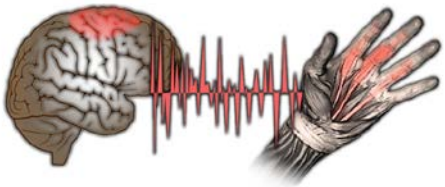
SEVENTH FRAMEWORK PROGRAMME

INFORMATION AND COMMUNICATION TECHNOLOGIES

Project:

NoTremor- Virtual, Physiological and Computational Neuromuscular Models for the Predictive Treatment of Parkinson's disease

(NoTremor, Grant Agreement No. 610391)



NoTremor

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Executive Summary

This deliverable constitutes the Deliverable D2.3 – "Completion of Second Test Campaign," of the NoTremor project (Grant Agreement No.: 610391), and sets out to provide the results (Report and Data) of the NoTremor Second Test Campaign (month 36). The study involves two test campaigns. The first serves for parameterization/instantiation of the computational models and the second allows validation of the NoTremor simulation framework. The First Test Campaign (completed 01.07.15) provided data streams related to hidden physiological states and computational model initialization/parameterization, respectively. This allowed us to ground the model with experimental data and quantify and fine-tune the developed computational models and simulation framework. The Second Test Campaign tests the performance of the developed model through pilot execution in three challenging applications and will serve both model optimization and validation purposes.

This deliverable is a source of reference material for each of the partners. It ensures that all partners have knowledge of the initial test campaign strategy for the clinical assessments and initial results.

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List of abbreviations and acronyms

(*in alphabetic order*)

BG	Basal ganglia
BGN	Basal ganglia network
DBS	Deep brain stimulation
GPi	Globus Pallidus interna
ICA	Independent component analysis
LFP	Local field potential
MDS-UPDRS	Movement Disorder Society United Parkinson's Disease Rating Scale
PD	Parkinson's disease
STN	Subthalamic nucleus

1. Introduction

NoTremor aims to provide patient specific computational models of the coupled brain and neuromuscular systems that will be subsequently used to improve the quality of analysis, prediction and progression of Parkinson's disease. The aim of NoTremor test campaigns will be twofold. In the first half of the project (WP2) they have been performed so as to ground the model with experimental data and quantify and fine-tune the developed computational models and simulation framework. In the second half of the project, test campaigns will involve pilot execution in three challenging applications in a patient subgroup and will serve both model optimization and validation purposes.

While all patients in the Frist Test Campaign were tested while receiving their usual dopaminergic medication (ON medication), the Second Test Campaign involves testing a patient subgroup in the following challenging conditions: 1. **ON medication** 2. **OFF medication** following overnight withdrawal of antiparkinsonian medication in the levodopa challenge test and 3. **Longitudinally-** where the same patient is tested at baseline and 18 months later to assess utility in measuring disease progression. The pragmatic levodopa challenge test allows an assessment of response to the patient's current levodopa dosage 60 minutes after ingestion after an overnight withdrawal of antiparkinsonian medication in a subgroup of eligible and consenting early PD patients.

This attenuated and pragmatic levodopa challenge test affords **some information on levodopa responsiveness**, but should be distinguished from the more comprehensive levodopa challenge test sometimes used in other studies where a **supramaximal** dose of the patient's usual levodopa medication (e.g. 250mg levodopa) is given, with the possibility of causing additional acute side effects including nausea, vomiting and dizziness. The pragmatic levodopa challenge test was chosen for this test campaign for these reasons, to ensure completion of the test campaign, and ethical approval awarded to perform the testing.

