VĚDECKÉ SPISY VYSOKÉHO UČENÍ TECHNICKÉHO V BRNĚ

Edice Habilitační a inaugurační spisy, sv. 635

ISSN 1213-418X

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FLOW AND DEPOSITION OF AEROSOLS IN MODELS OF HUMAN AIRWAYS

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Energetický ústav

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FLOW AND DEPOSITION OF AEROSOLS IN MODELS OF HUMAN AIRWAYS

PROUDĚNÍ A USAZOVÁNÍ AEROSOLŮ V MODELECH LIDSKÝCH DÝCHACÍCH CEST

ZKRÁCENÁ VERZE HABILITAČNÍ PRÁCE

VYSOKÉ UČENÍ TECHNICKÉ V BRNĚ
NAKLADATELSTVÍ VUTIUM

BRNO 2019

KEYWORDS
Aerosol, model of lungs, airways, experimental methods, mechanical engineering

KLÍČOVÁ SLOVA
Aerosol, model plic, dýchací cesty, experimentální metody, strojní inženýrství

MÍSTO ULOŽENÍ RUKOPISU HABILITAČNÍ PRÁCE:
Fakulta strojního inženýrství
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ACKNOWLEDGEMENT:
I would like to express my thanks to my current or former colleagues Jan Jedelsky, Miroslav Jicha, Jakub Elcner, Árpád Farkas, and Miloslav Belka who were an invaluable asset to this work. I would also like to express my gratitude to my wife Elena for her support and intelligible explanations of medical topics related to the respiratory system; and our kids Eliska, Matous, Dominik and Anna for inspiring me with their perpetual enthusiasm, and patience during my work on this thesis.

ISBN 978-80-214-5778-2
ISSN 1213-418X

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ABOUT THE AUTHOR

Frantisek Lizal was born in Kroměříž in 1983. After completing grammar school, he continued his studies at Faculty of Mechanical Engineering, Brno University of Technology at the Department of Thermomechanics and Environmental Engineering. He received his Master degree in 2007 for a thesis entitled "Automotive Ventilation – Velocity Field near the Dashboard Ventilating Outlets". During his PhD studies, he focused on the research of aerosol transport and deposition in models of human lungs. He spent five months at Center for Air Resources Engineering and Science at prof. Philip K. Hopke at Clarkson University NY, USA, where he focused on measurement of deposition of inhaled glass fibres in a replica of human lungs. He defended his PhD thesis entitled "Experimental Research of Aerosol Transport and Deposition in Human Respiratory Tract" in 2012. During his postdoc research visit, he worked for four months in the team of prof. Anthony Wexler at University of California Davis and remained focused on the topic of aerosols in lungs. Dr Lizal is a member of International Society for Aerosols in Medicine, Czech Aerosol Society and leader of the WG 4 (Advanced imaging, patient monitoring and delivery verification) within the project COST MP1404 SimInhale (Simulation and pharmaceutical technologies for advanced patient-tailored inhaled medicines).

Dr Lizal has published 14 articles in international journals with Impact Factor and additional 28 articles and conference proceeding papers with DOI. He is a co-author of three national patents and participated at 13 national and international grant projects. He teaches the course in Thermodynamics (in English), has supervised 21 bachelor and master thesis and mentored 10 international students during their laboratory internships at Brno University of Technology.

1. INTRODUCTION

People have been aware of the effect of inhaled particles on human health since time immemorial. The reason is obvious—the respiratory system is a straight route to the bloodstream. Accordingly, it represents a great opportunity for medical treatment using inhaled aerosols, as the onset of the effect of inhaled pharmaceuticals is virtually immediate (Patton and Byron, 2007). At the same time, the airways represent a dangerous gate for harmful and toxic particles (Pope and Dockery, 2006). Hence, regardless of their purposes, both pharmacists and toxicologists need to know the fate of inhaled particles in the human respiratory system.

Understanding the mechanics and consequent health effects of inhaled particles is a complex task that requires collaboration of physicians, engineers, pharmacists, mathematicians, chemists, and programmers. It is evident that communication between experts from various disciplines challenges all its participants. Despite the decades of research in the field, there remains a gap between these communities and the transformation of knowledge between disciplines flounders due to the differences in terminology and the way of thinking.

The contribution of mechanical engineering to the research of aerosol transport is substantial, and the development of the field will undoubtedly gain from the engineering approach in the future as well. This habilitation thesis covers specifically these four topics: 1) physical airway model preparation and production, 2) experimental techniques applicable to human lungs and their replicas, 3) measurements of inhaled fibres in a lung replica, and 4) numerical calculations of fluid and particle flow. All the topics are closely related, and they are driven by the effort to gradually increase reliability of computational fluid dynamics (CFD) on the basis of conscientiously performed experiments and simulations.

It is generally accepted that CFD will bring detailed insight and improved predictions of the fate of inhaled particles, provided the method is indubitably verified and validated. The area of expertise of the author lies particularly in the experimental methods which form the basis for the CFD either as boundary conditions or as a validation tool. Hence, this habilitation thesis presents the current state-of-the-art in the area of experimental methods applicable in the field. It should help the readers coming not only from engineering but also from medical and pharmaceutical communities understand the principles and form realistic expectations regarding the achievable results and their precision.

The full text of the habilitation thesis is composed of eleven scientific papers, published in impacted journals by the author and his co-workers, divided into the four above mentioned thematic groups, which are supplemented with an introductory commentary. This summary uses main parts of the commentary and includes synopses of the eleven papers. The papers constituting the habilitation are reffered to as (HAB-*x*), where *x* is an ordinal number corresponding to the order of appearance in the full version of the habilitation.

2. AEROSOLS

The term *aerosol* can be in the simplest way described as a suspension of liquid or solid particles in a gas. Hinds (1999) adds that: “Aerosols are usually stable for at least a few seconds and in some cases may last a year or more. The term *aerosol* includes both the particles and the suspending gas, which is usually air. Particle size ranges from about 0.002 to more than 100 μm.” This definition is in contrast to the popularly used meaning of the word aerosol only as a product of pressurized spray-cans. The broader definition proposed by Hinds, and accepted within this thesis, encompasses phenomena such as smoke, fog, smog, dust, mist, or fume.

2.1. Particle and aerosol properties

The behaviour of inhaled particles obviously depends on its physical characteristics. The reader who is new to the topic and needs to learn the basics of particle and aerosol description is referred to great monographies of Hinds (1999) and Kulkarni (2011), as the chapter on aerosol properties had to be omitted due to the length restrictions of this summary.

2.2. Particle deposition mechanisms

Every sophisticated prediction of the deposited fraction of the inhaled aerosol in human airways must consider the five basic particle deposition mechanisms: *inertial impaction, gravitational settling, Brownian and turbulent dispersion, interception and electrostatic precipitation*.

Inertial impaction – is the dominant mechanism for particles of larger sizes (~ 5 μm and larger), whose inertia is so high that the particle is unable to follow the streamline on the curved path, and hits the airway wall. The probability of a particle to deposit by inertial impaction is proportionate to the Stokes number, given as:

$$\mathrm{Stk} = \frac{\rho d_p^2 U}{18\mu D}, \tag{1}$$

Where d_p is the particle diameter, ρ is particle density, U and μ are velocity and dynamic viscosity of the carrier gas (air) and D is a characteristic length, usually diameter of the airway.

Gravitational settling – is important mostly in smaller airways where the particles have smaller distances to travel before touching the wall and where they have enough time to settle. The settling velocity, U_s, is defined as:

$$U_s = \frac{\rho d_p^2 g}{18\mu}, \tag{2}$$

where g is the gravitational acceleration.

Brownian dispersion – originates from the random collisions of aerosol particles with air molecules. The influence of this mechanism increases with decreasing size of particles. It is proportional to the Brownian diffusion coefficient D_B defined as:

$$D_B = \frac{C_c kT}{3\pi\mu d_p}, \tag{3}$$

where C_c is a slip correction factor accounting for the increased velocity of the particles as a result of "slipping" through the space between the molecules before colliding with another molecule or object in path (for details see, e.g. (Musante et al., 2002)), k is the Boltzmann's constant and T is the absolute temperature.

Turbulent dispersion – is caused by the turbulent fluctuations of the flow; it is significant mostly in the upper and larger airways, where the turbulent flow appears (Darquenne, 2012).

Interception – means that the particle follows the fluid streamline, but comes into contact with the wall due to its size or shape. This mechanism is considered important mainly for fibres in lower airways, while for spherical particles remains negligible.

Electrostatic precipitation – appears in the case of charged particles, which come close to the wall and induce image charge on the surface. Then they are electrically attracted to the airway wall and deposit.

3. RESPIRATORY SYSTEM

The respiratory system provides continuous absorption of oxygen and excretion of carbon dioxide. This exchange of gases between the atmosphere and the blood circulation is called external respiration. Apart from that, the upper airways serve as a protection against harmful aerosol particles (Kacmarek et al., 2013) and they also humidify and warm up the air.

3.1. Airway anatomy

The first detailed description of the morphometry of human lungs was published by Ewald Weibel (Weibel, 1963). He statistically evaluated diameters, lengths, angles of branching and other characteristics of conducting and respiratory airways. He found that people have on average 23 generations of dichotomous branching, and extracted a symmetrical and asymmetrical model, which became very popular as a basis for mathematical and numerical modelling of lung deposition. His model was later followed by a more advanced asymmetrical model of Horsfield (Horsfield and Cumming, 1967, Horsfield and Cumming, 1968, Horsfield et al., 1971).

