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# A medical information system for monitoring respiratory function and related nonlinear dynamics*

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***Abstract*— In this paper the nonlinear effects in the respiratory systems at low frequencies are measured and evaluated in healthy children and healthy adults. To this aim forced oscillations technique (FOT) has been used to non-invasively measure the lung tissue mechanics. FOT does not require any special effort from the patient in contrast with standardized tests where maneuvers are necessary. Hence, FOT is an ideal lung function test for extreme ages, more specifically children and elderly, given the simpleness of measurement technique. Hitherto, measurements at low frequencies (i.e. close to the breathing frequency $\approx$ 0.3 Hz) have been invasively performed in sacrificed animals and on anesthetized humans. Here we measure in the frequency interval 0.1-2 Hz a total number of 94 volunteers (37 adults with ages between 25-35 years and 57 children with ages between 8-11 years). To evaluate the non-linear contributions of the respiratory tissue, a novel T-index has been introduced. We have tested the hypothesis whether the nonlinear distortions are changing with growth/development of the respiratory tree and aim to quantify its dependence to biometric values. The results obtained indicate that the proposed index can differentiate between the two analyzed groups and that there is a dependence to age, height and weight. A medical information system may use this information to update predictions of respiratory function and provide aid in decision-making process of drug therapy.**

## I. Introduction

Viscoelastic properties are characteristics of materials such as polymers, found to be similar to lung tissue [1]. In the human lungs these properties are changing with disease [2] which can be identified in early stages by evaluating the respiratory impedance at low frequency [3]. To capture these changes, measurements close to the breathing frequency ($\approx$ 0.3Hz) have to be performed. Hitherto, measurements at low frequencies have been done in sacrificed animals and in anesthetized patients [4]. All these studies imply invasive respiratory impedance evaluation. Hence, efforts have been made to design a device/technique capable to measure in a non-invasive way at low frequencies. However, in this case interference with the breathing signal occurs. To overcome a possible bias, filtering techniques have been proposed in literature. More specifically, the filtering between the breathing of the patient (acting as disturbance) and the effect of the excitation signal in the lungs (which is actually the useful information one wants to extract) is not possible using classical low pass filtering techniques. Therefore, non-linear estimators have been proposed to separate the breathing signals from the respiratory response [5], [6].

Standardized, clinical practice requires specific maneuvers from the subject (e.g. spirometry), i.e. maximal inspiratory and expiratory effort are required. For example, in order to differentiate between patients with asthma and chronic obstructive disease (COPD) spirometry in combination with other techniques (e.g. broncho-provocation) is employed [7]. Therefore, measurement and estimation of impedance by means of forced oscillation technique have been widely investigated for several years to show its added value and complementarity [3], [8]. This is a non-invasive procedure which does not require any special maneuvers from the patient and it requires minimal effort which makes this method an ideal lung function test, especially for the limit ages (children and elderly). Forced oscillation technique (FOT) can be briefly described as an oscillatory air flow superimposed on the breathing of the patient [9]. FOT has been broadly used for screening purposes, e.g. upper airway obstruction, small airway disease in COPD [10], respiratory mechanics in obstructive sleep apnea [11].

The non-invasive FOT is used to measure the respiratory mechanics at low frequencies (i.e. 0.1-2Hz) in two groups of volunteers (i.e. adults and children). For these measurements, the device described in [12] has been employed. As mentioned above, when measuring at low frequencies interference between the breathing signal and excitation signal occurs. For this, a nonlinear estimator has been employed to eliminate the disturbance signal (i.e. breathing) without losing the information about the respiratory response. However, the mathematical details have been described elsewhere [5], [6], [12], [13], [14].

In this paper the non-linear contributions of the respiratory tissue have been evaluated by means of T-index. The hypothesis tested here is to evaluate if there is a significant difference between children and adults and if this can be achieved by means of the proposed non-linear T-index. The results obtained indicate that the T-index can differentiate between the two groups and it is important to mention that this index can be determined by-passing the respiratory impedance. Moreover, up to now there are no studies reporting measurements at low frequencies in healthy volunteers.

