Robust and Adaptive Anticoagulant Control

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Summary. We consider a control theory approach to adaptive dose allocation of anticoagulants, based on an analysis of records of 152 patients on long-term warfarin treatment. We consider a selection of statistical models for the relationship between dose of drug and subsequent blood clotting speed, measured through the International Normalised Ratio. Our main focus is on subsequent use of the model in guiding choice of the next dose adaptively as patient-specific information accrues. We compare a naive myopic approach with a proportional integral plus method, with parameters estimated by either linear quadratic optimisation or by stochastic resource allocation. We demonstrate advantages of the control approaches in comparison to naive in simulations and through calculation of robust stability margins for the observed data.

Keywords: DIC, Controller Design, Robustness, Stability, Warfarin

1. Introduction

Choosing the correct doseage for patients on long term anticoagulation is a delicate problem as the dose-response relationship varies considerably both between patients and within patients over time (Avery et al. 2011, Landefeld & Beyth 1993, Pirmohamed et al. 2013, Schwarz et al. 2008, Wells et al. 2004). Blood clotting speed is usually measured through the International Normalised Ratio (INR), which is a standardised version of the prothrombin time, in turn the time taken for plasma from the patient to clot. In a healthy population the average INR will be one, but for patients prescribed anticoagulants the aim is to keep the INR higher and so reduce the risk of thrombosis. However, if INR is too high there is significant risk of bleeding. Hence a target band is usually specified, often the range 2 to 3, and during an initiation phase the clinician will seek a dose which maintains the patient's INR in that range. A difficulty is that blood clotting speed has both long-term and short-term variation so the required dose is rarely completely stable. Consequently clinicians regularly review doseage of patients on long term medication and amend dose in response to changes in INR. Often computer-assisted dosing algorithms are used to help guide the clinician, taking into account the patient's INR and dose history (Poller et al. 2008a,b). The algorithms are usually provided by commercial organisations in properietary software and are not public.

In this paper we describe an analysis of the records of 152 patients who were being treated in Newcastle upon Tyne with the anticoagulant warfarin during December 2013, which is the most recent date for which records have been made available. Warfarin is the most commonly prescribed anticoagulant and the literature on warfarin use in practice is rich. There have been attempts to apply to anticoagulation some recent statistical developments in optimal dynamic treatment allocation (Rosthøj et al. 2006, Henderson et al. 2010, Rich et al. 2014) but in this paper we will approach the problem from the quite different perspective of control theory. An aim of the paper is to introduce to a statistical audience some relevant concepts from modern control theory and to highlight the importance of the decision rule in determining adaptive treatments. Our motivation is that while sophisticated modelling, estimation and inference procedures are well known and well understood in the statistical community, there has been little attention on subsequent dynamic decision rules or *controllers*. In contrast in control theory this is usually the main focus, often with robustness in mind. Robustness in this sense does not mean the traditional robustness of estimators or inference under departures from assumptions, but stability of uncertain systems under external perturbations. Given an anticoagulant model and data, how best can we decide upon the dose to be prescribed while recognising that the patient may not behave as expected?

In Section 2 we will introduce the data and describe our modelling approach. This will be relatively brief as our main focus will be on the control interpretation introduced in Section 3. We will investigate three approaches to control, namely deadbeat, linear quadratic optimal and stochastic robustness analysis (SRA). The first two of these assume that the system parameters are known, whilst SRA recognises uncertainty by specifying a probability distribution for their estimates (Stengel & Ryan 1991). Although all three methods are well-known in the control systems literature, in this article we will focus on their application to the anticoagulant model. More specifically, we will solve the optimal and SRA control problems using a proportional-integral-plus framework (Young et al. 1987, Taylor et al. 2013), chosen because of its straightforward design flexibility and use of an integrated error term. This ensures that the output tracks the target INR at steady state, despite modelling errors associated with patient to patient variability and disturbances. The concept may have wide application to other optimal dynamic treatment problems.

The potential advantages of such an approach will be illustrated in Section 4, in which we will compare all three control strategies in simulations based on the anticoagulation scenario. In Section 5 we will return to the Newcastle data and compare the dose decisions that were actually taken with those that would have been recommended had each of our three controllers been in place. We will also compare robustness in these data for the three different controllers, using structured singular values to assess stability when model parameters are subject to uncertainty. Extensions and further work are discussed in the final Section 6.

2. Data and Model

2.1. Overview

We will consider the anticoagulation records of $m = 152$ patients, who together made 9345 clinic visits. Over 97% of the clinic visits were within 1 week to 3 months of the previous visit, and our preliminary analyses indicated little or no effect of the timing of visits or the intervals between them, at least within this range. This is perhaps because warfarin concentrations in the blood typically reach steady state within about 3 days of a change in dose (Holford 1986) and fewer than 1% of our clinic visits are within such a short interval of an earlier visit. Hence we will work in discrete time, indexed by clinic visit $t = 1, 2, \ldots$. The number of visits per patient ranged from 4 to 213, with median 45, corresponding to follow up times from 186 to 4568 days, with median 1128. In our modelling, if a patient had more than 50 clinic visits we restricted attention to the first 50 visits only, to avoid too much weight being given to these long-term patients. This resulted in data with between 4 and 50 visits ranging in length from 186 to 4275 days with median 983. We randomly divided the data into a training sample of 100 patients and a test sample of 52 patients.

For a generic patient, let y_t be the logarithm of the International Normalised Ratio (INR) measure of blood clotting speed, measured at clinic visit t. Let u_t be the dose of warfarin prescribed at that visit, measured in mg, and assume there are N clinic visits. Dose u_t and log(INR) y_t are shown in Figure 1 for four illustrative patients. The usual target range for INR is between 2 and 3, which is shown in the log scale as horizontal bands in the plot. Patient A had variable INR and no stable dose was achieved. By stable dose we mean a dose that varies by no more than 0.5mg over at least 10 observations. Patient B on the other hand was quite easy to control and only a small number of dose adjustments were made. We note the different mean dose levels required for these patients in order to maintain INR near the target range, providing illustrations of the highly patient-specific dosing needed for warfarin anticoagulation. Patient C, like Patient A, was not maintained at a stable level at all within the sequence shown, and had one very high INR value. Patient D was stable until a sudden drop in INR occurred, which required a temporary large increase in dose of warfarin. Sudden unexplained increases or decreases in INR, as seen for Patients C and D, are quite common and are one reason why anticoagulation control can be challenging (Wells et al. 2004).

2.2. Model selection

We adopt a Bayesian approach, based on linear models of the form

$$y_{t+1} = \alpha_1 y_t + \alpha_2 y_{t-1} + \ldots + \alpha_k y_{t-k+1} + \beta_1 u_t + \beta_2 u_{t-1} + \ldots + \beta_\ell u_{t-\ell+1} + \varepsilon_t$$

with $\varepsilon_t \sim \mathrm{N}(0, \sigma^2)$, independent from one visit to the next. We allowed the coefficients $\{\alpha_j\}$ and $\{\beta_j\}$ to be either common to all patients or patient-specific. The deviance information criteria, DIC (Spiegelhalter et al. 2002), for a selection of models are shown in Table 1. These were obtained using the `MCMCglmm` R package with default parameter values except for the number of iterations in the Markov chains, where we used 20,000 (after a burn-in of 3000) rather than the default 10,000 iterations, so as to be sure that our DIC values are reliable.

