Improving the Estimation of Biological Indices via Kalman Filtering

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Abstract – Monitoring of respiratory gas exchange (oxygen consumption – VO2 and carbon dioxide production – VCO2) in humans practicing normal daily life activity is important in order to establish physical condition and metabolic indices (such as the Respiratory Quotient – RQ) of the patients. A respiratory chamber is used to this extent, enabling long term (24h) observation under free-living conditions. Computation of VO2 and VCO2 is currently done by inversion of a mass balance equation, with no consideration of measurement errors and other uncertainties. In order to improve the accuracy of the results, a new mathematical model is suggested, explicitly accounting for the presence of such errors and uncertainties, enabling the use of Optimal Filtering methods. Validation experiments have been realized, injecting known gas quantities and estimating them using the proposed mathematical model and applying the Kalman Filtering (KF) methods. The estimates obtained reproduce the known production rates much better than standard methods. Experiments with eleven humans were carried out as well, where VO2, VCO2 and RQ were estimated. The error covariance matrix, produced by the KF method, appears relatively small and rapidly convergent. Spectral analysis is performed to assess the residual noise content in the estimates, revealing large improvement. The presented study demonstrates the validity of the proposed model and the improvement in the results when using a KF method to resolve it.

I. INTRODUCTION

Accurate monitoring of gas exchange (oxygen consumption - VO2 and carbon dioxide production - VCO2) of humans in health and disease is of large interest in medical research [8,13]. It enables the assessment of important physiological indices, such as oxidation rate of energy substrate and energy expenditure [6,10]. Although various instruments exist to monitor these phenomena, the respiratory chamber is the only one permitting continuous long term monitoring (24h) of patients practicing their daily life activities (sleeping, eating, physical activity, etc.). The precision of measuring the respiratory gas becomes of crucial importance in order to obtain precise metabolic data, as for example computation of the Respiratory Quotient (RQ), which is the VCO2 to VO2 ratio.

A respiratory chamber is merely a controlled volume in which gas exchange occurs. It exchanges gas volumes with the external environment through two sole apertures by means of an adequate pump mounted to the output aperture and creating a regular airflow. The output flow is measured by a flow meter and its gas content (oxygen and carbon dioxide) is analyzed by adequate sensors, measuring the fractions of oxygen and carbon dioxide in the sampled airflow. A schematic presentation of the respiratory chamber is in Fig. 1.

Conventional methods to compute gas production/ consumption rates of a subject in a respiratory chamber are all based on a similar mass balance equation, relating the available observations with VO2 and VCO2 [1,2,5,9-12]:

$$V \cdot \dot{c}^g(t) = \varphi_i(t) \cdot c_i^g(t) - \varphi_o(t) \cdot c_o^g(t) + u^g(t) \qquad (1)$$

where V is the chamber volume, c^g is the mean volumetric spatial fraction of a gas g in the chamber, c_i^g and c_o^g are the gas fractions in the input and output flows respectively, φ_i^g and φ_o^g are the input and output flows respectively, and u^g is the gas production rate.

Some differences do exist between the standard methods, mainly regarding the formulation of the mass balance equation rising from different simplifying hypotheses used. Only a few authors [2,12] address the problem of noise attenuation by applying certain prefiltering methods, but these do not explicitly consider the effects of measurement noise and other uncertainties. Heymsfield *et al*. [9] have formulated for the first time the problem using the terminology of dynamic systems theory, explicitly considering measurement noise and process noise which are fundamental in real applications. However, no solution to the estimation problem was proposed based on those concepts.