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## II. MATERIALS AND METHODS

### A. Subjects

In this study two groups (i.e. adults and children) of subjects have been evaluated. First set of measurements, i.e. 37 adults, was performed in our laboratory, while second set of measurements, i.e. 57 children, was performed in St. Vincentius Basis School in Zwijnaarde, Belgium during 2015-2017. The biometric data is given in table I.

TABLE I

BIOMETRIC PARAMETERS OF THE HEALTHY SUBJECTS, VALUES ARE PRESENTED AS MEAN ± SD (SD: STANDARD DEVIATION)

| | Adults | | Children | |
|---|---|---|---|---|
| | F (n=10) | M (n=27) | F (n=32) | M (n=25) |
| Age (yrs) | 27 ± 2 | 25 ± 2.9 | 11± 0.9 | 11± 0.8 |
| Height (cm) | 167 ± 2.5 | 173 ± 6.6 | 143 ± 6.4 | 145 ± 6.2 |
| Weight (kg) | 57 ± 2.5 | 79 ± 4.8 | 36 ± 3.8 | 36 ± 3.9 |
| BMI | 20 ± 0.58 | 26 ± 2 | 17 ± 1.07 | 17 ± 1.5 |

### B. Protocol

Measurements were performed in the sitting position with the head in an upright position. During the measurement the subject has to firmly support his/her cheeks using both hands and uses a nose clip. The subjects were instructed to breath normally without any special manoeuvres, according to guidelines from [8]. The measurement time is 120 seconds per volunteer. For the children group, the teacher was allowed to accompany them and good cooperation was achieved. The subjects were instructed to avoid swallowing, glottis closure, leak around the mouthpiece, improper seal with the nose clip, irregular breathing. Data with artefacts was discarded.

Written informed consent was obtained from all participants. In the case of children group the teacher has also signed for every evaluated child. This study and the consent procedure was approved by the local ethical committee of Ghent University Hospital, Ethical advice number B670201111936.

### C. FOT device with disturbance rejection

In this study the FOT non-invasive lung function test was applied to the subjects [5], [8]. Air-pressure variations $P$, with respect to atmospheric pressure and corresponding airflow $Q$ during an FOT test are measured at the mouth of the patient. The resulting data is a frequency dependent representation of mechanical properties and it is characterized by an absolute value in function of frequency of the respiratory mechanics. This is known as best linear approximation (BLA) and was evaluated in the frequency range 0.1-2 Hz [6].

The device used for the analysis presented in this paper is a third generation of the prototype described in [5], [12], [14]. The system consists of a group of fans located on each extreme of a main pipe. One group pushes the air into the tube, while the group on the other side of the tube extracts the air. The desired difference in speed between the two groups will generate a controllable pressure inside the pipe. At the patient-end part of the device is a pneumotachograph and two pressure sensors. A mouthpiece is mounted on the device for every patient tested (single-use). By measuring at frequencies close to the breathing frequency of the patient, important interference occurs, which has been tackled by open loop feedforward compensation (FF) and closed loop feedback compensation (FB) techniques.

In figure 1 the desired pressure (red dashed line, upper graph) and the measured pressure (blue continuous line, upper graph) with the corresponding flow (middle graph) and the excitation signal (lower graph) are represented. Observe in middle graph the low frequency of the breathing of the volunteer. When no saturation of the fans occurs, the setpoint can be easily followed by the inner control system.

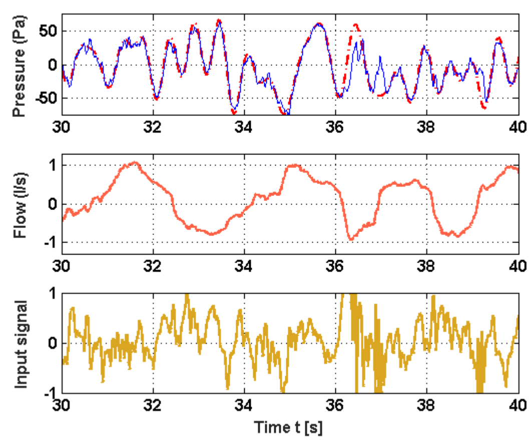


Fig. 1. Typical measured signals from one subject. Upper graph: desired pressure (red line) and measured pressure (blue line); middle graph: the measured flow; lower graph: the input (excitation) signal.

