REVIEW ARTICLE

Drug Infusions by Model Predictive Control using Computational Therapeutic Models

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Abstract

Intravenous infusion of drugs is preferred choice of drug delivery to critical care patients. However, the conditions of the patients treated require meticulous manual monitoring and control of the drugs infused which is imprecise and guesses prone. Development of adaptive control drug delivery systems to control infusion based on real-time variables will be advantageous in overcoming the stated difficulties, affording the caregiver to dynamically modify the amount of drug infused based on the real-time inputs. Predictive control modeling is a platform for implementing infusion control of hard to infuse drugs with better therapeutic efficiency.

Key words: Adaptive controls, computational therapeutics, critical care, drug infusion, predictive control model

INTRODUCTION

Critical care patients (CCPs) constitute a special category of the population who are critically or terminally ill; or recuperating from a surgery or trauma.[1] The CCPs normal pharmacological functions are altered or compromised due to the disease condition or by the progression of disease.[2] Due to this, CCPs are susceptible to higher risks of adverse drug events. The main contributing factors for this are the highly potent drugs and high-risk medications administered to them, either alone or in combination.[3] The CCPs are cared for in an intensive care unit (ICU) setup, and it is very important that most of their attention given by the caregivers to CCPs involves assessment of their condition and for close monitoring of vital signs and device feedbacks.[4]

The caregiving process in the ICU situations entails monitoring conditions that are monotonous, repetitive, and time intensive. The CCPs are in constant check for vital signs to ensure that they are stable and respond favorably to the medication administered. This process causes lots of fatigue to the caregivers and increases chances for errors or missing critical events.[5] These situations are commonplace in ICU setups. This in situation in recent times is being avoided by the use of automated drug infusion systems based on therapeutic models could be ideal. These can improve the drug delivery and can ease the burden of continual monitoring of infusion, volume adjustments, data logging, and documentation.[6]

PHARMACOLOGICAL ASPECTS

The route of choice for administering these medications to CCP in ICU setups is by intravenous (IV) route because of the advantages it offers. However, the IV route is with risks since many high-risk medications given in the critical or intensive care setups are for interventional effects. The major categories of drugs used in critical care setups are antihypertensives, vasodilators, anticoagulants, opioid analgesics, sedatives, anesthetics, electrolytes, and plasma

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volume expanders.[7] These drugs are potent, and many of the drugs in these categories have narrow therapeutic indices. Due to the high levels of pharmacological inadequacies and compromises, the CPP have challenges in doses and the situation further aggravates because of IV route.[5]

Further, there are several dosing considerations unique to CCP such as basal metabolic rate, renal, and hepatic insufficiencies, and hence, a more calibrated and prudent approach needs to be taken to avoid adverse drug events, and in most cases validated dosing data are not available or extrapolating the data from a non-critical patient population will result in therapeutic insufficiencies further compounding the problem.[8] The infusion volume is administered on a trial and error basis and has to be fine-tuned manually by frequently changing the Setpoint. Hence, there is making it a difficult proposition for administering drugs to CCP through the IV route.[9]

AUTOMATED DRUG DELIVERY SYSTEMS

However, with the advent of infusion pumps (IPs) with integrated control systems, a large part of the problem is solved.[10] The IP is a medical device that is approved by the regulatory authorities for infusing parenteral medications through IV route in a controlled manner. Depending on its design, the IP is capable of delivering drugs in large or small amounts. Due to this feature IPs can effectively deliver very small quantities of parenteral medications in a consistent manner and can also deliver them in boluses crucial for getting the desired pharmacokinetic response. This technology is leveraged to get desired pharmacokinetic and pharmacodynamic responses of the drug infused. Pharmacokinetic inputs map the infused drug's disposition will equilibrate to pharmacodynamic response.[7] The CCP with a lot of inherent complications benefit from this leveraged control of drug infusion resting in predictable pharmacokinetics and thereby the pharmacodynamic responses as well. This predictable pharmacokinetics is possible because of the sophisticated control systems that modify the drug infusion rate.[11]

Advantages of The ADME compromised state of the CCP can be put in perspective to control the infusion to get an optimal or in many instances enhanced therapeutic outcomes. In practical settings where CCP are treated infusion of potent drugs with often narrow therapeutic indices are used to evoke pharmacological responses to meet out emergencies.[12] Hence, a programmable control system for infusion is advantageous in such situations. There are many ways of controlling the drug infusion rate, and there are several manners of control systems which are possible to modify the rate and extent of drug infusion. The review of literature reveals that infusion control systems are powered by various methods.[13]

USE OF PREDICTIVE CONTROL MODELS IN DRUG INFUSION

The review of literature reveals that there are several highly potent drugs that might be safely infused as well as get an optimal therapeutic outcome in terms of safety and efficacy to the volume infused.[14] To achieve optimum therapeutic gains, a bolus dose is administered to meet the volume of distribution requirement, followed by a constant infusion, to achieve plasma concentration.[15] The situation becomes more complex in the three-compartment model the bolus dose is first administered to the central compartment, and the infusion rates are adjusted to attain a steady state in the process of achieving a constant drug concentration in the central compartment. Therefore, this situation calls for a method of varying infusion rates attune with central compartment concentration and excretion; this also affects the duration of infusion.[16]