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Estimates performed as indicated above are affected by several error sources: a) measurements are always corrupted by noise and though prefiltering is applied, considerable residual errors remain; b) the mass balance equation used is only an approximate representation of reality due to the simplifying hypotheses used; c) VCO2 and VO2 are obtained by simple inversion of the mass balance equation, without applying any mechanism to limit the propagation of the errors introduced by a) and b). The above error sources are always present in a real experimental setting and cannot be completely eliminated. Therefore, it is of high importance to apply procedures and methods to minimize such negative effects. In this work the authors propose a general stochastic mathematical model describing the dynamics of gas exchange within a controlled volume using an input-state-output approach. Differently of [9], the gas production/consumption rates (VO2 and VCO2) are treated as part of the system state and their estimation using the classical KF methods is, thus, made possible.

Next, a stochastic dynamical model describing gas exchange in a controlled volume is developed. This model is then used to formulate Kalman estimators (filter and interpolator) to estimate the gas production/consumption rate. The various experiments performed are then explained and the results presented. Conclusive remarks are offered in the last section.

II. DYNAMIC MODELLING

The scope of this section is to derive a general simple mathematical model to describe the following phenomenon: a controlled volume V is subject to an input air flow, an output air flow, and within it a source produces or consumes a gas g, see Fig. 1. This model is later used to describe both O2 consumption and CO2 production by a subject in the respiratory chamber.

Beginning with equation (1), where all gas volumes and flows are expressed in STP (Standard Temperature and Pressure) conditions, the following simplifying hypotheses are now assumed:

- An adequate ventilation system in the respiratory chamber allows to assume that "a rapid mixing of respiratory gas with air occurs in the chamber" (explicit in [11] and implicit in all others), therefore:

$$c_o^g(t) = c^g(t) \qquad (2)$$

- The concentration of the gas g in the input flow is constant with a value determined by its standard concentration in atmospheric air:

$$c_i^g(t) = \bar{c}^g \qquad (3)$$

- The input airflow is equal to the output airflow and is perfectly measured by an adequate sensor.

$$\varphi_i(t) = \varphi_o(t) = \varphi(t) \qquad (4)$$

Defining now the difference in the volumetric fractions of the gas considered,

$$\tilde{c}^g(t) = c_o^g(t) - \bar{c}^g \qquad (5)$$

and substituting equations (2) – (5) in equation (1), results in the following linear differential equation:

$$\dot{\tilde{c}}^g(t) = -\frac{\varphi(t)}{V}\cdot\tilde{c}^g(t) + \frac{1}{V}\cdot u^g(t) + w^m(t) \qquad (6)$$

where the modeling error $w^m(t)$ describes the cumulative effect of all approximations introduced by the simplifying hypotheses above. It is assumed that the modeling error can be accurately described as a zero-mean white Gaussian stationary random process, with a variance ψ_m.

Regarding humans, the mean gas production/ consumption rates over short time intervals can be described by a simple random walk model:

$$\dot{u}^g(t) = w^u(t) \qquad (7)$$

where w^u is a zero-mean white Gaussian random process with a variance ψ_u. The model in equation (7) plays only a descriptive role in this case and should not be interpreted as a model of the true physiological phenomenon. Since oxygen consumption and carbon dioxide production are highly related processes, it is reasonable to assume a similar temporal behavior (dynamic model), implying the use of the same ψ_u. The results obtained, presented in the sequel, further validate the use of this simple stochastic.

The value of ψ_m and ψ_u were assessed by injecting into the respiratory chamber gas inputs at accurately measured flow rates, thus simulating gas production by humans. The Kalman estimator was applied to the collected gas fraction measurements and the known gas inputs estimated using a wide range of values for ψ_m and ψ_u. Fitting error, with regard to the known input, was computed for each estimate (generated by using a certain couple [ψ_m, ψ_u]). The values optimal in this sense (minimal fitting error) are chosen to use in the estimator equations, resulting in $\psi_m = 10^{-12}\ \ \mathrm{min}^{-2}$ and $\psi_u = 25\cdot 10^{-4}\ \ \mathrm{liter}^2\cdot\mathrm{min}^{-4}$.

