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MONTE CARLO MODELING OF AEROSOL DEPOSITION IN HUMAN LUNGS. PART I: SIMULATION OF PARTICLE TRANSPORT IN A STOCHASTIC LUNG STRUCTURE

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Abstract—A stochastic model for the calculation of aerosol deposition in human lungs has been developed. In this model the geometry of the airways along the path of an inhaled particle is selected randomly, whereas deposition probabilities are computed by deterministic formulae. The philosophy of the airway geometry selection, the random walk of particles through this geometry and the methods of aerosol deposition calculation in conductive and respiratory airways during a full breathing cycle are presented. The main features of the Monte Carlo code IDEAL-2, written for the simulation of random walks of particles in a stochastic lung model, are briefly outlined.

INTRODUCTION

Physical and mathematical models of aerosol deposition in human lungs are usually based on an airway geometry which is approximated either by a sequence of straight cylindrical tubes (Weibel, 1963; Horsfield *et al.*, 1971; Yeh and Schum, 1980) or by a one-dimensional variable cross-section channel resembling a trumpet-shape (Taulbee and Yu, 1975). These morphometric models represent sets of pre-specified linear airway dimensions, such as length, diameter, number of airways, and branching and gravity angles.

The simplest model of the branching network is a fully symmetrical tree structure, such as Weibel's model A (Weibel, 1963). As a consequence of this symmetry all tubes of the same airway generation have identical geometrical parameters (diameters, lengths, branching and gravity angles) and the same number of tubes along each pathway leads to the closing alveolar sacs. In reality, however, branchings are not symmetrical, i.e. there are variations within the parameters of the tubes of a given generation. This variability is generally called intra-subject variation.

An attempt to describe at least part of this asymmetry is the construction of a five-lobe lung model (Yeh and Schum, 1980), in which different main and lobar bronchi are defined for the individual pathways. In other words, this model takes into account intra-subject variation only for the first three or four (depending on the specified lobe) bifurcations.

A certain kind of regular asymmetry has been considered in the model of Horsfield *et al.* (1971). In their proposed lung structure airways may branch into daughter tubes of different orders; however, tubes of the same order still have identical geometric parameters.

The first attempt to describe the geometry of the human tracheobronchial tree in a statistical manner was made by Soong *et al.* (1979). They computed the functional residual capacity of the lung by considering the Weibel geometry as the underlying average model and deriving distributions of the actual data around these averages from published morphometric measurements. This approach was extended to the acinar region in their next paper (Yu *et al.*, 1979). In their work, however, the symmetric branching concept of Weibel was preserved. A similar approach was taken by Hofmann and Daschil (1986), who studied the distribution of radiation doses from inhaled radon progeny among bronchial airway generations on the basis of the Weibel morphology.

The stochastic model of the human tracheobronchial tree (Koblinger and Hofmann, 1985) described the asymmetry and randomness of the airway system as best as was possible, given

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the morphometric data available. This stochastic model allowed for variations in diameters, lengths, branching and gravity angles, and also in the number of bifurcations leading to the end of each bronchial pathway. At that stage each acinus closing the last terminal bronchiole was approximated by a single sphere having an effective diameter (Koblinger and Hofmann, 1986 and 1988).

All efforts described above attempted to construct models reflecting variations within a given individual airway system. If one intends to study aerosol deposition in a given population, then the effect of inter-subject variations must be considered; i.e. information on the distribution of geometrical parameters in that population must be available.

Yu and Diu (1982a) studied the effect of individual variability on aerosol deposition by comparing different deterministic lung models and attributing the predicted range of deposition fractions to differences in linear airway dimensions. In a subsequent effort Yu and Diu (1982b) proposed a probabilistic lung model in which inter-subject differences in airway dimensions are simulated by two random scaling factors for tracheobronchial and alveolar air volumes, respectively, assuming again that the Weibel model represents the population mean.

In the present paper the effect of intra-subject variability on particle deposition in the human lung is modeled by using a stochastic lung model which has been derived from detailed morphometric measurements of the bronchial tree by Raabe *et al.* (1976) and of the acinar region by Haefeli-Bleuer and Weibel (1988). At present not enough information is available to derive distributions required for the consideration of inter-subject variations.

CONCEPT OF STOCHASTIC MODELING

Particles inhaled follow random paths in the lung; this randomness is the result of two different phenomena.

The first source of randomness is the selection of the actual paths of individual particles. Even in the well-specified airway system of a given lung, due to the many bifurcations from the trachea through the alveolar sacs, there are millions of possible pathways. In stochastic or Monte Carlo modeling the histories of an appropriately large number of particles is simulated, and a new pathway selected for each particle. The expected value of any physical quantity of interest is then given by the average value for that quantity obtained after a given number of simulations.

The second source of randomness originates from the physical nature of the walk of a particle even in a well-determined geometry. From the three basic physical mechanisms usually considered in aerosol particle deposition studies, i.e. sedimentation, impaction and Brownian motion, it is the latter which is totally characterized by randomness. The mean free pathlength between two collisions, however, is so small that it is practically impossible to follow the random walk of a particle due to Brownian motion step-by-step. Therefore, the probability of deposition by Brownian diffusion is calculated with analytical formulae derived for the appropriate geometries. Analytical formulae are also used for computing deposition by sedimentation and impaction. In the Monte Carlo process the simulations are not terminated by deposition in the tracheobronchial tree but, the so-called statistical weight of the particles is decreased (see section on Particle Transport).

