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Uncertainty Analysis of Feature Extraction From Expired Gas Traces

Marco Parvis, *Member, IEEE*, Carlo Gulotta, and Roberto Torchio

Abstract—Noninvasive medical analyses are a convenient method to study several pathologies even though their indirect nature often requires a complex processing to determine the relevant health “indicators.” The usefulness of such indicators depends on the employed model, but also on the uncertainty that is connected to the complex processing involved in the indicator determination. This paper deals with the problems related to the estimation of the uncertainty when the indicators are computed by means of a nontrivial processing on recorded traces of clinical parameters. The paper is focused on the analysis of expired gas traces, but the procedure can also be applied to many other cases where the processing involves manual or automatic selection of suitable “key points” on repetitive traces.

Index Terms—Biomedical signal processing, feature extraction, medical diagnosis.

I. INTRODUCTION

MANY medical analyses employ noninvasive procedures to reduce both the cost and morbidity associated to the tests. Examples of noninvasive procedures are ECG, EEG, EMG, and expired gas analysis. Although these methods belong to rather different fields, a common denominator is the processing sequence which is required to emit the diagnosis. The processing starts with a measurement session where the time evolution of one or more clinical parameters is recorded. Then, the recorded streams are analyzed to extract some relevant “features” or “indicators” and eventually the physician emits the diagnosis by employing his/her knowledge and practice to combine different indicators and his/her knowledge about the patient’s status and history.

While the accuracy of the last step can be validated by employing well-assessed medical procedures, the uncertainty of each indicator has to be determined by analyzing the instruments and processing involved in its determination.

Unfortunately, such an analysis is not easy since, in most cases, the processing involves a manual, “by sight” selection of “key” points that identify specific values on the stream, and therefore the obtained values are, to some extent, operator-dependent.

Automatic methods to extract the required features have often been proposed, especially for the most common and often used tests (e.g., [1]–[3]), but problems still remain regarding the reliability and robustness of the obtained results.

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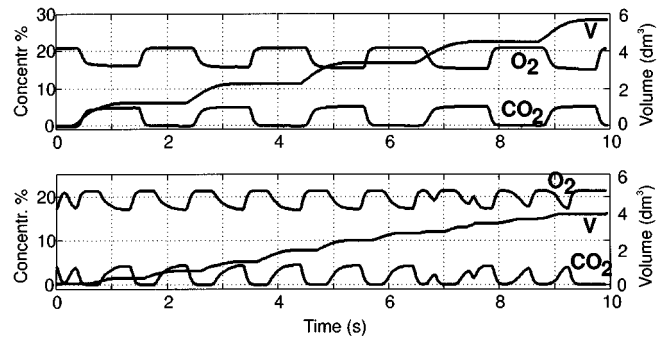


Fig. 1. Trace examples: collaborating patient (top) and noncollaborating patient (bottom).

This paper investigates the possibility of estimating the indicator uncertainty for both manual and automatic processing and tries to validate the results by means of an analysis based on subsequent estimations taken from the recorded data stream.

The proposed solution can be applied both to manual and automatic feature extraction, even though its application to the manual scenario can be rather time-consuming. The solution is tailored to the analysis of expiratory traces of either natural or artificial gases, but the proposed approach can be applied to other medical fields where similar measuring procedures are employed.

II. EXPIRED GAS ANALYSIS

The analysis of gas concentrations at the mouth during normal breathing is a powerful and noninvasive way of inferring the state of the “body machine” [4], [5]. Important data regarding the state of the lungs and the general conditions of a patient can be obtained by analyzing the expired gas composition when a mixture of artificial insoluble and soluble gases is inspired [6]. Other metabolic data can be obtained by measuring the concentrations of oxygen and carbon-dioxide in the expired gas both at rest and during increasing working conditions [5].

