Eötvös Loránd University

Faculty of Science

Numerical modelling of airway transport of inactive particles and radon progenies

(Development and application of the Stochastic Lung Model)

Theses of doctoral dissertation

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1. Introduction

There is usually a large number of particles in the environmental air. During breathing, they may irritate the epithelial tissue of the airways, causing inflammatory processes which might induce asthma, emphysema or COPD (chronic obstructive pulmonary disease). By breathing, biologically active, toxic or carcinogenic chemicals may be incorporated into the body as a result of particle deposition. Near half of the ionizing radiation burden originates from the inhalation, airway deposition and decay of radon progenies. ^{222}Rn first decays into ^{218}Po with a half-life of 3.8 days by alpha radiation, which decays again by alpha radiation into ^{214}Pb with a half-life of 3.1 minutes. Then after a beta decay ^{214}Bi is formed (half-life 26.8 min), and after another beta decay (half-life 19.7 min) one get ^{214}Po which emits another alpha particle (with a half-life of 164μs).

A number of epidemiological studies (ICRP 66, BEIR VI, UNSCEAR 2009) demonstrate a strong correlation between the activity concentration of radon in dwellings and the probability of lung cancer development.

Therefore it can be stated, that a significant part of environmental hazards are related to respiration.

It is important both for physics, medicine and biology to examine the biological effect of inhaled particles. Here the first step can be the determination of airway deposition distribution.

The deposition distribution can be tested experimentally by gamma camera or SPECT (Single Photon Emission Computer Tomography) after inhalation of radiolabelled particles. However, these methods have many disadvantages and difficulties. The main problem is the resolution of the experimental procedures. These methods are not suitable for examining the small airways below the diameter of 2 mm.

The deposition distribution of inhaled particles can be calculated by numerical procedures, such as in silico lung models.

The main advantages of lung models are that they are flexible, the simulations can be reproduced, and their cost is usually much lower than the cost of experimental procedures.

The so-called Stochastic Lung Model is used to simulate the respiratory deposition distribution of the inhaled particles. This software can be applied to determine the deposition

distribution of aerosols between the regions of the breathing system with a uniquely fine airway generation related resolution.

During my doctoral work I have applied and developed this model in many areas.

2. Objectives

During my doctoral work, I set the following objectives:

A. The development of the Stochastic Lung Model to make it suitable for the description of deposition density of particles along the airways.

B. The further development and application of the model, that it be more suitable for the quantification of the airway deposition distribution of inhaled aerosol drugs.

C. The further development and application of the model, that it be more suitable for the simulation of deposition distribution of inhaled particles in diseased airway system with asthma, emphysema and COPD.

D. The further development and application of the model, that it be more suitable for the description of the activity distributions and cell nucleus dose distributions of inhaled and deposited radon progenies along the bronchial airways.

E. To create and apply a bronchial mucociliary clearance model to simulate the effect of mucociliary clearance on activity and cell nucleus dose distributions of deposited radon progenies.

3. Applied Methods

I have modified and enhanced the source code of the Stochastic Lung Model, making it more flexible and more realistic. The most important types of the development were the followings:

(i) the development of an algorithm for the computation of the surface of the airways,
(ii) the computation of deposition densities along the airway generations,
(iii) the simulation of the trajectories of hygroscopic particles,
(iv) the numerical description and characterisation of asthmatic and emphysematic lungs,
(v) the simulation of inspiratory waveform in the model,
(vi) the simulation of activity and cell nucleus dose distributions originating from radon progenies considering both primary deposition and mucociliary clearance.

4. New scientific results achieved during the research:

A) Characterization of the deposition distributions of ultrafine urban aerosols

For the prediction of the biological effect of inhaled particles, it is not enough to analyse the deposition distribution of inhaled particles in the respiratory system, but the quantification of the distribution of deposition density (deposition on unit surface) is also needed.

At the examination of airway deposition of ultrafine urban aerosols I have demonstrated that the extrathoracic deposition fraction by the increase of physical activity decreased from 26% to 9%. The tracheobronchial deposition fraction was not sensitive to physical activity and was on average 12.5%. The acinar deposition fraction increased strongly with physical activity from 14.7% to 34%. Regarding the whole respiratory tract, the deposition fraction always has a significant peak in the acinar region. By physical activity, this peak moves deeper into the lungs. The number-deposition density distribution is quite different compared to the distribution of the deposition fractions and indicates that the largest surface load within the lungs is in the first few airway generations, i.e. in the large central airways. Based on the literature data, this region is where most of the lung cancer cases can be found (Cross 1987). This confirms the assumption that the biological effect is better described by the deposition density distribution than the deposition fractions. Some of the relevant results are shown in Figures 1 and 2.

