Preprints of the 19th World Congress
The International Federation of Automatic Control
Cape Town, South Africa. August 24-29, 2014

Adaptive Control of Bivalirudin in the Cardiac Intensive Care Unit ⋆

Qi Zhao * **T. Edrich** ** **Ioannis Ch. Paschalidis** ***

* *Division of System Eng., Boston Univ., USA (zhaoqi@bu.edu).*
** *Dept. of Anesthesia, Perioperative and Pain Medicine, Brigham and Women's Hospital, Boston, USA (tedrich@partners.org).*
*** *Dept. of Electrical & Computer Eng. and Center for Information & Systems Eng., Boston Univ., 8 St. Mary's St., Boston, MA 02215, USA (yannisp@bu.edu, http://ionia.bu.edu/).*

Abstract: Bivalirudin is a direct thrombin inhibitor used in the cardiac intensive care unit in patients who develop an allergic reaction to heparin. Since it is not a commonly used drug, clinical experience with its dosing is sparse. In earlier work (Zhao et al. [2014]) we developed a dynamic system model that accurately predicts the effect of bivalirudin when given dosage over time and patient physiological characteristics. This paper develops adaptive dosage controllers that regulate its effect to desired levels. To that end, and in the case that bivalirudin model parameters are available, we develop a Model Reference Control law. In the case that model parameters are unknown, an indirect Model Reference Adaptive Control scheme is applied to estimate model parameters first and then adapt the controller. Our algorithms are validated using actual data from a large hospital in the Boston area.

Keywords: Bivalirudin, Pharmacokinetics, Parameter Identification, Model Reference Control, Model Reference Adaptive Control.

1. INTRODUCTION

The US health care system is costly and inefficient (Anderson et al. [2003]). Among the many reform efforts, the meaningful use of Electronic Health Records (EHRs) is seen as a key to improving efficiency. In the hospital, the digitization of data from medical devices enables the development of algorithms that can automate decision making and facilitate treatment. This is exactly the goal of this paper which focuses on automating dosage decisions for a particular drug – bivalirudin – used in the cardiac Intensive Care Unit (ICU).

Bivalirudin antagonizes the effect of thrombin in the blood clotting cascade, thereby preventing complications from blood clotting. It is FDA-approved for short-term anticoagulation of patients undergoing cardiac catheterization to prevent complications due to blood clots (Bittl et al. [2001], Stone et al. [2006]). Bivalirudin is administered to patients who have a contraindication to heparin. It is infused continuously, and is eliminated via the kidney and by plasma protease-metabolism. It affects the coagulation parameters *Partial Thromboplastin Time (PTT)* and the *International Normalized Ratio (INR)* in a dose-dependent fashion. The PTT value is measured in seconds and it will be used as the parameter one wishes to regulate.

⋆ Research partially supported by the NSF under grants CNS-1239021 and IIS-1237022, by the NIH/NIGMS under grant R01-GM093147, by the ARO under grants W911NF-11-1-0227 and W911NF-12-1-0390, by the ONR under grant N00014-10-1-0952, and by the STAR (Surgical ICU TrAnslational Research) Center at Brigham and Women's Hospital.

As a drug that is not commonly used, bivalirudin is used more frequently in the ICU but residents adjusting the infusion rate have little experience, resulting in overdosing or underdosing. Adequate anticoagulation is necessary to avoid the risk of clot formation, but overshooting increases the risk of bleeding. Complicating matters, there is considerable inter- and intra-individual variability in the response to bivalirudin. Motivated by these challenges, in earlier work (Edrich et al. [2011], Zhao et al. [2013, 2014]), we developed methods for predicting future PTT values given past infusion rates and the patient's renal and liver function metrics. One method, proposes an explicit dynamic system model which was shown to produce quite accurate results when tested against actual patient data.

In this paper, we pursue what we view as the natural next step. Leveraging the dynamic system model from Zhao et al. [2013, 2014], we seek to synthesize controllers that can regulate the infusion rate to drive PTT within a desirable range. We develop two types of control laws. First, and assuming that a dynamic system model that can predict PTT given dosage is completely characterized, we directly develop a *Model Reference Control (MRC)* law. Model parameters, however, may be viewed as not known with certainty, which is due to modeling errors and individual variability. To that end, we develop an indirect *Model Reference Adaptive Control (MRAC)* law that identifies model parameters first and then adapts the controller in real-time. For both cases, we present analytical and numerical evidence showing the controllers to drive PTT to the desirable range. Our numerical validation is done

using actual patient data from the Brigham and Women's Hospital – a large hospital in the Boston area.

The remainder of the paper is organized as follows. Sec. 2 presents the dynamic system model that predicts bivalirudin's effect given dosage and physiological information. Sec. 3 presents the proposed control schemes; Sec. 3.1 develops the MRC law whereas Sec. 3.2 develops the indirect MRAC law based on the patient model but with unknown parameters. Finally, conclusions are in Sec. 4.

