Droplet dynamics, fluid flow and particle deposition for pulmonary drug delivery to pediatric patients

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CFD analysis of aerosol deposition in the upper airway of a pediatric patient was performed. The model geometry was directly determined from MRI imaging. Analysis of multiple flow rates, droplet sizes, and turbulence models was accomplished. It was determined that the *k-ε* model for turbulent flow would produce inaccurate deposition data, mostly likely due to the transitional nature of the internal flow. Data from large eddy simulation appeared more promising in accurately providing spray trajectories. For a monosized spray with a MMAD of 3.8 microns, 69 +/- 1 % of droplets deposited in the model using the k-epsilon turbulence model versus 17 % using LES.

Introduction:

Aerosol therapy is a promising method of drug delivery and progress in this field has had important effects on improving patient quality of life. Recently we have been witness to a rapid expansion in both the uses of and the need for Aerosol therapy in pediatric patients [1]. This is coupled with a patient subpopulation that shows high levels of mouth and throat deposition, limiting the effectiveness of Aerosol therapy. Thus it has become increasingly important to improve pulmonary drug delivery methods for this subpopulation in order to increase the reliability and effectiveness of Aerosol therapy. Ongoing research towards this goal lies at the interface of engineering and medicine, offering many unique challenges. A key obstacle discussed in this paper is to provide an efficient and regular dose to the targeted region of the respiratory tract. Primarily this becomes a problem of determining the air flow pattern within the respiratory tract and the consequent pharmaceutical spray interactions.

In this study Computational Fluid Dynamics (CFD) simulations were used to analyze fluid flow and spray interactions in the upper respiratory tract of a pediatric patient (male, aged 5). Aspects of properly modeling micron sized droplets in a constricted pipe-flow (the upper respiratory tract) are analyzed. Mesh quality and boundary conditions were manipulated to determine their impact on particle deposition. Additionally the k-ε model and the Large Eddy Simulation (LES) for turbulence were investigated. It was found that the LES produced results more consistent with experimental simulations. This research

sought to cultivate improved methods for determining spray deposition in the mouth and throat of pediatric patients.

Background and Theory

CFD modeling of fluid flow and particle deposition in the upper respiratory tract has only become a viable method in the past few years. Much of the recent work has focused on the creation of accurate modeling procedures for determining particle deposition. There are three primary complexities to these simulations; (1) the anatomical complexity of the airway, (2) the low-Reynolds number turbulence expected in this region, and (3) the inherent complexities of multiphase flow.

Developing an accurate anatomical model for CFD analysis has been treated with a variety of methods, which vary in their fidelity to the actual anatomy of a patient. These include a cadaver based model [2], a model based on a teaching cast [3] and averaged or smoothed models based on typical morphometric dimensions and CT scans [4, 5]. Model geometries are assumed to be static, though the varying area at the laryngeal constriction will modify CFD results [6]. All of these previous models were created for an adult morphometry, which typically show an increased airway caliber when compared to a pediatric morphometry [1]. Other morphological differences are also expected. In this study, the anatomy of a pediatric patient's upper respiratory tract was determined using Magnetic Resonance Imaging (MRI). MRI has been shown to be a useful tool in accurately determining the volume enclosed by the upper airways [7]. An additional difficulty that can be expected in creating an accurate representation of spray deposition is in mesh quality. It is essential to have an adequate mesh resolution to produce an adequate calculation of the air-flow field in regions of complex flow [8].

It has been identified in adults that turbulent flow can be expected following the glottal restriction of the throat for almost all respiratory flow rates [9]. This turbulence is evident despite pipe Reynolds numbers that are below the typical turbulent regime [10]. Previous computational simulations of fluid flow in the upper respiratory tract have used the Reynolds-averaged Navier-Stokes equations (RANS) to solve for the time averaged velocity field. This requires a model for the Reynolds stresses, most commonly the 2-equation k-ε model as used by Stapleton et al. (2000) and Gemci et al. (2001) [5, 11]. Stapleton et al. (2000) found that the k-ε model provided inaccurate results for turbulent flow when compared to experimental models. Considering the flow in this region will undergo a transition from a laminar to turbulent regime due to the laryngeal jet it is expected that the use of the standard k-ε model would be inappropriate [4, 10, 12, 13]. To overcome this, Zhang et al. (2002) [4] have adapted a low-Reynolds number turbulence model to internal flow. Their calculation of aerosol deposition reasonably matched experimentally predicted results.

