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Development of a Computer-Aided Dosage and Telemonitoring System for Patients Under Oral Anticoagulation Therapy

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Abstract. In this paper, we present a system that allows patients who require anticoagulation medicine an opportunity to independently manage their dosage concentration with the help of two machine learning algorithms. The basic idea is to predict the next dosage by using a neuronal network and the model predictive control approach, both based on the history of data already available from patients. This machine learning system is expanded by an smartphone application for the patients, and a website for the doctors to support their patients.

Keywords. artificial neural network, model predictive control, computer aided dosage, INR self management, anticoagulation therapy, telemedicine

1. Introduction

Today, due to heart disease and interventions, there are many patients who require anticoagulation medications (such as patients with mechanical heart valves, atrial fibrillation, LVAD-patients, etc. [1]). The correct dosage of the medication is vital: If the coagulability is too high, there is an increased risk of thrombosis. If it is too low, the risk of bleeding increases. To avoid these complications, it is important that the International Normalized Ratio (INR) remains in the therapeutic range [1,2]. To achieve this the medication dosage is usually determined by a doctor based on an INR-diary. However, due to the long intervals between visits to the doctor, the results in the aftercare were often not optimal. The INR-values therefore often lie outside the therapeutic range. Nowadays INR self-management has become established. Here, the patient measures his INR-value and determines his own medication dose. Several trials have shown the self-management to be beneficial both to therapeutic success and patient satisfaction, although there is room for improvement as deviations still occur regularly [2,3,4]. Another problem is the loss of overview for patients in self-management and overall control of the physician. To solve these problems our study aimed to develop a system that 1. automatically communicates the INR-specific values to the physician for documentation and control, and 2. creates an individually calculated medication recommendation for the patient based on personal health parameters and therapy relevant data records with the aim of optimizing the INR setting and to avoid complications.

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To illustrate the architecture of the system and the algorithmic methods in particular this paper is organized as follows. Section 2 presents an overview of related work and other approaches with the same goal. Section 3 presents the architecture of the system with focus on the two suggestion methods neural network and model predictive control. Tests and evaluation of our recommendation models are presented in section 4. A roundup and an outlook is offered in section 5.

2. Related Work

Heneghan et al. conducted a meta-analysis of randomized trials on self-monitoring INR-values and partly self-adjusted therapy using anticoagulant drugs [5]. They found that in the evaluated trials the self-management to improve the quality of oral anticoagulation with pooled estimates showing significant reductions in thromboembolic events, all-cause mortality and major hemorrhage. Ferreira et al. reviewed a telemonitoring system for VKA-patients and proved it to be safe and effective [6]. Poller et al. conducted a randomized study of two commercial computer-assisted dosage programs (PARMA 5 and DAWN AC), demonstrating the safety and effectiveness of these programs in comparison with experienced medical staff [7]. Both programs feature a graphical interface for patient management and monitoring for the medical staff, however only the DAWN AC-program contains the possibility of partial patient interaction, with the patient using a web browser to report INR values and receiving the dosage via text message. The algorithms used by PARMA 5 have been demonstrated by Manotti et al. [8]. The algorithms used in DAWN AC remain unknown. Rasmussen, Corell, Madsen and Overgaards investigated the management system CoaguTel [9]. The Hillingdon-algorithm, which is the main algorithm used by CoaguTel, has been described by Wilson and James [10]. None of the established and reviewed systems use a mobile application for patient interaction (e.g. sending INR-documentation), use a machine learning algorithm apart from regression analysis or consider patient vitamin K intake. We presume that because of this the existing systems lack the ability to easily incorporate new kinds of data records, which might be relevant to the dosage recommendation, such as the patient's dietary information.

3. Method, Experiment

The architecture of our system can be split into the two components front end and back end. The front end can further be split into a mobile app for the patients and a platform-independent web interface for the physician in charge. The back end is modularly developed with a restful web server, a database that stores the data of the patients and machine learning-based drug dosage recommendation systems [11]. For the patient's needs, a mobile app was developed for Android smart phones. This app is capable of tracking the INR measurements and other relevant data records, like a digital diary.

Upon entering a new data entry, the web server sends a request to two different machine learning systems based on the latest measurements. These two are an artificial neural network and a model predictive control system. The recommended drug dosage is stored in the database.

To monitor the recorded INR measurements and drug dosages, the physicians have access to a platform-independent web interface. Additionally, this interface informs the treating physician automatically, if a patient's record shows any threatening conditions (e.g. measured INR value is out of range).

To validate the system, 11 patients, all in VAK-treatment for of having a LVAD, have been asked to try out the system. Age range was 49 - 68. A total of 277 pairs of INR-measurements and dosages have been collected over a span of 12 weeks. INR target ranges were individual, but lied all between 2 and 3.

