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CORRESPONDENCE

Coming up for air

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The recent paper in *Journal of Experimental Biology* by Seibel et al. (2021) claims that a new term, the oxygen supply capacity (α), breathes new life into critical oxygen partial pressure (P_{crit}). Despite the authors' good intentions, their idea does not resuscitate the 88 year old concept of P_{crit} (Tang, 1933). It would be wonderful if the α-line were prescriptive and biologically meaningful across species and environmental conditions, but we suspect that it is not. We argue for what the data have told us for years: the relationship between any metabolic rate (MR) and P_{O_2} is not adequately described by straight lines.

We raise several problems with their overly simple linear model: maximum metabolic rate (MMR)=P_{O_2}×α. This linear line is anchored at the origin, must pass through any critical P_{O_2} (P_{crit}), has a single α value and passes through MMR.

While the authors claim the α-line can 'predict the maximum achievable MR at any P_{O_2}', this claim is misleading for three reasons. Foremost, the indefinitely long line cannot predict the maximum aerobic MR (i.e. $\dot{V}_{O_2,max}$) of the animal without knowing its metabolic scope. Second, the line is based on only one experimental data point (P_{crit}) that has associated error. If P_{crit} is based on standard metabolic rate (SMR) data, the point lies near the origin and therefore has a large leverage effect on the slope of the line. Small absolute errors in its position can create large absolute errors in MMR, in proportion to the animal's metabolic scope. Finally, real data for several species raise doubts that the line is straight.

Fry and Hart (1948) had a clear conceptual framework for investigating hypoxia tolerance in fish: '… the simplest and most direct methods of obtaining ecologically significant values of oxygen uptake are to measure the maximum rate over a series of varying oxygen tensions down to the asphyxia level, and to measure the standard rate over a range of tensions at which oxygen would not be the limiting factor even for the maximum rate'. This empirical approach is what Fred Fry envisaged for his 'Limiting Oxygen Concentration' (LOC) curve (Fry, 1947). In fact, reliable empirical data for MMR versus P_{O_2} with groups of fish exist (Claireaux and Lagardère, 1999; Claireaux et al., 2000) and these LOC curves, based on best-fit statistical relationships, were non-linear. Still needed are empirical data using single fish.

Unfortunately, the 'oxygen supply' concept (α_0) is not new, other than its name. Its units are identical to those used for 'conductance', a term defined and long-used by respiratory physiologists (Piiper et al., 1971) to represent the effectiveness of gas transport in each step down the oxygen cascade. 'Oxygen supply capacity' (α) would be the maximum conductance of the entire system from the environment to the mitochondrion, but its use places all levels of oxygen cascade into a black box, where we lose sight of what determines conductance at each level. Maximum conductance is influenced by individual conductances at all levels of the oxygen cascade, from ventilation of the gas exchange surface, to diffusion through the surface, oxygen binding to respiratory proteins and dissolved in plasma, convection by the cardiovascular system and diffusion through tissues to mitochondria where oxygen is finally consumed. Fundamentally, most of these conductances are non-linear with respect to P_{O_2}. Oxygen binding in blood, for example, is sigmoidal or hyperbolic, and mitochondrial kinetics are hyperbolic. Furthermore, the tissues supported at SMR (oxygen-sensitive internal organs) are different from those supported at MMR (aerobic red muscle), so the 'anatomy' of the oxygen cascade changes between rest and activity. Thus, we are not convinced that the mechanisms in the oxygen cascade remain identical at $P_{crit\text{-}SMR}$ and $P_{crit\text{-}MMR}$, an apparent requirement of the theory.

