Issues in Drug Delivery: Concepts and Practice

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SUMMARY

Understanding the transport and deposition of inhaled aerosols is of fundamental importance to inhalation therapy. Herein we address issues that affect drug delivery from experimental and theoretical perspectives. Accordingly, we shall limit our comments to a focused review of laboratory work (ie, an in vitro perspective) and the development of a computer-based 3-dimensional (3D) oral morphology with related computational fluid dynamics (CFD) and particle deposition studies (ie, an "in silico" perspective). To describe the oral region, morphometric data from the literature were employed. With Maya Unlimited, a third-party animation software package, coronal images were used to create initial spline curves, which served as the foundation of a nonuniform rational B-spline surface, representing a 3D morphology. To the best of our knowledge, this study is the first medical application of Maya Unlimited. We have demonstrated that the code can be employed to construct 3D biological structures and perform 3D CFD simulations of aerosols from dry powder inhalers and metered-dose inhalers. A study was also conducted using Fluent, a commercially available software package that has been used extensively in our laboratory for 3D CFD computations. The Maya Unlimited software can generate physiologically realistic oral structures; it has great potential for

use in the medical arena, because it requires neither advanced technical training nor substantial peripheral (eg, hardware) support, it allows for the introduction of medical devices (eg, dry powder inhalers) into simulations, and it predicts 3D CFD patterns consistent with experimental observations and results of more rigorous software (Fluent). In the in vitro perspective we considered numerous salient topics, including the performances of dry powder inhalers and metered-dose inhalers, their respective operating characteristics, and relevance to in vivo data. We advocate that 3D CFD software be employed in a complementary manner, in real time, with aerosol therapy protocols in the medical arena, to promote the targeted delivery of inhaled drugs and thereby enhance their efficacies. *Key words: in silico modeling, computer morphology, particle dosimetry, metered-dose inhaler, MDI, dry powder inhaler, DPI, simulation, inhaled drugs.* [Respir Care 2005; 50(9):1228–1250]

INTRODUCTION

Computational fluid dynamics (CFD) models of airflow and particle deposition in the extrathoracic passages could be of great use in the development of aerosol-based therapies. This would be the case for the treatment of respiratory diseases (eg, asthma), as well as using the lungs as the portal of entry into the body for the systemic distribution of drugs to other target organs. A notable example of the latter would be the delivery of inhaled insulin for the treatment of diabetes. The airflow patterns through these extrathoracic passages affect the trajectories of entrained particles and must be understood in order to determine drug dosimetry patterns among the distal (ie, downstream) thoracic airways. The airflow patterns are governed by the morphologies of the respective nasal, oral, pharyngeal, and laryngeal airways in association with ventilatory variables.

Because the topic of concern to this conference is metered-dose inhalers (MDIs) and dry powder inhalers (DPIs), we shall present an original methodology for reconstructing the morphology of the human oral cavity from imaging data, using a computer animation and analysis software package (Maya Unlimited, Alias Products, Toronto, Ontario, Canada). The software will also be used to perform fast CFD approximations of airflow within the oral cavity. A more rigorous third-party CFD package will also be used (Fluent, Aavid Thermal Technologies, Laconia, New Hampshire). We believe it worthwhile to comment (albeit briefly) on the use of CFD software in respiratory system simulations. Several third-party software packages exist in the commercial marketplace, and their use has become quite popular. In our laboratory we have successfully used Fluent and CFX-F3D (CFX Group of AEA Technology Engineering Software, United Kingdom) in clinical studies, and have published the results of our investigations in the peer-reviewed scientific and medical literature. The most common critiques we have received from the medical community regarding the integration of CFD software in medicine include: the licensing fees are too expensive; the codes are too complicated; the hardware platforms required are too expensive; and the programs require highly skilled and dedicated-to-CFD-use personnel. These factors present important problems in the clinical arena. Therefore, with our demonstrated experience, we decided to employ a relatively inexpensive and simple-to-use CFD package (Maya Unlimited) for demonstration purposes. It may be prudent to note that the Maya Unlimited software is widely used by the motion picture industry (eg, in *The Perfect Storm*).

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DPIs have evolved to varying degrees since their modern inception as drug-delivery devices in the 1970s. This evolution has accompanied changes in the regulatory environment, the introduction of new potent active drug compounds, increased market competition, and advances in our understanding of the mechanisms involved in dry powder dispersion and deposition in the airways. These developments and the incremental advancements of DPI design have raised several issues in dry powder drug delivery that need to be addressed. These issues are particularly important when put into context with the field of inhaled drug delivery as a whole: currently marketed DPIs are less efficient in delivering drugs to the lower airways than are MDIs.[1] Efficient delivery of the drug to the lung from a DPI requires sufficient energy for dispersion and deaggregation of cohesive fine drug particles. An approach to this problem that is under development is the design of inhaler devices that generate this energy (active devices). Alternatively, improvement in the amount of respirable drug delivered can be attained via design and modification of the powder formulation. Following an introduction of basic principles of DPI dispersion mechanisms and design, these developments and critical issues influencing DPI performance are addressed in the following text.

