

# Validation of a Mathematical Model of Heart Rate Response to Fluid Perturbation



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## Abstract

Background: Physiological closed-loop controlled (PCLC) medical devices are a rapidly advancing type of technology that can control a measured physiological variable in a closed-loop manner.

Assessment of PCLC medical devices through comprehensive clinical trials is often costly. Thus, in conjunction with smaller clinical trials, mathematical models can be leveraged to evaluate a device's performance under different physiological conditions.

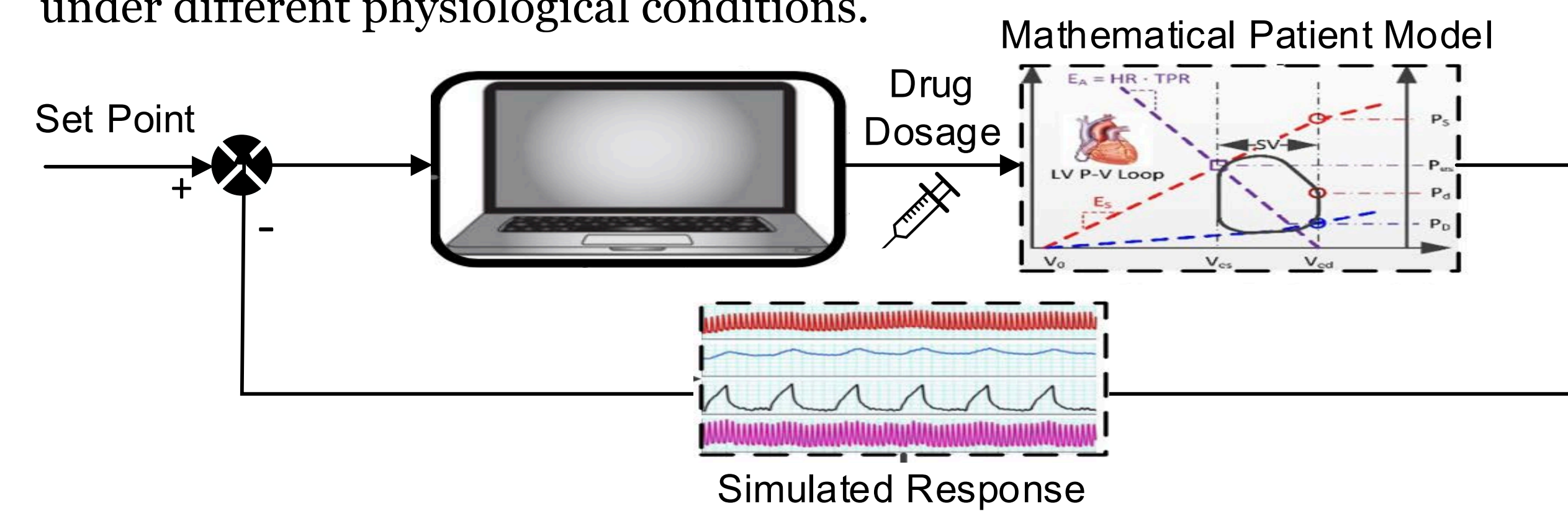


Figure 1. *In silico* assessment of a PCLC medical device [1]

## Introduction

A physiological variable that needs to be monitored during fluid resuscitation is heart rate (HR).

Gap: Existing HR models are mostly high-order mathematical models that are generally:

- created using data collected in a highly controlled environment
- not validated for their predictive capability performance
- limited to a few minutes of forecasting
- highly complex for generating virtual patients

Goal: To develop and validate a low-order mathematical model of HR to be incorporated into future non-clinical simulated testing setups for evaluating fluid resuscitation PCLC devices.

## Experimental Data

**Experimental data:** 16 hemorrhagic sheep received Lactated Ringer (LR) fluid infusion. Amongst the 16, 5 sheep were also given Colloid in a separate study. A group of 6 independent sheep that underwent a different protocol for fluid resuscitation was used for validation.

The data collection protocol was approved by the Institutional Animal Care and Use Committee (IACUC) at the University of Texas Medical Branch [2].

