Is the understanding of $\dot{V}O_2$ kinetics biased by the first-order multi-exponential model?

Luis Antonio Pereira de Lima¹ · Ricardo Dantas de Lucas² · Maxime Raison³ · Sofiane Achiche³

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We read with great excitement the recent study of Colosio et al. [2] applying the bioenergetics approach [13] to the oxygen uptake response during constant-load exercise: first, because the observed maintenance of the overall cost of locomotion beyond the third minute of exercise in the heavy domain dissociates the slow component etiology from the premises of the delayed recruitment of additional muscle fibers or the efficiency loss in the already recruited ones; second, because the $\dot{V}O_2$ slow component increase, when explained by a shift from the anaerobic glycolytic to the aerobic energy metabolism, may be elegantly interpreted simply as a reflection of a “prolonged adjustment of the oxidative metabolism” [2].

In fact, these findings are not only encompassed both conceptually and mathematically by our recently proposed second-order simultaneous components (SOSC) model [6], but also represent two of its basic assumptions. In the SOSC structure, the shape of the measured pulmonary $\dot{V}O_2$ response is composed by summing up two components, namely CI and CII, with no delay between their onsets, each one increasing

towards its own target asymptote accordingly with their own specific speed and magnitude characteristics. Thus, considered the difference in the responsiveness of each component (basically associated with the specificities of type I and II muscle fibers [6]), both of the increases observed over time for CI and CII may be explained by means of the same anaerobic-to-aerobic shift mechanism, while their simultaneous onsets eliminate the need for a delayed recruitment assumption.

In general terms, while CI is responsible for the majority of the first and large augmentation observed in the fast phase of the $\dot{V}O_2$ step response, CII is responsible for the majority of the secondary *slow augmentation in $\dot{V}O_2$ kinetics* ($\dot{V}O_{2SA}$). In the commonly used first-order multi-exponential (FOME) model [9, 15], these primary and secondary augmentations in the $\dot{V}O_2$ step response are each modeled by a first-order exponential (the fundamental and slow components, respectively) with a mandatory delay between their onsets. For clarity purposes, we intentionally refer to the slow component phenomenon as $\dot{V}O_{2SA}$ [6], avoiding confusion between the phenomenon itself and the homonymous mathematical element modeling it in the context of the FOME model.

Besides the coherence between the findings from Colosio et al. [2] and the described basic concepts of the SOSC model, we draw special attention to the biases potentially imposed by the FOME model representation to our understanding of the human $\dot{V}O_2$ kinetics mechanism.

In regard to the etiological bases of the $\dot{V}O_{2SA}$ offered by the FOME theory, some controversial aspects are noteworthy. One of them stems from the characteristic “bump” in the $\dot{V}O_2$ step response often observed at the beginning of the $\dot{V}O_{2SA}$ manifestation (i.e., a local increase in the curve slope in the region corresponding to the FOME’s slow component onset). Because the curve shape resulting from the summation of two or more first-order exponentials with a common onset time cannot present a positive slope variation, the reproduction of this $\dot{V}O_{2SA}$ -like shape in the FOME context requires the slow component onset delay to be longer than that of the

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✉ Luis Antonio Pereira de Lima
luis.delima@polymtl.ca

Ricardo Dantas de Lucas
ricardo.dantas@ufsc.br

Maxime Raison
maxime.raison@polymtl.ca

Sofiane Achiche
sofiane.achiche@polymtl.ca

¹ São Paulo, Brazil

² Sports Centre, Federal University of Santa Catarina, Campus Universitário, Florianópolis, SC 88040900, Brazil

³ Mechanical Engineering Department, Polytechnique Montréal, 2500, Chemin de Polytechnique, Montréal, QC H3T1J4, Canada

fundamental component [6]. Such a belated onset of the slow component is, however, deprived of physiological justification inasmuch as the progressive muscle fiber recruitment is no longer considered a requisite for the $\dot{V}O_2SA$ occurrence [1, 3, 14, 16]. Alternatively, a solution reproducing the $\dot{V}O_2SA$ -like shape without requiring its components to be differently delayed is offered by the SOSC model due to the interaction between the second-order features of its elements, as previously demonstrated [6].

