Optimizing levodopa dosing routines for Parkinson's disease

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Microdata Analysis
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Dalarna University
Sweden
2017

Abstract

This thesis in the field of microdata analysis aims to introduce dose optimizing algorithms for the pharmacological management of Parkinson's disease (PD). PD is a neurodegenerative disease that mostly affects the motor functions of the patients and it is characterized as a movement disorder. The core symptoms of PD are: bradykinesia, postural instability, rigidity, and tremor. There is no cure for PD and the use of levodopa to manage the core symptoms is considered the gold standard. However, long term use of levodopa causes reduced medication efficacy, and side effects, such as dyskinesia, which can also be attributed to overmedication. When that happens precise individualized dosing schedules are required. The goal of this thesis is to examine if algorithmic methods can be used to find dosing schedules that treat PD symptoms and minimize manifestation of side effects. Data from three different sources were used for that purpose: data from a clinical study in Uppsala University hospital in 2015, patient admission chart data from Uppsala University hospital during 2011-2015, and data from a clinical study in Gothenburg University during 2016-2017. The data were used to develop the methods and evaluate the performance of the proposed algorithms.

The first algorithm that was developed was a sensor-based method that derives objective measurements (ratings) of PD motor states. The construction of the sensor index was based on subjective ratings of patients' motor functions made by three movement disorder experts. This sensor-based method was used when deriving algorithmic dosing schedules. Afterwards, a method that uses medication information and ratings of the patients' motor states to fit individual patient models was developed. This method uses mathematical optimization to individualize specific parameters of dose-effects models for levodopa intake, through minimizing the distance between motor state ratings and dose-effect curves. Finally, two different dose optimization algorithms were developed and evaluated, that had as input the individual patient models. The first algorithm was specific to continuous infusion of levodopa treatment, where the patient's state was set to a specific target value and the algorithm made dosing adjustments to keep that patients motor functions on that state. The second algorithm concerned oral administration of microtables of levodopa. The ambition with this algorithm was that the suggested doses would find the right balance between treating the core symptoms of PD and, at the same time, minimizing the side effects of long term levodopa use, mainly dyskinesia. Motor state ratings for this study were obtained through the sensor index. Both algorithms followed a principle of deriving a morning dose and a maintenance dose for the patients, with maintenance dose being an infusion rate for the first algorithm, and oral administration doses at specific time points for the second algorithm.

The results showed that the sensor-based index had good test-retest reliability, sensitivity to levodopa treatment, and ability to make predictions in unseen parts of the dataset. The dosing algorithm for continuous infusion of levodopa had a good ability to suggest an optimal infusion rating for the patients, but consistently suggested lower morning dose than what the treating personnel prescribed. The dosing algorithm for oral administration of levodopa showed great agreement with the treating personnel's prescriptions, both in terms of morning and maintenance dose. Moreover, when evaluating the oral medication algorithm, it was clear that the sensor index ratings could be used for building patient specific models.

Keywords: Parkinson's disease; levodopa; symptom assessment; symptom management; dosing algorithms; wearable sensors; microtablets; continuous infusion;

List of papers

This thesis comprises of the following papers, which are referred in the text by their Roman numerals:

Paper I – Thomas, I., Westin, J., Alam, M., Bergquist, F., Nyholm, D., Senek, M., & Memedi, M. (2017). A Treatment-Response Index from Wearable Sensors for Quantifying Parkinson's Disease Motor States. Revised after review.

Paper II – Thomas, I., Alam, M., Nyholm, D., Senek, M., & Westin, J. (2017). Individual dose-response models for infusion dose optimization of Parkinson's disease. Submitted.

Paper III – Thomas, I., Alam, M., Bergquist, F., Johansson, D., Nyholm, D., & Westin, J. (2017). Algorithmic dosing suggestions for oral administration of levodopa/carbidopa microtablets for Parkinson's disease. Submitted, under review.

My contributions to the papers were as follows:

Paper I – Data processing, data analysis, writing and revising the manuscript.

Paper II – Data collection, data processing, methodology development, data analysis, writing the manuscript.

Paper III – Data processing, data analysis, methodology development, writing the manuscript.

Note: The paper listed above are not appended on the online version of the thesis.

Papers not included in the thesis:

Paper I – Thomas, I., Bergquist, F., Constantinescu, R., Nyholm, D., Senek, M., & Memedi, M. (2017). Using measurements from wearable sensors for automatic scoring of Parkinson's disease motor states: Results from 7 patients. In *Engineering in Medicine and Biology Society (EMBC), 2017 39th Annual International Conference of the IEEE.*

The following patent application has also been filed:

S Sensidose AB, Authors: Ilias Thomas, Mevluding Memedi, and Jerker Westin (UK), "SYSTEMS FOR EVALUATING DOSAGE PARAMETERS", GB1708624.0, 2017

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Introduction

Parkinson's disease

Parkinson's disease (PD) is the second most common neurodegenerative disease and is estimated that about 10 million will have the disease in the world's 10 most populous nations by 2030 (Dorsey et al., 2007). The onset of the disease leads to impairment of motor functions and because of that, the disease is classified as a movement disorder (Jankovic, 2008). There is no cure for PD and the reasons for the onset of the disease are still unknown. Onset of PD reduces production of dopamine in the basal ganglia part of the brain, as neurons that produce dopamine begin to die out. Reduced dopamine production leads to PD core symptoms, which are tremor, rigidity, postural instability and bradykinesia (Jankovic, 2008). Bradykinesia can be described as "slowness" in movement. When the core symptoms are present the patients are in an OFF state.

PD is mostly treated with levodopa (Connolly and Lang, 2014), a chemical compound that restores the motor function of the patients to a somewhat normal level, referred to as ON state. The treatment procedures can be vaguely categorized into three categories, which will be named in this thesis as: basic, advanced, and invasive.

The basic treatment is applied in the early stages of the disease, to restore normal motor functions (the patients take medication to go from the OFF state to the ON state). A generic dosing oral intake of levodopa is adequate for the majority of the patients.

However, as PD progresses, treatment of disease symptoms becomes more complicated, as medicine efficacy reduces, and side effects of levodopa use start to appear (Ahlskog and Manfred, 2001; Jankovic, 2005). These phenomena include: dyskinesia (Fabbrini, 2007) (manifestation of involuntary movements), that can be attributed to overmedication, and motor fluctuations (sudden loss of medication effect). In the presence of dyskinesia the patients are in the overmedication state.

In that stage, more elaborate treatment strategies are required, called here advanced strategies. These strategies consist of individualizing the dosing schemes of orally administrated levodopa, with regard to amount of dose and dosing times during the day (Connolly and Lang, 2014; Nyholm et al, 2014). These drug therapies often have a narrow therapeutic window and produce significant side effects when dosing is non-optimal. The timing of doses as well as the amount of the dose is therefore critical to maintain drug levels within desired levels and it is important that administered doses are as accurate as possible to reduce the effects that can otherwise arise from over, under or imprecise dosing. These treatments may involve a morning dose and then maintenance doses throughout the day. The need for morning dose is patient-specific, since there is a phenomenon called sleep benefit, and morning dose intake can be postponed for a large percentage of patients (Merello, 1997).

Finally, when managing disease symptoms with individualized doses is no longer feasible (due to uncontrollable side effects or insufficient medicine efficiency), invasive treatment options are considered (Timpka et al., 2016). The most notable invasive treatment options are the installation of a device in the abdomen area of the patients that provides continuous infusion of levodopa to the patients' blood flow (Nyholm et al., 2005; Olanowor et al., 2006) and deep brain stimulation therapy, by installing a device that provides electrical stimulation to the patients' brain (Volkmann et al., 2013).