The measurement available in a respiratory chamber is the difference in the volumetric fractions of the gas considered, as defined in (5), affected by an additive measurement noise $v(t)$ (present in any real application):

$$y(t) = \tilde{c}^g(t) + v(t) \qquad (8)$$

where the measurement noise is a white Gaussian process. Its expected value and variance are determined from the technical characteristics of the measurement instrumentation, resulting in $E\{v(t)\} = 0$, and the variance $\psi_v = 10^{-8}$ (unitless, as gas fractions are measured).

Complete stochastic model.

Putting together equations (6) – (8), the complete model describing a typical experimental setting of the respiratory chamber can be obtained in a compact matrix form:

$$\begin{cases} \dot{x}(t) = A(t)\cdot x(t) + w(t) \\ y(t) = C\cdot x(t) + v(t) \end{cases} \tag{9}$$

where

$$x(t) = \begin{bmatrix} \tilde{c}^{\,g}(t) \\ u^{g}(t) \end{bmatrix},\quad A(t) = \begin{bmatrix} -\dfrac{\varphi(t)}{V} & \dfrac{1}{V} \\ 0 & 0 \end{bmatrix}$$

$$w(t) = \begin{bmatrix} w^{m}(t) \\ w^{u}(t) \end{bmatrix},\qquad C = \begin{bmatrix} 1 & 0 \end{bmatrix} \tag{10}$$

Since the observations are in discrete time instants and the implementation is in computer software, the continuous model (equation 9) is discretized as follows:

$$\begin{cases} x(j+1) = H(j)\cdot x(j) + \Delta\cdot w(j) \\ y(j) = C\cdot x(j) + v(j) \end{cases} \tag{11}$$

where Δ is the constant sampling period, j denotes the discrete time $j\cdot\Delta$, and:

$$H(j) = \begin{bmatrix} m(j) & n \\ 0 & 1 \end{bmatrix};\ m(j) = 1 - \frac{\Delta\cdot\varphi(j)}{V}\ ;\ n = \Delta/V \tag{12}$$

The problem of estimating the state x using the available observations y in equation (11) turns out to be a Linear Gaussian problem that can be solved by applying a standard KF.

III. APPLICATION OF THE KALMAN FILTER.

The KF method determines the estimate $\hat{x}(j|k)$ of x at time j elaborating the available measurements up to time k, as well as the apriori information on the statistical properties of the random variables in the problem modeling. Estimates can be obtained for the following three possibilities: Prediction ($j > k$), Filtering ($j = k$) and Interpolation or Smoothing ($j < k$).

Various formulae of the KF are presented in literature (see e.g. [3,7]), and it has been lately introduced also in the estimation of biological processes [4,14]. Following [3], the general estimation problem can be solved by three sequential phases: a) Single Step Prediction; b) Filtering; and c) Interpolation. Below is the explicit formulation of the above for the particular system of equation (11). Note that any other formulation of the KF algorithm will produce similar results.

Single Step Prediction:

$$F(j) = H(j)\cdot\Psi_{\hat{e}}\cdot(j|j-1)\cdot C^{T} \times\left[C\cdot\Psi_{\hat{e}}\cdot(j|j-1)\cdot C^{T} + \Psi_{v}\right]^{-1} \tag{13}$$

$$G(j) = H(j)\text{-}F(j)\cdot C \tag{14}$$

$$\Psi_{\hat{e}}\cdot(j+1|j) = G(j)\cdot\Psi_{\hat{e}}\cdot(j|j-1)\cdot G^{T}(j) + \Delta^{2}\cdot\Psi_{w} + F(j)\cdot\Psi_{v}\cdot F^{T}(j) \tag{15}$$

$$\hat{x}(j+1|j) = G(j)\cdot\hat{x}(j|j\text{-}1) + F(j)\cdot y(j) \tag{16}$$

where $\Psi_{\hat{e}}$ is the estimation error covariance matrix, Ψ_{w} is the process noise covariance matrix, Ψ_{v} the measurement noise covariance matrix, and subject to the initial conditions:

$$\hat{x}(j=0) = \hat{x}(0),\quad \Psi_{\hat{e}}(j=0) = \Psi_{\hat{e}}(0) \tag{17}$$

