STATISTICAL APPROACH TO AEROSOL TRANSPORT EVALUATION UNDER CYCLIC CONDITIONS

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ABSTRACT

The effort to understand how aerosols transport and deposit in lungs drove us to application of particle velocity measurement with P/DPA (Phase Doppler Particle Anemometry). We have used optically transparent realistic human airway model and liquid aerosol for experiments under cyclic breathing conditions. The aerosol diameter, breathing frequency, tidal volume and way of the air supply was varied during experiments. We have employed statistical methods to distinguish and quantify differences in character of the aerosol transport for particular cases. Aerosol measurement using P/DPA gives results with non-equidistant sampling and unlike data rates in particular cases. Particle velocity and turbulence are variable with the cycle phase which makes the situation more complicated. Common statistical methods are not appropriate in this case. Statistical approach proposed in the paper is based on linear regression models of data fits. A test for the equality of two linear regression curves includes a heteroskedasticity effect. Our methods were implemented in MATLAB software. Mathematical background, results and discussions are presented in the paper.

INTRODUCTION

Studies of air pollution on health have linked particulate matter (aerosols) with a number of significant health effects. These include increased mortality and aggravation of existing respiratory and cardiovascular disease (Dockery *et al.*, 1992, 1993; Peters *et al.*, 2000; Hauck, 1998; Kotesovec *et al.*, 2001; and others). World Health Organization (WHO) has estimated that in Europe air pollution has caused 168000 excess deaths annually. The best estimate on the reduction in life expectancy in Central Europe including the Czech Republic is about 1 year. The health effects of atmospheric particulate matter are related to its ability to penetrate the respiratory system. Besides particles that represent air pollution and penetrate into the lung, aerosols are commonly used as a means of delivering therapeutic drugs to the lung for the treatment of lung diseases. The physiology and anatomy of the lung offer a unique way for drug delivery; it offers large surface area, decreased metabolic capacity, a relatively thin alveolar epithelium in the lower airways, and a rich blood supply (Cryana *et al.*, 2007). Inhaled pharmaceutical aerosols (IPA) can be used to deliver drugs to the bloodstream by depositing the drug in the alveolar regions. This approach allows treatment of the entire body by inhaled aerosols, and has opened up the field of IPA, since drugs traditionally administered by injection can potentially be administered by inhalation. It is then a must that we fully understand the IPA mechanics, since otherwise we reduce the effectiveness and market potential of the drug.

In most computational fluid dynamic (CFD) and experimental analysis of the human lung, it has been assumed that the trachea and branches of the lung have smooth walls. Number of these studies used regular bifurcation models, such as Weibel (1963) human lung model. Lin *et al.* (2007) found that turbulence induced by the laryngeal jet could significantly affect airway flow patterns as well as tracheal wall shear stress. Russo *et al.* (2007) shown influence of cartilage rings on airflow and particle deposition in the lungs. Accordant conclusion was given by Corcoran and Chigier (2002) and de Rochefort *et al.*, 2007. Results of several works show important difference between particle transport and deposition characteristics under steady flow conditions most frequently studied in the past and under oscillatory flow conditions (Lieber & Zhao (1998), Zhang & Kleinstreurer (2004), Ramuzat & Reithmuller (2002), Zhang *et al.* (2001)). Summarizing the above mentioned findings realistic human lung geometry extended from upper airways to tiny structures of the bronchial tree is the first prerequisite for proper study of air flow and aerosol transport and deposition. Usage of oscillating flow conditions is an additional requirement to fulfill this task.

One of our objectives is a study of aerosol transport under unlike breathing conditions (resting, normal breathing, light activity) for particle of variable size in several positions inside the human airways. It is a crucial task to find a proper statistical instrument for comparison of particular results with the aim to distinguish between consistent and different results.