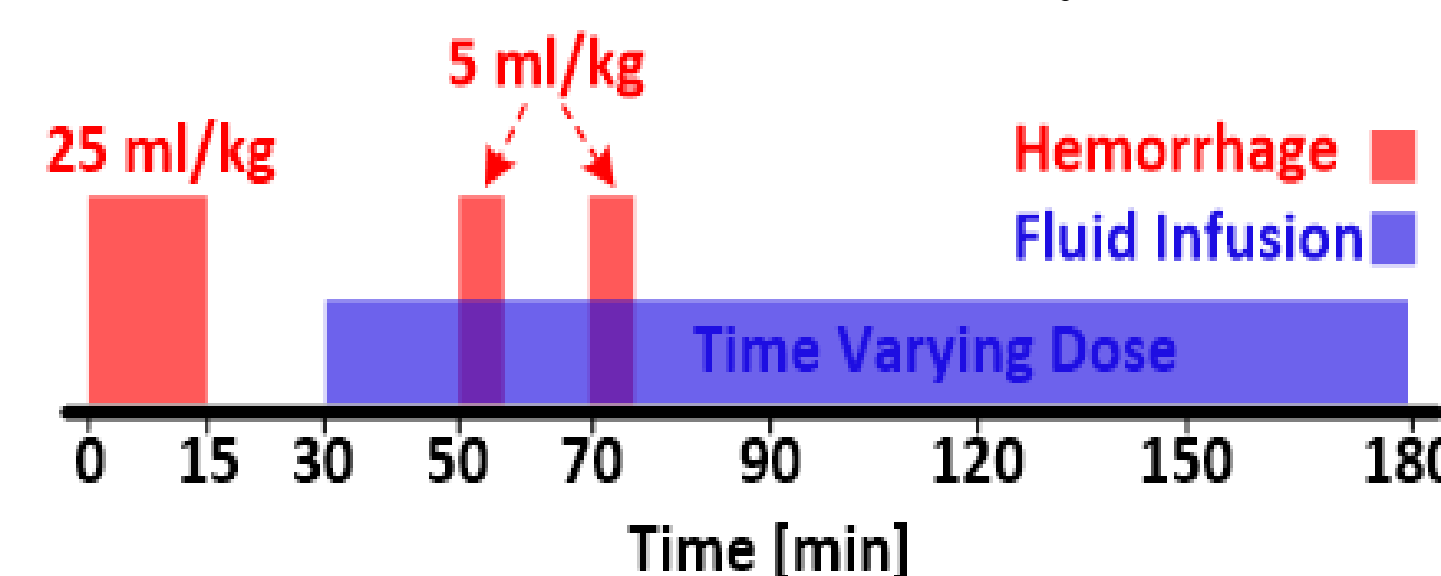


Figure 2. Experimental protocol for data collection from sheep subject under fluid perturbation

## Materials and Methods

**Model development:** A mathematical model of HR is developed and implemented in MATLAB. To capture the long-term HR response due to blood loss, a proportional-integral controller is implemented into the model, which enforces the change in HR to follow the expected long-term blood-loss effect.