Notation: We use bold letters to denote vectors and matrices; typically vectors are denoted by lower case letters and matrices by upper case letters. Vectors are assumed to be column vectors. For economy of space we write $\mathbf{x} = (x_1, \cdots, x_n)$ for the column vector $\mathbf{x} \in \mathbb{R}^n$. In addition, we use lower case letters to denote time domain functions (e.g., $f(t)$), and upper case letters to denote Laplace transforms (e.g., $F(s)$).

2. DYNAMIC SYSTEM MODEL FORMULATION

2.1 The Model

This section presents a *Multiple Input Single Output (MISO)* dynamic system model that attempts to explicitly account for the way bivalirudin affects PTT in patients. The model was developed and validated in Zhao et al. [2014]; it is presented here briefly to establish the notation and to set the stage for the control schemes of Sec. 3.

The key quantity (response) we would like to predict is the PTT at each time t. The dynamic model structure is shown in Fig 1. There are 11 inputs which are denoted by $u_i(t), i = 1, \ldots, 11$ and correspond to important physiological variables used as predictors. More specifically, inputs $u_1(t), \ldots, u_{11}(t)$ respectively correspond to:

(1) **Bival rate** (mg/kg/h): the weight-based bivalirudin injection rate.
(2) **GFR** (mL/min): the glomerular filtration rate.
(3) **PTT** (s): last measured PTT value.
(4) **INR** (unit-less): last measured INR value.
(5) **SGOT** (Units/L): the Serum Glutamic Oxaloacetic Transaminase.
(6) **SGPT** (Units/L): the Serum Glutamic Pyruvic Transaminase.
(7) **TBILI** (mg/dL): total bilirubin.
(8) **ALB** (g/L): Albumin.
(9) **PLT** (K/mcL): Platelet count.
(10) **HCT** (%): Hematocrit.
(11) **FIB** (mg/dL): Fibrinogen.

More detailed description of these physiological variables can be found in Zhao et al. [2014].

The model of Fig. 1 has a single output –the PTT value– which is denoted by $y(t)$. There is also a single state variable denoted by $x(t)$. Overall there are 14 unknown parameters: 13 of which correspond to the various gains and are denoted by β_i, $i = 1, \ldots, 13$. The initial condition of the system is the 14th unknown parameter and is denoted by $x(0)$ (β_{14}). The system dynamics are:

$$\begin{aligned} \dot{x}(t) &= \mathbf{A}x(t) + \mathbf{B}\mathbf{u}(t), \\ y(t) &= \mathbf{C}x(t) + \mathbf{D}\mathbf{u}(t), \end{aligned} \tag{1}$$

where $\mathbf{A} = -\beta_3$, $\mathbf{B} = [\beta_1 \ 0 \ \cdots \ 0]$, $\mathbf{C} = \beta_2$, and $\mathbf{D} = [0 \ \beta_4 \ \cdots \ \beta_{13}]$. Clearly, this is a *Linear Time Invariant (LTI)* dynamic system. However, we do not know the model parameters and we only have non-uniform sampled inputs $\mathbf{u}(t)$, and clinical observation values $y(t)$ at certain times t for each patient. It is therefore necessary to translate the continuous-time system dynamics to discrete-time dynamics before proceeding with parameter identification.

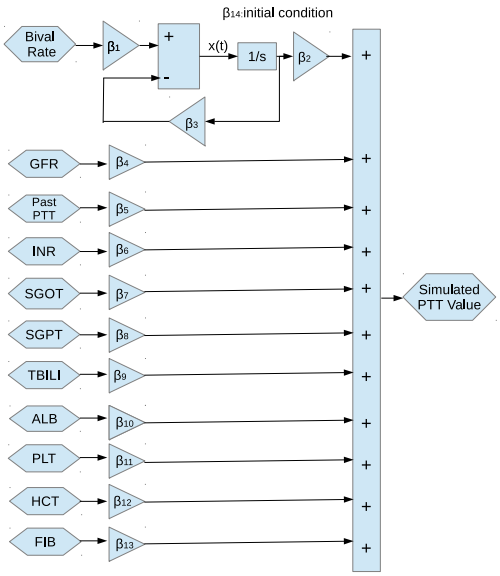

Fig. 1. The multiple inputs single output dynamic model.

2.2 Parameter Identification

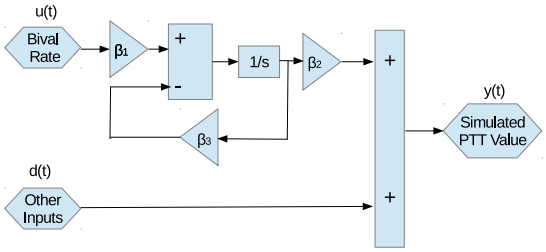

Fig. 2. In this dynamic model, the bivalirudin infusion rate $u(t)$ is the only controllable input. $d(t)$ is the linear combination of the rest of the inputs.