In essence, airway geometry is selected randomly and deposition is calculated deterministically in this model (Koblinger and Hofmann, 1988).

MORPHOMETRIC MODEL

Morphometry of the tracheobronchial tree

The morphometry of the tracheobronchial tree has been analysed by Raabe *et al.* (1976) at the Lovelace Inhalation Toxicology Research Institute (ITRI). Since the files containing their results must be considered as the most detailed data base published in the open literature these data were used in our work. In order to utilize their data in the modeling effort a systematic statistical analysis of the Lovelace ITRI files was made. Details of this analysis are given elsewhere (Koblinger and Hofmann, 1985). Here, for the convenience of the reader, the salient features of this analysis is briefly described.

The human lung is modeled by a sequence of tubes branching always into two daughter airways. A segment of the airway system is illustrated in Fig. 1. However, for these deposition calculations (discussed later) the airway system was considered as a sequence of bifurcation units. Each bifurcation unit being composed of half of the parent tube and half of the daughters (with the exception of the first unit, which contains the whole trachea).

Averages and distributions of the following parameters were derived:

— diameters and lengths of tubes in the different generations;

— ratio of parent tube cross-sections to the combined cross-sections of both daughters;

— ratio of the diameters of minor to major daughters;

— branching angles for minor and major daughters.

In addition, correlations of diameters and lengths of tubes of the same generation, as well as the probability of reaching the acinar region as a function of both tube diameter and generation number (termination probability), were obtained.

Construction of random pathways through the tracheobronchial tree

Based on the information on the distributions and correlations listed above the following scheme was used to select a separate pathway for each individual particle:

(1) Set generation number k to 1 (trachea).

(2) Select diameter d_k from the appropriate distribution.

(3) Select length l_k according to the diameter/length correlation.

(4) Select diameters of the two daughter tubes $d1_{k+1}$ and $d2_{k+1}$ from the distribution of the cross-section ratios of the parent tubes to both daughter tubes and that of the diameter ratios of the minor to major daughters.

(5) Select daughter tube lengths $l1_{k+1}$ and $l2_{k+1}$ according to the diameter/length correlation.

(6) Select the daughter tube through which the aerosol particle passes after branching.

(7) Select branching angle from the appropriate distribution and compute gravity angle.

(8) Select from the termination probability distribution whether the particle has already reached the acinar region. If not, let $k=k+1$, go to step 4, and continue.

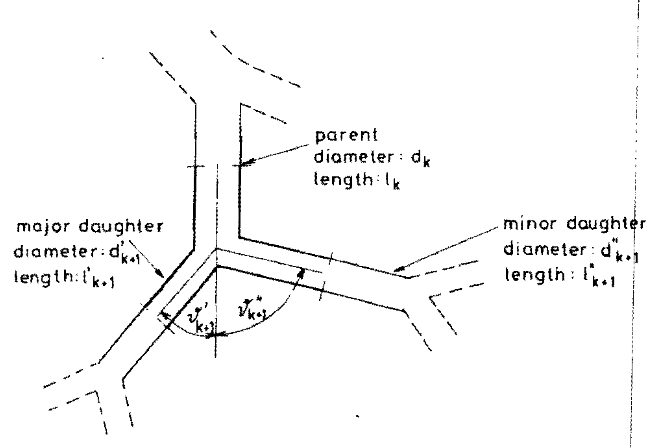

Fig. 1. Illustration of a segment of the bronchial tree. Subscript k denotes the kth generation of tubes. The bifurcation unit (bold lines) is composed of the three half tubes.

There are four points of the above procedure which require further comment:

— In the first four generations measured data (Kováts and Zsebök, 1955) are used instead of randomly selected ones (distributions could not be derived for those airways from the Lovelace ITRI files because of the small number of tubes in these generations);

— at step (6) the daughter in which the aerosol particle continues its path is selected according to the airflow distribution (see later);

— in step (7) gravity angles are calculated assuming uniform distribution of the azimuth. This assumption, however, leads to a more and more uniform gravity angle distribution in distant lung regions. Thus, at higher generation numbers a downward biasing procedure is used (see Appendix A), since a downward preference even at the highest generations has been reported, e.g. Yeh and Schum (1980);

— at step (8) the particle can reach the acinar region, the model of which is the subject of the next section.

Morphometry of the acinar region

Unfortunately, there is no detailed information of the acinar region available (unlike the case of the tracheobronchial tree). The main features, however, are well known from several papers (e.g. Yeh and Schum, 1980; Weibel, 1983). The model presented here is mainly based on the work of Haefeli-Bleuer and Weibel (1988), but results of Hansen and Ampaya (1975), and of Schreider and Raabe (1981) have also been incorporated.

An acinar region starts, by definition, with the first alveolated tube. Proceeding further into the pulmonary acinus more and more alveoli cover the tubes, and finally the path is closed by the so-called alveolar sac, which is completely covered by alveoli. The number of alveolated tubes connecting the last terminal bronchiole of the tracheobronchial tree with an alveolar sac varies from six to 12, with an average of nine (Haefeli-Bleuer and Weibel, 1988). The structure of an acinus is outlined in Fig. 2.

While the inner diameter of the alveolated tubes decreases with increasing generation number, the outer diameter remains practically constant (Haefeli-Bleuer and Weibel, 1988). The number of alveoli per duct increases with progression through the acinar airways at the beginning and decreases slightly after the sixth pulmonary generation (Schreider and Raabe, 1981).