In the problem of statistic data evaluation, we should first decide which methods are appropriate. An easy way is to use classical statistic methods that are implemented in commercial software and are widely used for comparison of two data files. These methods have general restriction as for example the same number of values in compared files, equidistant data sampling, a condition of normal distribution and so on. Results of particle measurement obtained using P/DPA with experiments performed under realistic conditions of cyclic breathing show not only variable velocity and turbulence with the cycle phase but also non equidistant sampling with unlike data rates. So data unfortunately do not obey restrictions of the classical statistic methods and they are not useful in our case.

This paper is focused on description and usage of some atypical methods for statistical comparison of data sets. Several different approaches are described here and their suitability for our case is discussed and tested.

EXPERIMENTAL APPARATUS

Arrangement of experimental technique for study of flow and particle transport at cyclic breathing conditions is shown in Fig. 1. As a generator of oscillating flow, a servo motor (6) (TGH3 from TG drives company) which drives piston through the pneumatic cylinder (Hoerbiger NZK 6100-0400 AG) (5) is used. The servo motor is computer controlled and it allows generating any shape of motion with appropriate frequency and amplitude. Monodisperse aerosol particles of DEHS ranging from 1 to 10 μm are generated by condensation generator (4) (model TSI 3475). Measurement of drop size and concentration is made by an aerosol monitor (model TSI 3375). The particles are mixed with the air in a chamber (3) using static mixer and flow into an airway model (1). Bladder (2) collects the air with particle for the second breathing cycle phase.

Velocity and size measurement of the particles during breathing cycle are made using Dantec P/DPA (7). This 1D system is equipped with Ar-Ion+ Laser ILT 5500A-00 (max. power 300 mW). Spectral line 514.5 nm of the CW laser beam with power up to 90 mW and horizontal polarization is splitted using transmitting optics 58N10 into 2 parallel beams 60 mm distant. Frequency of one of the beams is shifted by 40 MHz. Beam diameter was expanded to 2.5 mm to reduce a probe volume. The transmitting lens focal length is 310 mm. Light refracted by the 1st order is collected using receiving optics 57X10 equipped with three photo-detectors. Focal length of receiving lens is 310 mm and scattering angle 45° used. Signal processor Dantec 58N50 is set to measure velocity within a range of -16 to 16 m/s at bandwidth12 MHz. Droplet size range is 44.9 μm. The obtained data are evaluated using BSA Flow Software v2.1.

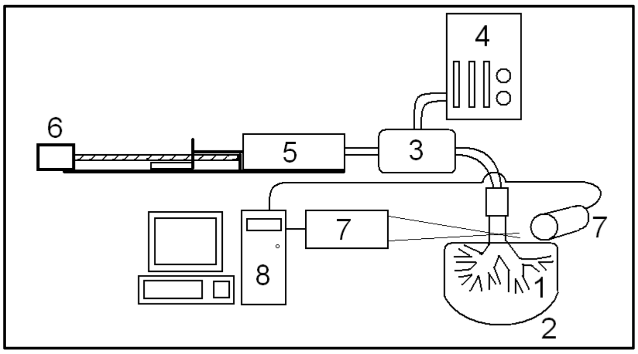

Figure 1. Diagram of a test rig with P/DPA.

Airway model: A digital reference model of the human lung published by Schmidt *et al.* (2003) was used for construction of tracheo-bronchial tree down to 3rd generation. This model is based on in-vitro preparation of the lung of an adult male combined with high resolution computed tomography. The model gives data up to the 17th Horsfield order with superior geometrical accuracy but it does not cover upper airways before trachea. The segment of airways beginning with throat and going to trachea was acquired as a 3D CT scan of an adult Caucasian male volunteer in St. Anna university hospital in Brno, CZ. This model gives realistic geometry of the airways with complex structures of glottis and epiglottis (Fig. 2 left). This model is useful up to about third generation of bronchi. Geometry of more subtle bronchi shows distortion due to motion during scanning caused by heart beating. Both the models were carefully catenated in trachea region with overlapping of corresponding parts. Rapid Prototyping technology was used to manufacture a negative model from gypsum composite with resolution 0.1 mm. Novel technique was developed for manufacturing of final positive thin-walled model. It is made of several layers of transparent elastomer Sylgard 184 (Dow Corning), see Fig. 2, left. Thin model walls are required for optical access into the model without strong optical distortions if air flow or particle transport with air as a carrier medium studied. This approach differs from common flow experimental methods in airways where liquids with the refraction index equal to the one of the model material are used. For more information on the geometrical model preparation and final model fabrication see Jedelsky *et al.*, 2008.