Given the highly non-uniform sampled data, two methods were introduced to identify model parameters in Zhao et al. [2014]. First, and after converting to discrete-time dynamics, we formulated the parameter identification problem as the nonlinear optimization problem of minimizing some metric of fitness to a training set of sampled data. We applied a Quasi-Newton method to obtain optimal values for the model parameters. This yielded a population-wide model in the sense that its parameters produced the best fit with the sampled data. Furthermore, and to accommodate variability across patients, we used a recursive estimation method (Extended Kalman Filter) to estimate the parameter values that best fit a given individual patient in real-time.

3. BIVALIRUDIN CONTROL SCHEME

We now turn to our primary goal of devising a proper controller to keep the PTT value in the range of 50s-70s. According to clinical experience, this range is optimal for cardiac surgery patients. For the system defined in Eq. (1),

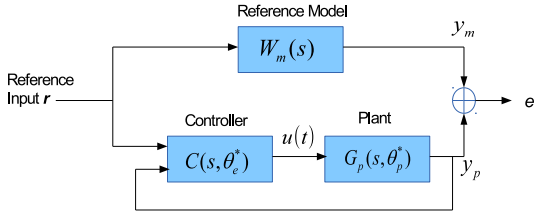

Fig. 3. Model Reference Adaptive Control (MRAC) structure.

the only controllable part is the bivalirudin infusion rate. Since the rest of the inputs are indicators of patients' liver and renal function, we can not control them in a short-time period. Thus, we split our inputs into two parts: a controllable part and a non-controllable part (cf. Fig. 2).

Ideally, we want to design a reference model which can generate sufficient but safe PTT values driven by a reference input signal. Based on the output of the reference model, we want to drive our system to perform similarly to the reference model by a proper control signal. To that end, we adopt the a continuous-time MRAC scheme (see Fig. 3). $W_m(s)$ denotes an ideal reference transfer function that can generate the desired reference output signal. The controllable system is represented by $G_p(s, \boldsymbol{\theta}_p^*)$, where $\boldsymbol{\theta}_p^*$ is a parameter vector. The objective is to design a controller $C(s, \boldsymbol{\theta}_e^*)$, parameterized by $\boldsymbol{\theta}_e^*$, to generate the proper control signals that can drive the controllable system to track the reference output values.

Our first controller is an MRC law that is designed assuming that the system parameters $\boldsymbol{\theta}_p^*$ are known.

3.1 Model Reference Control (MRC)

By observing the system in Fig. 2, we can rewrite the dynamics of a particular patient as

$$\dot{x}_p(t) = -\beta_3 x_p(t) + \beta_1 u(t), \tag{2}$$
$$y_p(t) = \beta_2 x_p(t) + d(t), \tag{3}$$

where we use $u(t), x_p(t), y_p(t)$ to denote the input signal (bivalirudin infusion rate), the state variable, and the output signal (PTT), respectively, and where $d(t) = \sum_{i=2}^{11} \beta_{i+2} u_i(t)$. Clinically, since the renal and liver functions of patients do not vary much within the period between two measurements, we assume that they are constant within the sample interval. By observing the clinical data, we find that $d(t)$ is a step-wise signal. Therefore, we assume that the first order derivative of $d(t)$ ($\dot{d}(t)$) is 0 within the sample interval. By taking the derivative on both sides of (3), using (2) to substitute for $\dot{x}_p(t)$, and using (3) to eliminate $\dot{x}_p(t)$, we obtain:

$$\dot{y}_p(t) = -\beta_3 y_p(t) + \beta_1\beta_2 u(t) + \beta_3 d(t). \tag{4}$$

In the frequency domain, we have

$$Y_p(s) = \frac{\beta_1\beta_2 U(s) + \beta_3 D(s)}{s + \beta_3}, \tag{5}$$

where the system output $y_p(t)$ ($Y_p(s)$), the input $u(t)$ ($U(s)$), and $d(t)$ ($D(s)$) can be observed. Hence, in our setting, the system transfer function is $G_p(s, \boldsymbol{\theta}_p^*) = Y_p(s)/U(s)$ parameterized by β_1, β_2 and β_3.

Next, we design a reference transfer function $W_m(s)$. We take $W_m(s)$ to be a first-order LTI system driven by a reference signal $r(t)$:

$$W_m(s) = \frac{Y_m(s)}{R(s)} = \frac{b_m}{s + a_m}, \tag{6}$$

which is equivalent to

$$\dot{y}_m(t) = -a_m y_m(t) + b_m r(t), \quad or$$
$$Y_m(s) = \frac{b_m}{s + a_m} R(s), \tag{7}$$

for any bounded piecewise continuous signal $r(t)$, where $a_m > 0$, $b_m \neq 0$ are known. We assume that a_m, b_m, and $r(t)$ are chosen so that $y_m(t)$ represents the desired output signal.

Before introducing the MRC law, we start we some definitions and a result (proven in Appendix A).

