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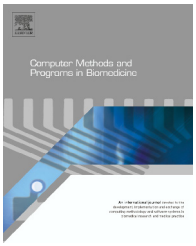

Monitoring of anticoagulant therapy applying a dynamic statistical model

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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.

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

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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

$$y_t = T + F^\top \theta_t + \nu_t, \quad (1)$$

where

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