Another controversial aspect regards the ambiguity in the proposed natures of the fundamental and slow components. While the anaerobic-to-aerobic shift is accepted by the FOME model as the explanation for the increase of the fundamental component towards its own asymptote, respecting the oxidative responsiveness of the recruited fibers, the same FOME model resorts to the additional fiber recruitment and/or the efficiency loss of the already-active fibers in order to explain the $\dot{V}O_2SA$. In the SOSC model, instead, the magnitudes of CI and CII are defined accordingly with the mix of muscle fibers required by the exercise force and contraction speed demands already at the beginning of the exercise or whenever these demands change. Thus, after the initial mix of fibers has been activated, no extra recruitment is necessarily expected, and the $\dot{V}O_2SA$ may be explained by the increase of CII dictated by its slower $\dot{V}O_2$ kinetics.

It must be remarked on, however, that a certain loss of efficiency may coexist with this anaerobic-to-aerobic shift for any component at any time, and most likely at more intense work rates (such as observed for the severe exercise domain [2]), where the augmented participation of type II fibers may increase the muscle susceptibility to fatigue [2]. Still, muscle fatigue does not seem important enough to be accounted for the entire magnitude of the $\dot{V}O_2SA$, at least not in the heavy exercise domain [2, 7].

We agree with Colosio et al. [2] that “the recruitment of bigger, preferentially glycolytic muscle fibres” resulting from the increase in exercise intensity may delay the attainment of a $\dot{V}O_2$ steady state. In coherence with Henneman’s size principle [3, 8], the SOSC model dynamics assumes that the more intense the exercise demands are, the larger the participation of CII is required to be and, given enough time, the more pronouncedly the $\dot{V}O_2SA$ manifests [6]. However, when these authors speculate that “the adjustment of $\dot{V}O_2$ in the heavy domain may be described by a slow primary component rather than by the summation of a primary plus a slow component” [2], our agreement is limited to the fact that the FOME’s solution of differently delayed components may not be adequate. Still, the reproduction of the characteristic slope variations of $\dot{V}O_2$ response curves containing the $\dot{V}O_2SA$ by means of one single component, if feasible, awaits to be presented.

A third reason for our interest in the study of Colosio et al. [2] was the overshoot [5, 6, 10–12] clearly observable in at least one of their moderate exercise domain data

(Fig. 1 from Colosio et al. [2], bottom panel). This phenomenon is also an important element of our SOSC model [6], since first-order system curves are not able to comprise overshooting responses. Even if only the fundamental component is considered, the first-order paradigm represents again a likely source of bias to the understanding of $\dot{V}O_2$ kinetics, for an overshooting response is a “signature” of second- or higher-order systems. Moreover, it is recognized that an overshooting response fitted with a first-order fundamental component curve may yield inadequate results in terms of amplitude [11], response time [5, 11, 12], and oxygen deficit [5, 10–12]. Nevertheless, however natural the adoption of a second-order formulation may seem, most of the efforts to include the overshoot phenomenon in the curve fitting have been solely adding “overshoot terms” to the FOME’s fundamental component [4, 10, 12]. Whereas such an approach reinforces the notion that the $\dot{V}O_2$ overshoot is an artifact and somehow alien to the $\dot{V}O_2$ kinetics mechanism, the use of second-order curves [5, 6] proposed by our SOSC model naturally incorporates this phenomenon to the very structure of the modeled system.

The elegant first-order exponential proposed in 1923 by Hill and Lupton [9] sufficiently described the primary $\dot{V}O_2$ increase at the onset of exercise in a situation when the $\dot{V}O_2SA$ or overshoot was not yet a concern. Almost fifty years later, Whipp and Wasserman [15] proposed the addition of another first-order exponential (i.e., the slow component) in order to comprise the $\dot{V}O_2SA$ phenomenon. The resulting FOME model, however, could only properly fit $\dot{V}O_2SA$ containing responses if its slow and fundamental components presented different onset time delays. Such a mathematical restriction imposing a 2–3-min delay to the slow component onset was then extended to the etiology of the $\dot{V}O_2SA$ phenomenon itself. As a consequence, a possibility has been ignored: that the actual delay was not in the physiological cause of the $\dot{V}O_2SA$, but only in its observation above the fundamental component asymptote.

Taken together, these issues regarding the modeling of the $\dot{V}O_2SA$ and overshoot phenomena denote the need for a disruption from that first-order paradigm firstly proposed almost one century ago. Since then, advancements in measuring techniques and investigation of a myriad of populations and contexts made available new evidence that claim for a second-order modeling for the $\dot{V}O_2$ kinetics. Such a model update, a routine in control theory whenever a system demonstrates a complexity higher than initially expected, rather than a route change, must be seen as a continuation of the magnificent research work paved so far in the $\dot{V}O_2$ kinetics field.

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Data availability Please contact the corresponding author for data regarding his cited studies.

Compliance with ethical standards

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