Simulation of Steady-State Energy Metabolism in Cycling and Running

Supplementary materials: github.com/smnnlt/suppl-metasim
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Please cite as: Nolte, S., Quittmann, O.J. & Meden V. (2022). Simulation of Steady-State Energy Metabolism in Cycling and Running. *SportRχiv*.

ABSTRACT

Purpose: A mathematical model to describe the interplay of distinct metabolic rates during exercise was developed decades ago. Despite its use in endurance performance diagnostics, attempts to validate the model's assumptions and predictions on experimental data are rare. We here provide a comprehensive study for the steady state.

Methods: We rewrote the mathematical equations in the steady state and tested them on a data set of N = 101 individuals derived from four studies in cycling and running.

Results: The rewritten equations reveal a unique relationship between the ratio of the maximum oxygen uptake and the lactate accumulation rate, and the fractional utilization of oxygen uptake at the maximum lactate steady-state. Experimental data for running do not provide evidence that this relation holds. For cycling, the experimental evidence is less devastating but can also not be considered as convincing.

Conclusion: The simulation in its current form is not suitable for a practical use in performance diagnostics. Additional model layers and/or more precise methods of measurement may improve the model's performance, but require experimental validation.

All authors have read and approved this version of the manuscript. This article was last modified on January 20, 2022.

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INTRODUCTION

Performance in endurance sports depends to a large extent on the ability of an athlete's muscles to facilitate energy for contraction over an extended period (Bassett & Howley, 2000). There are three major paths of energy conversion, namely the phosphocreatine hydrolysis, the glycolytic system, and the oxidative phosphorylation (Sahlin, 2014). For moderate intensities which yield a metabolic steady-state, the net energy release from the phosphocreatine hydrolysis can be neglected. The metabolic state for such intensities can therefore be described by the interplay of the rate of oxidative phosphorylation, reflected in the rate of the volume of oxygen uptake per body weight ($\dot{V}O_2$), and the rate of energy released from the glycolytic system, reflected in the rate of lactate production ($\dot{c}La_{pr}$). In contrast to previous literature, which denoted rates of lactate metabolism (e.g. the just introduced production rate but also the removal rate) by $\dot{V}La$, we use $\dot{c}La$ instead. As these rates describe changes in concentration and not in volume, we believe that the abbreviation used here more adequately reflects their nature.

The highest intensity at which the rate of lactate production equals the rate of lactate removal ($\dot{c}La_{re}$), and therefore a metabolic steady-state can be maintained for a prolonged duration, is defined as the maximal lactate steady-state (MLSS) (Mader & Heck, 1986). In various disciplines of endurance sports the power (or velocity) measured at the MLSS was shown to be highly correlated with race performance (Faude et al., 2009). The gold-standard method for determining the MLSS consists of several 30-min constant load tests (Beneke, 2003). To estimate the MLSS via less costly measurements, alternative testing procedures, such as different concepts of lactate thresholds (LTs), were developed. One of these concepts is "the onset of blood lactate accumulation" (OBLA), defined as the intensity corresponding to a blood lactate concentration of 4 $mmol \cdot l^{-1}$ in a graded exercise test (Sjödin et al., 1982).

Back in 1984, Mader introduced a mathematical model to describe the relationship between $\dot{V}O_2$, $\dot{c}La_{pr}$ and $\dot{c}La_{re}$. It is based on the assumption, that the basic chemical activation patterns of energy metabolism are similar in between individuals and independent of the mode of exercise. Parts of this computational model are frequently referred to as the simulation of steady-state energy metabolism. For its practical use an athlete's individual maximum rates of lactate accumulation ($\dot{c}La_{max}$) and oxygen uptake ($\dot{V}O_{2,max}$) have to be determined. Based on these input parameters the fractional utilization of $\dot{V}O_{2,max}$ at the MLSS as well as the power (or velocity) at the MLSS can be computed. In cycling, the calculated power at the MLSS based on measured $\dot{V}O_{2,max}$ and $\dot{c}La_{max}$ showed a good to very good reliability (Adam et al., 2015) and an acceptable agreement with the gold-standard method (Hauser et al., 2014; Weber, 2003). Furthermore, research in trained cyclists showed that

different training regimes result in specific adaptations in $\dot{V}O_{2,max}$ and $\dot{c}La_{max}$ but may result in similar improvements in calculated MLSS (Hommel et al., 2019). Therefore, the computational approach may allow to determine how a certain alteration in MLSS can be explained by adaptations in $\dot{V}O_{2,max}$ and/or $\dot{c}La_{max}$. Even though the modelling approach is frequently used in research and practice, there are several inconsistencies regarding the mathematical expressions, the justification of assumptions, and the use of physiological constants. Furthermore, attempts to compare model predictions with experimental data are rare.

Our goal is twofold. Firstly, we want to rewrite the established equations into forms which are more appropriate from a mathematical point of view. This will allow us to gain new insights into the relations between the model's parameters. Secondly, we want to combine data from different studies to discuss the advantages and limitations of the computational model to predict the MLSS based on two parameters of diagnostics. Our results have practical implications for the use of the computational model in diagnostics.