The measurement problem, however, is the analysis of the gas concentration changes to derive a compact indicator of the required functionality. Unfortunately, the trace aspect greatly depends on the patient’s collaboration and on his/her ability to follow predefined breathing maneuvers. Fig. 1 shows an example of natural gas traces which have been recorded from both a collaborating and a noncollaborating patient. Each plot is composed of three to ten breaths, depending on the breathing speed, and shows three traces that correspond to expired volume (V), measured with a unidirectional-valve plethysmograph, oxygen (O_2) and carbon dioxide (CO_2) concentrations, measured with

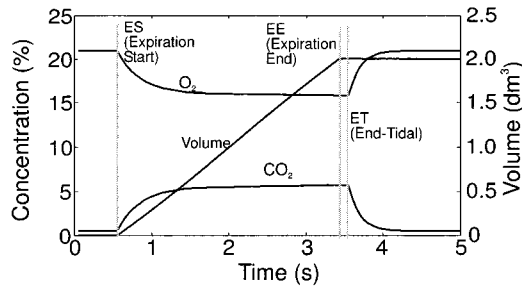


Fig. 2. Ideal trace and key point positions.

a mass spectrometer. The irregularities of the traces recorded for the noncollaborating patient are clearly visible and make the trace analysis problematic.

III. BASIC INDICATORS AND KEY POINT SELECTION

The feature extraction is performed on a breathing basis and consists of the computing of various quantities related to changes in the O_2 and CO_2 concentrations of the expired air with respect to the expired volume.

The processing relies on the identification of three “key points” that mark expiration start (ES), expiration end (EE), and the so-called “end-tidal” (ET).

Fig. 2 shows an example of ideal, simulated traces and of the three key points. ES and EE end are usually defined referring to the volume trace, while ET is selected as the point where the CO_2 concentration stops increasing.

Many trace-derived parameters have been proposed as indicators [5], [7], [8]. If only the traces of oxygen and carbon-dioxide are considered, most of the indicators are traditionally obtained by combining four basic quantities: the average oxygen and carbon-dioxide concentrations over one breath $\overline{O_2}$, $\overline{CO_2}$ and the oxygen and carbon-dioxide concentrations at ET O_{2ET} , CO_{2ET} . If the gas concentrations are sampled at a fixed frequency and $S_{O_2}(i)$ and $S_{CO_2}(i)$ are the samples corresponding to oxygen and carbon-dioxide concentrations, the four indicators are obtained as

$$\overline{CO_2} = \frac{1}{EE - ES + 1} \sum_{i=ES}^{EE} S_{CO_2}(i) \quad (1)$$

$$\overline{O_2} = \frac{1}{EE - ES + 1} \sum_{i=ES}^{EE} S_{O_2}(i)$$

$$\begin{aligned} CO_{2ET} &= S_{CO_2}(ET) \\ O_{2ET} &= S_{O_2}(ET) \end{aligned} \quad (2)$$

where ES , EE , and ET are the sample numbers that correspond to the identified key points.

All four of the indicators therefore rely on the key point positioning, which is usually performed by a trained physician.

The manual key point positioning is performed by selecting “by sight” their positions on one or more breaths. Since the selection is a time-consuming task, the selection is often performed on one breath, which is chosen, again by sight, as being the most representative.

In order to reduce the amount of subjectiveness of the analysis, the authors have developed an automatic procedure that an-

alyzes the traces and selects the points according to a two-step procedure.

The first step identifies the useful breaths according to the following procedure:

- 1) The expired volume trace is differentiated to determine the expired flux.
- 2) Each breath is identified around each interval with an expired flux greater than zero.
- 3) The CO_2 trace is then analyzed starting from the end of expiration until the CO_2 concentration abruptly decreases, signaling the start of a new inspiration.
- 4) Breaths too short or too long and breaths with low expired flux are marked as useless and discarded.

The second step identifies the key points of each identified breath. Such an identification is made difficult by the different shapes which arise according to the breathing maneuvers. Several approaches can be followed to tackle this problem, such as pattern recognition techniques, or neural networks, but a simple recursive solution was found to give satisfactory and reliable results.

The approach is based on a local corner approximation of the traces around the interesting points. As an example, the ES point is obtained by computing two regression lines: one for volume samples between the minimum volume and 2% of the total expiration, and the other for volumes between 5% and 10%. The actual volume at the corner point is then used to adjust the intervals for a new regression couple. This approach allows both slowly starting and abruptly starting traces to be correctly identified. Similar recursions are employed for EE and ET.

The automatic selection is performed on all the identified breaths so that up to ten estimations for each of the four quantities are obtained from each record. All of the results are presented to the physician, who can manually correct the key point positions, if necessary.

IV. UNCERTAINTY ANALYSIS

The uncertainty connected to the extracted features depends on three main causes: 1) the instrument uncertainty u_i ; 2) the uncertainty connected to the key point selection u_p ; and 3) the uncertainty connected to the breath-to-breath repeatability u_b .

