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Estimating instantaneous energetic cost during non-steady-state gait

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Selinger JC, Donelan JM. Estimating instantaneous energetic cost during non-steady-state gait. *J Appl Physiol* 117: 1406–1415, 2014. First published September 25, 2014; doi:10.1152/japplphysiol.00445.2014.—Respiratory measures of oxygen and carbon dioxide are routinely used to estimate the body's steady-state metabolic energy use. However, slow mitochondrial dynamics, long transit times, complex respiratory control mechanisms, and high breath-by-breath variability obscure the relationship between the body's instantaneous energy demands (instantaneous energetic cost) and that measured from respiratory gases (measured energetic cost). The purpose of this study was to expand on traditional methods of assessing metabolic cost by estimating instantaneous energetic cost during non-steady-state conditions. To accomplish this goal, we first imposed known changes in energy use (input), while measuring the breath-by-breath response (output). We used these input/output relationships to model the body as a dynamic system that maps instantaneous to measured energetic cost. We found that a first-order linear differential equation well approximates transient energetic cost responses during gait. Across all subjects, model fits were parameterized by an average time constant (τ) of 42 $\pm$ 12 s with an average R^2 of 0.94 $\pm$ 0.05 (mean $\pm$ SD). Armed with this input/output model, we next tested whether we could use it to reliably estimate instantaneous energetic cost from breath-by-breath measures under conditions that simulated dynamically changing gait. A comparison of the imposed energetic cost profiles and our estimated instantaneous cost demonstrated a close correspondence, supporting the use of our methodology to study the role of energetics during locomotor adaptation and learning.

energetics; gait; adaptation; indirect calorimetry; metabolic cost

STEADY-STATE measurements of metabolic energetic cost have provided valuable insight into why and how we walk the way we do. Energetic cost, in this context, refers to the input energy required to power the cellular processes underlying the body's movement. This energy is liberated from glucose, fats, and other stored foodstuffs in a reaction that requires oxygen and produces carbon dioxide (2). Consequently, energetic cost is typically measured indirectly by quantifying the oxygen and carbon dioxide in respiratory gases (1, 18). These measurements have demonstrated that we select the most fundamental characteristics of our gait—such as speed, step frequency, and step width—so as to minimize energetic cost per distance travelled (4, 5, 8, 9, 19, 25, 31, 37, 38, 42). Cost measurements have also allowed the quantification of energetic penalties imposed by various gait disabilities, and the evaluation of the effectiveness of rehabilitation interventions at mitigating these added costs (5, 37, 38). Equipment and wearable devices, be it backpacks (12, 17), prosthetics (27, 43), orthoses (10, 26), or running shoes (6), have been assessed, iteratively designed, and ultimately improved based on cost measurements.

The relationship between the body's instantaneous energy demands (instantaneous energetic cost) and that measured from respiratory gases (measured energetic cost) is complicated. Consider, for example, oxygen consumption measured at the mouth. Muscles meet their instantaneous energy demands for force generation using ATP, a form of stored energy. While ATP is immediately replenished using another form of stored energy, creatine phosphate, the mitochondrial dynamics that use oxygen and foodstuffs to replenish creatine phosphate are rather slow (7, 24, 32). There are still further delays before mitochondrial oxygen consumption is reflected in respiratory gases due to blood circulation from muscle to lungs (14), oxygen exchange between the blood and the lungs, and then lung ventilation itself. The relationship between instantaneous and measured cost cannot be determined by simply adding up these component time delays because blood gases are under tight neural control (30), and these controllers impose their own dynamics. For example, rapid increases in ventilation are often seen at the onset of exercise (30), preloading the body in anticipation of future mitochondrial oxygen requirements. Consequently, energetic cost as measured at the mouth can occur in advance of any actual energy use by muscle. An additional complicating factor is the discrete nature of breathing: while muscles may be continuously consuming the body's oxygen, the lungs only replenish oxygen with each breath and each breath may be of drastically different volume. Irregularities in both depth and timing of breaths create noisy breath-by-breath estimates of energetic cost that do not reflect true fluctuations in muscle energy use (15, 22). In summary, the relationship between instantaneous and measured energetic cost is complicated by mitochondrial dynamics, body transit delays, and respiratory control mechanisms, and then further obscured by high breath-by-breath variability.

It is due to these complexities that energetic cost is traditionally only measured during long bouts of constant-intensity conditions. By discounting non-steady-state regions of cost measurements, the rate at which the oxygen is entering the body is allowed to reach equilibrium with the rate at which cellular processes are consuming it. By averaging over minutes of data, high breath-by-breath "noise" is overcome and the measured energetic cost then accurately matches the instantaneous energetic cost. While these processing techniques have served us well over the past century, they restrict the research questions that can be effectively answered. Long-duration steady-state conditions, such as those experienced on a treadmill, are the exception rather than the norm during real-world walking (3, 23). In truth, we are continually adjusting our gait to meet the demands of a changing environment, and the energetic cost under these real-world conditions is essentially unknown.

Here, we expand on traditional methods of assessing energetic cost with the primary purpose of developing a technique to estimate instantaneous energetic cost during non-steady-

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state gait. We first characterized the dynamic relationship between instantaneous and measured energetic cost. To accomplish this, we enforced known changes in instantaneous energy use (input)—by prescribing changes to subjects' walking speed and step frequency—and measured the respiratory responses in measured energetic cost (output; Fig. 1*A*). We then modeled the body as a dynamic system that maps instantaneous to measured energetic cost (Fig. 1*B*). Next, we used this model to test two approaches for estimating instantaneous energy use from respiratory measures. The inverse model approach is perhaps the most intuitive: the actual measured energetic cost is smoothed and then passed through the inverse of the identified model to produce an estimate of the instantaneous energetic cost (Fig. 1*C*). The forward model approach estimates instantaneous energetic cost as the input that when passed forward through the identified model produces an estimate of measured cost that best fits the actual measured energetic cost response (Fig. 1*D*). We have chosen to present both approaches, as each has distinct strengths and limitations, and for particular study designs, one may be better suited than the other.

METHODS

Simon Fraser University's Office of Research Ethics approved the protocol, and participants gave their written, informed consent before experimentation.