MODELLING

Oxygen Uptake

The activation of pulmonary oxygen uptake is generally believed to be regulated by the phosphorylation state within the muscle cell (Holloszy & Coyle, 1984). It has been argued that a Hill equation, which is a generalization of the Michaelis-Menten kinetic equation, can adequately describe $\dot{V}O_2$ for steady-state intensities (Barstow et al., 1994; Chance & Williams, 1955). Here the intracellular adenosine diphosphate concentration [ADP] acts as the activating force. Hence, we use the following formula to describe the steady-state activation of oxygen uptake (modified from Mader & Heck, 1986):

$$\dot{V}O_2 = \frac{\dot{V}O_{2,max}}{1 + \left(\frac{K_{ox}}{[ADP]}\right)^{n_{ox}}} \tag{1}$$

$\dot{V}O_{2,max}$ and $\dot{V}O_2$ have the dimension volume per time and mass and are usually given in $ml \cdot min^{-1} \cdot kg^{-1}$. $\dot{V}O_{2,max}$ has to be measured individually and sport-specifically in diagnostics (Millet et al., 2009). K_{ox} refers to the half-maximal activation constant of $\dot{V}O_2$. For $[ADP] = K_{ox}$ one finds $\dot{V}O_2 = \dot{V}O_{2,max}/2$. When $\dot{V}O_2$ is plotted as a function of the logarithm of [ADP] (see Figure 1), $[ADP]=K_{ox}$ in addition is the point of inflection of the corresponding graph. Note that K_{ox} has the same dimension (number of particles per volume) as the ADP concentration and has been reported to take a value around 0.25 $mmol \cdot l^{-1}$ (Mader & Heck, 1986). On the logarithmic [ADP]

scale, the exponent n_{ox} sets the steepness of the $\dot{V}O_2$ activation curve around [ADP]= K_{ox}. The larger n_{ox} the steeper the curve (see Figure 1). Mader & Heck (1986) argued for a n_{ox} of 2.

It is barely possible to justify the details of the functional dependence of $\dot{V}O_2$ on [ADP] based on microscopic reaction kinetics. However, on a phenomenological level it appears to be reasonable that any sigmoidal line shape (on a logarithmic [ADP] scale) with two properly chosen parameters setting the point of inflection and the steepness might be sufficient for an adequate modeling of the relation between $\dot{V}O_2$ and [ADP]. Equation (1) is of this type. We emphasize that in contrast to the common practice (Hauser et al., 2014; Mader & Heck, 1986; Weber, 2003), it is advantageous to first divide the ADP concentration by K_{ox} before raising it to the power of n_{ox}. This way, the two line shape characteristics (namely, the point of inflection and the steepness) can be controlled independently by the two parameters. Furthermore, the argument of the power function becomes dimensionless as it is supposed to be.

Lactate production

In the steady-state, the lactate production (dimension number of particles per volume and time) was modeled by a Hill equation as well (Mader & Heck, 1986):

$$\dot{c}La_{pr} = \frac{\dot{c}La_{max}}{1 + \left(\frac{K_{La}}{[ADP]}\right)^{n_{La}}} \qquad (2)$$

$\dot{c}La_{max}$ is the maximal rate of lactate production and is usually given in $mmol \cdot l^{-1} \cdot s^{-1}$. We emphasize that it appears to be reasonable to give $\dot{c}La_{pr}$ in this unit as well as both are lactate production rates. This has to be contrasted to the earlier literature (Hauser et al., 2014; Mader & Heck, 1986; Weber, 2003) in which $\dot{c}La_{pr}$ was given with respect to minutes instead of seconds. This way we avoid any factors of 60. It is important to note that the $\dot{c}La_{max}$ appearing in Eq. (2) stands for a theoretical maximal rate of lactate production in the muscle cell. By contrast, the experimentally determined maximal rate of lactate production is based on exercise-induced alterations in capillary blood lactate concentration and thus is referred to as the maximal lactate accumulation rate (Quittmann et al., 2018; Quittmann, Appelhans, et al., 2020). Beside the fact that the lactate that has been produced in the muscle has to diffuse into the blood (which can be described by a Bateman-function) (Bateman, 1910; Beneke et al., 2005), the blood lactate concentration is affected by its simultaneous production and removal that occurs in various organs (van Hall, 2010). However, the skeletal muscle appears to be the most important effector of the blood lactate concentration (van Hall, 2010). Hence, the experimentally determined $\dot{c}La_{max}$ provides an adequate estimation of the theoretical maximal lactate production rate. From now on we do no longer distinguish between the two.