Definition 1
A state $\mathbf{x}_e$ is said to be an equilibrium state of the system $\dot{\mathbf{x}} = f(t, \mathbf{x})$, $\mathbf{x}(t_0) = \mathbf{x}_0$, where $\mathbf{x} \in \mathbb{R}^n, f : \mathscr{T} \times B(r) \to \mathbb{R}^n, \mathscr{T} = [t_0, \infty)$, $B(r) = \{\mathbf{x} \in \mathbb{R}^n \mid \|\mathbf{x}\| < r\}$, if $f(t, \mathbf{x}_e) \equiv 0 \ \forall t \geq t_0$. We assume that f is such that for every $\mathbf{x}_0 \in B(r)$ and every $t_0 \in [0, \infty)$, the system possesses one and only one solution $\mathbf{x}(t; t_0, \mathbf{x}_0)$.

Definition 2
A equilibrium state $\mathbf{x}_e$ is exponentially stable if there exits an $\alpha > 0$ and for every $\epsilon > 0$ there exists $\delta(\epsilon) > 0$, such that $\|\mathbf{x}(t; t_0, \mathbf{x}_0) - \mathbf{x}_e\| \leq \epsilon e^{-\alpha(t-t_0)}$, $\forall t \geq 0$ whenever $\|\mathbf{x}_0 - \mathbf{x}_e\| < \delta(\epsilon)$.

Theorem 1. If we choose $a_m > 0$, $b_m \neq 0$, and $r(t) = C_r$ (constant), the reference model equilibrium state $y_{me}(t) = b_m C_r / a_m$ is exponentially stable.

We will now design a proper controller $u(t)$ such that all signals in the closed-loop system are bounded and the system output $y_p(t)$ tracks the reference model output $y_m(t)$. The control law should be chosen so that the closed-loop plant transfer function from the input $r(t)$ to the output $y_p(t)$ is equal to the reference model transfer function. Motivated by this, we propose the control law

$$u^*(t) = -k_1^* y_p(t) + k_2^* r(t) - k_3^* d(t), \tag{8}$$

where k_1^*, k_2^*, k_3^* are controller coefficients chosen so that

$$\frac{Y_p(s)}{R(s)} = \frac{b_m}{s + a_m} = \frac{Y_m(s)}{R(s)}. \tag{9}$$

Eq. (9) is satisfied, if we select

$$k_1^* = -\frac{1}{\beta_1\beta_2}(\beta_3 - a_m), \quad k_2^* = \frac{b_m}{\beta_1\beta_2}, \quad k_3^* = \frac{\beta_3}{\beta_1\beta_2}, \tag{10}$$

which yields

$$u(t) = \frac{1}{\beta_1\beta_2}(\beta_3 - a_m) y_p(t) + \frac{b_m}{\beta_1\beta_2} r(t) - \frac{\beta_3}{\beta_1\beta_2} d(t), \tag{11}$$

provided of course that β_1, β_2, $\beta_3 \neq 0$, i.e., the plant is controllable. Such a transfer function matching guarantees that $y_p(t) = y_m(t)$, $\forall t \geq t_0$, when $y_p(t_0) = y_m(t_0)$, or $|y_p(t) - y_m(t)| \to 0$ exponentially fast when $y_m(t_0) \neq y_p(t_0)$ for any bounded reference signal $r(t)$.

We test the performance of the MRC on a (de-identified) data set from the STAR (Surgical ICU Translational Research) Center at Brigham and Women's Hospital in Boston. This data set contains the clinical records of 233 patients, and for each patient, the records consist of non-uniform sampled inputs and outputs over time. As mentioned before, $d(t)$ is a step-wise signal over time. By applying the parameter identification method outlined

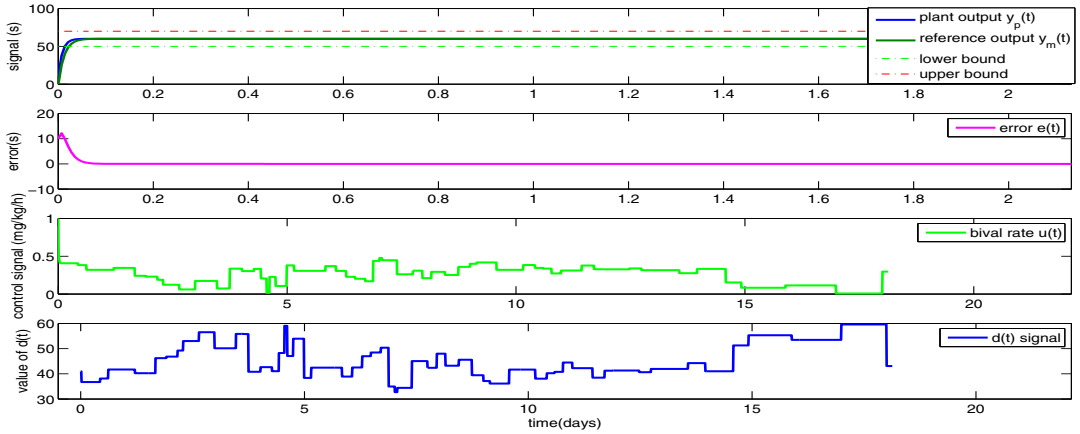

Fig. 4. The effect of the MRC law on a randomly selected patient.

in Sec. 2.2, we obtained both population-wide parameter values and individual model parameter values.

