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Monitoring of anticoagulant therapy applying a dynamic statistical model

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ABSTRACT

Patients with an increased risk of thrombosis may require treatment with vitamin K-antagonists such as warfarin. Treatment with warfarin has been reported difficult mainly due to high inter- and intraindividual variability in response to the drug [1]. Using predictive models that can predict International Normalised Ratio (INR) values enables for a higher degree of individualised warfarin dosing regime. This paper reports the outcome of the development of a dynamic prediction model. It takes warfarin intake and INR values as inputs, and uses an individual sensitivity parameter to model response to warfarin intake. The model is set on state-space form and uses Kalman filtering technique to optimise individual parameters. Retrospective test of the model proved robustness to choices of initial parameters, and feasible prediction results of both INR values and suggested warfarin dosage, which may prove beneficial for both patients and healthcare takers.

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1. Introduction

Several patients at risk of thrombosis will need some kind of anticoagulation therapy. Oral anticoagulation therapy (OAT) with coumarins (vitamin K-antagonists) is prescribed both for prophylaxis and therapy to a large group of patients at increased risk of thrombosis or thromboembolism, e.g. patients with atrial fibrillation, heart valve replacement, deep venous thrombosis, and pulmonary embolism [2]. The most serious adverse effect of OAT is bleeding. The treatment attempts to balance between avoiding haemorrhages due to over-treatment and recurrence of thrombotic events due to insufficient OAT. The treatment is usually assessed by measuring the International Normalised Ratio (INR) value. This ratio represents a patient's coagulation time (prothrombin time) compared to a normal individual.

Maintaining patients within the desired therapeutic window of INR values, which is between 2.0 and 3.0 for most patients, represents a challenge due to at least three factors: (1) a target INR value restricted by a relatively narrow therapeutic range, (2) an inter-individual variation of the effect of oral vitamin K antagonists, and (3) changes in dietary intake of vitamin K [3,4]. In other words, efficacy and safety of OAT are dependent on the maintenance of the INR within a narrow range recommended by current practice guidelines [5]. Despite tight control, the time in therapeutic range has in large studies been reported to be below 70% and dependent on the INR range [6,7]. The fact that no simple relationship exists between a vitamin K-antagonist (VKA) dose and the therapeutic effect

might be an explanatory factor for relatively low adherence to INR in the therapeutic range. The pharmacological characteristics of anticoagulant agents are in general well documented, while the management of warfarin is still a complex task. Warfarin is difficult to dose correctly. This is mainly due to inter- and intraindividual variability between patients' response to the required maintenance dose [1].

OAT is predominantly monitored by laboratory determination of INR using plasma obtained by venipuncture. Another method is patient self-management (PSM), in which the patients analyse a drop of blood using a portable coagulometer (INR-monitor) and subsequently determine their dose of OAT independently. At present, PSM has shown good clinical results in selected patients, and these patients will typically measure INR once a week [8]. Some patients assigned to PSM are using decision aiding electronic tools, or an online decision support system that will provide an on-screen dosage advice. Such tools have been described and refined in the literature during the past 30 years [9,10]. Common for these systems are an attempt of interpretation of prothrombin time (often provided as INR), to provide an advice on optimal VKA dose, and for some systems to give an estimate of when next measurement/test is needed. Their applications are mainly utilised in initiation of warfarin therapy or in the warfarin maintenance phase (or both). Other areas of possible use of such systems could be as guidance in achieving a new INR target in a postoperative situation.

In general, model based approaches in a broad field of medical treatment and monitoring has been described. Harris suggested a class of auto regressive (AR) models for within individual variation in blood constituents [11,12]. Similar models have been used for monitoring tumour markers in small cell lung cancer and breast cancer [13–15]. State space modelling techniques have been applied in monitoring of medical parameters that develops over time, one of the first examples being the monitoring of renal transplants by Smith and West who used a multi process Kalman filter for change point detection [16]. Alternatively Cusum techniques have been suggested for detecting changes in the behaviour of biomarker series [17]. A general auto regressive predictive model for glucose levels in diabetic patients has been applied, which provided sufficiently accurate estimates of glucose levels [18].

An attempt using a state-space model to provide warfarin dose advices has been proposed by Pannocchia and Brambilla [19]. This approach handles the initial state and noise estimation from patient data, and the algorithm attempts to keep the INR value close to the target INR or within the desired therapeutic range. They build a model based on a critically damped second order system, which requires 3 or 4 INR measurements to adopt the model to obtain patient specific parameters; these are not updated afterwards. Their work aims to improve anticoagulation treatment for patients by achieving a more stable OAT and ultimately reduce the number of adverse events caused from poor OAT management.

The purpose of this paper is to use quality data in the development of a dynamic predictive model based on a state-space modelling approach, which may guide patients in OAT. The algorithm will provide an individual sensitivity parameter to account for inter- and intraindividual responses to warfarin. This parameter can change over time to correct for i.e. age,

concurrent diseases, or new co-medication, hence providing a patient's current warfarin sensitivity. This may prove pivotal in clinical situations for long-term OAT patients and for healthcare takers.