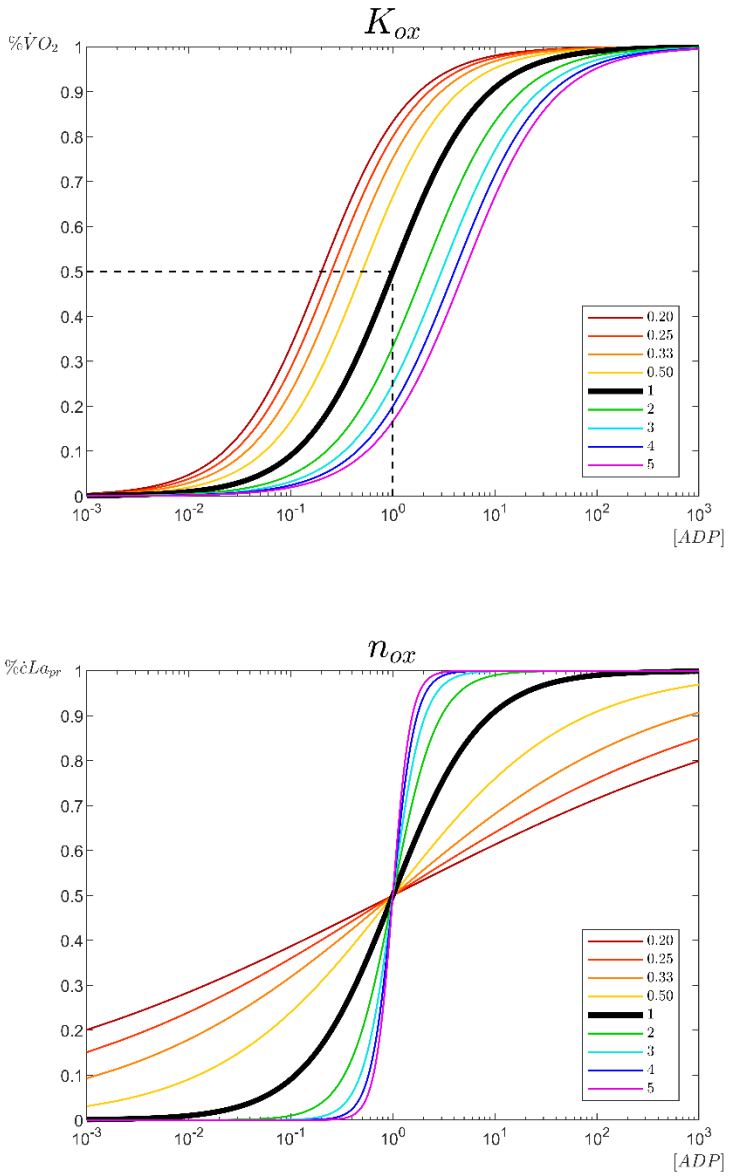

Figure 1. Schematics of the effect of the half-maximal activation constant (K_{ox}) and the exponent (n_{ox}) on the regulation of oxygen uptake by intracellular [ADP]. K_{ox} defines the ADP concentration at which half the maximal oxygen uptake is reached. This coincides with the point of inflection of the relation between oxygen uptake and ADP concentration. n_{ox} defines the steepness of this relationship. K_{ox} and [ADP] are both given in mmol·l^{-1}. See Equation 1. In the upper plot n_{ox} is set to 1, whereas in the lower plot K_{ox} = 1 mmol·l^{-1}. Note the logarithmic [ADP]-axis scale.

$\dot{c}La_{max}$ has to be determined individually and sport-specifically in diagnostics (Quittmann, Schwarz, et al., 2020). K_{La} in Eq. (2) is the half-maximal activation constant (point of inflection on a logarithmic scale) of the lactate production, which is around 1.1 $mmol \cdot l^{-1}$ (Mader & Heck, 1986). The glycolysis is believed to be activated by the product of the ADP concentration and the intracellular concentration of adenosine monophosphate. As the equilibrium constant of the adenylate kinase reaction is near 1 (Veech et al., 1979), it is reasonable to set $n_{La} = 3$. Concerning the details of the line shape of Eq. (2) the same caveats as put forward in connection with Eq. (1) hold. The relationships between intracellular [ADP] and the activation of lactate production and oxygen uptake are illustrated in Figure 2.

Lactate removal

As mentioned earlier, lactate removal occurs via lactate oxidation and gluconeogenesis in various tissues (van Hall, 2010). In the presence of high lactate concentrations, the rate of lactate removal $\dot{c}La_{re}$ was seen to be linearly dependent on the oxygen uptake (Donovan & Brooks, 1983) with a constant of proportionality k_{re}.

$$\dot{c}La_{re} = k_{re} \cdot \dot{V}O_2 \tag{3}$$

The constant has the dimension number of particles times mass per volume squared. As argued later in detail, k_{re} might be sport-specific. In previous literature, k_{re} has been defined as the ratio of a lactate-equivalent and the corresponding relative distribution volume. A wide variety of values has been reported for both these parameters in the literature (Mader, 1984, 1994, 2003; Mader & Heck, 1986, 1991; Weber, 2003). In particular, the k_{re} value of 0.02049/0.4 $mmol \cdot kg \cdot l^{-1} \cdot ml^{-1}$ = 0.051225 $mmol \cdot kg \cdot l^{-1} \cdot ml^{-1}$, which has been used in most of the recent research, is originally based on a misinterpretation of the literature by Weber (2003). One can furthermore criticize that this parameter is given up to per mill precision which suggests an accuracy which cannot be substantiated. In our approach, we will view k_{re} as a single constant instead of breaking it up in different factors. We will furthermore use it as a fitting parameter to properly describe measured data by the mathematical formulas derived from the model.