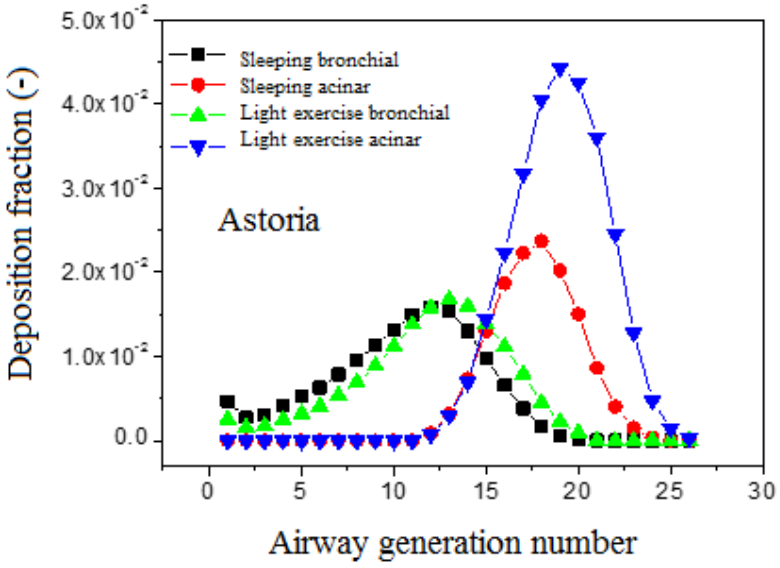

Figure 1: Bronchial and acinar airway deposition fraction distributions of ultrafine urban aerosols for woman at sleeping and light exercise physical activity, location: Budapest Astoria

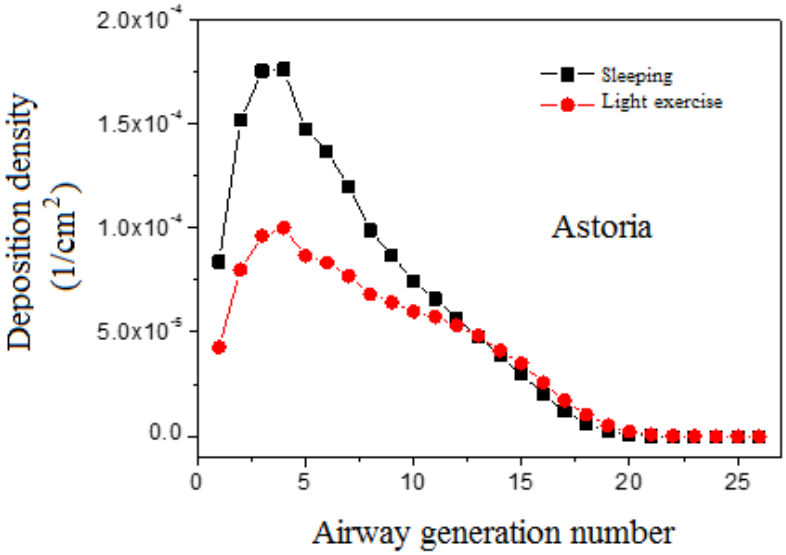

Figure 2: Airway deposition density distributions (bronchial + acinar) of ultrafine urban aerosols for woman performing sleeping and light exercise physical activity breathing conditions, location Budapest Astoria site

B) Description of airway deposition distributions of an industrial aerosol in healthy and diseased lungs

I studied the effect of the modified airway geometry and breathing pattern due to respiratory diseases (asthma, emphysema, silicosis) on the airway deposition distributions applying the size distribution of an Egyptian industrial aerosol. In case of heavily diseased breathing system with bronchitis and bullous emphysema, acinar deposition is greatly increased compared to the healthy lung. During mouth breathing the difference is even bigger. Based on the results, it can be stated that for workers with obstructive or restrictive respiratory illnesses, or healthy workers with mouth breathing, it is highly unhealthy to work in such heavily polluted area. If the first symptoms of a respiratory tract illness are recognized, the worker should stop working in the polluted area or his illness will become more and more serious. Figures 3 shows a few of the specific cases of the deposition fraction distributions (Figure 3 left panel) and the deposition density distributions (Figure 3 right panel) in the lungs of healthy and diseased (panacinar and bullous emphysema with asthma class III and IV breathing) respiratory tracts during mouth breathing.