2. Materials and methods

2.1. Initial data analysis

A retrospective statistical evaluation of variability in INR values was performed. This initial data mining has the purpose of revealing relations between INR values and past actions affecting INR values. The current value, INR_t, is predicted from past values, INR_{t-1}, INR_{t-2}, INR_{t-3}, INR_{t-4} as well as past warfarin intakes, d_{t-1}, d_{t-2}, d_{t-3}, d_{t-4}, in a multivariable regression model. From this model we inferred the following (data not shown, readers are referred to [20]);

1. An AR(1) model suffices to describe the variation in INR. The autoregressive coefficients do not vary significantly between patients.
2. The dependence of warfarin is sufficiently described by two lags. The warfarin sensitivities proved significant between-patient variations.
3. The standard deviation varies in the population. A histogram of the individual precisions (reciprocal variances) indicated a unimodal right skewed distribution.
4. Residuals from this regression model were mutually uncorrelated and showed no deviations from normality.

2.2. Model development

The model from the described initial data analysis will be applied for INR value predictions. The model and algorithms have been implemented in Matlab scripts (MathWorks Inc., MA). Let $y_{p,t}$ for $t = 1, \ldots, n_p$ and $p = 1, \ldots, P$ be the INR measurement at day t for the pth patient. Indexing for patient is suppressed in the following for notational convenience. We define the observation by the relation

$$y_t = T + \mu_t + \nu_t,$$

where the deviation from target INR, T, is denoted μ_t and ν_t is observational noise. The latent variables driving the process are dose, D_t, sensitivity, A_t, and deviations from target, μ_t. The latent random variables are organised in a three dimensional vector:

$$\theta_t = \begin{bmatrix} D_t \\ A_t \\ \mu_t \end{bmatrix}.$$

The relation between the observation and the latent variables can be formulated in the *observation equation* as

$$y_t = T + F^\top \theta_t + \nu_t, \tag{1}$$

where

$$F = \begin{bmatrix} 0 \\ 0 \\ 1 \end{bmatrix}.$$

In state space form the evolution over time is formulated recursively in the *system equation*;

$$\theta_t = G(\theta_{t-1}) + w_t, \tag{2}$$

where w_t is a three dimensional error term and the evolution function, $G(\cdot)$, is described in the following.

The time evolution of the individually recommended dose, D_t, is modelled in state space form as

$$D_t = G_D(\theta_{t-1}) + w_{D,t} = D_{t-1} + w_{D,t}, \tag{3}$$

where the standard deviation of the noise term on D reflects the expected magnitude of day-to-day changes in dosage. Hereby we allow for a small drift in dosage over time.

The sensitivity, A_t vary between patients but not over time, hence

$$A_t = G_A(\theta_{t-1}) = A_{t-1}. \tag{4}$$

The warfarin effect on INR at day t is influenced by intake of warfarin at day $t-1$ and day $t-2$. In the model formulation warfarin affects INR_t through a between-day-profile of intake, $(d_{t-1} + \lambda d_{t-2})$, where λ is common to all patients. The non-trivial structure of the regression model from the initial data is expressed in the time evolution of the last coordinate

$$\mu_t = G_\mu(\theta_{t-1}) + w_{\mu t} = A_{t-1}((d_{t-1} + \lambda d_{t-2})$$
$$- (1+\lambda)D_{t-1}) + \rho\mu_{t-1} + w_{\mu,t}. \tag{5}$$

The transformation $G(\cdot)$ is non-linear in μ due to the mixed term, $A_{t-1}D_{t-1}$. The term $\rho\mu_{t-1}$ (assuming $|\rho| < 1$) and the noise term $w_{\mu,t}$ model the AR(1) structure revealed in the initial data analysis.

The error term, $w_t = (w_{D,t}, 0, w_{\mu,t})^\top$, is assumed to be multivariate normally distributed with zero mean and a variance specific to the patient. This noise term will be expressed conditional on the individual precision, ϕ, by letting

$$w_t | \phi \sim N(0; \phi^{-1}W), \tag{6}$$

with the scaled variance matrix

$$W = \begin{bmatrix} W_D & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 1 \end{bmatrix}. \tag{7}$$

where W_D is the ratio between the evolution noise of D_t and μ_t. According to the initial data analysis, an AR(1) model suffices to describe the variation in INR, hence the observational noise, v_t, is absent.

The distribution of precisions over the population is chosen to be a gamma distribution. The gamma distribution is a right skewed distribution in accordance with the between patient distribution of precisions.

$$\phi \sim Ga\left(\frac{n_0}{2}, \frac{k_0}{2}\right). \tag{8}$$

The parameters n_0 and k_0 quantify the variation between patients in precisions.

The dynamic process is commenced by specifying the distribution of θ_0

$$\theta_0 | \phi \sim N(m_0; \phi^{-1}C_0), \tag{9}$$

where m_0 describes the population average dose, sensitivity, and deviation from target, and where C_0 quantifies the corresponding variance over the population. The matrix C_0 is defined such that $C_0 \cdot (k_0/n_0)$ is the variance matrix of the population distribution of dose, sensitivity, and deviation from target INR. If the warfarin intake is optimal, i.e. $(d_{t-1} + \lambda d_{t-2}) = (1+\lambda)D_{t-1}$, the process of (5) is a stationary AR(1) process provided that $C_{0,33} = 1/(1-\rho^2)$.