For intensities below the MLSS with corresponding lower values of the lactate concentration, the actual $\dot{c}La_{re}$ is equal to $\dot{c}La_{pr}$ and thus lower than with fixed k_{re}. Therefore, Eq. (3) only provides an upper bound for the lactate removal rate for intensities below the MLSS.

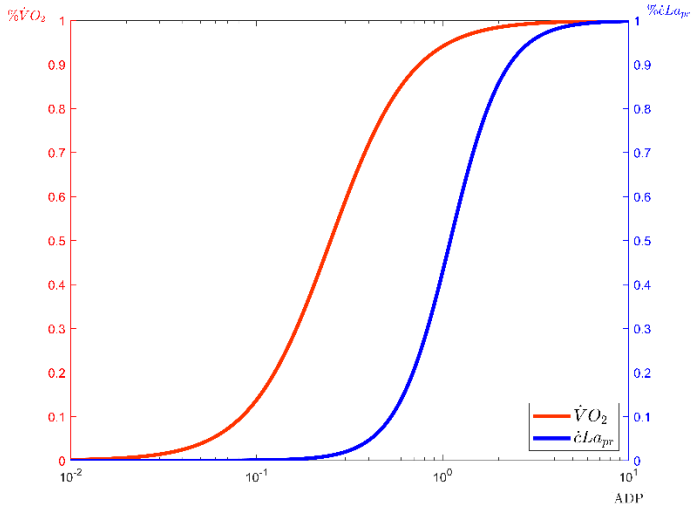

Figure 2. Schematics of the activation of oxygen uptake and lactate production by means of intracellular [ADP]. The dependence of $\dot{V}O_2$ on [ADP] (given in mmol·l^{-1}) was computed for K_{ox} = 0.25 mmol·l^{-1} and n_{ox} = 2. For $\dot{c}La_{pr}$, a K_{La} of 1.1 mmol·l^{-1} and n_{La} = 3 was used. With increasing [ADP], $\dot{V}O_2$ displays an earlier and less steep activation when compared to $\dot{c}La_{pr}$. Note the logarithmic [ADP]-axis scale.

Net lactate accumulation

The net accumulation rate of lactate $\dot{c}La_{net}$ is defined as the difference between $\dot{c}La_{pr}$ and $\dot{c}La_{re}$

$$\dot{c}La_{net} = \dot{c}La_{pr} - \dot{c}La_{re} \quad (4)$$

The MLSS is determined by the point at which $\dot{c}La_{net}$ vanishes. In a further step to access fat metabolism, a negative $\dot{c}La_{net}$ is assumed to display a lack of pyruvate (Mader & Heck, 1986). Therefore, the minimum of $\dot{c}La_{net}$ (or accordingly the maximum of the lack of pyruvate) is believed to represent the intensity of maximal absolute fat oxidation. We here do not further dwell on this.

Combining the formulas

To allow for a more transparent approach we normalize the rates appearing in the above equations to the corresponding maximal values $\dot{V}O_{2,max}$ and $\dot{c}La_{max}$, respectively. We, e.g., take

$$\%\dot{V}O_2 = \frac{\dot{V}O_2}{\dot{V}O_{2,max}} \quad (5)$$

and analogous for all the other rates. This way we only have to deal with dimensionless rates which is advantageous from a mathematical point of view. Solving in Eq. (1) for [ADP] and substituting this in Eq. (2), we obtain an expression for the normalized $\dot{c}La_{net}$ as a function of the normalized $\dot{V}O_2$:

$$\%\dot{c}La_{net} = \left(1 + \left(\frac{K_{La}}{K_{ox}} \cdot \left(\frac{1 - \%\dot{V}O_2}{\%\dot{V}O_2} \right)^{\frac{1}{n_{ox}}} \right)^{n_{La}} \right)^{-1} - \left(\frac{\dot{V}O_{2,max}}{\dot{c}La_{max}} \right) \cdot k_{re} \cdot \%\dot{V}O_2 \qquad (6)$$

$\%\dot{c}La_{net}$ is given as the difference between a function which strongly increases for $\%\dot{V}O_2$ approaching 1 and a linear function (see Fig. 3). The strongly increasing term is determined by the ratio K_{La}/K_{ox} and by both exponents n_{ox} and n_{La}. The linear term is parameterized by the ratio $\dot{V}O_{2,max}/\dot{c}La_{max}$ and the constant k_{re}.