The three motor function states (OFF, ON, dyskinesia) defined previously are usually scored by the treating personnel on motor function scales (Ebersbach et al., 2006; Ramaker et al., 2002), to assist when evaluating changes in the medication routines of the patients. A variety of symptoms can be rated in these scales, such as the severity of the core symptoms or dyskinesia. It is usual that the patients perform instrumental tests for the treating personnel to score their motor functions in those scales. The most common instrumental test are the ones used to assign scores on the Motor

Examination part of the Movement Disorder Society - Unified Parkinson's Disease Rating Scale (MDS-URDRS) (Goetz et al., 2008). Such instrumental test could include: Arising from chair task, speech task, gait task, finger tapping task and pronation-supination movement of hands task

Dosing optimization in clinical practice

In both the advanced and the invasive treatment stages, treating physicians alter the patients' dosing schedules to find a suitable schedule for each patient. That process is called dose titration. Finding the optimal treatment, during the titration period, requires dose adjustments based on the patients' response to treatment, scored in the motor function scales, which can take multiple tries to achieve. Dose titration happens both on individualizing the oral administration of levodopa on the advanced stage, or when trying to find the optimal infusion rate for every patient.

In clinical practice, dose titration is relying on physicians' and specialized nurses' subjective experiences to optimize therapeutic effects. Using such methods may take a considerable time to arrive at an optimal dose and may involve a patient being under or over medicated, thus experiencing potentially treatable symptoms and/or potentially unnecessary side effects, for a relatively long period of time. This is clearly undesirable. Expert systems and solutions that assist treating personnel during that process, when it comes to dosing suggestions, are not currently available, but there are sensor based products and methods that assist with monitoring the patients' motor functions, for example (Mancini et al., 2012; Tsipouras et al. 2012). However, clinicians typically make prescribing decisions based on an estimate of a reasonable dose for a particular patient and associated condition followed by regular qualitative observations of a patient taken over a period of weeks or possibly months. The qualitative observations often involve an assessment of the patient's appearance and physical characteristics and discussions with the patient intended to reveal their own perceptions of their response to the treatment and its side effects, which could be unreliable (Papapetropoulos, 2012).

Nevertheless, even though these monitoring methods and products can evaluate the patients' motor function momentarily or provide long-term treatment evaluation, they do not assist the treating physicians with dosing adjustment decisions. Therefore, these methods do not ensure that the dose is highly tailored to the patients' particular needs. Moreover, as PD progresses over time, particularly in terms of side effect manifestation by the patients, the same procedure of dose titration may be repeated many times for a single patient. Furthermore, physicians usually make dosing adjustments during patients' visits, no more than once or twice every year. As a result, patients in need of more frequent assessments and dosing adjustments can experience long periods of non-optimal treatment, which severely influences the patients' quality of life.

In the following chapters, a description of the three papers that comprise this thesis will be given. There will be a discussion about what motivated the methodological choices of the papers, key findings of the work, limitations, and how the three papers work together. Finally, there is a discussion of how the work fits in the field of microdata analysis and future plans.

Thesis work

Sensor monitoring on a continuous scale – work of paper I

As discussed briefly in the previous section, monitoring methods and products that can evaluate the patients' motor function momentarily or provide long-term treatment evaluation as available (Maetzler et al. 2016), but do not assist with dosing adjustments. That is in part because most monitoring systems have a clear distinction between the items they are monitoring, usually involving bradykinesia score, dyskinesia score, detection of freezing of gait or tremor assessment (Lopane et al., 2015; Griffiths et al., 2012; Giuffrida et al., 2009; Nancy et al., 2016; Patel et al., 2009). A limitation of those methods, in the author's opinion, is that there is a lack of a scoring method that rates patients' motor function in one, unified, continuous, motor function scale. It has been discussed in the literature

how technological assistance can contribute to the management of PD, and how therapeutic opportunities lay in those technologies (Dorsey et al., 2016; Espay et al., 2016). It has also been argued that the use of monitoring systems can assist with improving the patients' quality of life (Uem et al. 2016).

Inspired by those opportunities, in paper I a scoring method was developed with a clear intention to use it for dosing adjustments. In that paper the treatment response scale (TRS) is used, a motor function scale that ranges from -3, meaning very OFF, to 0, meaning ON, to +3, meaning very dyskinetic (Nyholm et al., 2005). That scale presents with the clear advantage that it can be used to evaluate the patients' state in a holistic way, even though there are instances where the phenomena of dyskinesia and bradykinesia overlap. Furthermore, this scale is already used for dose titration of continuous infusion rate where the treating personnel target a value of 0 as the desired response effect.

This study used data from commercial sensors, equipped with a 3D gyroscope and a 3D accelerometer, which the patients wore in both their wrists. The patients of this study were all in need of advanced treatment. The data were collected during a single dose levodopa experiment, where the patients received 150% of their normal morning dose, to increase the chance of observing dyskinesia (Senek et al. 2017). In total, 19 patient participated in the single dose experiment, during which they would perform instrumental motor tests at a pre-defined dosing schedule, before, at the moment, and after receiving the levodopa dose. The motor task that was examined in this study was the pronation-supination task of rapid alternative hand movements. The patients performed the task for approximately 20 seconds for each hand. The patients came into the clinic following a 10h washout period (no medicine intake), meaning they were in the OFF state, and by receiving the high dose the majority of the patients demonstrated all three stats of PD defined here (OFF, ON, Dyskinesia).

With that information the readers can infer that when rating the motor function on the TRS scale, patients included in the study would have motor states that go from a baseline value (in the minus values of the scale), to a value around 0 (when reaching the ON state), to a value on the positive side of the TRS scale (if the dose was big enough to induce dyskinesia), until finally the dose effect would wear off and the patients would return to the baseline value they had at the beginning of the day.

This intuitive assumption was confirmed by three moving disorder experts, who independently rated the patients' motor function on the TRS during all test instances. In order for that to happen, the patients were video recorded during the tests and the videos were presented to the experts in a randomized order, meaning the ratings were blinded in regards to time from dose administration. For the majority of the patients the ratings were consistent with what was expected, in response to the single dose. That behavior (the value change from 0FF-ON-dyskinesia-ON-OFF) can be defined here as dose-effect behavior of the patient. The ratings themselves however, presented with a few limitations as the patients did not demonstrate values at the end tails of the TRS scale (values close to -3 and close to +3).

These ratings were very important for the first study, since they were the target values of supervised machine learning methods (Kubota et al. 2016). That means that the rating values were used to "teach" the machine learning algorithms which movement patterns correspond to which value on the TRS. In other words, if another patient performs the same instrumental test, the algorithms will assign a score on the TRS, based on what movements were associated with which scores in the previous patients. The movement patterns in this case are the data captured from the sensors, which were used as predictors in the machine learning models.

Four machine learning algorithms were explored and evaluated based on the predictive performance they had. The predictive performance was evaluated in two settings, a 10-fold cross validation (CV) setting and a leave one patient out setting (L1O). In the 10-fold CV the dataset (sensor data and corresponding expert ratings) was randomly split in 10 sub-sets and at each iteration 9 parts were used for training the models and one part to test the model performance. There were in total 10 iterations and at the end of the process the results of every iteration were averaged. In the L1O setting the dataset was split into 19 parts, each part containing all the observations of a single patient. The algorithms

were trained based on the observations of 18 patients and the performance was tested against the patient left out.

In both settings, during the testing part, the machine learning algorithms were predicting on data previously unseen. The algorithmic predictions were compared to the average rating values of the experts, and two measures of interest were calculated. The correlation between the predictions and the ratings, and the root mean squared error (RMSE) between the predictions and the ratings. Those measurements are of interest, since, on the one hand, the correlation can give a somewhat clear picture on if the algorithmic predictions can follow the same dose-response behavior curve as the experts' ratings, and the RMSE can give an indication on the level of agreement between the algorithmic predictions and the raters.

Of the 4 machine learning algorithms examined it was evaluated that a support vector machines (SVM) model had the best performance (the other three being: linear regression, decision trees and random forest). SVM had superior performance from all algorithms in the 10-fold CV setting (correlation: 0.82, RMSE: 0.7) and similar performance to the linear regression model in the L1O setting (correlation: 0.6, RMSE: 1). Based on those results SVM was selected as the best machine learning algorithm. In figure 1 the performance is visualized in the L1O setting.