The parameters ρ and λ describe the dynamics of the INR-warfarin interaction, whereas m_0, C_0, n_0 and k_0 describe the distribution between patients. This model is a conjugate normal-gamma state-space model apart from the fact that the time evolution of θ_t is non-linear in μ. By using the inverse gamma distribution for describing the between patient distribution, we can exploit the conjugate form when using the model for prediction. A detailed exposition of normal/gamma state space models is found in [21].

2.3. Model predictions

The non-linearity of the time evolution may be handled by application of the extended Kalman filter [22] for model predictions. Established population coefficients will be utilised as initiation values and gradually be adopted into individual parameters. Hence each population parameter will gradually develop into patient specific parameters and each patient will be his or hers own reference. The distribution of θ_t and y_t given prior observations, $\mathcal{D}_{t-1} = \{y_1, \ldots, y_{t-1}\}$, and ϕ will be approximated by a normal distribution specified by the actual mean and variance of the non-linear combination of the elements of θ_{t-1}. The process is initiated with the distribution of ϕ and $\theta_0 | \phi$, see (8) and (9). Pseudo code for the Kalman filter is shown in Fig. 1.

Assume at time $t-1$ the distribution of the latent process follows:

$$(\theta_{t-1} | \mathcal{D}_{t-1}, \phi) \sim N(m_{t-1}; \phi^{-1}C_{t-1}),$$

$$(\phi | \mathcal{D}_{t-1}) \sim Ga\left(\frac{n_{t-1}}{2}, \frac{k_{t-1}}{2}\right). \tag{10}$$

The conditional mean of θ_t given ϕ and $\mathcal{D}_{t-1}$ is

$$a_t = G(m_{t-1}) + h, \tag{11}$$

```
/* (1) Initialisation */
n := n₀; k := k₀
m := m₀; C := C₀

For  t = 1 to  N
do  /* (2) Prior for θₜ */
    a := G(m) + h
    R := GₜCGₜᵀ + H + W

    /* (3) Prediction of  yₜ */
    f := Fᵀa;  Q = FᵀRF

    /* (4) Update */
    If  yₜ is available
    then  b := FRₜ
          m := a + b(yₜ − f)/Q
          C := R − bbᵀ/Q
          n := n + 1;  k := k + (y − f)²/Q

    else  m = a;  C = R
```

Fig. 1 – Pseudo code describing the extended Kalman filter for model predictions in four steps. The model is initialised (1) with population parameters; for each day the conditional mean and conditional variance is calculated (2); this allows for prediction of an INR value (3); if an INR measurement is available (4), the Kalman filter will use this information to update the (initial) population coefficients with (adopted) patient specific values.

where the non-linearity of $G(\cdot)$ is adjusted for by addition of h

$$h = \begin{bmatrix} 0 \\ 0 \\ -(1+\lambda)C_{t-1,12}k_{t-1}/n_{t-1} \end{bmatrix}.$$

Details are given in Appendix A. Similarly the conditional variance can be shown to be

$$R_t = G_t C_{t-1} G_t^\top + W + H, \tag{12}$$

where G_t is the gradient of $G(\cdot)$ evaluated in m_{t-1},

$$G_t = \begin{bmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ -(1+\lambda)m_{t-1,2} & d_{t-1}+\lambda d_{t-2}-(1+\lambda)m_{t-1,1} & \rho \end{bmatrix},$$

W is the scaled variance matrix, see (7), and H is a 3×3 matrix with $H_{ij}=0$ except for

$$H_{33} = (1+\lambda)^2 \left(C_{t-1,11}C_{t-1,22} + C_{t-1,12}^2 \right) \frac{k_{t-1}}{n_{t-1}}.$$

The non-linearity adjustment, H, is found by regarding second moments of products of bivariate normals, see Appendix A for further details. The conditional distribution (prior for θ_t) is approximated with a normal distribution;

$$(\theta_t|\mathcal{D}_{t-1},\phi)\sim N(a_t;\phi^{-1}R_t)$$

and the predictive distribution of the INR measurement to come is

$$(y_t|\mathcal{D}_{t-1},\phi)\sim N(f_t;\phi^{-1}Q_t) \tag{13}$$

with $f_t = a_{t,3}+T = F^\top a_t + T$, and $Q_t = R_{t,33} = F^\top R_t F$. Note that marginalising out ϕ in (13) by the distribution (10) yields a T-distribution for $y_t|\mathcal{D}_{t-1}$. Updating the distribution of θ_t for the new observation is done by conditioning on y_t in the joint conditional distribution of (θ_t, y_t) given $\mathcal{D}_{t-1}$;

$$(\theta_t|\mathcal{D}_t,\phi)\sim N(m_t;\phi^{-1}C_t),$$

where

$$m_t = a_t + \frac{FR_t(y_t - f_t)}{Q_t} \tag{14}$$

and

$$C_t = R_t - \frac{FR_t(FR_t)^\top}{Q_t} \tag{15}$$

The distribution of the precision, ϕ, is updated by $n_t = n_{t-1}+1$ and $k_t = k_{t-1}+(y_t-f_t)^2/Q_t$. Note that $n_t = n_0+\mathcal{N}$, where $\mathcal{N}$ is the number of available INR measurements at time t, and k_t measures the cumulated squared, normalised prediction error. In case of missing INR values or if long-term predictions are required, the distribution of θ_t is not updated as in (14) and (15), but rather $m_t = a_t$ and $C_t = R_t$. The precision parameters are left unchanged, $n_t = n_{t-1}$ and $k_t = k_{t-1}$. The recursive characteristic of the algorithm is hereby maintained.