METHODS

In Silico Modeling

Our contribution to this conference follows our previous participation, in which we presented the results of our mathematical modeling and computer simulation efforts for human lungs.[2] In a recent publication in RESPIRATORY CARE, the methodology to improve the reconstruction of lung structures from scintigraphy images was documented. Hence, the morphology of the theory and code has become evermore anatomically realistic.[3] Those components have been integrated to form in silico models and describe inhalation drug delivery to asthmatics, including theoretical studies and comparisons with data from experiments with patients.[4,5] More recently, the in silico models have been advanced to address pediatric medicine.[6]

Herein we shall address the airways of the human head and throat proximal to human lungs. The domain of concern is shown in Figure 1. The extrathoracic region consists of nasal, oral, pharyngeal, and laryngeal passages. Because the focus of this conference is the delivery of drugs via MDIs and DPIs, which are administered via the mouth, we shall naturally limit our analyses to the oral, pharyngeal, and laryngeal airways, which shall be identified as the "upper respiratory tract" for clarity of terminology.

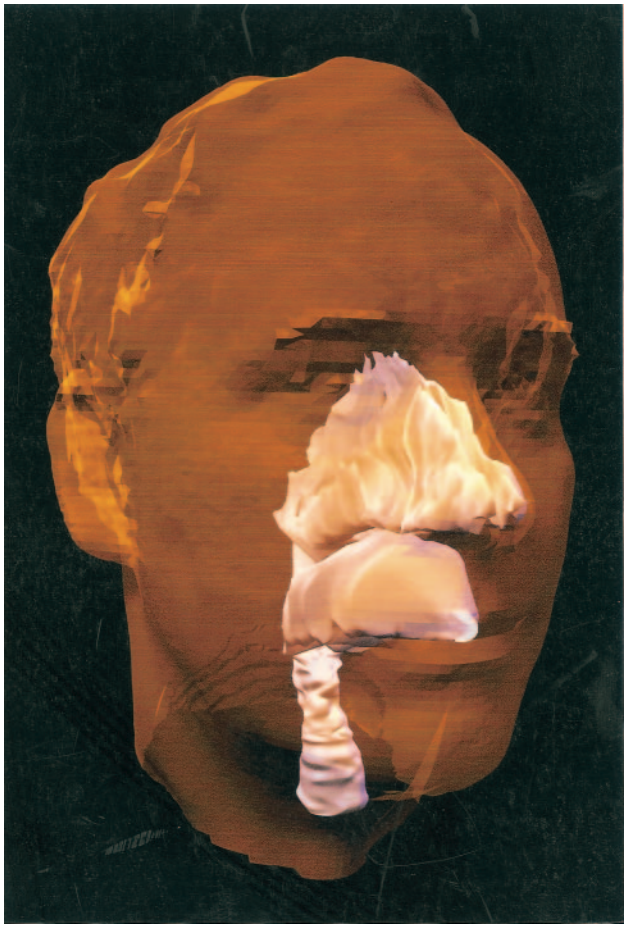

Fig. 1. Airways of the human head and throat.

Laboratory Data

The work described herein is but one element in our laboratory's ongoing development of evermore physiologically realistic 3-dimensional (3D) models of the human respiratory system to aid in the analysis of inhaled drug delivery issues. Our computer reconstruction of the anatomy of the human upper respiratory tract began with published data.[7] They presented morphological data describing the oral, pharyngeal, laryngeal, and tracheal passages, including 2-dimensional coronal sections of the region, oriented with the direction of primary flow.

In Figure 2 the upper respiratory tract region is shown. In Figure 3 the coronal sections of the oral cavity are presented at designated intervals. In Figure 4 the cross-sections of the distal pharyngeal, laryngeal, and tracheal airways are depicted at specific locations. These respective images were digitized and used to create corresponding spline curves which, when concatenated (ie, stacked), served as the foundation for the generation of 3D nonuniform rational B-spline (NURBS) surfaces that represent the 3D contours of the human upper respiratory tract, as detailed below.