3.1. Assisted Patient Monitoring

Until now the patients had to keep the INR diary manually. This led to some disadvantages: While bad readability is one of the minor problems, the major disadvantage is that the patient visits his doctor in relatively large time intervals of two or three weeks, sometimes longer. This results in the fact that adjustments of the dosage can be applied only with a delay according to the changes of the measurements. Our app does not only replace the diary, but also transmits measured values to the doctor immediately. This way it is not only possible for the doctor to conduct adjustments of the dosage promptly but also to react to serious discrepancies of the INR values from the therapeutic range as soon as possible, optionally by adapting the dosage by using the web interface.

Some food and drugs affect the INR value. Unfortunately, there are almost no studies about this research field. It is only known which foods and drugs cause changes of the INR value. Therefore, it is additionally possible for the patient to document his food and drug history during his INR medication. The data collected can potentially be used in further work.

3.2. Automated suggestion on basis of data-driven machine learning algorithms

To suggest a dosage to the patient, we investigated two different machine learning techniques. First, we took a look at neural networks to predict the next dosage directly by learning from a set of training data records. Second, we build a control system, based on model predictive control, to influence the INR value to be in the middle of the TR[2]. This section provides the reader with the setup for the machine learning processes as well as an evaluation.

3.2.1. Neural Network Approach

Neural networks are a great approach, based on human's cells and neurons, to investigate a non-trivial connection between some data and a so-called label [12,13]. The advantage of neural networks consists of the ability to detect non-linear and complex correlations in the data. The net should predict a label for a data record only based on previous observations. A data record is mostly a set of values, with fixed size, and a label is a value associated with that data record. To use a neural network, a set of training data records is needed. A training data record contains the values and the corresponding correct label. After the network has been trained, it can be used for predicting a dosage. The training process itself is typically a gradient descent approach, minimizing the mean squared error between the (correct) label of a training data record and its prediction from the network.

The approach divides into the setup for the neural network and the (non-trivial) computation of a set of training data records. We used MATLAB's neural network

[2] TR: therapeutic range

toolbox[3] as the implementation of the neural network. There we used a simple feed-forward network with multiple layers of neurons. We extract the training data records from several sources. A data record contains information about the INR value, the dosage that was taken by the patient as well as a time stamp.

To train the network we created a set of about 700,000 training data records containing a fixed row of data entries, which consist of the last N data records of the patients INR and drug history. As the label, it contains the INR and dosage values for the next day. Here we suppose the weak assumption, that the patient knew, what was the best dosage at that time. Most patients in our data-stock were on a good adjustment, so that we suppose learning from them would create a good neural network for predicting the dosage. In addition to the last N data records from a patient, we took the type of medication (MARCUMAR or COUMADIN) and the TR (containing the maximum and minimum INR values) as input for our network. As a result, we get $2 * N + 3$ input neurons for a fixed $N \in \mathbb{N}$. The network has two output neurons for the dosage and the INR prediction.

Because of the non-deterministic random like behavior of neural networks, a secure mechanism should be implemented, which checks the predicted dosage against some kind of rule. We suggest only using dosage predictions in the "typical" range of a patient or check for heavy deviations in the dosage prediction.

3.2.2. Model Predictive Control

Another approach that is used to calculate a dosage recommendation for the patient is based on MPC (model predictive control). This method originates from control system theory and extends regular control systems with a model to predict the behavior of the system and to choose the optimal inputs. MPC based controllers take the current state of the system and optimize the system input under a given cost function. This optimization is calculated for a horizon of T steps so that at time t the cost-function J is minimized in the timespan $[t, t + T]$. Only the first step of the optimized control outputs is used and the calculation is started again [14,15].

In our case of finding an optimal dosage we interpret the patient's body as the system to be controlled. The dosage is used as the control input, while the measured INR is taken as the controlled variable. We use the center of the therapeutic range as the reference point for the control output so the cost function is given as the difference between this value and the INR (Eq. 1).

$$J = (TR_m - INR)^2 \tag{1}$$

This context requires the underlying model to represent the correlation between a given medication dosage and the resulting output, the INR value. We used a simple model which assumes an output that decreases over time and increases with the input. This simulates higher INR values with higher dosages and lower INR values with lower medication dosages.

Similar to the neural network approach the MPC structure was implemented with MATLAB and its *Model-Predictive-Control*-Toolbox[4]. The described model was realized with the help of Simulink, a software bundled with MATLAB to build, simulate and control complex systems.

