

Heart Rate Dynamics Identification and Control in Cycle Ergometer Exercise: Comparison of First- and Second-Order Performance

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Background: Accurate and robust feedback control of human heart rate is important for exercise testing and prescription. Feedback controllers can be designed using first-order, linear, time-invariant models of heart rate dynamics, but it remains to investigate whether second-order models lead to better identification and control performance. The distinguishing contribution of this research is the direct employment of established physiological principles to determine model structure, and to focus the feedback-design goals: cardiac physiology proposes a two-phase second-order response, delineated into fast and slow components; the natural phenomenon of broad-spectrum heart-rate variability motivates a novel feedback design approach that appropriately shapes the input-sensitivity function.

OPEN ACCESS

Edited by:

Takao Sato, University of Hyogo, Japan

Reviewed by:

Thomas Beltrame, University of Waterloo, Canada Yoshihito Sawaguchi, National Institute of Technology, Kisarazu College, Japan

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Specialty section:

This article was submitted to Control and Automation Systems, a section of the journal Frontiers in Control Engineering

> Received: 11 March 2022 Accepted: 15 April 2022 Published: 05 May 2022

Citation:

Spörri AH, Wang H and Hunt KJ (2022) Heart Rate Dynamics Identification and Control in Cycle Ergometer Exercise: Comparison of First- and Second-Order Performance. Front. Control. Eng. 3:894180. doi: 10.3389/fcteg.2022.894180 **Aim:** The aim of this work was to compare the fidelity of first- and second-order models of heart rate response during cycle-ergometer exercise, and to compare the accuracy and dynamics of feedback controllers that were designed using the two model structures.

Methods: Twenty-seven participants each took part in two identification tests to generate separate estimation and validation data sets, where ergometer work rate was a pseudo-random binary sequence and in two feedback tests where controllers were designed using the first- or second-order models.

Results: Second-order models gave substantially and significantly higher model fit (51.9% vs. 47.9%, p < 0.0001; second order vs. first order) and lower root-mean-square model error (2.93 bpm vs. 3.21 bpm, p < 0.0001). There was modest improvement in tracking accuracy with controllers based on second-order models, where mean root-mean-square tracking errors were 2.62 bpm (second order) and 2.77 bpm (first order), with p = 0.052. Controllers based on second-order models were found to be substantially and significantly more dynamic: mean values of average control signal power were 9.61 W² and 7.56 W², p < 0.0001.

Conclusion: The results of this study confirm the hypotheses that second-order models of heart-rate dynamics give better fidelity than first-order models, and that feedback

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compensator designs that use the additional dynamic mode give more accurate and more dynamic closed-loop control performance.

Keywords: heart rate dynamics, system identification, feedback control, cycle ergometer, exercise

1 INTRODUCTION

Accurate and robust feedback control of human heart rate can be achieved using first-order, linear, time-invariant models of heart rate dynamics (Hunt and Fankhauser, 2016; Hunt et al., 2019a; Hunt and Hurni, 2019), but data from physiological studies suggest that at least two dynamic modes contribute to the overall response (Whipp et al., 1982; Bearden and Moffat, 2001). It is therefore of importance to investigate whether second-order models give better fidelity and whether feedback compensator designs that use the additional dynamic mode give more accurate and/or more dynamic closed-loop control performance.

It has been observed that heart rate response to step changes in work load consists of two principal components: a very fast, short-duration increase, called Phase I, attributed to the immediate cardiodynamic response; and a slower Phase II component that gives the major increase in heart rate; these two components have quite often been combined into a single exponential with a time constant that is termed the mean response time (Wasserman et al., 2011).

For work rates above the anaerobic threshold, there may in addition be a very slow but continuously increasing Phase III response, implying that a third-order model may be appropriate. When the dynamic model is to be used for feedback control of heart rate, however, any Phase III component can be neglected since integral action in the controller will eliminate these very slow disturbances (see also (Wang and Hunt, 2021a)). For this reason, and to deal with potential slow drift of heart rate response during system identification experiments, the data were detrended prior to parameter estimation (Section 2.1).

