Rendering the Parkinson home diary obsolete
A first step towards optimized medication for Parkinson’s disease patients

Who are we?

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*Present at today’s workshop
Unmet Clinical Need

Care-relevant continuous information about patient’s state (e.g. mental, conscious) and abilities (e.g. cognitive, sensory, motor).

Effective and accessible interventions to improve patient’s state and abilities.

Relevance:
- Brain injury (e.g. stroke) affecting 17’000 patient’s per year (CH)
- Neurodegenerative diseases: Alzheimer’s disease (105’000 Patients in CH); Parkinson’s disease (15’000 Patients in CH)
- Delirium and other behavioral and psychiatric symptoms are affecting 30-56% of hospitalized patients (e.g. neurology, intensive medicine)

Vision

Neurodegenerative diseases & brain injury

- Cognitive function
  Memory, attention, executive functions
- Perception
  Vision, hearing, proprioception
- Motor function
- Other symptoms
  Delirium, Sleep, Depression, psychiatric and behavioural symptoms

Patient at home or in the hospital

- Ambient Sensors
- Wearable Sensors
- Object Sensors
Ambient Sensors at the patients’ homes

**Ambient Sensors**

**Pro:**
- **Contactless**, high acceptance, reliable, low cost, easy to use

**Contra:**
- Not adapted for multi-person households,
- no physiological data,
- no outdoor measurements

Passive infrared sensors (PIR); temperature; light; humidity

Stucki RA et al. J Med Internet Res. 2014

83-year-old healthy woman

83-year-old patient with Alzheimer’s disease

(MMSE* 16 Points)


Wearable Sensors at the patients’ homes

**Wearable Sensors**

*Pro:*
Less infrastructure

*Contra:*
Battery runtime, **contact sensor**, acceptance

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Object Sensors

**Object Sensors**

Heartrate, 
Heartrate variability (HRV) 
Respiratory rate 
Movement in bed
Object Sensors

Vision

Neurodegenerative diseases & brain injury

Cognitive function
- Memory, attention, executive functions

Perception
- Vision, hearing, proprioception

Motor function

Other symptoms
- Delirium, sleep, depression, psychiatric and behavioral symptoms

Patient-specific interventions

Care-relevant information about patient’s state and abilities

Patient at home or in the hospital

Ambient Sensors

Wearable Sensors

Object Sensors

Multimodal patient model

Motor and cognitive function, activities, social interactions, sleep, delirium, psychiatric and behavioral symptoms

Behaviour recognition algorithms

Physiological parameters
Parkinson’s disease

- Second most common human neurodegenerative disorder.
- 4.1 Mio patients worldwide (expected 2030: 8.7 Mio)
- 15'000 patients in Switzerland
- Age-dependent prevalence (60 years: 1%; 80 years: 3%)
- Causes: Idiopathic (large majority), genetic, drug-induced, head trauma, etc.

Motor symptoms:
- Tremors
- Rigidity
- Slowed motion

Neuropsychiatric symptoms:
- Depression, cognitive dysfunction

Other symptoms:
- Sleep disturbances

Symptoms caused by insufficient dopamine

Source: Sciensphere 2015
**Parkinson’s Disease**

- Cognitive disorders, behavior & mood alterations
- Postural instability
- Resting tremor
- Freezing of gait
- Hyposmia
- Bradykinesia
- Akinesia

Cognitive disorders, behavior & mood alterations


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**Levodopa Medication**

"OFF" phase without Levodopa medication

"ON" phase with Levodopa medication

Levodopa Medication

**Early Disease**

- Therapeutic window
- Levodopa levels
- Threshold for dyskinesias
  - On
- Threshold for benefits
  - Off

Dyskinesia = involuntary muscle movements

Source: Hauser et al. Parkinson’s disease 2014

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**PD Home Diary**

Levodopa Medication

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Levodopa Medication

therapeutic window
levodopa levels
dyskinesias threshold for dyskinesias "ON"
threshold for benefits "OFF"

dyskinesia = involuntary muscle movements

Source: Hauser et al. Parkinson’s disease 2014

Levodopa Medication

therapeutic window
levodopa levels
dyskinesias threshold for dyskinesias "ON"
threshold for benefits "OFF"

dyskinesia = involuntary muscle movements

motor fluctuation = oscillation between "off", "on" and dyskinesia

Source: Hauser et al. Parkinson’s disease 2014
3D accelerometry allows long-term recordings without the need of battery recharge. Battery technology does not allow long-term recordings from gyroscopes. Wearable sensor-based devices can accurately measure overall dyskinesia and motor fluctuations.