The inner surface of the airways in the conducting zone (generation 0–16) is ciliated. The walls of the trachea and following bronchi are supported by cartilaginous rings, which prevent the airways from collapsing during the expiration. The rings keep the relatively stable diameter of the airway tubes during the breathing cycle, and hence the airways can be modelled by rigid tubes (nonmoving walls). The cartilages eventually disappear in generation 12 – 15 (Tu et al., 2013); therefore the downstream branches expand during the breathing cycle significantly. The process of development of digital models and fabrication of replicas of human airways has been published by the author in the paper (HAB-1)[1], which is an integral part of this thesis.

Synopsis of the "Development of a realistic human airway model" (HAB-1)

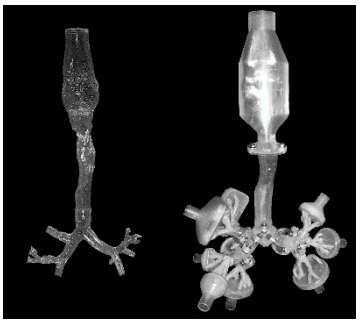

Fig. 1 The initial replicas of human airways

The acceptance of the paradigm of the crucial role of CFD in the research of inhaled aerosol in human lungs inevitably leads to the requirement of a benchmark physical model (replica) of human airways whose inner geometry is identical with digital geometry used for CFD calculations. The initial step of development of such a replica which can serve for experimental measurements and eventually for validation of numerical simulations is the acquisition of an airway geometry.

In our case, the digital reference model of Schmidt et al. (2004) has been employed and supplemented initially with our own scan of upper airways, and later with the oral cavity identical with Lovely Respiratory Research Institute (LRRI) "model A" (Zhou and Cheng, 2005). The initial geometry served for production of two replicas simulating the flow in the case of nasal breathing (see Fig. 1). One replica has been produced by brush coating of

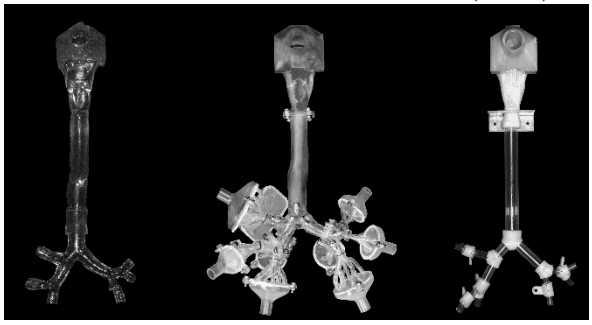

Fig. 2 Replicas containing the oral cavity

[1] Lizal, F., Elcner, J., Hopke, P. K., Jedelsky, J. and Jicha, M. (2012) 'Development of a realistic human airway model', *Proceedings of the Institution of Mechanical Engineers Part H-Journal of Engineering in Medicine,* 226(H3), pp. 197-207. IF(2017) = 1,124.

silicone on a soluble core produced on a 3D printer. This replica was optically transparent and hence suitable for measurement with laser Doppler based instruments. The second replica that possessed the identical inner geometry was produced directly by 3D printing from insoluble material. The second replica was separable into 32 segments which allowed measurement of deposition fraction in respective regions of airways. In a similar way, two additional realistic replicas of airways containing the LRRI oral cavity have been produced. Eventually, a semirealistic replica containing smooth straight glass tubes connected with 3D printed bifurcations has been produced to facilitate the measurements with optical measuring methods and to study the effects of simplification of the shape of the airways (see Fig. 2).

4. MODELLING AND MEASUREMENT OF THE AEROSOL-AIRWAY INTERACTIONS

The fate of inhaled particles, namely prediction of the distribution of deposited particles, is studied either *in vivo* (on living subjects using experimental techniques), in replicas of human airways[2], or *in silico* (using computational simulations). All these approaches lead eventually to the creation of models which can be used for better understanding of particle-lung interactions.

4.1. Experimental techniques and their application

Before we approach the models itself, we must describe the basic experimental techniques available for measurements performed *in vivo, in vitro, in silico* or in replicas of human airways. There has been great progress in the experimental methods in the last years. A thorough description of the available traditional and emerging techniques was given in the review paper (HAB-2)[3], which constitutes an integral part of the thesis. The experimental methods are not used independently nowadays, but more and more frequently as a validation tool for numerical simulations. The best results are acquired by a combination of experiments (which also provide boundary conditions and validation for CFD) and numerical simulations.

Some particular topics regarding the experimental techniques were also studied by the author and his co-workers. Specifically, the application of positron emission tomography for measurement of deposition of particles in a realistic replica of lungs was reported in (HAB-3)[4]; the turbulent behaviour of flow within the airways was studied by phase Doppler anemometry in (HAB-4)[5], and deposition of multicomponent particles was investigated in (HAB-5)[6].

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[2] Sometimes the term *in vitro* is used within the aerosol community for this approach, however, in biological sciences *in vitro* means "performed with cells, or biological molecules outside their normal biological context" (Lizal et al., 2018).

[3] Lizal, F., Jedelsky, J., Morgan, K., Bauer, K., Llop, J., Cossio, U., Kassinos, S., Verbanck, S., Ruiz-Cabello, J., Santos, A., Koch, E. and Schnabel, C. (2018) 'Experimental methods for flow and aerosol measurements in human airways and their replicas', *European Journal of Pharmaceutical Sciences,* 113, pp. 95-131. IF(2017) = 3,466

[4] Lizal, F., Belka, M., Adam, J., Jedelsky, J. and Jicha, M. (2015) 'A method for in vitro regional aerosol deposition measurement in a model of the human tracheobronchial tree by the positron emission tomography', *Proceedings of the Institution of Mechanical Engineers Part H-Journal of Engineering in Medicine,* 229(10), pp. 750-757. IF(2017) = 1,124.

[5] Jedelsky, J., Lizal, F. and Jicha, M. (2012) 'Characteristics of turbulent particle transport in human airways under steady and cyclic flows', *International Journal of Heat and Fluid Flow,* 35, pp. 84-92. IF(2017) = 2,103.

[6] Nordlund, M., Belka, M., Kuczaj, A. K., Lizal, F., Jedelsky, J., Elcner, J., Jicha, M., Sauser, Y., Le Bouhellec, S., Cosandey, S., Majeed, S., Vuillaume, G., Peitsch, M. C. and Hoeng, J. (2017) 'Multicomponent aerosol particle deposition in a realistic cast of the human upper respiratory tract', *Inhalation Toxicology,* 29(3), pp. 113-125. IF(2017) = 1,819.

Synopsis of the "Experimental methods for flow and aerosol measurements in human airways and their replicas" (HAB-2)

The experimental methods play a significant role both as a validation tool of numerical simulations and simultaneously as a source of data for setting the correct boundary conditions. It is important to establish the best practise guidelines for CFD with particle deposition studies. Such community consensus is necessary if the routine application of CFD in drug development and pharmaceutical regulatory procedures is ever to become reality. Experimental methods play an indispensable role in this context and it is important to know their strengths and weaknesses to be able to select a suitable method for a specific purpose and to form realistic expectations regarding accuracy and reliability of results.

The purpose of this paper was to review the relevant experimental methods in four categories: 1) planar and point-wise methods for measurement of velocity in the airways, 2) classic methods for measurement of inhaled aerosol deposition, 3) applications of standard medical imaging modalities for measurement of inhaled aerosol deposition and 4) nonconventional and emerging methods.

Basic features, resolution and requirements of all the methods covered by this review are summarized in Table 1. The first category includes intrusive methods, represented by hot-wire anemometry (HWA), and non-intrusive optical methods, such as laser Doppler anemometry (LDA) and particle image velocimetry (PIV). In general, PIV is more common today, as it provides the velocity field in a whole plane. However, e.g. for measurement of turbulence spectra, HWA is still a cheap and competitive alternative.

For the measurement of the distribution of inhaled particles in lungs or airway replicas, there are either classic methods such as particle concentration measurement using laser photometers, gravimetry (weighing of filters), fluorometry/mass spectrometry, or medical imaging modalities PET and SPECT. However, even the most precise methods on the list have basically reached their physical limits and cannot get to smaller resolution than 1 to 5 mm. Yet, the highly localised deposition hot-spots are extremely important and represent a crucial challenge for current CFD predictions (Longest and Holbrook, 2012). It means there is a space for emerging methods such as hyperpolarized gas magnetic resonance imaging (MRI), optical coherence tomography (OCT) or phase-contrast x-ray imaging (PCXI). The hyperpolarized gas MRI solves the main problem of conventional MRI, i.e. the low contrast between air and lung parenchyma due to the low hydrogen proton density in the lungs.

This problem is avoided by inhalation of high-contrast hyperpolarized noble gases (^{3}He or ^{129}Xe). Normally, the gas polarization is zero, which means that half of the nuclear spins are pointed up, along the magnetic field, and half are pointed down. An application of a strong magnetic field would cause the upward spin to be slightly more frequent. However, in hyperpolarization, we strive to induce a situation where almost all spins are in one direction (Roos et al., 2015). It is carried out by flipping the down spin of the rubidium electrons up by absorbing angular momentum from laser photons, which causes their outer-shell valence electrons to become spin-polarized.