Most previous studies of heart rate control have been modelbased, employing either linear (Su et al., 2010; Hunt et al., 2019b) or non-linear (Cheng et al., 2008) models. To date, there is a lack of evidence that non-linear controllers bring performance benefits, while the following limitations can be identified: the stability is conditional (Asheghan and Míguez, 2016; Verrelli et al., 2021); the non-linearity is reduced to derive a robust controller (Argha et al., 2016); and the performance validation was only applied in simulation (Mazenc et al., 2011) or in experiments with small sample sizes (Paradiso et al., 2013). Furthermore, a systematic, direct comparison of linear and non-linear controllers in 16 participants found no difference in performance and that the non-linear approach could be over-sensitive at low exercise intensity (Hunt and Maurer, 2016).

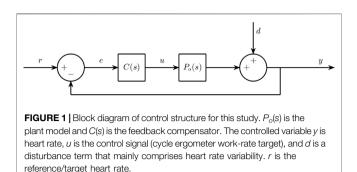
In contrast, several cycle ergometer heart rate control studies based on linear time-invariant models were validated using large sample sizes and demonstrated highly accurate and robust performance. Kawada *et al.* tested 67 participants in three groups and found good tracking accuracy in terms of rootmean-square tracking error (RMSE): 55 healthy participants had a mean RMSE of 2.5 bpm (beats per minute) at an intensity of 60% of maximal heart rate (HRmax); these same 55 participants achieved a mean RMSE of 3.8 bpm at 70% of HRmax; and 12 cardiac patients had mean RMSE of 3.0 bpm at a heart rate intensity of 20 bpm above their resting level (Kawada et al., 1999). Hunt *et al.* developed a robust input-sensitivity-shaping method based on a first-order linear model and tested 49 healthy participants in three cohorts grouped according to the shape of target HR profile and cadence: the mean RMSE values were 3.1 bpm (n = 25 participants, square-wave target HR and constant cadence), 2.5 bpm (n = 24, constant target HR, self-selected cadence) (Hunt and Hurni, 2019).

It is also possible to control heart rate on a cycle ergometer without an explicit dynamic model: Argha *et al.* developed and tested a novel method based on auditory biofeedback commands that instructed participants to change their cycling cadence (Argha et al., 2017); the choice of cadence as the manipulated variable is also unique, as most studies use work rate as the control signal. That work demonstrated good control accuracy in a total of 24 participants who were randomly divided into two separate groups: mean RMSE was 3.9 bpm (first group, n = 12) and 3.7 bpm (second group, n = 12). (Two groups were created in order to test controller robustness: a controller tuned for the first group was tested on the second group, and *vice versa*; no significant difference in mean RMSE between the groups was found.)

The mean response time model of heart rate response has motivated studies that used linear first-order models for identification and control design, e.g. (Hunt and Hurni, 2019), but the question arises of whether delineation of Phase I and II components, that is to say, the employment of second order models, will lead to better representation of heart rate dynamics and, in turn, to more accurate and dynamic feedback control: these are the hypotheses of the present study.

For treadmill exercise, it was previously demonstrated that goodness-of-fit of empirically identified second-order models was significantly higher than first-order models (Wang and Hunt, 2021a); but an associated feedback control study, while showing significantly more dynamic control signal activity, did not determine any difference in tracking and regulation accuracy (Wang and Hunt, 2021b); a limitation of the latter work was that a low sample size was employed (n = 10). For the cycle ergometer mode of exercise, on the other hand, no comparative study of first- and second-order identification and control performance has yet been conducted.

The aim of this work was to compare the fidelity of first- and second-order models of heart rate response during cycleergometer exercise, and to compare the accuracy and dynamics of feedback controllers that were designed using the two model structures.