2.4. Parameter optimisation

The parameters used in the predictive model can be divided into population parameters and dynamic parameters. As the model predictions require initial values for population parameters, moment estimates on n_0, and k_0 are obtained by using a leave-one-out approach for each patient. Clinical expert knowledge on the correlation structure between dose and sensitivity towards changes in warfarin was used for quantifying m_0 and C_0. This is based on population distribution of warfarin intake and expected change in INR when steady state dosage is changed, with e.g. one tablet per week. The values for dosage are $m_0 = (2.45, 0.51, 0)$ and $C_{0,11} = 0.77$, $C_{0,22} = 0.05$, and the correlation between initial dose and sensitivity is set to -0.7. Similarly $W_D = 0.082$ corresponding to a accumulated change in weekly dose of a magnitude of one tablet per week. Further, the dynamic parameters ρ and λ are estimated by a log-likelihood optimisation, where values for both parameters are iteratively adjusted. The likelihood function is given as the product of the predictive T-distribution densities obtained by marginalising out ϕ from the predictive distribution, see (10) and (13). Hence the likelihood function is

$$l(\rho,\lambda) \propto \prod_p \prod_t \left(1 + \frac{e_{pt}^2}{n_{t-1}} \right)^{-(n_{t-1}+1)/2}. \tag{16}$$
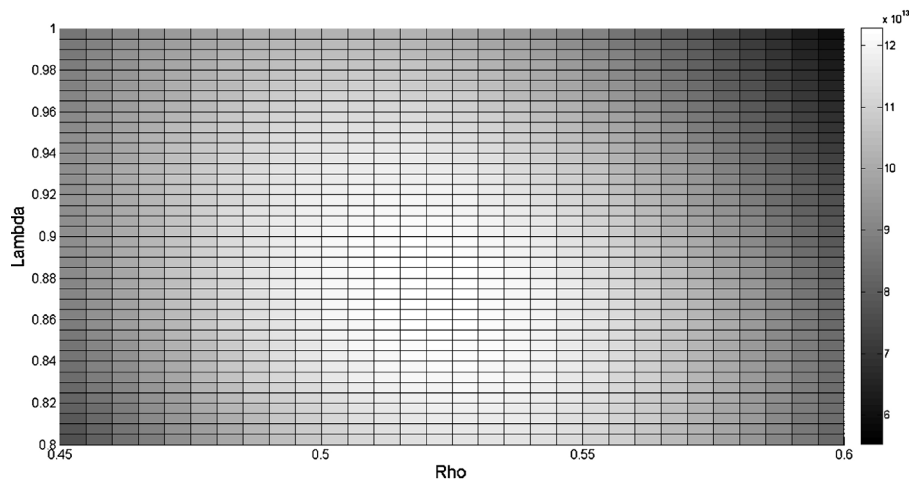
Fig. 2 – Three dimensional representation of the likelihood function for optimising ρ and λ. Brighter areas corresponds to higher values of the function. To ensure numerical stability, (16) has been up-scaled with a factor 1.5 for each data point.

where the prediction error normalised by individual standard deviation, e_{pt}, is defined as

$$e_{pt} = \frac{y_{pt} - f_{pt}}{\sqrt{Q_{pt}(k_{p,t-1})/(n_{t-1})}}$$

where p is patient index and t is the observation number. A graphical representation of the likelihood function for ρ and λ is given in Fig. 2.

By maximising the log-likelihood function for ρ and λ we derive the following optimal values $\rho = 0.52$ and $\lambda = 0.87$.

3. Results

Thirty patients accepted to be contacted, six declined to participate. Out of the 24 patients going into the study, 18 patients completed the data collection protocol (Table 1), equivalent to a 25% dropout rate.

A root mean square error (RMS) was selected to evaluate the performance of the model, where

$$\mathrm{RMS}_p = \sqrt{\frac{1}{n_p} \sum_t (y_{p,t} - f_{p,t})^2}.$$

Table 1 – Outline of 18 patients receiving warfarin therapy.

Characteristics	Mean $\pm$ SD$_w$, SD$_b$ or number (%)
Age	56 $\pm$ 15
Female	8 (44%)
Days in study	27 $\pm$ 1.78
INR value	2.5 $\pm$ 0.36, 0.36
Warfarin intake (tablets/day)	2.41 $\pm$ 0.43, 0.92

Abbreviations: SD$_w$ and SD$_b$ (standard deviation of within and between individual variation).

The RMS error is a non-weighted error that do not account for expected individual variance. The average RMS error across patients was 0.5.

The model was used to produce predictions of INR values for all 18 patients; an example for four patients is given in Fig. 3.

An autocorrelation analysis on residual error is performed to assess if the predictions produced by the model are mutually independent. The autocorrelation plot of residual error from lag 0 to 25 is provided in Fig. 4.