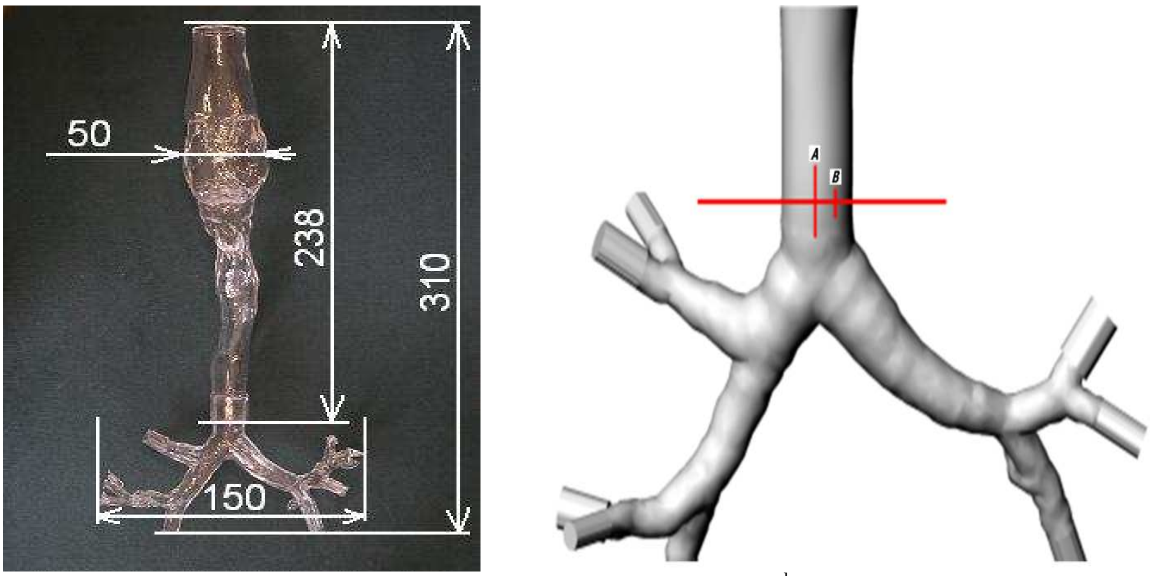

Figure 2. Final transparent model of the airways from throat to 3rd generation of bronchi (left), measured positions (right).

MATHEMATICAL APROACH, RESULTS AND DISCUSSION

About observed data

The main task is finding of appropriate statistic tools for investigation of aerosols transport velocity profiles in the human lung model.

A set of measurement data for different breathing conditions and aerosols size was taken, see Table (1). Particular regimes were established with regard to distinct human breathing modes described in the literature and in accordance with our previous work (Jedelsky *et al.*, 2009). Experiments were performed for harmonic oscillatory flow regimes. Measurement of aerosol transport was performed using P/DPA in trachea in two positions; the first is in trachea centerline (*A* - 0 mm from trachea axis) and the second is close the trachea wall (*B* - 4 mm from trachea axis). Every measurement was repeated three times; thus we have 54 measurements for 18 different setups. The measurement time reaches 30 000 – 35 000 ms, which corresponds to approximately 9 full breathing periods.

