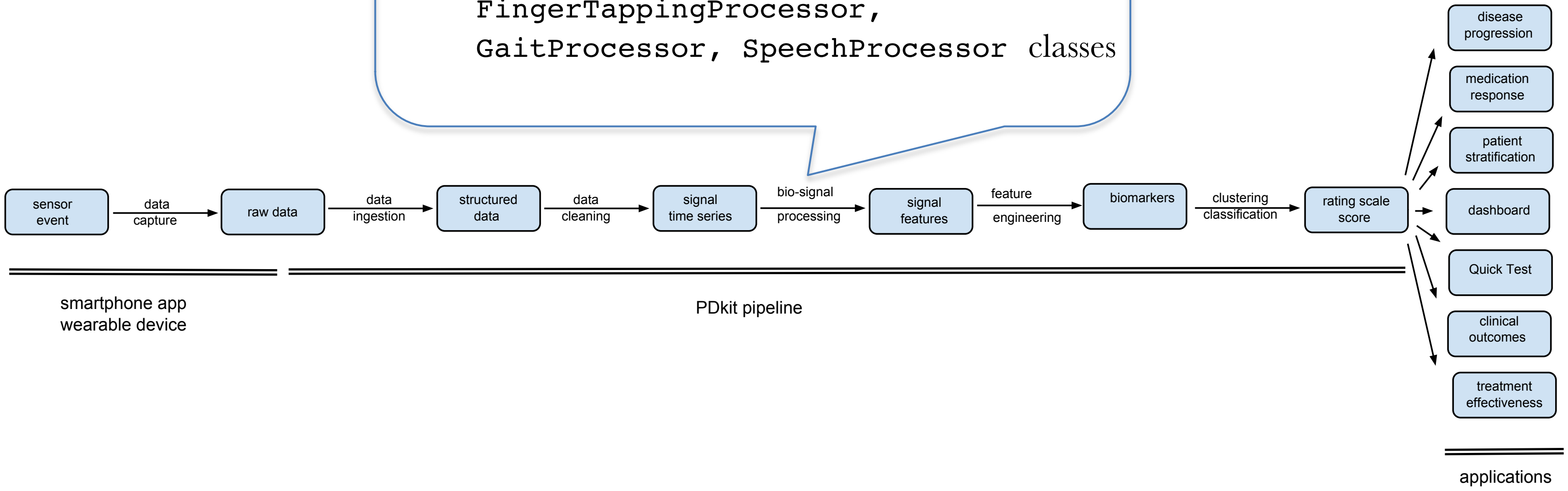
PDkit Processing Pipeline

- Missing and out of range values; data type normalization; indexing; standardised labelling; signal resampling
- Advanced features : gesture verification with DL, data augmentation, signal segmentation, extremity exclusions
- Output data converted to PDkit data types: `TremorTimeSeries, FingerTappingTimeSeries, GaitTimeSeries, SpeechTimeSeries`



PDkit Processing Pipeline

- Feature extraction
- 500+ tremor, bradikynesia, tapping, gait, turning and speech features
- Implemented in the `TremorProcessor`, `FingerTappingProcessor`, `GaitProcessor`, `SpeechProcessor` classes



