A Physiological Mathematical Model of Heart Rate Response to Fluid Perturbation

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Background: Physiological closed-loop controlled (PCLC) medical devices are a rapidly advancing type of technology that can control the state of patients by using physiological feedback in a closed-loop manner. Unlike the standard of care, PCLC devices do not require constant human adjustment of parameters, and thus, assessing the performance of this type of devices is essential.

Assessment of PCLC medical devices through comprehensive clinical trials is often costly. In conjunction with smaller clinical trials, mathematical models can be leveraged to evaluate a device's performance under different physiological conditions [1]. These models give control over different parameters and enable the simulation of a virtual cohort of patients under a wide range of physiological states for testing medical devices [2], [3].

This abstract for the first time presents a physiological mathematical model of heart rate (HR) response to hemorrhagic shock and fluid infusion. The model can be ultimately used to create a virtual patient cohort, which in turn can be used to study the perfromance of PCLC devices for fluid resuscitation. Hemorrhage and fluid infusion were induced in 21 conscious sheep, the data from which was used to develop the model [4]. The model adequately maps the rate of hemorrhage and fluid infusion to the change in HR.

Method: To create the mathematical model of HR response to blood loss and fluid infusion, two types of responses need to be studied. The first is the transient response which describes the instantaneous change in HR due to fluid perturbation. The second is the long-term response, which is the change in the steady-state value of HR response due to the perturbation. Figure 1-A presents an overview of the overall effect of the transient and long-term HR response.

Hemorrhages cause tachycardia due to an increase in sympathetic nerve activity. A severe hemorrhage causes a transient increase in HR. Moreover, due to the loss in blood volume and arterial pressure, there is a long-term increase in HR within a few hours after the hemorrhage till it reaches a plateau [5]. Fluid infusion also transiently alleviates HR response, as reported in prior studies [6], [7]. To capture the long-term HR response due to the blood loss, a proportional-integral controller is implemented into the model, which enforces the change in HR to follow the expected long-term effect of blood loss. Figure 1-B to 1-E illustrate the individual components of the model, which includes 7 parameters.

Result: Maximum likelihood optimization was used to tune the parameters in all the subjects. To analyze the performance of the model, Normalized Root Mean Square Error (NRMSE) was extracted between the estimated and true HR values. Averaged between all 21 subjects, results from the model gave an NRMSE of 7.4+/-2.8%. This result indicates that the model can accurately predict the change in HR due to fluid perturbation. Results from 2 representative subjects are shown in Figure 1-F.

Conclusion: In this paper, a model to predict the change in HR due to hemorrhage and fluid infusion was presented. This system applies a control-oriented approach where the rate of hemorrhage greatly influences the change in HR. This model can be incorporated into existing hemodynamic models to create a virtual cohort of patients that can be used to test PCLC devices for hemorrhagic applications.

References:

[1] O. Faris and J. Shuren, “An FDA viewpoint on unique considerations for medical device clinical trials,” *N. Engl. J. Med.*, vol. 376, no. 14, pp. 1350–1357, 2017.

[2] D. Brown *et al.*, “Trauma in silico: Individual-specific mathematical models and virtual clinical populations,” *Sci. Transl. Med.*, vol. 7, no. 285, pp. 285ra61--285ra61, 2015.

[3] O. Orozco-López, A. Rodriguez-Herrero, C. E. Castañeda, G. Garcia-Sáez, and M. E. Hernando, “Method to generate a large cohort in-silico for type 1 diabetes,” *Comput. Methods Programs Biomed.*, vol. 193, p. 105523, 2020.

[4] A. D. Rafie *et al.*, “Hypotensive resuscitation of multiple hemorrhages using crystalloid and colloids,” *Shock*, vol. 22, no. 3, pp. 262–269, 2004.

[5] S. Chien, “Role of the sympathetic nervous system in hemorrhage.,” *Physiol. Rev.*, vol. 47, no. 2, pp. 214–288, 1967.

[6] E. Salomao Jr *et al.*, “Heart rate variability analysis in an experimental model of hemorrhagic shock and resuscitation in pigs,” *PLoS One*, vol. 10, no. 8, p. e0134387, 2015.

[7] Z. Friedman, H. Berkenstadt, S. Preisman, and A. Perel, “A comparison of lactated Ringer’s solution to hydroxyethyl starch 6% in a model of severe hemorrhagic shock and continuous bleeding in dogs,” *Anesth. Analg.*, vol. 96, no. 1, pp. 39–45, 2003.

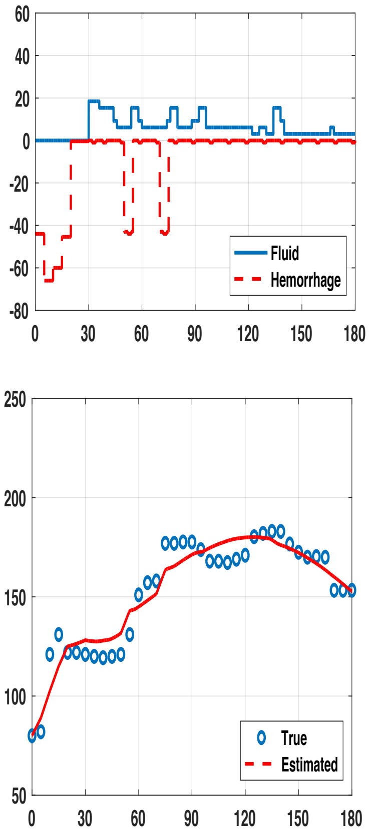

Figure 1: The heart rate model structure with estimation results from two representative subjects