<table>
<tr><th>Breath capacity/period</th><th>Diameter of aerosol particles</th><th>Measure position</th></tr>
<tr><td rowspan="4">0,5l/4s</td><td>1 μm</td><td rowspan="2">0 mm</td></tr>
<tr><td rowspan="2">3 μm</td></tr>
<tr><td rowspan="2">4 mm</td></tr>
<tr><td>6 μm</td></tr>
<tr><td rowspan="4">1l/4s</td><td>1 μm</td><td rowspan="2">0 mm</td></tr>
<tr><td rowspan="2">3 μm</td></tr>
<tr><td rowspan="2">4 mm</td></tr>
<tr><td>6 μm</td></tr>
<tr><td rowspan="4">1,5l/3s</td><td>1 μm</td><td rowspan="2">0 mm</td></tr>
<tr><td rowspan="2">3 μm</td></tr>
<tr><td rowspan="2">4 mm</td></tr>
<tr><td>6 μm</td></tr>
</table>

Table 1: Experimental setup

The P/DPA system records a velocity, size and arrival time of particles passing a measurement volume. It means that our data sets have non-equidistant sampling form and data rate; thus two measurement samples that which are compared, do not have the same number of values.

Statistical evaluation

The statistics should answer a question, whether we can suppose that the velocity profiles for two different setups are statistically the same or if they differ. We compare two data files having two columns of values (arrival time and velocity) in this case. We denote the time column as x axis and the velocity column as y axis. The data file describes the breathing cycle so periodic character is expected.

The data files have different number of values and there are not-equidistant as mentioned above. Typical commercial software can have problem to process this kind of data. Data interpolation to constant time steps is one way to deal with this problem. Unfortunately work with modified data can be inappropriate and the statistical result could be incorrect. We have chosen another way to solve this problem which is fitting the data by regression function and comparison of two files by comparing two linear regression models.

$$y = \beta_0 + \beta_1 f(\boldsymbol{x}), \tag{1}$$

$$y^* = \beta_0^* + \beta_1^* f(\boldsymbol{x}^*), \tag{2}$$

where $f(\boldsymbol{x}) = \sin\frac{2\pi \boldsymbol{x}}{T}$ and $f(\boldsymbol{x}^*) = \sin\frac{2\pi \boldsymbol{x}^*}{T}$. For the first two setups is $T = 4000[\text{ms}]$ (time is measured in milliseconds form) and for the last is $= 3000[\text{ms}]$. Null hypothesis for identity of two linear regression models is $H_0\colon \boldsymbol{\beta} = \boldsymbol{\beta}^*$ against alternative hypothesis $H_1\colon \boldsymbol{\beta} \neq \boldsymbol{\beta}^*$, where $\boldsymbol{\beta} = (\beta_0, \beta_1)'$, $\boldsymbol{\beta}^* = (\beta_0^*, \beta_1^*)'$. Parameters β are estimate by last square method and are denote by *b*. The statistical dependence of data files is necessary assumption for the test.
The test criteria according to Anděl, J. (1985): can be written as:

$$Z = \frac{n + n^* - 4}{2} \frac{(\boldsymbol{b} - \boldsymbol{b}^*)' \left[(\boldsymbol{X}'\boldsymbol{X})^{-1} + \left(\boldsymbol{X}^{*\prime}\boldsymbol{X}^*\right)^{-1}\right]^{-1} (\boldsymbol{b} - \boldsymbol{b}^*)}{(n-2)s^2 + (n^* - 2)s^{*2}}, \tag{3}$$

where n, n^* is number of values, s^2, s^{*2} is variance, $\boldsymbol{b}$, $\boldsymbol{b}^*$ is estimate regress parameters vector and $\boldsymbol{X} = \begin{bmatrix} 1 & x_1 \\ 1 & x_2 \\ \vdots & \vdots \\ 1 & x_n \end{bmatrix}$, $\boldsymbol{X}^* = \begin{bmatrix} 1 & x_1^* \\ 1 & x_2^* \\ \vdots & \vdots \\ 1 & x_n^* \end{bmatrix}$ for first and second data file.