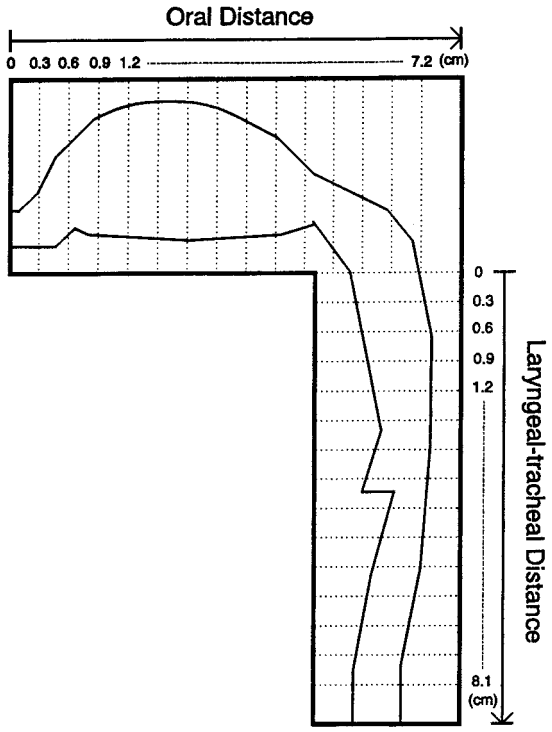

Fig. 2. Schematic diagram of the upper respiratory tract. (From Reference 7, with permission.)

Oral Passage Reconstruction

The anatomically realistic, 3D human oral morphology model was reconstructed from a series of 2-dimensional coronal sections of an oral cavity. The slices were taken at 0.3 cm intervals over a distance of 7.2 cm (Fig. 5 top), extending from the entrance of the mouth (ie, lips) to the exit of the mouth (ie, pharynx). Using Maya Unlimited version 4, a modeling, visual effects, and animation software package, 25 coronal section images of an oral cavity were hand traced and digitized to create spline curve representations of the oral passage cross-sections (see Fig. 5 bottom). The spline curves were concatenated into a single file to produce Figure 6. These cross-sections were then used as the basis for the creation of a surface representing the morphology of the human oral cavity. Specifically, Maya Unlimited was used to "loft" the curves to construct a NURBS surface that passed through the series of cross-sections, as described in the next paragraph.

We created a series of profile curves (Fig. 7 top) from the coronal sections, which defined the transitional shapes of the oral cavity, then lofted those respective curves together as if, quite literally, stretching a canvas over a wire frame. In computer graphics protocols, the process of lofting is most often employed to create new surfaces from primitive (eg, data-deprived irregular) shapes, to close open surfaces, and to create intermediate sites between any 2 surfaces generated with boundary curves. To begin, we selected the first two in the series of profile curves and used the loft command to construct an intermediate surface. This process of selecting and lofting was repeated until all 25 curves were combined to create the completed surface. In certain instances, when spline curves were lofted into their surfaces, some unexpected (ie, aphysical) shapes occurred, because the arbitrary number of control vertices on the initial curves did not have the same degree of curvature and number of algorithm edit points, as displayed in the bottom half of Figure 7. The practical and accepted way to address such problems, as encountered when considering a set of initial curves, is to make copies of a single (ie, representative) curve from the set, select key points on it as markers, and transform its control vertices onto the others as necessary to generate the desired profile curves. In that manner, the NURBS surface from the new spline curves was created, and is presented in Figures 8 and 9.

The tongue has an important role in the administration of drugs via MDI and DPI. To be succinct, the tongue may adversely affect the efficiencies with which inhaled drugs are delivered. As a physical entity, the tongue will, at least, direct aerosol motion within the mouth, and may very well impede it. Therefore, in Figures 10 and 11 the role of the tongue is addressed. In Figure 10 an idealized tongue is placed within the computer-generated wire frame network. We have employed the idealized tongue as a place holder for computation studies. The actual configuration of the real tongue is displayed by the lower contour curves (ie, the convoluted spline curves) which are distinctly shown within the oral cavity. We selected this format for clarity of presentation. In Figure 11 the tongue is shown within the NURBS surface describing the oral cavity. Again, for clarity of discussion, the wire frame is exposed under the NURBS surface to demonstrate the mode of computer construction.

Simulations

Fluid flow simulations were performed within the oral passage model, with Maya Unlimited and Fluent. In both cases, simulations were performed for particles having the same density as the carrying air. With Maya Unlimited the fluid flow was visualized by animating the progress of an ensemble of particles as a function of time. With Fluent the flow was visualized by displaying the streamlines associated with a group of particles entrained in the flow. The procedures employed with Fluent when simulating the respiratory system have been well documented in the literature; therefore, we shall only address the use of Maya Unlimited.