Construction of pathways in the acinar region

Because of the very limited data on distributions of acinar parameters the model developed here is less stochastic than the model for the tracheobronchial tree. The following basic procedure is used:

(1) Select the number of tubes n actually connecting the last bronchial tube with the alveolar sac;

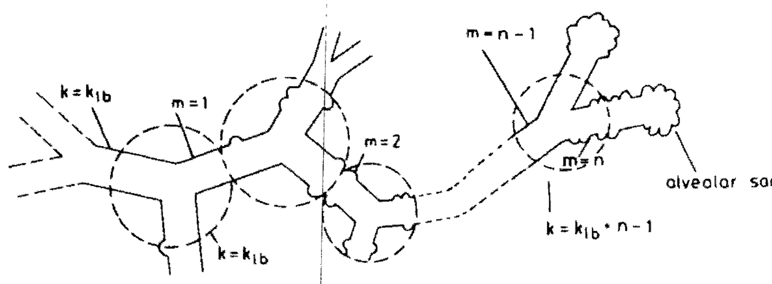

Fig. 2. A sketch of a pathway in an acinus. Symbols: k—generation number; k_{lb}—generation number of the last bronchial tube; n—number of tubes connecting the last bronchial tube to the alveolar sac; m—serial number of connecting tubes. The circled areas cover the bifurcation units.

(2) Set acinar generation number m to 1;

(3) Compute the inner diameter d_m and length l_m;

(4) Select branching angle and calculate gravity angle of the daughter;

(5) Calculate the probabilities whether:

(a) the particle is deposited on a tube surface (in this case the simulation is terminated); or

(b) the particle enters an alveolus; or

(c) the particle remains in the air volume. In this case set $m = m + 1$; if $m > n$, the particle then enters an alveolus of the closing alveolar sac, otherwise continue from step (3).

The actual selection based on the procedure outlined above is made with the following additional assumptions:

— in step (1), the distribution given in Fig. 11 of Haefeli-Bleuer and Weibel (1988) is used;

— since we have no detailed information on the distribution and correlation of the subsequent inner diameters, we assume that the inner diameter decreases in a stepwise manner from the value of the last bronchial diameter down to the diameter of the alveolus (all alveoli are assumed to have the same pre-set diameter);

— the lengths of the tubes are set equal to 2.2 times the inner diameters (this average ratio is obtained from Haefeli-Bleuer and Weibel, 1988);

— because of a lack of information distinction cannot be made between minor and major branches at the bifurcations;

— for the actual branching angle selection the average distributions obtained for major and minor daughters in the 18th bronchial generation were used. Previous analysis (Koblinger and Hofmann, 1985) has shown that the distribution of branching angles hardly changes after about the 16th bronchial generation;

— the probability that a particle which would have been deposited on the surface of a non-alveolated tube (having the same inner diameter) enters an alveolus is increased in a stepwise manner from zero in the last bronchial tube to one in the closing alveolar sac. This probability is basically determined by two factors, namely the number of alveoli covering a given tube (discussed above) and the flow pattern in the acinus. The axial component of the flow velocity is expected to decrease significantly towards the end of the acinus, since air reaching this zone has already passed tubes with inflating diameters. In addition, only a decreasing fraction of the volume change is still ahead and the alveolated ducts enlarge also in radial directions. The combined effect of the two factors is obviously an increase of the probability of entering an alveolus. Since we do not know the form of this function, linearity is assumed.

DEPOSITION CALCULATIONS

Deposition within bifurcation units

The three basic deposition mechanisms, namely sedimentation, Brownian motion and impaction, are considered in this model. Deposition probabilities for a bifurcation unit are calculated as the sum of the probabilities obtained for the two straight tube portions representing half of the parent tube and half of the daughter tube actually selected. Inertial impaction is calculated for a bend tube, where the bend angle equals the branching angle, whereas, the diameter and the flow velocity are taken as the averages of the respective values of the parent and the selected daughter. In the present version of this Monte Carlo program the equations listed in Table IV of Yeh and Schum (1980) are adopted, and the three deposition mechanisms are assumed to act independently (for the benefit of the reader, the deposition formulae used in present calculations are listed in Appendix B).

Experiments have shown that deposition is enhanced at bifurcation sites in upper bronchial airways, particularly at carinal ridges (Martonen, 1983; Martonen *et al.*, 1987). Therefore, the total deposition probability calculated for a specified bifurcation unit is multiplied by an enhancement factor. In the program, however, this factor may be defined as a function of airway dimensions, particle size and airflow velocity. The incorporation of this enhancement factor is the only difference between the bifurcation unit concept used here and the straight tube models generally used.

Deposition in alveoli

All alveoli are approximated by spheres. Since we have no detailed data on the distribution of the effective diameters of the alveoli all alveoli are assumed to have the same diameter in the present model.

If total air mixing is assumed in the alveoli (mixing will be discussed in the next section) then inhaled particles will fill the alveolar volume uniformly. The equations derived for sedimentation and diffusion deposition in spheres are given in Appendix C.

If there is no air mixing the particle inhaled will be located at a certain depth inside the sphere, since the outermost shell of the alveolar sphere is filled with either the air of the residual volume or with the air inhaled after the particle has entered the alveolus. Because of the random orientation of the alveolar orifice it is assumed that the particles inhaled are distributed uniformly in a concentric smaller inner sphere. The diameter of this inner sphere is set equal to the average diameter of the orifice of the alveolus. From data published by Hansen and Ampaya (1975) we estimated an average inner sphere diameter to alveolar diameter ratio of 0.65. Deposition formulae for this geometry are also given in Appendix C.

