


Brian J. Whipp
Human Bio-Energetics Research Centre
Crickhowell, Powys, United Kingdom

COUNTERPOINT: THE KINETICS OF OXYGEN UPTAKE DURING MUSCULAR EXERCISE DO NOT MANIFEST TIME-DELAYED PHASES

The existence of time-delayed phases (1) is not supported by oxygen uptake kinetics data. Despite many attempts for a number of years, no convincing physiological mechanism for such behavior has been proven to exist. The reason is that these time-delayed phases are a frame of the incorrect treatment of the data and the overly simple curve fitting of the, usually, averaged data. The reported problems regarding high levels of uncertainty in TD₂ or insufficient clarity in the drop in the pulmonary gas exchange ratio, R, defining TD₁ are due to trying to fit time-delayed phases to data with no such features. Due to the poor data handling and curve fitting the time constants are also physiologically irrelevant.

Breath-by-breath recordings exhibit spontaneous fluctuations (18). A number of different algorithms with different assumptions are therefore used to estimate the breath-by-breath V̇O₂, resulting in notable differences observable throughout the whole on/off transient, most extremely so in the initial response (16). These algorithms can also affect the three-phase curve parameters estimates (9, 13). Breath-by-breath variability may have biological significance (5) as non-linear systems such as those governing the respiratory and circulatory functions can produce signals that look like random noise but are in fact not stochastic (3, 11, 14, 15, 21). Therefore part of what is attributed to noise can contain inherent features and vital information (30). For example, in both constant and free-paced 10,000-m runs the V̇O₂ (and HR) has a scaling exponent above 0.5, the value for white noise (4).

Noise reduction is commonly achieved via ensemble averaging the responses of multiple supposedly identical exercise bouts (17). This is only justified when the noise is Gaussian and stochastic (26) and the basic response pattern of each bout is identical, which in general is not the case (2, 20). To support this procedure (17, 20) it is often quoted as showing that the noise is white. These papers however do not provide sufficient proof of the noise’s whiteness for the whole on/off transient at any intensity, as only the steady states at rest or during the last 2 min (120 s is a very short sample size) of non-slow component data are analyzed. In contrast more modern studies show that some breath-by-breath algorithms produce data with non-white noise (4, 7, 9), hence averaging several repetitions can be methodologically unjustified (9). Also due to variation in parameter values on repeated testing days it is debatable whether ensemble averaging is an accurate method (2). Parameter variability is also reported, especially in the time constants (19). Differences between bouts, when ensemble averaged, can produce features not found in the raw unaveraged time series for a single bout of exercise (30). Therefore a model that is fit to the features of averaged data is not necessarily a good model of the raw unaveraged data of a single exercise bout [in which features such as time-delayed phases cannot be observed due to the high-frequency signal oscillations (5, 23)]. A curve without time-delayed phases (22–25, 28–30) can fit the data perfectly well. If the data for a single bout of exercise is instead filtered using a low-pass filter or a moving average with sufficient high n (30) or a more sophisticated nonlinear curve smoothing techniques (15) then the curve obtained will provide the basic response pattern for that bout of exercise. The basic response pattern is what should be modeled, not the average, which in general is a different curve (30).

The phase 1/2 components are intertwined, complicating the TD₁ interpretation (26). In theory, the start of phase 2 (i.e., TD₁) should be triggered by a fall in the pulmonary gas exchange ratio (R = V̇CO₂/V̇O₂), however, “this decrease is often not sufficiently clear for this purpose and a value of at least 20 s is commonly used” (26). Many researchers try to improve the phase 2 fit by constraining the fitting window to start some time after the exercise onset (26). As there exists a high degree of interdependency in the parameters (16), arbitrarily cutting data affects all the parameter values. As a result τ₂ will be dependent on the amount of data removed, making it of limited use physiologically. For the phase 1 and slow component, the best fit to the data can result in unphysiologically large values of the amplitude and/or time constant (16). It is debatable therefore whether the exponential is a good model for these phases (8, 12, 26). The determination of both the phase 2 asymptote and TD₁ is highly uncertain and via dependency, this can dramatically affect the parameter values and confidence, possibly causing an unacceptable reduction in the τ2 confidence (26).

Slow kinetics can easily be observed to exist by inspection, what is not certain however is the existence of a time-delayed slow component, nor has a physiological mechanism been proven (26). Slow kinetics emerge from the background noise after a time period, however, crucially this does not imply the
existence of a time-delayed phase (26). The slow phase gain profile and time constant(s?) also remain to be determined (26). A step-wise increment in oxygen demand after a time delay $TD_2$ has recently been recognized to be unrealistic and an $n$-phase curve has been proposed instead (2, 26, 27). A more powerful approach, however, (28) numerically estimates the time dependency of the oxygen demand from the on/off transient kinetics. Mathematically speaking the $n$-phase curve (2, 27) refers to the way a smooth function is approximated using first principles of infinitesimal calculus (30). A more rigorous model therefore would consist of a smooth function (23, 25).

A single exponential rise for phase-2 has been argued against as almost identical curves can be produced using very different assumptions based on numerous compartments with either a range of $\tau$ values and the same amplitudes or the same $\tau$ but different amplitudes ($6, 27$). Hence doubts exist regarding the phase 2 parameters physiological relevance. Regarding all the $3n$-phase curves the number of parameters used is large as their values depend on the exercise intensity. Ideally in a good model these parameters should be far fewer and remain constant for all exercise intensities, hence characterizing the individual (23, 25).