Random variable Z has Fisher-Snedecor distribution $F_{2,n+n^*-4}$ under H_0 assumption. We reject hypothesis H_0 on significance level α if the inequality $Z \geq F_{2,n+n^*-4}(\alpha)$ is satisfied. The test is calculated using MATLAB mathematical software. Figure (3) shows situation where two data files are fit by linear regression model. The first one includes data from regime 0,5l/4s-3 μm-0mm marked by red color and its relevant regression function is in black. Another data from regime 0,5l/4s-3 μm-4mm marked by green color and their regression function is in blue. Only two periods are displayed for transparency reasons.

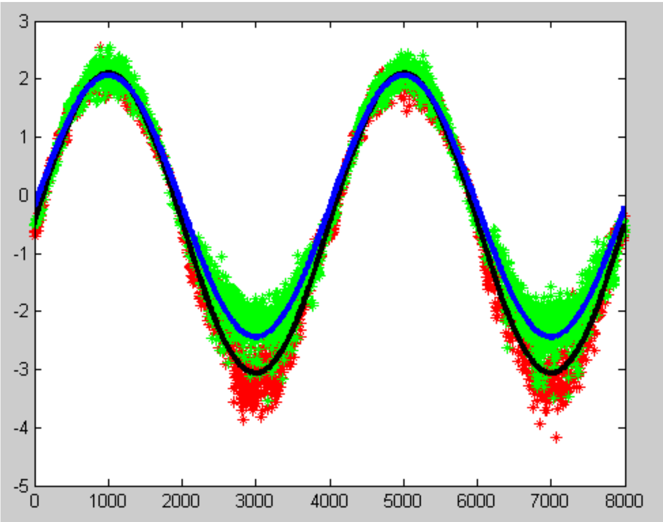

Figure 3: Data fit by regression

Test criterion value are $Z = 8{,}2900e + 003$ and $F = 4{,}6056$. We reject hypothesis that the regression functions are same if $Z \geq F$. This situation is also evident from figure (3) or from problem character when we assume higher velocity in the trachea centerline than near the trachea walls. Variable variance through time can be also seen in figure (3). One assumption for linear regression model is based on constant variance (homoskedasticity (Baltagi *et al.*, 2005, Steigerwald *et al.*, 2007)). Parameter estimation can be very inaccurate in this case. How to deal with this problem?

Two methods will be presented here. The first method is based on application of a weighting function in the regression model, which stabilizes the variance and corrects the inaccuracy in the parameter estimation. Regression function with the weighting function can be written as:

$$y = \beta_0\sqrt{w(\boldsymbol{x})} + \beta_1 f(\boldsymbol{x})\sqrt{w(\boldsymbol{x})}, \tag{4}$$

$$y^* = \beta_0^*\sqrt{w(\boldsymbol{x}^*)} + \beta_1^0 f(\boldsymbol{x}^*)\sqrt{w(\boldsymbol{x}^*)}. \tag{5}$$

There are three weight function presented. 1) $= \frac{1}{\boldsymbol{r}^2}$, 2) $\boldsymbol{w} = \frac{1}{|\boldsymbol{r}|}$, 3) $\boldsymbol{w} = \frac{1}{\boldsymbol{y}}$, where $\boldsymbol{r}$ is residual vector. The value for F is the same but criterion value Z is not the same for different weighting functions. The Z value is for used weighting function listed below Figures (4-7).