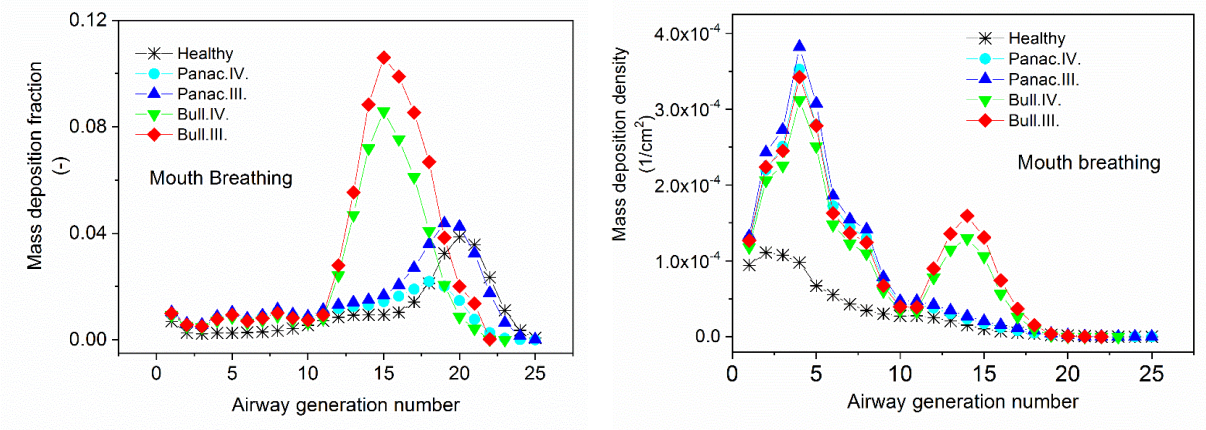

Figure 3: Mass deposition fraction distributions and mass deposition density distributions as a function of airway generation number in healthy and diseased lungs during mouth breathing

C) Simulation of airway deposition distributions of aerosol medicines in diseased respiratory systems

For the description of the airway deposition distributions of aerosol drugs, I have developed a new version of the Stochastic Lung Model, which is suitable in all respects for the determination of the parameter values required for individualized medicine selection.

Based on a series of inhalational experiments performed with volunteers, it can be stated that the deposition distribution in the respiratory system strongly depends on the particle size distribution of the drug, the type of the applied inhaler and the patient's individual spirometric data (Figure 4).

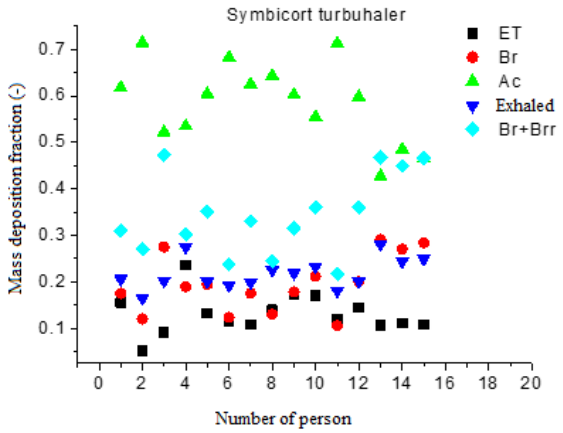

Figure 4: Regional mass deposition fraction distribution of the therapeutic aerosol emitted from the Symbicort Turbuhaler inhalator in the cases of 15 volunteers

Applying my developments in the lung model, a new method have been elaborated by our group which takes the individualized medicine selection possible, based on our knowledge first time in the world. For the enhancement of the efficiency of the therapy, it is highly advantageous for the patient to select the most suitable inhaler and in this drug selection procedure the Stochastic Lung Model has a unique role.

D) Determination of the effect of mucociliary clearance on the activity distribution of inhaled radon progenies

For the description of the effect of mucociliary clearance on the activity distribution of inhaled radon progenies along the bronchial airway generations I have developed a numerical model and built in into the Stochastic Lung Model. This version of the Model can follow the airway trajectories and radioactive decays of the ^{218}Po, ^{214}Po, ^{214}Bi, ^{214}Pb isotopes. Based on my results, it can be stated that in the large bronchial airways the alpha activity of ^{214}Po isotope cleared up from the deeper airway generations is higher than the alpha activity of ^{218}Po plus ^{214}Po isotopes decayed in the same airway generation where they were deposited. That is, the role of clearance is very important. For this type of analysis, a lung model with at least airway generation resolution is required.