A. Instrument Uncertainty

The instruments employed in the determination are calibrated each day the measuring apparatus is used. All of the measurements are digitized by employing a PC-based 12-bit conversion system and using a sampling rate of 50 Hz. Low-pass filters ensure the measurements are not aliased and greatly reduce the noise that is present on the samples so that it can be neglected with respect to the other uncertainty causes. Gas concentrations are measured by means of a mass spectrometer whose channels are calibrated using two gas cylinders containing known gas mixtures. A linear approximation is used to identify channel sensitivities k_{CO_2} , k_{O_2} , and offsets b_{CO_2} , b_{O_2}

$$\begin{aligned} CO_2(i) &= k_{CO_2} * [S_{CO_2}(i) - b_{CO_2}] \\ O_2(i) &= k_{O_2} * [S_{O_2}(i) - b_{O_2}]. \end{aligned} \quad (3)$$

The expired volume is measured by means of a water-filled spirometer equipped with an unidirectional valve. The volume channel is calibrated by injecting a known volume into the spirometer by means of a calibrated syringe. A linear transduction function is then identified starting from the volume changes

$$V(i) = k_V * [S_V(i) - b_V] \quad (4)$$

where k_V and b_V are volume channel sensitivity and offset.

The uncertainty after calibration can be estimated by combining

- the uncertainty of the gas standard mixtures;
- the residual linearity error, which is obtained from the manufacturer specifications;
- the amount of noise, which is estimated by measurements in steady conditions;
- the short-term drift of the calibration parameter, which is estimated by repeated calibrations.

The resulting standard uncertainty of the gas concentration channels $u_i(O_2)$ and $u_i(CO_2)$ is of less than 0.5% concentration and the uncertainty of the volume channel $u_i(V)$ is of less than 0.05 dm³.

B. Key Point Related Uncertainty

The uncertainty connected to the key point selection depends on both the shape of the breaths and the selection procedure.

An estimation of the uncertainty $u_p(I_k)$ of the k th indicator can be obtained by determining: 1) the indicator sensitivity with respect to each point position p_i and 2) the uncertainty $u(p_i)$ of the point positioning.

If the uncertainty of the point positioning is small, so that a linear approximation of the function f_{I_k} which expresses the relation between point and indicator can be used, the resulting uncertainty is¹

$$u_p^2(I_k) = \sum_{i=1}^{N_p} \left(\frac{\partial f_{I_k}}{\partial p_i} \right)^2 u^2(p_i) \quad (5)$$

where $N_p = 3$ is the number of key points.

The uncertainties $u(p_i)$ of the manual placement can be evaluated by repeated measurements by the same or by different physicians of the same breath. The uncertainty connected to the automatic key point selection can be evaluated by comparing the automatically generated results with the mean of the results obtained by repeated measurements of different physicians on the same breath of the same trace set.

C. Breath-to-Breath Repeatability

The uncertainties $u_b(I_k)$ connected to the breath-to-breath repeatability can be evaluated by determining the experimental standard deviation of the indicators obtained by analyzing all the available breaths of a single patient

$$u_b(I_k) = \sqrt{\frac{\sum_{i=1}^{N_B} [I_k(i) - \bar{I}_k]^2}{N_B - 1}} \quad (6)$$

¹Equation (5) does not contain cross correlation coefficients since the three-point positioning can be considered to be statistically independent.

where

- N_B number of breaths in the considered stream;
- $I_k(i)$ indicator computed on the i th breath;
- \bar{I}_k average indicator value.

In order to correctly estimate $u_b(I_k)$, the indicators $I_k(i)$ used in (6) should be obtained by employing the ‘‘correct’’ values for the key points, i.e., the values obtained by averaging the positions selected by different physicians. If such average values are not available and simple key point positions are employed, (6) overestimates the breath-to-breath repeatability. Attempts could be made to separate the contribution connected to the key points, but the reduced number of available breaths and the possible correlation between the positioning of the key points on sequential breaths make these attempts difficult to employ.

In addition, one should note that all the indicators have a sensitivity with respect to several parameters (breath duration, breath speed, etc.) [5], which are not considered in this analysis. Equation (6) therefore produces a value that could be reduced by applying corrections for these parameters.