As the activation patterns of oxygen uptake and glycolysis are assumed to be similar both, for a given individual performing different endurance sports as well as between individuals, the parameters K_{La}/K_{ox}, n_{ox}, and n_{La} are fixed. Typical values used in the past were given above. According to this reasoning the only remaining two parameters of the dependence of $\%\dot{c}La_{net}$ on $\%\dot{V}O_2$ are k_{re} and the ratio $\dot{V}O_{2,max}/\dot{c}La_{max}$. Accordingly, as $\%\dot{c}La_{net}$ in Eq. (6) is set to zero, determining the MLSS, the corresponding $\%\dot{V}O_2$ in the MLSS is a function of those two parameters only as well. In particular, $\dot{V}O_{2,max}$ and $\dot{c}La_{max}$ do not enter individually but only via their ratio. Assuming that k_{re} is the same for all individuals, athletes with the same ratio of these standard parameters of diagnostics will have the same percentage of oxygen uptake in the MLSS with respect to their individual $\dot{V}O_{2,max}$. In other words, an athlete with a $\dot{V}O_{2,max}$ of 70 $ml \cdot min^{-1} \cdot kg^{-1}$ and a $\dot{c}La_{max}$ of 0.70 $mmol \cdot l^{-1} \cdot s^{-1}$ will have the same $\%\dot{V}O_2$ at the calculated MLSS as an athlete with a $\dot{V}O_{2,max}$ of 60 $ml \cdot min^{-1} \cdot kg^{-1}$ and a $\dot{c}La_{max}$ of 0.60 $mmol \cdot l^{-1} \cdot s^{-1}$, since their ratio $\dot{V}O_{2,max}/\dot{c}La_{max}$ is equal to 100 $ml \cdot l \cdot s \cdot min^{-1} \cdot kg^{-1} \cdot mmol^{-1}$. However, the absolute intensity (in terms of the velocity and/or the power) will be different for both individuals. To the best of our knowledge, this important insight regarding the dependence of the $\%\dot{V}O_2$(MLSS) on the ratio $\dot{V}O_{2,max}/\dot{c}La_{max}$ has not yet been emphasized, even though it is a mathematical consequence of the established equations used to model the glycolytic and the oxidative system, which we here only present in a mathematically more appealing form. This insight can be used for a stringent testing of the model's predictions (see below).

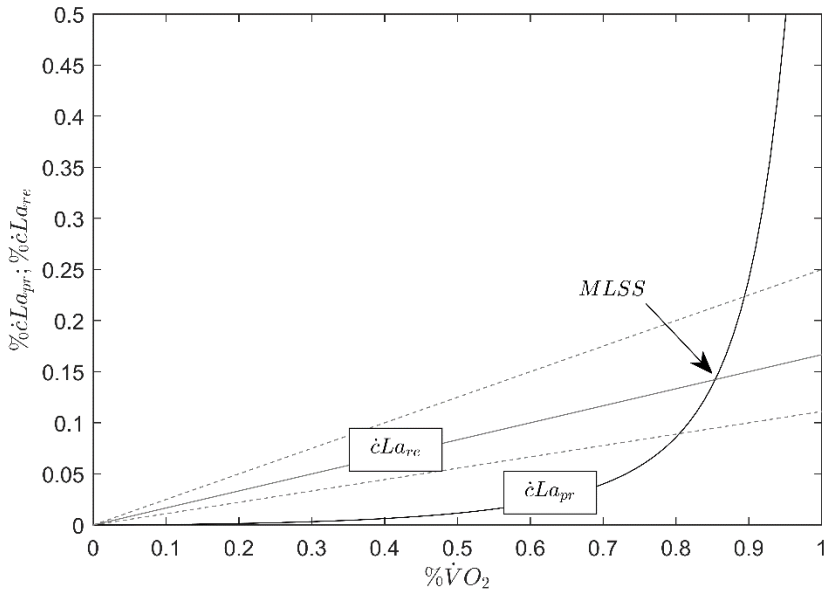

Figure 3. Graphical representation of $\%\dot{c}La_{net}$. According to Eq. (6) $\%\dot{c}La_{net}$ is the difference between a strongly increasing ($\dot{c}La_{pr}$) and a linear term ($\dot{c}La_{re}$). Constants of $\dot{V}O_2$ and $\dot{c}La_{pr}$ activation are chosen according to the text. The solid $\dot{c}La_{re}$ line illustrates lactate removal for an exemplary k_{re} of 0.1 mmol·kg·l^{-1}·ml^{-1} and a $\dot{V}O_{2,max}/\dot{c}La_{max}$ of 100 ml·l·s·min^{-1}·kg^{-1}·mmol^{-1}, dashed lines are these values ±33%. The crossing point of $\dot{c}La_{pr}$ and $\dot{c}La_{re}$ displays the relative intensity at the MLSS. According to the model, a higher k_{re} or a higher ratio $\dot{V}O_{2,max}/\dot{c}La_{max}$ lead to a MLSS at a higher intensity and vice versa.

Setting the right-hand side of Eq. (6) to zero for determining the $\%\dot{V}O_2$(MLSS) does not have a closed analytical solution. To calculate the $\%\dot{V}O_2$(MLSS), the zero has to be determined numerically by using approximation methods in computer software. Note that if $\dot{c}La_{max}$ in Eq. (6) is given in mmol·l^{-1}·s^{-1}, previously applied values for k_{re} (see section lactate removal) will have to be divided by 60 to ensure proper units. To indicate how the position of the MLSS depends on k_{re}, in Fig. 3 we show the second addend of Eq. (6) for three different values of k_{re}.