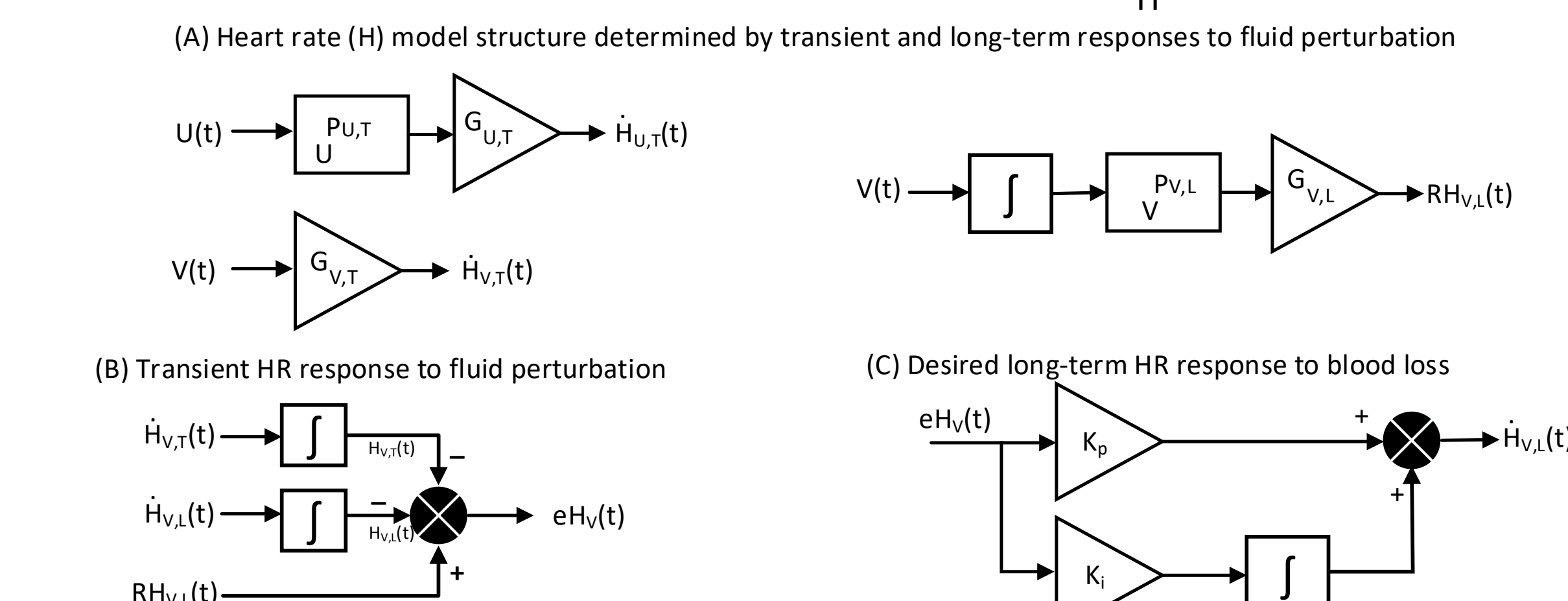
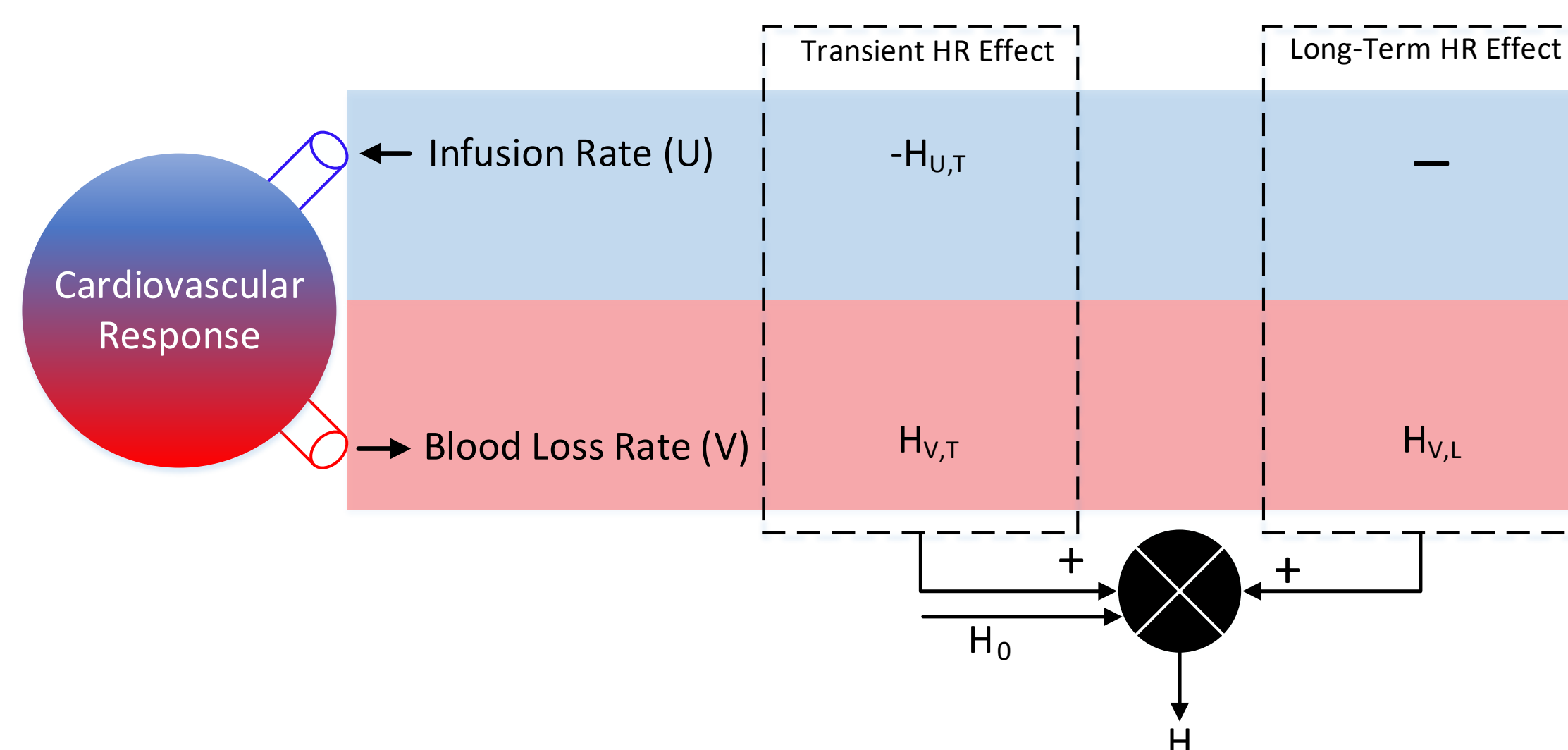