As discussed earlier, movement patterns associated with values at the end tails were not available, something also seen in figure 1. In turn, the machine learning models did not have data to learn from and would fail to make accurate predictions at those tails, which was the biggest limitation of the SVM model. An accurate depiction of that limitation is seen in figure 2, showing the results from the 10-fold CV. It is clear in this figure the values at -3 and +3 areas are over and under predicted respectively (also referred to as regression to mean effect).

The most important finding of this work was that monitoring and scoring the patients on a continuous scale is possible, and that the use of a single instrumental test can provide enough information to give accurate scores.

After acquiring these results the question was shifted to how would they could be used to assist with dosing optimization. That leads to the next section.
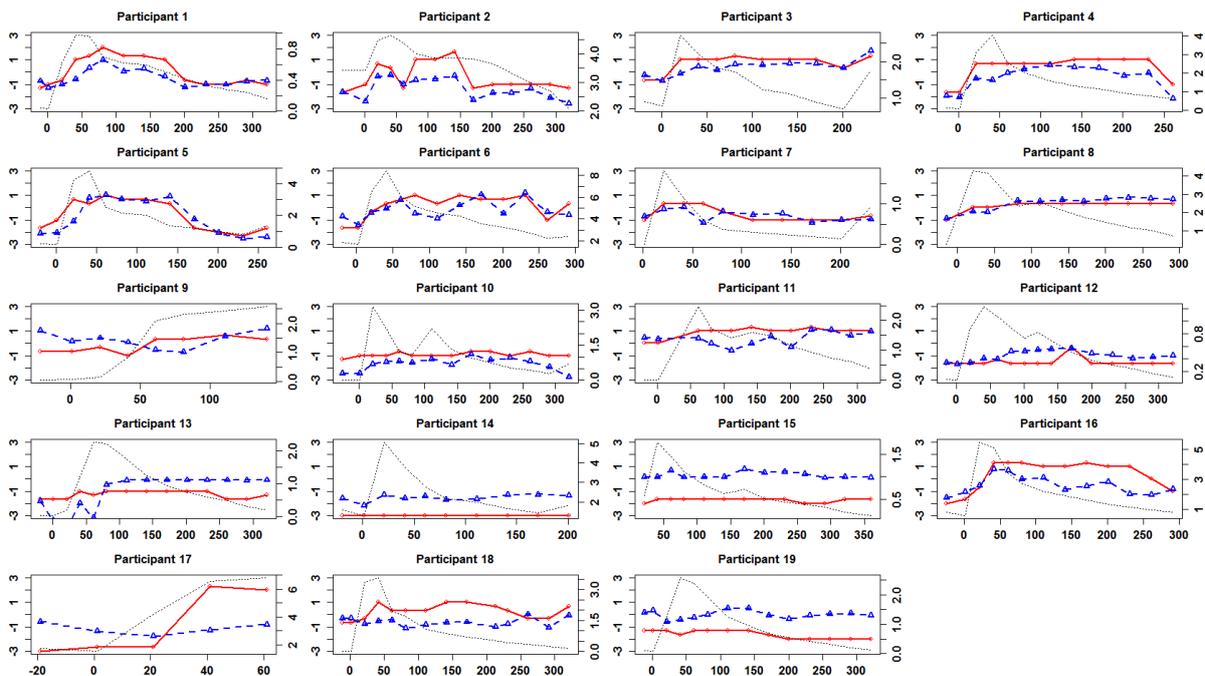

Figure 1: The L1O predictions of the SVM model. The straight lines (circles) represent the TRS rating and the dashed lines (triangles) the prediction values. These values are represented on the left axis, ranging from -3 to
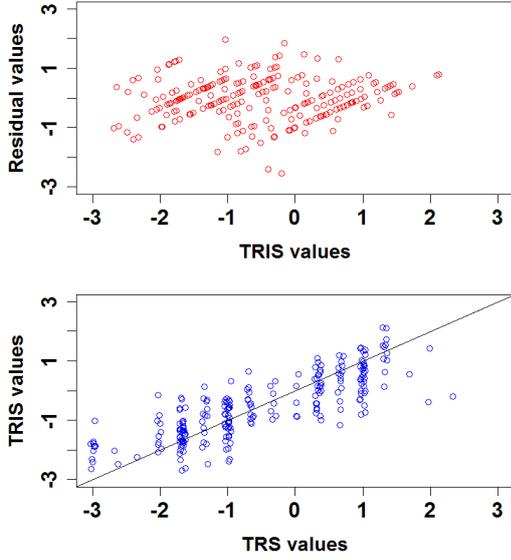
Figure 2: Visual representation of the SVM model performance from 10-fold CV. On the top plot the fitted (TRIS) vs. residual values is shown, without any apparent patterns. On the bottom plot the fitted (TRIS) vs. the TRS values is shown, plotted with a line going through the origin. Random error was added to the TRS values so that they do not overlap and a clear picture of the data distribution can be shown. It is seen in the plot that the values at the end tails of the TRS interval are over and under predicted.

Individual model fitting – part 1 of paper II

The research question that motivated the work in paper II, was how ratings on a specific scale and dosing information can be used together. The combination of these two should be able to provide information about patients' specific needs, as they describe the patient-specific dose-response behaviors. The answer to that question was inspired from the work of Jayachandran et al. (2014) where a method to predict patients' specific needs to treat leukemia is described, by individualizing dose-effect models.

Vaguely, dose-response models are models that are written as a system of mathematical equations and describe the response to a dose intake, which could be medicine intake, exposure to environmental factors, food consumption etc. In Jayachandran et al. (2014) the dose is radiation intake and the response is how the radiation treats leukemia.

The dose-response model used in paper II is specifically designed for levodopa intake and the mathematical equations describe the movement (and concentration) of medication through the body compartments (Othman and Sandeep, 2014; Simon et al., 2016; Westin et al., 2011). That is from the intake of levodopa until finally reaching an effect compartment, and the concentration of levodopa in that compartment manifests as an increasing value on an effect scale. This model has the effect manifested in the TRS scale (Westin et al., 2011), something consistent with the work done in paper I, but also useful when evaluation dose optimization for continuous infusion of levodopa, as the TRS is used for this purpose. The system of equations of the dose-response model used can be seen in equations 1-5.

$$\frac{da_0}{dt} = \text{Inf} - k_a * a_0 \tag{1}$$

$$\frac{da_1}{dt} = \text{BIO} * k_a * a_0 - \left(\frac{\text{Q+CL}}{V_1}\right) * a_1 + \left(\frac{Q}{V_2}\right) * a_2 + Rsyn \tag{2}$$

$$\frac{da_2}{dt} = \left(\frac{\text{Q}}{V_1}\right) * a_1 - \left(\frac{\text{Q}}{V_2}\right) * a_2 \tag{3}$$

$$\frac{dc_e}{dt} = \text{kEO} * \left(\frac{a_1}{V_1} - c_e\right) \tag{4}$$

$$E = \text{BASE} + \frac{Emax * c_e^{\gamma}}{c_e^{\gamma} + EC50^{\gamma}} \tag{5}$$

That model can be described as a two compartment model when in equation 1 dose intake takes place, and after movement through the dosing compartments it reaches the effect compartment in equation 5 and effect is manifested in response to levodopa concentration. The parameter and variable description of the PKPD model (equations 1—5) is given in table 1.

TABLE I
PARAMETER DESCRIPTION OF EQUATIONS 1-5.