Enforcing rapid changes in instantaneous energetic cost. Ten adult subjects (body mass: 67.1 ± 6.0 kg; height: 173.7 ± 5.2 cm; mean ± SD) with no known musculoskeletal or cardiopulmonary impairments participated in these experiments. Subjects were instrumented with indirect calorimetry equipment (VMax Encore Metabolic Cart, ViaSys), and all walking was performed on an instrumented treadmill (FIT, Bertec, MA). To habituate subjects to the experimental set-up, they walked at a range of treadmill walking speeds (0.75, 1.00, 1.25, 1.5, and 1.75 m/s) for a minimum of 10 min at each speed (33, 35, 36). Subjects next completed a series of enforced rapid changes in gait. The treadmill speed (walking speed) and metronome frequency (step frequency) were rapidly and simultaneously increased or decreased using custom-written software (Simulink Real-Time Workshop, Mathworks) to evoke a step-like change in instantaneous energetic cost (Fig. 1*A*). We chose to not only alter speed, but also step frequency because people often take tens of seconds to adjust their step frequency to steady state following perturbations in treadmill walking speed (29, 35). Metronome frequency was set at the subjects' preferred step frequency at each speed, defined as the average step frequency during the final 3 min of walking in the habituation trials. Step frequency for an individual step was calculated as the inverse of the time between foot contact events, identified from the characteristic rapid fore-aft translation in ground reaction force center of pressure (34). The treadmill speed alternated between 6-min periods at a base speed of 1.25 m/s and 6-min periods above or below this base speed (1.5 or 1.75 m/s, and 0.75 and 1.00 m/s, respectively). This resulted in eight different changes or gait (conditions), including step-like changes up-to and down-from the nonbase speeds of 0.75, 1.00, 1.5, and 1.75 m/s. Speed presentation order was randomized. We designed these changes to have differing direction (increase or decrease in speed) and magnitude (absolute speed change of 0.25 or 0.50 m/s) to test if the identified energetic cost dynamics differed across conditions. To compensate for the variable nature of breath-by-breath measurements and to further control for order effects, we had subjects complete a second day of testing in which they repeated the enforced gait changes twice with a newly randomized order, giving us a total of three repeats for each of the eight conditions. Subjects walked for less than 2 h/day to reduce fatigue effects.

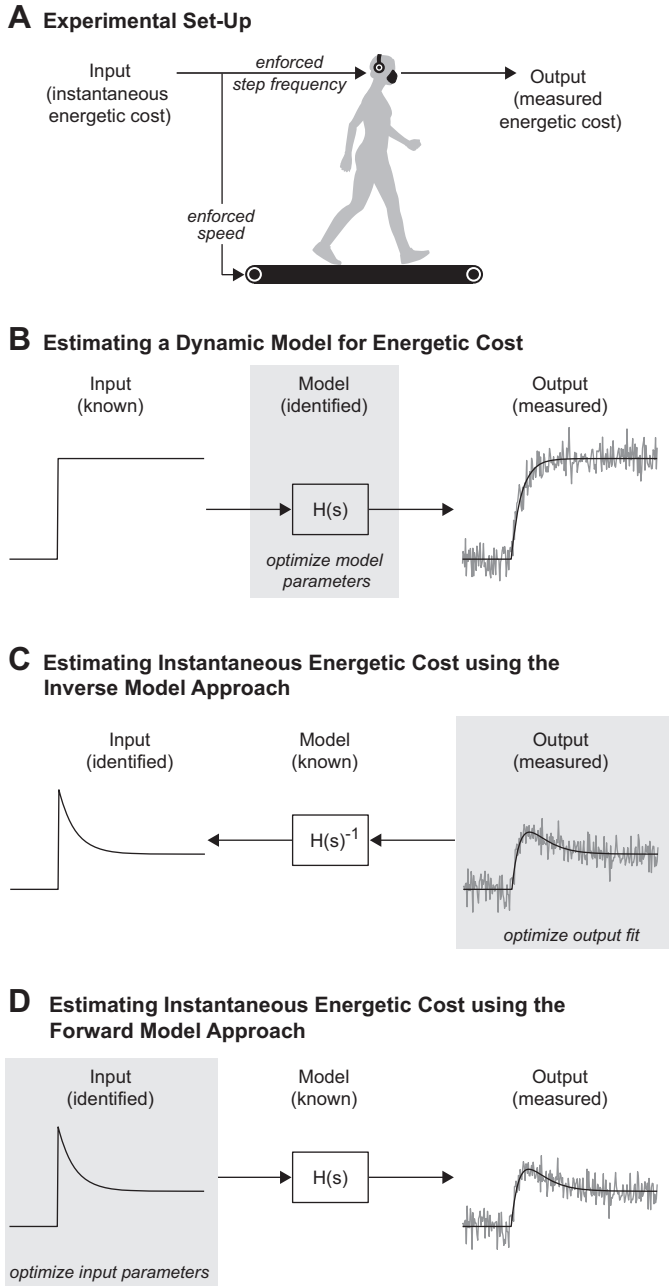

Fig. 1. Experimental design. *A*: experimental set-up. To evoke known changes in instantaneous energetic cost, subjects' walking speed (treadmill speed) and step frequency (metronome frequency) were enforced, and the resulting breath-by-breath energetic cost response was measured using indirect calorimetry. *B*: we then modeled the relationship between instantaneous energetic cost (input) and measured energetic cost (output). Using this model we estimated instantaneous energetic cost from the measured energetic cost response using 2 approaches. *C*: when using the inverse model approach, noisy output data were fit with a constrained polynomial, which was then passed through the inverse of our identified model to produce an estimate of instantaneous energetic cost. *D*: when using the forward model approach, we assumed the general shape of the input profile is known and described it by a set of parameters, which were then optimized so that the input profile, when runs forward through our identified model, generated an output profile that best fit our measured output. Gray shaded boxes have been used to highlight what parameters were optimized for each processing technique.