D. Feature Uncertainty

The combined uncertainty of a single measurement can eventually be obtained by combining the three uncertainty contributions

$$u_c(I_k) = \sqrt{u_i^2(I_k) + u_p^2(I_k) + u_b^2(I_k)}. \quad (7)$$

If more measurements of the same stream are available, a better indicator estimation can of course be obtained by averaging the available measurements

$$\bar{I}_k = \frac{\sum_{i=1}^{N_B} I_k(i)}{N_B}. \quad (8)$$

In this case, the expected uncertainty is lower, even though not all the uncertainty contributions can be reduced by the averaging. In particular, a high correlation of the instrument-connected uncertainties $u_i(O_2)$, $u_i(CO_2)$, and $u_i(V)$ is expected for measurements on the same stream. By assuming a complete correlation of the instrument related uncertainty and no correlation between the other uncertainty sources, the uncertainty can be expressed as

$$u_c(\bar{I}_k) = \sqrt{u_i^2(I_k) + \frac{u_p^2(I_k) + u_b^2(I_k)}{N_B}}. \quad (9)$$

V. EXPERIMENTAL RESULTS

The proposed algorithm has been applied to traces obtained from 378 patients monitored during 1999. Fig. 3 shows the histogram of the number of breaths identified in the different streams by the automatic placement program. The automatic placement system has been able to recognize at least one breath in 369 (98%) patients and more than two breaths in 342 (90%) of the patients.

The estimation of the uncertainty connected to the manual point positioning has been performed by asking three physicians to place the key points on 13 different breaths of 11 different patients. The 13 breaths have been randomly and anony-

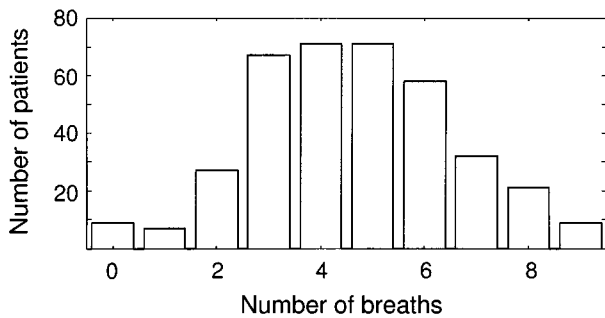


Fig. 3. Number of breaths detected by the automatic system.

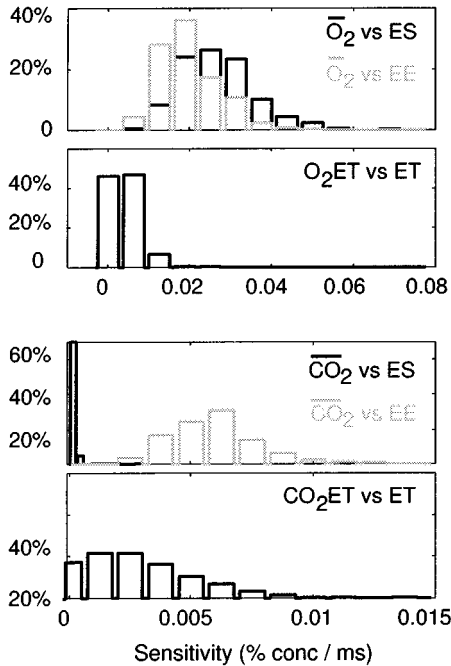


Fig. 4. Sensitivity of the four indexes with respect to ES, EE, and ET.

mously presented to the physicians in two sessions over two days eventually collecting 95 placements. Standard deviations of 19 ms, 32 ms, and 64 ms were observed, respectively, for ES, EE, and ET. Such values correspond to an uncertainty of about one sample for ES and EE and to about three samples for ET.

As explained in the previous section, the mean values of the key points placed by the physicians have been taken as reference values for the estimation of the correctness of the automatic point placement. The values obtained by the automatic system are consistent with respect to the reference values for ES and EE (average differences below 8 ms), while a not negligible mean difference of about -28 ms characterizes ET. The standard deviation of the differences between automatically obtained values and the physician average has been 16 ms, 28 ms, and 44 ms, respectively, for ES, EE, and ET.