Filtering:

$$\hat{x}(j|j) = H^{-1}(j)\cdot\hat{x}(j+1|j) \tag{18}$$

$$\Psi_{\hat{e}}\cdot(j|j) = H^{-1}(j)\cdot\Psi_{\hat{e}}\cdot(j+1|j)\cdot {H^{-1}}^{T}(j) - \Delta^{2}\cdot H^{-1}(j)\cdot\Psi_{w}\cdot {H^{-1}}^{T}(j) \tag{19}$$

Interpolation:

$$M(j) = H^{-1}(j)\text{ - }\Delta^{2}\cdot H^{-1}(j)\cdot\Psi_{w}\cdot\Psi_{\hat{e}}^{-1}(j+1|j) \tag{20}$$

$$N(j) = H^{-1}(j)\text{-}M(j) \tag{21}$$

$$\hat{x}(j|k) = M(j)\cdot\hat{x}(j+1|k) + N(j)\cdot\hat{x}(j+1|j)\ ;\ j<k \tag{22}$$

Choice of initial conditions ($\hat{x}(0)$ and $\Psi_{\hat{e}}(0)$) is not critical to the performance of the KF since it is proved that, for an observable system, the estimate becomes independent of this choice as the index j grows [7]. The following values are used in this study:

- VO2 initial state - $\hat{x}(0) = [0, 0.3]^{T}$, gas concentration is unitless and consumption rates in liter/min..
- VCO2 initial state - $\hat{x}(0) = [0, 0.2]^{T}$, gas concentration is unitless and production rates in liter/min..
- Initial error covariance matrix - $\Psi_{\hat{e}}(0) = \begin{bmatrix} 0.1 & 0 \\ 0 & 1 \end{bmatrix}$.
- Process noise covariance matrix - $\Psi_{w} = \begin{bmatrix} \psi_{m} & 0 \\ 0 & \psi_{u} \end{bmatrix} = \begin{bmatrix} 10^{-12} & 0 \\ 0 & 25\cdot 10^{-4} \end{bmatrix}$.
- Measurement noise covariance matrix - $\Psi_{v} = 10^{-8}$.

Loosely speaking, the interpolator version uses more information to compute an estimate of each time instant. Consequently, when applying it using all measurements collected over a 24 hours experiment, the resulting estimate is likely to be the most accurate. Naturally this cancels out the possibility of on-line application. The latter can be obtained, however, by applying a filtering algorithm.

IV. EXPERIMENTS AND RESULTS

Validation experiments.

Gas mixtures of known composition (20% CO_2, 1% O_2, rest N_2) were injected at an accurately measured flow rate to the respiratory chamber, thus simulating CO2 production by a human being. The goals of this procedure were to identify and confirm the model parameters and to confirm the ability of the proposed method to reproduce good estimate of a known gas production rate. Three validation experiments were carried out, starting with zero CO2 injection for 20 minutes followed by 20 minutes of a known level of CO2 gas (200 ml/min in experiment A; 120 ml/min in experiment B; 120 ml/min in experiment C) creating a step type phenomenon, to be estimated by the proposed method. Flow and concentration measurements were performed at the frequency of 0.2 Hz. The results are confronted to those obtained by applying a conventional method [12]. Comparison is based on the mean fitting error, computed as the mean of the absolute values of the instantaneous estimation errors.

Table I confronts the three estimation methods (Kalman interpolator, Kalman filter, and the conventional method of [12]) by computing the mean fitting error with regard to the known input. Fig. 2 presents the results of experiment A, where the three subfigures plot the performance of the different methods applied. The known value of the gas production rate is plotted by a dashed line. Clearly the results obtained by applying the proposed method are much better than those obtained using a standard one. Note in Fig. 2 the large variations in the standard method, due, in all probability, to the propagation of the measurement and model errors into the computation of the gas production. The filter (on-line) version demonstrates much more accurate estimate but reveals a delay in detecting the sharp change in the gas production rate. The interpolator (off-line) version further improves the estimation accuracy and removes this delay.