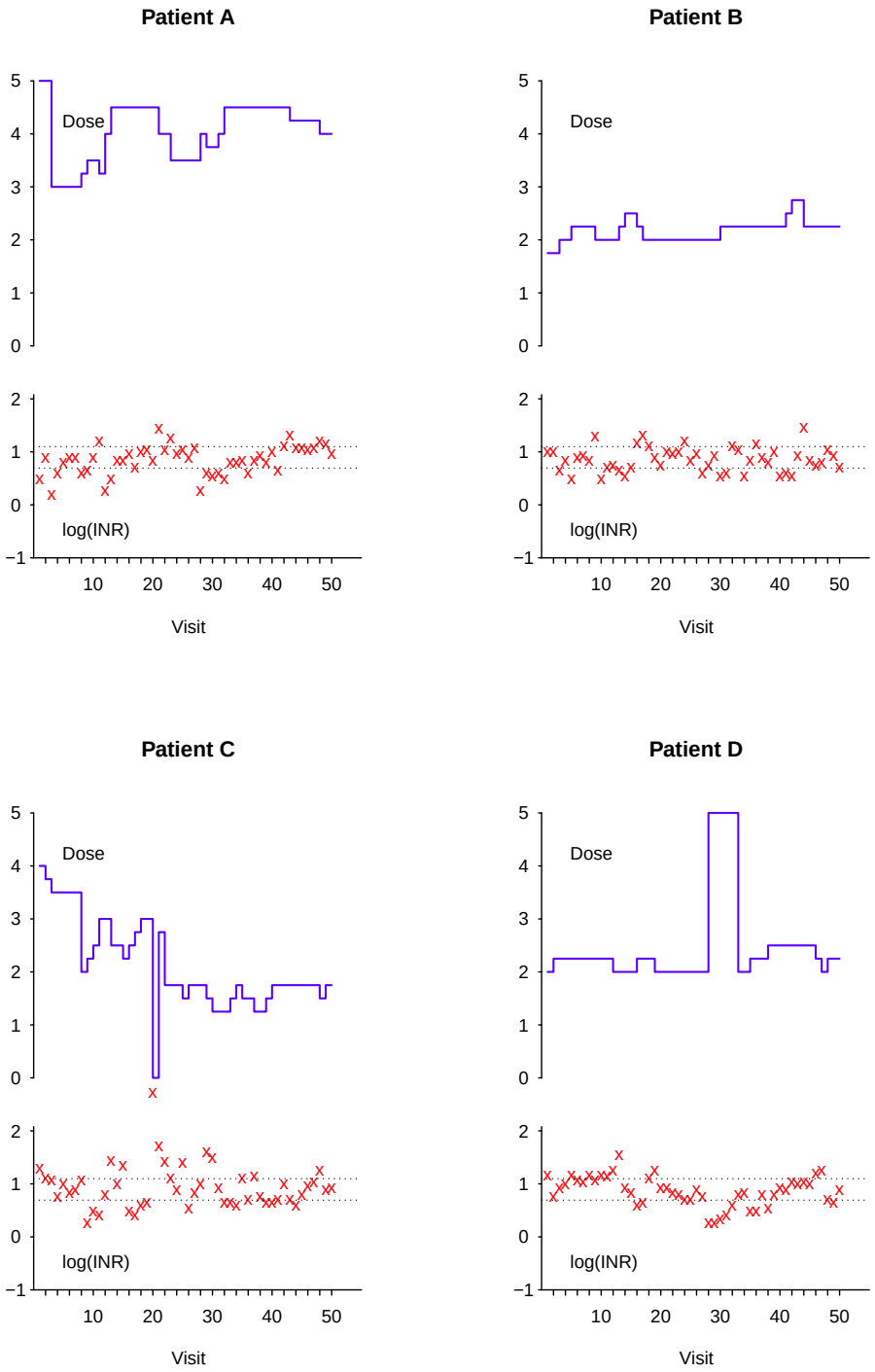

Fig. 1. Anticoagulation for four example patients. The upper part of each panel shows the prescribed warfarin dose and the lower part shows the logarithm of INR.

Table 1. Selected model comparisons using Deviance Information Criterion DIC. Terms included in a model are indicated by p (patient-specific values allowed) or c (a common value is assumed for all patients).

	Model terms						
Model	y_t	y_{t-1}	y_{t-2}	u_t	u_{t-1}	u_{t-2}	DIC
I	p	p	p	p	p	p	214.7
II	c	c	c	c	c	c	646.5
III	p	p		p	p		203.8
IV	c	c		c	c		837.5
V	p	p		p	c		203.2
VI	p	p		c	p		449.4
VII	p	c		p	p		204.1
VIII	c	p		p	p		204.6
IX	p	p		p			219.7
X	p	p			p		513.8
XI	p			p	p		215.7
XII		p		p	p		321.6
XIII	p	p					1182.3
XIV	c	c					1282.7
XV	p			p			234.0
XVI	c			c			1197.7

The smallest DIC value in the table corresponds to Model V, for which $k = \ell = 2$, coefficients α_1, α_2 and β_1 are patient-specific but coefficient β_2 is common to all patients. Allowing β_2 to be patient-specific too leads to only a small increase in log-likelihood, and so our preferred choice is model III. As mentioned previously, our main focus is on the design of controllers rather than detailed modelling, and we are not overly concerned by a little over-fitting.

Introducing subscript p to indicate patient number, the model we will assume for the remainder of the paper is

$$y_{t+1} = \alpha_{p1} y_t + \alpha_{p2} y_{t-1} + \beta_{p1} u_t + \beta_{p2} u_{t-1} + \varepsilon_t. \tag{1}$$

Letting $\theta_p = (\alpha_{p1}, \alpha_{p2}, \beta_{p1}, \beta_{p2})^T$, we assume $\theta_p \sim \mathrm{N}(\theta_0, \Sigma)$. Taking vague priors for θ_0, Σ and σ leads to maximum a posteriori estimates of $\sigma = 0.2076$ and

$$\theta_0 = \begin{pmatrix} 0.2608 \\ 0.0901 \\ 0.1917 \\ 0.0158 \end{pmatrix} \qquad \Sigma = \begin{pmatrix} 0.0540 & -0.0106 & 0.0201 & -0.0317 \\ -0.0106 & 0.0222 & -0.0047 & 0.0033 \\ 0.0201 & -0.0047 & 0.0410 & -0.0356 \\ -0.0317 & 0.0033 & -0.0356 & 0.0423 \end{pmatrix}. \tag{2}$$

The following gives the standard deviations of the elements of θ_p on the diagonal and their correlations above the diagonal:

$$\begin{pmatrix} 0.2324 & -0.3058 & 0.4281 & -0.6646 \\ & 0.1491 & -0.1571 & 0.1078 \\ & & 0.2025 & -0..8561 \\ & & & 0.2056 \end{pmatrix}.$$

Because θ_0, Σ and σ are very precisely estimated in comparison with inter-patient variability and random noise terms, we will take them to be fixed and known from now on. All of the results in the following sections can be adapted if necessary to allow θ_0, Σ and σ to have appropriate posterior distributions.