Manual control of mean arterial blood pressure (MABP) is tiring and if timely adjustment of infusion is not carried out, may lead to undesirable or dangerous oscillations in the MABP level, affecting organ perfusion and homeostasis. Rao *et al*. have to investigated the automatic control of the MABP through the use of automated drug infusion systems. The earlier work done in this domain was on the single input single output method (study of the relationship between single drug to a change in single parameter) of regulating the MABP; however, recent works in this domain have taken control of several hemodynamic variables modified by the infusion of multiple drugs.[17]

Koivo *et al.* initiated the research in automatic control of the blood pressure in rabbits and pigs, but did not factor in the time delay in the patient response, hence resulting in oscillatory response conditions. Sheppard *et al*. designed a method to infuse vasoactive drugs by computer control to regulate the MABP of the patients in the ICU. A proportional integral and derivative (PID) controller were incorporated in the system, and a model was developed to represent the hemodynamic variables - blood pressure cardiac output (CO) in response to the infused drug.[18]

Slate and Sheppard[19] proposed an adaptive control algorithm for MABP regulation. Ying and Sheppard[20] experimented with a real-time fuzzy control of MABP in pigs by regulating the rate of infusion of the vasodilator drug sodium nitroprusside. Not all these methods were able to address the variations in the sensitivity of different types of patients to the drugs. Need for adaptive controllers propelled many researchers to work on the model-based adaptive controllers. Many researchers have used the drug controller design developed by Slate and Sheppard to model the patient's response to the infused drug.

The cardiovascular dynamics model and the automated regulation of MABP was propounded by Guyton *et al.*[21] and Ying *et al.*[22] reported the use of fuzzy control of

MABP of patients in a clinical setting. Valcke and Chizek[23] have explored closed-loop drug delivery system for use in coronary artery disease. Gao and Er[24] have adopted the use of a generalized fuzzy neural network method to adaptive modeling and control of drug delivery systems.

Experimental studies were carried on canines by Rao *et al.*[25] using a multiple model approach based on Guyton's model in the model predictive control framework. The literature review suggests that clinical experiments have shown adaptive model of drug delivery to be effective and superior in comparison with manual methods. Since experiments involving animals and humans involve ethical issues and are expensive and time-consuming, simulations are often preferred.[26]

A simulator to relate the infusion of vasoactive drugs and physiological parameters was developed by Woodruff *et al.*[27] and Yu *et al.*[28] developed a multiple model adaptive controller used to monitor the CO in congestive heart failure and safely administer vasodilatation and inotropic agents (sodium nitroprusside and dopamine). This controller uses six different patient models to calculate the control algorithms and deliver simplistic computations. Behbehani and Cross[13] described the application of a self-tuning control strategy that seeks to minimize the deviation of the MABP from the desired value and also optimizes the amount of medication administered.

Hahn *et al.*[29] have reported the implementation of the drug infusion system using adaptive internal model control (IMC). However, the limitations of the IMC are that there is no provision for systematic inclusion of constraints and no inner optimization block. Manju *et al.*[30] reported the control of the drug rate delivered to the patients using PID control. Again, there is no means to include constraints.

The development of a reliable controller is difficult due to the complex, multi-variable, nonlinear behavior of physiological systems, Smith and Demetriou,[31] Bronzino[32] Experiments and research on control of blood pressure during surgery has also been done, Furutani *et al.*[33] Luginbuhl *et al.*[34] and Frei *et al.*,[35] have proposed a model predictive controller (MPC) taking into account the effects of surgical events and then used it for blood pressure regulation during anesthesia. Uemura and Sugimachi[36] have carried out a detailed review of the closed-loop control of hemodynamics. Nirmala *et al.* has modelled the effects of employing a closed loop infusion system in CCP recuperating from surgical procedure and have classified them based on their responses to the infused drug.[37] and in a subsequent work has also carried out the development of an MPC based closed loop drug delivery system for infusing potent vasoactive drugs.[38]

CONCLUSION

CCPs in ICU setups are continually monitored for hemodynamic variables such as MABP, heart rate, Central Venous Pressure, and CO. Various drugs such as vasodilators and inotropes are infused to regulate the hemodynamic variables. The primary objective of this review is regulating the MABP as this is the most important variable which decides the perfusion pressure of various organs. Another variable CO, which decides the volume of blood pumped from the heart, is also considered. Drugs quoted in literature to treat these parameters are sodium nitroprusside and dopamine, apart from these norepinephrine and nitroglycerine are also drugs of choice.

The current practice of manual manipulation of the IV drugs infused through IV lines is disadvantageous as the regular intervention of the caregiver is required for these adjustments. There is a need to make these drug delivery systems closed loop to relieve the attending caregiver to check for other patient parameters, which cannot be readily measured. In addition, when such a system is put to work, the caregiver can handle more number of patients. MPC methods constitute a platform for adaptive control of drugs where the measured parameters can be used as inputs for the controls of the drug delivery system.

Model-based adaptive control techniques are useful in improving the system performance and minimizing the human interference in the process of drug delivery. An MPC is designed for the closed-loop control of the drug infusion system; it can be programmed to act on the drug delivery system to provide the correct dosage at the correct time and thereby enhancing the therapeutic outcomes in CCP.

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