An alternative to modeling turbulence using the RANS equations, is to perform a direct numerical simulation of the time-varying velocity components. This offers the highest level of accuracy and flow description [14], however due to the high computational costs involved would be impractical for this model. A compromise between these two procedures is to solve the flow field using Large Eddy Simulation (LES). LES involves the direct solution of the larger eddies present in turbulent flow and the modeling of the smaller eddies. The large

eddies in a system contain the bulk of the fluid energy [15] and are more problem-dependant [16]. The smaller eddies are generally isotropic [15] and thus lend themselves to modeling.

Finally the multiphase nature of a liquid aerosol entrained in a gaseous air stream must be modeled. For this application the multiphase problem can be divided into a continuous phase (air) and a discrete phase (water). Due to the very small droplet sizes, of the order of 2 μm, involved in aerosol therapy the interaction of the discrete phase with the continuous phase is ignored. In simulations where this coupling was taken into account [2], the effect on the mean flow was less then 3% for droplets of 10 microns or less.

Discrete phase droplet trajectories were calculated using a Lagrangian formulation[16]. The effect of turbulence was analyzed using a stochastic method that modeled the effects of instantaneous fluctuations of velocity. Stochastic tracking involves using the instantaneous fluid velocity, $\overline{u} + u'(t)$ to calculate the particle trajectory. The local velocity is held constant for a discrete period of time using the Discrete Random Walk (DRW) or "eddy lifetime" model. To determine particle dispersion it is necessary to determine the time a discrete particle spends in turbulent motion. For LES the time scale used is the equivalent LES time scale, however for the two-equation *k-ε* model the Lagrangian integral time, T_L is set by the following.

$$T_L = C_L \frac{k}{\varepsilon} \tag{1}$$

C_L is generally considered to be 0.15 for the *k-ε* model. The eddy-lifetime for the velocity fluctuation u' over a discrete time in the DRW model is set to fluctuate randomly about T_L. More information on this model is available in the Fluent documentation [15].

In order to relate spray deposition to system parameters, Stokes number will be used.

$$St = \frac{\rho_p d_p^2 U}{9 \mu D} \tag{2}$$

Where d_p is the droplet diameter, ρ_p is the droplet density, U is the mean velocity, μ is the dynamic viscosity and D is the minimum hydraulic diameter.

Numerical Simulation

The pediatric airway model, Figure 1, was constructed from MRI images of a five year old male taken at 3 mm slices [17]. This original model extended from the oral cavity to the first bifurcation, more information on its generation is available in Corcoran et al (2003) [17]. Using the ProEngineer spline an IBL model of the vertex data was ported into the Gambit preprocessor (Fluent Inc., Lebanon, NH) and then manually connected to form the outer topology of the model. During this process the oral cavity was cropped to analyze the region from the oropharynx downstream. The model was then meshed as an unstructured tetrahedral hybrid. Prior to adaptation the model was composed of 46,883 cells comprising a total volume of 8.11×10^{-6} m^3.

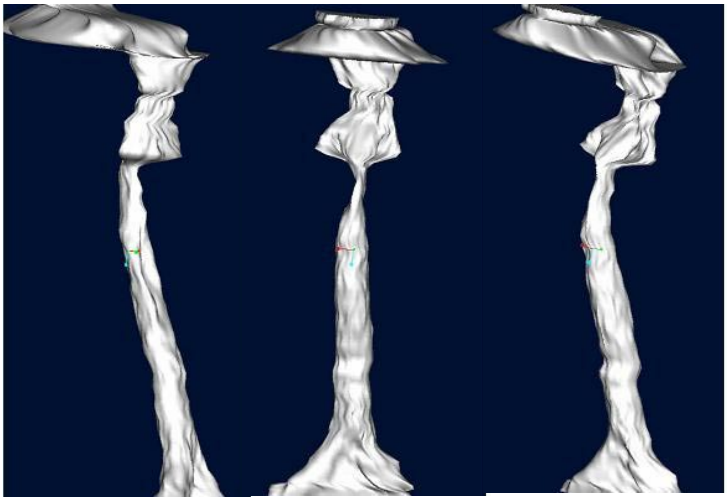

Figure 1. MRI Based Upper Respiratory Tract Model. Viewed in Pro-Engineer from the (left *(left)*, anterior *(center)*, anterior-left *(right)*) planes

In order to assess the validity of the simulation results of spray deposition additional experimental work was performed on a mold of the full pediatric model, including the oral cavity. This work indicated that for a 3.8 micron spray from a nebulizer, 25.5% of droplets deposited on the walls of the cast [17].