2.3. Adaptive estimation

We are most interested in learning about θ_p as information on patient p accrues. Before any observations are available on patient p, we assume that θ_p is a draw of a four dimensional $\mathrm{N}(\theta_0, \Sigma)$ random variable. Suppose now that k observations are available, collected into a k-vector y_{pk}. Let X_{pk} be the associated $k \times 4$ design matrix based on (1), and define

$$J_1 = X_{pk}^T X_{pk}/\sigma^2 \qquad J_2 = \Sigma^{-1}.$$

Then (Turkman et al. 2019) the posterior distribution of θ_p is Normal with mean

$$\theta_{pk} = (J_1 + J_2)^{-1} \left(J_1 (X_{pk}^T X_{pk})^{-1} X_{pk}^T y_{pk} + J_2 \theta_0 \right)$$

and variance

$$\Sigma_{j,k} = (J_1 + J_2)^{-1}.$$

3. Control Design

In this section we discuss some ideas and methods developed in control engineering that may be useful in anticoagulation control. Generalising from the anticoagulation application, we will refer to u_t and y_t as inputs and outputs respectively. Given $\mathcal{F}_t = (y_t, y_{t-1}, y_{t-2}, \ldots, u_{t-1}, u_{t-2}, \ldots)$, our objective is to select the next input u_t so as to maintain output as close as we can to a target y_t^*. Any algorithm to select u_t will be referred to as a controller. It is not physically possible to have a negative dose, therefore u_t is constrained to be non-negative. If an algorithm selects a negative dose this will be set to zero to satisfy the constraint. When specifying the controllers, we assume that the future desired trajectory y_{t+1}^* is available. This is the case for anticoagulation control where the aim is to ensure that INR remains within a pre-defined range.
For the most part we will concentrate on a single generic patient, dropping the subscript p to indicate patient number, using $\theta = (\alpha_1, \alpha_2, \beta_1, \beta_2)^T$ for the true model coefficients for the patient, and $\hat{\theta} = (\hat{\alpha}_1, \hat{\alpha}_2, \hat{\beta}_1, \hat{\beta}_2)^T$ as estimated or assumed parameter values.

3.1. Transfer functions, linear controllers, and system performance

The performance of a controlled system is usually studied for deterministic models, assuming that general properties for a deterministic model will mirror those of a stochastic model with additive zero-mean noise. Hence in this section we will temporarily drop ε_t from (1) and work with

$$y_{t+1} = \alpha_1 y_t + \alpha_2 y_{t-1} + \beta_1 u_t + \beta_2 u_{t-1}. \tag{3}$$

More general and sophisticated models are of course used in many applications but this is sufficient for our discussion. Introducing a backward shift operator z^{-1}, such that for example $z^{-j} y_t = y_{t-j}$, equation (3) can be written as

$$\left(1 - \alpha_1 z^{-1} - \alpha_2 z^{-2}\right) y_{t+1} = \left(\beta_1 + \beta_2 z^{-1}\right) u_t,$$

or

$$y_{t+1} = \left(\frac{\beta_1 + \beta_2 z^{-1}}{1 - \alpha_1 z^{-1} - \alpha_2 z^{-2}}\right) u_t. \tag{4}$$

The multiplier of u_t on the right-hand-side is referred to as a transfer function (Taylor et al. 2013). Properties of the transfer function, most importantly the poles, determine the properties of the system: see for example Fadali & Visioli (2013). In our case the poles are the roots of $x^2 - \alpha_1 x - \alpha_2$. If the poles are plotted in the complex plane, then the distance from the origin gives the decay rate: poles at the origin imply that the output reaches the target after just one sample, with increased time-to-target as poles move towards the unit circle. Poles outside the unit circle are unstable. Complex poles inside the unit circle can lead to oscillations in output, and oscillations are also possible for poles on the negative real axis. If the poles are on the real positive axis, the output does not oscillate.
A linear controller selects the input u_t at time t as a linear combination of observed and target values. An example for (3) might be

$$u_t = k_1 y_{t+1}^* - f_0 y_t - f_1 y_{t-1} - g_1 u_{t-1}, \tag{5}$$

for which the coefficients k_1, f_0, f_1 and g_1 are sometimes called *gains*. An equivalent form is

$$u_t = \frac{k_1 z y_t^* - \left(f_0 + f_1 z^{-1}\right) y_t}{\left(1 + g_1 z^{-1}\right)}. \tag{6}$$

The controller is stable if $\mid g_1 \mid < 1$.
In a closed loop system the input is always selected algorithmically by the controller rather than exogenously, so we can use (4) and (6) to write down a system which relates y_{t+1} to earlier values $\{y_{t-j}; j = 0, 1, 2\}$ and targets y_{t+1}^* and y_t^*. In our case this is

$$y_{t+1} = \gamma_1 y_t + \gamma_2 y_{t-1} + \gamma_3 y_{t-2} + \eta_1 y_{t+1}^* + \eta_2 y_t^*, \tag{7}$$

where

$$\begin{aligned}
\gamma_1 &= \alpha_1 - g_1 - \beta_1 f_0, \\
\gamma_2 &= \alpha_2 + \alpha_1 g_1 - \beta_1 f_1 - \beta_2 f_0, \\
\gamma_3 &= \alpha_2 g_1 - \beta_2 f_1, \\
\eta_1 &= k_1 \beta_1, \\
\eta_2 &= k_1 \beta_2.
\end{aligned}$$

An important measure of system performance is the steady state gain between output and target, which is the long-term ratio between y_t and y_t^*. At steady state $y_t = y_{t-1} = y_{t-2}$ and $y_{t+1}^* = y_t^*$ so that the steady state gain is $(\eta_1 + \eta_2)/(1 - \gamma_1 - \gamma_2 - \gamma_3)$.

3.2. Deadbeat and PIP control

A simple way to choose input u_t is to select it so that the expected value of the next output is equal to the target value, assuming the true model parameters are equal to the estimates. For the model given in (3), with estimated coefficients $\hat{\alpha}_1$, $\hat{\alpha}_2$, $\hat{\beta}_1$ and $\hat{\beta}_2$, and assuming target y_{t+1}^*, this leads to

$$u_t = \frac{y_{t+1}^* - \left(\hat{\alpha}_1 y_t + \hat{\alpha}_2 y_{t-1} + \hat{\beta}_2 u_{t-1}\right)}{\hat{\beta}_1}, \tag{8}$$

which is referred to as a *deadbeat* controller. It is a special case of (5), with appropriately defined coefficients k_1, f_0, f_1 and g_1. In this case, the steady state gain between output and target is

$$\frac{(\beta_1 + \beta_2)}{\left(\hat{\beta}_1 + \hat{\beta}_2\right)(1 - \alpha_1 - \alpha_2) + (\hat{\alpha}_1 + \hat{\alpha}_2)(\beta_1 + \beta_2)}, \tag{9}$$

which is one when the estimated parameter values are equal to the true parameters.
There are a huge array of alternative controllers, commonly implemented using feedback control, of which the most widely used is the proportional-integral-derivative (PID) feedback controller (Franklin et al. 2013). We concentrate on one particular controller, the so-called proportional-integral-plus or PIP controller (Young et al. 1987, Taylor et al. 2000, 2013). This is an extension of the PID controller and is selected due to its increased

design flexibility and the fact that under certain constraints it becomes equivalent to the special case of a deadbeat controller given in (8). In our case the PIP controller is

$$u_t = k_1 y^*_{t+1} - f_0 y_t - f_1 y_{t-1} - g_1 u_{t-1} - k_2 e_t, \tag{10}$$

where $e_t = e_{t-1} + y^*_t - y_t$, which is the cumulative error between output and target. Inclusion of the extra term better allows the system to track the target in case of model misspecification or parameter estimation error (and is a standard concept in most engineering applications of feedback control).
Using (4), (10) and $e_t = (y_t - y^*_t)/(1 - z^{-1})$ to determine the closed loop system representation, we see that the steady state gain between the output and target is one, regardless of parameter estimation error (Taylor et al. 2013). This contrasts with the steady state gain associated with (5) or (8) which, as illustrated by (9), is only one when the estimated parameter values are equal to the true parameters. In Section 4 we will illustrate further advantages of the PIP controller in comparison to deadbeat. Before that, we make some brief comment on how the coefficients k_1, f_0, f_1, g_1 and k_2 might be selected.