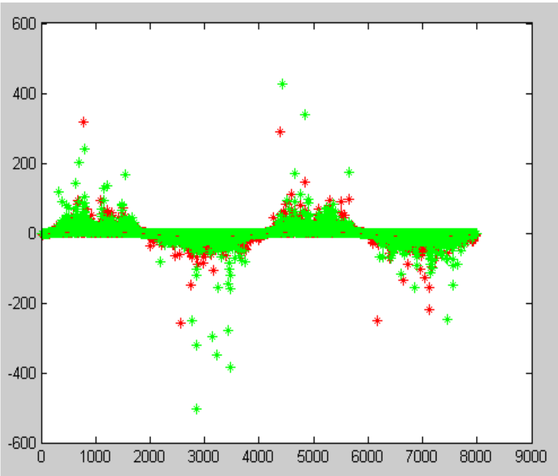

Figure 4: $\boldsymbol{w} = \frac{1}{|\boldsymbol{r}|}$, $Z = 1.2236$

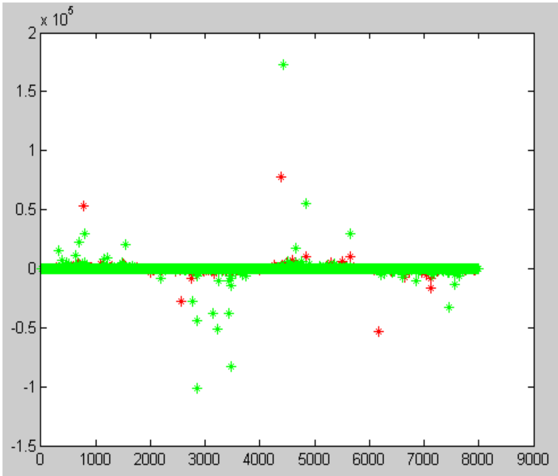

Figure 5: $\boldsymbol{w} = \frac{1}{\boldsymbol{r}^2}$, $Z = 8.1594e-007$

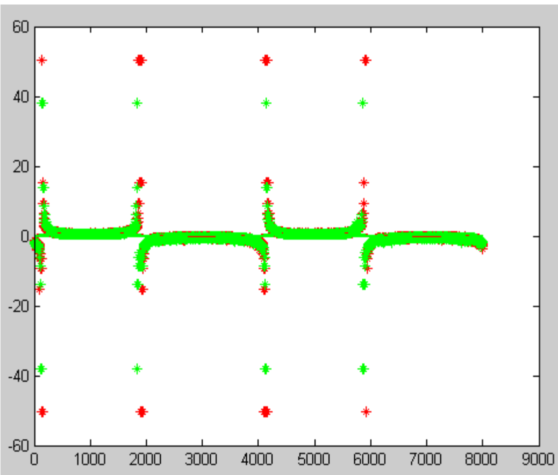

Figure 6: $= \frac{1}{\boldsymbol{y}}$, $Z = 0.0099$

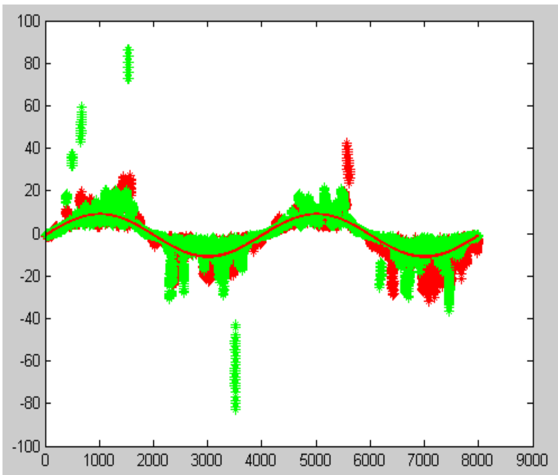

Figure 7: $\boldsymbol{w} = \frac{1}{|\bar{\boldsymbol{r}}|}$, $Z = 10.9865$

It is obvious from Figure (6) that weighting function 3 is completely impropriate for this kind of data regardless the fact that it is often mentioned in regression analysis. Function 1 smoothes our data too much; the data have totally different character after passing the test. So the test with this weighting function is not useful. The only applicable function is function 2, but the unlike data still pass the test. All weighting functions are inappropriate from this perspective. Instead of searching for a new weighting function we decided to try a modified function 2. The modification replaces residuum r_i in position i by average value $\bar{\boldsymbol{r}}$ taken from neighborhood r_i. $Z = 1{,}5750$ in the case where average uses 10 neighborhood values. For 100 neighborhood values $Z = 10.9865$ and test rejects null hypothesis, thus the data have different velocity profiles. We have unfortunately to modify this number for data files with unlike number values (which is a problem for this kind of data).