The autocorrelation supports the adequacy of the model. Predictions on simulated sequences of OAT data will be carried out to evaluate the model behaviour when limited INR measurements are available, this allows for inspection of model performance on "normal" OAT data, where the INR value is not measured every day. Fig. 5 depicts this scenario where the data is "mirrored", hence doubling the amount of warfarin data and INR data. However, only every fifth INR measurement will be available to the model.

The dashed horizontal lines represent the confidence limits of INR predictions; longer period with no INR measurement increases the uncertainty of the INR prediction.

4. Discussion

This paper reports the outcome of the development of a predictive model on state-space form. The model is able to predict INR values, but also provide a theoretically correct dose of warfarin to maintain a patient on a preset target INR. The same data is used in estimation and in testing, which is a method drawback. It has been circumvented by splitting the data set accordingly in moment estimates by using a leave-one-out approach. It is not known if the used data is representative for OAT patients. These patients have recently received training in patient self-management, and are expected to have an interest in achieving a stable OAT. Further, by measuring the INR value once a day, they can adjust for variation more often than patients in usual treatment.
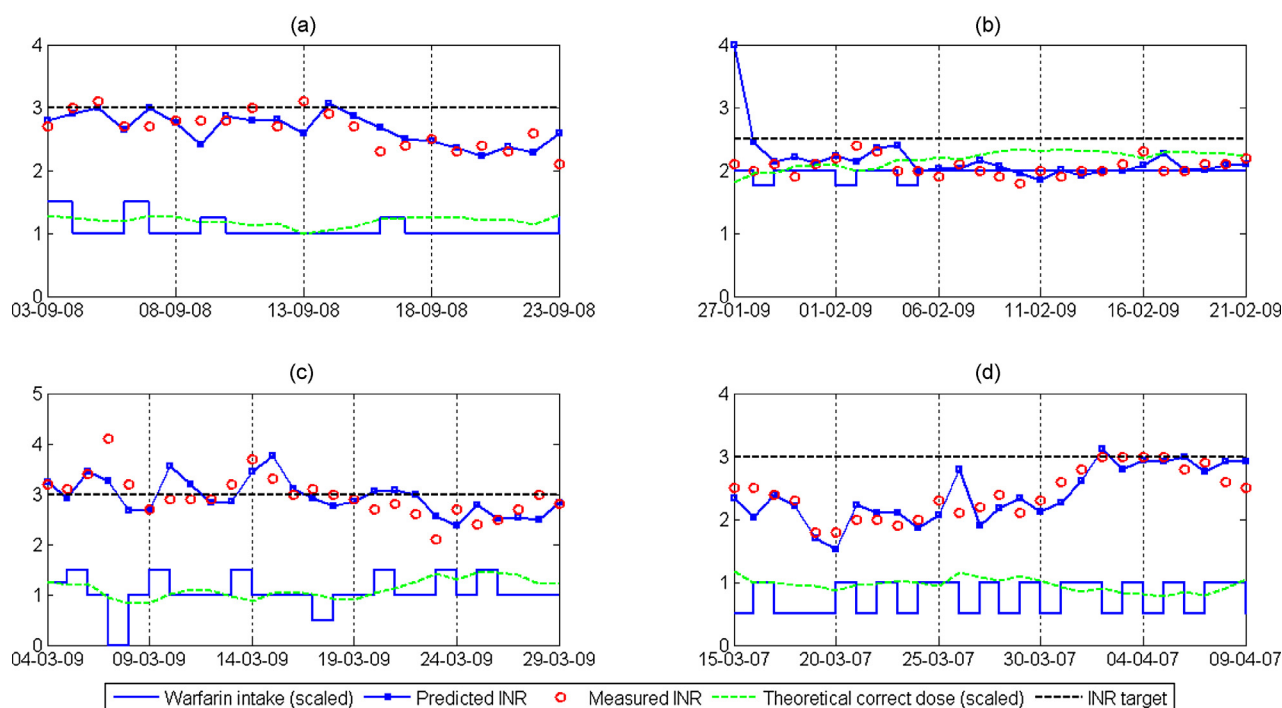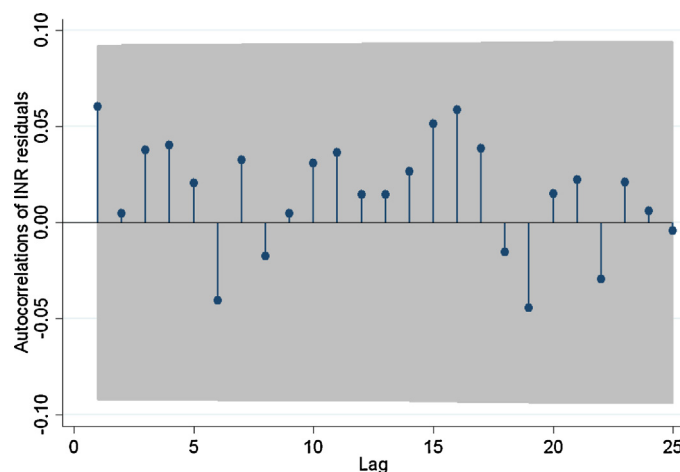
Fig. 3 – Retrospectively model based INR predictions (solid line marked with squares) on patient data, and measured INR values for the patient (marked with circles). The bars represents warfarin intake and the green dashed line is the theoretical correct intake of warfarin to stay on target INR; both lines are downscaled by 0.5 for visual purposes. The horizontal dashed line is the patient specific target INR value.