METHOD

We searched the literature for studies in which the $\dot{V}O_{2,max}$, the $\dot{c}La_{max}$, and the power or the oxygen uptake at the MLSS were measured in a single group of athletes. As studies in which the MLSS is determined according to the gold-standard method of constant load tests are rare, we also considered data from publications in which alternative estimates of the MLSS (LT, OBLA, etc.) were employed. Since alternative measures can only approximate the MLSS, this may be a source of minor deviations between predicted and measured data (see discussion). The criterion which substantially limits the number of appropriate studies to a few

is that $\dot{c}La_{max}$ has barely been determined experimentally. Individual $\dot{V}O_{2,max}$, $\dot{c}La_{max}$, and $\%\dot{V}O_2$(MLSS) data were extracted from these studies.

As modes of endurance exercise, we considered cycling and running. For cycling studies, in which only the power output at the MLSS was measured, $\%\dot{V}O_2$(MLSS) was estimated using additional data of body weight (bw) employing a linear relationship between the $\%\dot{V}O_2$ and the power (Mader & Heck, 1991):

$$\%\dot{V}O_2(\text{MLSS}) = \frac{\frac{P(\text{MLSS})\cdot CE}{bw} + \dot{V}O_{2,rest}}{\dot{V}O_{2,max}} \quad (7)$$

CE denotes the absolute cycling efficiency (absolute rate of oxygen uptake needed to produce the energy for 1 W of power) and was set to 11.7 $ml \cdot min^{-1} \cdot W^{-1}$ (Mader & Heck, 1991). $\dot{V}O_{2,rest}$ was assumed to be around 5 $ml \cdot min^{-1} \cdot kg^{-1}$ (Weber, 2003). For running studies, in which no constant load tests were performed, the $\%\dot{V}O_2$ at the OBLA was used as an estimate of $\%\dot{V}O_2$(MLSS). Individuals exhibiting a $\%\dot{V}O_2$(MLSS) smaller than 0.5 or greater than 0.98 were excluded from the analysis because of a high probability of testing errors.

As emphasized earlier, the mathematical model predicts a unique relationship between $\%\dot{V}O_2$(MLSS) and the ratio $\dot{V}O_{2,max}/\dot{c}La_{max}$. To check whether such a relationship can be found in the experimental data, we created a scatter plot of both quantities. We included the relationship predicted by the simulation model by fitting sport-specific constant of lactate removal. For this MLSS data fitting we used a non-linear least square routine by setting the right-hand side of Eq. (6) to zero. $\%\dot{V}O_2$ was chosen as the independent variable, $\dot{V}O_{2,max}/\dot{c}La_{max}$ as the dependent variable and k_{re} as the coefficient (fitting parameter) with a starting value of 0.1 $mmol \cdot kg \cdot l^{-1} \cdot ml^{-1}$. All the other parameters of Eq. (6) were taken as given above. Fitting results are presented with the coefficient's 95% confidence interval (CI) as a measure of the quality of the fit. Fitting procedures and visualization were performed with R Version 4.1.2 and MATLAB 2021b. All code and raw data is available at https://github.com/smnnlt/suppl-metasim.

Results

We included a total of 4 studies that meet our criteria, with three performed in cycling and two in running. A total of N = 101 participants (n = 86 male, n = 15 female) were included into the statistical analysis. The studies used partly different methods to measure $\dot{V}O_{2,max}$ and $\dot{c}La_{max}$ as well as to determine the MLSS or equivalent estimates. The characteristics of the included studies are summarized in Table 1.

Table 1. Methods of determining the physiological parameters in the included studies.

reference	subjects	training status	$\dot{c}La_{max}$-determination	$\dot{V}O_{2,max}$-determination	MLSS/LT-determination	$\%\dot{V}O_2$(MLSS)-determination
Weber	19 (19m, 0f) cyclists	recreational to elite	15s-ST; t_{alac}: PPO -3,5%	RT: 2min @175-320W +25W/30s	CLT; 20min; no significant rise in [La] in last 10min	unclear
Hauser et al.	13 (13m, 0f)	untrained to well-trained	15s-ST; t_{alac}: PPO -3,5%	RT: 2min @50W +25W/30s	CLT: 30min; Δ[La] ≤0.05mmol·l^{-1}·min^{-1} for last 20min	calculated from P(MLSS) using Eq. (7)
Quittmann et al. (b)	44 (29m, 15f) runners/ triathletes 1 excluded	recreational to well-trained	100m-ST; t_{alac}: interpolated from sprinting time	RT: 2min, @2.8m·s^{-1} +0.15m·s^{-1}/30s 1% grade	GXT: 2m·s^{-1} +0.4m·s^{-1}/5min, 30s break, 1% grade; LT: v([La]=4mmol·l^{-1})	measured during GXT
Quittmann et al. (a)	25 (25m, 0f) runners/ triathletes	well-trained	100m-ST; t_{alac}: interpolated from sprinting time	RT: 2min @2.8m·s^{-1} +0.15m·s^{-1}/30s	CLT: 30min; Δ[La] ≤0.05mmol·l^{-1}·min^{-1} for last 20min	measured during CLT

