The evolution of fractional order respiratory impedance models and their impact on lung function device development

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Abstract

This paper presents a systematic overview of fractional order impedance models describing viscoelastic properties in respiratory tissue during tidal breathing and afferent lung function testing devices. A technological development timeline is given and current state of art is evaluated with clinical data in healthy subjects and chronic obstructive pulmonary disease diagnosed patients. Further technological and methodological improvements are suggested.

Key words: respiratory impedance, fractional order impedance, lung function test, forced oscillatory technique, viscoelastic properties, low frequency interval, nonlinear distortions

1 Introduction

Biological tissues are complex systems characterized by dynamic processes that occur at different length and time scales. Accordingly, simple Debye (D) models cannot adequately describe the behaviour of such materials because these models are unable to represent interactions between various relaxation phenomena and memory effects [1]. Non-integer formulations of the D relaxation model are often necessary to account for the rich phenomena that take place within biological materials at different scales [2, 3, 4, 5].

Comprehensive overviews of the use of fractional calculus (FC) tools in biological applications can be found in several works [6, 7, 8, 9].

Validation of models emerging from fractional calculus in biological applications has been numerous, e.g. in vegetables and leaves [10, 11], in frog muscles [12], in animal lung tissue [13, 14, 15], in respiratory impedance [8, 16], diffusion of drugs into the body [17, 18], etc.

The respiratory system has complex dynamics including viscoelastic properties, memory effects and diffusion mechanisms. A detailed integer order and fractional order modelling has been given with electrical analogy and mechanical analogy in [8, 16]. This paper is an overview of models developed for characterising respiratory properties and related lung function methods and devices.
2 Modelling Viscoelasticity

The most basic view of lung tissue mechanics is a static one expressed in terms of lung compliance defined as the ratio of a change in lung volume to the corresponding change in applied pressure. Lung compliance depends on lung volume so the quasi-static pressure-volume relationship of the lung is frequently expressed in terms of an exponential function that captures the strain stiffening observed experimentally [19]. The tissues of the lung are highly viscoelastic, which means that lung pressure depends markedly on lung volume history. This was first articulated mathematically in the 1930’s by Mount [20], but it was not until the studies of Hildebrandt several decades later that stress relaxation in lung tissue was shown to be poorly described by decaying exponential functions, which are the solutions of ordinary differential equations involving derivatives of integer order [21, 22]. Rather, Hildebrandt showed that the pressure, \( P \), inside a rubber balloon following a step change in volume, \( V_T \), is much better described either by a power-law function of time:

\[
P(t) = A t^{-n} + B,
\]

where \( 0 < n << 1 \), or by its truncated series approximation as a logarithmic function of time

\[
P(t) = C - D \log t
\]

where \( A, B, C, D \) are constants. The transfer function obtained by applying Laplace Transform to (1) is:

\[
P(s) = \frac{P(s)}{V_T} = \frac{A \Gamma(1-n)}{s^{1-n}} + \frac{B}{s}
\]

where \( \Gamma \) is the Gamma function. If the input is a step function of amplitude \( V_T \), then \( V(s) = V_T/s \) and eqn. (3) becomes

\[
P(s) = T(s) = A s^{-n} \Gamma(1-n) + B
\]

To account for the mass of air introduced into the balloon, the transfer function requires the addition of an inertive term to give:

\[
T(s) = \frac{P(s)}{V(s)} = A s^{-n} \Gamma(1-n) + B + L_r s^2
\]

where \( L_r \) is the equivalent of electrical inductance. However, it is more likely that the lungs perform dynamical changes as a function of sinusoidal inputs, hence it is meaningful to express its frequency-dependent respiratory impedance form:

\[
T(j \omega) = A \Gamma(1-n) \omega^n \cos(\frac{\pi \omega}{2}) - L_r \omega^2 + B + j[A \Gamma(1-n) \omega^n \sin(\frac{\pi \omega}{2})]
\]

After applying this expression to the dynamic pressure-volume behaviour of a rubber balloon, Hildebrandt showed that it could also be applied to an isolated cat lung [22].