To ensure that the lungs are excited with the correctly designed excitation signal (i.e. input), the FOT concept has been augmented. More specifically, a feedforward and feedback control strategy has been implemented in order to avoid the interference problem, as mentioned in section II-C. The feedforward action takes into account the dynamics of the device and feedback action will suppress the pressure disturbance caused by the patient's respiration (D) and any residual (N). This is depicted in figure 2 by the filtered signal $UM/P^*$, where a schematic block scheme of the implemented control strategy is presented.

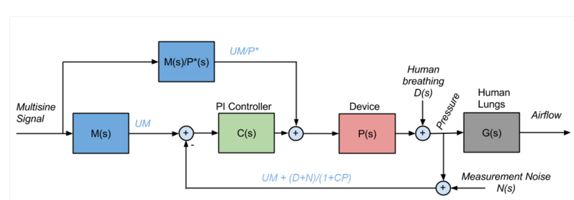


Fig. 2. Block scheme of the implemented control: blue represented the feedforward compensation, green represented the linear feedback controller; red denotes the device.

A set of control designs have been used, the step setpoint test is depicted in figure 3 [15], [16], [17].

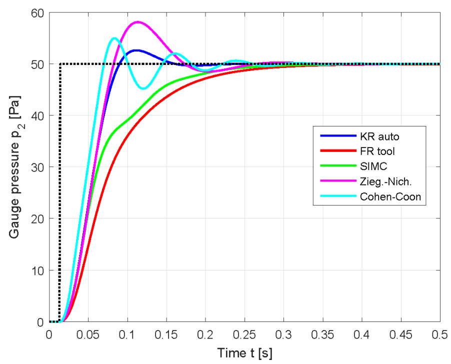


Fig. 3. Setpoint tracking performance with various control designs. All previously published tuning methods, such as: KR autotuner, FRTool CAD design, SIMC method, Ziegler-Nichols and Cohen-Coon methods were compared.

Feedforward loop (figure 2) introduces the dynamic inversion of the process model ($1/P^*$) in order to ensure that the system receives the exact control effort required to achieve the desired output. This leads to a non-proper transfer function and therefore a first order filter (M) with a very small time constant ($\tau_m$) has been introduced.

However, in this case the contribution of the patient in the model is not taken into account (i.e. model identified with the sealed off mouthpiece = no patient). When the patient is in the loop then disturbances (D) are introduced, implicitly process model parameters are changing. Therefore, it is required to close the loop with a feedback controller signal $UM + (D + N)/(1/CP)$ where C is a PI-controller. For this, controller has been tested with a sealed (no patient) mouthpiece. The results obtained indicated a 96% fit between the desired and measured data.

### D. Analysis of nonlinearities in the lung tissue

The influence of nonlinear distortions on the frequency response of measurements are quantified by using identification methods given in [18]. A brief description of the essential steps is given hereafter.

$$U(t) = \sum_{k=1}^{N} A_k \cos(k\omega_0 t + \phi_k) \quad (1)$$

Consider an input signal defined as a random phase multisine with $A_k$ the non-zero amplitude for odd $k$ values, $\omega_0 = 2\pi f_0$ and $f_0 = 0.1$ Hz, $\phi_k$ the phase uniformly and independently distributed in the $[0; 2\pi]$ interval and $N$ the number of sinusoids. The best linear approximation (BLA) of a nonlinear system can be viewed as a minimization of the mean squared error between the true output of the nonlinear system and the output of an approximated linear model. The estimated BLA $\hat{G}_{BLA}(j\omega_k)$ of a wide class of nonlinear systems, obtained using (1) can be written as:

$$\hat{G}_{BLA}(j\omega_k) = G_{BLA}(j\omega_k) + G_S(j\omega_k) + N_G(j\omega_k) \quad (2)$$