Experiments with humans.

Experiments were carried in the respiratory chamber with 11 subjects (4 male and 7 female). The nature and purpose of the investigations were explained to all subjects before they agreed to participate in the study, which followed the protocol guidelines of the Institutional Review Board. Each subject occupied the respiratory chamber for 24 hours, practicing normal activity and performing a physical exercise composed of walking for 30 minutes at 10% grade at a constant speed of 3 km/h. Flow and concentration measurements were performed at the frequency of 1 Hz. Due to a particular setting of the existing measuring instrumentation, the readings were averaged over a 5 minutes period. VO2 and VCO2 were calculated using both the proposed method and the standard method [12], in order to validate the new method with respect to standard ones. Similarly, the subjects' RQ was computed based on the different estimates of the respiratory volumes.

Fig. 3 plots the temporal behavior of the O2 consumption rate and CO2 production rate of a typical subject. Note the large variations presented in the estimates produced by the standard method. Fig. 4 plots the temporal behavior of the RQ, computed for the same subject on the basis of the estimates presented in Fig. 3. The values obtained by the standard method are notably scattered and it is very hard to deduce the physiological condition of the patient. Moreover, as is well known in the medical community, an acceptable range for RQ values is of 0.7 to 1.0. Clearly the estimates by the standard method fail to comply with this range, whereas the KF estimates generally meet this constraint. The temporal behavior of the RQ estimated by the KF method is much smoother and in accordance with what expected from biological understanding of such phenomenon. The reasons for the scattered estimates with standard methods can be understood by the large variations in the estimates of VO2 and VCO2 (due to noisy estimates).

In Fig. 5 the error covariance matrix, as predicted by the KF algorithm, is plotted versus time. Note that this variance converges rapidly to a steady state value, thus confirming the filter stability and its robustness with regard to the initial condition values. This indicates quasi-stationary behavior of the filter resulting from the fact that the variations in the time dependent matrix $H(j)$ (equation 12) are of negligible order. In such case it might be possible to use the steady state version of the KF algorithm (the Wiener Filter) and reduce the computational load, though in this study it was preferred to use the more general method.

Since true values of VO2 and VCO2 are unknown in the case of the experiments with humans, it is impossible to validate the performance of the estimation methods as in the case of known production rates. An alternative method is based on assessing the residual noisy components in the estimates. Biological processes, such as variations of the gas production or RQ in humans, are considered to have a limited bandwidth – with relatively large oscillation periods. The existence of high frequency components in a computed spectrum indicates the presence of estimation errors. The noise content in the estimate is, thus, proportional to the area enclosed by the spectrum on high frequencies. To quantify the noisy components, the power content of the estimate was calculated in frequencies above 0.05 min^{-1} (i.e. oscillations with periods shorter than 20 minutes). Computation is done by calculating the area contained below the spectrum, starting from the frequency of 0.05 min^{-1}.

Fig. 6 demonstrates the mean power spectral density (computed over the 11 subjects) of the VO2 and VCO2 time series. Fig. 7 plots the results obtained by spectral analysis of the RQ time series. Since the RQ is dimensionless the resulting spectrum has the dimension of minutes, whereas for the gas rates the spectra are in units of ml^2/min. Table II presents the high frequency signal power (oscillatory components with periods shorter than 20 minutes) residual in the estimates performed by the three methods. This data is proportional to the residual noise content in the estimates.