AIRFLOW AND MIXING PATTERNS

A symmetric breathing cycle is modeled with equal inspiration and expiration times, separated by equal breath-hold times (Fig. 3). The lung volume increases and decreases linearly with time during inspiration and expiration, respectively. This assumption results in constant flow rates. Particles are either inhaled with constant probability over the inspiration period, or inhalation of particles entering the trachea at arbitrary preset times can be simulated. The dimensions of the components of the airway system vary during a breathing cycle. Larger changes are expected to occur in the pulmonary region than in the bronchial tree. In the present model we assume that there is no change in tubular airway dimensions. Instead, all of the increase in volume during inhalation takes place in the alveoli. Particles need a certain amount of time to reach the alveolated region; i.e. a particle will most likely enter an alveolus toward the end of the inhalation period, when the alveoli are nearly fully inflated. Therefore, we do not change the alveolar diameter during the time when deposition may occur.

Since the dimensions of the tubes are not changed during the breathing cycle no residual air is assumed. In the present model mixing due to non-reversibility of the mass flow of air between small pulmonary units is not taken into account. Mixing in the alveoli is modeled by a linear combination of no-mixing and total-mixing; the weight of the total mixing term in the linear combination is called the mixing factor. A mixing factor depending on particle size and/or breathing conditions may be specified if experimental and/or theoretical information become available. When a particle enters an alveolus it is randomly selected either to be mixed or not to be mixed with the residual air in the alveolar volume according to the preset mixing factor.

It is further assumed that the change in volume of a certain segment during the breathing cycle is proportional to the total volume of that segment. In this case the distribution of the airflow at a bifurcation is proportional to the volumes distal to the two daughters. However, in our random selection scheme we have no information about the volumes of airways and

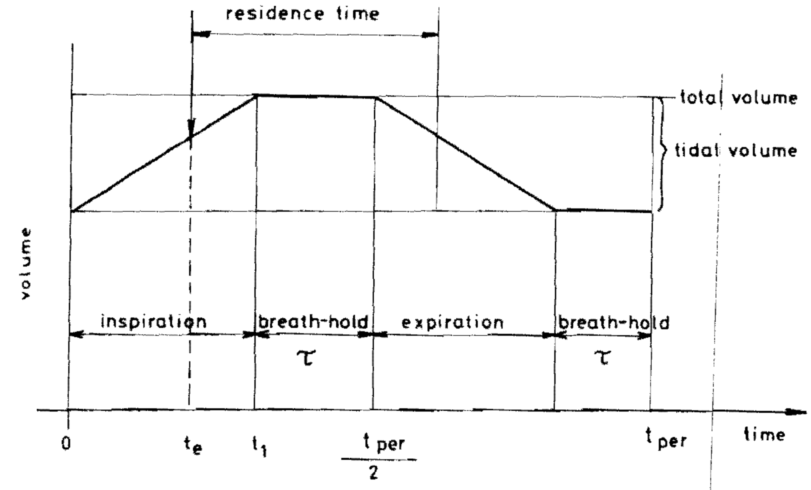

Fig. 3. Change of volumes during a full breathing cycle and illustration of different time intervals.

alveoli which will be selected at a later stage in our procedure. Only in the first bifurcations leading to the different lobes can the lobar volumes given by Yeh and Schum (1980) be used. At the following bifurcations it is assumed that the volumes distal to the two daughters are proportional to the respective daughter tube cross-sections.

PARTICLE TRANSPORT

Using the procedures outlined in the previous sections a particle penetrating deeper and deeper into the lung during inhalation can be followed. This inward movement may be stopped for three reasons:

— the inhaled particle is deposited;

— it enters an alveolus; or

— inhalation time expires.

Deposition is not simulated directly in the tracheobronchial tree; instead, for the sake of improving the statistics of the Monte Carlo calculations, the so-called statistical weight method is used. This means that a unit weight is assigned to each particle entering the trachea, which is multiplied by $(1-p)$ at each bifurcation, where p denotes the deposition probability at that bifurcation unit. The contribution to the deposition fraction is given by the product of the actual weight and the respective deposition probability. In the acinar region the real processes is stimulated directly, i.e. terminate the histories by the probability of deposition. The statistical weight method cannot be used here, because the particle has a third choice besides the possibilities of deposition and continuing the flight—it can enter an alveolus.

When the particle enters an alveolus the first-in/last-out assumption is used. Thus, the particle may rest in an alveolus for a time given by the sum of the breath-hold time (τ) plus twice the time spent from entering the alveolus (t_e) to the end of the inhalation period (t_1), i.e. the residence time is $\tau+2(t_1-t_e)$ (see Fig. 3). This approach is quite reasonable for the no-mixing case. When total mixing is assumed, however, particles may leave the alveolus with constant probability during the whole exhalation period, but, for the sake of simplifying the model, the above mentioned first-in/last-out approximation is always used independently of the actual mixing factor. For particles selected to be mixed the chance to be exhaled in the first exhalation period is the ratio of the tidal to the total lung volume, the other particles will remain in the alveolus for at least the time of one total cycle. Therefore, we assume that these particles will be deposited with a probability of one.

If the time, which is incremented by the ratio of the tube length to the airflow velocity at every bifurcation, exceeds the inhalation time (t_1 in Fig. 3) the flight of the particle is stopped, and the probability of deposition is computed for the tube in which the particle rests during the breath-hold time. After the breath-hold time the particles which were not deposited will be exhaled. It is assumed that during exhalation they follow the same path that was selected during inspiration. Deposition during exhalation is calculated in the same manner, with the only exception that no enhancement factor is applied.