$\dot{c}La_{max}$=maximum lactate accumulation rate; $\dot{V}O_{2,max}$=maximum oxygen uptake; MLSS=maximal lactate steady-state; LT=lactate threshold; ST=sprint test; t_{alac}: end of alactic time interval; PPO= peak power output; RT=ramp test; CLT=constant load test; GXT=graded incremental exercise test

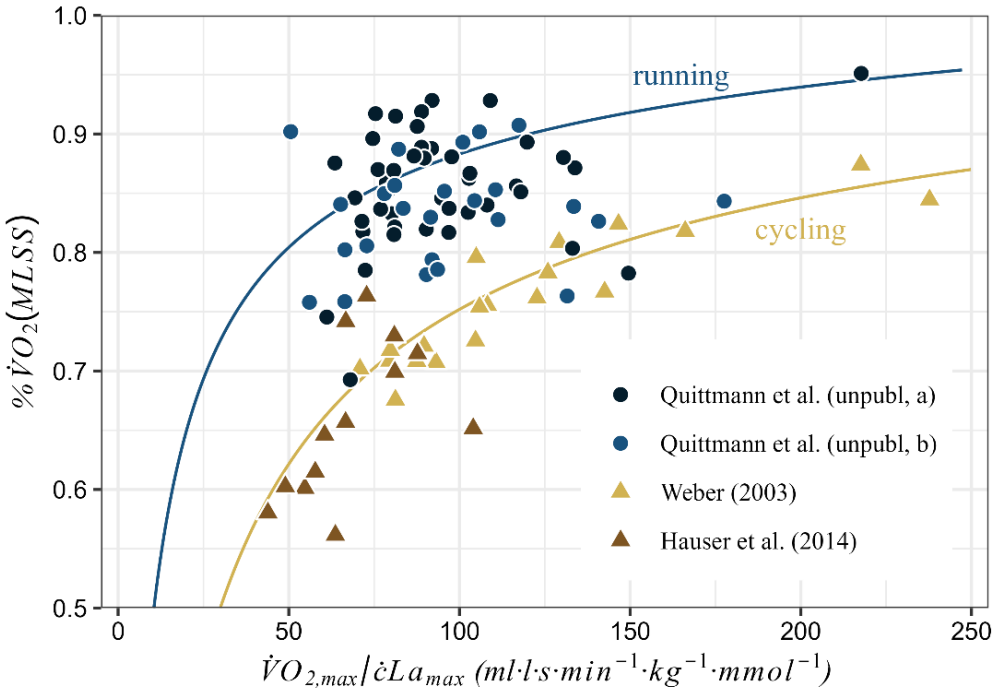

Figure 4. Scattered plot of $\%\dot{V}O_2$(MLSS) against $\dot{V}O_{2,max}/\dot{c}La_{max}$ for all individuals included into the analysis. Circles represent running data, triangles stand for cycling data. Solid lines represent results from the computation with constant of lactate removal fitted for each exercise type.

In Fig. 4 individual data of $\%\dot{V}O_2$(MLSS) is plotted against $\dot{V}O_{2,max}/\dot{c}La_{max}$. The fitting procedure revealed a k_{re} of 0.0471 mmol·kg·l^{-1}·ml^{-1} ([0.0442 0.0506] 95% CI) for cycling and 0.1347 mmol·kg·l^{-1}·ml^{-1} ([0.1208 0.1521] 95% CI) for running. Particularly for running exercise the data reveals a high degree of spreading. We noticed that the PhD thesis of Hauser on cycling (Hauser, 2013) contained data for more individuals than the publication of Hauser et al. (2014). Unfortunately, the data are not completely given in a table of the PhD thesis. Visual inspection of the corresponding plots leads us to conclude that including all the data of the PhD thesis the spreading would be significantly enhanced also for cycling. For both exercise types there is a lack of data for very small and very large values of $\dot{V}O_{2,max}/\dot{c}La_{max}$. These missing values at the ends of the spectrum, make it hard to judge whether or not the model with its characteristic line shape for the dependence of $\%\dot{V}O_2$(MLSS) on $\dot{V}O_{2,max}/\dot{c}La_{max}$ provides a reliable description (see the lines in Fig. 4 obtained for two different k_{re}). In other words, the displayed data, in particular those for running, can obviously also be fitted by functions other than the one resulting from the zero of Eq. (6), e.g., a linear relationship.

Discussion

Our mathematical rewriting reveals that the simulation of steady-state energy metabolism predicts a unique relationship between $\dot{V}O_{2,max}/\dot{c}La_{max}$ and $\%\dot{V}O_2$(MLSS). However, available experimental data do not provide clear evidence for this. The observed deviations from the predicted relationship can be attributed to either an insufficient theoretical framework (quality of the model) or an inaccurate assessment of the physiological parameters (quality of the measurements).