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Two decades later, Hantos and co-workers built on Hildebrandt's work to model the complex impedance of the lung as [13, 14]:

\[ Z(j\omega) = R_r + L_r(j\omega) + \frac{1}{G \cdot s^\beta}, \quad (7) \]

This expression has been shown to accurately describe the impedance of the lung below about 20 Hz in numerous species and has become an "off the shelf" available model. The last term in (7) consists of a constant-phase element which can be split into a real and imaginary part, denoting tissue damping and tissue elastance:

\[ G = \frac{1}{C \cdot \omega_0} \cos(\beta \pi/2) \]
\[ H = \frac{1}{C \cdot \omega_0} \sin(\beta \pi/2) \quad (8) \]

and their ratio denotes the degree of heterogeneity present in the tissue [23], also known as hysteresivity. Hence, the expression given in (7) is generally referred to as the constant-phase model because the phase arising from the tissue component is independent of oscillation frequency.

In [8], each parameter in the above described model has been linked to the anatomy, structure and function of the respiratory tree, airways and alveoli. An electrical analogy has been made to approximate the resistance, inductance and capacitance of airway segments as a function of their morphology, anatomy and function. The following relations have resulted [24, 25]:

\[ R_e = \frac{\ell - \mu \ell^2}{\pi R^4 M_{10}} \sin(\xi_{10}) \quad (9) \]
\[ L_e = \frac{\ell \rho}{\pi R^2} \frac{\cos(\xi_{10})}{M_{10}} \quad (10) \]
\[ C_e = \frac{2 \pi R^2 (1 - \nu^2)}{E h} \quad (11) \]

where \( \ell \) is the airway tube length, \( R \) is the tube radius, \( h \) is the wall thickness, \( \mu = 1.8 \times 10^{-5} \) kg \cdot (m \cdot s)^{-1} is the air viscosity, \( \rho = 1.075 \) kg \cdot m^{-3} is the air density, \( \delta = R \sqrt{\frac{\mu \cdot 2}{\rho}} \) is the dimensionless Womersley parameter and \( \omega = 2\pi f \) is the angular frequency in rad/s with \( f \) the frequency in Hz. The term \( \xi_{10} \) is the phase angle of the complex number from Bessel function of rank 1 and order 0 and the term \( M_{10} \) is the modulus of the complex number from Bessel function of rank 1 and order 0; and \( \nu_F \) is the Poisson coefficient [24]. The effective elastic modulus \( E \) is determined by the fraction \( \kappa \) of cartilage and soft tissue in the airway wall:

\[ E = \kappa E_c + (1 - \kappa) E_s, \rho_{wall} = \kappa \rho_c + (1 - \kappa) \rho_s \quad (12) \]

where subscripts \( c \) and \( s \) correspond to cartilage and soft tissue respectively, with \( E_c = 400 \) kPa, \( E_s = 60 \) kPa, \( \rho_c = 1140 \) kg/m\(^3\), \( \rho_s = 1060 \) kg/m\(^3\).

These elements have been extensively used in recurrent ladder networks to mimic the respiratory tract and led to natural appearance of fractional order derivative and integral terms [8, 25, 26, 27]. It has also been shown that the hysteresivity term from (8) is an indication of the existence of nonlinear contributions in the respiratory dynamical properties.
Furthermore, if changes in \( R \) are small, then any changes in \( G \) (kPa s\(^{1-\beta}\)/L) will represent changes in parenchyma or in very small airways. Chronic changes in \( H \) (kPa s\(^{1-\beta}\)/L) reflect changes in the intrinsic mechanical properties of the parenchyma, as shown in several groups of diagnosed patients reported in [8].

### 2.1 The Mechanistic Basis of Power-Law Stress Relaxation

Suki et al. [28] list the following five classes of systems in which power-law relaxation or constant-phase impedance arise:

- **Class 1:** Systems with nonlinear constitutive equations.
- **Class 2:** Systems in which the coefficients of the constitutive differential equations are time-varying.
- **Class 3:** Systems with multiple degrees of freedom characterized by a continuous distribution of time constants.
- **Class 4:** Complex dynamic systems exhibiting self-similar (fractal) properties.
- **Class 5:** Systems governed by differential equations of fractional order.

The above five system classes have each been invoked to account for examples of power-law or constant-phase behaviour, but they fail to make a direct link between the phenomenon being described and the micro-level physics responsible. Bates [16] proposed that the common element to all of these processes is what might be termed *sequentiality*; they arise as a result of activity taking place within systems in a sequential fashion rather than in a parallel fashion distributed simultaneously across the entire system. Bates showed that when collections of springs and dashpots are arranged so as to exhibit sequential behaviour they automatically give rise to power-law stress relaxation. This occurs even when the constitutive properties of the springs and dashpots are highly nonlinear. Furthermore, the exponent of the power-law is independent of the amplitude of the step in strain that is administered to cause stress relaxation, a well-described phenomenon known as quasi-linear viscoelasticity. Similar approaches have been used in models of the arterial wall [29].