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Modeling the relationship between instantaneous and measured energetic cost. Whipp and colleagues have previously modeled ventilatory gas dynamics during non-steady-state cycling (16, 41). Given step-like changes in work rate, they found that for some conditions, the oxygen uptake and carbon dioxide output could be adequately described by first-order differential equations with an accompanying time delay. Here, we use their model as a starting point for our modeling efforts while recognizing that gas kinetics during walking and cycling are not constrained to have identical dynamics. We modeled the relationship between the instantaneous energetic cost (our input) and the measured cost (our output) as a single dynamic process comprising a time-delayed first-order linear ordinary differential equation. The mathematical representation of this model expressed in the frequency domain takes the form:

$$Y(s) = H(s)X(s), \tag{1}$$

where

$$H(s) = \frac{A}{\tau s + 1} e^{-\delta s}, \tag{2}$$

$X(s)$ is the input instantaneous energetic cost, and $H(s)$ is the output measured energetic cost. The parameter τ is a time constant characterizing the rate of change, A represents the amplitude of the change, and δ is a fixed time delay between energy use by muscle and that which we measure at the mouth. One may understand this model as a low-pass filter, where a rapid change in input (instantaneous energetic cost) will result in a slow and smoothed output response (measured energetic cost), and the amount of slowing and smoothing will increase with the magnitude of τ. Thus, if one were to see very quick changes in measured respiratory energetic cost, it would mean there was an exceptionally large and rapid change in the underlying instantaneous energetic cost. One might also understand this model in terms of its response to a step input, where the produced response would take the form of an exponential rise to steady state with a delay between the step input and the beginning of the response. The larger the value of τ, the longer the time required for the exponential rise.

To fit this model to our data, we analyzed 3 min of metabolic data prior to each gait change and 6 min of data following the gait change. The magnitude of each trial was normalized to unity to allow us to compare and average gait changes of differing magnitude and direction. To accomplish this normalization, we first subtracted the steady-state value before the gait change (the average of *minutes −3* to *0*) and then divided by the amplitude of the change (the average of *minutes 3* to *6*). Note that this normalization process does not affect any dynamics in the measured cost response. To solve for our unknown model parameters (τ and δ), we used weighted least-squares optimization to minimize the residuals between our model and measured data. The optimization uses the Levenberg-Marquardt algorithm and was implemented with MATLAB's *nlinfit* function. Due to prior normalization, best-fit amplitudes had a value of 1 ($A = 1$). To avoid known convergence issues with delayed dynamic models (21), we visually confirmed the accuracy of the fitted time delays. We assessed the goodness-of-fit of our estimated parameters by calculating the R^2 value between the model and our measured data. As a test of model sufficiency we also evaluated whether the addition of a second process, modeled as an additional time-delayed first-order linear differential equation, produced a better fit to our data.

To test whether the same model holds regardless of magnitude or direction, for each subject we first separately fit our model to all trials of the same direction (increase or decrease in speed) or magnitude (absolute speed change of 0.25 or 0.50 m/s) and tested for differences using a Student's paired *t*-test. For all tests, we accepted $P < 0.05$ as statistically significant. For each subject, we also performed cross validations by fitting the increase in speed trials with the model parameters solved from the decrease in speed trials (and vice versa), as well as the 0.25 m/s magnitude trials with the parameters solved from the 0.50 m/s magnitude trials (and vice versa).

Estimating instantaneous energetic cost during dynamically changing gait. We next assessed if the subject-specific models that we previously identified could be used to estimate instantaneous energetic cost from measured breath-by-breath energetic cost. To accomplish this, we had four representative subjects (body mass 69.5 ± 9.8 kg; height 175.2 ± 2.1 cm; mean ± SD) return for a third and fourth day of testing. Our goal was to enforce instantaneous energetic cost profiles that differed from those upon which our model was based. To design varying instantaneous energetic cost input profiles, we leveraged the fact that subject's energetic cost will increase as their step frequency deviates from preferred (20, 31). To quantify this relationship, on the third testing day our test subjects walked on the treadmill at 1.25 m/s for 6 min at nine enforced step frequencies that were at, above, and below preferred (0, ±5, ±10, ±15, ±20% deviation from preferred step frequency). For each enforced step frequency, we took an average of the final 3 min of steady-state energetic cost data, leaving us with nine data points that we then fit with a cubic polynomial (Fig. 2*B*). Note that during these steady-state regions, the average measured energetic cost is equivalent to the average instantaneous energetic cost, as the gas exchange measured at the mouth has reached equilibrium with the gas exchange occurring at the muscle tissue level.

Next, the solved polynomial was used to design step frequency profiles that, at constant treadmill speed of 1.25 m/s, would evoke three distinct input muscle energy use profiles: a step, a ramp, and an adaptation profile (Fig. 2*A*). The step profile, although the same shape as the original input profile on which we based our model, imposed different physical constraints on the subject, as treadmill speed was held constant and only step frequency was rapidly increased. The profile was designed to produce a final steady-state magnitude change of ~1 W/kg. The ramp profile was markedly different from that of the step in that step frequency was gradually increased over the course of minutes, again resulting in a final magnitude change of ~1 W/kg. The

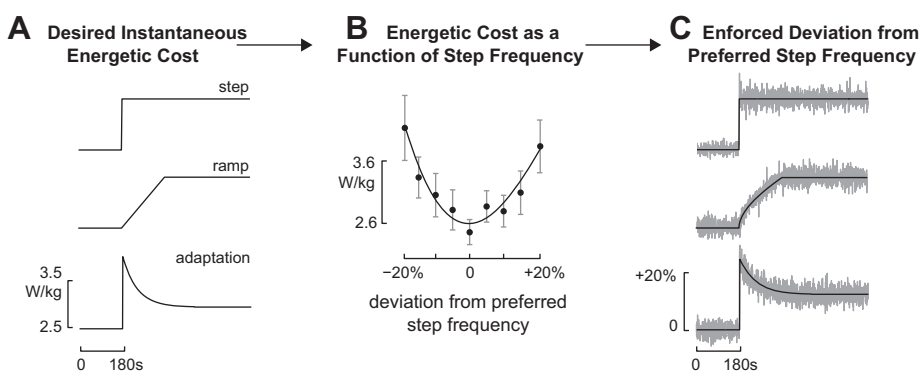

Fig. 2. *A*: we sought to enforce 3 differing but known input changes in instantaneous energetic cost. *B*: to identify what step frequency profiles would evoke these desired changes in instantaneous energetic cost, we identified each subject's relationship between energetic cost and deviation from preferred step frequency. *C*: using the solved relationship between energetic cost and step frequency, we designed step frequency profiles that would evoke our desired change in instantaneous energetic cost. The black line illustrates the step frequency commanded with a metronome, and the gray line illustrates the subjects actual step frequency.

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adaptation profile was designed to mimic a fast adaptation, where a subject's instantaneous energetic cost may initially step up in response to a perturbation and then rapidly decay. For our adaptation profile, cost was stepped up by ~1.3 W/kg and then decayed with a time constant of 60 s to a final steady state that was ~0.3 W/kg above the initial steady state. For each trial, treadmill speed was held constant at 1.25 m/s and the subject was asked to match their steps to the changing metronome frequency (Fig. 2*C*) while we measured energetic cost. The subjects completed three repeats for each input profile shape in randomized order on the fourth testing day.