Figure 3. Control-oriented mathematical model of HR

**Model parameter estimation:** Maximum likelihood method was used to identify the parameter set  $\theta$  and variance of error  $\sigma^2$ .

$$H_{obs}(t_k) = H(t_k|\theta) + \varepsilon(t_k)$$

$$L^*(\theta, \sigma) = -\frac{K}{2} \ln(2\pi) - \frac{K}{2} \ln(\sigma^2) - \frac{1}{2\sigma^2} (H_{obs}(t_k) - H(t_k|\theta))^T (H_{obs}(t_k) - H(t_k|\theta))$$

$$\mu = \{\theta^*, \sigma^*\} = \text{argmin}_{\mu} (-L^*(\theta, \sigma) + 2\gamma \|\theta\|_2) \quad \theta = \{G_{V,T}, G_{U,T}, G_{V,L}, P_{V,L}, P_{U,T}, K_p, K_i, H_0\}$$

**Virtual cohort generator tool:** A novel compartment method that mixes three compartments of the model from three different subjects as well as a uniform distribution method are used to generate virtual patients.

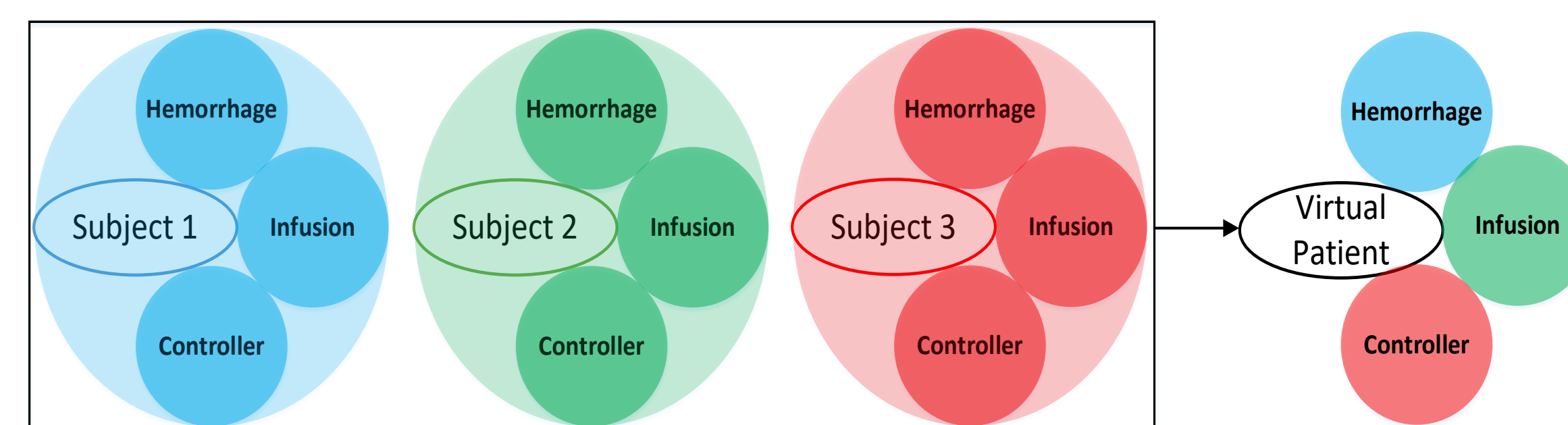


Figure 4. 3-subject compartment method for virtual cohort generation

**Model performance assessment:**

- Calibration
- Predictive capability
  - Leave-one-out
  - Independent data validation