PDkit Processing Pipeline

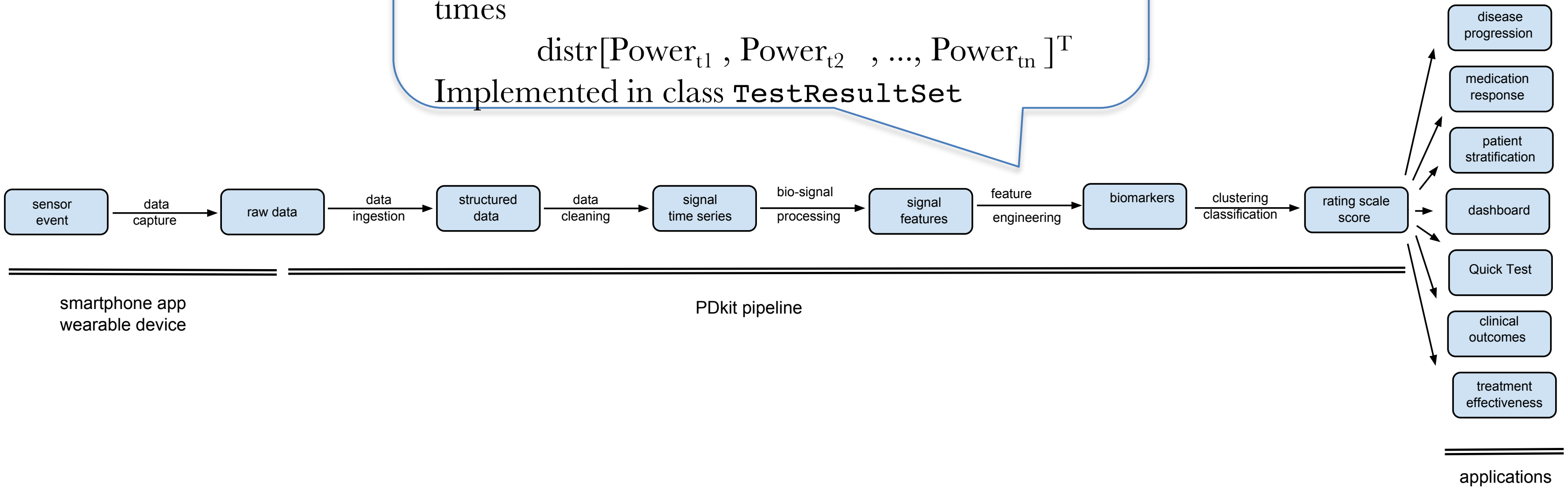
Classic unitary and vector instantaneous biomarkers

$$[\text{Power}, \text{Amplitude}]^T$$

Novel longitudinal biomarkers introducing temporal element e.g. same feature calculated at different times

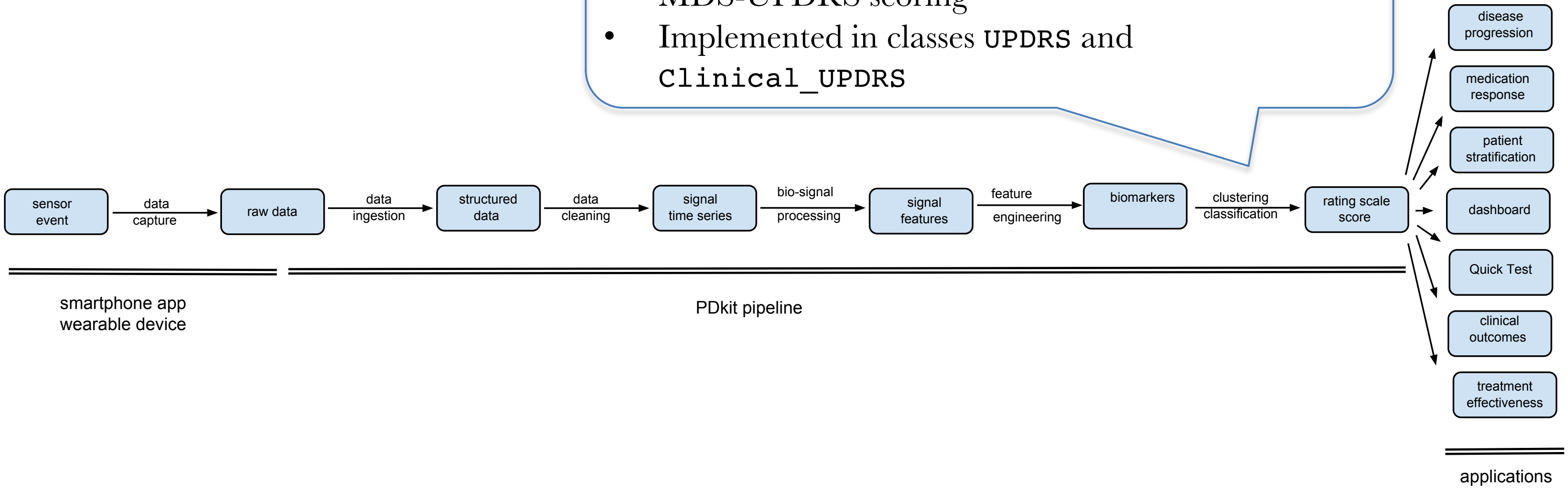
$$\text{distr}[\text{Power}_{t1}, \text{Power}_{t2}, \ldots, \text{Power}_{tn}]^T$$

Implemented in class `TestResultSet`



PDkit Processing Pipeline

- Supervised and unsupervised learning for scoring
- Clinical labels or classes created from the data only
- MDS-UPDRS scoring
- Implemented in classes `UPDRS` and `Clinical_UPDRS`