The scheme of the whole process is graphically illustrated in Figs 4 and 5.

THE COMPUTER CODE IDEAL-2

The computer code IDEAL-2 (Inhalation, Deposition and Exhalation of Aerosols in/from the Lung—2nd version) has been developed for the simulation of the random walk of particles in the human lung as described above (the first version of IDEAL is briefly described in Koblinger and Hofmann, 1986, 1988). The program is written in a modular form. This means that geometrical data, distributions and correlations, as well as deposition formulae are given in separate subroutines and functions. Thus, whenever we get more information on any geometrical feature or physical process governing the random walk, the current data or formulae can easily be replaced by new ones.

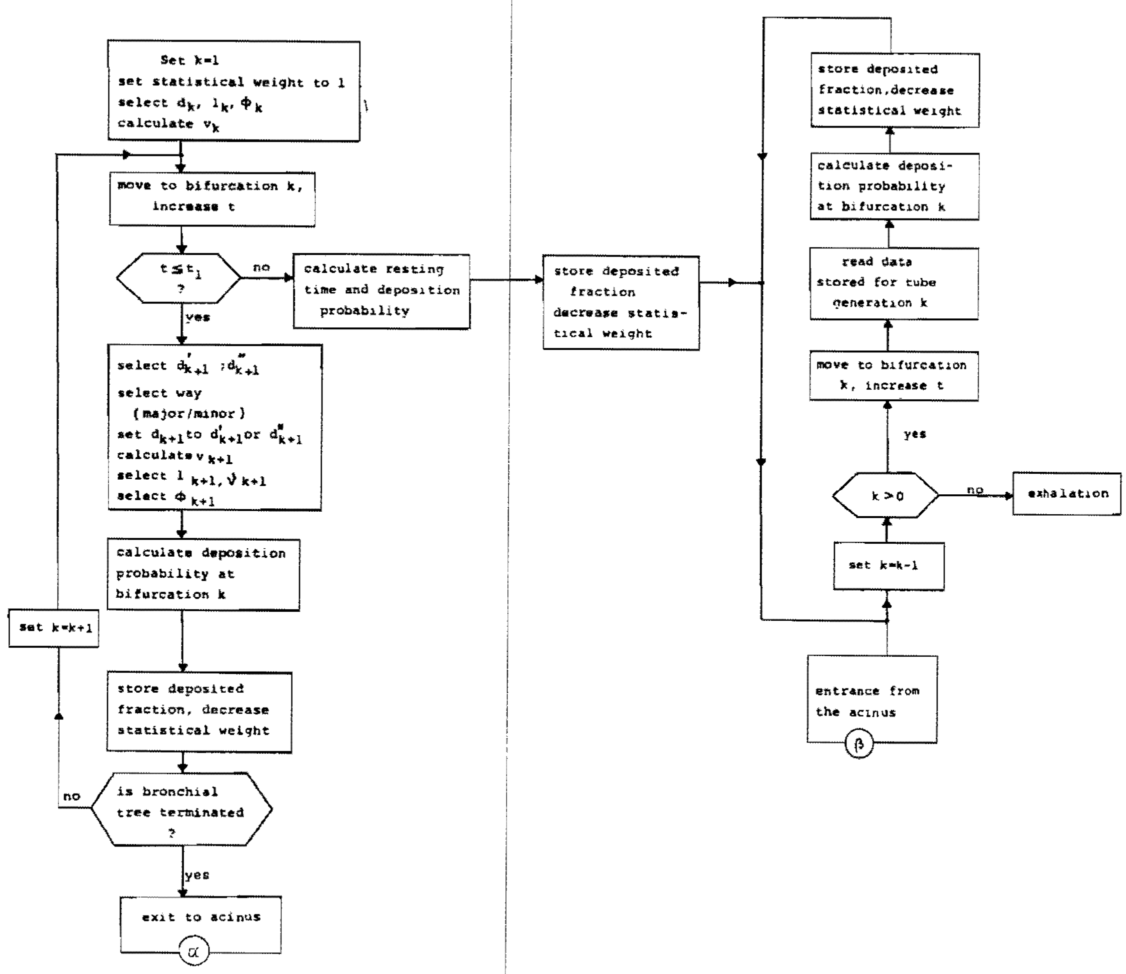

Fig. 4. The flow chart of pathway selection and deposition calculation in the tracheobronchial tree. Symbols: k—tube generation and bifurcation unit number; d—tube diameter; l—tube length; v—flow velocity; θ—branching angle; ϕ—gravity angle; t—time.