Inf	Intestinal levodopa infusion rate (mg/min)
a0	Amount in first compartment (mg) / Variable
a1	Amount in second compartment (mg) / Variable
a2	Amount in third compartment (mg) / Variable
k_a	Absorption rate (1/min) / parameter
TABS	$1/k_a$, absorption time constant (min) / parameter
kEO	Effect rate (1/min) / parameter
TKEO	1/ kEO, effect time constant (min). / parameter
BIO	Bioavailability/ parameter
Q	Intercompartmental clearance (L/min) / parameter
V1	Volume in first compartment (L) / parameter
V2	Volume in second compartment (L) / parameter
CL	Clearance rate (L/min) / parameter
Rsyn	Endogenous levodopa synthesis rate (mg/min) / parameter
Ce	Concentration in the effect compartment (mg/L) / Variable
EC50	Concentration at 50% effect (mg/L) / parameter
Gamma	Sigmoidicity factor / parameter
BASE	Baseline effect / parameter
Emax	Change from baseline effect / parameter
E	Effect ranging from -3 to +3

As seen in table 1, the model contains variables and parameters. The strategy to fit individual models was to individualize some of the parameter values. The rest of the parameter values were fixed to the population mean values as in Westin et al. (2010). The parameters to individualize were selected based on a sensitivity analysis that was performed to understand which parameter changes influence the model output in equation 5 the most. In total 4 parameters were chosen to be individualized (together with an added secondary parameter), and the rest were set to population mean values. To individualize the 5 parameters, mathematical optimization was applied, by minimizing an objective function through least squares minimization. The objective function can be seen in equation 6, were the predicted effect is the value output from equation 5 and the TRS values are the scores assigned on the TRS scale (by experts or sensor scores).

$$Objective\_function = \sum_{k=1}^{n}(Predicted\_effect_k - TRS\_values_k)^2 \qquad (6)$$

In order to evaluate the ability of the method to fit dose-response curves to individual dose-response patient profiles, a simulation study of continuous infusion was conducted. This process was done with the intention that the individual models would have enough flexibility to fit dose-response curves, like the ones seen in figure 1. For that experiment 100 patient profiles were generated based on the population values of Westin et al. (2010) through a covariance matrix (individual parameter values for all patients on that study were available). For each of the 100 subjects an infusion morning rate and maintenance rate was provided and, with a sampling rate of 60 minutes, 12 observations were collected from each subject (without sampling or added error), with the values of the response on the

TRS scale. For all subjects the algorithm managed to fit individual patient models, with the objective function value of virtually 0. In other words the mean residual value from the model fitting process was 0.

In that step multiple optimization algorithms were evaluated, all giving similar results. Based on those results the model individualization strategy was assessed as sufficient and was succeeded by application of this methodology on real-life data. Of course, in real life data the objective function value will hardly ever be zero, since the TRS values will likely contain rating error (both from experts and from sensor predictions) and might not follow a "Gaussian" curve (in the case of a single dose experiment.)

After developing the model fitting algorithm, there still was a gap in knowledge about how the individual patient models can be used to make dosing suggestions. For that reason two dose optimization algorithms were developed, that take individual patient models as input, one for continuous infusion of levodopa, and one for oral administration of levodopa. Both algorithms were applied in real-life data and the suggestions they produced were evaluated against dosing decisions taken by expert physicians, used in this thesis as the gold standard.

Dosing algorithm for continuous infusion of levodopa – part 2 of paper II

Continuous infusion optimization is not something new as control theory has been extensively used in medical applications, when there is a known target value for a physiological measurement. The most notable application of control theory can be found in the treatment of diabetes (Leelarathna et al., 2014), where an infusion pump is supplying the patients with insulin, and the amount of insulin delivered is determined by the concentration of glycose on the blood flow. The application can be described as a closed loop process, as the system adjusts the dosing based on the output measurements. The target in that case is the glucose levels on the blood.

Another noteworthy application of continuous infusion optimization is the anesthesiology field were both closed and open loop feedback systems are used in practice (Struys et al. 2016). The target in this case is the desirable clinical state of the patients.

In this work the target value for the optimization procedure is a value selected in the TRS scale as the optimal state of the patients. This target value would be 0, as it is the ON state of the patients. As far as continuous infusion is concerned, treating personnel can find the optimal treatment quite accurately during the titration period. That is because the therapeutic decisions concern mainly the correct choice of the constant rate, a task with low complexity. The challenge in this case is not finding the optimal doses, but doing so in a timely fashion. Dose titration takes days, and patients usually are admitted to the hospital to do so, even though it has been also applied in remote fashion (Willows et al., 2016). Having algorithmic assistance that could help with reducing the dose titration period, and that is what motivated this work.

For the design of the continuous infusion algorithm the Levodopa-Carbidopa Infusion Gel (LCIG) pump specifications were taken into consideration, as it is the most widely used to treat Parkinson's disease. Through that device a morning dose is given at the beginning of the day, and after the dose is supplied a continuous infusion rate is initialized. The morning dose is high, and has the intention to bring the patients to an ON state quickly at the beginning of the day. The continuous infusion rate (maintenance dose) is lower and assists with maintaining the patient on the ON state, since it sustains the levodopa plasma concentration stable.

The limitation of this device, compared to the device used for diabetes treatment, is that sampling of levodopa plasma concentration is not possible since, to calculate levodopa plasma concentrations, blood samples need to be examined at a laboratory whether glucose levels are easily found in the blood flow. That means that the state of the patient needs to be assessed by an expert (or with wearable sensors) and a specific morning dose and maintenance dose needs to be manually programmed into the device.

As seen in figure 3, the optimization strategy entails minimizing an area (dark shade in the figure), which in that example consists of 3 parts, one before reaching the ON state, one with a bit of an overshoot, and one in which the TRS values go into the negative again. This is a typical representation of what the optimal behavior of a patient would look like, even though there could be exceptions. Mathematical optimization was used to minimize those areas, or, in better words, minimize the distance between the dose-effect curve and the target.
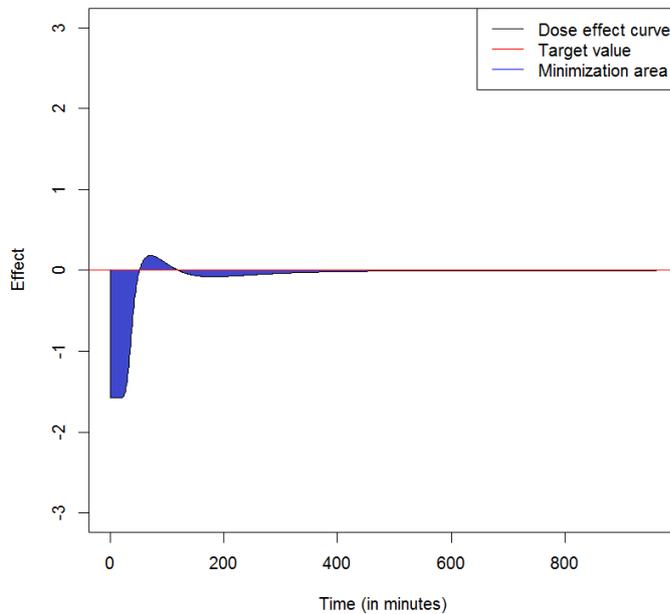

Figure 3: Optimization strategy for deriving optimal morning dose and infusion rate. The morning dose should be big enough that the effect reaches the target value as soon as possible and at the same time make sure that it is small enough so that such overshooting causes minimal side effects. The algorithm adjusts the infusion rate and makes sure that once the effect line comes to the target value again, it remains there throughout the day (960 minutes here- 16 hour day).

To evaluate the performance of the algorithm dose-titration data from continuous infusion were acquired from Uppsala university hospital. To access the data, an ethical application was filed to the regional board at Uppsala and permission was given to retrospectively access data of patients' admittance records to the hospital. The data contained information about patients' visit, with each visit consisting of a number of days that the patients were monitored (assigned a score to the TRS scale). During the monitoring period the patients' dose would be adjusted until finding the optimal morning and maintenance dose.

In total data from 31 patients were accessed (9 females – 22 males), which were hospitalized between 2011 and 2015. The mean titration period was 5.7 days with a standard deviation of 2.7. Each dosing day contained information about the amount of dose the patients received, the morning dose, the maintenance dose, or adjustments that were made within a day. For every hour after the dose initiation period there was a rating of the patients' state assigned on the TRS scale.