The Gambit mesh file was imported into the Fluent (Fluent Inc., Lebanon, NH) software for CFD analysis. Fluent offers a rigorously validated industrial platform for resolving fluid flow and heat transfer. Four flow rates were analyzed; 8, 10, 18, and 24 LPM. These volumetric flow rates correspond to typical inhalation rates [18]. The continuous fluid phase was set as air with a density of 1.225 kg/m^3 and a dynamic viscosity of 1.79 x 10^{-5} kg/m-s.

The inlet boundary was set as a uniform velocity inlet with magnitude normal to the boundary. Inlet velocity was determined from the projected area of the inlet and the desired volumetric flow rate. The outlet boundary was set as an outflow condition with equal flow weighting through each bronchial bifurcation. Flow fields were derived originally as laminar flow, then as turbulent flow using the two-equation k-ε model and turbulent flow using LES. The standard k-ε model was used with standard wall functions and default constant values. Values of k equal to 0.018 m^2/s^2 and ε equal to 40.1 m^2/s^3 were set at the inlet. These values were adapted from previous simulations [4], but the validity of these values is unknown for this model. It is expected that the derived flow field downstream of the inlet and aerosol deposition should be relatively independent of these values [5, 12]. This was determined by comparison with an inlet k and ε of unity. LES was performed with the Renormalization Group (RNG) submodel for small eddies. This is recommended for low Reynolds number effects of transitional flow and near wall boundary layers [16]. The inlet turbulent intensity was set at 5%. The energy equation was not solved, and thermophoretic effects were ignored. Operating pressure was set to atmospheric pressure at the model inlet. The conservation equations were discretized according to the standard pressure option, SIMPLE pressure-velocity coupling, and the second order upwind method for momentum and turbulent kinetic energy. Convergence was determined when residuals fell below 0.0001 for all transport variables.

After the initial solution of the flow field, grid adaptation along the velocity magnitude gradient was performed. Additional grid adaptation was performed to reduce the maximum grid volume to 1 x 10^{-15} m^3.

Of primary concern to aerosol deposition is the size of the particle. In these simulations spherical particles where analyzed, such that the size can be represented accurately by their diameter. Droplets produced from a nebulizer for medical therapy were analyzed by Kippax et al. (2001) [19]. Using laser diffraction with a standard nebulizer for a driving gas flow rate of 10 LPM the respirable fraction (< 5 microns) was 53.94 %, $D_{V,10}$ was 0.90 microns, $D_{v,50}$ was 4.51 microns and $D_{v,90}$ was 12.76 microns. As can be seen the particle size range to be analyzed just for medical therapy is highly dynamic and can differ by an order of magnitude. Thus particle deposition in this model was analyzed for monosized droplets ranging from 1 micron in diameter to a maximum of 15 microns.

Results

The derived flow field using the RNG-LES submodel, for a grid adapted along the velocity contour is presented in Figure 2. Velocity vectors are presented on the left, along a saggital plane through the center of the model. Taking discrete z-values the average velocity, maximum velocity, minimum velocity, and cross-sectional area were obtained and presented on the right of Figure 2.