[3] https://www.mathworks.com/products/neural-network.html
[4] https://www.mathworks.com/products/mpc.html

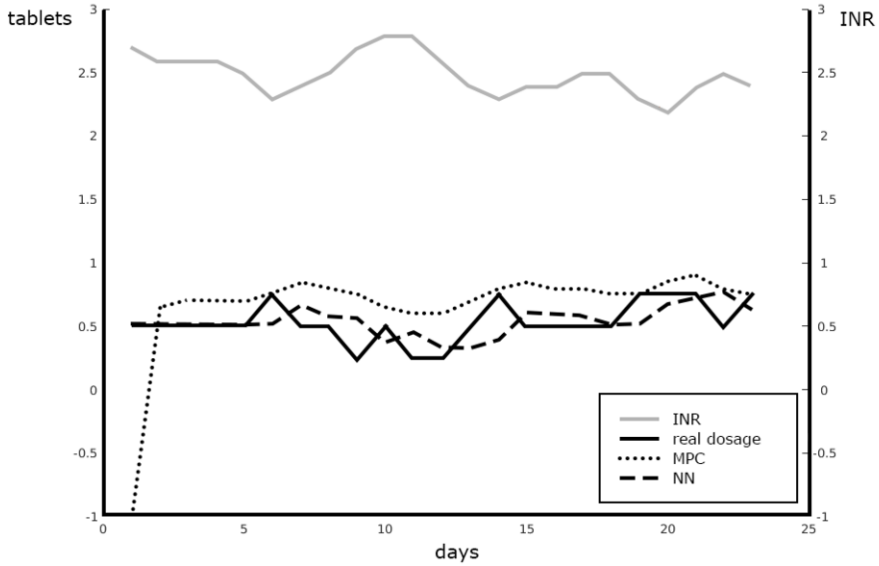


Figure 1. Comparison of different algorithms with real dosages and the corresponding INR values

Finally, both of these systems have to be triggered and the given dosages need to be transferred back to the server. This was realized with a message queue based infrastructure that took requests from the server and distributed them to the recommendation processes. Since both recommendation approaches were built with MATLAB a Java connector between the message queue and MATLAB was built. This connector reads the recommendation requests from the queue, starts up the recommender and reads their results. These results are then put into another queue from where the web server reads and persists them and finally displays them to the user in their app and the doctor in the web front end.

4. Results

Our app improves the process of INR self-management in several ways. The patient gets an easier way to keep track of his medication and INR history. The doctor is enabled to keep track of many patients at once and review their current state. Furthermore, they are notified in the event of INRs that are out of the TR. The modular infrastructure allows the evaluation of multiple models for dosage recommendation.

To evaluate the recommendation models their results were compared with actual dosages (Figure 1). Since these dosages – which were chosen by the patients themselves – are not necessarily optimal, a recommendation close to the actual dosage does not indicate a good recommendation. For a better assessment of the evaluation the patient histories we looked at 30 day blocks of measurements and classified them by variance of the INR in respect to the middle of the therapeutic range.

For the blocks with maximal, average and minimal variance the algorithms were compared to the actual dosages in the following way: Since the neural network needs at least a week of patient history prior to the evaluated day, a window of 7 days was moved along the 30-day block. This resulted in 23 different recommendations that could be

compared to the dosage value given in the dataset. The mean squared error E of these differences was then calculated (Eq. 2). These errors were then averaged over the different variance categories, as can be seen in Table 1.

$$E = \frac{1}{23} \sum_{n=8}^{30} \big(R(n-7,n) - D(n)\big)^2 \quad (2)$$

$R(m,n)$ = Recommendation for day n, with measurement input from day m to n
$D(n)$ = Actual dosage on day n

Table 1. Mean squared error between recommended and real dosage

Variance	MPC	NN
maximum	0.4515	0.4711
median	0.3954	0.0867
minimum	0.3835	0.0297

As already mentioned, the actual dosages can not be considered optimal. Therefore a heuristic was constructed to further evaluate the algorithms. Based on the time that a dosage of anticoagulant needs to take effect (given as about 2 days for MARCUMAR, cf. figure 2) the following assumptions were made:

When evaluating the dosage $D(n)$ at time n, we take the difference between this and the corresponding recommendation $R(n)$ as $\Delta_D = R(n) - D(n)$. We then look at the INR offset by the above mentioned span of 2 days $I(n+2)$ and compare this to the center of the therapeutic range TR, $\Delta_I = I(n+2) - TR$. If $\Delta_I > 0$, we can assume that the dosage has been too high and therefore we want Δ_D to be negative, meaning a lower recommendation than the actual dosage. Vice versa we want $\Delta_D > 0$ for $\Delta_I < 0$.