Since the data was not collected during a study specifically for the evaluation of the algorithm, there were a few limitation when working with it. The most important one is that the first observation is missing in most cases (at minute 60 after the dose initiation) making it for the system difficult to evaluate how the patients responded to the morning dose they received. Then, there was a consisted lack of observations at the baseline state (without any medication). A third limitation was the lack of dosing adjustment information in some occasions. Finally, for some days there was a lack of ratings, and the patients were only rated 2 or 3 times in a 16 hour period.

Based on those limitations it was decided that for each patient only one day of information would be used, the first day of their titration period that contained all dosing information and a sufficient amount of observations (the lowest was 6). The lack of information for the time point 60 minutes count not be accounted for, but for each patient the baseline was set the lowest value the patients demonstrated at

any point during the titration period. Out of the 31, there were 23 patients that fitted those criteria and individual models were fitted for. In figure 4 those patient observations (dots) and the fitted models (continuous line) can be seen. The patients in that figure that have multiple "spikes" in the dose effect curve received one or multiple extra doses during the day, a bit before the spike is seen.

Those individual models were passed to the dosing algorithm as an argument and for each model a morning dose and a maintenance rate was derived. The doses were then compared to the doses the treating personnel had derived on the discharge date from the hospital, used in this study as the gold standard.
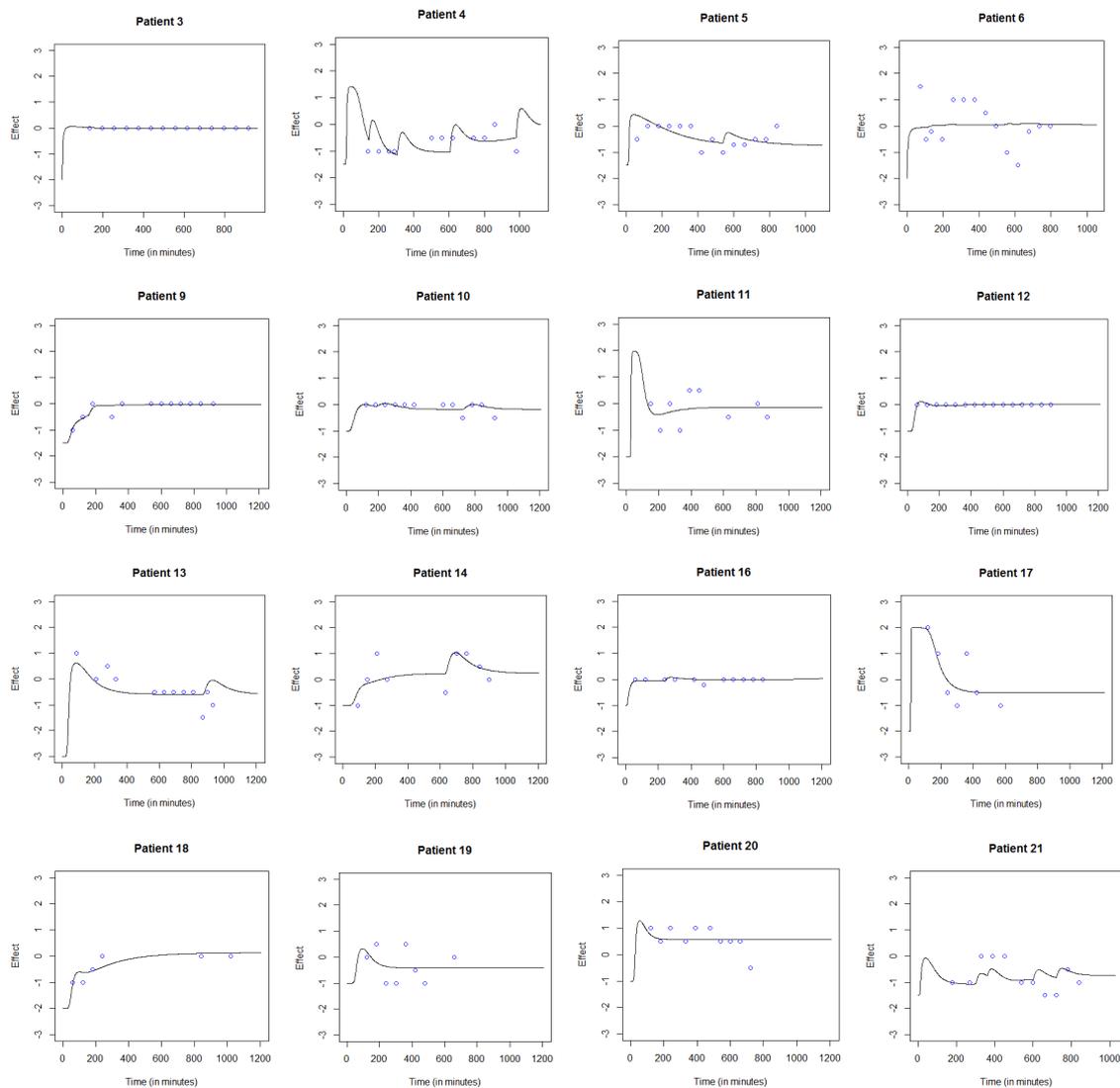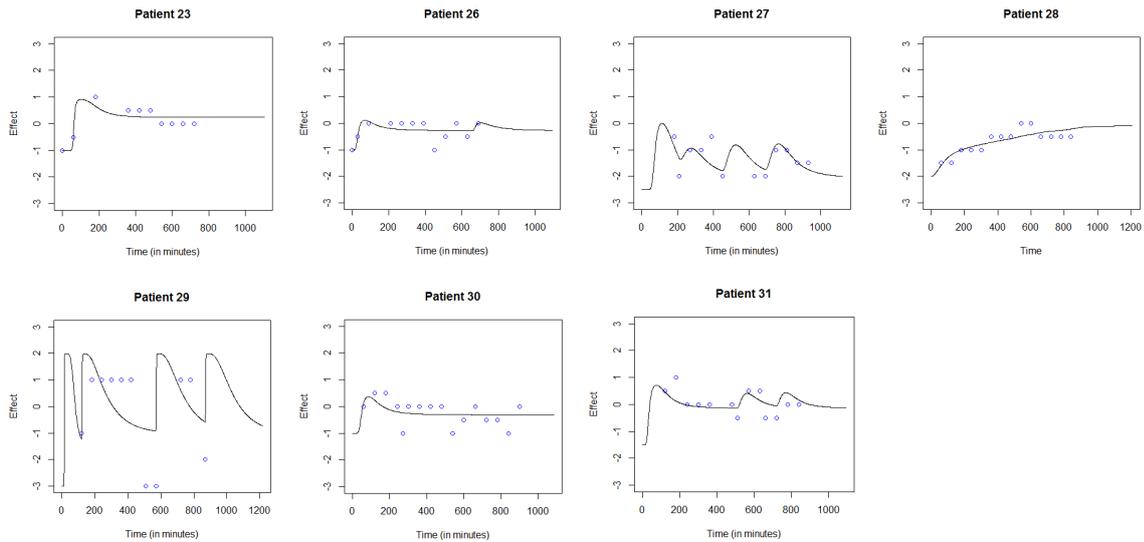
Figure 4: Individual fitted models. For each patient one model was fitted with one day of information from the chart data (doses, time of dosing, and ratings).