The nowadays widely used lung model in radiation protection, the Human Respiratory Tract Model (HRTM) divides the tracheobronchial region only into two, large bronchial (BB) and bronchiolar (bb) regions. Due to its limited resolution, this model is not suitable for the characterization of the effect of mucociliary clearance in the tracheobronchial region. To characterize the biological effect, a more complex model with at least airway generation related resolution is needed, such as the Radact version of the Stochastic Lung Model.

E) Quantification of absorbed cell nucleus doses originating from deposition and clearance of inhaled radon progenies

The absorbed doses originating from the alpha decays of inhaled radon progenies are strongly inhomogeneous along the bronchial region of the respiratory system. Supposing the global average home microenvironment, the average absorbed cell nucleus dose intensities vary between 10^{-13} Gy/hour and 10^{-7} Gy/hour for a healthy adult man along the bronchial airway generations. The maximum average absorbed cell nucleus dose intensities can be found

between the first and fourth airway generations. Most of the lung cancer cases based on clinical experience (Cross 1987) are developed in this region of the lung. The lung model widely used by radiation protection (HRTM, ICRP 1994) is not able to detect inhomogenity within the large and small bronchial airways, thereby this model is probably not able to adequately estimate the biological effect of inhaled radon progenies. Figure 5 and 6 depicts the cell nucleus dose rate distributions in the sensitive epithelial cells of the bronchial region originating from the unattached and attached progenies as a function of bronchial airway generation number in the global average home environment.

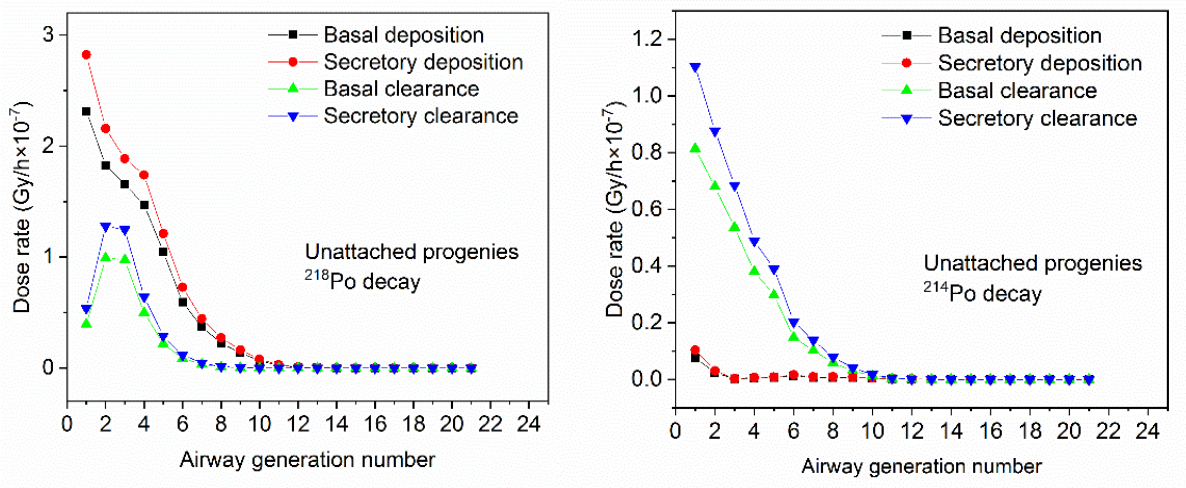

Figure 5. Cell nucleus dose rate distributions along the bronchial airways in the sensitive cells of the epithelium originating from the first (left panel) and second (right panel) alpha decay of unattached ^{218}Po, by computing the deposition and clearance components, healthy sitting man