2 METHODS

2.1 Plant Model and Feedback Design

The open-loop plant P_o was modelled as the general linear, time-invariant transfer function

$$P_o(s) = \frac{B(s)}{A(s)} : \ u \mapsto y \tag{1}$$

with control signal u (physically, target work rate) and controlled variable y (heart rate); heart rate variability and other uncertainties are represented by a disturbance term d (**Figure 1**); A and B are polynomials in the complex variable s.

The first- and second-order instances of the plant are, respectively,

$$P_1(s) = \frac{k_1}{\tau_1 s + 1}$$
(2)

and

$$P_2(s) = \frac{k_2}{(\tau_{21}s+1)(\tau_{22}s+1)}$$
(3)

where the k are steady-state gains and τ time constants.

As discussed in the Introduction, raw data obtained from identification experiments were detrended prior to parameter estimation in order to eliminate any potential Phase III component. The gains and time constants of the first- and second-order models were estimated using a least-squares optimisation procedure (Matlab System Identification Toolbox; The Mathworks, Inc., United States).

A feedback control system for heart rate was employed (**Figure 1**) that used a strictly-proper, linear, time-invariant compensator transfer function C,

$$C(s) = \frac{G(s)}{H(s)} : e \mapsto u, \tag{4}$$

where e = r - y is the tracking error. Integral action was implemented by constraining the compensator denominator as H(s) = sH'(s).

Synthesis of the feedback compensator C used a frequencydomain design approach, see (Hunt and Fankhauser, 2016), that shapes the input sensitivity function U_o to be well behaved (no peaking) and to satisfy a closed-loop bandwidth requirement. U_o describes the closed-loop transfer function linking the

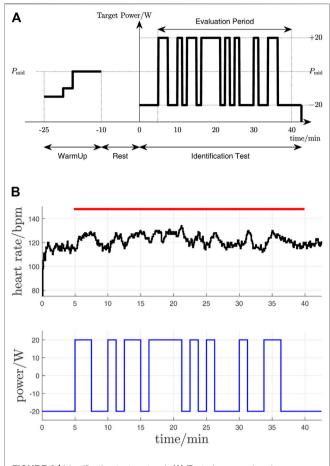


FIGURE 2 | Identification test protocol. **(A)** Test phases and cycle ergometer work rate (PRBS around the mid-level P_{mid}). **(B)** Original data record from one participant (PO1). Upper plot - heart rate measurement; lower plot - target work rate (PRBS signal with P_{mid} subtracted); the evaluation period is depicted by the red horizontal bar.

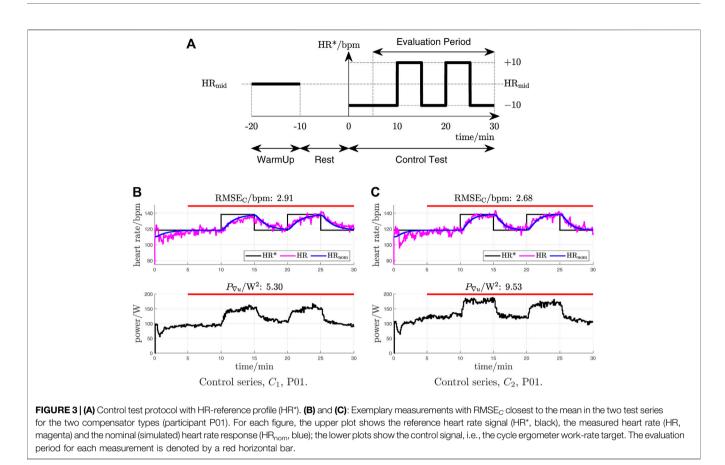
disturbance term d (and the reference r) with the control signal u. The overall idea behind this design concept is therefore to make the control signal u well behaved in the face of disturbances d arising from heart-rate variability, but with the option of freely selecting the response bandwidth. U_o is defined in general as

$$U_{o}(s) = \frac{C(s)}{1 + C(s)P_{o}(s)} : d, r \mapsto u.$$
(5)