The absence of observational noise in the model is somewhat unusual, but is supported by the evidence from the initial data analysis and the ACF plot. Despite this, we investigated this component in a similar analysis. A measurement noise is easily adopted in the Kalman filter, and hence a maximum likelihood estimation of the observational noise, based on (16), was made. However, it was not possible to separate the evolution noise, w_t, from the short term observation noise on basis of the data at hand.

The examples of utilising the model on patient data, seen in Fig. 3, shows how the model is able to predict the trend of INR values, most noticeably at the end of the prediction period. Fig. 3d shows a patient with a target INR at 3. This target is used in the calculation of the theoretical correct dose. This is illustrated as this dose (dashed line) is above actual warfarin intake almost during the entire period. This corresponds well to the fact that this patients INR value is below target INR during most of the prediction period.

Inspection of the confidence limits on INR predictions in Fig. 5 demonstrates the importance of providing INR measurements to the model. A closer inspection of Fig. 5b demonstrates that at the beginning of the simulated period,

Fig. 4 – The autocorrelation plot from lag 1–25 on residual error produced from model predictions. The shaded area indicates approximate 95% confidence limits.
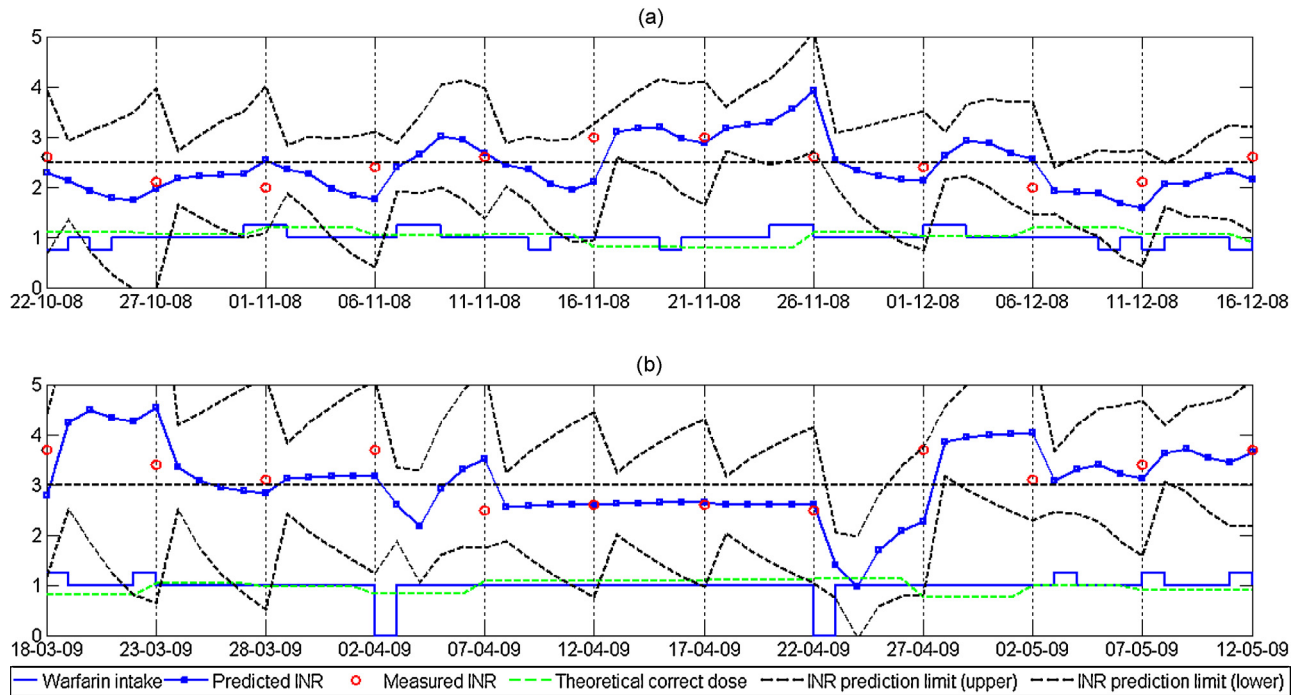
Fig. 5 – Model based INR predictions for two different patients on simulated patient data. INR predictions are solid line marked with squares and measured INR values (marked with circles). Bars represents warfarin intake downscaled by 0.5 and green dashed line is the theoretical correct dosage. The horizontal dashed lines are upper and lower confidence limits for INR predictions.
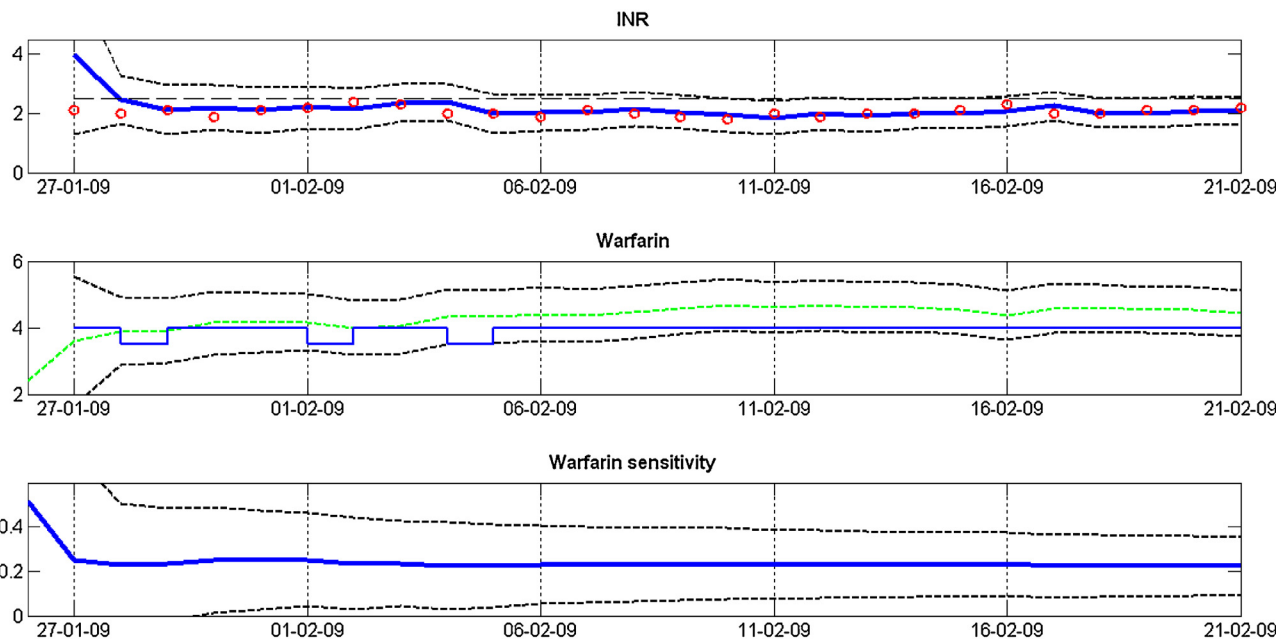
Fig. 6 – Schematic representation of INR predictions (upper) and the resulting theoretical correct dose (middle) to stay on INR target and the sensitivity towards changes in warfarin intake (bottom). All predictions are shown with confidence limits as dashed lines. For reference, population values for theoretical correct dose and warfarin sensitivity are included, and the patient data used are those provided in Fig. 3b.