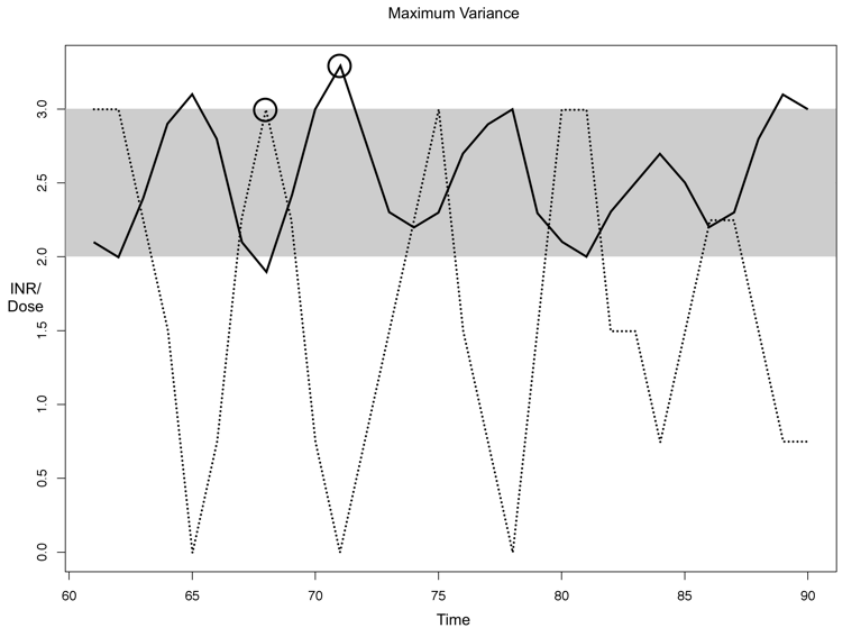
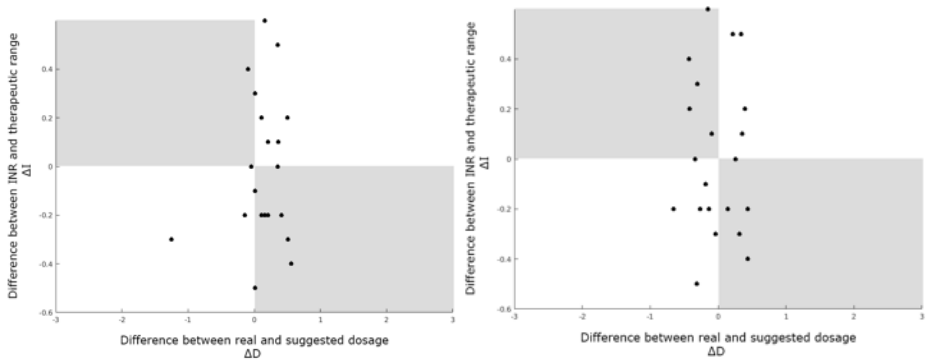


Figure 2. Patient history showing a high dosage (dashed) and the corresponding high INR-value 2 days later (solid)



(a) MPC (b) NN

Figure 3. Scatterplots of Δ_D and Δ_I, with the desired areas marked grey

An example plot of evaluating the two algorithms with this heuristic can be seen in figure 3 for one of our mini-trial patients with 29 data points. Other patients of our trial have similar distributions so that the algorithms have between 50% and 60% recommendations that meet the described criteria.

5. Discussion, Future Work

The mini-trial conducted at the *Schüchtermann* clinic showed the system to be viable in practical use. Our results support the idea that even relatively simple dosage recommendation models can be on a par with the patient's own dosage decisions and are in such consistent with previous assessments. The data records might not truly reflect the viability of the used dosage recommendation algorithms in practice as 9 out of 11 patients have been in close guidance by clinic caretakers during the trial period. A longer field trial with more completely self-monitoring participants is needed to fine-tune the algorithm parameters and determine a better quality estimation. Note that as of now while autonomous algorithmic decision-making for dosing is technically possible a human doctor must make the final decision by law in many countries (e.g. Germany).

The models have been trained on a very limited database. It can be assumed that they will perform better, when the training sets become bigger and of better quality. The integration of health tracking data, which in many cases is already being collected (like step count, other drugs, heart rate monitoring), is of particular interest. While the consideration of these data points by human caretakers is hardly viable, the machine learning algorithms can learn whether the integration is useful. The frameworks and standards already exist (e.g. *iOS Health app* and *ResearchKit* or *Google Fit*), a follow-up program would need to determine whether the data records can be used for dosage prediction. Besides automatically collected data records it also seems promising to include laboratory records, especially liver values and data records about the patient's diet, in the calculations. Some features, like detection of drug interactions, while theoretically useful, have been kept back as they were not necessary for the evaluation or were not feasible. The web application can be extended by an emergency access for fast insight in emergency situations. For practical usage, it should be possible to export the data points collected and calculated in the application to other programs

used in the clinic environment. In future, it would be desirable to develop an open sourced and publicly available system for automatic dosage recommendations to simplify comparisons among algorithms, as both researchers and patients would benefit.

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