The design goal for input-sensitivity shaping algebraically constrains the compensator C in such a way that U_o is first order, and hence is devoid of peaking, and has a specified bandwidth p, which is the feedback design/tuning parameter. For both the first- and second-order cases, U_o then reduces to

$$U_o(s) = \frac{p/k}{s+p},\tag{6}$$

where $k = k_1$ (first-order plant Eq. 2) or $k = k_2$ (second-order plant Eq. 3).



Derivation of the compensator solutions that achieve this form for U_o is described in detail elsewhere (Hunt and Fankhauser, 2016; Wang and Hunt, 2021b), and merely summarised here: in the first-order case, the compensator is (see (Hunt and Fankhauser, 2016))

$$C_{1}(s) = \frac{\frac{p}{k_{1}}\left(s + \frac{1}{\tau_{1}}\right)}{s\left(s + p + \frac{1}{\tau_{1}}\right)};$$
(7)

and for the second-order case it is (Wang and Hunt, 2021b)

$$C_{2}(s) = \frac{\frac{p}{k_{2}} \left(s^{2} + \left(\frac{1}{\tau_{21}} + \frac{1}{\tau_{22}}\right)s + \frac{1}{\tau_{21}\tau_{22}}\right)}{s \left(s^{2} + \left(p + \frac{1}{\tau_{21}} + \frac{1}{\tau_{22}}\right)s + p\left(\frac{1}{\tau_{21}} + \frac{1}{\tau_{22}}\right) + \frac{1}{\tau_{21}\tau_{22}}\right)}.$$
 (8)

Thus, the compensators depend simply on the chosen design parameter p (bandwidth of U_o) and the plant parameters k_1 , τ_1 (first-order case) or k_2 , τ_{21} , τ_{22} (second-order case).

2.2 Equipment

All identification and feedback control experiments were performed using a computer-controlled cycle ergometer (model LC7, Monark Exercise AB, Sweden). The ergometer was connected using a USB serial link to a PC running Simulink Desktop Real-Time (The MathWorks, Inc., United States). Heart rate was monitored using a chest belt sensor (H10, Polar Electro Oy, Finland) and a receiver module (Heart Rate Monitor Interface, Sparkfun Electronics, United States) connected via USB to the PC and Simulink models. A sample period of 5 s was used for identification and control.

2.3 Experimental Procedures

In accordance with an *a priori* statistical power and sample size estimate (**Section 2.5**), 27 participants were recruited: 20 males and 7 females; mean age 31 years; mean height 1.79 m; mean body mass 76 kg.

Each participant took part in two identification tests—to generate separate estimation and validation data sets—and two feedback control tests—to compare compensators C_1 and C_2 —with each test separated by 24 h.

For system identification, cycle-ergometer work rate was varied using one complete period of a pseudo-random binary sequence (PRBS) with a mean level of P_{mid} and an amplitude of 20 W (i.e. $P = P_{mid} \pm 20$ W). The overall identification test protocol (**Figure 2**) included a 15-min warm up which also served to determine the mid-level work rate P_{mid} , as follows. During the warm up, heart rate was controlled using an existing feedback compensator to reach a constant level HR_{mid} corresponding to the border between moderate and vigorous intensities, viz. HR_{mid} = 0.765 × (220 – age) – 20, (Riebe et al., 2018; Hunt and Hurni, 2019). P_{mid} was calculated as the mean work rate of the final 2 minutes of the warm up and used in the subsequent open-loop identification phase. For each participant, the first data set was used to estimate first-