The comparison of the suggestions with the optimal dosing is shown in figure 5. The suggested infusion rate had 0.88 correlation to the optimal infusion rate with mean absolute relative error of 10%. The results from the morning dose were not comparable as the algorithm systematically suggested lower morning doses, with an obvious outlier in patient 29 that produced an extreme value for the morning dose (figure 5, right panel).
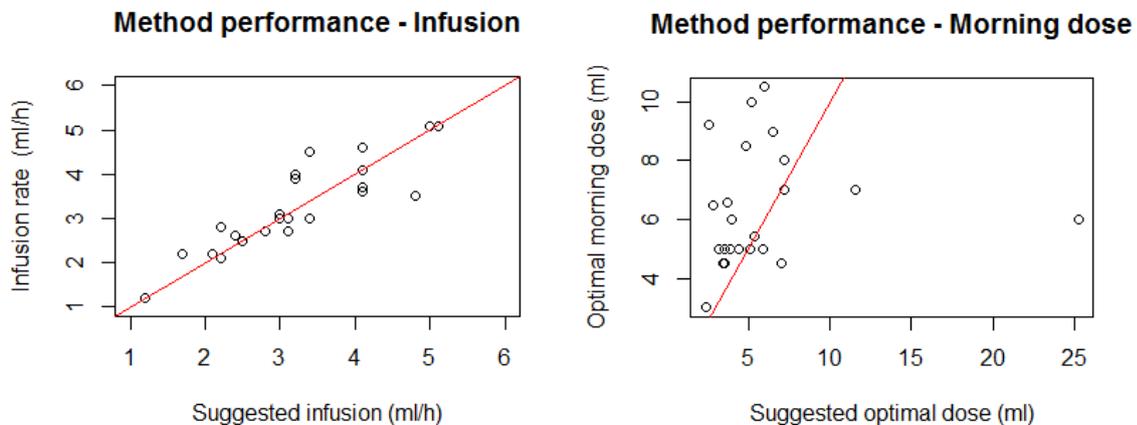

Figure 5: Left panel: infusion rate comparison. Right panel: morning dose comparison. In both panels optimal dose vs. suggested dose is plotted with the line going through the origin added.

It should be noted that the algorithmic suggestions for the morning dose are far from optimal, with a few explanations as to why this is happening. The most obvious one, as said earlier, is the fact the patients state is not evaluated at the time points after receiving the morning dose. A second reason, which is more knowledge driven, is the fact the treating personnel does not follow the same strategy as the dosing algorithm. In clinical practice the old dose (of oral administration) is converted to the equivalent infusion morning dose (Tomlinson et al., 2010), without taking into account the immediate initiation of a continuous flow of medicine after the morning dose has been given. That means that there is an overshoot at the beginning of the day, something that is also supported from the data, as seen in figure 4 for patients 6,13,14,17,19,20,23, 29, 30 and 31. These patients have a big overshoot in the chart data (dots) but the morning dose was not adjusted downwards, as the algorithm suggested.

10

Dosing algorithm for oral administration of levodopa – paper III

In paper III the research question shifted from continuous infusion to oral medication of levodopa, particularly for the advanced treatment stage. In contrast with the continuous infusion, the complexity of this problem, even for experts, makes the determination of an optimal dosing scheme (dosing interval and amount of dose) a challenging task (Nyholm et al., 2014).

In this case, the construction of a dosing algorithm is not as straightforward and multiple aspects need to be considered. It starts with the fundamental understanding that such a way to medicate is not optimal in the sense of treatment efficacy. A naïve but instinctively correct question would be why all patients don't get an infusion pump or DBS (and get improved treatment), and the treating personnel bothers with tailoring the individual doses when there are superior options. That questions has a multilevel answer which relates to cost of treatment (infusion pump is by far the most expensive (Valldeoriola et al., 2013), potential side effects (DBS has the most severe ones (Fenoy and Simpson, 2014), even though there is evidence to suggest that continuous infusion can cause peripheral neuropathy (Mancini et al., 2014), convenience for the patient (quality of life with a device attached to a body), and last, but most definitely not least, potential improvement of treatment for the patients. A comprehensive evaluation of these factors is performed to determine if the potential treatment improvement outweighs the combined adversity risk of the above factors.

Having said that, it is possible to dive more into the details of the dosing algorithm for oral administration. Patients do experience wearing off in effect from one dose to the next, and most patients will have dyskinesia manifestation during the day. When designing the algorithm, adverse behavior is a given, and the system is built to minimize these adverse effects. The question is how one finds a dose that is high enough so ON state is reached but at the same time is low enough so overmedication is avoided.

That question was answered by setting a target interval for each patient, and keeping the expected dose-response effect within that interval as long as possible. In figure 6 the dosing algorithm design is graphically depicted. For a fixed dosing interval, a morning dose is given, with subsequent maintenance doses throughout the day. The estimated effect is kept within a target interval range and an additional safety has been set, a threshold value to prohibit the fluctuation to become so large that the patients' condition traverses back and forth in the different motor function states. The imposition of a threshold value, which the dose-effect curve could not cross was called the fluctuation criterion.
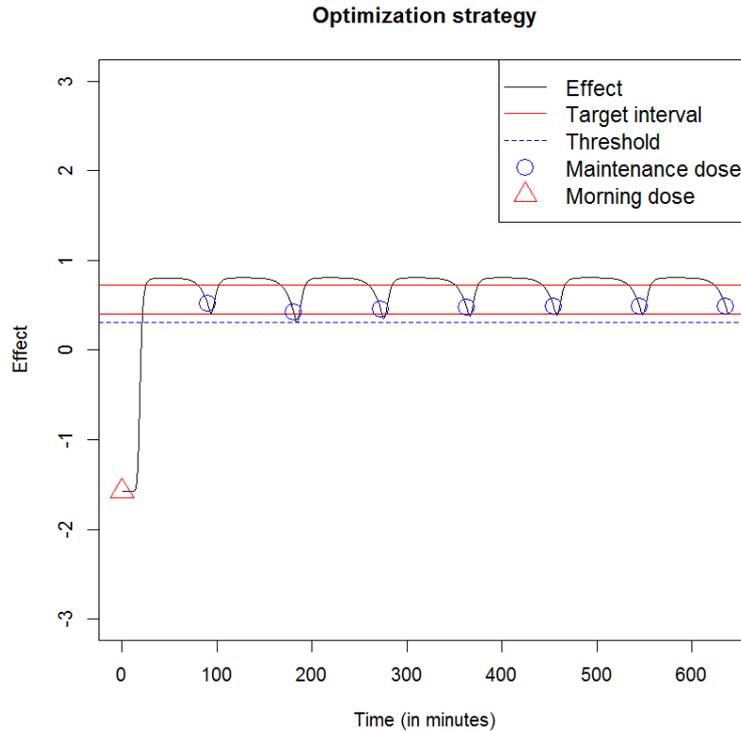
Figure 6: Dose optimization strategy of the algorithm for an example patient. Within the red (straight) lines lays the target interval and the area outside that interval is minimized by the algorithm. The triangle represents the moment the morning dose is suggested and the circles represent the moments that the maintenance doses are suggested.

The input to the algorithm were individual patient models. The dosing algorithm produced an optimal dosing suggestion for a multitude of dosing interval for the individual patient models. Usually a dosing interval is as low as 90 minutes and as large as 240 minutes. The algorithm suggested one optimal dose for intervals within the 90-240 minute range, with a 10 minute interval increase. So, for 16 dosing intervals (90 min, 100 min, … , 240 min), there would be 16 dosing suggestions, each one corresponding to a dosing interval.

For each dosing interval, in order to find the optimal dose, the algorithm performed repeated simulations in two steps. The first step was to find the maintenance dose and the second step was to find the morning dose. For the maintenance dose, starting from a value of 1mg, the dose optimizer simulated the behavior of the dose effect curve for 16 hours (960 minutes). The process was repeated for every dose until a maximum (usually at 300 mg) with a 1 mg increase for the dose value. For each of the doses the total area value outside the target interval was stored (after the 600 minute mark, as the effect of a morning dose wears off at maximum a 10 hour period). That means that for a single interval 300 different doses were evaluated and the one that produced the minimum area outside the target interval was selected as the optimal. On the second step the morning dose was evaluated on a similar fashion, but then the maximum dose was allowed to reach 400 mg and the area evaluated was after the 20 minute mark (after receiving the dose the manifestation of effect has about a 20 minute delay, on average, so a choice before that could lead to overmedication of the patients). At the end, for every interval, a combination of a morning dose and a maintenance dose was suggested as the optimal.