CUSSP study

- CUSSP at the UCL Institute of Neurology and Homerton Hospital (UK)
  - Details https://clinicaltrials.gov/ct2/show/NCT02937324
  - Data collection completed in May
  - 74 patients
- 20 lines of PDkit source code specify processing protocol
- 2-3 hours of software development
- Can recreate results in 1 hour on standard laptop

CUSSP Clinical Study

Visit 1 Day -60 to 0 (Screening): Discuss study, PIS given

↓

Visit 2 Day 0 (Eligibility): Written consent, MOCA, PDQ39, Beck's administered, baseline demographics recorded, App installed

↓

Visit 3 Day 1-150 (Hospital UPDRS): Official Enrolment, assessments as follows with order *randomised:*

a) Clinical video UPDRS (OFF/ON)*

b) Smartphone UPDRS (OFF/ON)*

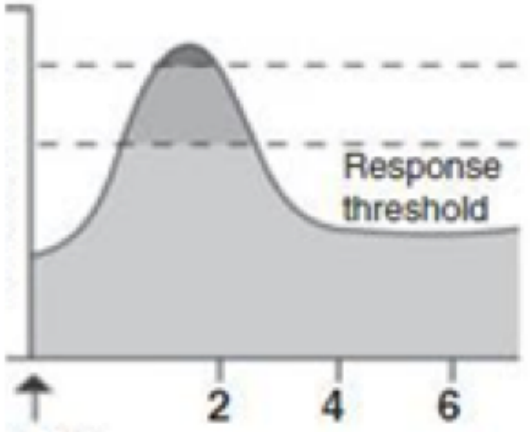
↓

Home monitoring period (order of A, B and C pseudorandomised)
(3 consecutive weeks, starting on Day 1- 150)

Week 1	6 days of home monitoring+ (method A)	Baseline smartphone OFF/ ON test on 7th day* Visit 4+
Week 2	6 days of home monitoring + (method B)	Baseline smartphone OFF/ ON test on 7th day* Visit 5+
Week 3	6 days of home monitoring + (method C)	Visit 6+

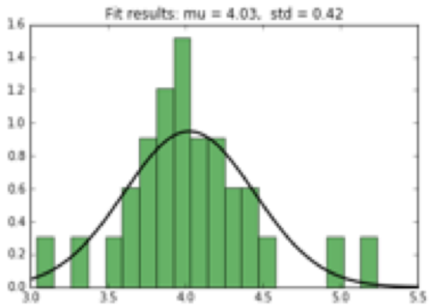
Limitations of current practice

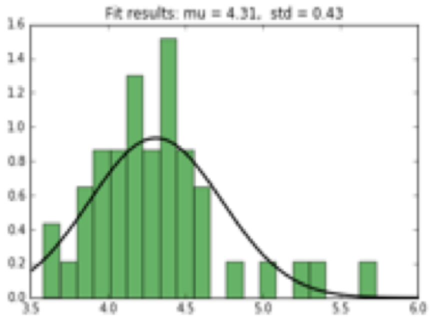
- Minimum Detectable Change (MDC95) ~12 (range 0-108)
- Typical annual disease progression 3-4 points
- Idealised response model
- Rapid uphill, slow downhill
- Affected by numerous parameters e.g. mood, social interaction, diet, exercise etc
- One sample has extremely limited value