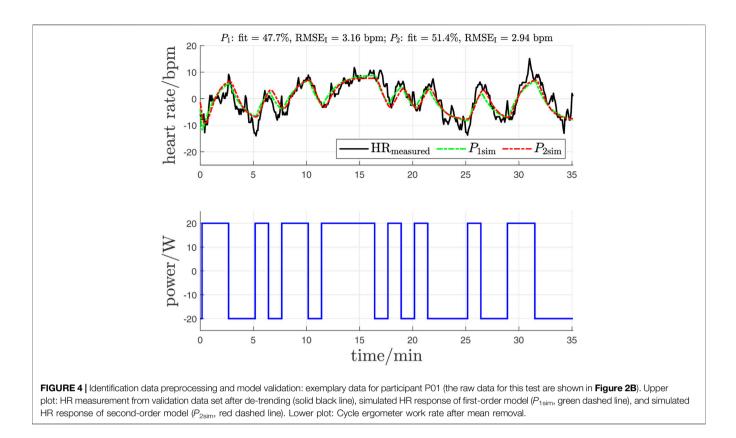


TABLE 1 Overall outcomes for P_1 and P_2 from the model identification test series
and comparison of outcome differences (see also Figure 5).

	Mean ± SD		MD (95% CI)	<i>p</i> -value
	P ₁	P ₂	<i>P</i> ₂ - <i>P</i> ₁	
RMSE _/ /bpm	3.21 ± 0.70	2.93 ± 0.59	-0.27 (-∞, -0.22)	2.0 × 10 ⁻¹¹
fit/%	47.9 ± 7.0	51.9 ± 8.0	4.0 (3.3, ∞)	7.1×10^{-14}

P₂: second-order models.

SD: standard deviation.

MD: mean difference.

95% CI: confidence interval for the mean difference.

p-value: paired one-sided t-tests.

RMSE: root-mean-square model error, Eq. 10.

Fit: normalised root-mean-square error, Eq. 9.

bpm: beats per minute.

and second-order models P_1 and P_2 and the second data set to compute the validation outcomes, namely fit, **Eq. 9**, and RMSE_{*I*}, **Eq. 10**. The procedure was then reversed by using the second data set for estimation and the first data set for model validation. Thus, with a cohort of 27 participants, a total of 54 pairs of first- and second-order models were available for comparison.

For feedback control, a square-wave target heart rate profile was applied with mean level HR_{mid} and amplitude 10 bpm, i.e. $HR^* = HR_{mid} \pm 10$. The overall feedback control test protocol (**Figure 3**) incorporated a 10-min warm up that was feedback-

controlled to a constant target heart rate of HR_{mid} . Each participant was tested with their individual C_1 and C_2 compensators: the C_1 were calculated according to **Eq.** 7 using the best of the participant's two identified P_1 models, and C_2 were calculated using **Eq. 8** and the best of the two individual P_2 models. To avoid possibly confounding order-ofpresentation effects, the order of testing with C_1 or C_2 (i.e. C_1 then C_2 vs. C_2 then C_1) was changed sequentially according to participant number. Control data from one participant had to be excluded for reasons of data quality; 26 pairs of outcomes were therefore available for the C_1 vs. C_2 comparative analysis.

2.4 Outcome Measures

Identification outcomes: fidelity of the estimated models was quantified on the validation data sets using a normalised root-mean-square model error (NRMSE), also called "fit", and the absolute RMS model error (RMSE_{*l*});

fit (NRMSE) [%] =
$$\left(1 - \sqrt{\frac{\sum_{i=1}^{N} (\text{HR}(i) - \text{HR}_{\text{sim}}(i))^{2}}{\sum_{i=1}^{N} (\text{HR}(i) - \overline{\text{HR}})^{2}}}\right) \times 100;$$
(9)

$$\text{RMSE}_{\text{I}} [\text{bpm}] = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (\text{HR}_{\text{sim}}(i) - \text{HR}(i))^2}; \quad (10)$$

where HR is the measured heart rate and $\mathrm{HR}_{\mathrm{sim}}$ is simulated using the estimated models.