2. Second test campaign

These will test the performance of the model, serve to validate it, and to increase its relevance by demonstrating that the pharmacological basis of some key model parameters can be defined. Accordingly, we will:

- *Correlate model parameters with objective and clinical scales and monitor their evolution in a patient cohort*

We aim to correlate clinical scales and related objective measurements with the NoTremor suite of tests, metrics and internal states estimates. We will focus on a cohort of patients for whom both clinical and the NoTremor assessment will be carried out while on standard medication. In particular, among the clinical scales to be used for correlation, the UPDRS III will be primarily considered (but supplemented with other objective indicators, e.g., the Purdue Pegboard score). For the NoTremor tools, objective measurements (saccadometry and line tracking test) will be carried out and data will be processed to estimate the model parameters that represent the

internal basal ganglia and motor control states, thus representing the disease into an abstract “disease parameter space”.

The observations will be repeated approximately 18 months later in a smaller cohort of 10-20 patients, to observe possible changes in the disease parameters and clinical scales, as a first step towards observation (and in future prediction) of the disease evolution. A small cohort (n~5) will be followed longitudinally with daily/monthly test frequency with the novel measurement systems, with the purpose to further provide elements of system validation, and to monitor possible evolutions in a high frequency observation scheme.

- *Determine the pharmacological basis of some of the parameters of the NoTremor model and test performance of the model off and on levodopa*

We will model individual patients as they experience different levels of exogenous dopaminergic input. This will take the place of a levodopa challenge when patients omit their antiparkinsonian medication overnight and then take a test dose of the medication. We hypothesise that there will be model parameters that do not change significantly which can be considered as ‘non-dopaminergic’ in so far as they do not change over the dynamic range of dopaminergic drives tested in the levodopa challenge. These parameters should correlate with clinical features that are considered to be predominantly determined by non-dopaminergic changes in PD, such as tremor and gait instability.

Conversely, we hypothesise that there will be model parameters that do change significantly which can be considered as ‘dopaminergic’ in so far as they change over the dynamic range of dopaminergic drives tested in the levodopa challenge. These parameters should correlate with clinical features that are considered to be predominantly determined by lack of dopaminergic activity in PD, such as bradykinesia and rigidity (and at least partially captured in the MDS-UPDRS Part III, Purdue Pegboard, Tapping speed). Identifying some model parameters as dopamine-related considerably increases the potential utility of the NoTremor approach; as such parameters may provide a means of predicting the relative degree of dopaminergic denervation and the potential for reversal of specific symptoms with conventional and novel dopaminergic drugs in a given patient.

The test campaigns have taken place at the Oxford Parkinson’s Disease Centre (OPDC) (http://opdc.medsci.ox.ac.uk). The OPDC Discovery cohort (PI: Michele Hu) allows the NoTremor tasks to be collected in parallel with a range of clinical measures that are already collected longitudinally every 18 months in a cohort of >1000 early PD patients who are within 3.5 years of diagnosis at their baseline study recruitment.

Validation and benchmarking

The core clinical trial is detailed in the description of WP2. Specifically, the test campaigns will utilise and extend a well studied cohort of patients with Parkinson's disease enrolled in the Discovery project (http://opdc.medsci.ox.ac.uk/) already funded by Parkinson's UK. This has the considerable advantage of delivering

clinical data within the time constraints of NoTremor which, if collected de novo, would delay the other NoTremor work-packages by several years and would increase study costs considerably. This study already affords extensive data (MDS-UPDRS 1-4, timed up and go test, Hoehn and Yahr, manual reaction time, saccadometry, cognitive and non-motor assessments) on disease progression and, moreover, will provide data on the response to levodopa challenge. The computational models and simulation framework that will be developed should be in position to replicate patient macro-scale behavior based on their physiological characteristics and clinical state.

In particular, the data will be used to:

- *Validate simulations of the effect of levodopa in the virtual environment.*
- *Monitor disease evolution on an individualized patient basis, based on simple behavioural monitoring through an inverse simulation framework*

Local Ethics approval is in place that covers these studies (Targeting the early pathological pathways in Parkinson's disease, REC reference: 16/SC/0108, IRAS project ID 188167, South Central- Oxford A Research Ethics Committee).