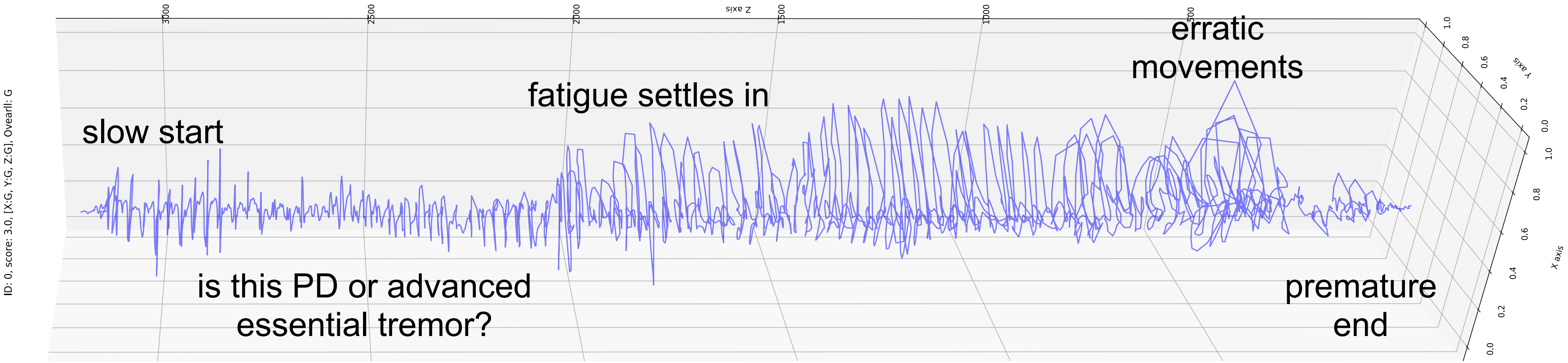
Capturing temporal variability

- Tremor signal is not stationary but is often treated as such (not unreasonable due to measurement limitations)
- Consider tremor to be a random process
- Look at temporal aggregates
- Preliminary results suggest far superior MDC95

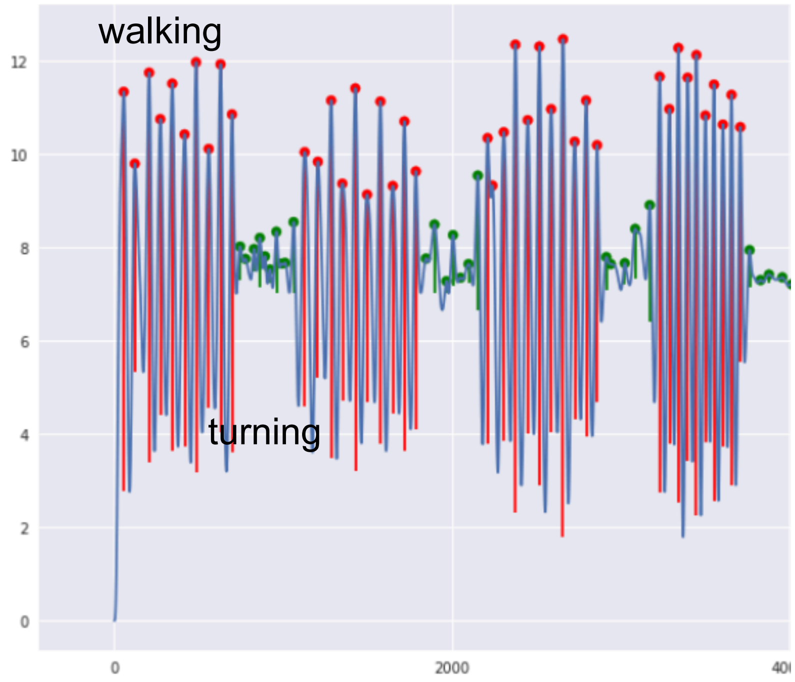




What is actually measured?



Gait test/activity recognition with HMM



How precisely can we detect the onset of turning movements?
Healthy subjects turn differently than PwP.

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Closing remarks

- Move from clinician to automated diagnosis and treatment offers great opportunities to realise patient benefits
- Challenges often relate to having to change methods
- This can be intensified by the greater availability of data
- Stationary to dynamic processes, non-linearity
- Validated evidence is time consuming/expensive to collect

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cloudUPDRS/pdkit people

Benchmark Performance

- Marco Luchini
- Stefan Kueppers
- Rajesh Pampapathi

re:technica

- Marco Iannone
- Nikos Fragopanagos
- Joan Saez Pons

audience focus

- Theano Moussouri
- Froso Nomikou

UCL IoN

- Bhatia
- John Rothwell
- Ashwani Jha
- Sebastian Schreglmann
- Elisa

Birkbeck College

- Ioannis Daskalopoulos
- Cosmin Stamate
- George Magoulas
- Jenny Vafeiadou

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Further resources

App demo videos

`http://www.updrs.net`

PDkit analytics toolkit

`https://github.com/pdkit/pdkit`

Papers

`http://www.dcs.bbk.ac.uk/~gr/pubs.html`

CUSSP Study Record

`https://clinicaltrials.gov/ct2/show/NCT02937324`

cloudUPDRS app on the Play Store

`https://play.google.com/store/apps/details?id=uk.ac.bbk.dcs.cloudupdrs`