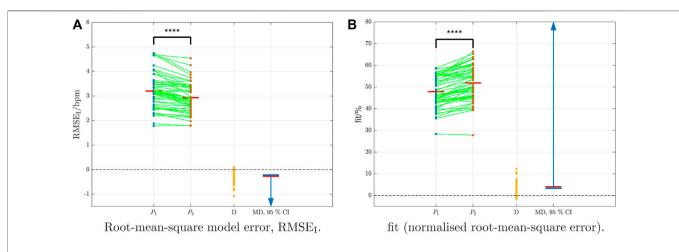


FIGURE 5 Identification outcomes: data samples and differences for RMSE_{*i*} and fit between 54 first-order models, P_1 , and 54 second-order models, P_2 (see also **Table 1**). Sample pairs for each participant are connected by green lines; mean values are shown as red horizontal bars (with numerical values given in **Table 1**). Samplepair differences are shown as D ($P_2 - P_1$). The mean difference (MD) is depicted as a red bar and the blue arrow is the corresponding 95% confidence interval (Cl). For both RMSE_{*i*} and fit, the 95% Cl does not contain the value 0, thus showing a significant improvement for P_2 vs. P_1 (p < 0.05, **Table 1**; the notation **** denotes p < 0.0001). (A) Root-mean-square model error, RMSE_{*i*}. (B) fit (normalised root-mean-square error).

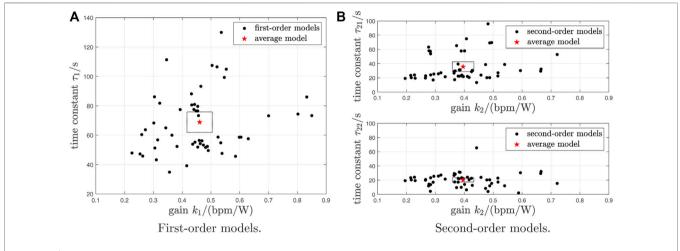


FIGURE 6 | Dispersion of estimated model parameters for 54 first- and 54 second-order models. The stars depict the average models. The 95% confidence intervals for the mean gains and time constants are shown as dotted rectangular boxes. (A) First-order models. (B) Second-order models.

Feedback control outcomes: accuracy of heart rate tracking was quantified using root-mean-square tracking error ($RMSE_C$),

$$\text{RMSE}_{\text{C}} [\text{bpm}] = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (\text{HR}_{\text{nom}}(i) - \text{HR}(i))^2}, \quad (11)$$

where HR_{nom} is the nominal (simulated) closed-loop heart rate response, while intensity of the manipulated variable was quantified by the average power in changes in the control signal ($P_{\nabla u}$), viz.

$$P_{\nabla u} \left[\mathbf{W}^2 \right] = \frac{1}{N-1} \sum_{i=2}^{N} \left(u(i) - u(i-1) \right)^2.$$
(12)

2.5 Hypotheses, Statistics and Sample Size Estimate

The hypotheses of this study were (cf. **Section 1**): 1) that secondorder models of open-loop heart-rate response would give better fidelity (i.e. higher fit and lower RMSE_I) than first-order models, and 2) that feedback compensators based on second-order models would give more accurate (lower RMSE_C) and more dynamic (higher $P_{\nabla u}$) control of heart rate.

Hypothesis testing—comparison of sample mean differences for the outcomes defined above—was done using paired, onesided t-tests with a significance level of 5% ($\alpha = 0.05$). Normality of sample differences was confirmed using the Kolmogorov-Smirnov test with Lilliefors correction.

TABLE 2 Overall outcomes for C_1 and C_2 from the feedback control test series
and comparison of outcome differences (see also Figure 7).

