Control Engineering Practice 73 (2018) 149–160

Contents lists available at ScienceDirect

Control Engineering Practice

journal homepage: www.elsevier.com/locate/conengprac

Control-oriented physiological modeling of hemodynamic responses to blood volume perturbation

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ARTICLE INFO

Keywords:
Mathematical model
Hemodynamic response
Fluid infusion
Hemorrhage
Fluid resuscitation
Blood volume
Physiological closed-loop control

ABSTRACT

This paper presents a physiological model to reproduce hemodynamic responses to blood volume perturbation. The model consists of three sub-models: a control-theoretic model relating blood volume response to blood volume perturbation; a simple physics-based model relating blood volume to stroke volume and cardiac output; and a phenomenological model relating cardiac output to blood pressure. A unique characteristic of this model is its balance for simplicity and physiological transparency. Initial validity of the model was examined using experimental data collected from 11 animals. The model may serve as a viable basis for the design and evaluation of closed-loop fluid resuscitation controllers.

1. Introduction

Fluid infusion is an essential component of circulatory resuscitation for hypovolemia caused by infection (e.g., sepsis), perioperative and traumatic hemorrhage, neuro-critical care, burns and so forth (Bouglé, Harrois, & Duranteau, 2013; Chatrath, Khetarpal, & Ahuja, 2015; Goodman & Kumar, 2014; Haberal, Sakallioglu Abali, & Karakayali, 2010; Rochwerg et al., 2014). Fluid resuscitation requires titration and re-titration of fluid infusion dose to the varying physiological state of a patient. In today's clinical practice, caregivers are responsible for the continuous titration tasks. As a practical matter, this tedious but life-critical requirement presents a few challenges. First, the choice of target endpoints is heterogeneous and depends on the underlying pathophysiology of the patient and the preference of caregivers (e.g., blood pressure (BP) was shown effective for fluid infusion after uncomplicated hemorrhage in animals (Vaid et al., 2006) while urinary output (UO) was shown effective for burns (Salinas et al., 2008)). Second, caregivers may not effectively perform titration due to, e.g., heavy workload, distractions, and clinical inertia (Oliveira, Garcia, & Nogueira, 2016). Third, caregivers may not make optimal titration due to enormous variability in fluid responses across different patients.

The above limitations naturally suggest the desire for autonomy in fluid resuscitation. In fact, published reports document that autonomous closed-loop control systems for fluid resuscitation may alleviate the caregiver workload while still maintaining the quality of care by reducing the laps and errors associated with therapy adjustments (Michard, 2013; Rinehart, Liu, Alexander, & Cannesson, 2012; Rinehart, 2014; Bighamian, Kim, Reisner, & Hahn, 2016). However, existing work on closed-loop fluid resuscitation is not abundant, if not rare, both in terms of design and evaluation. Most closed-loop fluid resuscitation controllers reported to date are built upon empiric decision rules and gain tuning (Hoskins et al., 2006; Rinehart, Lee, Cannesson, & Dumont, 2013; Salinas et al., 2008; Ying & Sheppard, 1990). This state-of-the-art leaves much room for improving the efficacy and robustness of closed-loop fluid resuscitation controllers via model-based design approaches established in the field of control theory (Ioannou & Sun, 2012; Khalil, 2001; Nise, 2011; Skogestad & Postlethwaite, 2005; Slotine & Li, 1991). In addition, most evaluation studies have resorted to costly and time-consuming animal experiments (Rafie et al., 2004; Chaisson et al., 2003; Elgjo, Traber, Hawkins, & Kramer, 2000). Discussions at the recent Public Workshop on Physiological Closed-Loop Controlled Medical Devices organized by the Food and Drug Administration (FDA) found that computational models may offer time- and cost-efficient means for non-clinical testing (FDA Public Workshop, 2015). Hence, a credible mathematical model that can reproduce hemodynamic responses to

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https://doi.org/10.1016/j.conengprac.2018.01.008
Received 31 July 2017; Received in revised form 3 December 2017; Accepted 11 January 2018
Available online 31 January 2018
0967-0661/

blood volume perturbation may open up new opportunities for the design and evaluation of closed-loop fluid resuscitation controllers.

A mathematical model must be equipped with a pair of conflicting attributes to be useful for both design and evaluation of closed-loop control systems. First, it must be simple enough to streamline the design of closed-loop controllers. Second, it must be accurate and transparent, or interpretable, enough to produce legitimate evaluation outcomes. However, existing mathematical models that aim to reproduce hemodynamic responses to blood volume perturbation do not appear to fulfill an adequate balance between these two requirements: one class of black-box models are too empiric to offer viable physiological implications (Lewis, 1986; Mardel et al., 1995; Simpson et al., 1996; Wears & Winton, 1990), whereas the other class of first-principles models are too complex, involving as many as a few thousand parameters (Abram, Hodnett, Summers, Coleman, & Hester, 2007; Kofránek & Rusz, 2010; Pirkle & Gann, 1976; Hedlund, Zaar, Groth, & Arturson, 1988; Arturson, Groth, Hedlund, & Zaar, 1989; Carlson, Kligman, & Gann, 1996), making it inappropriate for the purpose of controller design. Therefore, a pre-requisite for the development of next-generation closed-loop fluid resuscitation controllers is a simple yet accurate and mechanistically transparent mathematical model suited to the design and evaluation of closed-loop fluid resuscitation controllers. Such a model must be able to reproduce a comprehensive list of hemodynamic responses to blood volume perturbation used as clinical endpoints of fluid resuscitation in today's clinical practice, including blood volume (BV), stroke volume (SV) and cardiac output (CO), BP, and central venous pressure (CVP) (Roche, Miller, & Gan, 2009; Rinehart, Lee, Canales, et al., 2013; Blankenship, Wallace, & Pacifico, 1990; Cannesson, de Backer, & Hofer, 2011; Bighamian, Kim, et al., 2016).