with $G_{BLA}(j\omega_k)$ the true best linear approximation (BLA) of the nonlinear system, $G_S(j\omega_k)$ the zero mean stochastic nonlinear contributions and $N_G(j\omega_k)$ the measurement noise [6], [18]. The stochastic nonlinear contributions $G_S(j\omega_k)$ can be extracted by averaging from a manifold of experiments containing different phase realizations in the excitation signal from (1). The basic principles for detecting nonlinearities are shown in figure 4. The output of a linear system, which is excited with a multi-frequency input signal, is given on the first row. Only amplitude variations on the excited (odd harmonics) frequencies are observed (red). However, when this input signal is applied on a nonlinear system (e.g. the respiratory tissue), nonlinear dynamics become visible and can be measured as additional detection lines (second and third row in blue and green). These distortions are in fact superimposed to the linear output signal and contribute to the signal measured at the output (last row). The resulting output signal contains extra information via phase differences. The nonlinear contributions can be determined via the identification of the even and odd harmonics (blue and green). A detailed description of the method can be found in [6], [18].

In order to quantify these nonlinear contributions, the following index has been introduced in [13]:

$$T = \frac{P_{even} + P_{odd}}{P_{exc}} \cdot \frac{U_{exc}}{U_{even} + U_{odd}} \quad (3)$$

where $P$ represents the pressure and $U$ is the input signal. Each variable is the sum of the absolute values of all the contributions in pressure signal and input flow signal respectively, at the even non-excited frequencies, the odd non-excited harmonics and the excited odd harmonics as schematically depicted in figure 4. Only the corrected output pressure has been taken into account when calculating (3), i.e. the linear contribution has been estimated and subtracted. The principle of detecting the non-linear contributions has been described elsewhere [18].

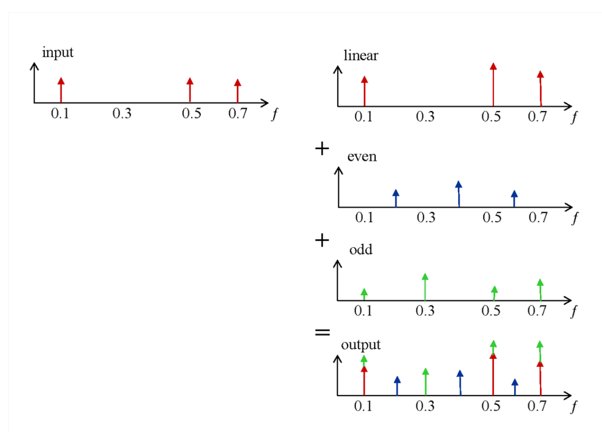


Fig. 4. A schematic representation of the input-output contributions.

## III. Results and discussion

Since the airway and tissue compartments exhibit distinctly different frequency dependence, a model-based evaluation of the pulmonary and respiratory impedance data offers a valuable alternative of the airway and tissue mechanics. To achieve this comprehensive description, the lung viscoelasticity was extensively evaluated in the early 1970s by Hildebrandt and co-workers [19], [20], [21], [22]. In their studies, the linear viscoelastic phenomena of the pulmonary system were resolved. Furthermore, the derived linear model in the time domain exhibited characteristics such as stress relaxation and dynamic hysteresis ascribed to viscoelasticity. If these properties are examined in the frequency domain, the airways and respiratory system tissues reveal characteristically different dependences on frequency that allow a separation of their contributions to impedance on the basis of mathematical models.

In clinical practice FOT is applied in the frequency range 2-40 Hz where the oscillatory signal is superimposed on the spontaneous breathing. Within this medium-frequency range, the imposed oscillations start roughly one decade above the spontaneous breathing rate and extend up to a few times the resonant frequency of the lungs. Over the low-frequency range (around 2-4 Hz), the respiratory tissues predominate and the steep increase in reactance with frequency is mirrored by a marked decrease in resistance [23], [24]. In the medium-frequency range (2-40 Hz), the resistance expresses no more than mild changes, while at the first resonance (reactance = 0) the reactance undergoes a transition from dominance by the tissue elastic properties to dominance by the inertial properties of the gas in the airways. At higher frequencies (7-250 Hz) the airways mechanics become dominant [13].