We tested the MRC control law on a subset of patients and the results were qualitatively the same in each case. We report results from a randomly selected patient who has identified model parameters and available input data. To that end, we set the reference parameters as $a_m = 100$, $b_m = 6000$, $r(t) = 1$. In simulation, we set the model time step $\Delta t = 0.0069s$. Choosing these values keeps the reference PTT value to be 60s, which is in the middle of the desirable range. We note that these parameter values are simply an example and physicians have the freedom of selecting alternative values depending on the stable value and response time they wish to achieve.

The effect of the MRC law (11) on this randomly selected patient is shown in Fig. 4. It can be seen that driven by inputs generated by the MRC law, the system output quickly converges to the reference output (top figure). The tracking error ($e(t) = y_p(t) - y_m(t)$) quickly converges to zero and remains at zero (2nd figure). We also obtain the control signal which corresponds to the bivalirudin infusion rate (3rd figure). The MRC control law we introduced is robust to the uncontrollable signal $d(t)$ (bottom figure). Although $d(t)$ changes over time, the control signal can adapt and drive the system to track the reference signal closely. We also note that, depending on the parameters of some patients, this law may yield a negative control signal which is infeasible in practice (corresponds to "extraction of bivalirudin" from the patient). In such a case, we set a lower threshold of zero for the control signal.

3.2 Indirect Model Reference Adaptive Control (MRAC)

As we mentioned earlier, there is significant patient variability in the response to bivalirudin. We have already established, Zhao et al. [2014], that adapting model parameters to individual patients leads to improved performance. This suggests that the model structure is largely accurate but model parameters of an individual patient can deviate from population-wide parameter values.

To better assess the effect of this variability, we test the performance of the MRC law derived using parameter values of a specific patient when applied to another patient with different model parameters. Fig. 5 plots the MRC law performance for such a case. The top figure shows that there exists a large gap between the reference output signal and the system output signal. In addition, the system output is out of the safe range. This situation should be avoided because overdosing or underdosing is very dangerous for the patients. To address this issue, we next develop a method that first estimates the individual model parameters, and then adopts the MRC law we introduced using a certainty equivalence principle (Ioannou and Kosmatopoulos [2006]). Such a control scheme is called indirect *Model Reference Adaptive Control (MRAC)* law.

By adding and subtracting $-a_m y_p(t)$ to (4), we can obtain the *State-Space Parametric Model (SSPM)*:

$$\dot{y}_p(t) = -a_m y_p(t) + ((a_m - \beta_3)y_p(t) + \beta_1\beta_2 u(t) + \beta_3 d(t)). \tag{12}$$

Based on (12), the series-parallel estimation model, Ioannou and Sun [2012], is given by:

$$\dot{\widehat{y}}_p(t) = -a_m\widehat{y}_p(t) + ((a_m - \widehat{\beta}_3(t))y_p(t) + \widehat{\beta}_1(t)\widehat{\beta}_2(t)u(t) + \widehat{\beta}_3(t)d(t)), \tag{13}$$

where $\widehat{y}_p(t)$ is an estimated value of $y_p(t)$, and $\widehat{\beta}_1(t)$, $\widehat{\beta}_2(t)$, $\widehat{\beta}_3(t)$ are estimates of the system parameters β_1, β_2, and β_3 at time t. Note that, in (13), $y_p(t)$ is treated as an input available for measurement. By using certainty equivalence, we take the control scheme structure to be

$$u(t) = -k_1(t)y_p(t) + k_2(t)r(t) - k_3(t)d(t), \tag{14}$$

where

$$k_1(t) = \frac{a_m - \widehat{\beta}_3(t)}{\widehat{\beta}_1(t)\widehat{\beta}_2(t)}, \quad k_2(t) = \frac{b_m}{\widehat{\beta}_1(t)\widehat{\beta}_2(t)}, \quad k_3(t) = \frac{\widehat{\beta}_3(t)}{\widehat{\beta}_1(t)\widehat{\beta}_2(t)}.$$

In this problem, we will estimate the product of $\beta_1(t)$ and $\beta_2(t)$ instead of estimating them separately. The model estimation error is $e(t) = y_p(t) - \widehat{y}_p(t)$ which implies:

$$\begin{aligned}\dot{e}(t) =& \dot{y}_p(t) - \dot{\widehat{y}}_p(t)\\ =& -a_m e(t) + \tilde{\beta}_3(t)(y_p(t) - d(t)) - \tilde{\beta}_{12}(t)u(t),\end{aligned} \tag{15}$$

where

$$\tilde{\beta}_3(t) = \widehat{\beta}_3(t) - \beta_3, \qquad \tilde{\beta}_{12}(t) = \widehat{\beta}_1(t)\widehat{\beta}_2(t) - \beta_1\beta_2. \tag{16}$$