Legend to Table 1:

Particles	Flow	Flow and particles

u – flow velocity; D – particle diameter; c – particle concentration; CPS – counts per second, which can be converted to radioactivity per unit volume and to % of injected dose per unit volume, a calibrated standard within the FOV is required for absolute quantitation; [a]the cost refers to as a purchase price of the instrument; [b]the term adjustment express the frequency of adjustments of the system by operator; [e]depends on the size of the FOV in mm and the pixel number of the camera chip, can be determined by the formula: FOV/number of pixels of the chip, example: FOV is $100 \times 100 mm^2$, camera has 1024×1024 px², resolution is 100 μm/px

Table 1 Main features of the experimental methods (HAB 2).

Technique	Spatial / time resolution	Quantities acquired / uncertainties	Cost[a] / availability	Requirements	Special features	Calibration / adjustment[b]
HWA	1 mm / <100 kHz	*u* (min. ±0.03 m/s; 5%) / 1C–3C	4 k€ for a single channel device/common in fluid mechanics	Inserting holes	Equidistant sampling, intrusive measurement	Daily / daily
LDA/PDA	0.1 mm / <100 kHz	*u* (±1%); *D* (±0.5 µm); *c* (±20%)	40–80 k€ per channel / common in fluid dynamics	Optical access, seeding	Random time sampling, on-line	No / daily
PIV/PTV	[e]>1 µm (for µ-PIV) / <10 kHz	*u*, 2C–3C / 0.2 px	80–200 k€ depending on PIV-type	Optical access, refractive index matching, seeding	Stereo PIV, Tomo-PIV, µ-PIV, scanning-PIV, endoscopic PIV	For each measurement
Concentration meas.	Airway generation/ single breath	*c* (±10%)	About 20 k€	Trained volunteers / lung replica	Simple, easily available	Annually/per experiment
Microscopy	1 mm to generation / per breath	*c* (±30%)	3.5 k€ per equipped microscope/common in environmental sciences	Separable replica of airways, filter preparation equipment	Simple, time-consuming, established methodology	Monthly; regular intra and inter-laboratory checks
Gravimetry/ Fluorometry	Bifurcation, several cm^2	*c* (±10%)	3 k€ (laboratory balance), units of k€ for fluorometer	Separable replica or volunteer (for fluorometry)	Simple, low resolution or reduced extent	Annually / per experiment
PET	1–5 mm	CPS	Expensive, human scanners > 1 M€, radiochemistry facilities required.	Species to be tracked labelled with a positron emitter	*In vivo*, 4D (time + space), minimally invasive	Periodically (e.g. monthly)
SPECT/CT	Typically 5–10 mm in clinical scanners	CPS	Cheaper than PET, most hospitals have SPECT, radiochemistry facilities required.	Species to be tracked labelled with a gamma emitter	*In vivo*, 3D, minimally invasive	Periodically (e.g. monthly)
^{3}He MRI		*u*, 3C, ±6.4%; ±25 mm/s	Low availability	MRI with broadband amplifier; gas polarizer; dedicated chest coil; ^{3}He or ^{129}Xe supplies;	3D flow dynamics	Yes
PCXI	1 µm / 100 Hz	X-ray image sequence → *u*	Access to set-ups available via peer-reviewed application, without cost	X-ray absorbing or phase-shifting features	PIV of lung motion, 2D, 3D (time/space), 4D (time+space), individual particle motion	No
OCT	1–10 µm / single depth line ~1–10 µs, plane ~1 ms, volume 0.1 s	*u*, *c*	50–200 k€	Optical access, seeding	*In vivo*, 3D	No / rare

This process is called optical pumping. Then, in another process called spin exchange, the electrons collide with ^{3}He or ^{129}Xe nuclei which become polarized. The advantage of this method is that both, flow and deposition measurements can be performed simultaneously. On the other hand, the resolution of this method is still lower compared to other medical modalities.

In contrast, resolution in the μm range can be achieved by OCT. It is based on the white light interferometry with near-infrared wavelength. The source of the light is a laser from which the light travels to a fibre coupler where it is divided into two parts, one part is reflected from a reference mirror, while the other part is scattered and partly reflected at the sample. The interfering light is recorded by a detector as a function of wavelength. There are several variants of OCT which differ in the way they analyse the recorded spectra and consequently in the achievable resolution and speed. The main drawback of this method is the requirement of optical access.

Unlike the conventional x-ray imaging which captures attenuating properties of structures, the PCXI is sensitive to the refractive and scattering properties of the sample. Attenuation of the signal by the sample causes a reduction in the amplitude of the incident x-ray waves which results in reduced intensity at the image detector. Soft tissues are not clearly seen in a conventional image, as they attenuate weakly. However, if an x-ray wavefield passes through a material with different refractive properties, a difference in the phase of the x-ray wavefield is introduced. PCXI is sensitive to these phase shifts and hence provides much better visualization of the soft tissues. It has been proved that single micrometre-sized particles can be tracked by this method. However, it is available only in a few specialized centres in the world.

Synopsis of "A method for in vitro regional aerosol deposition measurement in a model of the human tracheobronchial tree by the positron emission tomography" (HAB-3)

A practical application of PET to the measurement of regional distribution of inhaled particles in the replica of human airways introduced in (HAB-1) was documented in this paper.

Fluorine-18, with a half-life of 109 minutes, was selected as a positron emitter. It was incorporated into the cores of aerosol particles generated by heterogeneous condensation of di-2-ethyl hexyl sebacate in the condensation monodisperse aerosol generator (CMAG, TSI 3475, TSI Inc., Shoreview, MN, USA), which was slightly modified for this experiment. Under normal conditions, the nuclei are produced from sodium chloride solution sprayed from the nozzle in the atomizer vessel and dried in a diffusional dryer. For this particular experiment fluoride-18 nuclide was produced by irradiation of $H_2{}^{18}O$ enriched water by a proton beam in a cyclotron. The activity was eluted by the saline solution and transported into the modified shielded atomizer which contained 6 GBq of activity at a reference initial time.

Particles in sizes of 2.5 and 4.3 μm were generated and introduced into the replica of airways with constant inhalation flow rates of 15, 30 and 60 L/min. Immediately after the exposure was the replica transported to a PET/CT scanner Siemens Biograph (Siemens AG, Munich, Germany). The images were analysed in software Carimas (Turku PET Centre, Turku, Finland). The replica was divided into 22 segments and a separate volume of interest (VOI) has been set for each segment. Radioactivity was evaluated in each VOI. Then, the deposition fraction (DF) and deposition efficiency (DE) were calculated for all segments on the basis of the measured radioactivity which is proportional to the number

of deposited particles. Also, comparison with previously published data on the basis of Stokes number was performed (Fig. 3).

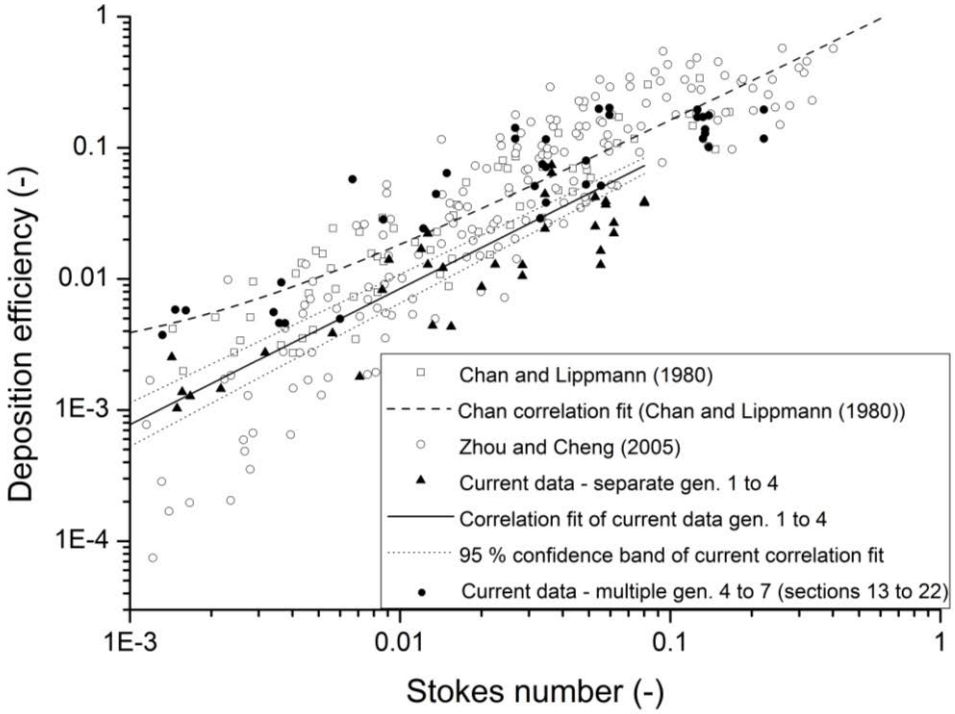

Fig. 3 Deposition efficiency as a function of Stokes number in the first seven generations of human airways. Comparison with previously published data and correlation fits (HAB-3).