Sadly, Seibel et al. (2021) do not address the very reasonable criticisms of P_{crit} theory and methods (e.g. Wood, 2018; Cobbs and Alexander, 2018; Marshall et al., 2013). Also, they discourage examining data that depart from their model: 'Using the α-method, MR measurements below $P_{crit\text{-}SMR}$ are not diagnostic and, thus, are not relevant'. They dismiss attempts of other approaches to understand responses as 'purely descriptive' and imply that approaches to understand the entire MR versus P_{O_2} response curve 'may not have any functional relationship to available oxygen'. In particular, the regulation index (RI), a metric that evaluates the empirical ability of animals to regulate MR in relation to P_{O_2} (Mueller and Seymour, 2011), is dismissed as being devoid of underlying physiological mechanisms. Having discarded a need to consider the entire responses, they fail to recognize that their measure of $P_{crit\text{-}SMR}$ may not actually relate to SMR. For example, some species show a progressive MR decrease at high P_{O_2} (e.g. Fig. 2B of Seibel et al., 2021, showing data from Mueller and Seymour, 2011), so the MR at $P_{crit\text{-}SMR}$ would appear lower than SMR. The whole response could represent metabolic suppression in response to hypoxia. In fact, well laid out and rigorously tested methodological and analytical procedures demonstrate the real possibility of metabolic suppression and show that $P_{crit\text{-}SMR}$ can be interpolated from empirical data for MR versus P_{O_2} (Chabot et al., 2016, 2021; Claireaux and Chabot, 2016) rather than by selecting three points with the highest α values. Absent from Seibel et al. (2021) is the crucial validation that estimated P_{crit} values do indeed match those measured using reliable SMR determinations.

In conclusion, we feel Seibel et al. (2021) presented a theory trying to enforce itself onto real data. They cite Fry and Hart (1948) ('the worth of such data to the ecologist must ultimately depend on proof that they have real significance as values limiting the activity of the organism in nature') to justify their theory, but the equation of Seibel et al. (2021) lacks empirical realism. Indeed, forcing an equation relating MMR and P_{O_2} through the origin does not represent empirical data (Claireaux and Lagardère, 1999; Claireaux et al., 2000) in a biologically meaningful manner. Still, you can always draw a straight line through two data points, in this case a biologically meaningless intercept at the origin and a potentially

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subjective $P_{crit\text{-}SMR}$. Besides, MMR cannot be derived from such a line without prior knowledge of metabolic scope in normoxia.

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Response to 'Coming up for air'

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We (Seibel et al., 2021) proposed a novel method to quantify the oxygen supply capacity (α), which defines the maximum metabolic rate (MMR) that can be achieved at a given oxygen pressure. In their Correspondence article, Farrell et al. (2021) suggest that our method lacks 'empirical realism'. The core issue is whether the MMR is linearly related to P_{O_2} and whether that line intercepts the origin as required for the constancy of α, from which its predictive power derives. However, Farrell et al. (2021) overlooked the published derivation and validation of α, which is based on decades of empirical physiology and which demonstrates convincingly that α is constant from rest to maximum exertion (Deutsch et al., 2015; Seibel and Deutsch, 2020).

For a given species, α, calculated as the standard metabolic rate (SMR) divided by its critical P_{O_2} ($P_{crit\text{-}SMR}$), accurately predicts MMR measured at any P_{O_2} up to its critical P_{O_2} ($P_{crit\text{-}max}$; see Fig. 2D in Seibel and Deutsch, 2020). Thus, α is equal to both SMR/$P_{crit\text{-}SMR}$ and MMR/$P_{crit\text{-}max}$ and is effectively the slope of a straight line between those two endpoints that intercepts the origin (Fig. 1). Beyond $P_{crit\text{-}max}$, in hyperoxia, MMR plateaus (see Fig. 2B in Seibel and Deutsch, 2020). A non-linear relationship that begins and ends at identical α values would be highly improbable. The interpretation of some of this same data as curvilinear (Farrell et al., 2021) stems, at least in part, from the inclusion of measurements made at oxygen pressures beyond $P_{crit\text{-}max}$ (i.e. in the hyperoxic plateau). Thus, α does not typically change with oxygen or activity (Fig. 1) and can be used to predict MMR and aerobic scope.

The anatomy of the oxygen cascade does change between rest and activity, and some individual steps in the cascade appear non-linearly related to P_{O_2}. However, these non-linear steps do not preclude a linear relationship between MMR and inspired P_{O_2} (Seibel and Deutsch, 2020). Regardless of the underlying mechanism, Fig. 1 shows that MMR is linearly related to P_{O_2} for most species analyzed to date. Although there may be species and conditions for which α changes with activity or oxygen, such examples would not diminish the utility of α. Instead, they may reveal how α is acted upon by natural selection. For example, α may vary with swimming in species that ram ventilate, with depth in species that migrate vertically across oxygen and temperature gradients, or with size and life stage as circulatory systems develop.