	Mean ± SD		MD (95% CI)	p-value
	C ₁	C ₂	C ₂ - C ₁	
RMSE _c /bpm	2.77 ± 0.61	2.62 ± 0.45	-0.15 (-∞, 0.002)	0.052
$P_{\nabla u}/(W^2)$	7.56 ± 4.26	9.61 ± 5.82	2.05 (1.34, ∞)	2.3×10^{-5}
n = 26.				
C1: compensate	or C ₁ .			
C2: compensate	or C ₂ .			
SD: standard de	eviation.			
MD: mean differ	rence.			
95% CI: confide	ence interval for th	e mean difference	9.	
p-value: paired	one-sided t-tests.			
	ean-souare tracki	ng error, Eg. 11 .		
RIVISEC: root-m				
-	ntrol signal powe	••••		

The sample size of n = 27 participants was estimated *a priori* by a statistical power calculation that used estimates of expected effect sizes and sample standard deviations obtained from previous studies in this lab, with the significance level of 5% and a statistical power of 80% $(1 - \beta = 0.8)$.

3 RESULTS

3.1 Identification

To aid understanding of the overall identification test analysis, the results for a single participant (P01) are first illustrated (**Figure 4**). In this example, the second-order model provides higher fidelity than the first-order model: the respective RMSE_I values were 2.94 bpm and 3.16 bpm (P_2 vs. P_1), while the fit values were 51.4% and 47.7% (P_2 vs. P_1).

Of the 54 identification tests completed, 48 (89%) of the P_2 models returned a lower RMSE_{*I*} and higher fit than the corresponding P_1 models; overall, RMSE_{*I*} was significantly lower and fit significantly higher for P_2 than for P_1 :

- RMSE₁ was 2.93 bpm \pm 0.59 bpm (mean \pm standard deviation) vs. 3.21 bpm \pm 0.70 bpm (P_2 vs. P_1) with $p = 2.0 \times 10^{-11}$ (**Table 1**; Figure 5A),
- Fit values were $51.9\% \pm 8.0\%$ vs. $47.9\% \pm 7.0\%$ (P_2 vs. P_1) with $p = 7.1 \times 10^{-14}$ (**Table 1; Figure 5B**).

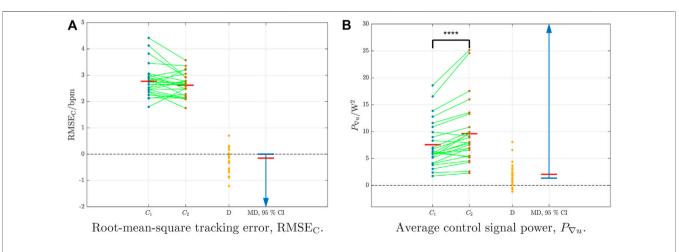
Graphical illustration of the individually estimated gains and time constants (**Figure 6**) shows wide dispersions but quite narrow bounds on the 95% confidence intervals for mean estimates. The overall first-order model had gain $k_1 = 0.46$ bpm/W \pm 0.14 bpm/W (mean \pm standard deviation) and time constant $\tau_1 = 68.8 \text{ s} \pm 22.0 \text{ s}$. The overall second-order model gain was $k_2 = 0.40$ bpm/W \pm 0.12 bpm/W and the time constants were $\tau_{21} = 35.7 \text{ s} \pm 21.7 \text{ s}$ and $\tau_{22} = 20.4 \text{ s} \pm 9.6 \text{ s}$. This gives average first- and second-order model transfer functions as follows:

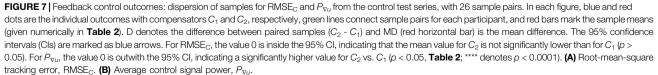
$$u \mapsto y: P_1(s) = \frac{0.46}{68.8 \ s+1},$$
 (13)

$$u \mapsto y: P_2(s) = \frac{0.40}{(35.7 \ s+1)(20.4 \ s+1)}.$$
 (14)

3.2 Control

As an example, the C_1 and C_2 test results of a single participant (P01) are first shown (**Figure 3**). In this illustrative data set, C_2 was found to be more accurate (lower RMSE_C) and more dynamic (higher $P_{\nabla u}$) than C_1 : the respective RMSE_C values were 2.68 bpm vs. 2.91 bpm (C_2 vs. C_1), and the average control signal power ($P_{\nabla u}$) values were 9.53 W² vs. 5.30 W² (C_2 vs. C_1).