We then used two different approaches to estimate instantaneous energetic cost from measured cost, each approach having distinct strengths and drawbacks. Recall that for each subject, we have solved for an individualized model that maps instantaneous to measured energetic cost. Therefore, the inverse of this model will do the opposite: map measured to instantaneous energetic cost. This is the basis of our inverse model approach (Fig. 1*C*). By passing a subject's measured energetic cost data through their inverse model, we can directly compute the instantaneous energetic cost. However, it was necessary to first smooth the measured data. Passing unsmoothed data through the inverse model, which functions like a high-pass filter, would effectively amplify high-frequency components in the measured signal, and these high-frequency components tend to be dominated by the breath-by-breath noise. Although a low-pass filter could be used to first attenuate noise, it would indiscriminately attenuate all high-frequency inputs, which may include rapid changes in instantaneous energetic cost that we are seeking to identify. Instead, to estimate the shape of the underlying energetic cost profiles, less the noise, we fit each trial of measured data with polynomials. A constrained least-squares optimization, implemented using MATLAB's *lsqlin* function, was used to solve for the best-fit polynomial parameters. Polynomial order was set such that no systematic pattern was observed in the residuals. The fitted curve was required to pass through the initial steady-state value (0 after normalization) at the point of perturbation and had to reach steady state (1 after normalization) in the last 3 min of the trial. These constraints are reasonable given that the prescribed step frequencies were at steady state during these regions. We did not constrain the initial slope of the polynomial allowing for rapid initial changes in the smoothed cost.

Our forward model approach can be used in situations where the experimenter has a good first approximation of the shape of the instantaneous energetic cost profile (Fig. 1*D*). This shape is described with a set of parameters that are then optimized so that the generated input profile, when run through the subject-specific model, produces an estimate of measured cost that best fits the actual measured energetic cost response. We used a Nelder-Mead Simplex method, implemented with MATLAB's *fminsearch* function, to solve for the optimal parameter values. For the step input, a single parameter was optimized: the time of onset of the step. For the ramp input, two parameters were optimized: the time of onset and the time of offset of the ramp, which together dictate the slope of the ramp. For the adaptation input, three parameters were optimized: the time of onset, the amplitude of the peak, and a decay constant. Note that the initial and final steady-state amplitudes were not optimized, as normalization fixes them at 0 and 1, respectively.

The inverse and forward model approaches where applied to individual repeats of the step, ramp, and adaptation profiles for each subject, as well as average profiles, which were produced by averaging the measured energetic cost data across the three repeats of a given profile prior to applying the inverse model or forward model approach. We also averaged data across all four subjects and again applied the inverse and forward model approach, this time using the average model parameters across our four subjects. In all cases, we assessed the goodness-of-fit between model-produced estimates of instantaneous energetic cost and the enforced instantaneous energetic cost profile by calculating an R^2 value for each approach.

RESULTS

We found that the dynamic relationship between instantaneous energetic cost and measured energetic cost could be modeled using a first-order linear ordinary differential equation (*Eq. 2*). We first tested whether this simple model held irrespective of the direction and magnitude of the change in gait. For each subject, we grouped across all trials of the same direction and found that the time constants describing both increases and decreases in speed were similar in magnitude and not statistically different ($P = 0.500$, Table 1). We found the same pattern when we grouped trials of the same magnitude and compared responses to 0.25 m/s speed changes to those induced by 0.50 m/s speed changes ($P = 0.094$, Table 1). When the increase in speed trials was fit with the time constant solved from the decrease in speed trials (and vice versa), and the 0.25 m/s magnitude trials with the time constant solved from the 0.50 m/s magnitude trials (and vice versa), R^2 values, averaged across subjects, remained above 0.85. Because the underlying dynamics did not depend strongly on the magnitude or direction of the change in gait, in subsequent analyses all trials for an individual subject are grouped together before fitting.

Our model described the dynamics of respiratory metabolic cost reasonably well for most subjects. Compared with the average response, the model accounted for 82–99% of the measured variability (Fig. 3). Adding a second dynamic process, modeled as an additional time-delayed first-order linear differential equation, did not appreciably improve our fits; no improvement was visually evident and on average only an additional 0.9% ± 1.0% of the variability was explained (mean ± SD).

Across all subjects, model fits yielded an average time constant τ of 41.8 ± 12.1 s (mean ± SD). This means that 95% of the response to a step-like change in input is completed within three time constants, or 125.4 ± 36.3 s (mean ± SD). We did not identify time delays (δ) that were discernable from zero for any of the 10 subjects. Due to normalization, all amplitudes *A* displayed in Fig. 3 have a value of 1. Therefore, the mathematical representation of our model (*Eq. 2*) simplifies to a transfer function of the form:

$$H(s) = \frac{1}{(\tau s + 1)} \tag{3}$$

Using the time constants we measured for each subject, this model enabled accurate subject-specific estimates of instantaneous energetic cost from respiratory energetic cost measures. Using both our inverse and forward model approaches, we

Table 1. *Time constants and model fits for changes in gait of different direction and magnitude, averaged across subjects*

Change in Gait	Time Constant, s		Fit, R^2	
	Mean	SD	Mean	SD
Direction up	38.04	8.52	0.87	0.10
Direction down	44.97	17.43	0.89	0.10
Magnitude 0.25 m/s	42.64	18.94	0.87	0.08
Magnitude 0.50 m/s	41.85	9.71	0.93	0.07
All	41.78	12.05	0.94	0.05

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were able to produce estimates of instantaneous energetic cost from measured energetic cost that well matched the enforced step, ramp, and adaptation profiles (Table 2 and Fig. 4). For the step and ramp input profiles, both approaches performed exceptionally well. The R^2 values between the enforced instantaneous energetic cost profile and the model-produced estimates of instantaneous energetic cost were typically greater than 0.9 for individual trials. As a result, averaging measured energetic cost data across the three repeats or across subjects prior to applying either approach did little to improve our estimates of instantaneous energetic cost. Thus, for the step and ramp profiles, it appears possible to accurately estimate instantaneous cost from a single trial of measured energetic cost data. Single trial estimates of instantaneous energetic cost were less accurate for the adaptation profile. Individual trial R^2 values ranged widely from 0.38 to 0.96 and 0.26 to 0.96 for the inverse model approach and forward model approach, respectively. However, averaging measured energetic cost data across the three repeats prior to applying the inverse model or forward model approaches typically resulted in R^2 values above 0.75, while then averaging across all subjects resulted in R^2 values above 0.85.