In figure 5 the results obtained for adults group and for children group are presented. From the obtained results it can be seen that the T-index for children is lower than in the adults group. This is due to the fact that the lung tissue of the children is more homogeneous since they are in the growing phase and the lungs are still in development. This indicated that the nonlinearities in children are less than in adults where the number of airways/alveoli increases, hence an increase turbulence in airflow occurs. This is in line with studies on airways and thoracic growth that suggest a dysanapsis (mismatch of the changes in airway size and lung size) growth pattern of different parts of the respiratory system.

In figures 6 and 7 the dependence of the nonlinear T-index as a function of biometric parameters (age, height, weight) are given. The obtained results indicate that nonlinear T-index is increasing with height, weight and age of the subject. By means of this index the relative ratio of the non-excited with respect to excited harmonics is determined. Even more, this index provides a relative measure of the gain between contribution in the input and output signals of the system. Given that the respiratory system is nonlinear system whose output depends on the input, one may conclude that the choice of this relative measure is technically sound.

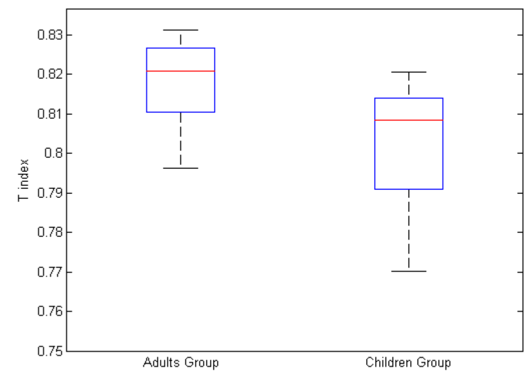


Fig. 5. Boxplot for the non-linear distortions in adults and children groups.

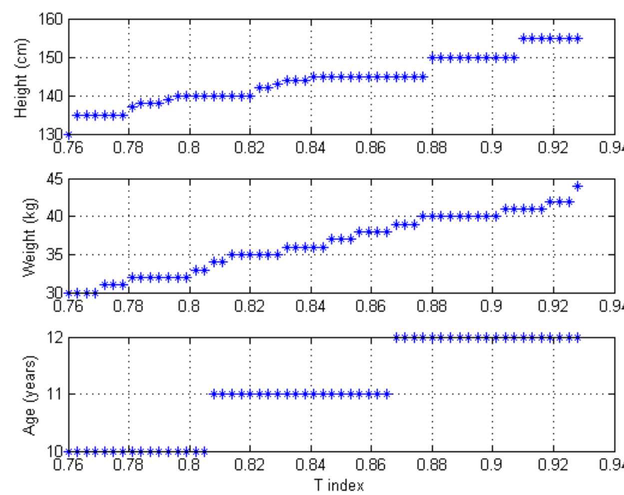


Fig. 6. Children: Relation between non-linear index and the biometric parameters.

In table II the fitted linear regression model to identify the relation between the nonlinear index and the biometric parameters are given.

TABLE II

Regression equations for the evaluated groups in function of age, height and weight

| | Adults | Children |
|---|---|---|
| Age (yrs) | y = 0.015x + 0.42 | y = 0.058x + 0.2 |
| Height (cm) | y = 0.0063x - 0.29 | y = 0.0077x - 0.27 |
| Weight (kg) | y = 0.0049x + 0.41 | y = 0.013x + 0.38 |

## IV. A medical information system for patient monitoring

From the medical informatics point of view, health-related information technology consists of a wide range of networking technologies, clinical databases, electronic

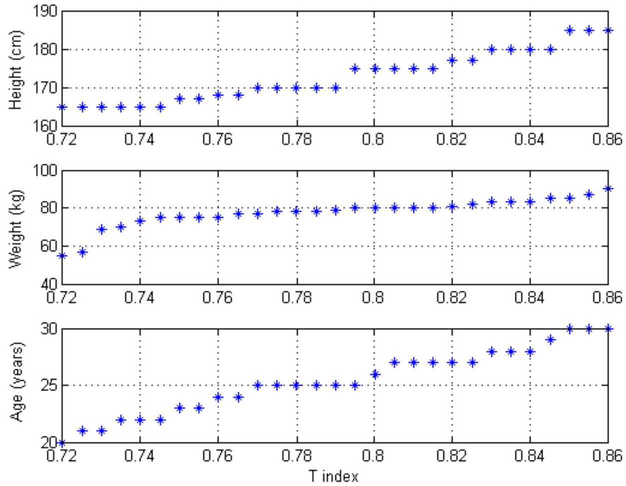


Fig. 7. Adults: Relation between non-linear index and the biometric parameters.