the model is initialised with no INR measurements, resulting in large uncertainties of the first prediction, i.e. an INR prediction within 1–8. This is caused by the warfarin intake, which is significantly higher than the population average. Every fifth day the model is provided with a new INR measurement, hence updating m, C, n and k. An update reduces the uncertainty of the prediction and can be seen by more narrow confidence limits each day after an update. To further elaborate on the behaviour of the model a graphical representation of patient sensitivity (data from Fig. 5b) is provided along with INR predictions (all measurements included) as well as predictions of the theoretical correct dose, see Fig. 6.

Fig. 6 shows how the model becomes more individualised as the confidence limits on INR predictions, prediction of the theoretical correct dose, and warfarin sensitivity are narrowing. The model is able to obtain a feasible warfarin sensitivity, which can be deduced by the following: according to data in this study the average population intake is 2.45 tablets per day. This patient, however, has a substantial higher warfarin intake (avg. 3.95 tablets per day) and has a faster rate of metabolism of warfarin. Due to an initial high prediction error of INR at day one, the model is immediately able to discover the (negative) correlation between this high warfarin intake and relatively low impact on INR, leaving a choice to lower this patients warfarin sensitivity.

The model has potential to be used in different clinical settings. Patients with specific types of atrial fibrillation can in some cases benefit from direct current (DC) conversion. This type of patients is often treated with OAT. DC conversion requires an INR value at a certain level for the procedure to be safe. The developed model could be used in such a setting, where the new specific target INR is provided, and the model will predict the theoretical correct dose of warfarin to achieve that level of INR value. Anticoagulated patients who are planned for a surgical procedure requires an INR value below a certain level, e.g. 1.5, before surgery is safe. INR should on the other hand not drop too far below this value because of the subsequent risk of thrombosis. Again, the developed model could be utilised to attain this strict requirement of INR level. To further enhance the use of the model in such clinical situations, the warfarin sensitivity parameter may prove useful. During longer periods of time (than data available in this study), the model will be able to depict an individual patient's response to warfarin changes by the sensitivity parameter. By using the model to predict INR values, physicians will have a tool that can predict when an adjustment is needed to be able to achieve a certain INR level. Further studies on clinical data can show whether the model can predict variations in dosage and INR in a variety of patients and with different measurement intervals. Positive results from such studies could be implemented in clinical practice to guide OAT patients in their treatment.

In its current form the model has proven to perform well in terms of predicting INR values one day into the future. Further development of the model should involve investigations on model performance on normal OAT data, with a maximum of one INR measurement a week, and hence require longer prediction period. The next step will be a test on prospective clinical data to test if the model could facilitate a better clinical outcome in patients treated with vitamin K antagonists.

Conflict of interest

Acknowledgements

Appendix A. Adjustment for non-linearity

The formulae for non-linearity adjustments in (11) and (12) in the Kalman filter are explained in this Appendix A.