We now choose a Lyapunov-like function

$$V(t) = \frac{1}{2}e(t)^2 + \frac{1}{2\gamma_1}\tilde{\beta}_3^2(t) + \frac{1}{2\gamma_2}\tilde{\beta}_{12}^2(t), \tag{17}$$

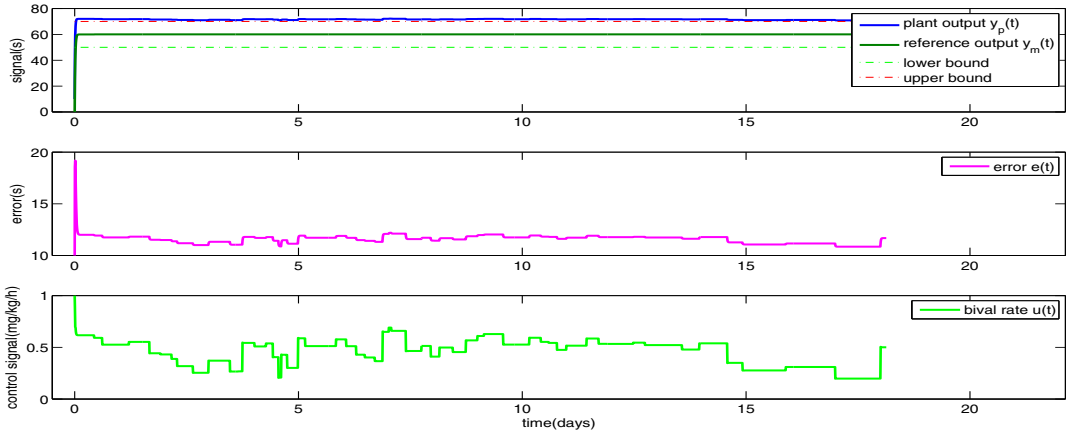

Fig. 5. The MRC law for one patient used on another patient.

which, with $\gamma_1, \gamma_2 > 0$, is non-negative for all t. By taking the derivative on both sides of (17) we obtain

$$\begin{aligned}\dot{V}(t) =& e(t)\dot{e}(t) + \frac{1}{\gamma_1}\tilde{\beta}_3(t)\dot{\tilde{\beta}}_3(t) + \frac{1}{\gamma_2}\tilde{\beta}_{12}(t)\dot{\tilde{\beta}}_{12}(t) \\ =& -a_m(e(t))^2 + \tilde{\beta}_3(t)[e(t)(y_p(t) - d(t)) + \frac{1}{\gamma_1}\dot{\tilde{\beta}}_3(t)] \\ &+ \tilde{\beta}_{12}(t)[\frac{1}{\gamma_2}\dot{\tilde{\beta}}_{12}(t) - e(t)u(t)]. \end{aligned} \quad (18)$$

Then, choosing

$$\dot{\tilde{\beta}}_3(t) = -\gamma_1(y_p(t) - d(t))e(t) \text{ and } \dot{\tilde{\beta}}_{12}(t) = \gamma_2 e(t)u(t)$$

leads to $\dot{V}(t) = -a_m e^2(t) \leq 0$. In addition, since $\beta_1\beta_2$ and β_3 are constants, (16) implies $\dot{\tilde{\beta}}_3(t) = \dot{\widehat{\beta}}_3(t)$ and $\dot{\tilde{\beta}}_{12}(t) = \dot{\widehat{\beta}}_{12}(t)$. It follows that we could estimate the model parameters by:

$$\begin{aligned}\widehat{\beta}_3(t + \Delta t) &= \widehat{\beta}_3(t) + \dot{\widehat{\beta}}_3(t)\Delta t, \\ \widehat{\beta}_{12}(t + \Delta t) &= \widehat{\beta}_{12}(t) + \dot{\widehat{\beta}}_{12}(t)\Delta t, \end{aligned} \quad (19)$$

for small Δt. Then, we can adapt the controller coefficients recursively and control the system in real-time by using (cf. (11))

$$u^*(t) = -\frac{a_m - \widehat{\beta}_3(t)}{\widehat{\beta}_{12}(t)}y_p(t) + \frac{b_m}{\widehat{\beta}_{12}(t)}r(t) - \frac{\widehat{\beta}_3(t)}{\widehat{\beta}_{12}(t)}d(t). \quad (20)$$

Theorem 2. Under the control law (20), the tracking error converges to 0 as $t \to \infty$.