medical/health records, and other specific biomedical, administrative and financial technologies that generate, transmit and store healthcare information [25]. In the diagram below, a generic model of information flows that typify health information systems infrastructure in our project is presented below.

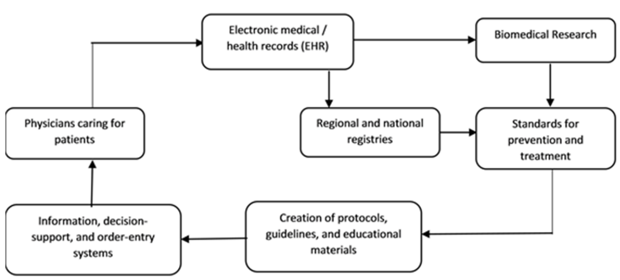


Fig. 8. A generic healthcare information system and its elements.

Healthcare information systems (HIS) have been critically acclaimed for their ability to increase legibility, reduce medical errors, shrink costs and boost the quality of healthcare. HIS, as proposed in our project is expected to save money in the long run and generate organizational profitability through efficiencies, cost-effectiveness and safety of medical care deliveries. It will reduce expenses associated with record-keeping while meeting privacy regulation standards and improving workflows, practice management and cost management. HIS is also expected to permit automated sharing of information among providers (both COPD patient side and caregiver side), reduce office visits (to provide quality of life information and/or to receive tests results) and hospital admissions (due to missing information), and even reduce risks of malpractice on caregiver side.

For our project goals, we expect HIS to contribute to improve overall quality of care and patient outcomes in the COPD population in Belgium. These include:

- more complete, accurate and structured clinical data documentation;
- automatic sorting and summarization of data for information generation;
- direct access to instant updates to records as well as remote access to patient records;
- reduced medical mistakes from legibility and order entry errors;
- increased decision support from structured data and predictive modeling and disease management tools;
- data mining capabilities provided by the vast amounts of structured medical record data contributing to disease research and preventive interventions in clinical care; and
- continuous improvement in clinical decision making through decision support (enabled by health information exchange), rapid dissemination of information and quicker monitoring of care.

Through the aforementioned capabilities of HIS, mistakes are minimized, information quality is enhanced, treatment response times are improved, and optimal decision-making is attained.

The end-goal is to provide an easy access, secured, personalized database of information for both caregiver and patient side. This implies the delivery of both static and dynamic tools of information, i.e. server based database with mobile app access points. An application for caregiver side and another one for patient side will be programmed and developed for use in mobile electronic devices. A software platform will be developed for server logging and information access purposes.

For the purpose of wearable FOT technology for monitoring respiratory dynamics, the prototype presented in [26] can be re-visited.

## V. CONCLUSIONS

In this paper the hypothesis whether or not the amount of non-linear distortion is changing during the development of the lung has been investigated. The measurement setup used in this study allows to excite the patient with a multisine excitation in the frequency range of spontaneous breathing (0.1 - 2 Hz). The measurements indicate that pressure oscillations can be imposed even when patient's breathing is constantly disturbing the pressure signal. This has been achieved by implementation of feedforward and feedback loops to compensate the interference between the input signal and the breathing signal. Since this method does not require any special manoeuvres it is comfortable for patient and useful for routine use in lung function measurements. Measurements have been performed during two campaigns on a total of 37 adults and 57 children (all volunteers are healthy). The results obtained for these two groups confirm the hypothesis investigated in this paper, more specifically the non-linear T-index can be used to classify between healthy children and healthy adults. Next step is to implement a medical information system platform for monitoring and prediction of respiratory function.

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