The results were fitted by a function and produced an empirical equation applicable for prediction of micron-sized particle deposition in the first four generations of the tracheobronchial tree:

$$DE = 1.038\, Stk + 0.0012. \qquad (4)$$

Synopsis of the "Characteristics of turbulent particle transport in human airways under steady and cyclic flows" (HAB-4)

Data on fluctuations of velocity during the breathing cycle in human airways are very rare in the literature. Yet, they have a great value for the validation of numerical simulations. PDA measurements of micron-sized di-2-ethyl hexyl sebacate particles which can be seen as flow tracers due to their low Stokes number were documented in this paper. Fuzzy Slotting Technique has been used for estimation of the power spectral density (PSD) of velocity fluctuations on the basis of time-resolved velocity measurement. The study focused on 1) comparison of velocity fluctuations during steady-flow regimes and cyclic breathing regimes equivalent to them, 2) comparison of velocity fluctuations during inspiration and expiration phase, and eventually to 3) behaviour of particles of different sizes in several locations within the airway model.

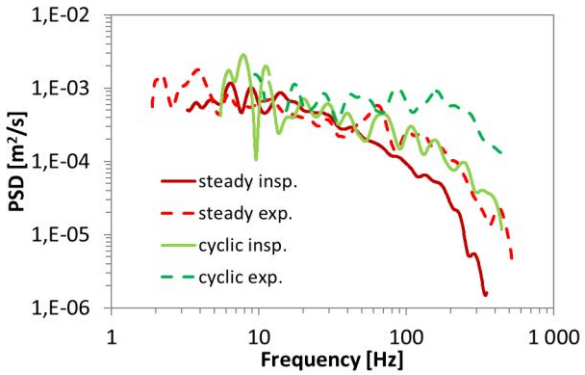

Fig. 4 Power spectral density of velocity fluctuations inside the replica of airways under steady and cyclic inhalation and exhalation (HAB-4).

The results showed that velocity fluctuations in the frequency range of 30 to 500 Hz were systematically higher for cyclic flows than for equivalent steady flows. Similarly, the expiratory flows produced more high-frequency fluctuations compared to inspiratory flows in both the steady and cyclic regime (Fig. 4). Comparison of the behaviour of different particle sizes (in the range of 1 to 8 μm) showed negligible differences at frequencies below 500 Hz, which was explained on the basis of Stk. Stk of the particles used during the experiment felt within the range $0.0002 < Stk < 0.12$, which indicates that they follow the streamlines well. In general, the results suggest that the turbulent diffusion contributes to deposition and PDA can be used for its characterisation.

Synopsis of the "Multicomponent aerosol particle deposition in a realistic cast of the human upper respiratory tract" (HAB-5)

The harmfulness of electronic cigarettes is being discussed in medical as well as aerosol science community. The question of the number of aerosol particles delivered to human lungs can be answered by the analysis of multicomponent aerosol particles. In this paper, deposition of monodisperse glycerol particles was measured at first in the realistic replica of airways in order to establish the method and guarantee consistency with previously performed experiments and published data.

A mass median aerodynamic diameter (MMAD) of the particles was 2.3 μm and a constant inhalation with a flow rate of 15 L/min was measured. The highest deposition surface density rate was found in the bifurcation segments, which confirmed the hypothesis that inertial impaction was the dominant deposition mechanism.

Then the multicomponent aerosol with an MMAD of 0.5 μm was generated by an e-vapour device. The chemical analysis based on gas chromatography-mass spectrometry focused on amounts of deposited glycerol, propylene glycol and nicotine. All the compounds showed similar deposition patterns in the replica (see Fig. 5) which was explained as an indication that they deposited within the same droplets.

The presented method proved to be applicable to multicomponent aerosols with low volatility compounds. The results can be used for validation of CFD calculations and will help to understand the fate of inhaled electronic cigarette aerosols

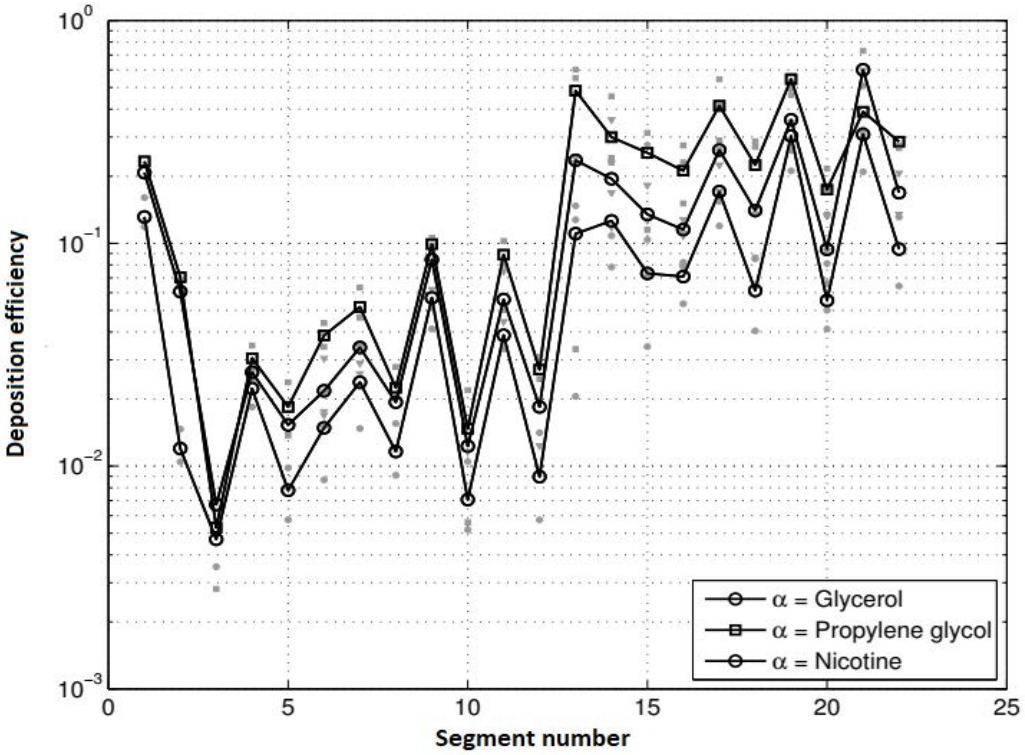

Fig. 5 Deposition efficiency of multicomponent aerosol in segments of the realistic replica evaluated for the glycerol, propylene glycol and nicotine compound (HAB-5).

4.2. Description of the modelling approaches

One of the key motivations for the development of human airway models is the requirement to precisely predict the dose of delivered particles into specific regions of airways after inhalation of adverse or therapeutic aerosols. There are three main modelling approaches: 1) Traditional (mechanistic) models – based on simplified airway geometries where the deposition rates are calculated from equations derived for the relevant particle deposition mechanisms; 2) Empirical and semi-empirical models which are based on experimental data fitted with equations; and 3) CFD models which can predict local deposition in anatomically realistic geometries. The work of the author documented in this thesis mostly extends into the latter two groups. The calculated delivered dose can then be used in another type of models called physiologically based pharmacokinetic (PBPK) models. They focus on internal processes within the human body after inhalation and predict kinetics of absorption, distribution, metabolism, excretion and storage of inhaled aerosols (Phalen and Raabe, 2016). PBPK modelling is not the subject of this thesis.

Traditional mechanistic models

The first model utilizing simplified division of airways into several compartments and applying the mechanisms of sedimentation, impaction, diffusion, and interception was published by Findeisen (1935). He was the first one to assume that once the particle touches the airway wall, it is irreversibly deposited. He also deduced the U-shaped curve of the dependence of deposition efficiency on particle diameter, where the minimum was predicted for particles between 0.2 to 0.6 μm in diameter (Phalen and Raabe, 2016). In this perspective, it is surprising, that some communities still believe that nanometer-sized particles are easily exhaled, although there had been an indication that this supposition was wrong already in the 1930s.

This type of models was later improved by Landahl (1950) and Beeckmans (1965) to include the upper airways, the effects of interpulmonary gas mixing and re-entrainment of nondepositing particles, and, eventually, to incorporate the lowest airways (Stuart, 1984).

Slightly different type of models was proposed by Yu (1978), later improved by Robinson and Yu (2001) to include cigarette smoke-related features. Their approach is called the trumpet model. It simplifies the many lung generations into a single trumpet-like path. The cross-sectional area increases with increasing lung generation. It calculates the one-dimensional transport equation for aerosol concentration loss (Rostami, 2009).

Empirical and semi-empirical models

This group includes models (or in general experimental data-fits, tables and figures) measured either in vivo (on living humans) or on replicas of human lungs. These models have usually limited applicability for cases matching the experimental conditions. However, many of these measurements became eventually parts of more sophisticated complex models which utilized data from numerous studies and gathered them to create generally valid predictions. Following papers co-authored by the author of this thesis fall into this category: (HAB-5; HAB-6[7]), as they include experimental data fits for multicomponent and fibre particles, respectively, which enhances our abilities to predict the deposition of these special types of particles.

The most typical example of the complex "summarizing" models was published by International Commission on Radiological protection (Bailey, 1994, ICRP, 1994) and National Council on Radiation Protection and Measurements (NCRP, 1997). Both models were implemented in commercial software. However, there is also a freeware alternative in so-called Multiple path Dosimetry (MPPD) model (available from https://www.ara.com/products/multiple-path-particle-dosimetry-model-mppd-v-304; Accessed 15/02/2019).