Main challenges:
- patients’ acceptance of multiple wearable devices
- detection of the activity of daily living context

The correlation between accelerometer data and clinical score was highly significant (Pearson’s: $p < 0.0005$) although with a modest R of 0.65.

Average estimation error values of 3.4% for tremor, 2.2% for bradykinesia, and 3.2% for dyskinesia.
**Research Aim & Novelty**

- **Neurodegenerative diseases & brain injury**
  - Cognitive function
    - Memory, attention, executive functions
  - Perception
    - Vision, hearing, proprioception
  - Motor function
  - Other symptoms
    - Delirium, Sleep, Depression, psychiatric and behavioural symptoms

- **Patient at home or in the hospital**
  - Multimodal patient model
    - Motor and cognitive function, activities, social interactions, sleep, delirium, psychiatric and behavioural symptoms
  - Behaviour recognition algorithms
  - Physiological parameters

- **Patient-specific interventions**
  - Ambient Sensors
  - Wearable Sensors
  - Object Sensors

- **Care-relevant information about patient’s state and abilities**

**Research Aim**

Development and evaluation of a new sensor network system that helps clinicians with (motor)-symptom identification of PD patients

- Well accepted by patients, family members, by caregivers and clinicians
- Objective and reliable
- Easy to use
- Safe to use
Work-Packages – Phase 1: Technical development
(July 2017 – June 2019):

**Work Package 1:** Workshops with end-users (PD patients and family members)

**Work Package 2:**
- Select the wearable sensor
- Integration into the ambient sensor system
- Find an optimal sensor combination
Requirements for wearable sensors

- Based on user group meetings and interview with care professionals and clinicians
- 8 functional and 4 nonfunctional requirements were identified

<table>
<thead>
<tr>
<th>Functional Requirements</th>
<th>Nonfunctional Requirements</th>
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</thead>
<tbody>
<tr>
<td>Number of sensors: 2-3</td>
<td>Choice of material: Soft materials</td>
</tr>
<tr>
<td>Sampling rate: &gt; 40Hz</td>
<td>Color: Black or white</td>
</tr>
<tr>
<td>Measurement range: &gt;= 6g</td>
<td>Locking mechanism: Easy to operate</td>
</tr>
<tr>
<td>Battery life: &gt; 15h</td>
<td>Charging option: Easily accessible</td>
</tr>
<tr>
<td>Memory constraints: &gt; 75 MB</td>
<td>Software interface: Access to RAW data</td>
</tr>
<tr>
<td>Communication interface: USB</td>
<td></td>
</tr>
</tbody>
</table>

Wearable sensor selection

- Sensor selection based on review paper by C. Godinho et al.

Mobility Lab Opal¹  
Physilog®²  
DynaPort Hybrid³  
Axivity AX3⁴

[3] https://www.mcroberts.nl/old/products
Wearable sensor selection

Axivity AX3 selected
- Small 23 x 32.5 x 7.6 mm
- Lightweight: 11g
- Battery life: 14d

<table>
<thead>
<tr>
<th>Sensor</th>
<th>Accel</th>
<th>Gyro</th>
<th>Data Rate [Hz]</th>
<th>Weight [g]</th>
<th>Memory [GB]</th>
<th>Battery Life [d]</th>
<th>Data Transfer</th>
<th>Size</th>
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<tr>
<td>The OPAL</td>
<td>Yes</td>
<td>Yes</td>
<td>200</td>
<td>25</td>
<td>8</td>
<td>0.6</td>
<td>Wireless</td>
<td>Small</td>
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<tr>
<td>Physilog 4</td>
<td>Yes</td>
<td>Yes</td>
<td>500</td>
<td>19</td>
<td>4</td>
<td>0.8</td>
<td>Bluetooth</td>
<td>Medium</td>
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<tr>
<td>DynaPort MiniMod</td>
<td>Yes</td>
<td>Yes</td>
<td>100</td>
<td>74</td>
<td>Custom</td>
<td>7</td>
<td>Bluetooth</td>
<td>Medium</td>
</tr>
<tr>
<td>Axivity AX3</td>
<td>Yes</td>
<td>No</td>
<td>100</td>
<td>11</td>
<td>0.5</td>
<td>14</td>
<td>USB</td>
<td>Small</td>
</tr>
</tbody>
</table>

Axivity AX3


Wearable sensor: Indoor Localization

Idea:
- Resolves the ambiguity in a multi-household when detecting ADLs
- Enables the mapping of acceleration events to certain locations