Methodological issues may also influence the apparent shape of the MMR–P_{O_2} relationship. MMR measurement relies on a fish's willingness to swim during exercise protocols (Slesinger et al., 2019), which may vary with exertion and oxygen. Furthermore, because MMR declines in direct proportion to P_{O_2}, supposed 'normoxic' MMR measurements may be underestimates. Seibel et al. (2021) recommended that, when feasible, MMR be measured across a range of P_{O_2} values, including hyperoxia, to minimize our shared concern (Farrell et al., 2021) of extrapolating from 'one experimental data point … that has associated error'. Also, when feasible, MMR should be elicited by more than one protocol (e.g. chase and flume). Our method provides much-needed consistency for determining oxygen supply capacity directly and provides a means of predicting MMR and aerobic scope.

Farrell et al. (2021) are correct that MMR can't continue upward indefinitely with P_{O_2}. Instead, it plateaus at $P_{crit\text{-}max}$. A realistic estimate of $P_{crit\text{-}max}$, rather than aerobic scope as suggested by Farrell et al. (2021), is required to avoid over-estimates of MMR. $P_{crit\text{-}max}$ has been directly measured for numerous species but, more importantly, it can be approximated as the highest P_{O_2} that persists in a species' natural environment (i.e. air-saturation for most shallow, coastal species; Seibel and Deutsch, 2020).

Farrell et al. (2021) are concerned that α is a 'black box' that hides all relevant physiological mechanisms. However, this is true of all integrative physiological metrics, including SMR and aerobic

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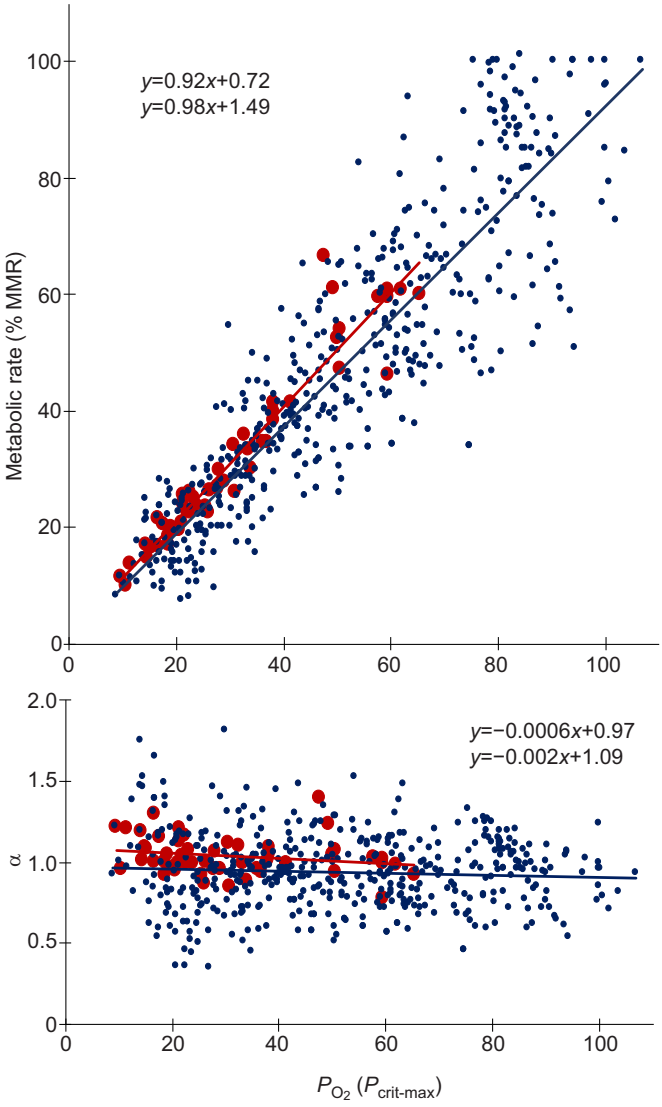