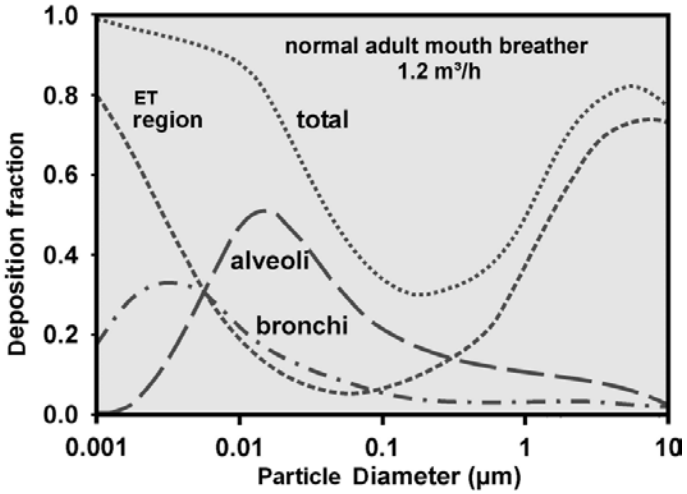

Fig. 6 The average predicted total and regional lung deposition fraction based on ICRP (1994) model for light exercise breathing conditions (Hussain et al., 2011).

An example of a result which can be acquired from the ICRP model is depicted in Fig. 6. It shows regional and total deposition fraction as a function of particle diameter. It is an

[7] Belka, M., Lizal, F., Jedelsky, J., Elcner, J., Hopke, P. K. and Jicha, M. (2018) 'Deposition of glass fibers in a physically realistic replica of the human respiratory tract', *Journal of Aerosol Science,* 117, pp. 149-163. IF(2017) = 2,281.

illustration of the previously mentioned U-shaped curve of deposition. Apparently, nanoparticles deposit even more efficiently than micrometre-sized particles.

The empirical and semi-empirical models are useful for prediction of total and regional aerosol deposition. They frequently serve as an input for PBPK models. Naturally, they cannot simulate interpersonal variability, local deposition on a millimetre scale or the patient-specific influence of diseases; however, they provide sufficient data for the "average" person aerosol dosimetry.

The author and his team have recently developed more sophisticated approach, where specific features of a particular disease can be accounted for. The research has been published in HAB-11[8]. The paper focused on the prediction of aerosol deposition to the lungs of patients with chronic obstructive pulmonary disease (COPD). At first, realistic inhalation profiles were recorded. These profiles were used as an input to the stochastic lung model, a special type of empirical model developed by Koblinger and Hofmann (1990). The results showed that the aerosol dose delivered to the lungs of COPD patients was significantly lower compared to healthy subjects although exactly the opposite is needed.

Synopsis of the "Simulation of Airway Deposition of an Aerosol Drug in COPD Patients" (HAB-11)

The real dose that is successfully delivered to the airways of a patient suffering from COPD is difficult to predict. It depends on the actual breathing pattern of the specific patient, which varies with the severity of the disease. This paper presents the results of measurements of real inhalation profiles induced by patients with mild, moderate, and severe COPD during inhalation from the Symbicort® Turbuhaler® dry powder inhaler (Fig. 7).

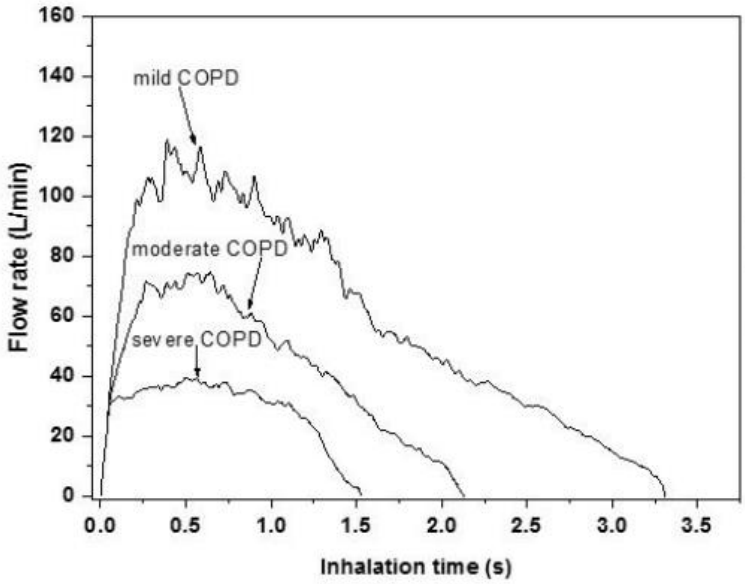

Fig. 7 Median of inhalation curves measured among patients with mild, moderate, and severe chronic obstructive pulmonary disease during the real inhalation manoeuvre (HAB-11)

The recorded profiles were used as an input to a stochastic airway deposition model. The results showed, that the amount of deposited particles correlates with severity of the

[8] Farkas, Á., Lizal, F., Jedelsky, J., Elcner, J., Horváth, A. and Jicha, M. (2019) 'Simulation of Airway Deposition of an Aerosol Drug in COPD Patients', Pharmaceutics, 11(4). IF(2017) = 3,746.

disease. The lung deposition fraction calculated for mild asthma was comparable to that of healthy patients (28% vs. 31%), however, the deposition fraction of severe COPD patients was significantly lower (17%). Deposition fraction of moderate COPD patients was 23%. It indicates that COPD patients using identical inhaler receive a significantly lower dose of medication compared to a standard based on a healthy person.

CFD models

The fast development of computational capabilities allowed more detailed calculations of aerosol deposition in realistic geometries in the last decades. This approach is frequently referred to also as CFPD (Computational Fluid and Particle Dynamics). It consists of several steps: 1) acquisition of a suitable airway geometry (either the simplified Weibel or Horsfield models, or, more frequently, a realistic geometry acquired by medical imaging methods, such as computed tomography or MRI performed *in vivo,* or on airways excised at an autopsy); 2) creation of a computational mesh which is necessary for discretization of the problem and allows solution of complex equations of fluid and particle motion; 3) solving the Navier–Stokes equation for fluid flow and applying Lagrangian, or Eulerian approach for particles and 4) post-processing, i.e. analysis of the results and calculation of deposition rates in all regions of lungs.

The main advantage of this type of modelling is that it allows calculations of patient-specific lungs. Various pathologies can be easily simulated and compared to healthy lungs. On the other hand, there cannot be a complete whole-lung model, because, first, there is no complete digital geometry of lungs available (due to the limitations on the side of imaging methods, see (HAB-2) for details), and second, calculations on such complex geometry in realistic conditions would be impossible even for current top-class computer clusters.

There is a vast number of publications on the CFD modelling of human airways. The development in the field has been reviewed by (Rostami, 2009, Hofmann, 2011, Longest et al., 2019). Only a very brief selection of essential aspects of CFD modelling is presented here.

The first step is always the selection of a suitable geometry. In order to take advantage of the best features of CFD (ability to focus on detail), it is advisable to use realistic, patient-specific geometries. Preferably those, for which enough experimental data is available for boundary conditions setting and for validation purposes. However, such cases are sporadic. Therefore, it has been a major objective of the author of this thesis to prepare a digital geometry that would serve for both fabrication of physical models and numerical modelling. The whole procedure has been reported in the paper (HAB-1) which is a part of this thesis. This effort has been appreciated by the community of scientists gathered within the COST Action 1404 SimInhale (http://www.siminhale-cost.eu/), who selected the model developed by the author's team as a benchmark case for comparison of CFD calculations among six international teams (for details see (HAB-8)[9]).

The second step, creation of the computational mesh, is crucial because if the calculations are performed on a poor mesh, the results are worthless. The requirements on the density and type of the mesh differ depending on the proposed numerical method. Usually, a mesh convergence study is performed at the beginning of calculations. In brief, the search is for the compromise between the speed of the calculation (coarse mesh) and the accuracy of

[9] Koullapis, P., Kassinos, S. C., Muela, J., Perez-Segarra, C., Rigola, J., Lehmkuhl, O., Cui, Y., Sommerfeld, M., Elcner, J., Jicha, M., Saveljic, I., Filipovic, N., Lizal, F. and Nicolaou, L. (2018) 'Regional aerosol deposition in the human airways: The SimInhale benchmark case and a critical assessment of in silico methods', *European Journal of Pharmaceutical Sciences,* 113, pp. 77-94. IF(2017) = 3,466.

the results (dense mesh). This means that several variants of the mesh are created, from a coarse mesh with the fewest reasonable number of cells to denser and denser meshes. Then calculations are performed on all meshes, and the results (e.g. velocity on a line crossing some complicated area) are compared. The results converge to the best value delivered by the densest mesh. The coarsest mesh, whose results are consistent with the best calculation is then selected.

Within the third step, the Navier–Stokes equation is being solved. It describes the fluid flow and is used for calculation of velocity field providing the correct boundary conditions were set. The movement of fluid can be studied by either Eulerian or Lagrangian approach. In the Lagrangian approach, the observer is connected with the observed parcel of the fluid, and the path of the parcel can be completely described as a function of its original coordinates and time. On the contrary, when using the Eulerian approach, the observer focuses on a specific location through which the fluid flows. Then, the flow velocity in the specific location is given as a function of the location coordinates and time.