$$NIS(t_k) = \begin{cases} \frac{H_u(t_k) - H_l(t_k) + \frac{2}{\alpha}(H_l(t_k) - H_{obs}(t_k))}{H_{obs}(t_k)} & H_{obs}(t_k) < H_l(t_k) \\ \frac{H_u(t_k) - H_l(t_k) + \frac{2}{\alpha}(H_{obs}(t_k) - H_u(t_k))}{H_{obs}(t_k)} & H_u(t_k) < H_{obs}(t_k) \\ \frac{H_u(t_k) - H_l(t_k)}{H_{obs}(t_k)} & \text{Otherwise} \end{cases}$$

NIS: Normalized interval score

## Results and Discussion

**Model calibration:** Across all 21 calibration datasets, the average normalized root mean square error (NRMSE) was found to be  $7.4 \pm 2.8\%$ , indicating that the model was able to estimate the observed HR response to fluid perturbation with a small error.

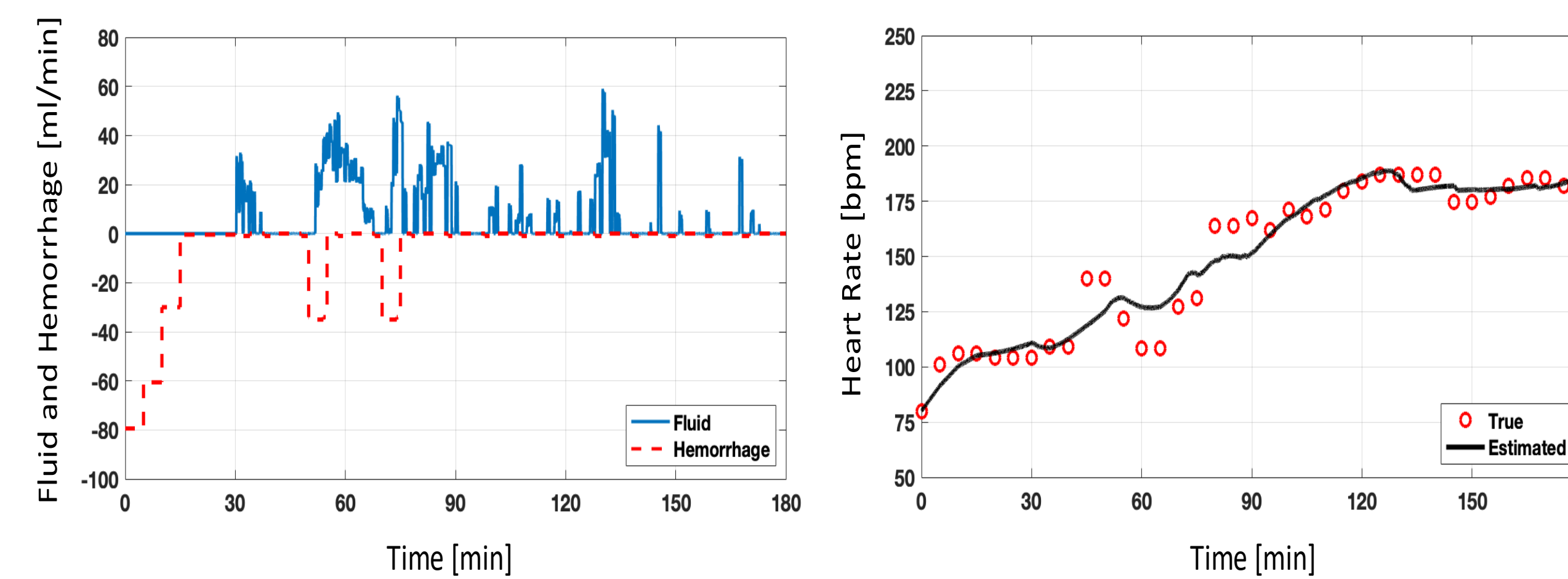


Figure 5. A representative calibration performance

**Model validation:**

Table 1. Average minimum NRMSE for model validation

	Uniform distribution method	Compartment Method
Leave-One-Out	$12.91 \pm 5.34$	$9.56 \pm 3.15$
Independent Set	$13.65 \pm 5.32$	$11.1 \pm 1.22$