2.1 Data to correlate model parameters with objective and clinical scales and monitor their evolution in a patient cohort

2.1.1 Cohort summary: Oxford Discovery Cohort

The Oxford Discovery cohort is a subset of early PD subjects, all within 3.5 years of the clinical diagnosis of PD at the time of their baseline recruitment, who are part of the >1000 PD subjects studied longitudinally as part of this UK-based cohort in the Thames Valley region. All subjects are seen longitudinally every 18 months by a neurologist and research nurse, to evaluate their clinical diagnosis of PD according to the UK PD Brain Bank Criteria, and assign a clinical probability for this diagnosis at each study visit. This cohort is divided into two campaigns.

(i) The Discovery cohort 1 comprises 29 PD patients ON medication (mean age 64.8 years, mean disease duration from diagnosis = 1.8 years, mean UPDRS III=25.3, Hoehn and Yahr I to III) and 3 healthy subjects of similar age. A few of these subjects were tested again in Cohort 2 below.
(ii) The Discovery cohort 2 comprises 21 PD subjects ON medication, of whom 7 were also seen earlier as part of cohort 1 (after 3 omissions; mean age 67.7 yrs, mean disease duration from diagnosis 3.9 years, mean UPDRS III= 28.6, Hoehn and Yahr I to III), a subset of whom were also measured On and OFF medication (see below).

Total PD patients assessed for NoTremor= 43

Longitudinal assessments: 7 PD patients from Discovery cohort 2 were seen at baseline and 18 months later to allow for monitoring of disease evolution.

2.1.2 Cohort summary: Oxford Surgery Cohort

The Oxford Surgery cohort, in comparison to the Oxford Discovery Cohort have more more advanced complex PD, typically with a disease duration >10.0 years from diagnosis. These patients have undergone Deep Brain Stimulation (DBS) surgery as a treatment for their complex PD. Local field potentials (LFP) are recorded from the contacts at the end of the DBS electrodes used for chronic stimulation in the U.K following surgery synchronized with the execution of the line and force test. Typically the LFP is picked up from the subthalamic nucleus (STN), where, although highly focal and localised, it still represents a population averaged signal.

13 Surgical subjects carried out the line test on medication of which 10 carried out the test also in the OFF state. An additional 8 subjects who carried out only the force test ON medication.

2.1.3 Cohort summary: Thessaloniki Cohort

Data collection from Parkinson patients and a control group consisted of healthy counterparts was twofold. Session-I started in December of 2015 and was completed in late February 2016 and session-II started in late September 2016 and was completed in December 2016 respectively. All tests were carried out in three local hospitals in the city of Thessaloniki, Greece, under the clinical supervision of Dr. Bostantjopoulou (Professor of Neurology, Aristotle University of Thessaloniki) and Dr. Katsarou (Director of Department of Neurology, Ippokrateio General Hospital). PD patient assessments were performed while ON medication. Researchers were provided with a quiet room, in each of the aforementioned hospitals, where all experimental protocols were performed without any distractions. Data from the mobile phone (i.e gait test) were obtained with participants walking in the shared-used corridors.

Fifty-five patients with Parkinson's disease (62.1±8.8, 18 female) and 10 aged matched controls (66.4±1.88, 6 female) performed the line test, force test, fitt's law, and mobile phone test . Eight of the patients were diagnosed in Hoehn and Yahr scale H&S 1, thirty-nine in H&S 2 and eight in H&S 3. Tests were given in a random order each time to eliminate any learning effect while ample of time was allowed between trials to avoid mental fatigue. Two subjects from the PD patients group in session I and one patient in session II did not complete the force test and dropped out due to an excessive tremor of the hand employed. Among all tests force test was perceived as the most demanding one. Overall, the dropout rate was less than 2% for the PD group in session I and less than 1% in session II respectively, whereas the adherence rate for the second session reached 100%.

Longitudinal assessments: 25 PD patients were seen at baseline and 6 months later to allow for monitoring of disease evolution.