The Navier–Stokes equation (14) in CFD calculations of airway flow is usually solved by the Eulerian approach.

$$\rho\left(\frac{\partial \boldsymbol{U}}{\partial t} + \boldsymbol{U}\cdot\nabla\boldsymbol{U}\right) = -\nabla p + \mu\nabla^2\boldsymbol{U}, \tag{5}$$

where p is pressure.

The solution of the Navier–Stokes equation is performed on the discretized mesh by a suitable numerical method. The actual direct solving of the equation requires calculation of a wide range of time and length scales. It can be achieved by direct numerical simulation (DNS); however, it is extremely computationally expensive, which limits the applicability of this method only to the low-Reynolds number cases and the limited extent of airways. As an alternative, large eddy simulation (LES) can be used. It actually solves only the large scale fluctuations, while the small-scale fluctuations are modelled. The least computationally expensive approach is solving the Reynolds-averaged Navier–Stokes (RANS) equations, which provides the time-averaged approximate solution to the Navier–Stokes equation. It uses the so-called Reynolds decomposition, i.e. division of the actual quantities to the time-averaged and fluctuating components. Application of this decomposition to Navier–Stokes equation leads to the introduction of the Reynolds stress term. It is a nonlinear term, which requires additional turbulence models. Although it seems to be complicating the solution procedure, it is actually faster than LES. Nonetheless, it is on the expense of receiving only the mean flow values. The author's team contribution in the field of RANS simulations was documented in (HAB-8; HAB-9[10]).

In short, the velocity field can be calculated by either DNS, LES, or RANS approach; however, in any case, results of simulations should always be validated by experimental data to exclude the possibility of inaccuracy and consequent misinterpretation. The author with his colleagues applied phase-Doppler anemometry for investigation of the turbulence characteristics (HAB-4) and reported results, which serve for the CFD validation.

After the successful validation of the velocity field, the flow of particles can be calculated. It can be performed by both Lagrangian and Eulerian approaches, while Lagrangian tracking is more common for dilute, and Eulerian approach for dense aerosols. The solution can be performed in two ways—either the particles just interact with the flow,

[10] Elcner, J., Lizal, F., Jedelsky, J., Jicha, M. and Chovancova, M. (2016) 'Numerical investigation of inspiratory airflow in a realistic model of the human tracheobronchial airways and a comparison with experimental results', *Biomechanics and Modeling in Mechanobiology,* 15(2), pp. 447-469. IF(2017) = 3,212.

but the flow is not influenced by the presence of particles (one-way coupling), or the particles and fluid interact mutually (two-way coupling). Again, the second option is demanded only for dense aerosols (e.g. cigarette smoke). The author's team dealt with both Lagrangian (HAB-9) and Eulerian approach (HAB-10)[11]. In the Lagrangian approach, the equation of motion of a particle is usually expressed as (Rostami, 2009):

$$m_p \frac{dU_p}{dt} = F_D + m_p g + F_{add}, \tag{6}$$

where m means mass, F_D denotes the drag force, g is gravitational acceleration and F_{add} are additional forces, such as Brownian, thermophoretic, electrostatic or others.

In the Eulerian approach, where the focus is on the elemental control volume through which the particles flow, the transport equation is solved for aerosol concentration (Rostami, 2009):

$$\frac{\partial \rho C}{\partial t} + \nabla.(\rho U C) = \nabla.(\Gamma \nabla C) + S_C, \tag{7}$$

where C is the particle (mass or number) concentration, Γ is the effective particle diffusivity (due to the Brownian motion and turbulent eddy diffusivity), and S_C is the particle source or sink term.

The above-mentioned equation can be used for monodisperse aerosols; however, as was shown in the previous chapters, real aerosol (including pharmaceutic) is polydisperse. For such cases a modification called 3D general dynamic equation (GDE) is used (Rostami, 2009):

$$\frac{\partial n_k}{\partial t} + \nabla.(U n_k) = \nabla.(\Gamma \nabla n_k) + \left(\frac{\partial n_k}{\partial t}\right)_{growth} + \left(\frac{\partial n_k}{\partial t}\right)_{coag}, \tag{8}$$

where n_k is the discrete size distribution function (concentration of particles in the size range k), and the source term S_C was replaced by the term accounting for hygroscopic growth, condensation and evaporation from the particle; and coagulation of particles respectively. Other modifications, accounting for additional forces, chemical composition of particles, etc. can be made. For details see the paper (HAB-10), which is a part of this thesis.

Synopsis of the "Regional aerosol deposition in the human airways: The SimInhale benchmark case and a critical assessment of in silico methods" (HAB-8)

The benchmark replica of human airways introduced in (HAB-1) has been applied for comparison and validation of numerical simulations performed by six different teams from various European countries. The collaboration was realized within the European project COST MP1404 SimInhale. Three RANS and three LES simulations were compared. Each group used different turbulence model, different mesh density and different solver, however, the airway geometry was identical. All teams used Lagrangian tracking of particles and one-way coupling. The benchmark case served for the examination of the sensitivity of predictions to the setup of the simulations. The flow in the upper airways

[11] Frederix, E. M. A., Kuczaj, A. K., Nordlund, M., Belka, M., Lizal, F., Jedelsky, J., Elcner, J., Jicha, M. and Geurts, B. J. (2018) 'Simulation of size-dependent aerosol deposition in a realistic model of the upper human airways', *Journal of Aerosol Science,* 115, pp. 29-45. IF(2017) = 2,281.

was sensitive to mesh size and turbulence model, while the inflow conditions had a lesser effect. The transition of the flow from laminar to turbulent at the back of the mouth appeared even for low Reynolds numbers (below 2000). The inflow conditions affected only the flow upstream of the larynx. As expected, the mean flow fields predicted by the LES simulations were superior to RANS, however, the RANS low-Re k-ω model predicted the mean-flow dynamics well with significantly lower computational COST compared to LES.

It was shown, that deposition is sensitive to mesh size and particle-tracking scheme, while the interpolation errors increase with decreasing grid resolution. Hence, the selection of the interpolation method is crucial. Particles with small Stokes number are influenced by the velocity fluctuations, thus errors in the flow field cause erroneous predictions of deposition. In our case, RANS with Continuous random walk and Eddy interaction model of turbulent dispersion overpredicted deposition at small and medium particle sizes. On the other hand, the RANS with mean-flow tracking clearly underpredicted the deposition of large particles. LES predictions were in good agreement with experiments (see Fig. 8) Forces other than drag and gravity had a minor effect on the deposition.

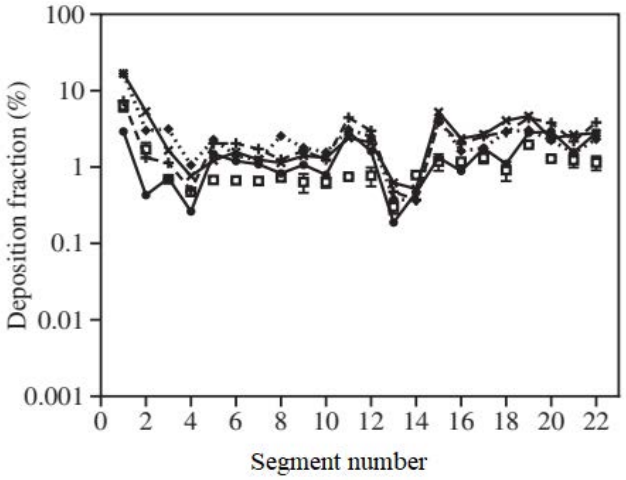

Fig. 8 Comparison of deposition fraction provided by □ experiment, and four different LES simulations: • LES1, ♦ LES1c, × LES2, + LES3 (HAB-8).

Synopsis of the "Numerical investigation of inspiratory airflow in a realistic model of the human tracheobronchial airways and a comparison with experimental results" (HAB-9)

Numerical simulations of cyclic breathing pattern validated with thorough and elaborate measurements of velocity are presented in this paper. The experiments were performed using phase Doppler anemometry in eight cross-sections of the thin-walled transparent replica of human airways. It was necessary to set the emitting and receiving optics of the anemometer for each measuring point. It was a consequence of the complex shape of the wall of the replica which caused slight misalignment of the intersection of the beams and which had to be corrected.

Both experiment and simulations were performed for three breathing patterns: resting conditions with a tidal volume of 0.5 L and period of the breathing cycle 4 s were followed by deep breath and light activity regimes with tidal volumes of 1 L (for both) and period of 4 and 3 s, respectively. The course of the flow rate was sinusoidal in all cases and duration of inspiration and expiration was equal.

The simulations were performed in commercial software CCM+ (Adapco) with an SST k-ω low-Reynolds Number RANS model on a mesh with 2.6 million polyhedral control volumes and a time step of 0.001 s (Fig. 9). The RANS simulations predicted well the unstable character of the flow field. The transition from laminar to the turbulent character of flow was predicted with surprising precision in most of the measuring points. Separation zones with a reattachment were formed in both main bronchi. Maximum velocities in the left main bronchus were slightly overpredicted by the simulation,

however, the width of the separation zone was correct. Turbulent kinetic energy (TKE) was evaluated as well. The sudden rise of TKE was found immediately downstream of the glottis. Local increases were observed on each branching.