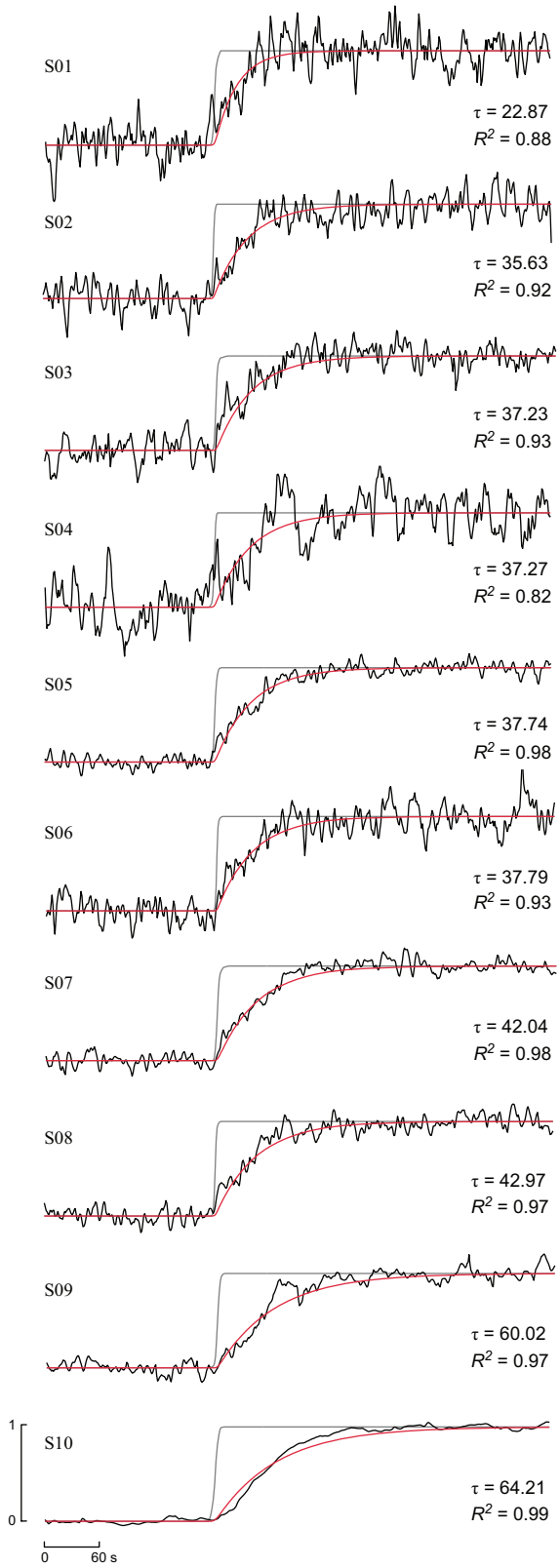

Fig. 3. Modeling the measured energetic cost response. The average measured energetic cost response (black line) to 24 rapid changes in instantaneous energetic cost (gray line) is shown for each subject. The red line illustrates the model that best fits each subject's response. Model time constants (τ) and R^2 values for each fit are presented on the right-hand side of each panel. Before we averaged the data, we normalized all instantaneous and measured energetic cost changes to unity by subtracting the initial steady-state values and dividing by the amplitude of the final steady-state values.

DISCUSSION

We found that a simple first-order linear differential equation can approximate transient energetic cost responses during gait. When rapid step-like changes in instantaneous energetic cost were enforced, we observed a single underlying response featuring no discernable delay. On average, subjects took 2 min to reach 95% of the steady-state metabolic cost value, with all but one subject reaching 95% steady state within 3 min. These same underlying dynamics held regardless of the magnitude or direction of the change in gait. Despite the collective effect of many sources of complexity, including mitochondrial dynamics, gas stores, transit delays, and cardiopulmonary control, a simple model explains the transient energetic cost response during walking.

This model allowed us to produce reasonably accurate estimates of instantaneous energetic cost from respiratory cost measures. Our two approaches, the inverse model approach and forward model approach, resulted in similar estimates of instantaneous energetic cost, and compared with our enforced cost profile, R^2 values were typically greater than 0.90. Both methodologies were able to capture rapid changes in instantaneous energetic cost that were prescribed during the step trials, as well as gradual changes and discontinuities that were prescribed during the ramp trials. The poorest estimates of instantaneous energetic cost were found for the adaptation trials, where fitting the rapid decay proved problematic in some trials. These sorts of transient changes in cost are more readily distorted by breath-by-breath noise because there are fewer data points available within the transient period with which to fit model parameters. Our adaption trial decayed to steady state with a time constant of 60 s, which equates to only about 20 breaths. Better estimates may be possible with improved noise

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Table 2. *R^2 values between the enforced and the model-produced estimates of instantaneous energetic cost for both the inverse model and forward model approach*

		S03		S05		S07		S10		All Subjects	
Input	Trial	Inverse	Forward	Inverse	Forward	Inverse	Forward	Inverse	Forward	Inverse	Forward
Step	Best	0.97	0.99	0.99	0.99	0.98	0.99	0.97	0.99		
	Median	0.96	0.99	0.99	0.98	0.97	0.99	0.88	0.96		
	Worst	0.98	0.92	0.94	0.87	0.94	0.93	0.83	0.74		
	Average	0.98	1.00	0.99	0.99	0.98	0.98	0.96	0.92	0.98	0.97
Ramp	Best	0.99	1.00	0.99	1.00	0.99	0.99	0.94	1.00		
	Median	0.98	1.00	0.97	0.98	0.98	0.99	0.89	0.91		
	Worst	0.86	0.79	0.89	0.93	0.98	0.99	0.69	0.60		
	Average	0.97	1.00	0.99	0.99	0.99	1.00	0.87	0.99	0.97	0.98
Adapt	Best	0.84	0.70	0.84	0.82	0.90	0.96	0.92	0.88		
	Median	0.79	0.61	0.77	0.86	0.64	0.46	0.82	0.50		
	Worst	0.72	0.40	0.79	0.78	0.38	0.26	0.77	0.46		
	Average	0.81	0.76	0.84	0.88	0.75	0.66	0.92	0.79	0.87	0.85

R^2 values from the 3 repeats, for each of the step, ramp, and adaptation input profiles, have been ordered from highest to lowest for each subject. To produce the average value, we averaged the measured energetic cost data across the 3 repeats prior to applying the inverse model or forward model approach. We also averaged across all subjects and all repeats to produce the final two columns of data. Note that *subject S03* has been used as a representative subject in Fig. 4, with the median trials being used as representative individual trials.

removal techniques, improved fitting techniques, or as we found here, through averaging over a greater number of trial repeats or subjects. Overall, the two approaches produced similar and seemingly accurate estimates of instantaneous energetic cost. However, each approach is subject to distinct limitations and requires different assumptions on the part of the user.