In order to evaluate the performance of the proposed solution, data from a clinical study where used. The objective of the study was to optimize the dosing schedules of people in advanced dosing stage of PD, with the assistance of a wrist worn monitoring device. A dose dispenser of microtablets of levodopa was used, that allows for precise doses of levodopa. A secondary objective was to assess the

feasibility of using the dosing algorithm to optimize the medication schedules of the patients. Thirty ones patients were recruited and after 3 screening failures, 28 patients enrolled in the study.

The study was a longitudinal, single-center, observational, open-label study, and it consisted of three patient visits to the clinic, with a two week period between each visit. On the first visit the previous dosing schedules of the patients were converted to the microtablet equivalent (Tomlinson et al., 2010). Then, for a week before the second visit, the patients wore the monitoring device to evaluate the dose efficacy of the previous dosing schedule. On the second visit, a single dose experiment, as the one described in paper I, was conducted, where patients wore different sensors (as the ones on paper I) to perform instrumental tests. The results from the supination-pronation test were used in this study.

The adjustments the physician made were mostly based on the monitoring device recordings, and the suggestions that the algorithm produced were based on the sensors readings during the test day. For the dosing algorithm to produce the dosing suggestions the following steps were taken:

1) Extract the sensor data and run the machine learning algorithms to score the patients state on the TRS (Work of paper I).
2) Use the scores and the dosing information to fit individual patient models (Work of paper II).
3) Pass the models as an argument to the dosing algorithm for oral administration of levodopa.

Two weeks after the second visit, the patients had a third visit to the clinic to evaluate the efficacy of the adjusted dosing schedule. On that visit if was evaluated if the dosing adjustments of the neurologist improved the clinical state of the patients. More details about the study structure and its outcomes can be found in Johansson et al. (2017).

As described before, on the second visit the supervising neurologist adjusted the dosing routines of the patients, giving them a morning dose, a maintenance dose, and a dosing interval. For the dosing interval that the neurologist chose the morning and maintenance dose were compared to the morning and maintenance dose that the algorithm suggested for the same interval. The results of the comparison can be seen in figure 7, where the algorithmic suggestions against the neurologist choices are plotted. From that figure it can be evaluated that the dosing suggestions of the algorithm have great agreement with the neurologist's adjustments, for the same dosing interval.

Finally, independently of the neurologists' prescriptions, the algorithm visualized the predicted response of the patients' state for each dosing interval as a guide to indicate towards which the optimal interval would be. An example of this visualization is seen in figure 8, where the areas above and below the target interval are summed up and plotted against one-another for each dosing interval. In this example, the interval of choice would be a dose about 150 minutes, since it is the interval with the minimal area outside the target interval.
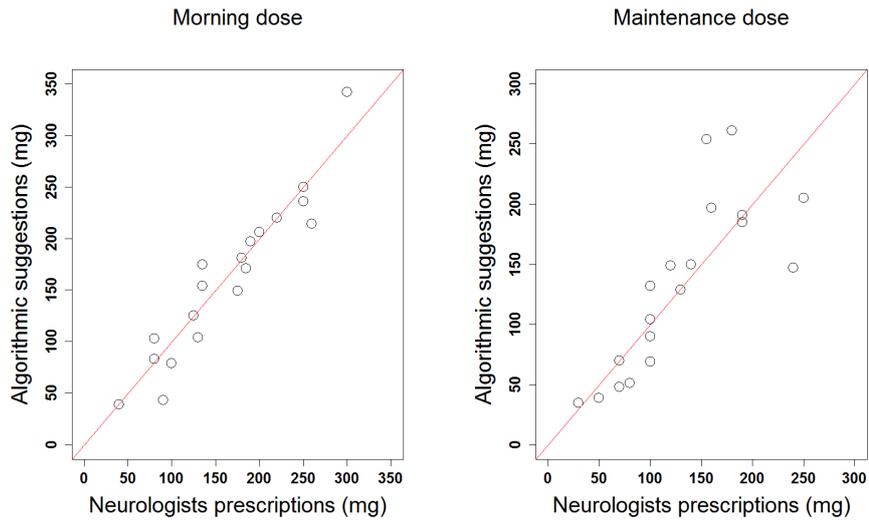
Figure 7: Visual comparison of the algorithms suggestions compared to the physician's choices for the same dosing interval
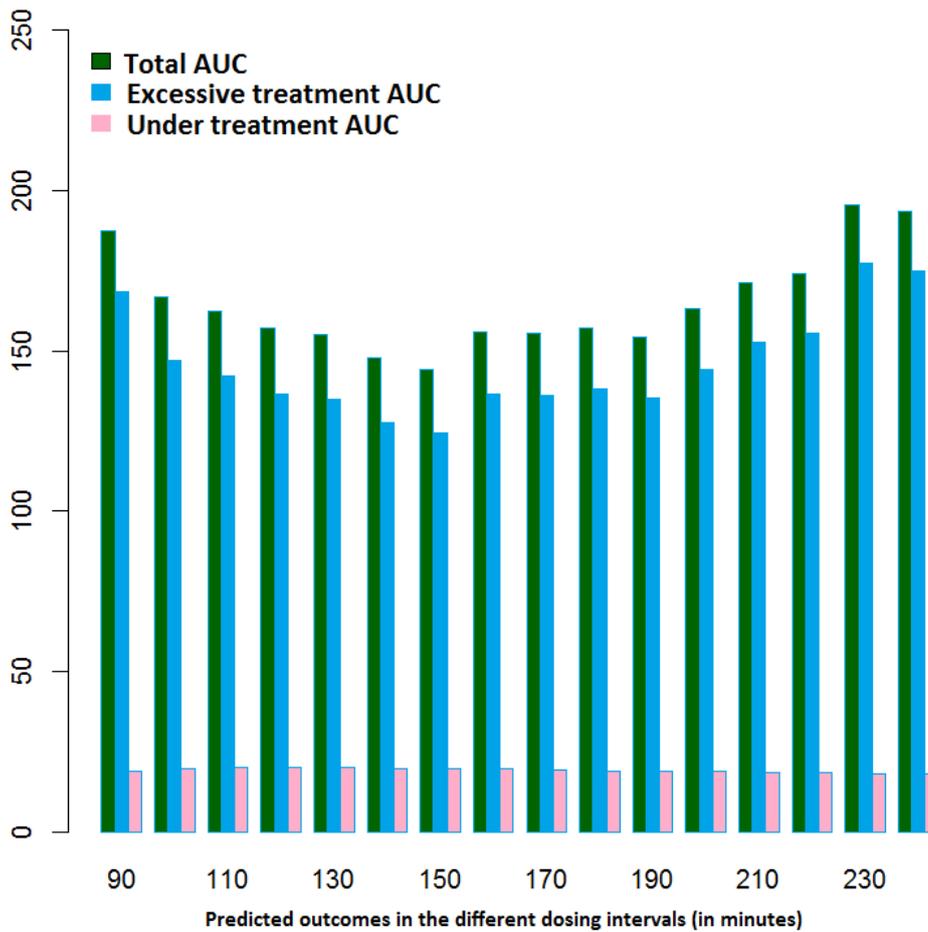

Figure 8: Visualization of the predicted outcome. For each dosing interval a corresponding barplot is created that gives information about the AUC estimation of being overmedicated or undermedicated with the suggested dose. On the x-axis the different dosing intervals are shown. On the y-axis the AUC of an individual being on a non-optimal state for a day is plotted, as a function of time (in minutes) and absolute distance from the target interval.

Synergy between the three papers

In this thesis three original research papers have been discussed. The focus was on providing the readers with the background of the problem, and subsequently motivating the methodological choices of the work. The performance of the developed methods and systems was evaluated and the key results were also presented.