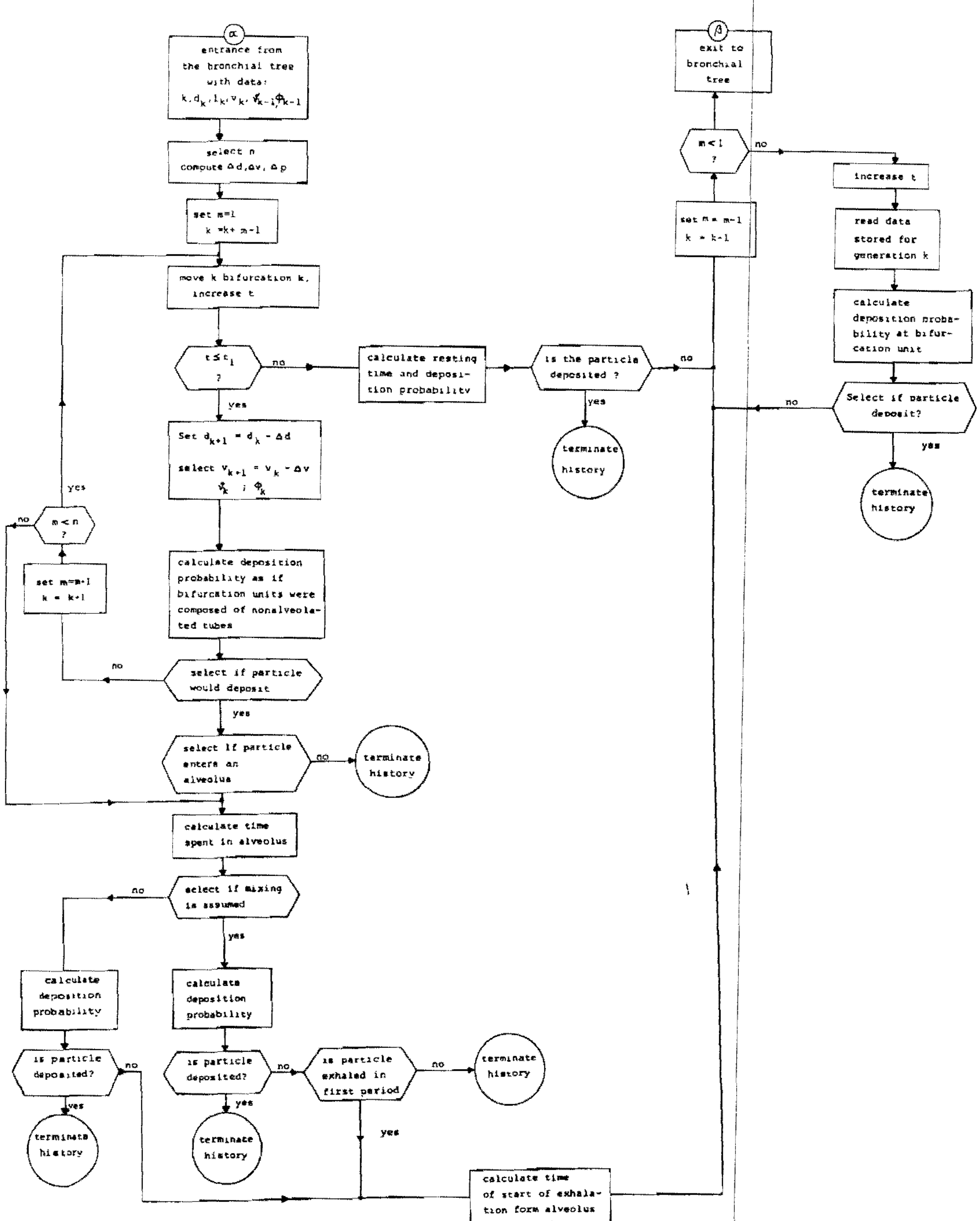

Fig. 5. The flow chart of pathway selection and deposition calculation in the acinar region. Symbols: k—bifurcation unit number; n—number of connecting tubes; m—serial number of connecting tubes; d—inner tube diameter; Δd—diameter decrement; d_{alv}—diameter of spheres representing the alveoli; l—tube length; v—flow velocity; Δv—flow velocity decrement; θ—branching angle; ϕ—gravity angle; p—probability of entering an alveolus; Δp—increment of the probability of entering an alveolus; t—time.

The following parameters have to be specified in the input:

— breathing cycle data: tidal volume and total lung volume, full cycle period time, inspiration, expiration and breath-hold times, and the actual time of inhalation, if the inhalation probability is not uniform throughout the inspiration time;

— mixing factor;

— diameter and density of the inhaled aerosol (if particles are polydisperse, the user can specify a histogram presentation of their distribution, and the program will select the diameter randomly for each simulation);

— alveolar diameter;

— parameters governing the downward biasing of the tubes at higher generation numbers;

— enhancement factors;

— maximum number of simulations and the error limit (the whole Monte Carlo calculation is terminated before reaching the preset maximum number if the statistical error falls below the specified limit).

The following results are printed out:

— fractions of particles deposited in bifurcation units, differential by lobe and generation number;

— the above fractions summed up for all lobes for a given generation, and summed up for all generations in each lobe;

— the fractions of particles deposited in the alveoli in the different lobes and in the total lung;

— total deposited fractions in the different lobes and in the total lung;

— the exhaled fraction differential by time of exhalation.

The program is written in FORTRAN and can run on an IBM (or IBM compatible) PC. For a statistical uncertainty not exceeding 3% for total deposition, typical numbers of simulations required range from about 200 to about 8000, dependent on the absolute value of deposition.

AREAS OF FURTHER IMPROVEMENT

In general, there are two possible routes of improving upon our current model:

— the first and certainly simpler way is the replacement of several sets of data as soon as more reliable information becomes available, without changing the basic structure of the model;

— the second way concerns the refinement of the model itself towards a more realistic description of the morphometry and the physical processes involved.