### 2.2 Lung Tissue Mechanics

The complex mechanical impedance of various types of biological soft tissue is typically described in terms of a real part, also called the storage modulus, that represents the elastic properties of the tissue, and an imaginary part, also called the loss modulus, that represents capturing its dissipative properties. That is,

\[
E^*(j\omega) = \frac{\sigma(\omega)}{\varepsilon(\omega)} = E_S(\omega) + jE_D(\omega)
\]

where \( \sigma \) and \( \varepsilon \) are stress and strain, respectively. The simplest lumped-parameter model having an impedance of this form is the Kelvin-Voigt body consisting of an elastic element.
(spring with elastance $E'$) in parallel with a viscous element (dashpot with resistance $R$),
that is governed by the ordinary differential equation:

$$\sigma(t) = E\varepsilon(t) + R\frac{d\varepsilon(t)}{dt}$$  \hspace{1cm} (14)

which has impedance

$$E^*(j\omega) = E + j\omega R$$  \hspace{1cm} (15)

More complicated models may consist of arbitrary numbers of such bodies arranged in
series and parallel, the order of the governing differential equation equaling the number of
mechanical degrees of freedom in the model. However, all derivatives in the equation are
of integer order, which translates into a mechanical impedance having terms containing
$j\omega$ raised to corresponding integer powers. We have already seen, however, that lung
tissue impedance exhibits behaviour that depends on frequency raised to a fractional
power (7), which naturally invokes the concept of fractional derivatives and integrals. In
[50] we have shown that mechanical analogy to respiratory tract maintaining morphology,
structure and function leads to appearance of fractional order derivatives and integrals.

The classical Riemann-Liouville definition of the fractional order derivative of a func-
tion $f(t)$ is given by [31, 32, 53]:

$$\frac{d^n f}{dt^n} = \frac{1}{\Gamma(1-n)} \frac{d}{dt} \int_0^t \frac{f(\tau)}{(t-\tau)^n} d\tau$$  \hspace{1cm} (16)

The fractional-order derivative can thus be seen as the convolution of $\varepsilon f(t)$ with $t^{-n}$,
implying some kind of system memory that fades in time according to a power-law. The
two terms of the lumped-parameter impedance of the spring-pot element in (15) can then
be replaced with the single term:

$$\sigma = \eta \frac{d^n \varepsilon}{dt^n}$$  \hspace{1cm} (17)

where $0 \leq n \leq 1$. This relation is the mechanical equivalent of the constant-phase term
in (7), respectively (8). The value of $n$ determines whether the element is either purely
elastic ($n = 0$), purely viscous ($n = 1$), or something in between. Biological soft tissue
exhibits both elastic and dissipative behaviours [34, 29], so the appropriate value of $n$ is
a fraction between 0 and 1.

Hitherto, measuring viscoelastic properties in lung tissue have been performed in-
vensively during anaesthesia in humana [35] or in sacrificed animals [13, 14, 15]. These
extreme experimental conditions are far from the operating conditions of the dynamic
respiratory system during tidal breathing. It is therefore necessary to have non-invasive
methods and devices able to excite respiratory tissue with low-frequency air-pressure osc-
illations in order to estimate the above described dynamical properties. The remainder
of this paper presents the steps undertaken in the past decade towards this objective.

3 Impedance Measuring Devices

The ease of application and straightforward result of the forced oscillation (FOT) lung
function test makes it increasingly popular in current routine pulmonary function tests
[38]. Its added value and parallel evaluation next to standardized routines such as
spirometry and body plethysmography have been broadly documented and brought up-front in healthy subjects and diagnosed patients. The evaluation in terms of respiratory impedance provides specificity and sensitivity to various degree of obstruction in asthma and COPD (chronic obstructive pulmonary disease). The mechanical properties of the respiratory system, i.e. resistance and elastance, are dependent on the breathing frequencies and patterns which obviously vary with pathology [39, 8]. Several processes taking place in the lung during the process of gas exchange make FOT a handy tool for evaluation of tissue viscoelasticity, temporal and spacial heterogeneity, diffusion, etc.

Most of the measurements based on FOT make use of loudspeaker based devices and work in a linear range of oscillation frequencies: 4-48 Hz [38, 41]. Another reason for using this bandwidth is that interference with the breathing signal from the patient is avoided, thus a comfortable situation for the system engineers. Higher frequencies are usually associated with acoustic properties of the respiratory tracts and may be useful to understand effects of aerosol deposition for treatment of upper airways [42, 27].