It would be a remiss to evaluate the results of each paper separately, since the work follows a clear path from the first paper to the third one, and the three papers complete each other to form this thesis as a single entity. The third paper would not be possible without the work of papers I and II. The second paper stands alone, but the inspiration came from the results of paper I.

In figure 9 a graphical representation of the work flow is given for a better understanding of how the three papers complement each other. A patent application that follows a similar work flow and utilizes that work of the 3 papers has been filed and more information can be found in patent number GB1708624.0, filled in the UK (authors: Thomas, Memedi, and Westin).
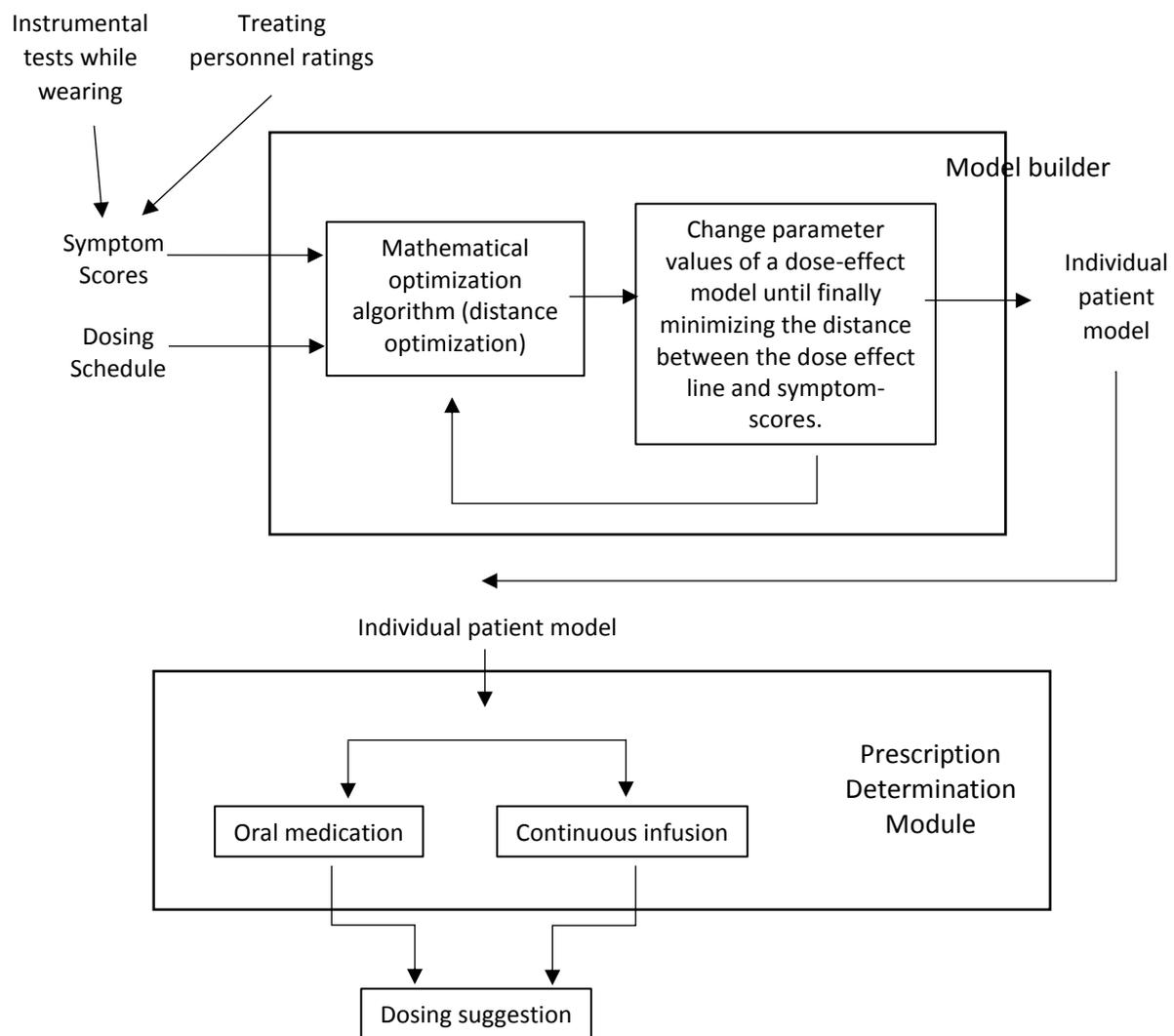

Figure 9: Work flow of the thesis. The input to the model builder is either sensor ratings (paper I) or treating personnel ratings. The model builder uses the dosing information and the ratings to build individual patient models (paper II). The individual patient models are then passed as an argument to the prescription determination module, where the dosing algorithms either suggest a dosing schedule for continuous infusions of levodopa (paper II) or oral administration of levodopa (paper III).

Limitations of the thesis work

The methods developed had also limitations. The most considerable limitation of paper I, was the under and over prediction issue at the two tails of the TRS scale. It does seem however that when using the sensors with the dosing algorithm for oral administration the dosing suggestions are quite robust, regardless of the max and min effect detected from the prediction algorithm.

Paper II had two limitations worth discussing, one in the sensitivity analysis part, where a local sensitivity analysis method was used, instead of a global sensitivity analysis method. Since the focus of the paper was not in this part, such a limitation is not considerable (and it is unlikely that the results would be different in a global sensitivity analysis setting). One could argue that the sensitivity analysis was merely a guide that confirmed the choice of parameters rather than point to which parameters to choose. The second limitation was the dataset used in the evaluation part. That dataset was far from optimal for this setting, since motivation of dosing adjustment choices was missing from the charts, and the charts themselves had a lot of missing observations. A way was found to overcome this limitation, using the first possible day from each chart, but one could only speculate on the reasons of the differences between the morning dose suggestions and the treating personnel choices.

Paper III does not have a pronounced limitation, and one could point to the fact that the system does not produce a suggestion for a specific dosing interval. What is produced is a visual representation of the expected behavior of the patients in each interval, which could be useful as a guide but restricts the automation of the process.

Discussion of the thesis in the context of microdata analysis

Microdata analysis is a normative science that comprises of a 5-step chain, namely data collection (step 1), data capture, processing, and storage (steps 2 and 3), data analysis with mathematical modeling (step 4) of data, and finally decision-making / decision support (step 5). For a thesis work to be placed in the field of microdata analysis, it needs to fulfil 3 criteria:

1) The research conducted is normative with the goal of better decision-making in a complex environment.
2) It has good understanding and familiarity with parts 1-4 of the Microdata analysis chain.
3) It has deep methodological understanding in at least one part of the chain.

The work of this thesis proceeds from data collection, to data processing, to statistical analysis and development of novel methods, to finally describing how the methods can be used for decision support. It was a practical, problem-solving, goal-oriented work that managed to a great extend find answers to the research questions set at the beginning of the project. It is in line with the spirit of normative sciences and has the aim to aid in decision making in a complex environment, such as dose optimization. Parts 1-4 of the microdata analysis chain have all been used and deep methodological understanding has been shown in parts 4 and 5. Looking at the three manuscripts through the perspective of the microdata analysis definition, one can truly appreciate how this research fits in the field.

Future plans

More focused efforts will be made on the second part of the doctorate degree to develop the methods proposed. As discussed in previous chapters the algorithms presented have limitations and in the next version of the algorithms these limitations need to be addressed. This work could take a few different directions, focusing either on validation of the developed algorithms or investigation of alternative ways to make dosing suggestions, just to name two.

However, future work should not limit itself to the refinement of the work of this thesis. The next steps should have a strong focus on the key elements of microdata analysis, which revolve around decision support. Implementation of the work suggested here and validation of the dosing suggestions through the patients' perspective should be the priority of future work. To that end, the ambition is that the proposed system will be intergraded into an interactive platform (or internet application) that visualizes the results of the algorithms for the better understanding of the treating personnel, in order to truly assist with decision making.

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