Changes in the data set may affect any distribution we derived from the analysis of the Lovelace data (Koblinger and Hofmann, 1985). Despite the usefulness of these data, more detailed information on the bronchial morphometry is required. We doubt, however, that such time-consuming efforts of measuring lung casts will be undertaken again in the near future. Also, deposition formulae for straight tubes may be replaced by new ones addressing specifically particle deposition in bifurcation units, or taking into account the simultaneous effects of different deposition mechanisms (Taulbee, 1978; Balásházy *et al.*, 1990). Another point still to be clarified is the distribution of airflow at the bifurcations.

The model itself is expected to be modified mainly in the acinar region. In order to develop a complete stochastic model of the acinar region analogous to the one already obtained for the tracheobronchial tree (Koblinger and Hofmann, 1985), we need a data base similar to the Lovelace files (Raabe *et al.*, 1976). The way of handling deposition and mixing in the alveolar sacs also requires more information.

The current morphometric model should also be supplemented by a stochastic model for the nasopharyngeal region. Information on the morphometry of these complex structures is currently not available at the required level of detail. To facilitate comparison of our results with experimental data on total deposition, average deposition fractions for the nose and mouth as proposed by Yu *et al.* (1981) and Stahlhofen *et al.* (1989) will be used in Part III [Hofmann and Koblinger (manuscript in preparation)].

The sensitivity of the model to several parameters is discussed in Part II (Hofmann and Koblinger, 1990a).

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APPENDIX A: DOWNWARD BIASING

The gravity angle, i.e. the angle between the vertical and the axis of the tube investigated, is denoted by ϕ; and the projection of a unit vector in the direction of the tube on the x, y and z coordinates by ω_x, ω_y and ω_z, respectively.

$$\omega_z = \cos\phi. \tag{A1}$$

A biased direction is defined by changing ω_z to:

$$\omega_z' = 2\left[\frac{\omega_z + 1}{2}\right]^{\beta} - 1, \tag{A2}$$

and, consequently, ω_x and ω_y to:

$$\omega_x' = \omega_x \left[\frac{1-\omega_z'^2}{1-\omega_z^2}\right]^{1/2}, \tag{A3}$$

and

$$\omega_y' = \omega_y \left[\frac{1-\omega_z'^2}{1-\omega_z^2}\right]^{1/2}. \tag{A4}$$

In equation (A2) β is called the biasing factor. At $\beta=1$ there is no biasing; if β increases the tubes turn more and more downward. Application of a factor of 1.35 results in an average gravity angle of about 120°, i.e. 60° from the downward vertical, after several generations, independently of the starting gravity angle distribution. An average value of 60° has been reported by Yeh and Schum (1980).

APPENDIX B: DEPOSITION FORMULAE FOR CYLINDRICAL TUBES

The deposition formulae for cylindrical tubes employed in present calculations are taken from Yeh and Schum (1980).

(1) The probability of deposition by Brownian diffusion p_d is:

$$p_d = 1 - \sum_{i=1}^{3} a_i \exp(-b_i x) - a_4 \exp(-b_4 x^{2/3}), \tag{B1}$$

where

$$x = \frac{LD}{2R^2 v},$$

D denotes the diffusion coefficient, R is the radius of the tube, L is the length of the tube and v is the mean flow velocity.

The coefficients in equation (B1) adopt the following values:

$a_1 = 0.819$	$b_1 = 7.315$
$a_2 = 0.0976$	$b_2 = 44.61$
$a_3 = 0.0325$	$b_3 = 114.0$
$a_4 = 0.0509$	$b_4 = 79.31.$

The probability of deposition during a pause of time t is:

$$p_d = 1 - \exp\left(-5.784 \frac{Dt}{R^2}\right) \tag{B2}$$

(2) The probability of deposition by sedimentation p_s is:

$$p_s = 1 - \exp\left(-\frac{4gC\rho r^2 L \cos\phi}{9\pi\mu R v}\right), \tag{B3}$$

where g is the acceleration of gravity, ϕ is the angle relative to gravity, ρ is the density of the particle, C is the Cunningham slip correction factor, r is the radius of the particle and μ is the viscosity of the fluid.

(3) The probability of deposition by inertial impaction p_i is:

$$p_i = 1 - \frac{2}{\pi}\cos^{-1}(\theta\,\mathrm{St}) + \frac{1}{\pi}\sin[2\cos^{-1}(\theta\,\mathrm{St})], \quad \text{for } \theta\,\mathrm{St} < 1,$$

$$p_i = 1, \quad \text{for } \theta\,\mathrm{St} > 1, \tag{B4}$$

where θ is the branching angle and St is the Stokes number.

APPENDIX C: DEPOSITION FORMULAE FOR A SPHERICAL SPACE

I. *Particles are uniformly distributed within a sphere*

This derivation of particle deposition equations applies to the case of total air mixing within alveoli.

Let a sphere of radius of R be filled with particles of diameter d, and let the sedimentation velocity be denoted by u_s and the diffusion coefficient by D.