From the 26 pairs of feedback control tests, 17 C_2 controllers (65%) were more accurate than C_1 while 22 C_2 controllers (85%) were more dynamic than C_1 . In the overall statistical analysis, there was moderate evidence that C_2 was more accurate than C_1 and strong evidence that C_2 was more dynamic than C_1 :

- RMSE_C was 2.62 bpm \pm 0.45 bpm (mean \pm standard deviation) vs. 2.77 bpm \pm 0.61 bpm (C_2 vs. C_1) with p = 0.052 (**Table 2, Figure 7A**),
- Average control signal power, $P_{\nabla u}$, was 9.61 W² ± 5.82 W² vs. 7.56 W² ± 4.26 W² (C_2 vs. C_1) with $p = 2.3 \times 10^{-5}$ (**Table 2, Figure 7B**).

4 DISCUSSION

The aim of this work was to compare the fidelity of first- and second-order models of heart rate response during cycleergometer exercise, and to compare the accuracy and dynamics of feedback controllers that were designed using the two model structures. This aim was motivated by observations from the physiological literature that heart rate response is dominated by two components with distinct time constants—a fast Phase I response, and a dominant but slower Phase II response—in concord with the underlying mechanisms thought to be at work in neural regulation of heart rate. These considerations led to the hypotheses of this study, namely that second-order models of open-loop heart-rate response would give better fidelity than first-order models, and that feedback compensators based on second-order models would give more accurate and more dynamic control of heart rate.

It was found that second-order models gave substantially and significantly better representation of the dynamic heart rate response to changes in exercise work rate, with mean fit values of 51.9% and 47.9% (p < 0.0001), respectively, and mean root-mean-square model error of 2.93 bpm vs. 3.21 bpm (p < 0.0001). This finding supports the concept of two principal dynamic modes contributing to the overall heart rate response. The mean time constants for the second-order models, viz. $\tau_{22} = 20.4$ s and $\tau_{21} = 35.7$ s, can be interpreted physiologically as the faster Phase I and slower Phase II components, respectively.

In the feedback control comparison, there was modest improvement in tracking accuracy with controllers based on second-order models, where mean root-mean-square tracking errors were 2.62 bpm (second order) and 2.77 bpm (first order), with p = 0.052 being close to the statistical significance threshold. But controllers based on second-order models were found to be substantially and significantly more dynamic: mean values of

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average control signal power were 9.61 W² and 7.56 W², C_2 vs. C_1 , and p < 0.0001. The finding that improvements in closed-loop control accuracy were less clear than open-loop model fidelity is likely due to the basic characteristic of feedback systems that plant uncertainty is reduced, at least in frequency ranges where the closed-loop sensitivity function takes on values less than one (Åström and Murray, 2008); thus, a given difference in model fidelity will effectively be "attenuated" when the respective models are used for feedback design, thus making it more difficult to experimentally detect improvements in control accuracy.

5 CONCLUSION

The results of this study confirm the hypotheses that secondorder models of heart-rate dynamics give better fidelity than firstorder models, and that feedback compensator designs that use the additional dynamic mode give more accurate and more dynamic closed-loop control performance.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics Committee of the Swiss Canton of Bern. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

KH and HW designed the study. AS did the data acquisition. AS, KH and HW contributed to the analysis and interpretation of the data. AS and KH wrote the manuscript and HW revised it critically for important intellectual content. All authors read and approved the final manuscript.

FUNDING

This work was supported by the Swiss National Science Foundation (Grant Ref. 320030-185351).

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