Using the dynamics command of Maya Unlimited, we created a "directional emitter" to launch a collection of particles with prescribed coordinate direction attributes. The NURBS surface of the oral cavity was specified to be

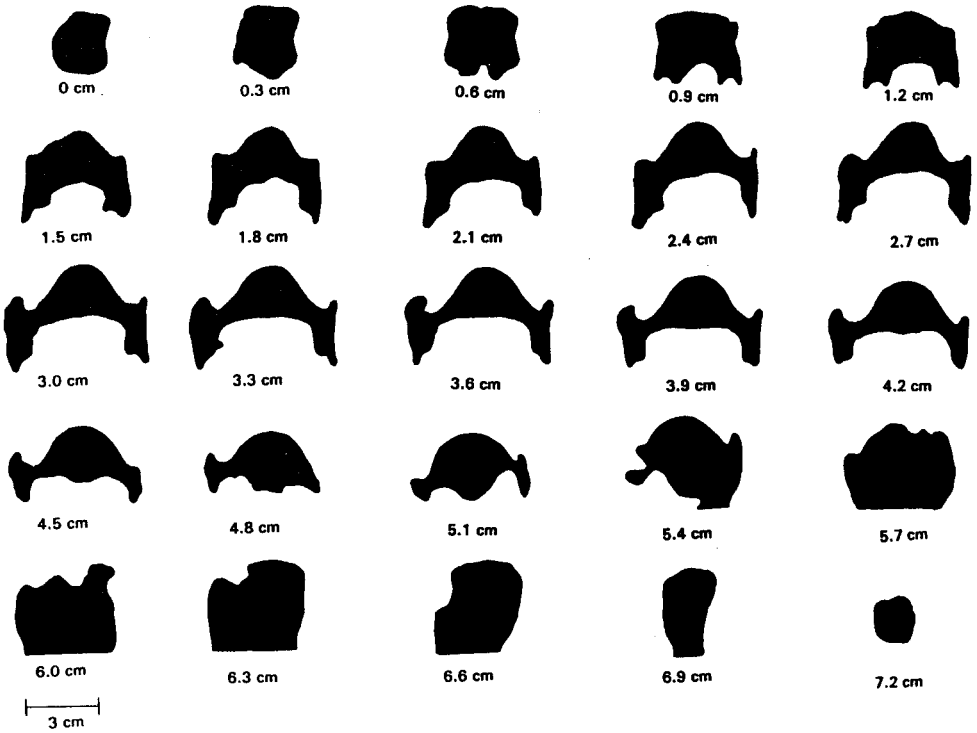

Fig. 3. Changes in cross-sectional area within the human mouth, progressing from the entrance (lips) to the exit (pharynx). The spatial locations are identified in Figure 2. (From Reference 7, with permission.)

a "collision geometry" to contain the particles emitted. Then, placing an MDI into the orifice of the NURBS (oral cavity) surface, with the directional emitter releasing particles, we created an animation of a drug aerosol within the surface structure, as shown in the RESULTS section below.

It is beyond the scope of this text to provide a comprehensive review of this subject matter (ie, mathematics, physics, and engineering as applicable to aerosol therapy), which warrants separate treatment as a worthy and timely topic in medicine. However, a review of factors that affect aerosol deposition modeling per se may be found in the textbook by Martonen[8] and the more recent works of Isaacs et al[9] and Martonen et al.[10] Herein we shall make only a few comments to put our contribution in perspective with the kind of information that is available. Finlay et al[11] constructed an idealized model consisting of the oral, pharyngeal, laryngeal, and tracheal passages and measured particle deposition as a function of flow rate. The results were compared to the findings of Stahlhofen et al,[12] when plotted as a function of an impaction parameter. Pant et al[13] performed 2-dimensional CFD analyses of flow within a computer model based on the morphology of a human replica cast consisting of oral, pharyngeal, laryngeal, and tracheal airways. Their CFD simulations corresponded to the sagittal plane of the replica cast, and differ, therefore, in concept from the work reported herein, in many respects, including the fact that our simulations are 3D CFD.

To be consistent with DPI and MDI issues, the work presented in this text will focus on aerosolized drug delivery through the mouth. We must comment, however, that inhaled drugs may also be administered via the nose. In a previous effort, we presented 3D CFD models of the head and throat consisting of the nasal, pharyngeal, laryngeal, tracheal, and upper bronchial airways.[14,15] In those 3D in silico studies the structures were anatomically realistic, CFD flow patterns were determined, and trajectories of inhaled particles were mapped throughout the system.

In Vitro Investigations

Mechanisms of Dispersion

The central problem for creating dry powder aerosols suitable for inhalation is related to a balancing act between particle size and inter-particulate forces.[16] The particle size range generally considered ideal for targeted delivery to the airways is between 1 μm and 5 μm.[17] This size range, however, is one that encounters a transition from gravitational forces to thermodynamic forces.[16,18] As a consequence, typical particles designed for lung delivery are substantially aggregated and difficult to separate. The particulate interactions that give rise to aggregated fine powders result from the contribution of a number of concurrently acting forces, which include van der Waals,