3.3. Design of controller

As mentioned previously, stability of the system and speed of convergence to steady-state are determined by the positions of the poles of the transfer function. In *pole placement*, the coefficients are selected so that the poles of the transfer function are in desired locations, so as to ensure the system is well-controlled. Deadbeat is an example of this approach, in which the coefficients are selected so that the poles lie at the origin of the complex plane.
A more direct method is based on minimisation of an interpretable cost function. For example, we might want to penalise both short-term and sustained deviations between output and target, and between input and some nominal input level u^*. In that case we might minimise

$$\sum_{t=1}^{N} \left\{ w_1 \left(y_t - y^*_t\right)^2 + w_2 e_t^2 + w_3 \left(u_t - u^*\right)^2 \right\}, \tag{11}$$

for chosen positive weights w_1, w_2 and w_3. More involved cost functions might of course be preferred. The minimisation of a quadratic cost function for a linear system model is referred to as LQ optimisation. The given cost is equivalent to that minimised when using a standard PIP-LQ controller design (Taylor et al. 2013)
Both pole placement and LQ optimisation and their variants assume that the system parameter θ is known. An alternative, *stochastic robustness analysis* (SRA), recognises uncertainty in θ by specifying a probability distribution for it, in our case $\mathrm{N}(\theta_0, \Sigma)$. SRA was first demonstrated by Stengel and Ryan Stengel & Ryan (1991), with significant further contributions from Marrison, Stengel and Wang (Marrison & Stengel 1995, 1997, Wang & Stengel 2002). SRA is flexible and easy to implement for a range of systems. However, a downside is that it can be computationally expensive.
To implement SRA we begin with a performance metric. Examples are

- *Probability of instability, P_i:* the probability that at least one closed loop root is outside the unit circle.

- *Probability of error exceedence, P_e:* the probability that the root mean square error between output and target exceeds a specified value.

- *Probability of error exceedence after settling, P_r:* the probability that the root mean square error between output and target exceeds a specified value after a burn-in period to allow settling.

- *Probability of control-limit exceedance, P_g:* the probability that the input signal goes above a given amplitude.

A weighted average of these or other metrics may be preferred. Once the metric is decided, we then numerically search for coefficients f_0, f_1, g_1 and k_2 that give acceptable performance when integrated over the distribution of parameters θ, using Monte Carlo integration.

4. Properties and Performance

In this section we will compare the performance of deadbeat and PIP controllers using simulations based on the anticoagulation model. Although a range of possible controllers could be developed from the algorithms and design methods introduced in Section 3, we will focus our investigations on three cases, namely deadbeat using equation (8), and PIP control (10) with the coefficients chosen by either LQ or SRA optimisation.
We re-introduce the noise term ε_t and work with (1). The results are based on 10000 simulated patients, each with an individual $\theta_p \sim \mathrm{N}(\theta_0, \Sigma)$, with θ_0 and Σ given by (2). The model for patient p is stable if the magnitude of the roots of $x^2 - \alpha_{p1}x - \alpha_{p2}$ are less than 1. For the test set of 10000 patients, 26 had simulated parameter values that would give an unstable model. Without constraints each of the 10000 patients were controllable, however, including the constraint that inputs must be positive meant that these 26 unstable patients were not controllable (using test conditions provided in Evans & Murthy (1977)). Therefore, these patients 26 were removed from the analysis.
In the remaining test data, there were 278 patients with negative values of the steady state gain between output and input:

$$\frac{\beta_{p1} + \beta_{p2}}{1 - \alpha_{p1} - \alpha_{p2}}.$$

Patients with negative gains cannot be controlled without negative input values u_t. With the anticoagulation example in mind, we constrained the inputs to be non-negative in the simulations to follow, and hence removed these patients too, as structurally non-controllable. This left a test set of 9696 patients. As an aside we note that in anticoagulation in practice a proportion of patients are indeed non-controllable or extremely difficult to control (Razouki et al. 2014). In their study of 103897 patients Razouki et al. (2014) found that 40% of patients spent less than 60% of the time with an INR in the range 2-3, and of these patients with poor control, 30% (13226 patients and 12% of the total patients) had neither a high or low tendency to be out of range so presumably had erratic control.

4.1. Known parameter values

To begin with we will assume that the parameters θ_p are fully known for each patient. In simulations the output and inputs were initialised to zero and for each patient we generated two series of $N = 50$ observation times. One series had inputs selected using deadbeat control and the other used PIP with the coefficients chosen by LQ optimisation. The aim in practical anticoagulation is often to maintain INR in the range 2–3. Hence as target output we selected $y_t^* = \log 2.5$ for $t = 1, 2, \ldots, 50$.

4.1.1. Deadbeat control

We consider first the series with deadbeat control. Choosing inputs by deadbeat control resulted in unstable behaviour in 3151 of the 9696 simulated patients, even when the model was correct and the parameter values fully known. Although there is an analytical cancellation, the instability occurs due to the controller being unstable (see Eq. (6)) and the numerical rounding errors and dose constraints that occur. The dose of the drug is discrete, so similar stability issues are likely to occur in practice if an unstable controller is used. Examples of patients with good and poor control are given in Figure 2. For the patient with poor control, the input ocillates wildly between zero and extremely large values outwith the range plotted. The output also oscillates unacceptably.