Proof. By choosing such control law, $\dot{V}(t) = -a_m e^2(t) \leq 0$, $\forall t > t_0$. Since $V(t)$ is bounded from below and non-increasing, it converges to a constant. This implies that $-a_m \int_{t_0}^{\infty} e^2(t)dt = V(\infty) - V(t_0)$ is bounded, which is turn implies that $e(t) \to 0$ as $t \to \infty$ according to Barbalat's lemma, Popov and Georgescu [1973]. It also follows that $\dot{\tilde{\beta}}_3(t)$, $\dot{\tilde{\beta}}_{12}(t) \to 0$ as $t \to \infty$. □

One key flaw of the adaptive control law (20) is that the boundness of control signal $u(t)$ can not be established unless we show that $k_1(t)$, $k_2(t)$, $k_3(t)$ are all bounded. However, such a control law may generate estimates of β_{12} arbitrarily close or even equal to zero, which leads to the uncontrollability of the estimated model and unboundness of $u(t)$. To avoid this issue, we propose a modification to the control law (20). One method is to modify the adaptive law for $\widehat{\beta}_{12}(t)$ so that adaptation takes place in a subset of $\mathbb{R}$ which does not include the zero element. We need to use the priori knowledge of $\beta_1 \geq \beta_1^{lb} > 0$ and $\beta_2 \geq \beta_2^{lb} > 0$ to do the projection:

$$\begin{aligned}\dot{\tilde{\beta}}_3(t) =& -\gamma_1(y_p(t) - d(t))e(t), \\ \dot{\tilde{\beta}}_{12}(t) =& \begin{cases} \gamma_2 e(t)u(t), & \text{if } |\tilde{\beta}_{12}(t)| > \beta_1^{lb}\beta_2^{lb}, \\ & \text{or } |\tilde{\beta}_{12}(t)| = \beta_1^{lb}\beta_2^{lb} \\ & \text{and } e(t)u(t)\text{sgn}(\tilde{\beta}_{12}(t)) \geq 0, \\ 0, & \text{otherwise.} \end{cases} \end{aligned} \quad (21)$$

After modifying the adaptive control law, the time derivative of the Lyapunov function becomes:

$$\dot{V}(t) = \begin{cases} -a_m(e(t))^2, & \text{if } |\tilde{\beta}_{12}(t)| > \beta_1^{lb}\beta_2^{lb}, \\ & \text{or } |\tilde{\beta}_{12}(t)| = \beta_1^{lb}\beta_2^{lb} \\ & \text{and } e(t)u(t)\text{sgn}(\tilde{\beta}_{12}) \geq 0, \\ -a_m(e(t))^2 & \\ +\tilde{\beta}_{12}e(t)u(t), & \text{if } |\tilde{\beta}_{12}(t)| = \beta_1^{lb}\beta_2^{lb} \\ & \text{and } e(t)u(t)\text{sgn}(\tilde{\beta}_{12}(t)) < 0. \end{cases} \quad (22)$$

Therefore, $\dot{V}(t) \leq -a_m e^2(t) \leq 0$, $\forall t \geq t_0$.

Using a similar argument as before, it can be shown that by using this modified parameter estimation law (21), the tracking error converges to zero driven by a bounded control signal. Additionally, we have shown (cf. Thm. 1) that the reference output response is exponentially stable, and it follows that the system output can be driven to the stable state exponentially fast.

We next test the indirect MRAC law using the patient data. The parameter values of the reference model are the same as in Sec. 3.1. We choose the population-wide parameter values $\beta_3^* = 60$, and $\beta_1^*\beta_2^* = 3428.5$ as initial values of $\widehat{\beta}_3(t)$ and $\widehat{\beta}_{12}(t)$, respectively. The MRAC adapts based on these estimates in real-time. The trajectory of the system under the indirect MRAC is shown in Fig. 6.

Fig. 6 indicates that the system output quickly converges to the reference output and it remains within the desired range (top figure). The tracking error oscillates around zero (middle figure), but it is not as smooth as in Fig. 4. This is due to the fact that the indirect MRAC takes some time (which depends on the parameter setting and model

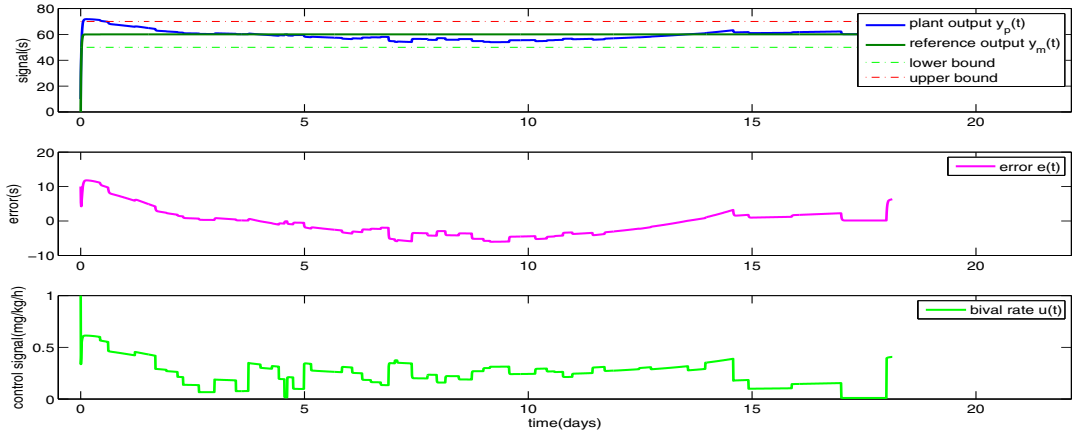

Fig. 6. The performance of the indirect MRAC law.

complexity) to estimate the system parameters first and then adapts the controller coefficients. Similarly, we can also obtain the bivalirudin infusion rate (bottom figure). Notice that although $d(t)$ changes over time, the control signal can drive the system to track the reference output signal well.