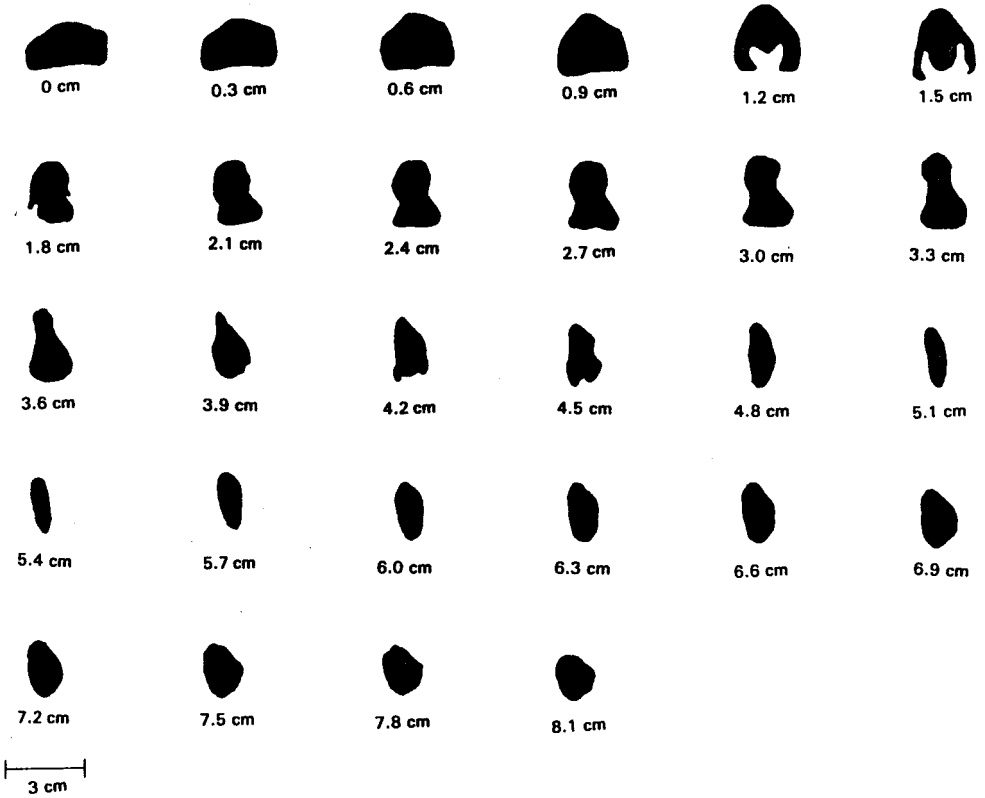

Fig. 4. Changes in cross-sectional area within the human extra-thoracic region, progressing from the entrance (pharynx) through the larynx to the exit (trachea). The spatial locations are identified in Figure 2. (From Reference 7, with permission.)

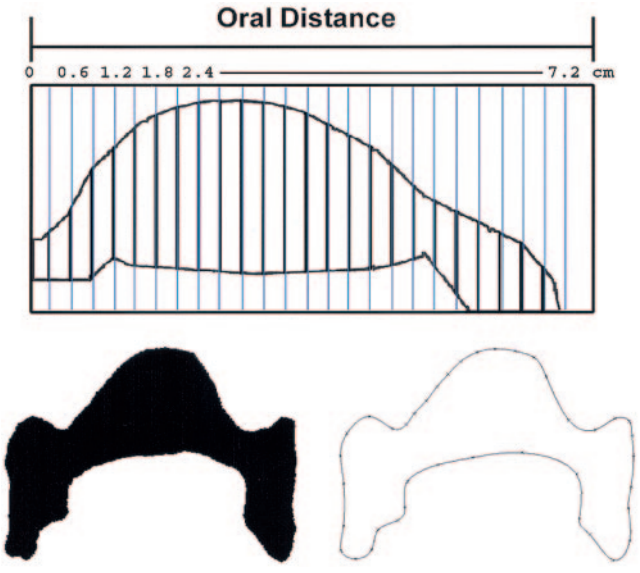

Fig. 5. Top: Schematic diagram of the oral cavity. Bottom left: Representative coronal section with the corresponding hand-traced spline curve (bottom right) created from the image.

electrostatic, capillary, and mechanical interlocking forces. Van der Waals forces result from instantaneous differences in electronic configurations of molecules, which give rise to dipolar characteristics. Electrostatic forces can also contribute to particulate interactions in pharmaceutical powders because of the transfer of electrons and ions between particles that are typically insulators. Capillary forces arise when water molecules condense on solid-solid interfaces. The force is proportional to the surface tension of the adsorbed liquid layer and may dominate other forces. Mechanical interlocking occurs because pharmaceutical aerosols are typically composed of polydisperse particle size distributions, and the constituent particles are rarely uniformly shaped or spherical. Rough surfaces can assist in the interlocking of particles once they have come into contact.

Aggregate formation and micronized particle complexes are difficult to disrupt to reform particles in the size range suitable for entering the target regions of the lung. Thus, appropriate formulation, powder engineering, and inhaler device design are critical to improving the performance of DPIs.