Solea solea (LeFrancois and Claireaux, 2003)
Rattus norvegicus (Arieli et al., 1976)
Scophthalmus maximus (Mallekh and Lagardère, 2002)
Gnathophausia ingens (Childress, 1968)
Homo sapiens (Fulco et al., 1998; Hochachka, 1985; and Wehrlin and Hallén, 2006)
Dicentrarchus labrax (Claireaux and Lagardère, 1999)
Sciaenops ocellatus (Esbaugh et al., 2021; Ern et al., 2016)
Spalax ehrenbergi (Arieli et al., 1977)
Chitala ornata (Tuong et al., 2018)
Anarhichas minor (Claireaux and Chabot, 2016)
Penaeus esculentus (Dall, 1986)
Jasus edwardsii (Crear and Forteath, 2000)
Salmo salar (Oldham et al., 2019)
Octopus bimaculoides (Seibel and Childress, 2000)
Fundulus heteroclitus (Reemeyer and Ries, 2019)
Argyrosomus japonicus (Fitzgibbon et al., 2007)
Cyclopterus lumpus (Ern et al., 2016)
Lepomis gibbosus (Crans et al., 2015)
Lepomis macrochirus (Crans et al., 2015)
Micropterus salmoides (Crans et al., 2015)
Ambloplites rupestris (Crans et al., 2015)
Chromis atripectoralis (Ern et al., 2017)
Gadus morhua (Claireaux et al., 2000)

Fig. 1. Maximum metabolic rate is linearly related to P_{O_2} between the critical partial pressures ($P_{crit\text{-}SMR}$ and $P_{crit\text{-}max}$, respectively) for standard and maximum rates. Top: standard metabolic rate (SMR) plotted at $P_{crit\text{-}SMR}$ (red, data from Seibel and Deutsch, 2020; n=52, 1 point per species) and maximum metabolic rate (MMR) plotted at measurement P_{O_2} for individual trials (blue, n≈400 points from 23 of the 52 species in Seibel and Deutsch, 2020; data extracted from published representative plots using webplot digitizer; species and their sources are listed). Data are expressed as percentages of $P_{crit\text{-}max}$ and MMR at $P_{crit\text{-}max}$, resulting in all species falling around the same line despite interspecific differences in the absolute values of both variables. $P_{crit\text{-}max}$ was estimated as the highest prevailing environmental P_{O_2} (air-saturation for most species; Seibel and Deutsch, 2020). Bottom: oxygen supply capacity (α=MMR/P_{O_2}), derived from the data in the top panel. Because all data are expressed as percentages, and because the relationship is linear, α is near 1 for all species regardless of P_{O_2} (i.e. MMR declines by 1% for a 1% decline in P_{O_2}).

scope, and does not diminish the utility of these metrics or the importance of the underlying mechanistic physiology. Rather, these 'black boxes' act to reduce inherent physiological complexity in order to understand relationships at different scales. The α is informative despite the complexity of the oxygen cascade, just as aerobic scope is informative despite incomplete knowledge of the specific oxygen requirements of the underlying processes (Farrell, 2016).

Farrell et al. (2021) state that we dismissed approaches that aim to understand the entire MR versus P_{O_2} response curve and that, having done so, we fail to recognize that our 'measure of $P_{crit\text{-}SMR}$ may not actually relate to SMR'. This indicates an important misunderstanding of our method. We are not measuring $P_{crit\text{-}SMR}$. We are measuring the oxygen supply capacity (α). We did compare $P_{crit\text{-}SMR}$ derived from α with that using other methods simply as a demonstration of its relative accuracy and precision. However, our method concerns only α and does not require that P_{crit} be measured at SMR because the P_{crit} measured for any rate provides the same information (α) from which the P_{crit} for any other rate (including SMR) can be calculated. For example, SMR could be independently determined and $P_{crit\text{-}SMR}$ can then be calculated as SMR/α, even if α was determined at MMR. The physiological changes that occur at P_{O_2} above P_{crit} are not relevant to the measurement of α, and statistical descriptions of the entire MR versus P_{O_2} trial apparently seek to answer a different question.

Furthermore, we do not 'discourage examining data that depart from [our] model', nor do we simply 'draw a straight line through two data points'. We determined oxygen supply for every P_{O_2} bin in 50 published trials. The highest value in each trial is the oxygen supply capacity (α) for that individual or species. The metabolic

rate divided by α is P_{crit} for that rate, whether standard, routine or maximum. Any P_{O_2} (up to $P_{crit\text{-}max}$) multiplied by α is the maximum metabolic rate that could be achieved at that P_{O_2}. Our theory, rather than 'trying to enforce itself onto real data', is derived from real data and provides a powerful tool for understanding how metabolism changes with oxygen and temperature. Our paper 'breathed new life into P_{crit}' by clarifying its biological significance as a measure of oxygen supply capacity.

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