Consider a multivariate random vector $X = (X_1, X_2, X_3)^\top \sim N(\xi; \Sigma)$. Let a random variable be defined as $U = g(X) = X_1 X_2 + X_3$.

Then,

$$\mathbb{E}U = g(\xi) + h \tag{A.1}$$

where $h = \Sigma_{12}$ and

$$\mathbb{V}U = G\Sigma G^\top + H \tag{A.2}$$

where $H = \Sigma_{11}\Sigma_{22} + \Sigma_{12}^2$ and $G = (\xi_2, \xi_1, 1)$ is the gradient of g evaluated in ξ.

Proof. Using that $\Sigma_{12} = \mathbb{C}(X_1, X_2) = \mathbb{E}X_1 X_2 - \mathbb{E}X_1 \mathbb{E}X_2 = \mathbb{E}X_1 X_2 + \xi_1 \xi_2$, (A.1) follows immediately. In order to obtain the variance, we need to evaluate $\mathbb{E}X_1^2 X_2^2$ and $\mathbb{E}X_1 X_2 X_3$. From Isserlis' theorem [23], see also [24], we have for a zero-mean multivariate normal variable $Y = (Y_1, Y_2, Y_3, Y_4)^\top$ that

$$\mathbb{E}Y_1 Y_2 Y_3 = 0$$

and

$$\mathbb{E}Y_1 Y_2 Y_3 Y_4 = \mathbb{E}Y_1 Y_2 \ \mathbb{E}Y_3 Y_4 + \mathbb{E}Y_1 Y_3 \ \mathbb{E}Y_2 Y_4 + \mathbb{E}Y_1 Y_4 \ \mathbb{E}Y_2 Y_3.$$

If $Y_1 = Y_3$ and $Y_2 = Y_4$ it follows directly that

$$\mathbb{E}Y_1^2 Y_2^2 = 2\mathbb{C}(Y_1, Y_2)^2 + \mathbb{V}Y_1 \ \mathbb{V}Y_2.$$

Letting $Y_1 = X_1 - \xi_1$, $Y_2 = X_2 - \xi_2$, and $Y_3 = X_3 - \xi_3$, we have

$$\mathbb{E}X_1^2 X_2^2 = \xi_1^2 \xi_2^2 + \Sigma_{11}\Sigma_{22} + 2\Sigma_{12}^2 + \xi_1^2 \Sigma_{22} + \xi_2^2 \Sigma_{11} + 4\xi_1 \xi_2 \Sigma_{12}$$

and

$$\mathbb{E}X_1 X_2 X_3 = \xi_1 \xi_2 \xi_3 + \xi_1 \Sigma_{23} + \xi_2 \Sigma_{13} + \xi_3 \Sigma_{12}.$$

Recognising that

$$G\Sigma G^\top = \xi_1^2 \Sigma_{22} + \xi_2^2 \Sigma_{11} + \Sigma_{33} + 2\xi_1 \Sigma_{23} + 2\xi_2 \Sigma_{13} + 2\xi_1 \xi_2 \Sigma_{12}$$

we get

$$\mathbb{V}U = G\Sigma G^\top + \Sigma_{11}\Sigma_{22} + \Sigma_{12}^2$$

whereby (A.2) is proven. $\square$

In the Kalman filter setting we have

$$\theta_t | \mathcal{D}_{t-1}, \phi \sim N(m_{t-1}, \phi^{-1}C_{t-1}).$$

Letting $X_1 = A_{t-1}$, $X_2 = ((d_{t-1} + \lambda d_{t-2}) - (1+\lambda)D_{t-1}) + \rho\mu_t$, and $X_3 = \rho\mu_{t-1}$, (A.1) yields

$$a_{\mu,t} = \mathbb{E}(\mu_t | \mathcal{D}_{t-1}, \phi) = G_\mu(m_{t-1}) + \mathbb{C}(A_{t-1}, (d_{t-1} + \lambda d_{t-2})$$

$$- (1+\lambda)D_{t-1} | \mathcal{D}_{t-1}, \phi) = G_\mu(m_{t-1}) - \phi^{-1}(1+\lambda)C_{t-1,12},$$

where now G is defined in (2). Similarly, from (A.2), we get the adjustment for non-linearity in $\mathbb{V}(\mu_t | \mathcal{D}_{t-1}, \phi) = \phi^{-1}R_{t,33}$ to be

$$\Sigma_{11}\Sigma_{22} + \Sigma_{12}^2 = \phi^{-2}(1+\lambda)^2(C_{t-1,11}C_{t-1,22} + C_{t-1,12}^2).$$

In order to maintain conditional distributions given data points $\mathcal{D}_s$ and individual precision ϕ on the form $N(\xi; \phi^{-1}\Sigma)$ we replace ϕ^{-1} with the reciprocal of the conditional mean of ϕ. Hence,

$$h = -(1+\lambda)C_{t-1,12}\frac{k_{t-1}}{n_{t-1}}$$

and the adjustment of the variance $\phi^{-1}H = \Sigma_{11}\Sigma_{22} + \Sigma_{12}^2$, whereby

$$H = (1+\lambda)^2(C_{t-1,11}C_{t-1,22} + C_{t-1,12}^2)\frac{k_{t-1}}{n_{t-1}}.$$

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