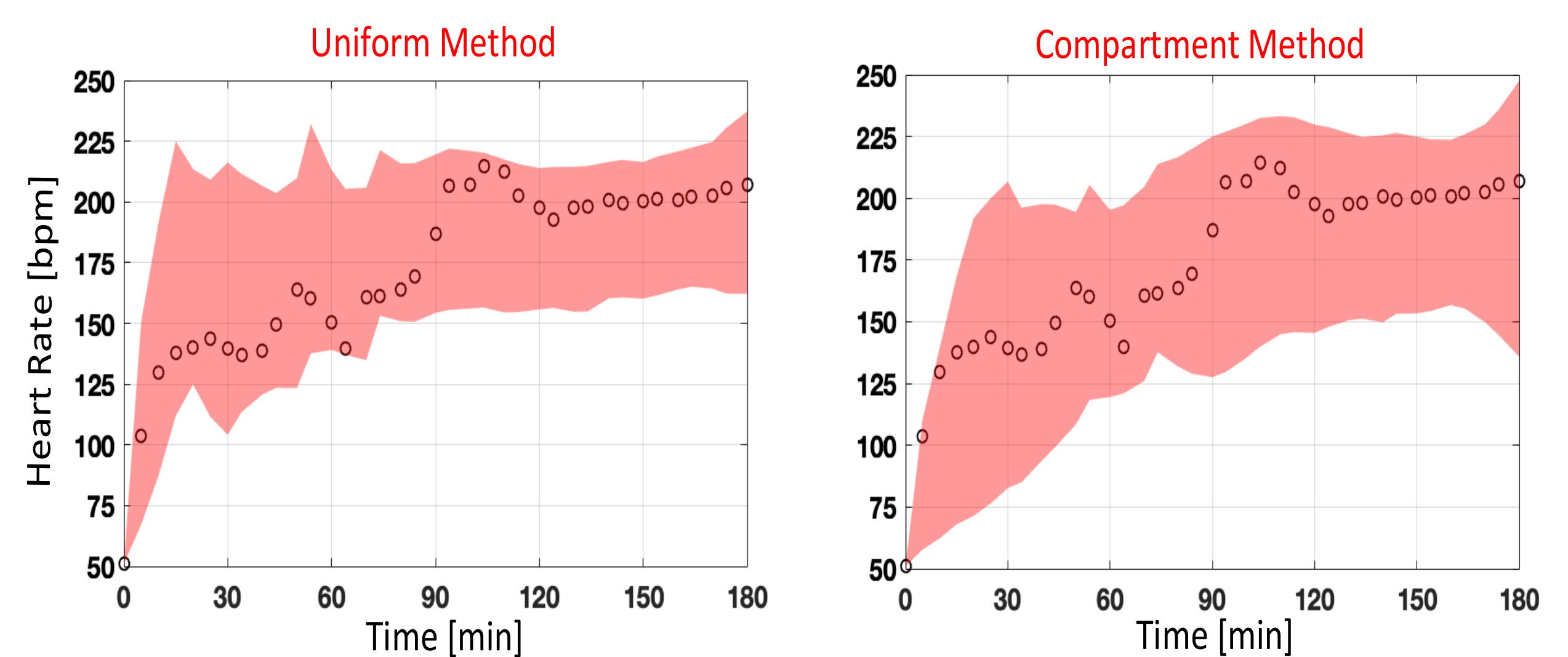


Figure 6. 95<sup>th</sup> percentile envelope for predictive capability assessment for a fully virtual subject. Among 18522 simulations, only those with the NRMSE  $\leq 20\%$  were included in the envelope. Dots represent observed HR data.