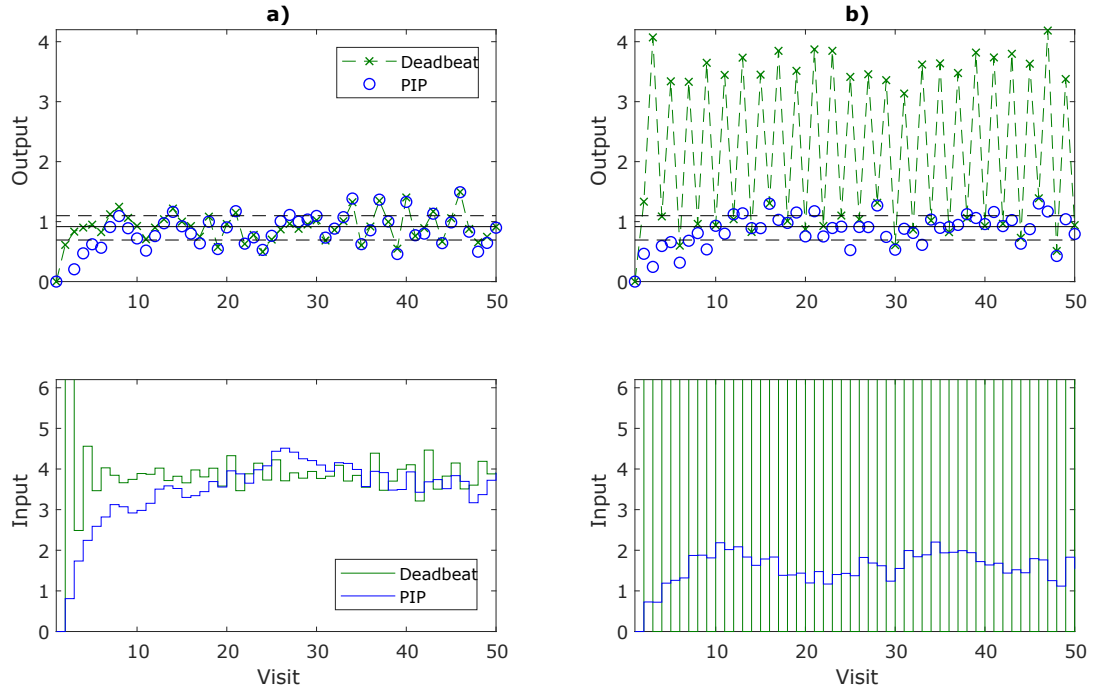

Fig. 2. Deadbeat and PIP control responses for two simulated patients when the model parameters θ_p are known. a) Deadbeat input model stable for example patient, b) Deadbeat input model unstable for example patient.

Table 2. Summary of results when θ_p is known. The PIP results are for 9696 simulated patients. The deadbeat results are for the subset of 6545 simulated patients who had stable inputs and outputs - note deadbeat results for the full set of 9696 patients were RMSE values of the order of 10^{38} due to instabilities. RMSE is root mean square error between output and target.

Controller	RMSE $t = 1:50$	RMSE $t = 21:50$	Mean $\lvert u_t - u_{t-1}\rvert$
Deadbeat (subset)	0.2438	0.2084	0.4586
PIP	0.3283	0.2353	0.2574

4.1.2. PIP control

For the second set of series, we used PIP with the coefficients for each simulated patient chosen by LQ optimisation based on cost (11), with weights $w_1 = w_2 = w_3 = 1$. This gives equal weighting to the output error, cumulative error and input deviations. Changing the weights varies the importance of each term in the cost being optimised. Oscillations in the inputs do not occur when using a PIP controller, as demonstrated in Figure 2 (in comparison the deadbeat input oscillates between the input constraints, with the maximum outside of the plotted range).

Table 2 provides a performance comparison between the 9696 simulated patients controlled using a PIP strategy and the 6545 with a stable deadbeat strategy. In general, the PIP controller is slower, but more robust than the deadbeat controller. On average the PIP controller suggests smaller changes in input doses. If the input model used to determine the deadbeat inputs remains stable, and the model is correct, then the deadbeat controller performs better in terms of minimising the errors in the output. As we have seen however, even in the ideal case of a correctly specified model and known parameter values, the deadbeat controller failed for about 30% of patients.

4.2. Uncertain parameter values

The response when θ_p is not known is now considered. Before any data are available for the patient, our prior knowledge is simply that $\theta_p \sim \mathrm{N}(\theta_0, \Sigma)$. In the next subsection we will briefly consider adaptive estimation as data accrue. In this subsection we suppose that the control policy is fixed at the outset and not adapted as further data on the patient become available.

4.2.1. Deadbeat control

Replacing the true model parameters by θ_0 in the deadbeat controller gave a stable response for all 9696 simulated patients in the test data. A performance summary is given in Table 3.

A key problem with the deadbeat strategy when the model is not correct is that the output does not track the desired output and there is a steady state error. This explains the increased RMSE values given in the table. The response of two example patients when using the deadbeat controller with model mismatch is given in Figure 3a. This demonstrates that the control strategy does not work well and the output does not track the desired output when the model is not correct.

For perfect tracking we want y_t close to y_t^*, which is achieved at steady state if the closed loop system has a steady state gain (9) of one. For the simulated set of patients the mean steady state gain under deadbeat control was 0.9959, suggesting good model calibration overall. But there was a large standard deviation of 0.3343, and hence for many individual patients there was significant bias between mean output and target.

4.2.2. PIP with LQ coefficient choice and fixed θ

First, the PIP control coefficients were obtained using LQ optimisation of (11), with weights $w_1 = w_2 = w_3 = 1$, and assuming that the population mean parameter θ_0 applied. As the target is time-fixed we set $k_1 = 0$ and used the integral of error as the tracking measure. The obtained coefficients were $f_0 = 0.4290, f_1 = 0.1183, g_1 = 0.0207$ and $k_2 = -0.8562$. The response for the two example patients is given in Fig 3b, demonstrating the improvement from deadbeat control.

The performance of this PIP controller is summarised in Table 3. As pointed out in Section 3.2, the steady state gain is one for each realisation. Nonetheless, for some patients the controller works poorly, which is reflected in the relatively high root mean square errors.

4.2.3. PIP with SRA coefficient choice and random θ

The previous PIP control design does not take into account the possible spread of parameters between patients. In order to achieve good performance over the range of possible patients, the PIP coefficients can also be determined using SRA. This provides a way of using the knowledge that $\theta_p \sim \mathrm{N}(\theta_0, \Sigma)$. We used the performance and stability measures P_i, P_e, P_r and P_g defined in Section 3.3. For the probability of error exceedence, P_e, we flagged if the overall root mean square error between output and target exceeded 0.3. For P_r, we used the root mean square error between y_t and y_t^* over the range $t = 15 : 50$, with a flag if this exceeded 0.25. For the probability of control-limit exceedance, P_g, we monitored the proportion of times the controller proposed an input above 10mg. These probabilities are calculated as

Table 3. Summary of results when θ_p is not known. All results are based on 9606 simulated patients. The deadbeat and PIP LQ methods use θ_0 in place of θ_p in determining the controller. The PIP SRA method integrates over $\theta_p \sim \mathrm{N}(\theta_0, \Sigma)$.

Controller	RMSE $t = 1:50$	RMSE $t = 21:50$	Mean $\lvert u_t - u_{t-1}\rvert$
Deadbeat	0.4663	0.4298	0.3839
PIP LQ	0.4023	0.3763	0.2701
PIP SRA	0.3345	0.2469	0.2296

$$P_i = \frac{\sum_{j=1}^{N} \omega_j}{N} \qquad \omega_j = \begin{cases} 1 & \text{if } \exists\, |p_{cl}| > 1 \\ 0 & \text{otherwise,} \end{cases}$$

$$P_e = \frac{\sum_{j=1}^{N} \phi_j}{N} \qquad \phi_j = \begin{cases} 1 & \text{if } \sqrt{\frac{\sum_{t=1}^{50}(y_t - y_t^*)^2}{50}} > 0.3 \\ 0 & \text{otherwise,} \end{cases}$$

$$P_r = \frac{\sum_{j=1}^{N} \pi_j}{N} \qquad \pi_j = \begin{cases} 1 & \text{if } \sqrt{\frac{\sum_{t=15}^{50}(y_t - y_t^*)^2}{36}} > 0.25 \\ 0 & \text{otherwise} \end{cases}$$

$$P_g = \frac{\sum_{j=1}^{N} \rho_j}{N} \qquad \rho_j = \begin{cases} 1 & \text{if } \exists\, u_t > 10 \\ 0 & \text{otherwise,} \end{cases}$$

where p_{cl} is used to define a closed loop pole and j indicates patient number. As overall cost we used

$$w_i P_i^2 + w_e P_e^2 + w_r P_r^2 + w_g P_g^2$$

with weights $w_i = 10$, $w_e = 1$, $w_r = 0.1$ and $w_g = 1$. We chose the quadratic form to give increased importance to large probabilities.