However, it has been recognized many times that evaluating frequencies closer to the breathing frequencies delivers very interesting information on viscoelastic effects, which become dominant with parenchymal changes occurring in obstructive disease. The bottleneck in this research direction remained for a long time the interference with the breathing and necessity for higher amplitudes in the oscillatory pressure which no longer obeys linearity of the complex dynamical system of lungs. There are few studies discussing generator nonlinearities in the literature. Studies on the original FOT device based on loudspeaker oscillations suggested that its nonlinear nature can introduce artefacts that coincide with the frequencies applied to excite the respiratory system, limiting the accuracy of the impedance estimation [43, 44]. Spectral analysis has been used in one of our previous studies to detect nonlinear distortions coming from the FOT generating device [45]. About three decades ago, a lot of attention has been given to other biasing effects such as of dead-space [46], upper airway shunt [47, 49, 48, 50] and interference with spontaneous breathing [51, 47]. However, most of the studies were evaluated at frequencies well above the spontaneous breathing frequency, while it is generally agreed that most interesting information appears at frequencies below 4 Hz [41]. Since the recent increased interest in the FOT [38], other kind of generating signal devices have been investigated along with improved estimation methods for the respiratory impedance at low frequencies. The remainder of this section provides a historical overview of such devices.

3.1 Commercial FOT Devices

A commercially available FOT setup assessing respiratory mechanics from 4 – 48 Hz is the

**DIAM (Differential Impedance and Acoustic Measurement) device produced by Chess Medical Technologies, The Netherlands (2000).** The specifications of the device from figure 1 are: 11kg, 50x50x60 cm, 8 sec measurement time, European Directive 93/42 on Medical devices and safety standards EN60601-1. The standard measurement time of 8 seconds is attractive because it requires minimal cooperation from the subject. Our previous works indicated that the breathing period in this interval might not be considered as a stationary signal. To avoid biased estimates due to the extremely short measurement time, a second measurement line has been connected to a data acquisition card and the signals were recorded for 30 seconds during our research studies. The subject is connected to the typical setup from figure 2 via a mouthpiece, suitably designed to avoid flow leakage at the mouth.
and dental resistance artefact. The oscillation pressure is generated by a loudspeaker connected to a chamber [52]. The loudspeaker is driven by a power amplifier fed with the oscillating signal generated by a computer. The movement of the loudspeaker’s cone generates a pressure oscillation inside the chamber, which is applied to the patient’s respiratory system by means of a tube connecting the loudspeaker’s chamber and the mouth-filter. A bias tube allows the patient to have fresh air circulation. This pipeline exhibits a high impedance at the excitation frequencies to avoid the loss of power from the LS pressure chamber. During the measurements, the patient wears a nose clip and keeps the cheeks firmly supported. Before starting the measurements, the frequency response of the pressure transducers PT and of the pneumotachograph PN are calibrated [50, 48, 38]. The measurements of air-pressure \( P \) (cmH\(_2\)O) and air-flow \( Q \) (l/s) during the FOT lung function test is done at the mouth of the patient.

Figure 1: Photo of the commercial device I2M (UGent 2003).

The global experimental set-up from figure 2-A can be modelled by the electrical analogy from figure 2-B, where: \( U_g \) denotes the generator test signal (known); \( U_r \) denotes the effect of spontaneous breathing (unknown); \( Z_r \) denotes the total respiratory impedance (to be estimated); \( Z_1 \) denotes the impedance (unknown) describing the transformation of driving voltage (\( U_g \)) to chamber pressure; \( Z_2 \) denotes the impedance (unknown) of both bias tubes and loudspeaker chamber; \( Z_3 \) denotes the impedance (unknown) of tube segment between bias tube and mouth piece (effect of pneumotachograph essentially). It follows that the respiratory impedance \( Z_r \) can be defined as their spectral (frequency domain) ratio relationship [54, 53]:

\[
Z_r(j\omega) = \frac{S_{PU_g}(j\omega)}{S_{QU_r}(j\omega)}
\]  