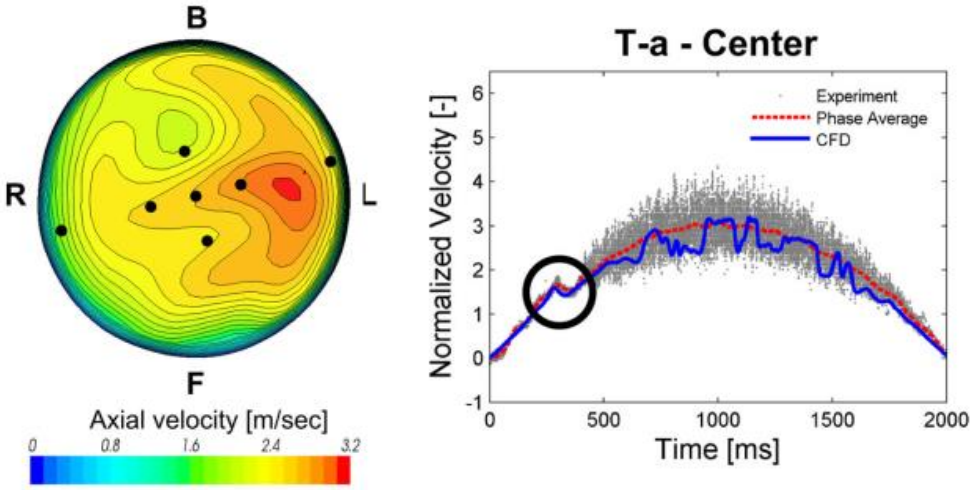

Fig. 9 CFD calculated velocity field in the right main bronchus and indication of the measuring points (left), and the course of velocity during inhalation assessed by the experiment and numerical simulation in the centre of the cross-section (HAB-9).

Synopsis of the "Simulation of size-dependent aerosol deposition in a realistic model of the upper human airways" (HAB-10)

The Eulerian approach to the simulation of particle-laden flow was adopted within this work. The simulations were performed in the realistic replica of airways identical with the previous papers. The GDE, introduced earlier in this summary, included terms accounting for diffusion due to Brownian motion, and drift due to droplet inertia. Also, gravitational settling was accounted for in the equation for calculation of the motion of the droplet.

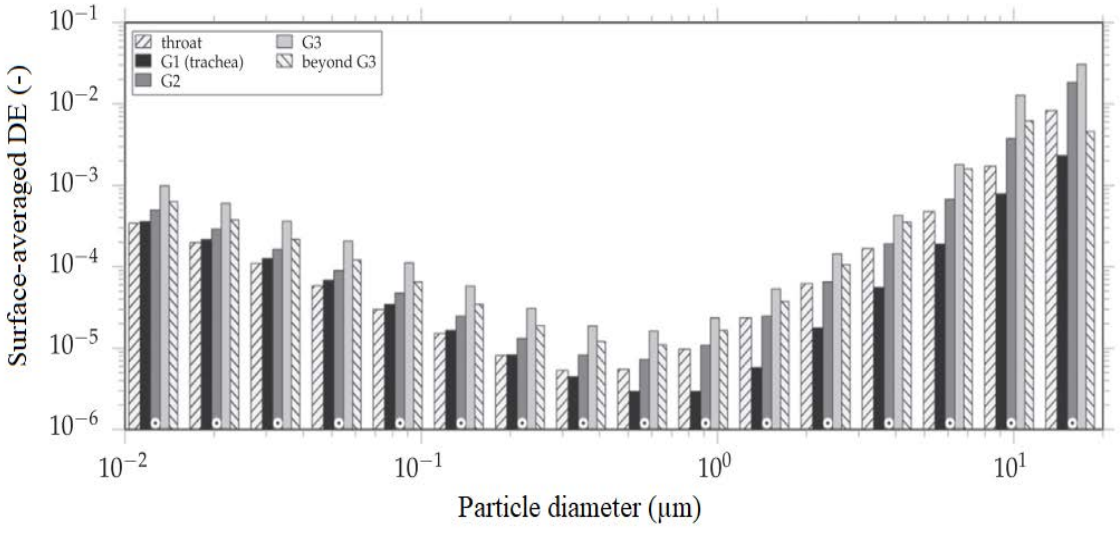

Fig. 10 Surface-averaged deposition efficiency as a function of particle size in first three generations of airways and the throat (HAB-10)

The results of particle deposition measured with glycerol particles as presented in (HAB-5) were used for validation. The size-dependent deposition was studied in this paper. The results were presented in the form of surface-averaged deposition efficiency. This metric showed, that the second generation of the airways (the main bronchi), has the highest "filtration" efficiency. The throat area was much less effective in capturing small droplets compared to other generations of the lung tree (see Fig. 10)

4.3. Deposition of fibres in human lungs

A scientific gap has appeared in the area of modelling of inhaled fibres. The reason why this topic remained temporarily aside of the main research interest grounded in two facts: first, there has been a seeming lack of motivation for the further study of fibre flow after the successful hunt for asbestos fibres and global ban of their production. Public opinion was that this problem had been solved and it is not necessary to invest in new research in this area. Second, calculation of fibre motion in human airways is significantly more complicated compared to spherical particles. Such simulations require more complex equations and multiple iterations in a single time step to account for the changes in orientation and rotation of a fibre. Moreover, there has not been enough experimental data available for validation of the simulations.

It should be clearly stated, that asbestos is not the only harmful fibre that can get into human lungs. Glass and mineral fibres are being used as asbestos substitutes in thermal insulations; carbon nanotubes are produced in amounts exceeding several thousand tons per year for various purposes (De Volder et al., 2013). Therefore, the ability to predict the fate of inhaled fibres in authentic airways becomes important nowadays.

The author of this thesis and his team focused initially on experiments and performed a series of measurements in the realistic replica of human lungs with glass fibres. The work has been reported in two papers: (HAB-7)[12] focused on the method for detection of fibres on samples created after the exposition of the airway replica to the fibres. In (HAB-6), the author's team has published empirical equations for prediction of deposition efficiency as a function of Stokes number. The work in this area is ongoing and more papers will be published soon on numerical modelling of the fibre flow.

Synopsis of the "'Deposition of glass fibers in a physically realistic replica of the human respiratory tract" (HAB-6)

The glass wool JM100/475 (Johns Manville) was crushed in a mechanical press and the fibres thus produced were mixed with glass beads in order to facilitate the dispersion process in the fluidized bed disperser. The length-classification was performed in a dielectrophoretic fibre classifier.

Dielectrophoresis is a motion of electrically conductive but electrically neutral particles in a non-homogeneous electric field. It is very appropriate for the length classification of fibres because it is more sensitive to the length of the fibre than to its diameter (which is on the contrary to the better-known electrophoresis – the movement of electrically charged particles in an electric field).

The length-classified fibres were then introduced into the replica of airways and the number of fibres in each segment of the model and on the output filters was counted using

[12] Belka, M., Lizal, F., Jedelsky, J., Starha, P., Druckmullerova, H., Hopke, P. K. and Jicha, M. (2016) 'Application of image analysis method to detection and counting of glass fibers from filter samples', *Aerosol Science and Technology,* 50(4), pp. 353-362. IF(2017) = 2,000.

the method described in (HAB-7). Three constant inhalation flow rates (15, 30 and 50L/min) were measured. The results were presented in terms of deposition fraction, density and efficiency and compared to deposition of spherical particles.

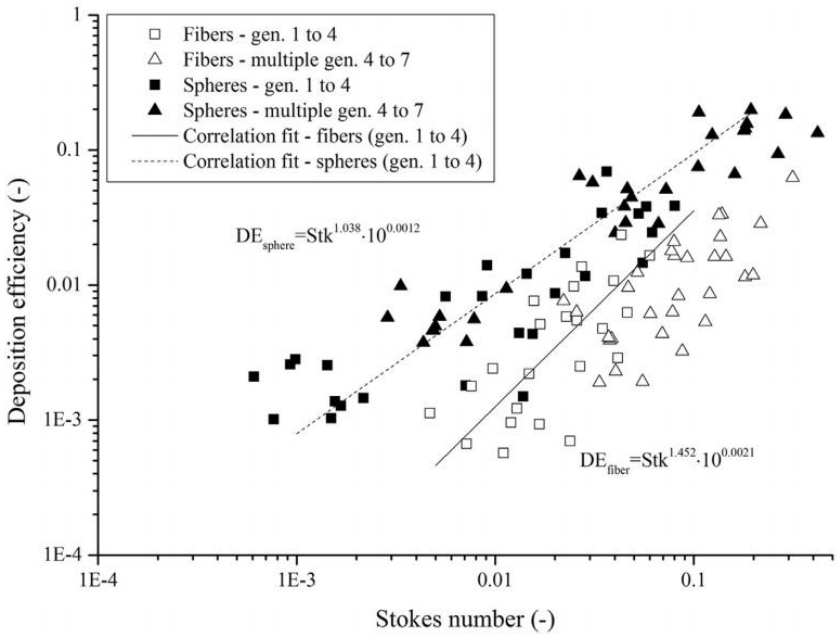

Fig. 11 Comparison of deposition efficiency of fibres and spheres in first generations of the tracheobronchial tree (HAB-6)

Empirical fit for calculation of deposition efficiency in the upper parts of the tracheobronchial tree was calculated (Fig. 11). Fibres deposit less effectively compared to spheres having the same Stokes number and hence tend to penetrate deeper into the lungs.