The cost was calculated using a Monte-Carlo simulation with N=10000 realisations to generate 10000 random patient models. The control gains that minimised the cost function were calculated using the Matlab function `patternsearch`, with initial values taken as the LQ estimates chosen in the previous subsection. The SRA method led to $f_0 = 0.1165, f_1 = 0.1534, g_1 = 0.2204$ and $k_2 = -0.9815$. A controller with these coefficients was then applied to the 9696 test simulated patients. Performance summaries are presented in Table 3 and, for two example patients, in Figure 3c. The PIP strategy with coefficients obtained by SRA gives very reasonable performance.

4.3. Adaptive parameter values

In Section 4.1 we looked at control in the hypothetical case that the parameters that determine the input/output relationship for a patient are fully known. In Section 4.2 we

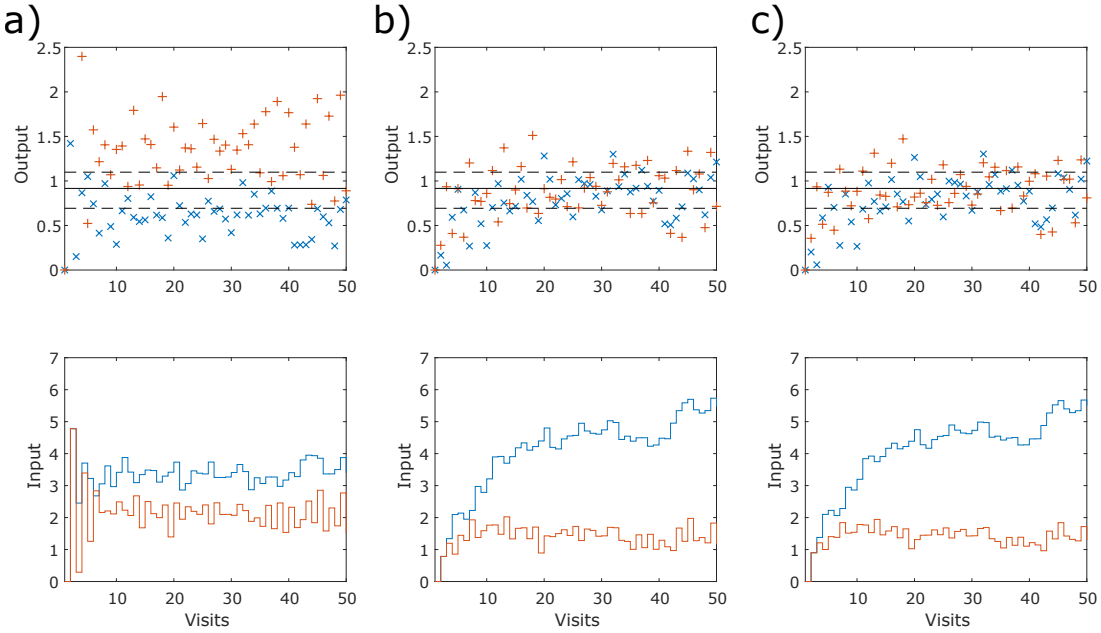

Fig. 3. Simulated patient results when θ_p is not known: a) Deadbeat, b) PIP LQ, c) PIP SRA.

assumed that we knew nothing about the patient and based our controller on population characteristics. In practice of course there will be an accrual of patient-specific knowledge as time proceeds. In this section therefore we will use simulations to briefly investigate the effect of dynamically adapting the controller as experience is gained. Our simulations will be based on the parameter values for a fairly typical patient, Patient A in Figure 1. We will compare controllers with coefficients determined at time zero for the patient, after 25 observations are available, and after 50 observations are available. The true parameters for the patient are the conditional mean values after 50 observations.
For Patient A the conditional parameter mean and variance matrix after 25 observations are

$$\theta_{p25} = \begin{pmatrix} 0.2447 \\ 0.1677 \\ 0.1040 \\ 0.0241 \end{pmatrix} \qquad \Sigma_{p25} = \begin{pmatrix} 0.0127 & -0.0045 & -0.0009 & -0.0009 \\ -0.0045 & 0.0098 & -0.0017 & 0.0007 \\ -0.0009 & -0.0017 & 0.0049 & -0.0041 \\ -0.0009 & 0.0007 & -0.0041 & 0.0040 \end{pmatrix}.$$

After 50 observations these are

$$\theta_p = \theta_{p50} = \begin{pmatrix} 0.2579 \\ 0.1895 \\ 0.0769 \\ 0.0396 \end{pmatrix} \qquad \Sigma_p = \Sigma_{p50} = \begin{pmatrix} 0.0096 & -0.0038 & 0.0000 & -0.0012 \\ -0.0038 & 0.0076 & -0.0015 & 0.0007 \\ 0.0000 & -0.0015 & 0.0041 & -0.0037 \\ -0.0012 & 0.0007 & -0.0037 & 0.0038 \end{pmatrix}.$$

These values were used to design PIP controllers based on the mean using LQ optimisation and based on the mean and variance using SRA with 10000 simulated patients as

Table 4. PIP control coefficients for Patient A initially and after 25 and 50 observations.

	PIP LQ				PIP SRA			
Observations	f_0	f_1	g_1	k_2	f_0	f_1	g_1	k_2
None	0.4290	0.1183	0.0207	-0.8562	0.1781	0.1417	0.1349	-0.9187
25	0.5669	0.2460	0.0353	-0.9042	0.1919	0.7919	0.4572	-1.9042
50	0.6556	0.2922	0.0611	-0.9097	0.2806	1.2961	0.7329	-2.4097

described in the previous sections. The control coefficients are summarised in Table 4. Each controller was then used to generate 10000 new sequences of 50 observations. Table 5 presents a comparison of results, and an example response is given in Figure 4.