Note in Fig. 6 that the useful signal is concentrated on the low frequencies, as predicted, but the spectra of the standard method estimates do not go to zero on high frequencies, thus indicating noisy contents. A similar, and even more distinguished phenomenon is revealed by the spectra of the RQ in Fig. 7. Contrarily, the spectra of the KF estimates do converge to zero on high frequencies. Those results emphasize the higher efficiency and accuracy of the proposed method. Table II quantifies the noise contents, clearly visible in Fig. 6 and in Fig. 7. The noise content in the estimates obtained by the standard method is 2-3 orders of magnitude larger than that obtained by the KB methods.

V. DISCUSSIONS

The KF methods show much better performance over standard methods, as can be easily predicted theoretically. Noise attenuation is highly improved (2-3 orders of magnitude) and monitoring of biological indices becomes practically possible. Two application possibilities are presented – an interpolator version enabling better results on the price of off-line execution, and a filter version for on-line application.

The main innovation in the proposed model is in equation (7), where the phenomenon of gas production/ consumption in humans is modeled using a random process. This process is assumed to take the form of a random-walk and its variance of its variations is assumed to be time-invariant. The results obtained are very promising and validate this simple presentation. One possible modification might be the use of a time dependent $\psi_u = \psi_u(t)$, in particular considering large ψ_u at the instants of beginning and ending of the physical exercise. Such modification requires the use of a-priori information regarding these instants, and is therefore left for future work.

In conclusion, using a linear stochastic model and an adequate estimation method, it is possible to obtain highly more accurate monitoring of VO2 and VCO2 in a respiratory chamber, enabling accurate estimation of important metabolic indices. Similar approach can be followed to estimate other biological processes, in particular compartmental phenomena, when noisy measurements are presented.

Table I: Verification tests results

	KB Interp.	KB Filter	Standard Method
Experiment A	20.9	54.1	297.9
Experiment B	16.5	29.0	126.6
Experiment C	12.3	24.0	132.1
Mean	16.6	35.7	185.5

Mean fitting error with regard to the known input in [ml/min]

Table II: Spectral content at noise frequencies.

	Units	KB Interp.	KB Filter	Standard Method
RQ	--	$3.2 \cdot 10^{-5}$	$6.1 \cdot 10^{-4}$	$8 \cdot 10^{-2}$
VCO2	$(ml/min)^2$	1.8	57.6	2057
VO2	$(ml/min)^2$	2.9	90.8	3440

Mean values over 11 subjects.

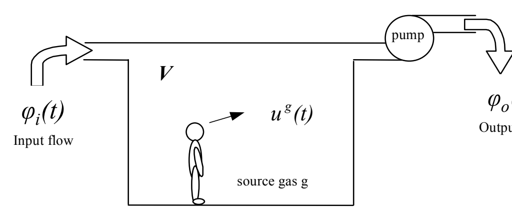

Fig. 1. Simplified presentation of gas exchange in the respiratory chamber.

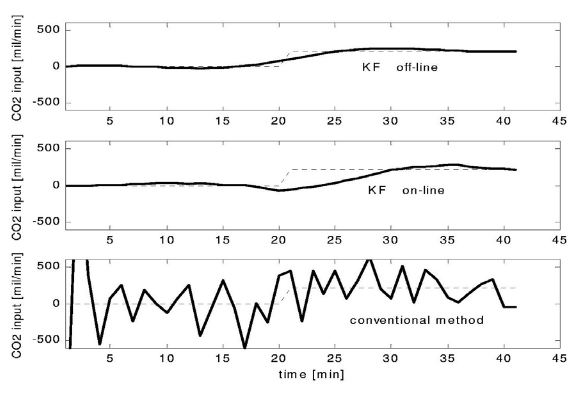

Fig. 2. Estimates of the known input in Experiment A. The Kalman Interpolator estimates (top figure), the Kalman Filter estimates (middle figure) and the estimates computed by a conventional method (bottom figure). Reference input is indicated by a dashed line.

