Children Lung Function Diagnostics – New Methods For Handling of Clinical Data

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ABSTRACT
In our talk we would like to introduce a new approach to handling of clinical data obtained during children lung function testing. We focus on multiple breath inert gas washout test (MBW) which is a new and promising method. We combine traditional approaches with unconventional methods of interval analysis. That helps us to develop new robust algorithms not suffering from typical drawbacks of classical methods. These algorithms enable further processing of the clinical data – extrapolation, prediction, regression, checking validity of measurement.

Categories and Subject Descriptors
G.1.0 [**Numerical analysis**]: General—*Interval arithmetic*; G.3 [**Probability and statistics**]: Correlation and regression analysis; J.3 [**Life and medical sciences**]

General Terms
Algorithms, Experimentation, Measurement, Reliability, Verification, Theory

Keywords
lung function diagnostics, multiple breath washout test, interval analysis, regression, least squares

1. INTRODUCTION
Multiple breath inert gas washout test (MBW) is a new and promising method for lung function diagnostics. It can be used in patients of all age groups independently on their ability to perform special breath manoeuvres. The high sensitivity to the most peripheral airway changes has been shown in most of chronic lung diseases (e.g. bronchial asthma, cystic fibrosis, primary cilliary dyskinesia etc.) [3], [5], [9]. Currently there is a growing evidence of functional superiority of the MBW to conventional methods (spirometry, bodyplethysmography).
This method has a great potential to become a useful tool for clinical assessment of the respiratory status of a patient. Moreover, it can be successfully used in general clinical research [8].

2. MULTIPLE BREATH WASHOUT TEST
Multiple breath inert gas washout test is based on the assessment of ventilation inhomogeneity. Indirectly, the patency of the most peripheral airways (from the 12th generation of bronchi to the periphery) can be evaluated. The test consists of two phases – wash in and wash out. During the first phase lung is filled with an inert gas (sulphur hexafluoride, helium or nitrogen), during the second phase the inert gas is washed out by air or 100% oxygen (depending on the inert gas used). Concentration of the respective inert gas, volume of exhaled gas and flow are measured online. The pattern of inert gas concentration decrease gives information about the homogeneity of ventilation and thus about the patency of airways. The crucial moment of the measurement is a precise estimation of the inert gas concentration. Accuracy and high response time are needed. The mass spectrometry meets all these requirements and is considered to be the gold standard. However, this method is a bit bulky, difficult to use and expensive. Recently, an indirect method for inert gas concentration estimation has been proposed. It is based on ultrasonic measurement of flow and molar mass. Oxygen and carbon dioxide are measured by well established absorption method (infra-red or laser diode absorption). Subsequently, the concentration of an inert gas is estimated by subtraction of oxygen, carbon dioxide and other rare gases concentrations from 100% after BTPS correction (body temperature, pressure, saturated). To achieve sufficient accuracy of inert gas concentration sophisticated algorithms are required. The optimal one is still being discussed [1] and there is a great potential for improvement. We used an unconventional way to handle raw data using interval analysis. This approach helps to develop more robust algorithms and shed more light on the procedure of inert gas washout.

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3. INTERVAL ANALYSIS

Interval analysis is a system of mathematical tools developed in 50s and 60s [10]. Its main idea is based on enclosing real numbers in our data by real intervals. This might be required for different reasons:

- Various real numbers are difficult to be precisely represented on computers (such as $\pi, \sqrt{2}$). They are enclosed with rigorous intervals to ensure that their right value is not missed because of rounding errors in subsequent computations.
- Measured data contain uncertainties and errors (due to limited sensor accuracy, discretization with limited sampling rate). To rigorously handle these raw data limitations, measurements are enclosed with verified intervals.
- For checking or verification of a model we need to test its all variables for all their possible values. The range of each variable is then represented with a correspondent interval.

Data or tasks containing intervals (e.g., a linear system with interval coefficients) can be pictured as all possible realizations (all linear systems with real coefficients) that can vary within these intervals. An important assumption is absence of a distribution on the intervals. This way arithmetics on intervals can be easily defined and used in computation. Of course, many tasks with interval data become difficult to be solved, since verification and robustness is a strong additional information to our data. However, many interval methods has been developed that can handle even these difficult problems in fast and reliable way [10], [11], [4], [6],

4. CURRENT AND A NEW APPROACH

The current software used for clinical data analysis relies on classical statistical approaches and conventional methods for data interpretation (breath detection, smoothing breath flow curves, etc.). Nevertheless, these methods have several drawbacks. At first, they are not able to localize the precise time of each breath end (the data are sampled discretely in time, sensors work with an inherent error). The other drawback is a risk of skipping an irregular breath due to use of heuristics. Moreover, verified breath end estimation is crucial for the determination of inert gas peak concentration which is required for derivation of clinically relevant parameters (LCI – lung clearance index, FRC – functional residual capacity). Under these imprecisions the obtained data can be far from reality. Hence, the classical statistical tools (regression, extrapolation) can fail to provide relevant information. However, interval analysis can overcome all these limitations. From the raw data we are able to construct verified time intervals safely containing the breath ends. Based on this information, peak inert gas concentrations can be estimated in more reliable way. Using interval analysis, we are able to compute several types of interval regressions (possibilistic, tolerace, neccesity) [2], [7]. They give us the upper and lower bound enclosing all desired classical regression curves on all possible realizations of interval data. In Figure 1 there is an illustration of a possibilistic interval regression. The mauvre area depicts the nitrogen concentration in time.

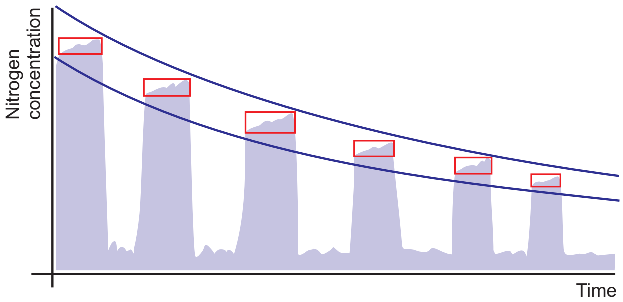

Figure 1: An illustration of a possibilistic interval regression.

The red rectangles represent verified interval boxes containing peaks of nitrogen concentration. The two blue curves represent verified upper and lower bound on regressions of all data realizations from interval boxes.

5. CONCLUSIONS

The interval methods proved to be useful for offline analysis of the raw data obtained from MBW. It is still necessary to keep in mind that interval methods as a matter of post-processing can not fully eliminate the inherent limitation of the indirect method of gas concentration assessment. However, they can significantly increase the informative value of the measurement. Interval regression is a relevant tool for a meaningful description of the washout curve. This enables solving of many crucial clinical tasks:

- Robust extrapolation and data prediction (potential to reduce time required for the measurement procedure)
- Precise derivation of other clinically relevant indices (index of acinar and conductive inhomogeneity – Sacin and Scond)
- Recognition of different disease specific patterns of the washout curve
- Automatic quality assessment of the measurement to assist the physician's decision whether to accept the test
- Automatic correction of technically incorrect data (e.g., leak detection and its elimination)
- Analysis of consecutive measurements from one patient

Currently we are developing a software combining the classical statistical methods and interval analysis. The final version of the software should handle most of the items mentioned in the previous list.

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