Technology: Bluetooth Low-Energy
- Low-Power
- Low-Cost
- Low-Complexity
- Availability in consumer hardware

[5] Rattanalert et al. 2015

RSSI based indoor localization
Wearable sensor: Indoor Localization

Evaluation:
- Review of all commercially available Smartwatches from 12 manufactures

Selection:
- Polar M600

Modification:
- Implemented reliable acquisition of accelerometer data
- Power optimization for > 18h battery life
- Automatic data upload to iHL-Server

Polar M600

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
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<tbody>
<tr>
<td>Sampling rate</td>
<td>100 Hz</td>
</tr>
<tr>
<td>Range</td>
<td>+/- 2g to +/- 16g</td>
</tr>
<tr>
<td>Resolution</td>
<td>16 Bit</td>
</tr>
<tr>
<td>Battery life</td>
<td>48h</td>
</tr>
<tr>
<td>Memory</td>
<td>4 GB</td>
</tr>
<tr>
<td>Communication</td>
<td>Bluetooth &amp; WiFi</td>
</tr>
<tr>
<td>OS</td>
<td>Android Wear</td>
</tr>
</tbody>
</table>


Integrated Sensor System

Wearable sensors:
- Soft-touch materials
- Hook-and-loop closure (wrist & ankle)
- Suspender closure (hip)
Ambient Sensors 2\textsuperscript{nd} Generation

**BLE-Beacons**
- Based on the iHomeLab Multisensor

**Features:**
- PIR-Sensor
- BLE-Beacon feature
- Humidity & Temperature
- VOC (Volatile Organic Components)
- Acceleration / Vibration
- Door Contact Sensor
- Luminosity Sensor
- Magnetometer
- Sound Pressure
- Distance Sensor (1.5m)
- Non-Invasive Power estimator

Integrated Sensor System

Logging Setup with Base-Station (Raspberry-Pi), 4G-Router, Axivity AX3 sensors and Polar M600

Logging Setup integrated in a portable case
Integrated Sensor System

Wearable sensor: Indoor Localization
Work Packages – Phase 1: Technical development
(July 2017 – June 2019):

Work Package 3:
- Collect ground truth data:
  - ADL activities in healthy subjects (ADL reporting)
  - Parkinson’s patients (PD – home Diary)
- Develop the feature extraction algorithms

Pilot data collection in PD Patients

- 4 PD patients
  - 2 female, 2 male
  - age 65 – 70
  - Disease duration 10 – 14 years
  - UDPRS 11 – 49
- 4 weeks continuous measurement
- Patients fill in PD diary
Preliminary results: Acceptance

- SUS score 71.5%
- Additional questionnaire shows high score for all sensors
- Strong preference of sensor-set over PD home-diary
- Good short-time acceptance

Botros et al. 2019 submitted

Preliminary results: Adherence

- High adherence with sensor-set
- Constant, regular wearing times
- No requirement to wear during night
- Wearing time out of remaining 16 hours per day

Botros et al. 2019 submitted
Preliminary Results: Symptom Identification – Bradykinesia

Bradykinesia

- Features from n=3 people
- Relevant features:
  - Min/max/mean velocity
  - Range of movement
- Time window of 5 minutes

Data collection in healthy subjects

- Measurement of n=50 healthy participants
- Age: 65 - 92
- In-home localization based on PIR sensor (no Bluetooth Low Energy)
**Work Packages – Phase 1: Technical development**
*(July 2017 – June 2019)*:

**Work Package 4 (delay):**
Develop user-specific data selection and presentation methods that allow physicians to quickly get a clinical picture of the patient’s symptoms.

**Phase 2: Clinical testing**
*(July 2019 – June 2020)*:

- **WP5:** Clinical testing will include experiments at the hospital and in the patient’s home:
  - Five PD patients will be invited to spend one night in the „independent living suite“, which is a fully functional one-bedroom apartment equipped with monitoring technology at the SITEM-Inselspital.
  - Another five PD patients will be using the system at home for 8 weeks (2 ongoing).