2.1.4 Cohort summary: Santa Chiara Cohort

This cohort is a longitudinal study, using the line test for frequent (daily) remote monitoring at home. The study involved **4 PD**, **4 healthy age matched controls**, **2 controls with a different disease** and some other short-term technical controls. The observation period span from a few months (for controls) to nearly a couple of years for a couple of PD subjects

2.2 Data to test performance of the model on and off levodopa

To determine the pharmacological basis of some of the paramaters of the NoTremor model, and evaluate the effect of levodopa, recordings with parallel clinical assessments were taken ON and OFF medication in the same individual from the following 2 cohorts:

1. Oxford Discovery cohort: 9 PD patients performed ON and OFF line recordings during pragmatic levodopa challenge testing (see above) with parallel clinical assessments. Mean UPDRS III (motor) scores ON medication were 23.8, mean OFF medication scores were 34.3.
2. Oxford Surgery cohort: 10 DBS PD patients had LFP recordings synchronized with execution of the line test in ON and OFF states.

2.3 Clinical Assessments performed across the 4 cohorts

Due to local clinician availability and resources, different clinical assessments were performed in each cohort.

(i) **All 43 Oxford Discovery PD** and control participants underwent a comprehensive battery of assessments of motor, non-motor and cognitive function at each study visit on medication. For those undergoing levodopa challenge testing, OFF medication motor UPDRS (III) scores were also collected. The clinical assessments and methods are detailed elsewhere in full (Hu et al, 2015), and include:

Motor:

- MDS-UPDRS I-IV (clinical assessment)
- Hoehn and Yahr scale
- Purdue Pegboard Test (of manual dexterity and cognition)
- Assessment of levodopa response at 18 months during formal levodopa challenge test (in patient subgroup)
- Flamingo test (of postural stability)
- Timed Get up and Go (test of gait
- Freezing of Gait (FOG) questionnaire

Cognitive:

- MoCA (Montreal Cognitive Assessment)
- MMSE (Mini-mental State Examination)
- Phenomic and semantic verbal fluency
- NART (National Adult Reading Test to estimate premorbid IQ)

Non-motor:

- RBD Questionnaire
- Leeds Anxiety and Depression scale
- Epworth Sleepiness Scale

Other:

- Educational/social history
- Handedness, % clinical PD probability, whether fulfilled UK PD Brain Bank diagnostic criteria
- Levodopa Equivalent Daily Dose (LEDD), medical history and drug history
- Comprehensive family history
- IQ-CODE
- Schwab and England Scale
- EQ-5D with VAS

(ii) Oxford Surgical Cohort

Motor UPDRS (III), on and off (levodopa challenge test), LEDD, handedness

(iii) Thessaloniki Cohort

Hoehn and Yahr Scale was available, and disease demographics, handedness

(iv) Santa-Chiara Cohort

Handedness, Hoehn and Yahr

2.4 NoTremor tests performed across the 4 cohorts

For the Oxford Discovery cohort, the original plan had been to perform the full clinical assessment battery detailed above in addition to a full battery of additional NoTremor assessments- saccadometry, the force and line manual tracking tasks, and a mobile phone app test recording voice, manual dexterity, reaction time, standing balance, gait over 20 metres (see Arora et al, 2015, Tsanas et al, 2011 and 2012).

However, these assessments proved too tiring for patients, particularly while undergoing the levodopa challenge test, and the longitudinal testing as patient's symptoms progressed. Therefore, following completion of the First Test Campaign, a pragmatic decision was made by the group to reduce the NoTremor test battery in order to ensure sufficient numbers of patients were recruited at baseline, were tested

in the ON and OFF state during levodopa challenge test, and were tested longitudinally. The NoTremor Discovery test battery was reduced in June 2016, when it became evident that patient recruitment would not be reached if the full testing battery was continued. The Force manual tracking task was discontinued as patients feed back to the clinical team that it was the most arduous of the two tasks, and they found it difficult to complete. Saccadometry was to be performed only in patients who were able to tolerate it after completion of the core tests.