The inverse model approach requires little advance knowledge of the underlying instantaneous energetic cost profile, but is greatly complicated by breath-by-breath noise. High-frequency components of breath-by-breath variability in measured energetic cost are effectively amplified when passed through the model inverse, obscuring estimated instantaneous energetic cost. To reduce their contribution, while retaining our ability to fit fast-changing inputs, we first fit the noisy metabolic cost data using a polynomial. We constrained the polynomial to pass through an initial steady-state value at the point of perturbation, and to reach steady state at the end of the trial. For an experimenter, these constraints require that the protocol be designed such that the subject begins and ends in steady state. (These particular constraints are not universal for every experimental paradigm; researchers should identify whatever constraints on the measured data are imposed by the experimental paradigm and use them to their fitting advantage.) Although we made no assumptions about the shape of the profile between the beginning and end steady-state regions, complex profiles would not be fit well by a low-order polynomial. In such situations higher-order polynomials, splined polynomials, or altogether different functions may be necessary to accurately fit the measured energetic cost profiles. This will inevitably introduce subjectivity, as the experimenter will be required to make decisions about what profile changes are "true" and what is simply "noise."

Estimating instantaneous energetic cost using the forward model approach requires some advance knowledge of the profile shape. This knowledge may be based on the study design or additional measurements. For example, if the study design calls for a novel force to be rapidly applied to a limb, one may reasonably assume an abrupt increase in instantaneous energy use followed by an exponential decay as the subject adapts to the new force. One need not know the timings and magnitudes of the initial increase and subsequent decay as the forward approach employs optimization to estimate their values. Alternatively, one may deduce the profile shape from a measured physiological variable, such as the time course of adjustments to step frequency or muscle activity. It is also possible that the experimenter has a range of hypotheses about what the input profile shape may be. These hypotheses can be evaluated by optimizing each candidate input profile and testing which one provides the best fit. To illustrate this, we fit optimal step, ramp, and adaptation profiles to each of the three responses and found that each response was best fit by its respective profile shape (e.g., the enforced ramp was best fit by a ramp profile). Because the experimenter must make assumptions about the underlying profile shape, the forward approach introduces a bias based on the experimenter's expectations. Moreover, there may be situations where the experimenter does not have a reasonable first approximation of the input profile shape.

In addition to the approach-specific limitations described above, there are four more general limitations to our methodology and analysis. First, we treat our enforced instantaneous energetic cost profiles as a gold standard to which we compare our model estimates. Although we attempted to enforce a specific cost profile by controlling walking speed and step frequency, other uncontrolled gait parameters, for example stance time or muscle activity, may have caused instantaneous energetic cost to deviate from our desired input profile. As a consequence, our estimates may be better or worse than presented. Second, the identified model and its average parameters only apply to adult humans. Differences in size and phylogenetic history are both likely to alter the dynamic relationship of other animals from that in adult humans. Similarly, the identified model and its average parameters only apply to walking. While we found that a single process accurately captures the identified dynamic relationship between instantaneous and measured energetic cost, Whipp and colleagues have found that there are two important processes in particular cycling conditions, perhaps reflecting a difference in cardiopulmonary control between the two tasks (39, 40). A fourth limitation of our model is that it can only be applied to walking tasks within the tested metabolic cost range. At metabolic rates above 5

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W/kg, many subjects may breach the anaerobic threshold, causing oxygen stores to be depleted faster than they can be replenished and rendering our measured energetic cost a poor estimate of the underlying instantaneous energetic cost. At metabolic rates below 1.5 W/kg it is possible that more complex dynamics exist at the onset of exercise, as first described by Whipp and colleagues (39). Overall, our exact model can be used to estimate instantaneous energetic cost of walking at metabolic rates ranging from 1.5 to 5 W/kg, which, under natural conditions, corresponds to walking speeds ranging from 0.75 to 1.75 m/s. Outside of this range, care should be taken to first identify the underlying dynamic relationship between instantaneous and measured energetic cost before applying our inverse or forward model approach. Within the constraints imposed by these limitations, there is still considerable flexibility with regard to what tasks can be used to identify the model between instantaneous and measured energetic cost; rapid changes in speed and step frequency are convenient, but not necessary. The most important feature is that the dynamics underlying the energetics of the non-steady-state tasks of interest should not be appreciably different from those underlying the tasks used to identify the model. In other words, the mitochondrial dynamics, body transit delays, and respiratory control mechanisms, but not necessarily the biomechanical task, need to be the same or similar between the tasks.

Our methodology may prove useful for both post hoc and real-time estimation of energetic cost. Its accuracy benefits from a personalized model for each subject, but for some situations, it may suffice to use the average dynamic model identified in the current experiments. As an initial test of this possibility, we simulated measured energetic cost to an adaptation input profile for a subject with an exceptionally slow time constant of 60 s. We then compared instantaneous cost estimates using this subject-specific time constant to that obtained if we assumed our average time constant (42 s). Using the average time constant still made it clear that instantaneous cost adapted by demonstrating the characteristic rapid increase followed by a slower decay. As to be expected, R^2 values dropped when using the average time constant, but over 80% of the variability was still explained. This general model is particularly useful because it allows experimenters to return to previously measured energetic cost data and estimate instantaneous energetic cost without the need for a subject-specific model of cost dynamics. Another use for the identified dynamic model is real-time estimation of instantaneous cost. Kalman filters, and similar algorithms, leverage dynamic models of the system to help correct for noise and delays (11, 28). Real-time estimates of instantaneous energetics may prove useful for biofeedback, manipulating gait training based on energetic cost, or simply for online determination of when a research subject has reached steady state.