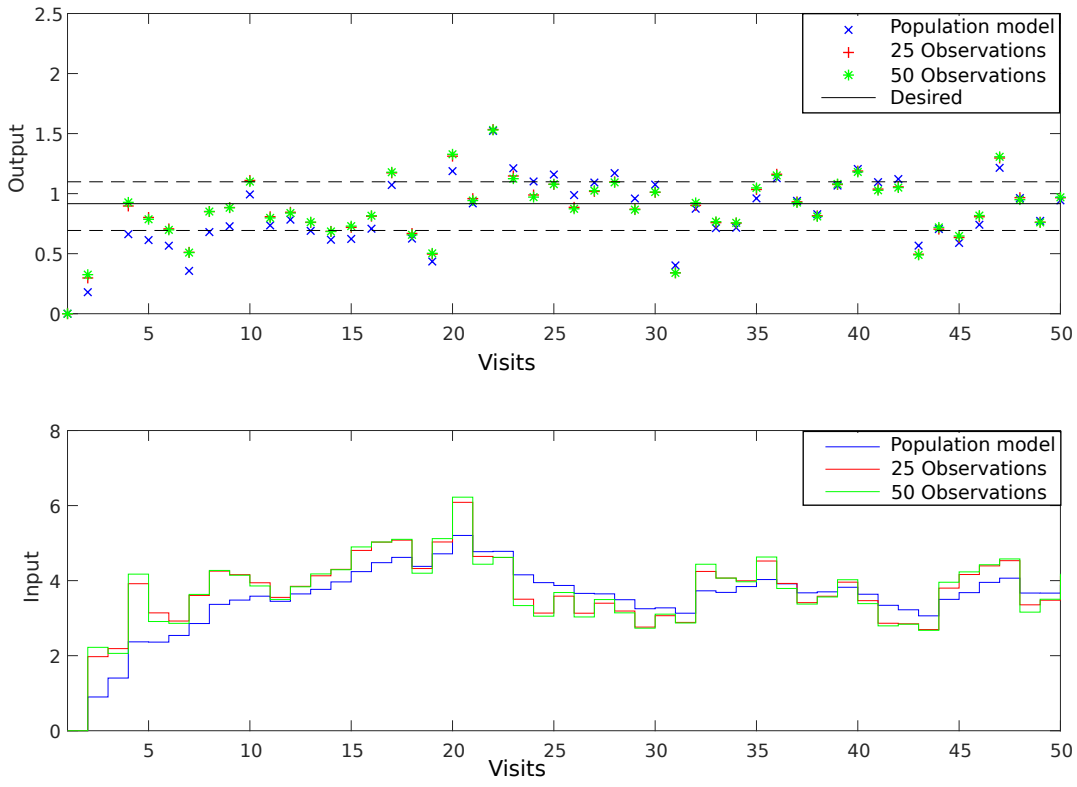

Fig. 4. Example simulated response using SRA based on population and adaptive patient-specific control coefficients.

Using LQ optimisation there is little change in the results for the different models because only the mean parameter influences the controller and for this particular patient the values of θ_{p25} and θ_{p50} are quite similar to θ_0. When using SRA to determine the control gains however, the overall root mean square errors are reduced once we have patient-specific information. This is a consequence of the SRA controller becoming faster and more aggressive when it does not need to be robust to such a wide spread of possible

Table 5. Summary of results using PIP LQ and PIP SRA with coefficients determined initially and after 25 or 50 observations.

Controller	Observations	RMSE $t = 1:50$	RMSE $t = 21:50$	Mean $\lvert u_t - u_{t-1}\rvert$
PIP LQ	None	0.3456	0.2283	0.2587
	25	0.3437	0.2272	0.2882
	50	0.3452	0.2264	0.3030
PIP SRA	None	0.3452	0.2294	0.2285
	25	0.3143	0.2296	0.4053
	50	0.3102	0.2291	0.5289

parameter values. The fact that the controller becomes more aggressive is also evident in the increased changes to the inputs using SRA. The simulated example in Figure 4 illustrates these characteristics. In the plot, and also in Table 5, for SRA there is little difference between conditioning on 25 or on 50 observations, which might be expected since Σ_{p25} and Σ_{p50} are relatively similar for this patient.

5. Use of Control in Anticoagulation

5.1. Retrospective comparison

Returning now to the observed anticoagulation data, for each patient p in the test data set we will compare the actual doses u_{pt} with those that would have been recommended by the various controllers we have considered, generically c_{pt} say. We classify the actual doses u_{pt} as being good if INR at the next visit was in the target range of 2—3 units, as being too low if the INR was below 2, and as being too high if it was above 3. Good decisions are compared with controller values using the absolute relative difference

$$G_{pt} = \frac{2|u_{pt} - c_{pt}|}{(u_{pt} + c_{pt})} \qquad \log(2) \le y_{p,t+1} \le \log(3). \tag{12}$$

If u_{pt} proved to be too low, we used an indicator for the controller suggesting a higher value:

$$L_{pt} = I(c_{pt} > u_{pt}) \qquad y_{p,t+1} < \log(2). \tag{13}$$

We used the opposite if the actual dose was too high:

$$H_{pt} = I(c_{pt} < u_{pt}) \qquad y_{p,t+1} > \log(3). \tag{14}$$

Mean values of these statistics are given in Table 6. Results are based on 2029 decisions in total, of which 58% of doses were good, 27% too low and 15% too high. The adaptive controller coefficients were updated after each observation. When the actual prescribed dose was judged to be good, the two PIP methods clearly outperform deadbeat and would usually recommend doses that are very close to that prescribed. When the actual dose seemed to be too low, all three controllers would have prescribed a higher value for a large majority of decisions. When the actual dose was too high the two PIP controllers would have prescribed a lower dose in over 60% of the cases, whereas deadbeat would have recommended a lower dose less often.

Table 6. Comparison of actual decisions and controller recommendations for 52 test patients. $\bar{G}$, $\bar{L}$ and $\bar{H}$ are the mean values of statistics (12)-(14) over 2029 decisions.

Controller		$\bar{G}$	$\bar{L}$	$\bar{H}$
Fixed	Deadbeat	0.3472	0.7129	0.4967
	PIP LQ	0.0684	0.6996	0.6283
	PIP SRA	0.0615	0.7414	0.6447
Adaptive	Deadbeat	0.3189	0.8916	0.3421
	PIP LQ	0.0679	0.7034	0.6316
	PIP SRA	0.0753	0.7529	0.6513

5.2. Robustness

We can examine also the robustness of the three controllers under consideration by using the structured singular value, which is a device used to analyse the stability of a system subject to perturbations. We consider a single generic patient and drop the subscript p for notational convenience. We assume adaptive estimation and recall that at time t we have $\theta \sim \mathrm{N}(\theta_t, \Sigma_t)$. Our controllers are of the form $u_t = Ky_t^e$ where $y_t^e = (y_t, y_{t-1}, u_{t-1}, e_t)$ is the extended observation vector and K is a matrix of design coefficients and elements of θ_t. The state evolution of a closed-loop system can thus be represented as

$$y_{t+1}^e = F(\theta_t, \triangle_t, K)y_t^e \tag{15}$$

where $\triangle_t$ reflects the uncertainty caused by using the posterior mean θ_t in place of the unknown true parameter θ.

The intention is to assess stablity of the system as θ varies over a feasible region. We use pointwise $1-\alpha$ credible regions

$$(\theta_t)_j \pm z_{\alpha/2}\sqrt{(\Sigma_t)_{jj}}$$

for each element j, where $z_{\alpha/2}$ is the upper $\alpha/2$ quantile of the standard Normal distribution. Further, we define $\triangle_t^\alpha$ as the Cartesian product of these sets.

Since the model is uncertain, we are interested in the ability of a controller to stabilise the state evolution for the largest set of parameter values around θ_t. To address this, we compute the so-called robust stability margin $R(K, \triangle_t^\alpha)$, which quantifies the percentage of modelled departure in the uncertainty set $\triangle_t^\alpha$ for which the system (15) remains stable for a given controller K. For example, $R(K, \triangle_t^\alpha) = 0.3$ means that (15) is stable for all values of θ in

$$(\theta_t)_j \pm 0.3z_{\alpha/2}\sqrt{(\Sigma_t)_{jj}}),$$

but there is a value of θ in the complementary subset of $\triangle_t^\alpha$ which renders (15) unstable. The greater $R(K, \triangle_{p,t}^\alpha)$ is, the more stable the system, and $R(K, \triangle_t^\alpha) > 1$ indicates there is no parameter corresponding to perturbations in $\triangle_t^\alpha$ which destabilises (15). This robustness analysis method is rooted in the work of Doyle et al. (1982) then Doyle (1985), Young et al. (1991) and Fan et al. (1991), where the problem of margin computation is