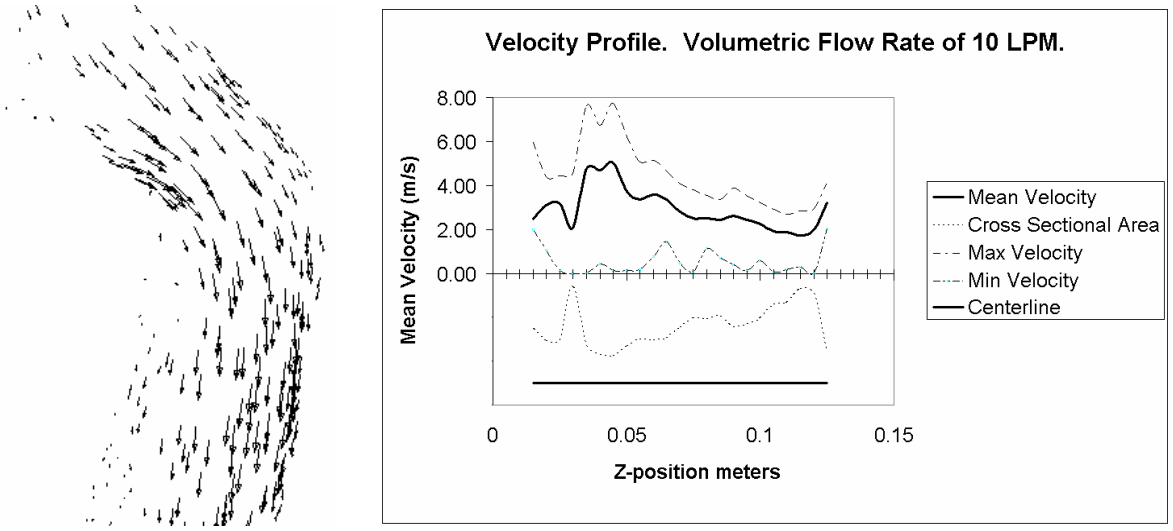

Figure 2. *(left)* Velocity Magnitude Vectors, cut at x=0 position. Zoomed view of anterior directed laryngeal jet is shown. *(right)* Graph from top (z=0.015 m) to bottom (z=0.129 m) of minimum, average and maximum velocities on top of scale and model cross-sectional area on bottom.

To determine the importance of inlet conditions to the two-equation *k-ε* model the unadapated grid was solved at three flow rates (10, 18, and 24 LPM) for differing inlet conditions and spray deposition was compared, Figure 3.

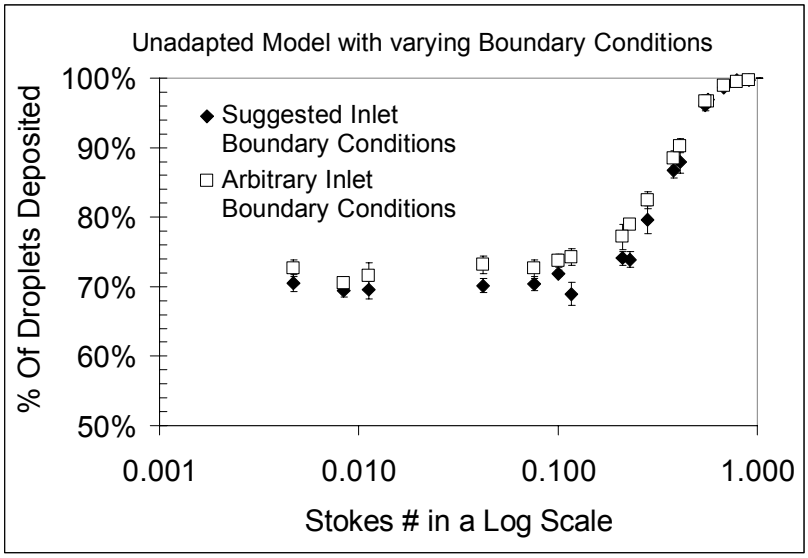

Figure 3. To determine the importance of inlet boundary conditions.

Additionally it is necessary to see the importance of grid adaptation to aerosol deposition. In Figure 4 a comparison of aerosol deposition using the *k-ε* model is presented on the left, and using LES on the right; both simulations were performed at 24 LPM. Additionally the unsteady LES simulations were tracked according to the average velocity along a medial plane. Adaptation had a minimal effect on the traced statistic (2.7% change). Grid Adaptation 1 refers to an adaptation along the velocity magnitude contour producing a 71,789 cell grid. Grid Adaptation 2 refers to an adaptation of volume creating a maximum cell volume of 1×10^{-15} m^3, for 574,312 cells.