In conclusion, just because a curve has good statistical fit it does not mean that this is significant if the curve is not constructed from physiologically proven principles. For example, fitting straight lines point to point would result in a perfect fit having no physiological significance. Marginal statistical improvement in the fit (i.e., by adding time delays) of an arbitrary curve also have no significance, bearing in mind the spread of the raw data in a single bout of exercise. Finally as time delays cannot be seen with any sort of clarity in raw data from a single response, and bearing in mind all of the methodological problems previously discussed and the lack of a proven physiological mechanism, we have no reason to believe such features exist. To quote (10) [see also (9)] “data reporting proven physiological mechanism, we have no reason to believe methodological problems previously discussed and the lack of a fit having no physiological significance. Marginal statistical does not mean that this is significant if the curve is not


29. Zakynthinaki MS, Stirling JR, Sillerø M, Sampedro J, Refoyo I. Obtaining the basic response pattern of physiological time series data: a
changes. This yields a "cardio-dynamically mediated" $\dot{V}O_2$ with physiologically relevant features, including those consequent from that after appropriate ensemble-averaging (see Ref. 5, breath variability, will necessarily yield "a different curve" (2) a portion of the early transient R decrease (4); where not, it is not that the delayed component is not there but that it is "smeared" by increased perfusion from other regions and/or transient hyperventilation. Its presence is physiologically justified: the transient alkalosis (1, 3), resulting from proton trapping as [phosphocreatine] decreases, retains CO$_2$ intramuscularly. When the $\varphi_1$–$\varphi_2$ transition cannot be clearly determined from R, a portion of the $\varphi_1$ response should not be allowed to influence the $\varphi_2$–$\tau$ estimation: this is a physiological control parameter not a parameter of convenience (6), as are the $\varphi_1$ and slow-component $\tau$s. Deleting a portion of the early response slightly greater than the real delay may influence the confidence of the $\varphi_2$–$\tau$ estimation; deleting too little will affect its value—a greater concern.

Also, we disagree with their assertion that parameter estimation from an individual response, i.e., including breath-by-breath variability, will necessarily yield "a different curve" (2) from that after appropriate ensemble-averaging (see Ref. 5, Figs, 1, 2). We do not dispute that such "noise" contains physiologically relevant features, including those consequent to pleural pressure variations associated with tidal volume changes. This yields a "cardio-dynamically mediated" $V_O_2$ response superimposed on the underlying kinetics; there is no equivalent in the muscle kinetics!

We, among others, have proposed physiological equivalents to the estimated intensity dependent response parameters. That these should "remain constant for all exercise intensities" (2) seems unjustified—the physiology does not! Furthermore, the authors neglect to note that our suggested alternative (6) to the common slow-phase characterization was cited as just one of the alternate means of producing such a response. That its physiological mechanism(s) have not been elucidated does not justify assertions that it is not there.

Would that Stirling and Zakynthinaki inform us how their no-delay(s) model might be mediated physiologically.

REBUTTAL FROM WHIPP

I expected the Stirling and Zakynthinaki Counterpoint (2) to provide alternative physiological explanations for the discernibly different oxygen uptake ($\dot{V}O_2$) kinetics at different exercise intensities.

Some of their points seem warranted: the lack of justification for an exponential phase ($\varphi$) 1 fit and the "slow-phase" exponential fit reflecting a process with a single time constant (7) and gain. But so many of their assertions demand challenge. For example, they state that the problems regarding the decrease of "R" as an indicator of what they term TD$_2$, "are due to trying to fit time-delayed phases to data with no such features." Well, there are such features! The $\varphi_1$–$\varphi_2$ transition often coincides with a time-delayed transient R decrease (4); that a "priming exercise can reduce [the slow components] magnitude with no discernible effect on the fundamental component" (8) does not suggest a different component’s existence. It only shows the effect on the subsequent kinetics of a change in the initial conditions of the human system.

That a "monoexponential characterization of the entire transient" is "no longer justifiable" (8) is insufficient proof of the non-existence of a phase before the time delay and its sudden switching on needs concrete proof. Such features need to be clearly observable in raw unaveraged data from a single bout of exercise (which is not the case) and suitable physiological mechanisms need to be found that are true time-delayed phases and

REFERENCES


REBUTTAL FROM STIRLING AND ZAKYNTHINAKI

This is not a "mathematical quibble over fitting strategies" (8), it is a description of serious errors in the 3/n-phase approach with major physiological implications, as a search for non-existent error-induced features will obviously be fruitless (10). The delayed component during moderate exercise and the evidence for a time-delayed slow component have been seriously challenged (5).

That a "monoexponential characterization of the entire transient" is "no longer justifiable" (8) is insufficient proof of the need for an additional time-delayed phase. It is incorrect that not implementing a delayed slow component "necessitates the process be established from the onset" as is the expectation of a distortion to "the phase-2 monoexponentially" (8) by a substantial slow component. These problems are all due to the 3/n-phase curve fitting procedure, other physiologically relevant functions (7, 6) have been perfectly fit.

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Figure 1, top and middle (8), does not present raw unaveraged data and hence is unsuitable for drawing physiological implications (5). The phase 1 is misleading due to the superposition of the model curve; the spread and amount of raw unaveraged data points in this region cannot be seen [numerous counter examples exist (2, 4, 6)]. Slow kinetics are easily observable; however, a time-delayed phase is not apparent (9). The connection between a delayed slow component and the "backing away from the simple linearity at higher intensities" (8) is not trivial or obvious, physiologically or mathematically, as the effect of forcing a system with a square wave or a ramp is different.

These physiological processes are obviously time dependent (1, 3) with certain features becoming apparent or emerging from the high-frequency oscillations with time. However to use time-delayed phases is an extremely strong condition to impose, as the nonexistence of a phase before the time delay and its sudden switching on needs concrete proof. Such features need to be clearly observable in raw unaveraged data from a single bout of exercise (which is not the case) and suitable physiological mechanisms need to be found that are true time-delayed phases and