Synopsis of the "Application of image analysis method to detection and counting of glass fibers from filter samples" (HAB-7)

Methods for counting asbestos or man-made vitreous fibres have been established by the International Organization for Standardization (ISO) and The National Institute for Occupational Safety and Health (NIOSH) standards. However, the methods are based on manual counting, which is time-consuming, tedious, requires well trained and skilled personnel and is sensitive to fatigue, health state or even mood of the microscopist. Therefore, an automated method for detection and quantification of fibres on filters has been developed and tested (Fig. 12).

The image analysis starts with histogram-based equalization followed by application of an adaptive radial convolution filter in order to enhance the contrast between fibres and the background. The accuracy of the automated analysis was validated by comparison with manual counting using the NIOSH-based method which uses phase-contrast microscopy.

The methods correlated well (the coefficient of determination was 0.977). Nevertheless, corrections were necessary to compensate for a false fibre identification (splitting of the fibre and counting the single fibre as two fibres).

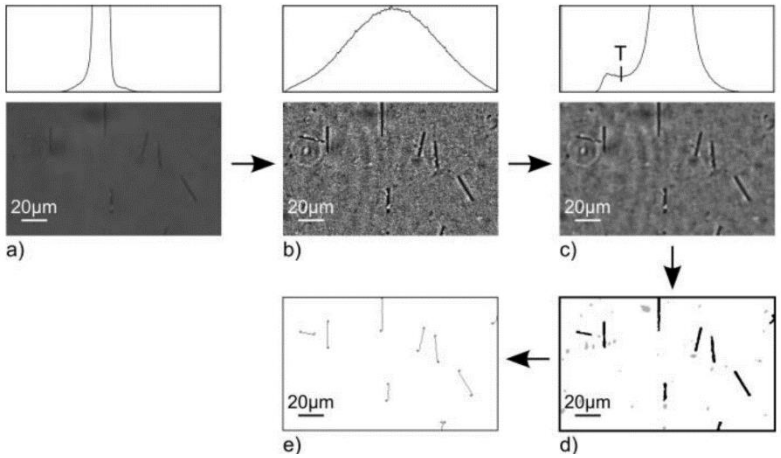

Fig. 12 The image processing procedure used by the newly developed software: (a) the original image and its histogram; (b) the same image after application of adaptive contrast control algorithm; (c) the image after adaptive radial convolution; (d) the image after segmentation; (e) the image with recognized fibers (HAB-7).

5. CONCLUSIONS AND FUTURE WORK

The recent fast development in the field of modelling of human airways documented in this thesis brings interesting opportunities for more efficient treatment of patients suffering with (not only) the lung diseases. It also allows a better description of the fate of inhaled harmful particles.

It is possible to predict overall and regional deposition fractions for an average population with reasonably good precision. Numerical simulations can be performed on realistic airway geometries with up to 16 generations of branching. There are experimental data available for validation of velocity fields within human lungs and deposition of spherical and, partly, fibrous particles.

Current limits are set by the absence of the complete model or just digital geometry of real human lungs spanning from the nasal and oral cavity to alveoli. Also, the computational power is not sufficient for solving the flow field precisely by DNS. Various numerical approaches deliver different results. Hence, the experimental validation remains an indispensable part of the process. Acquisition of correct boundary conditions represents significant challenge during not only *in vivo* but also *in vitro* measurements.

Nonetheless, future goals appear clearly on the horizon. The medical community hopes for a bright future of a patient-tailored medicine. In brief, the idea is the following: a patient suffering from a particular problem visits the physician, who scans their lungs by CT or MRI. The images are processed, airway geometry is segmented and prepared for numerical simulations. The calculations are performed overnight, resulting in the prescription of the most suitable drug administered by the most efficient inhalation device. It reduces the cost of the treatment (smaller doses are necessary due to the precise targeting), and it minimizes the side effects (as the drug is delivered solely to the predetermined region, the organism does not need to process the pharmaceuticals from other locations). Similarly, the protection against harmful particles can be more efficient if the toxicological limits are set to the appropriate values, and efficient lung protection tools are produced.

In order for these dreams to become reality, it is necessary to focus the research into following areas: improved prediction of the local deposition (hot-spots on millimeter or

even micrometer scale); better simulations of non-ideal particles (fibers, porous particles); and incorporation of physiologically realistic features of airways (wall motion in lower airways, mucociliary mechanisms, hygroscopic growth, surface roughness, and electrostatic effects).

An important topic for further research is also the influence of lung diseases on the flow and deposition of particles. The inhaled medication is, apparently, administered to sick, not healthy patients. However, the development process of inhalation systems in the pharmaceutical industry is often based on healthy volunteers' data, cascade impactors or extremely simplified airway geometries. Likewise, more realistic predictions are needed on the side of PBPK modelling and the fate of deposited particles in general (Forbes et al., 2015). A scientific gap remains in the area of aerosol–lung interactions during the development of lungs from the fetal stage to adulthood, and there is a lack of data on gender differences.

The future progress in the field of inhaled particles modelling obviously depends on the interdisciplinary collaboration, which inevitably pushes experts from all disciplines to their limits. This thesis documents that the contribution of mechanical engineers is significant, and that there will be enough opportunities for application of the engineering approach also in the future. The appealing feature of this research is the fact that it is directly related to human health, and hence it is rewarded by the public recognition of the societal benefit.

NOMENCLATURE

C	concentration (count/m^3)
C_C	slip correction factor (–)
d, D	diameter (μm), characteristic length (m), or diffusion coefficient (m^2/s)
dN	number of particles in a size interval (–)
F	fraction (–)
g	gravitational acceleration (m/s^2)
k	Boltzmann's constant (–)
M, m	mass (kg)
$n(d_p)$	number distribution function (–)
N, n	number (count) (–)
p	pressure (Pa)
S, s	surface (m^2)
S_C	particle source or sink term (a.u.)
t, T	time (s), temperature (K)
U	velocity (m/s)
V, v	volume (m^3)

Greek symbols:

Γ	effective particle diffusivity (m^2/s)
μ	dynamic viscosity (Pa·s)
ρ	particle density (kg/m^3)
σ_G	geometric standard deviation

Subscripts:

0	standard value, or reference value
a	aerodynamic
add	additional
B	Brownian
D	drag
e	equivalent
G	geometric
k	size range
p	particle, or pressure
s	settling
T	total

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Topic-2: Experimental techniques applicable to human lungs and their replicas

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HAB-3 Lizal, F., Belka, M., Adam, J., Jedelsky, J. and Jicha, M. (2015) 'A method for in vitro regional aerosol deposition measurement in a model of the human tracheobronchial tree by the positron emission tomography', Proceedings of the Institution of Mechanical Engineers Part H-Journal of Engineering in Medicine, 229(10), pp. 750-757. IF(2017) = 1,124.

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Topic 4: Numerical calculations of fluid and particle flow

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ABSTRACT

The improved knowledge of flow and deposition of aerosols in human lungs is necessary for both more efficient inhaled therapy and reduction of toxicological effects of harmful particles. Due to the recent fast development in the field of modelling of human airways, it is possible to predict overall and regional lung deposition fractions with reasonably good precision. Computational simulations can be performed on realistic geometries of the tracheobronchial tree. There are experimental data available for validation of calculated velocity fields within human lungs and deposition of inhaled particles.

The habilitation thesis documents author's contribution to the current knowledge in the following areas: 1) physical airway model preparation and production, 2) experimental techniques applicable to human lungs and their replicas, 3) research of inhaled fibres in a lung replica, and 4) computational simulations of fluid and particle flow. All the topics are closely related, and they are driven by an effort to gradually increase reliability of computational simulations on the basis of conscientiously performed experiments.

The work evidences that progress in the experimental and computational modelling of inhaled particles depends on interdisciplinary collaboration with a significant and irreplaceable contribution of mechanical engineers. An appealing feature of this research is the fact that it is directly related to human health, and hence it is rewarded by a public recognition of its social benefit.

ABSTRAKT

Kvalitnější poznání mechanismů proudění a usazování aerosolů v lidských plicích je nezbytné jak pro účinnější inhalační léčbu, tak pro snížení účinků vdechování škodlivých částic. Díky současnému rychlému vývoji v oblasti modelování lidských dýchacích cest je možné s velmi dobrou přesností předpovídat celkovou i regionální depoziční frakci. Počítačové simulace lze dnes provádět na realistických geometriích tracheobronchiálního stromu. Jsou k dispozici i experimentální výsledky vhodné pro validaci vypočítaných rychlostních polí v plicích a množství usazených vdechnutých částic.

Habilitační práce prokazuje autorův přínos k současnému poznání v následujících oblastech: 1) příprava a výroba modelu dýchacích cest, 2) experimentální techniky použitelné v lidských plicích a jejich modelech, 3) výzkum inhalovaných vláken v modelech plic, a 4) počítačové simulace proudění tekutiny a částic. Všechna témata spolu úzce souvisejí a jsou motivována snahou postupně zlepšit spolehlivost počítačových simulací pomocí pečlivě prováděných experimentů.

Předložená práce dokazuje, že vývoj v oblasti experimentálního a počítačového modelování inhalovaných částic závisí na mezioborové spolupráci s výrazným a nezastupitelným příspěvkem strojního inženýrství. Nesmírně přitažlivou vlastností tohoto výzkumu je fakt, že přímo souvisí s lidským zdravím, což je logicky odměněno všeobecným uznáním společenské prospěšnosti