4. CONCLUSIONS

Based on a specific dynamic system model of bivalirudin acting in cardiac surgical patients, we developed two methods of synthesizing a controller to regulate the bivalirudin infusion rate and induce a PTT within a desirable range. The first method assumes that the model parameters are available and develops a control law that tracks a physician specified reference output signal. Our second method considers patients for which past clinical records are sparse and accurate model parameters are not readily available. It develops an indirect control scheme that first estimates the model parameters and then adapts the corresponding controller based on these estimates. In the latter case, choosing population-wide model parameters (hence, not too far from the parameters of the specific patient) as initial estimates can help avoid underdosing or overdosing. This is an important consideration in clinical practice.

The methods we developed can be seen as key steps towards automation of dosage decisions in a hospital setting, which can help eliminate errors and neutralize the inexperience of residents who are currently responsible for these decisions.

REFERENCES

Gerard F Anderson, Uwe E Reinhardt, Peter S Hussey, and Varduhi Petrosyan. Its the prices, stupid: why the united states is so different from other countries. *Health Affairs*, 22(3):89–105, 2003.

J.A. Bittl, B.R. Chaitman, F. Feit, W. Kimball, and E.J. Topol. Bivalirudin versus heparin during coronary angioplasty for unstable or postinfarction angina: final report reanalysis of the bivalirudin angioplasty study. *American heart journal*, 142(6):952–959, 2001.

T. Edrich, G. Frendl, and I. Ch. Paschalidis. Tachyphylaxis in post-cardiac surgical patients receiving bivalirudin – a retrospective dynamic study using a PKPD model. *Critical Care Medicine*, 39(12):198, December 2011.

Petros A Ioannou and Elias B Kosmatopoulos. *Adaptive Control*. Wiley Online Library, 2006.

Petros A Ioannou and Jing Sun. *Robust adaptive control*. DoverPublications. com, 2012.

Vasile Mihai Popov and Radu Georgescu. *Hyperstability of control systems*. Springer-Verlag New York, Inc., 1973.

G.W. Stone, B.T. McLaurin, D.A. Cox, M.E. Bertrand, A.M. Lincoff, J.W. Moses, H.D. White, S.J. Pocock, J.H. Ware, F. Feit, et al. Bivalirudin for patients with acute coronary syndromes. *New England Journal of Medicine*, 355(21):2203–2216, 2006.

Q. Zhao, T. Edrich, and I. Ch. Paschalidis. A predictive model for the anticoagulant bivalirudin administered to cardiac surgical patients. In *Proceedings of the 52nd IEEE Conference on Decision and Control*, pages 121–126, Florence, Italy, December 2013.

Q. Zhao, T. Edrich, and I. Ch. Paschalidis. Predicting and evaluating the effect of bivalirudin in cardiac surgical patients. *IEEE Transactions on Biomedical Engineering*, 2014. in print.

Appendix A. PROOF OF THEOREM 1

The solution to Eq. (7) is

$$y_m(t) = \Phi(t, t_0) y_m(t_0) + \int_{t_0}^{t} \Phi(t, \tau) b_m r(\tau) d\tau,$$

where $\Phi(t, \tau) = e^{-a_m(t-\tau)}$ is the state transition function in this problem. Since $r(t) = C_r$, which is a constant, the solution to (7) can be written as

$$y_m(t; t_0, y_m(t_0)) = e^{-a_m(t-t_0)} \left(y_m(t_0) - \frac{b_m C_r}{a_m} \right) + \frac{b_m C_r}{a_m}. \quad \text{(A.1)}$$

Equation (A.1) indicates that $y_m(t; t_0, y_m(t_0)) \to b_m C_r / a_m$ which is a constant, as $t \to \infty$. In addition, using Definition 1, it can be easily verified that $y_{me} = b_m C_r / a_m$ is the equilibrium state of our reference system. Furthermore, $|y_m(t; t_0, y_m(t_0)) - y_{me}| = |e^{-a_m(t-t_0)}(y_m(t_0) - y_{me})| = |y_m(t_0) - y_{me}| e^{-a_m(t-t_0)}$, $\forall t \geq t_0$. Therefore, by Definition 2, it follows that the reference model equilibrium state y_{me} is exponentially stable. □