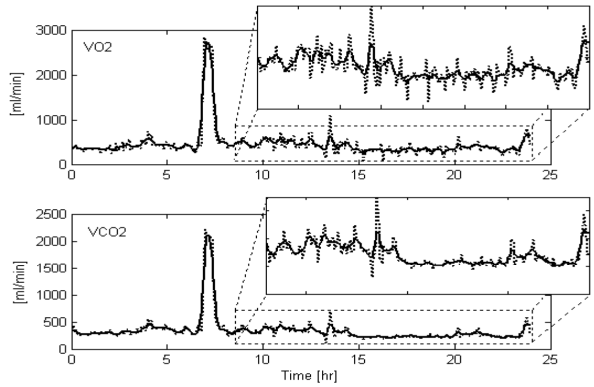

Fig. 3. Typical oxygen consumption and carbon dioxide production of a subject. Proposed method in solid line and standard method in dotted line. The peak corresponds with the physical exercise.

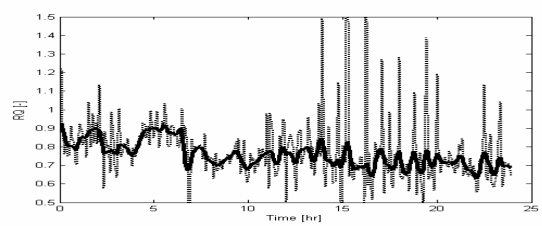

Fig. 4. Estimated RQ of subject 11 throughout the 24-hour experiment. Proposed method in solid line, standard method dotted.

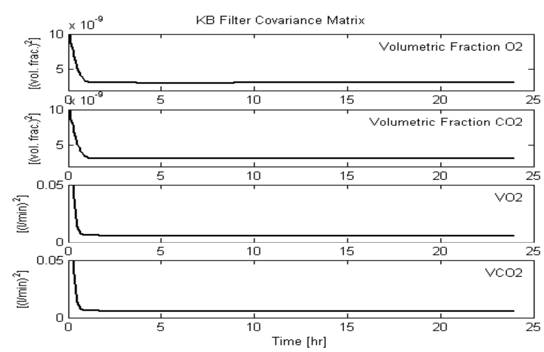

Fig. 5. Temporal behavior of the diagona elements in the estimation error covariance matrix, computed by the Kalman Filter.

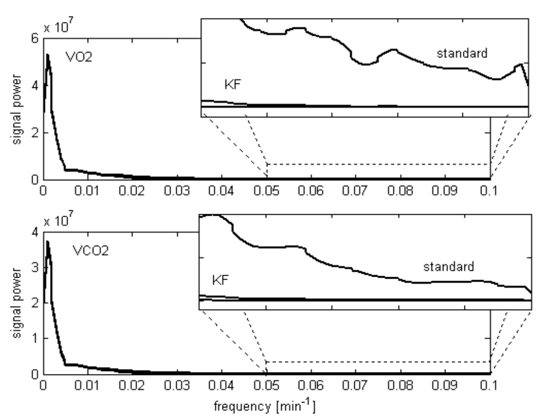

Fig. 6. Spectral analysis of the VO2 and VCO2 estimates. Mean spectra over the 11 subjects.

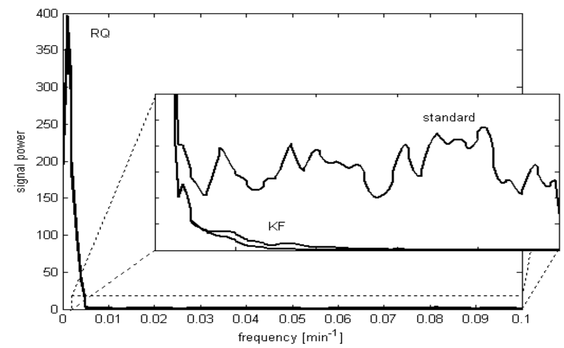

Fig. 7. Spectral analysis of the RQ estimates. Mean spectra over the 11 subjects.

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