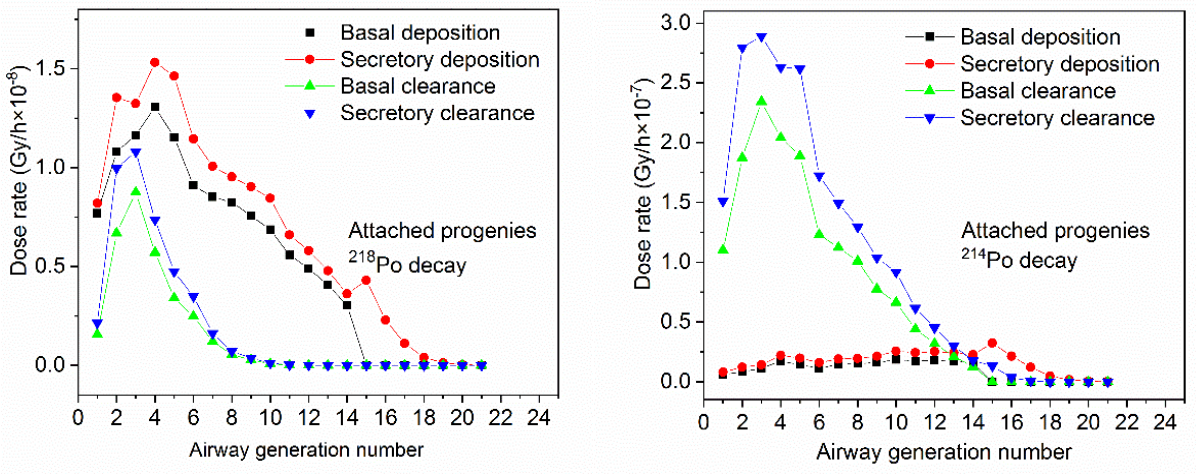

Figure 6. Absorbed cell nucleus dose rate distributions along the bronchial airways originating from the alpha decay of attached ^{218}Po (left panel) and the ^{214}Po alpha decay of all the attached particles (^{218}Po,^{214}Pb, ^{214}Bi) (right panel), at healthy sitting man

5. My most important publications related to my doctoral work:

Salma, I., Füri, P., Németh, Z., Balásházy I., Hofmann, W., Farkas Á. 2015. Lung burden and deposition distribution of inhaled atmospheric urban ultrafine particles as the first step in their health risk assessment. Atmospheric Environment 104: pp. 39–49.

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Jókay Á, Farkas Á, Füri P, Balásházy I, Horváth A, Müller V. (2015) Az asztma kezelésében néhány gyakran használt kombinált aeroszol gyógyszer (ICS-LABA) légúti kiülepedéseloszlásának numerikus modellezése. Medicina Thoracalis 68, 1, 46-57, 2015. február.

Farkas, Á., Jókay, Á., Balásházy, I., Füri, P., Müller, V., Tomisa, G., Horváth, A. 2016. Numerical simulation of emitted particle characteristics and airway deposition of Simbicort® Turbuhaler® dry powder fixed combination aerosol drug. European Journal of Pharmaceutical Sciences 93: pp. 371-379.

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Füri, P., Hofmann, W., Jókay, Á., Balásházy, I., Moustafa, M., Czitrovszky, B., Kudela, G., Farkas, Á. 2017. Comparison of airway deposition distributions of particles in healthy and diseased workers in an Egyptian industrial site. Inhalation Toxicology 29, 4: pp. 147-159.

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Füri, P., Balásházy, I., Bálint, Zs., Czitrovszky, B., Szántó, P. (2015) Az ionizáló sugárzás lepkékre gyakorolt hatása. XL. Sugárvédelmi Továbbképző Tanfolyam. 2015. április 21-23, Hajdúszoboszló, Absztraktgyűjtemény 21-22.

Somogyi, V., Müller, V., Lázár, Zs., Jókay, Á., Füri, P., Horváth, A., Nagy, A., Bárczi, E., Erdélyi, T., Balásházy, I. Kombinációban alkalmazott inhalációs hosszú hatású-kortikoszteroid b2 antagonista (ICS-LABA) aeroszolok légúti kiülepedéseloszlásának numerikus modellezése. A Magyar Tüdőgyógyász Társaság Allergológiai és Légzéspatológiai, valamint Légzésrehabilitációs Szekciója, illetve az MTT Társult Egyesülete Közös Tudományos Ülése és a Fiatal Pulmonológusok Kazuisztikai Fóruma, Hajdúszoboszló, Programfüzet és absztraktkönyv 66. o., 2015.

Farkas, Á., Jókay, Á., Füri, P., Horváth, A., Czitrovszky, B., Balásházy, I., Aeroszol gyógyszerek légúti kiülepedésének és tisztulásának számítógépes modellezése. XII. Magyar Aeroszol Konferencia, Szeged, Kivonatok Könyve 78-79, 2015.

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UNSCEAR 2000 Sources and effects of ionizing radiation Report to the General Assembly, with scientific annexes, New-York.