where \( S_{XY}(j\omega) \) denotes the cross-correlation spectra between the various input-output signals, \( \omega = 2\pi f \) is the angular frequency and \( j = \sqrt{-1} \), the result being a complex variable. The derivation of (18) from the measured signals is detailed in [53]. The FOT excitation signal is kept within a range of a peak-to-peak size of 1-3 (cmH\(_2\)O), in order to ensure linearity [38]. Averaged measurements from 3-5 technically acceptable tests are taken into consideration for each subject, and typical recorded signals are depicted in figure 2-C. An overview of integer-order parametric lumped models for respiratory impedance is given in [40].
Figure 2: A schematic overview (A) and an electrical analogy of the FOT setup (B). Typical measured signals (C) from one subject: oscillatory driving air-flow; air pressure and air-flow. The breathing of the patient (low frequency) can be observed superimposed on the multisine signals. Symbols: LS - loudspeaker; PT - pressure transducer; PN - pneumotachograph; BT - bias tube; bf - biological filter; \( U(t) \) and \( U_g \) - denote the generated pressure oscillations (4-48Hz); \( P(t) \) - measured pressure oscillations; \( Q(t) \) - measured flow; pressure unit conversion: 1 kPa = 10 cm H\(_2\)O.
This commercial device has been improved over the last decades and is now delivered in a compact form, while maintaining the same methodology for evaluating the respiratory impedance over the 4-48 Hz frequency interval. For details see [55].

3.2 Initial Attempts to Develop Devices for Low Frequency Impedance Evaluation

The devices and methods presented hitherto are suitable for evaluating the respiratory impedance at frequencies well above the breathing frequency of the patient. In this way, any nonlinear effects from frequency overlapping and other nonlinear dynamic effects coming from the respiratory tissue are avoided. However, at these frequencies the dominant contributions are from the proximal airways and not the respiratory tissue. Our efforts to develop suitable device for measuring frequencies located progressively closer to the breathing frequency led to the following prototypes.

Limitations arising from air-pressure oscillations generated by means of loudspeaker based systems are known in specialised literature. In essence, the loudspeaker lower limit bandwidth is around 4Hz. A first attempt to improve this bandwidth was to use a more powerful loudspeaker, larger in diameter and with enhanced signal to noise ratio. A laboratory setup is shown in figure 3. The specifications of the device are: 8 kg, 50x20x45, 30 seconds measurement time.

![Figure 3: An improved loudspeaker based prototype device (UGent 2008).](image)

An alternative solution has been proposed as a piston based air-flow displacement generator, as given in figure 4. The specifications of the device are: 7 kg, 60x40x45, 40-60 seconds measurement time. Although the device can create oscillations with frequency below 4Hz, the signal to noise ratio is poor. The mechanical friction between the moving shaft and rotating pieces to move the chamber wall in order to create the desired oscillations prevents qualitative impedance values.
A comparison between the two devices in terms of operability is given in figure 5 by means of the best linear approximation and noise in the system. It can be observed that the mechanical device can deliver better power of the input signal at lower frequencies, at the cost of higher noise in the overall system. The best linear approximation of a dynamical system (i.e. the device) has been estimated using signal processing algorithms presented in [45].

![Figure 5: Bandwidth for the improved loudspeaker based device (left) and for the mechanical device (right). Black line represents the transfer function for operation range of the device (Best Linear Approximation), the two dashed lines represent the noise of the system by means of odd and even nonlinearities and the dotted red line is the variance.](image)

### 3.3 A Successful Fan-Based Device

In an effort to make the device lighter, portable and efficient at low frequencies, the second generation prototype (FOT2G) described in [56, 57] has emerged. The system is formed
by a group of three fans located on each extreme of a principal pipe as depicted in figure 6. The specifications of the device are: 4 kg, 50x20x10, 60-140 seconds measurement time. One group of fans pushes the air into the tube, while the group on the other side of the tube, extracts the air. The controlled difference in speed between the two groups will generate a controllable pressure inside the pipe. The pipe has 2 inches diameter and has been filled with tubes with smaller diameter (straws) in order to preserve a laminar flow. Despite a careful design, nonlinear effects are not completely avoided and their contribution is taken into account in the evaluation of the final impedance result.

The device has been built in a configurable National Instruments CompactRIO (cRIO) platform. The cRIO is a reconfigurable embedded control and acquisition system that includes I/O modules in a reconfigurable FPGA chassis. Additionally, cRIO is programmed with NI LabVIEW graphical programming tools and can be used in a variety of embedded control and monitoring applications.

The signal pressure generated by the device, at the frequencies 0.05–2 Hz, is originated by the group of fans driven by a PWM signal generated by the cRIO platform. The zero value of the duty cycle has been chosen when the pressure signal is zero, and a linear behaviour has been ensured with no hysteresis. In this context, to generate pressure amplitudes lower than 0.2 kPa, as recommended for human use, the duty cycle of the PWM should be slightly more than 50%.