Formulation Design

To overcome these forces, DPI formulations are typically designed as either interactive blends or controlled aggregates. Interactive blends attempt to overcome the highly cohesive interactive forces of drug particles that are

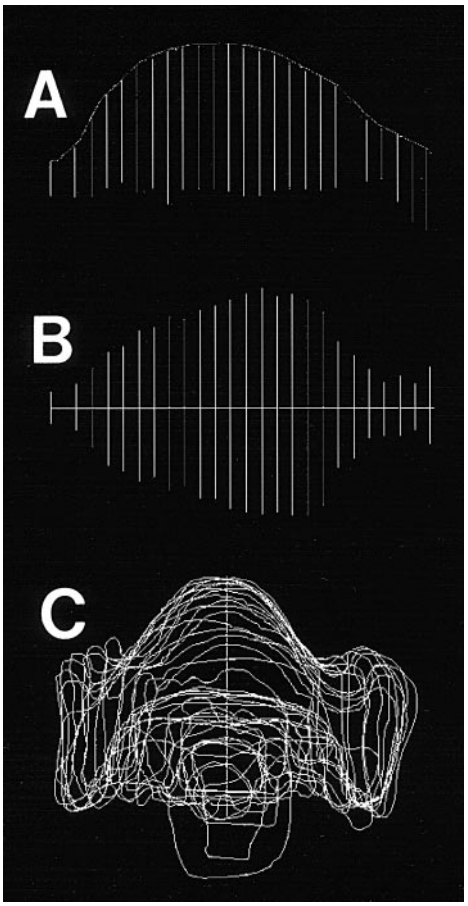

Fig. 6. Spline curves defining the oral cavity presented in (A) side view, (B) top view, and (C) front view.

sized between 1 μm and 5 μm, by the addition of so called carrier particles. These carrier particles are generally much larger than the micronized drug particles and therefore behave under predominantly gravitational forces. Carrier particles are blended so that the surfaces of the large particles become coated with micronized drug. After Dunbar et al,[19] a simplified schematic of the generation of a dry powder aerosol using this formulation strategy is shown in Figure 12.

Alternatively, controlled aggregates of micronized drug particles can be used instead of generating interactive blends. These carrier-free formulations contain loosely bound quasi-spherical drug particles that are micron-sized for lung delivery. The aggregates are approximately 100 μm and have improved flow properties. The interactions between the micronized drug particles must be weak enough to enable deaggregation during dispersion to the lung and also strong enough to withstand processing.[1,20]

DPI Design

All currently marketed DPIs are passive devices in which the energy for powder fluidization and aerosolization is derived from the patient's inspiratory effort. Various manifestations of similar designs are found in approved DPI products. Early designs used capsules as the powder dose container. The capsule is placed in a chamber within the device and ruptured. Device design typically allows turbulent airflow to be generated during patient inspiration, and the airflow is the primary mechanism of dispersing the powder. Other more recent embodiments include reservoirs and blister dose containers.[21,22]

Active DPI devices use an energy source independent of the patient. Typically, the device contains some form of stored energy (eg, spring, battery-driven electric motor, piezoelectric element, or compressed air) that is focused on the powder dose to be aerosolized. At present, no active DPI system has been approved for marketing by regulatory agencies. However, a number of such devices are under development or have been previously described in the literature. The discussion of active DPI systems is continued below.

RESULTS

In Silico Modeling

The resulting oral passage cross-sections, obtained at 0.3-cm intervals over the 7.2-cm distance from the lips to the oropharynx, are displayed in top, side, and front views in Figure 6. The location and orientation of the tongue is particularly evident in the front view. The general underlying shape of the oral cavity is evident in the perspective view of the hand-traced sections (Fig. 7 top).

In the bottom half of Figure 7 we have intentionally shown typical problems that can arise when such complex computational protocols are applied to biological data. Our intent was twofold. First, to candidly alert new users of software, along with readers of the literature, that although such difficulties can occur, they can be solved using established techniques. Second, to caution the beginning user of software that initial results must be carefully examined to make certain they are anatomically realistic (ie, are not aphysical). For example, the presence of sharp corners in a biological system should be reviewed.

Views of the final reconstructed NURBS model, emphasizing different structural features, are shown in Figures 8 and 9. In Figure 8 the enveloping NURBS surface is shown. In Figure 9 the bottom surface of the model is highlighted to demonstrate how the position and shape of the tongue affect the shape of the overall oral cavity.