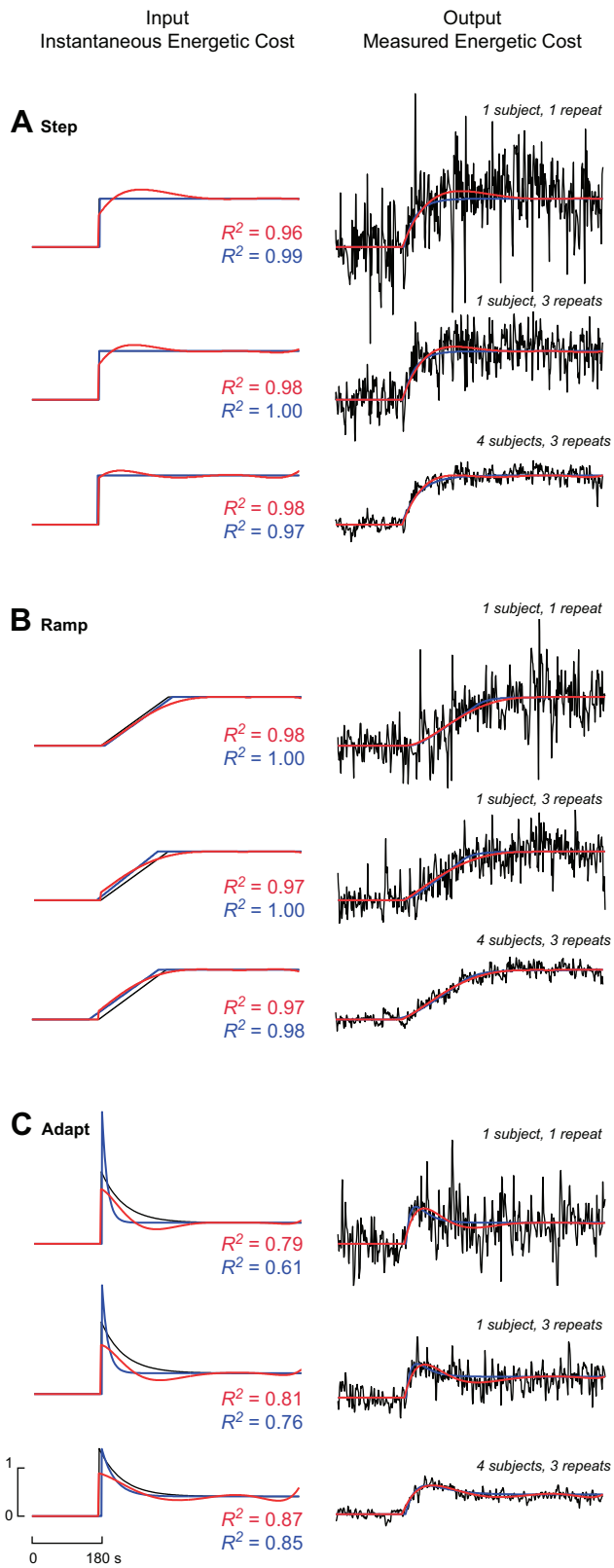

Fig. 4. Estimating changes in instantaneous energetic cost for step (*A*), ramp (*B*), and adaptation (*C*) input profiles. The enforced instantaneous energetic cost (input, left panel) and measured energetic cost responses (output, right panel) are shown in black. The red lines represent estimates from the inverse model approach, and the blue lines represent estimates from the forward model approach. For some conditions, the lines illustrating the estimates obscure the black line input profiles. The first row of data is from a single representative trial for a representative subject (*S03*). The second row of data has been averaged across the three repeats for the same representative subject. The third row contains data averaged across the three repeats and four subjects. R^2 values calculated between the enforced instantaneous energetic cost profiles and the inverse model approach estimates of muscle energy use are shown in red text, while that for the forward model approach estimates are shown in blue text. The normalized *Y*-axis scale represents a change in energetic cost of ~1 W/kg.

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An ability to assess instantaneous energetic cost during non-steady gait could unveil new insights into walking. People rarely experience metabolic steady-state conditions; less than 1% of real-world walking bouts last the requisite 5 min (23). The fields of locomotor adaptation and learning aim to shift our scientific focus from the steady state to this real-world behavior. Energetic concepts such as economy, efficiency, and least effort are often used to explain adaptations to novel environments or tasks. Yet, as researchers work to understand the neuronal circuitry involved in gait adaptation, and quantify the time scales over which adaptation occurs, they have been unable to effectively make direct comparisons to energetic cost during the adaptation itself. An understanding of the role of energy use may help us understand how we adapt to changing environments, how we compensate for injury or motor control deficits, and how we learn new tasks. By presenting a methodology for assessing instantaneous energetic cost during adaptation and other non-steady-state gait conditions, we aim to provide our field with a tool with which we can investigate previously unanswerable questions.

APPENDIX

Identifying an appropriate model between instantaneous and measured energetic cost is a first and critical step when using both our inverse and forward model approach. When designing the experiments for identifying the model, users need to know how confident they need to be in the identified model parameters, and the number of trial repeats required to achieve this level of confidence. That is, does one need to know the time constant within 1 s or 10 s of its actual value to accurately estimate instantaneous energetic cost? And, to achieve the appropriate accuracy in estimating the time constant, does one need a small number of trials or a prohibitively large number of trials?

To address the first question, we simulated the measured energetic cost to step, ramp, and adaptation input profiles for hypothetical subjects with time constants over the range of time constants that we measured in our subjects (20, 40, and 60 s). We constructed the simulated data for a particular combination of input profile and time constant by passing the profile through our model (*Eq. 3*), parameterized with the time constant, then added white noise to reflect breath-by-breath noise, and finally downsampled the signal to a desired breathing frequency. We then applied the inverse and forward model approaches and compared the R^2 values found for instantaneous cost estimates from the time constant used to simulate the data (i.e., actual time constant) to that obtained if the time constant deviated by different amounts (i.e., estimated time constant). We used deviations of ± 2, ± 5, ± 10, ± 15, and ± 20 s. As the difference in R^2 values will depend upon the particular random breath-by-breath variability used in each simulation, we employed a standard bootstrap Monte Carlo procedure and repeated this process 100 times to estimate the average difference in goodness-of-fit between the actual time constant and the estimated time constant (13). We found that across all time constants, the goodness-of-fit did not depend strongly on the accuracy of the time constant, the level of noise, or the breathing frequency within the range of these parameter values that we measured in our subjects. Rather, the required confidence in the time constant can depend strongly on the shape of the input profile. Profiles with impulse-like characteristics, such as the adaptation input profile, are much more affected by errors in the time constant than a more gradual profile such as the ramp. For example, when the estimated time constant was 15 s longer than the actual time constant of 40 s, the average R^2 value dropped from 0.96 to 0.87 for the adaptation input profile. The same error in time constant had almost no effect on the R^2 for the ramp input profile. As a conservative guideline, we recommend designing the identification experiments to have the 95% confidence level of the time constant be within 5 s. If attempting to fit input profile shapes that differ from those we have tested, we recommend using the range of subject data from Table 3 to simulate the output metabolic power response, allowing one to run their own simulation to determine the desired level of confidence in a subject's time constant.