A schematic description of a cleaned up version of this device is given in figure 7, i.e. the third generation FOT3G device. This device is currently used in Ghent University Hospital to perform measurements of respiratory impedance in asthma and chronic obstructive pulmonary disease diagnosed patients. Photo of the device is given in figure 8.

4 Clinical Validation

The study included in this paper consists of 60 chronic obstructive pulmonary disease (COPD) diagnosed patients (≥ 60 years) who came for periodic evaluation of their lung function at Ghent University Hospital, Belgium during 2013-2015 and evaluated with the FOT2G device. Biometric and spirometric variables are listed in Table 1. All subjects
Figure 7: Schematic overview of the final version of the fan-based device used for clinical studies (FOT3G).

Figure 8: Photo of the fan-based device used in clinical studies (UGent 2016, FOT3G).
Table 1: Biometric characteristics and baseline lung function data for the patients included in the study.

<table>
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<th>GOLD III</th>
<th>GOLD IV</th>
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<tr>
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<td>(42,48)</td>
<td>(27,31)</td>
<td>(95,98)</td>
</tr>
</tbody>
</table>

Figure 9: Evolution of the index H per group ($p < 0.01$).

gave their written informed consent and the protocol was approved by the local ethical committee. The group of COPD patients has been classified in three sub-groups, in increasing degree of obstruction: GOLD II, GOLD III and GOLD IV.

The estimated values of airway resistance $R$ and airway inductance $l$ had no normal distribution, hence were not used to perform further analysis. The trends for the tissue elastance $H$ are depicted in figure 9, by means of Anova plot (Matlab). The values estimated at each frequency point according to (8) and for all subjects in group are depicted as one column in the Anova plot, indicating that statistical difference exists, with $p < 0.01$. The elastance increases with the degree of obstruction in COPD due to the breaking of the walls as the disease progresses. The air remains trapped in the lungs, making it very difficult for the patient to breathe and obtain a nominal gas exchange percent. Changes in the alveolar wall structure and morphology will affect the heterogeneity $\eta$ and thus will increase the degree of nonlinear contributions in the impedance values at low frequencies [35, 26].

Related to the presence of nonlinear contributions is the degree of heterogeneity in the small airways and tissue. In [34], the authors provide a theoretical framework for understanding evolutions of this index with changes in tissue resistance and elastance.
For $\eta$ to increase by heterogeneity at low frequencies (i.e. $f=0.16$ Hz), the resistive and elastic properties must have appropriate relative values. The regional increase/decrease in heterogeneity does not automatically lead to an increase in $\eta$. This specific aspect is reflected in COPD GOLD II data, where the hysteresivity factor has a high variability interval compared to the other groups.

5 Future Technological and Scientific Improvements

Challenges for further improvements are numerous and the section hereafter is not intended to be exhaustive. Some suggestions are given hereafter.

A carry-on device for continuous monitoring of respiratory impedance in highly dense urban areas has not yet been developed. This may be due to the fact that respiratory function evaluation falls somewhat lower priority to other modern age diseases worldwide. However, it may be interesting to monitor the effects of high levels of smog on the respiratory function, detect asthma attacks, possible early respiratory dis-functions. The technological challenge is in manufacturing a light weight, low-cost, personal use mask to be put over the mouth and nose, with possibility to access fresh air for tidal breathing. Additionally, the power supply for the microcontroller which delivers the pressure oscillations and performs the necessary signal processing must be autonomous for a minimum amount of hours to ensure practical use.

From a signal processing point of view, significant improvements can be added taking into account the fact that the breathing period is not a stationary signal. As pressure oscillations are applied at frequencies around the breathing period of the patient, nonlinear effects arise which are difficult to separate. Limitation in the lowest frequency that can be excited in the respiratory tissue has to do with the measurement time. A healthy volunteer may be able to breath normally (not forced) for 2 minutes, but most of diagnosed patients with severe respiratory obstruction have difficulties after 30 seconds. This introduces a forced, sharp breathing pattern which no longer poses the properties necessary for a linear estimator. Still, signal processing of clinical data remains a struggle for the researcher and current solutions are yet far from being perfect.

6 Conclusion

This paper is an overview of about fifteen years of research towards a non-invasive, patient-friendly, lung function evaluation device based on forced oscillation technique. The objective to measure viscoelastic properties in tissues with various degree of respiratory obstruction has been achieved by a parallel development of both device and methodology.

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