The Core NoTremor test battery from June 2016 consisted of: line manual tracking task, the 6 minute android phone app task, and saccadometry only where possible after the initial tests were completed. Tests were to be performed in the ON and OFF states, and longitudinally where possible. For the Oxford surgical cohort, both the Line and Force manual tracking tasks were completed, but only the Line task while ON and OFF for consistency.

In other sites, where comprehensive clinical assessments were not available, patients were able to complete the Line force test on multiple occasions in a single day at home over 6 months using an iPad (Santa Chiara), or in the Thessaloniki cohort where each subject performed the line and force manual tracking task, the Fitt's law test, and Android phone test.

A summary of clinical and NoTremor tests performed to date, with projected number estimated laid out in our revised Description of Works (DOW- 2013-05-31).

NoTremor Test	First test campaign	Second test campaign	Total completed (with projected numbers in brackets)
Baseline line test	29 PD, 3 control	21 (14 unique) PD	43 PD (45) 3 control (NS)
Baseline saccadometry	20 PD, 2 control	0	
Baseline Android	17 PD	10 PD	27 PD (NS)
STN LFP and line-ON		10 PD	10 PD (10)
STN LFP and line-OFF		10 PD	10 PD (10)
Longitudinal line test		7 PD	7 PD (10-20)
ON and OFF line test		9 PD	9 PD (10-20)

Table 2.4 : Final summary of assessments performed in first and second test campaign for Oxford Discovery and Oxford Surgery cohorts

3.1 Potential limitations in second test campaign

The prediction of levodopa response has only been made in a test cohort of 9 Oxford Discovery patients. The original target number of 10 to 20 was selected for tractability and economy, as it proved too tiring for patients to perform the full battery both on and off medication on the same day. Furthermore, ethical approval to perform the testing on and off medication was only granted in mid 2016. The core test battery was refined in June 2016, at which time only 1 PD patient had been tested on and off medication. A further 8 patients were then tested over the remaining 6 months of the project.

In accordance with our ethical permissions for this study, the formal levodopa challenge test is a pragmatic test, following overnight withdrawal of levodopa medication, and a low test dose (100-200mg levodopa, or 100% of the patient's standard levodopa dose) to minimise side effects. Therefore, it can be argued that the subject is not completely off medication during the challenge test, and that a suboptimal levodopa dose is given to elicit levodopa responsiveness. At this early stage of disease (< 5 years duration), most PD patients generally have sufficient buffering capacity from their remaining nigral dopaminergic projections to allow levodopa dose intervals to be 12-16 hours without wearing off symptoms to develop. Therefore, the OFF state derived after

overnight withdrawal is unlikely to be a true representation of the patient's motoric ODFF state, but a milder deterioration. This is in contrast to the Oxford Surgical cohort, who by definition in having complex PD require DBS surgery to manage their motoric PD symptoms, and will experience wearing off symptoms typically 3 to 5 hours after their usual levodopa medication dose. These patients will therefore manifest a more representative OFF state following overnight withdrawal of medication in the levodopa challenge test.

The longitudinal cohort were recorded on medication, so that medication-related will not compromise the interpretation of any change in model parameters. However only 7 PD patients were studied longitudinally in the Discovery cohort over 18 months despite best efforts. Given that the NoTremor project is only 3 years in duration, and the refinements necessary in the first test campaign, these lower numbers are to be expected. The conclusions that can be drawn on these lower numbers are however limited.

4 Conclusion

Here we have defined the two test campaigns to be undertaken in NoTremor. The first serves for parameterization/instantiation of the computational models and the second allows validation of the NoTremor simulation framework. The first test campaign will provide two data streams related to hidden physiological states and computational model initialization/parameterization, respectively. The second test campaign tests the performance of the developed model and identifies the pharmacological basis of some of the parameters of the model, in particular test performance of the model off and on levodopa.

5 Appendices

6 References

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