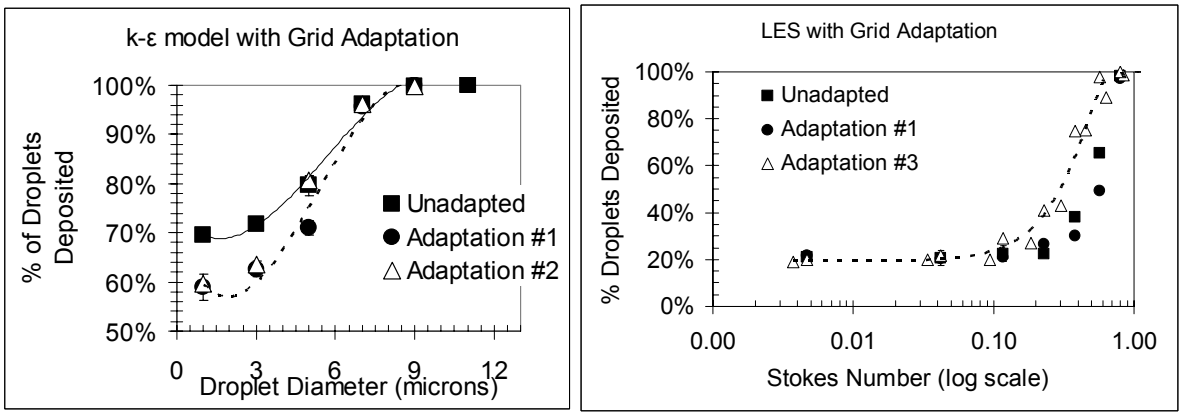

Figure 4. *(left)* An analysis of droplet deposition as a function of droplet diameter for the k-ε model at varying levels of adaptation. *(right)* An analysis of droplet deposition as a function of Stokes number using LES at varying levels of adaptation.

Finally using the finest mesh and a flow rate of 8 LPM deposition was determined for a monosized spray of 3.8 microns in Table 1. It must be emphasized that the experimental

model corresponded to the entire upper airway including the oral cavity with a polydisperse nebulized spray, while the computational model did not include the oral cavity.

Table 1. % of 3.8 micron monosized droplets deposited on the walls of the URT model.

Turbulence Model	**% of Droplet Deposited**
Laminar	39.8 %
k-ε	69 ± 1 %
LES	17 %
Experimental [17]	25.5 %

Discussion:

From the data presented it can be seen that as expected the *k-ε* model provides unsatisfactory resolution of spray deposition. Modifications of inlet turbulent kinetic energy and dissipation as well as refinement of the mesh did significantly alter deposition results. It is to be expected that the boundary conditions and mesh quality used in these experiments are not optimal. However, the large differences between expected results and simulated results found in this simulation and previous simulations [3],[5] are further evidence that turbulence models designed for fully turbulent flow can cause significant inaccuracies in spray deposition when used to model flow that has possible laminar and transitional characteristics. It is interesting to note that a reduction in the time scale constant, C_L, by several orders of magnitude leads to a better correlation between the two-equation *k-ε* model and both the LES model and experimental data.

Grid Adaptation indicated a significant effect on Aerosol Deposition as can be seen in Figure 3. Ideally mesh sizes would still have to be greatly reduced before the flow field becomes independent of mesh size. This is particularly true for LES, which requires very small mesh sizes to resolve the turbulent fluctuations that occur at this scale. When deposition correlations to droplet size were compared to previous experimental results [20] significant deviations were seen. Caution must be used when comparing the results, as the experimental correlation was derived for adult morphologies and for a larger portion of the upper airway. However, disparities between expected deposition for adults and actual deposition in children is an important factor. Whether this is a function of the unique morphology of the pediatric patient or due to modeling accuracies must be the focus of future research.

Conclusion and Recommendations:

Supporting previous research the *k-ε* turbulence model is found unsuitable for modeling fluid flow in the upper respiratory tract. As an alternative LES can provide accurate flow fields and spray deposition data. However, LES requires a computational sacrifice. Additionally the use of MRI to produce a pediatric model of the upper airways is established. This procedure allows the relatively rapid construction of morphologically accurate meshes for all populations. One concern is the persistent deposition seen despite very low Stokes numbers with a variety of modeling procedures. The source of this non-physical result is difficult to ascertain.

It is recommended that future simulations utilize LES on meshes of finer resolution. Also the effects of unsteady state transport must be taken into account for proper modeling of unsteady turbulence with unsteady particle tracking.

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