(1) *Sedimentation.* Two spheres of the same radius R represent the alveolar sac and the air volume containing the aerosol particles. The two spheres are concentric at $t=0$; as time continues the sphere filled with aerosol particles moves downwards with a velocity of u_s. The fraction of aerosol particles still not deposited at time t is given by the intercepting fraction of the two spheres. The deposited fraction is:

$$p = \begin{cases} \dfrac{1}{2}\dfrac{u_s t}{2R}\left[3 - \left(\dfrac{u_s t}{2R}\right)^2\right], & \text{if } t < \dfrac{2R}{u_s}, \\[2ex] 1, & \text{if } t \geq \dfrac{2R}{u_s}. \end{cases} \tag{C1}$$

(2) *Brownian diffusion.* The deposited fraction due to Brownian motion is determined by using the analogy of the equations for Brownian diffusion and those of heat conduction. Carslow and Jaeger (1959) provide formulae for the temperature in a sphere having a radius of a for different boundary conditions. Equation (8) in section 9.3, subsection I, of the cited book gives the change of the average temperature (v_{av}) for zero initial temperature and a constant surface temperature of V as:

$$v_{av} = V - \frac{6}{\pi^2} V \sum_{n=1}^{\infty} \frac{1}{n^2} \exp(-\mathscr{K} n^2 \pi^2 t/a^2). \tag{C2}$$

In subsection IV it is stated that the formula for constant initial temperature V and zero surface temperature is obtained by subtracting their equation (8) [equation (C2) above] from V:

$$v_{av} = \frac{6}{\pi^2} V \sum_{n=1}^{\infty} \frac{1}{n^2} \exp(-\mathscr{K} n^2 \pi^2 t/a^2). \tag{C3}$$

In the analogy here the constant initial temperature, V, is replaced by the initial concentration, c_0: the average temperature, v_{av}, by the average concentration in the sphere, c; the heat conductivity of the medium, $\mathscr{K}$, by the diffusion coefficient, D; and instead of a we denote the radius by R.

Thus, the deposited fraction (p) defined as

$$p = 1 - \frac{c}{c_0} \tag{C4}$$

reads:

$$p = 1 - \frac{6}{\pi^2} \sum_{n=1}^{\infty} \frac{1}{n^2} \exp(-D n^2 \pi^2 t/R^2). \tag{C5}$$

In practice, only the first m terms of the infinite series are used (the actual value of m depends on the accuracy required).

II. *Particles are uniformly distributed within an inner sphere and deposited on the surface of an outer sphere*

This derivation of particle deposition equations applies to the case of no air mixing within alveoli.

Let the inner sphere, having a radius $r<R$, be filled with particles.

(1) *Sedimentation.* Here a sphere of radius r representing the volume filled with aerosol particles moves downwards with a velocity of u_s inside the alveolar sphere of radius R. The two spheres are concentric at $t=0$, there is no interception (i.e. deposition) if time t is less than $(R-r)/u_s$, and all particles are deposited if time t exceeds $(R+r)/u_s$. In between these two limits the deposited fraction is calculated from the intercepted volumes as:

$$p = \begin{cases} 0, & \text{if} \quad t \le \dfrac{R-r}{u_s}, \\[2ex] 1 - \dfrac{a^2(3r-a)+A^2(3R-A)}{4r^3}, & \text{if} \quad \dfrac{R-r}{u_s} < t < \dfrac{R+r}{u_s}, \\[2ex] 1, & \text{if} \quad t \ge \dfrac{R+r}{u_s}, \end{cases} \tag{C6}$$

where

$$a = x + r - u_s t, \tag{C7}$$

$$A = R - x, \tag{C8}$$

and

$$x = \frac{R^2 - r^2 + (u_s t)^2}{2 u_s t}. \tag{C9}$$

(2) *Brownian diffusion.* Again, the derivation is based on the analogy with heat conduction. In section 9.3, subsection IX of Carslow and Jaeger (1959) the temperature v is given in equation (19), for an initial temperature V in $0<r<b$, and zero in $b<r<a$:

$$v = 2\frac{V}{r} \sum_{n=1}^{\infty} x_n(a,b)\, y_n(a,t) \sin\frac{n\pi r}{a}, \tag{C10}$$

where:

$$x_n(a,b) = \frac{a}{n^2\pi^2} \sin\frac{n\pi b}{a} - \frac{b}{n\pi} \cos\frac{n\pi b}{a} \tag{C11}$$

and

$$y_n(a,t) = \exp(-\mathscr{K} n^2 \pi^2 t/a^2). \tag{C12}$$

If W denotes the volume of the total sphere and $\mathrm{d}W$ the volume element, the average temperature, v_{av}, can be calculated as:

$$
\begin{aligned}
v_{av} &= \frac{\int c\,\mathrm{d}W}{W} \\
&= 2\frac{V}{W}\sum_{n=1}^{\infty} x_n(a,b)\, y_n(a,t)\int_0^a \frac{1}{r}\sin\frac{n\pi r}{a}\,4\pi r^2\,\mathrm{d}r \\
&= \frac{6V}{a\pi}\sum_{n=1}^{\infty}(-1)^{n+1}\frac{1}{n}\,x_n(a,b)\,y_n(a,t). \qquad \text{(C13)}
\end{aligned}
$$

After replacing a and b by r and R, respectively, (according to our notation) and v_{av}, V and $\mathscr{K}$ by c, c_0 and D, respectively, (according to the analogy) and finally taking into account equation (C4), the deposited fraction is:

$$p = 1 - \frac{6}{\pi}\sum_{n=1}^{\infty}(-1)^{n+1}n^{-2}\,f_n(R,r)\,g_n(r,t), \qquad \text{(C14)}$$

where

$$f_n(R,r) = \frac{1}{n\pi^2}\sin\frac{n\pi r}{R} - \frac{1}{\pi}\frac{r}{R}\cos\frac{n\pi r}{R} \qquad \text{(C15)}$$

and

$$g_n(r,t) = \exp(-Dn^2\pi^2 t/R^2). \qquad \text{(C16)}$$

In practice, only the first m terms of the infinite series are used (the actual value of m depends on the accuracy required).