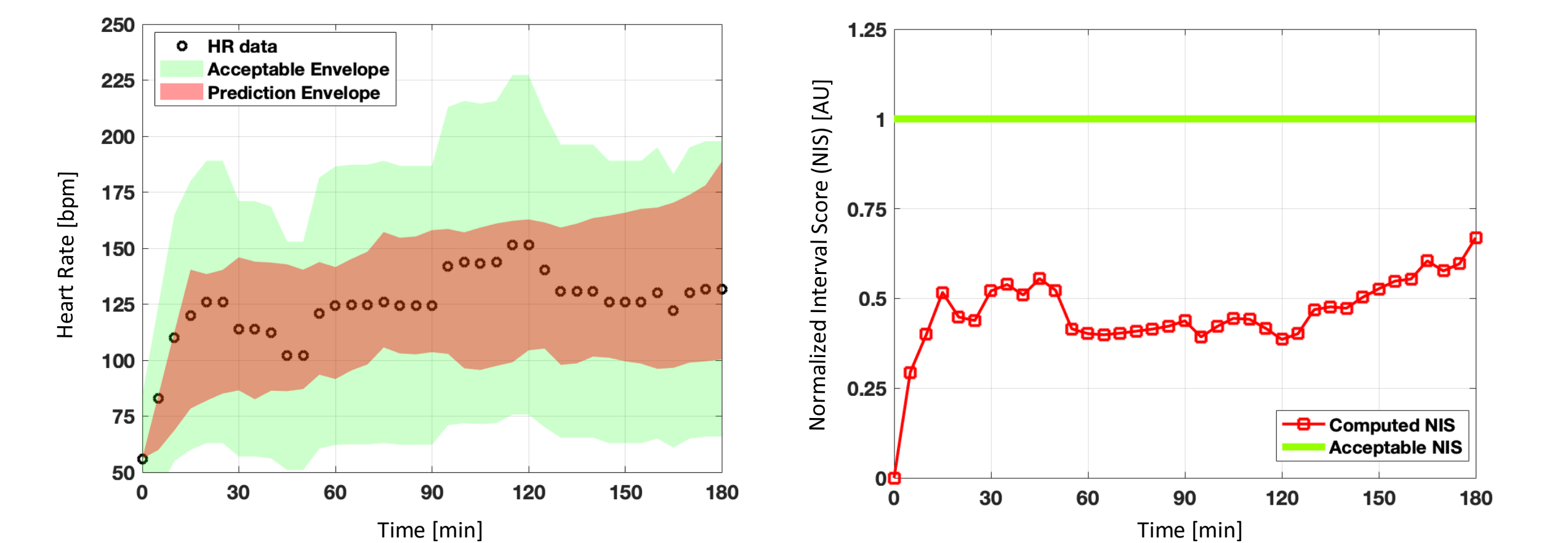


Figure 7. A representative example for assessing the prediction envelope. An acceptable NIS of 1 allows maximum 50% deviation of the HR envelope from the observed HR value.

**Table 2.** Percentage of subjects satisfying the NIS acceptable criteria. An acceptable NIS of 0.5 allows maximum 25% deviation of the HR envelope from the observed HR value.

Acceptable Range	Uniform Cohort Method				Compartment Method			
	0.25	0.5	0.75	1	0.25	0.5	0.75	1
Leave One Out	4.76%	66.66%	76.19%	76.19%	0%	66.66%	90.47%	95.23%
Independent Set	0%	66.66%	66.66%	66.66%	0%	50%	83.33%	100%

## Conclusion

This research presented and validated a control-oriented mathematical model of HR during fluid perturbation. A 3-subject compartment method was developed to generate virtual HR simulations. The average minimum NRMSE in validation dataset indicated that the compartment method was able to generate virtual subjects that were closer to the actual subjects than the uniform method when same number of samples are generated in each method. A normalized interval score was used to quantify the predictive performance of the model. It was shown that across all acceptable NIS levels and compared to the uniform distribution method, compartment method showed a superior NIS performance. The results support the validity of the model to be incorporated into future non-clinical simulated testing setups for *in silico* evaluation of fluid resuscitation PCLC devices.

## Acknowledgements

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## References

- [1] Bighamian, Ramin, Systems-level modeling and validation of cardiovascular system responses to fluid and vasopressor infusion for automated critical care systems, Doctoral Dissertation (2017).
- [2] Rafie, A. D. et al. Hypotensive resuscitation of multiple hemorrhages using crystalloid and colloids. Shock 22, 262–269 (2004).