Second method deals with data before regression is used. The data are modified the way, that every n values are replaced by one which is an average. The question is similar to the previous situation: how to choose n. Our test showed that n=50 for typical amount of data from P/DPA is appropriate. Null hypothesis is rejected after application of regression on the modified data $= 511.4458 \geq F = 4.6282$. Situation can be seen in figure (8).

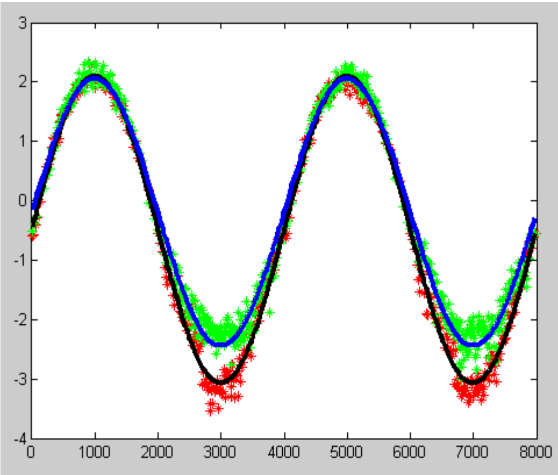

Figure 8: Regress analysis with average data

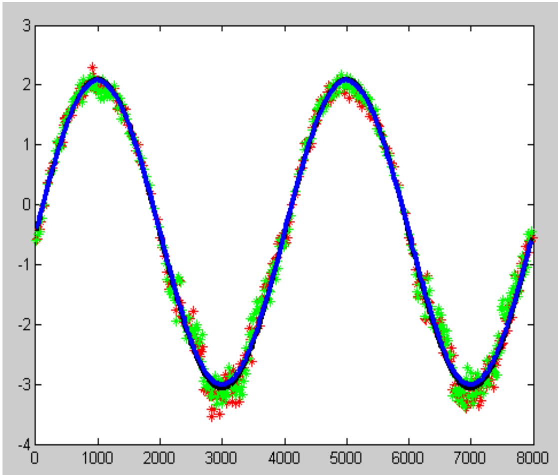

Figure 9: Regress analysis with average data

Now we examine case when other two data files are tested. For instance two measurements with the same regime 0,5l/4s-3 μm-0mm, figure (9). Test results are $Z = 4.5051 \leq F = 4.6330$ and we cannot reject null hypothesis. So we consider the data as equivalent. We can say now that the test can decide which regimes have the same or similar velocity profiles, and which have not. Also the higher Z value means the data are more different. For instance when we are interested in searching for a difference in results for unlike aerosol particle diameter and for unlike breathing capacity. Performing test we can say that change in breathing capacity gives more different results than the change in the aerosol particles diameter (Table (2)).

1. file	2. file	Z
1.0l/4s-0mm-3um	0.5l/4s-0mm-3um	1.2211e+004
1.0l/4s-0mm-3um	1.0l/4s-0mm-1um	6.1035
1.0l/4s-0mm-3um	1.0l/4s-0mm-6um	0.6418

Table 2: Comparison of regimes

This method can also compare two periods from one measurement and decide if a phenomenon with not periodic character is present in the data set.

CONCLUSIONS

The paper deals with suitable statistic tools for data obtained from simulation of breathing cycle in human lungs. Several statistical approaches are tested. Regression model for average data seems to be the most suitable method for this data character. The future work is improvement of this method and tests of other data sets for better problem understanding. But investigation of the approach with weighting function will also continue.

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