Flow through the oral model, as predicted by the 3D fluid-flow tools within Maya Unlimited, is shown in Figure 13 and Figure 14. Specifically, the orientation of an entrained ensemble of particles (each particle having the

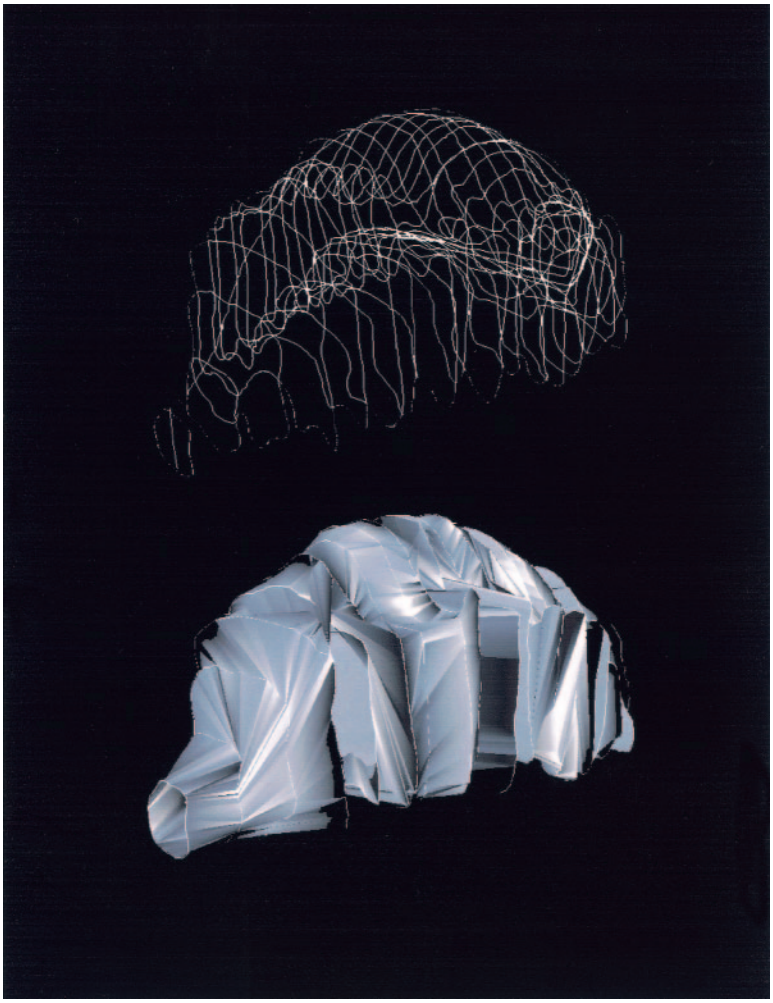

Fig. 7. Top: Perspective of the family of spline curves defining the wire frame foundation of the oral cavity. Bottom: Unacceptable nonuniform rational B-spline (NURBS) surface with aphysical features that must be addressed in computational protocols to produce an anatomically realistic oral cavity. Such problems can be corrected via techniques outlined in the text.

same density as the carrying air) is visualized at 6 different points in time. The motions of these particles are consistent with streamlines derived from CFD simulations of flow through the oral cavity performed in Fluent (Fig. 15).

In Figure 16 we present (using Maya Unlimited) the progression of inhaled aerosol through the human oral cavity. The flow patterns are self-explanatory, and we shall make only a few straightforward comments to orient the reader. The incoming aerosol enters with directed motion (ie, in the form of a jet) and experiences a sharp deviation as it encounters the tongue (ie, which, in effect, functions as an obstruction to motion). Within the mouth the aerosol has a curvilinear pathway and is affected, in quite a pronounced fashion, by the structure (ie, curvature) of the tongue. Eddy formations are distinct elements of the flow pattern within the oral cavity.

In Vitro Investigations

Inspiratory Flow Rate and Resistance

Principles. Precise dose delivery to the lung during normal patient use is desirable for all inhalation delivery systems. For all currently available DPI systems, the dispersion of powder relies on the patient's inspiratory effort to provide energy for fluidization and deaggregation. Because of the variability in inhalation characteristics between patients, there is potential for the extent and efficiency of dose delivery to the lung to be variable.[23]

Figure 17 outlines the general scheme by which passive DPIs use inspiratory energy to disperse powders. Generally, increasing airflow increases drug dispersion[1] because it increases the drag forces of the fluid acting on the par-