The sensitivity of each indicator to the key points greatly depends on the trace aspect and has to be computed each time a measurement is performed, even though it is interesting to derive an average value to estimate the importance of the operator dependent uncertainty. Fig. 4 shows the distribution of the sensitivity values of the 361 patients with respect to ES, EE, and ET. The O_2 related traces have a greater sensitivity with respect

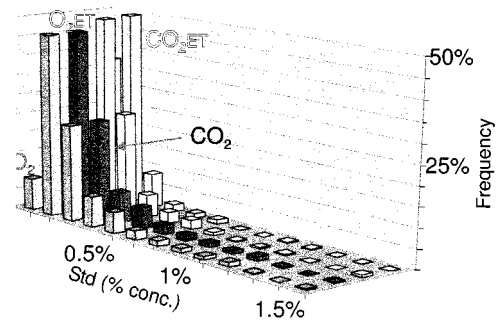


Fig. 5. Observed inter-breath repeatability.

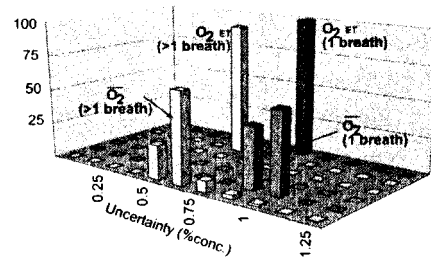


Fig. 6. Uncertainty for O_2 indexes.

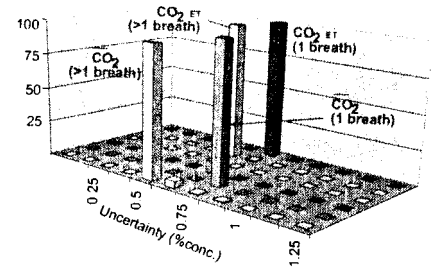


Fig. 7. Uncertainty for CO_2 indexes.

to the CO_2 ; however, most of the breaths have a sensitivity below 0.03% conc/ms. This implies that the key point related uncertainty is generally expected to be below 0.6% of concentration on the O_2 indexes and below 0.2% concentration on the CO_2 indexes.

The inter-breath repeatability has been computed by analyzing the results for patients for which more than one breath has been identified. Fig. 5 shows the inter-breath repeatability obtained for the four indexes. The inter-breath repeatability is rather low and almost always lower than 0.5% concentration, thus being lower than the dispersion which is expected as a consequence of the key point positioning. This confirms that a correlation exists between the positions of the key points placed by the automatic system on subsequent breaths of the same patient and therefore that (6) is a reasonable way of estimating the inter-breath dispersion, even though the average key point values are not available.

The combined feature uncertainty can eventually be estimated according to (7) or (9) depending on the number of identified breaths. Figs. 6 and 7 show the uncertainty distribution observed on the 369 patients, respectively, for the O_2 and CO_2 indexes. The figures contain two distributions for each index: one distribution refers to the patients where only one breath was identified, while the other refers to all the other patients. The uncertainty when only one breath is available

reaches values above 1% concentration for both $\overline{O_2}$ and $\overline{CO_2}$. Such an uncertainty greatly decreases when more breaths are considered: in this case uncertainties near the instrumental uncertainty (0.5%) are observed in most cases. The same difference is observed also for the ET values, which always have uncertainties below 1%.

VI. CONCLUSIONS

The uncertainty of health indicators derived from the evolution of important clinical parameters is connected to the employed instruments, to the processing and to the intrinsic indicator repeatability. While the first contribution can easily be determined, the other two require a more complex analysis, since, in many cases, the data processing relies on subjective decisions.

This paper describes a procedure that can compute the overall uncertainty in the case of indicators derived from expired gas traces. This is an interesting example since the processing which is required to compute such indicators relies on a "by sight" selection of three key points on the recorded traces and therefore is suitable to highlight the operator-related uncertainty contributions. In addition, the recorded traces often contain enough samples to perform more than one measurement, and therefore an estimation of the intrinsic uncertainty can be obtained.

A population of 378 patients monitored over one year has been used to estimate the parameter repeatability, while the effect of the operator has been estimated by analyzing the values obtained by different operators that analyzed the same recorded traces.

The obtained uncertainty values have been eventually used to estimate the overall uncertainty of the required features when only one feature determination is available. When more measurements are available, their mean value has been used as indicator, while the uncertainty has been estimated taking the effect of the average processing into account. The uncertainty estimation has been implemented within the program that manages the data acquisition and computes the features, so that the final result is automatically tagged with its uncertainty, thus helping the physician to evaluate the index importance.

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