Quality of the model

The available experimental data questions the practical value of the simulation of steady-state energy metabolism in its present form. Even when employing the best reasonable diagnostic methods - such as in (Quittmann et al., unpubl. a) for running - the predicted relationship cannot be validated with the empirical data. For cycling the situation is less devastating but considering data of Hauser's PhD thesis (Hauser, 2013) we conclude that no convincing experimental evidence of the predicted relation can be given. The deviations between predicted and measured $\%\dot{V}O_2$(MLSS) make it impossible to reasonably judge the model's assumptions.

A reasonable explanation for the model's shortcoming lies in its simplicity. For example, the model assumes a fixed rate of lactate removal. Assuming that differences in active muscle mass influence the rate of lactate removal, we adjusted the model by using a sport-specific k_{re}, while it seems reasonable that this parameter also differs between individuals. Differences among individuals in k_{re} might be influenced by lactate transport capabilities, concentrations of gluconeogenesis key enzymes or levels of peripheral capillarization and blood flow (Gladden, 2000). This would be in line with observations in rats and humans that the lactate removal rate is sensitive to training stimuli (Donovan & Brooks, 1983; Donovan & Pagliassotti, 1990; Phillips et al., 1995). Since diagnostic methods to approximate the rate of lactate removal on a cellular level are currently lacking, these assumptions can neither be validated nor be incorporated into the simulation model for a practical use.

Inaccurate modelling constants and unincorporated physiological features may as well lead to the large deviations between predicted and measured data. This holds in particular as it is difficult to justify both the detailed line shape of the rate of oxygen uptake and lactate production (Hill equation) as well as the precise values of the parameters based on microscopic considerations. This is, e.g., indicated by the change of the parameter values in the literature over time. It might be tempting to not only fit the constant of lactate removal k_{re}, as we did, but to fit (a selection of) the other parameters of the model (K_{ox}, n_{ox}, K_{La}, n_{La}) as well.

Similarly, new layers could be incorporated into the model, e.g. for example to account for the role of Magnesium or the pH-level in the energy metabolism.

However, an extended model with a multi-parameter fit should be treated with caution: Besides the general question of the mathematical stability of such multi-parameter fits one should keep in mind that the more free parameters of a model are fitted, the less insights can be gained from the modeling itself. Or, as the famous mathematician, physicist, and computer scientist John von Neumann used to say, "With four parameters I can fit an elephant, with five I can make him wiggle his trunk" (Dyson, 2004, p. 297). To add additional layers to the existing model is challenging, as experimental data does not provide evidence that even the assumptions of the simple model evaluated in this study hold true in practice.

Quality of measurements

The simulation model is based on assumptions on a cellular level. As it is necessary for its practical use in diagnostics, it aims to also work on a whole-body level, assuming that current methods of measurement sufficiently approximate parameters of cellular energy metabolism. Despite a reported measurement error of up to ~5% (Katch et al., 1982; Vickers, 2003), ramp tests to measure $\dot{V}O_{2,max}$ are widely recognized as valid (Howley et al., 1995). Measurement methods for the model's other input parameter, $\dot{c}La_{max}$, demonstrated high reliability (Adam et al., 2015; Quittmann, Schwarz, et al., 2020), but lack validation. Similarly, only one of the studies presented here measured oxygen uptake during constant load tests at the maximum lactate steady-state (Quittmann et al., unpubl. a). Therefore, the discrepancy between model and experiment might partly be attributed to imprecise measurements.

However, to have practical relevance for performance diagnostics and training, the model should at least perform well for the best-practice methods to determine the physiological parameter (i.e. when validated against the measured $\%\dot{V}O_2(MLSS)$). When such methods were used in running (Quittmann et al., unpubl. a), the model performed insufficiently, questioning the practical relevance of the simulation model as long as no other methods of measurement for the model parameters have been developed.

Conclusion

The simulation of steady-state energy metabolism aims to put different rates of metabolism into a mathematical relationship. We presented data showing that the predicted relationship between $\dot{V}O_{2,max}/\dot{c}La_{max}$ and $\%\dot{V}O_2(MLSS)$ cannot be observed in experimental settings. Large deviations between modelled and measured parameters occur even when the most accurate (practically possible) methods of measurements were used. Assuming that the

parameters can be measured with sufficient validity and accuracy, one is forced to conclude that the model is too simplistic and/or incorporates inaccurate assumptions. While the model may extend the knowledge of metabolic patterns during physical exercise on an educational level, the steady-state simulation of energy metabolism in its present form is not suitable for predicting diagnostic parameters. To validate modified or extended versions of the model, we encourage researchers to take the same steps as we did with rewriting the mathematical relationships and testing these against experimental data.

Contributions

All authors contributed to conception and design, acquisition, analysis and interpretation of data. All authors drafted and/or revised the article and approved the submitted version for publication.

Funding information

No funding was received in support of this research.

Data and Supplementary Material Accessibility

All data, code and figures can be found at https://github.com/smnnlt/suppl-metasim

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