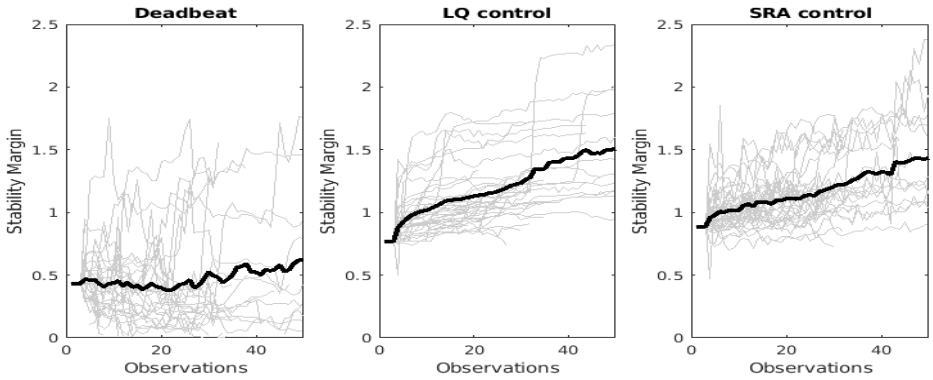

Fig. 5. Stability margins $t \longrightarrow R(K, \triangle_{p,t}^{\alpha})$ for deadbeat, LQ and SRA control. The grey lines are the margins for the individual patients in the test data, adapted as information accrues. The bold lines are the means.

turned into the analysis of a matrix function called the structured singular value μ and defined by:

$$\mu_{\Lambda}(M) = \frac{1}{\min\{\overline{\sigma}(\lambda) : \lambda \in \Lambda, \det(I - M\lambda) = 0\}}.$$

Here $\overline{\sigma}(\lambda)$ is the largest singular value of λ and Λ is a matrix set having a particular structure representing uncertainty: see Packard & Doyle (1993) for a clear introduction. By denoting P the transfer function for (15) in the absence of perturbations, a small-gain theorem tells us that (15) is stable for all perturbations in $\triangle_t^{\alpha}$ if $\sup_w \mu_{\triangle_t^{\alpha}}(P(jw)) < 1/\max\{\overline{\sigma}(\lambda_t^{\alpha}) : \lambda_t^{\alpha} \in \triangle_t^{\alpha}\}$. Moreover, we can infer from $\sup_w \mu_{\triangle_t^{\alpha}}(P(jw))$ the size of perturbations that (15) is robustly stable against.

In practice, we use the Matlab function `robstab` to compute $R(K, \triangle_t^{\alpha})$ while avoiding issues with μ discontinuities by considering only real uncertainty (Barmish et al. 1990, Packard & Pandey 1993). The computation of μ is NP hard, so the Matlab function `robstab` returns lower and upper bounds, which are easier to compute. In our computations the differences between the lower and upper bounds were small, with mean 0.0014. We plot the lower bounds, as the exact stability margin is guaranteed to be no smaller than this, guaranteeing stability for all modelled uncertainties with normalised magnitude up to the lower bound.

For the three controllers considered in this work, we show in Figure 5 the values of of $R(K, \triangle_t^{\alpha})$ as t increases and knowledge accrues, using $\alpha = 0.05$. The grey lines represent the uncertainty margins for individual patients in the test set, with the bold lines showing the mean. We see that adaptive LQ and SRA controllers provide more robustness than deadbeat. Moreover, the stability margins for the deadbeat controller increase only slowly as we learn about the patient, whereas the LQ and SRA margins increase more quickly.

6. Discussion

Personalised anticoagulant dose selection is necessary given the heterogeneity in response between and within individuals. Careful modelling of the dynamic and patient-specific relationship between dose and response is of course necessary if dose-selection algorithms are to be effective. We have tried to show in this work that it is equally important to pay close attention to the dosing rule given the model. Hence we have not described modelling in much detail in this work, other than the variety of simple transition models compared in Table 1. We did, however, consider a much wider range of models in unreported exploratory analyses of the warfarin data. For example we removed the discrete time assumption and considered modelling in real time with a point process of clinic visits. We included gender, age and time intervals between visits as covariates, and we used mean-covariance modelling (Pourahmadi 1999, Liu et al. 2018) as implemented in the `jmcm` R package of Pan & Pan (2017) to allow previous responses, doses and covariates to affect not just the mean, but also (via a Cholesky decomposition) the variance of responses. None of these more involved models brought substantial improvement over the simple model (1) with patient-specific coefficients.

Genetic factors and other factors such as alcohol intake, BMI and interacting medicines have been shown to influence the response to warfarin (Bader & Elewa 2016, Bourgeois et al. 2016). In the hospital notes accompanying our data there are regular explanatory comments on possible causes for unusual INR values (e.g. co-medication, alcohol increases or decreases). However, there is not always any record of these additional factors that could affect the output INR, or decisions on the input dose, and we did not have any genetic data available. Additional factors therefore could not be included in the models or dose selection algorithms. The methods can easily be extended to include such information if it is available.

We have not concentrated on modelling and inference because these are of course familiar to a statistical readership. Instead we have focused on design and performance of the dose selection algorithm, given the model and parameters, and considered as a problem in controller selection. Of the methods considered, adaptive SRA is perhaps the most flexible in that it optimises customised performance measures, albeit at the cost of modelling assumptions. Using SRA the PIP controller can be designed to maximise the probability of an acceptable response for possible patient models. However, due to the probabilistic nature an acceptable response cannot be guaranteed so constraints should also be introduced to ensure that in practice unacceptable decisions are not made. For the warfarin application the following constraints might be chosen.

- A maximum allowable *change in dose* at each time step can be specified. If the controller suggests a larger change then the actual change can be capped.

- A maximum allowable *dose* at each time step can be provided. For example guidelines on warfarin dosing sometimes suggest a maximum dose of 10mg.

- If the recorded output is very high or very low then the subsequent input can be constrained. For example we might force dose u_t to be zero if INR exceeds some limit.

We investigated the PIP controller with LQ or SRA adaptive estimation and showed that this brought substantial improvement over the naive deadbeat approach in respect of stability and robustness. In future work we hope to compare PIP with other model based controllers, in particular those designed using model predictive control, MPC (Camacho & Alba 2013). MPC is a generalised control strategy in which: i) a model is used to predict future outputs; ii) the set of future control signals that minimise some objective and satisfy constraints are calculated; iii) the first of these control signals is applied to the system and the process is repeated. The use of MPC is attractive, both due to its ability to automatically handle constraints and because it allows non-myopic strategies whilst keeping flexibility to react to unexpected responses.

In retrospective analysis, the PIP controllers led to similar or improved decisions in comparison to those actually made. We envisage that control algorithms could be embedded in existing computerised dosing software, to help guide personalised treatment decisions based on the individual's history of inputs and outputs. Such algorithms would provide guidance for INR dosing (and could also be used for other treatment applications), they could improve performance by balancing the dose change so it is effective (accuracy), but not too aggressive (robustness). The controller parameters can be tuned to account for this performance–robustness trade off. Controllers can be designed to optimise different criteria; hence, they can be used to provide optimised treatment decisions that are personal to individual patients. Controllers can also be used in closed loop systems where the dose is automatically adjusted based on feedback. An example is closed loop insulin delivery (artificial pancreas) (Steil et al. 2004). Here, a key issue is ensuring patient safety which requires robust controllers.

Acknowledgement

We thank Professor Farhad Kamali and his group for providing the anticoagulation data and the Joint Editor, Associate Editor and referees for their help in improving the paper. This work was supported by EPSRC grant EP/M015637/1.

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