To determine the number of trial repeats required to achieve that confidence, we leveraged the work of Lamarra and colleagues (15) who addressed precisely this question for the purpose of identifying the time constants underlying gas kinetics during stationary cycling. In brief, their method uses Monte Carlo simulations to estimate the confidence interval for a given model parameter. This is dependent on both the experimental design, including factors such as the number of trial repeats and the magnitude of the induced change in metabolic power, as well as particular subject characteristic, including their time constant, variability in measured metabolic power, and breathing frequency. We modified their analysis by using our measured ranges for changes in steady-state metabolic power, time constants, variability in metabolic power, and breathing frequency (Table 3), as these are more typical for walking than the values used in the original analysis. We found that the number of trial repeats (n) was largely insensitive to changes in time constant (τ) within the ranges of time constants we measured in our experiments. Consequently, we chose a single value

Table 3. *Each subjects' time constant, SD in breath-by-breath metabolic power, breathing frequency, and net metabolic power across the range of walking speeds tested*

Subject	Time Constant, s	Metabolic Power SD, W/kg*	Breathing Frequency, breaths/min)*	Net Metabolic Power, W/kg				
				0.5 m/s	1.00 m/s	1.25 m/s	1.5 m/s	1.75 m/s
S01	22.87	0.93	25	1.32	1.62	2.29	3.12	4.44
S02	35.63	0.77	25	1.78	2.21	2.89	3.81	5.29
S03	37.23	0.47	30	1.52	1.99	2.50	3.33	4.60
S04	37.27	0.78	19	1.46	2.03	2.26	3.01	3.95
S05	37.74	0.34	22	1.59	1.94	2.49	3.34	4.97
S06	37.79	0.51	26	2.35	2.91	3.38	4.35	6.31
S07	42.04	0.31	20	1.68	2.07	2.63	3.54	5.32
S08	42.97	0.34	20	2.35	2.79	3.37	4.16	5.85
S09	60.02	0.32	17	1.24	1.60	2.30	3.54	5.21
S10	64.21	0.19	11	1.53	2.02	2.54	3.36	4.67
Mean	41.78	0.49	22	1.68	2.12	2.67	3.56	5.06
SD	12.05	0.25	5	0.39	0.43	0.42	0.43	0.69

These data can be used to simulate an expected output metabolic cost response, allowing one to assess the required confidence in a subject's time constant and the resulting number of trial repeats required to achieve this confidence. *These values have been reported for a walking speed of 1.25 m/s. On average, SD in metabolic power increases as walking speed increases at a rate of 0.31(W/kg)/(m/s) and breathing frequency increases at a rate of 3.3 (breaths/min)/(m/s).

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Table 4. *Simplified lookup table for the number of repeats (n) required to approximate τ with a 95% confidence interval of ±5 s across a range of breath-by-breath noise levels and breathing frequencies*

Metabolic Power SD, W/kg	Breathing Frequency, breaths/min				
	10	15	20	25	30
0.1	0.4	0.3	0.2	0.1	0.1
0.2	1.6	1.1	0.8	0.6	0.5
0.3	3.5	2.3	1.7	1.4	1.1
0.4	6.1	4.1	3.1	2.4	2.1
0.5	9.5	6.3	4.8	3.8	3.2
0.6	13.6	9.1	7.0	5.5	4.7
0.7	18.4	12.3	9.5	7.5	6.4
0.8	24.0	16.0	12.4	9.8	8.4
0.9	30.3	20.2	15.7	12.4	10.7

τ is assumed to be near 40 s and the change in metabolic power (ΔW) is 1.5 W/kg. Values are reported to 1 decimal place to facilitate accurate scaling of these numbers when applying *Eq. 4*.

of τ (40 s) to test the effect on trial repeats of breathing frequency and variability in metabolic power. Table 4 presents the results of this analysis as well as serving as a simplified look-up table for estimating the number of trial repeats across a range of subject characteristics for a nominal change in metabolic power of 1.5 W/kg (about that which would be seen if walking required speed increased from 1.00 to 1.5 m/s). As described by Lamarra et al. (15), the following formula can be used to determine n for a different change in metabolic power (ΔW_{new}):

$$n_{new} = n_{table}\left(\frac{\Delta W_{table}}{\Delta W_{new}}\right)^2 \quad (4)$$

where ΔW_{table} has a value of 1.5 W/kg and n_{table} is determined from Table 4 based on subject breath-by-breath noise and breathing frequency. Intuitively, the number of required trial repeats decreases as the signal-to-noise ratio increases, either through a higher signal due to larger changes in metabolic power or lower noise due to smaller subject variability in metabolic power, and when breathing frequency increases, thereby yielding more information on which to fit the model. As an example calculation, if we determine a subject has a breath-by-breath standard deviation in metabolic power of 0.5 W/kg and a breathing frequency of 20 breaths/min from a short steady-state walking trial, and we are going to subject them to a change in metabolic power of ~1.5 W/kg, we would require 5 repeats to determine their τ with a 95% confidence interval of ±5 s. If we were only going to subject them to a 1 W/kg change in metabolic power, *Eq. 4* indicates that we would need 11 trial repeats to determine the time constant to the same accuracy. It is worth noting that this method is very convenient: the number of trial repeats required to determine a subject's time constant can be estimated by making a small number of measurements (breathing frequency and variability in breath-by-breath metabolic cost) during a single steady-state trial.

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DISCLOSURES

No conflicts of interest, financial or otherwise, are declared by the author(s).

AUTHOR CONTRIBUTIONS

Author contributions: J.C.S. and J.M.D. conception and design of research; J.C.S. performed experiments; J.C.S. analyzed data; J.C.S. and J.M.D. interpreted results of experiments; J.C.S. prepared figures; J.C.S. drafted manuscript; J.C.S. and J.M.D. edited and revised manuscript; J.C.S. and J.M.D. approved final version of manuscript.

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