SITEM-Inselspital: Swiss Institute for Translational and Entrepreneurial Medicine
Discussion

Validity and Accuracy of Ground Truth
- PD diary is difficult Ground Truth
- Subjective rating of symptoms
- Blind-eye to certain symptoms (Dyskinesia, Resting Tremor)

Outlook (I)

Validity and Accuracy of Ground Truth
- PD diary is difficult Ground Truth
- Subjective rating of symptoms
- Blind-eye to certain symptoms (Dyskinesia, Resting Tremor)

- Counter-measure to difficult Ground Truth
  - Controlled measurements in Living suite

- Full integration of ADL
  - Integration of localization information and activities
Conventional Deep Brain Stimulation (DBS)
Fixed high frequency stimulation (130 Hz)
Efficacy & selectivity good but not perfect

Adaptive DBS
Brain circuit intervention that changes according to feedback to control symptoms
Focus on state of neural circuit to make stimulation more effective, efficient and selective, i.e. fewer side-effects

Outlook (II): Closed Loop Deep Brain Stimulation

Validity and Accuracy of Ground Truth
- PD diary is difficult Ground Truth
- Subjective rating of symptoms
- Blind-eye to certain symptoms (Dyskinesia, Resting Tremor)
- Counter-measure to difficult Ground Truth
  - Controlled measurements in Living suite
- Full integration of ADL
  - Integration of localization information and activities
Challenges …

Usability, technological challenges (e.g. interface, battery life, data handling)
User needs vary among individuals, no „technology agents“, non-standardized, open environment
No established business models (e.g. DomoSafety S.A., Biovition AG)
Non-motor symptoms are multifaceted and require lots of clinical insights

… and Opportunities

• Continuum of treatment from the hospital to the patients home
• Large impact of home therapy
• Novel technologies (e.g. internet of things, big data methods)
• Adoption of technology in the older population

Publications and presentations

Paper:
*Long-term home-monitoring sensor technology in patients with Parkinson’s disease – acceptance and adherence*
Botros et al., 2019, under review

Conferences:
*Preliminary Evaluation of a Home-Based Long-Term Monitoring Device For Parkinson’s Disease Motor Symptoms*, Botros et al., ADPD 2019, Poster Presentation

*Home-based sensor system for reliable motor-symptom monitoring in Parkinson’s disease patients*, Botros et al., SFCNS 2019, Nomination for YouClin-Award
Thank you for the kind support and for listening

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*present at today’s workshop

Preliminary results: Symptom Identification – Bradykinesia

Bradykinesia
- Features from n=3 people
- Relevant features:
  - Min/max/mean velocity
  - Range of movement
- Time window of 5 minutes
- Results per feature vector

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<tr>
<th>Feature</th>
<th>Mean</th>
<th>Std</th>
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<tr>
<td>Sensitivity</td>
<td>69.8 %</td>
<td>3.7</td>
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<tr>
<td>Specificity</td>
<td>68.3 %</td>
<td>5.3</td>
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<tr>
<td>Precision</td>
<td>70.1 %</td>
<td>4.3</td>
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<tr>
<td>Accuracy</td>
<td>68.9 %</td>
<td>3.3</td>
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</table>
Results: Symptom Identification – Tremor & Dyskinesia

**Dyskinesia**
- Features from n=3 people
- Relevant features
  - Dominant frequencies
  - Energy in high/low energy band
- Moving time window length 6s, shift 3s

**Tremor**
- Features from n=1 person
- Relevant features
  - Dominant frequency
  - Energy of dominant frequency
  - Energy in low/high frequency band
- Time window length 3s

<table>
<thead>
<tr>
<th></th>
<th>Mean</th>
<th>Std</th>
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<tbody>
<tr>
<td>Sensitivity</td>
<td>74.2%</td>
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<tr>
<td>Specificity</td>
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<td>Precision</td>
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<tr>
<td>Accuracy</td>
<td>71.9%</td>
<td>1.9</td>
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<tr>
<td>Accuracy</td>
<td>70.6%</td>
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</table>

Particular electrophysiological characteristics in Parkinson’s disease

- PD evidence points to excessive synchrony in beta band **causing symptoms**
- Synchronisation varies from moment to moment and comes in pathologically prolonged bursts (Tinkhauser et al 2017)
- Bursts of beta activity can be recorded and tracked from the stimulating electrode
Closed-loop DBS: exemplary set-up for beta-amplitude controlled adaptive DBS

- Rectified smoothed beta (400ms smoothing av.)
- Crossing ~50\textsuperscript{th} percentile amplitude threshold
- 250ms ramping-up
- aDBS only on 44 ± 2 % of the time

Little et al 2013

Closed-loop DBS: clinical outcome

- Adaptive DBS more effective than continuous DBS (p < 0.05)
- Random DBS far less effective, so tracking beta bursts critical
- Battery saving: aDBS only on 44 ± 2 % of the time (p <0.0001)
- Adaptive DBS protects against stimulation-induced speech side effects

Little et al 2013,2016