Adaptive Control of Bivalirudin in the Cardiac Intensive Care Unit

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***Abstract*—Bivalirudin is a direct thrombin inhibitor used in the cardiac intensive care unit when heparin is contraindicated due to heparin-induced thrombocytopenia. Since it is not a commonly used drug, clinical experience with its dosing is sparse. In earlier work [1], we developed a dynamic system model that accurately predicts the effect of bivalirudin 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. Alternatively, direct Model Reference Adaptive Control is applied to adapt the controller directly without estimating model parameters first. Our algorithms are validated using actual patient data from a large hospital in the Boston area.**

***Index Terms*—Adaptive control, bivalirudin, parameter identification, pharmacokinetics.**

I. Introduction

THE US health care system is viewed as costly and highly inefficient. Among the many reform efforts, the meaningful use of Electronic Health Records is invariably 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 currently FDA-approved for short-term anticoagulation of patients undergoing cardiac catheterization to prevent complications due to undesired blood clots [2]–[5]. 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* in a dose-dependent fashion. The PTT value is measured in seconds, and it will be used as the output one wishes to regulate within a specific range.

Although not commonly used overall, bivalirudin is finding increasing use in the ICU. Residents adjusting the infusion rate of bivalirudin may have limited experience, thus, risking over- or underdosing. Currently, the drug is regulated empirically or with a very simple nomogram [6]. 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 intraindividual variability in the response to bivalirudin. Motivated by these challenges, in earlier work [1], [7], [8], we developed methods for predicting future PTT values given past infusion rates and the patient's renal and liver function characteristics. Related work has used pharmacokinetic-pharmacodynamic models to model the effect of various drugs, see, e.g., [9] and [10]. One of our methods in [1] 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 [1] and [8], we seek to synthesize controllers that can regulate the infusion rate to drive PTT within a desirable range. Other methodologies such as expert systems have also been used for controlling some drugs [11]. We develop two types of control laws. First, assuming that a dynamic system model that can predict PTT given dosage is completely characterized, we 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 inter- or intraindividual variability. To overcome this problem, we develop an indirect *Model Reference Adaptive Control (MRAC)* law that identifies the model parameters first and then adapts the controller in real time. Furthermore, we develop a direct MRAC law that adapts the controller directly without estimating model parameters first, which is more efficient. For each case, we present analytical and numerical evidence showing that the controllers do drive PTT to the desirable range. Our numerical validation is in fact done using actual patient data from the Brigham and Women's Hospital—a large hospital in the Boston area.

The remainder of this paper is organized as follows. Section II presents the dynamic system model that predicts the effect of

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