This paper presents a lumped-parameter model to reproduce hemodynamic responses to blood volume perturbation applicable to the design and evaluation of closed-loop fluid resuscitation controllers. A unique characteristic of this model is its balance for simplicity (via abstraction of complex microscopic physiological mechanisms into systems-level feedback control actions) and physiological transparency (via rigorous use of established physiological knowledge). The preliminary validity of the model was examined using experimental data collected from 11 animals. First, a fully individualized model (a model obtained for each animal by estimating all the parameters from the data) was studied. Then, a parametric sensitivity analysis was performed to obtain a well-conditioned model by identifying low-sensitivity model parameters and fixing them at nominal values. Finally, a partially individualized model (a model obtained by estimating only the parameters to be individualized from the data) was studied.

2. Materials and methods

2.1. Lumped-parameter model of hemodynamic responses to blood volume perturbation

The model consists of three sub-models: (a) a control-theoretic model to relate blood volume perturbation (specifically, hemorrhage and fluid infusion) to blood volume; (b) a simple physics-based model to relate blood volume to stroke volume and cardiac output; and (c) a phenomenological model to relate cardiac output to blood pressure (Fig. 1). Compared to existing models available in the literature, a unique characteristic of this model is its balance for simplicity (via abstraction of complex microscopic physiological mechanisms into systems-level feedback control actions) and physiological transparency (via rigorous use of established physiological knowledge). Details follow.

2.1.1. Modeling of blood volume response to blood volume perturbation

Fluid in the body is distributed in 3 major compartments: intravascular (blood), extravascular (interstitial fluid), and intracellular (Guyton, Taylor, & Granger, 1975). In the context of critical care, the gain or loss of fluid occurs primarily in the intravascular compartment in the form of hemorrhage, UO, fluid infusion etc., but the perturbation in the intravascular fluid volume thus occurred is dynamically distributed across all 3 major compartments via the inter-compartmental fluid shift (Guyton et al., 1975). In our prior work, a control-theoretic model of BV response to fluid infusion was developed (Bighamian, Reisner, & Hahn, 2016). The basic idea was to formalize established physiological principles underlying fluid volume distribution (that fluid infused into the intravascular compartment is distributed in the intravascular and extravascular compartments to regulate the ratio between their volumetric changes (Guyton et al., 1975)) into a mathematical model by abstracting myriads of complex microscopic fluid shift mechanisms into macroscopic feedback control actions.

Given that the ratio between the intravascular and extravascular volumetric changes is different for fluid loss (hemorrhage) and gain (fluid infusion) due to the compositional differences in the fluids involved in each process (blood lost consists of plasma and red blood cells (RBCs) while infused fluid may consist of electrolyte (crystalloid such as Lactated Ringer's solution (LR)) and starch (colloid such as Hextend (Hex))), our original model developed primarily for fluid infusion scenarios is not readily applicable to the scenarios in which a patient undergoes both hemorrhage and fluid infusion. In the current work, our original model was extended as follows to address this limitation. Denoting the ratio between the intravascular and extravascular volumetric changes in the steady state in response to fluid gain (fluid infusion) and loss (hemorrhage and urine) as α_u and α_v, respectively, the desired steady-state change in BV, $r_B(t)$, can be written as follows:

$$r_B(t) = \frac{1}{1+\alpha_u}\int_0^t u(\tau)\,d\tau - \frac{1}{1+\alpha_v}\int_0^t v(\tau)\,d\tau \tag{1}$$

where $u(t)$ and $v(t) = v_H(t) + v_U(t)$ denote the rates of fluid gain (infusion) and loss (hemorrhage $v_H(t)$ and UO $v_U(t)$) at time t. At each time t, the inter-compartmental fluid shift is dictated by the discrepancy between the desired ($r_B(t)$) versus actual ($\Delta V_B(t)$) changes in BV as follows:

$$q(t) = q\left(e_B(t)\right) = q\left(r_B(t) - \Delta V_B(t)\right) \tag{2}$$

Then, applying the conservation of volume to the intravascular compartment in Fig. 1(a) dictates that the rate of change in ΔV_B at time t is given by the resultant sum of the fluid gain $u(t)$, fluid loss $v(t)$, and the inter-compartmental fluid shift $q(t)$ (see the inflows and outflows associated with the "Blood" bucket):

$$\Delta\dot{V}_B(t) = u(t) - v(t) - q(t) \tag{3}$$

If the inter-compartmental fluid shift is abstracted into the action of a simple proportional–integral (PI) controller that strives to drive $e_B(t)$ to zero in the steady state (Nise, 2011):

$$q(t) = -K_p e_B(t) - K_i\int_0^t e_B(\tau)\,d\tau \tag{4}$$

where K_p and K_i are proportional and integral gains, the dynamics dictating the rate of change in BV can be written as follows by combining (1)–(4):

$$\Delta\ddot{V}_B(t) + K_p\Delta\dot{V}_B(t) + K_i\Delta\dot{V}_B(t) = [\ddot{u}(t) - \ddot{v}(t)] + \frac{K_p}{1+\alpha_u}\dot{u}(t) - \frac{K_p}{1+\alpha_v}\dot{v}(t) + \frac{K_i}{1+\alpha_u}u(t) - \frac{K_i}{1+\alpha_v}v(t) \tag{5}$$

This model is visualized in Fig. 1(a) as a two-bucket system connected by a bi-directional flow valve, where the buckets represent the intravascular and extravascular compartments, respectively, while the valve represents the resultant action of all the inter-compartmental fluid shift mechanisms.