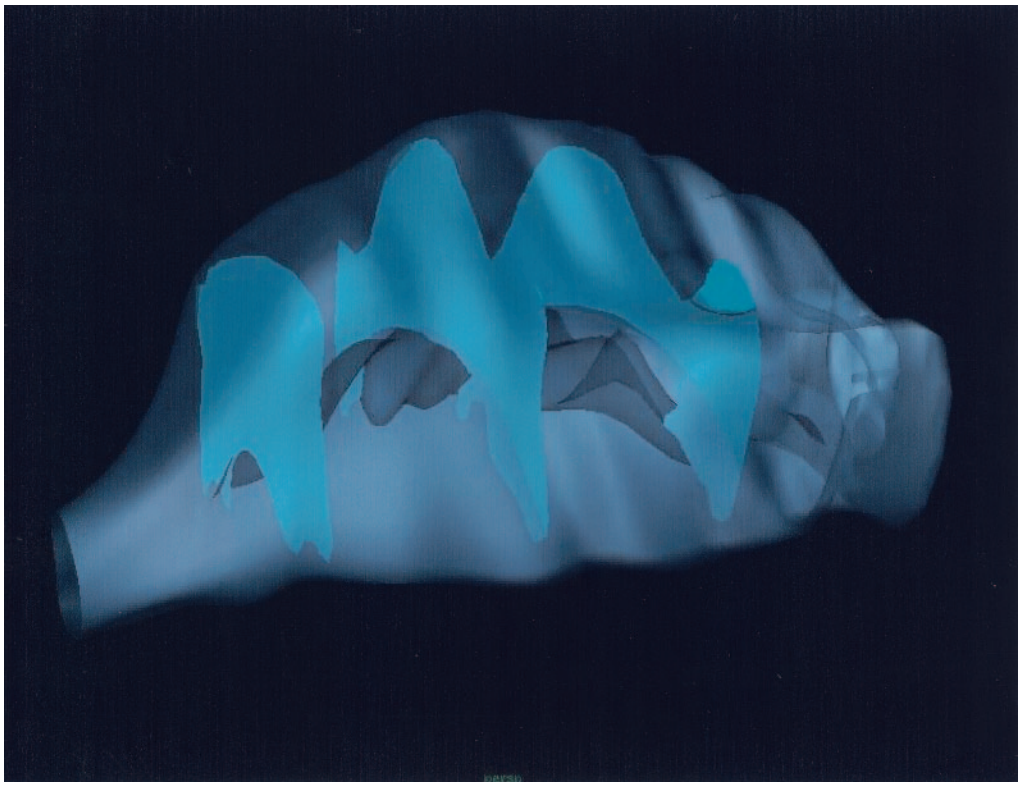

Fig. 8. Acceptable 3-dimensional nonuniform rational B-spline (NURBS) surface of the human oral cavity, whose internal configuration is shown using superimposed coronal sections (see Figs. 3 and 5).

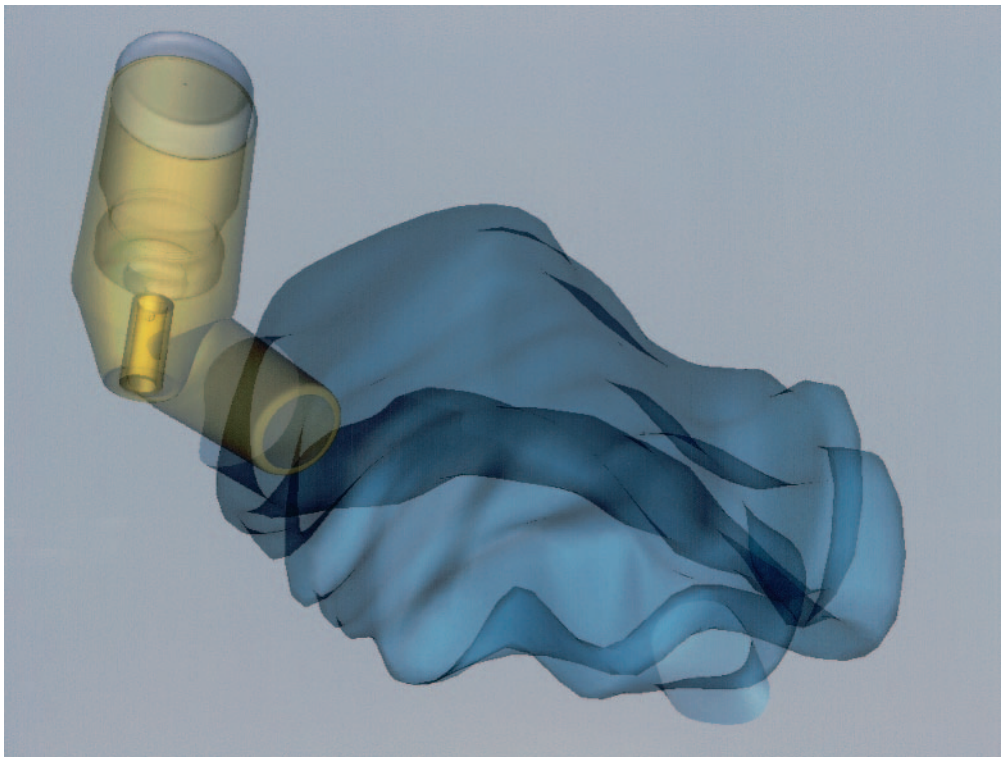

Fig. 9. Perspective of the 3-dimensional nonuniform rational B-spline (NURBS) surface, highlighting its bottom boundary to show how the position and shape of the tongue inherently affect the contour of the oral cavity.

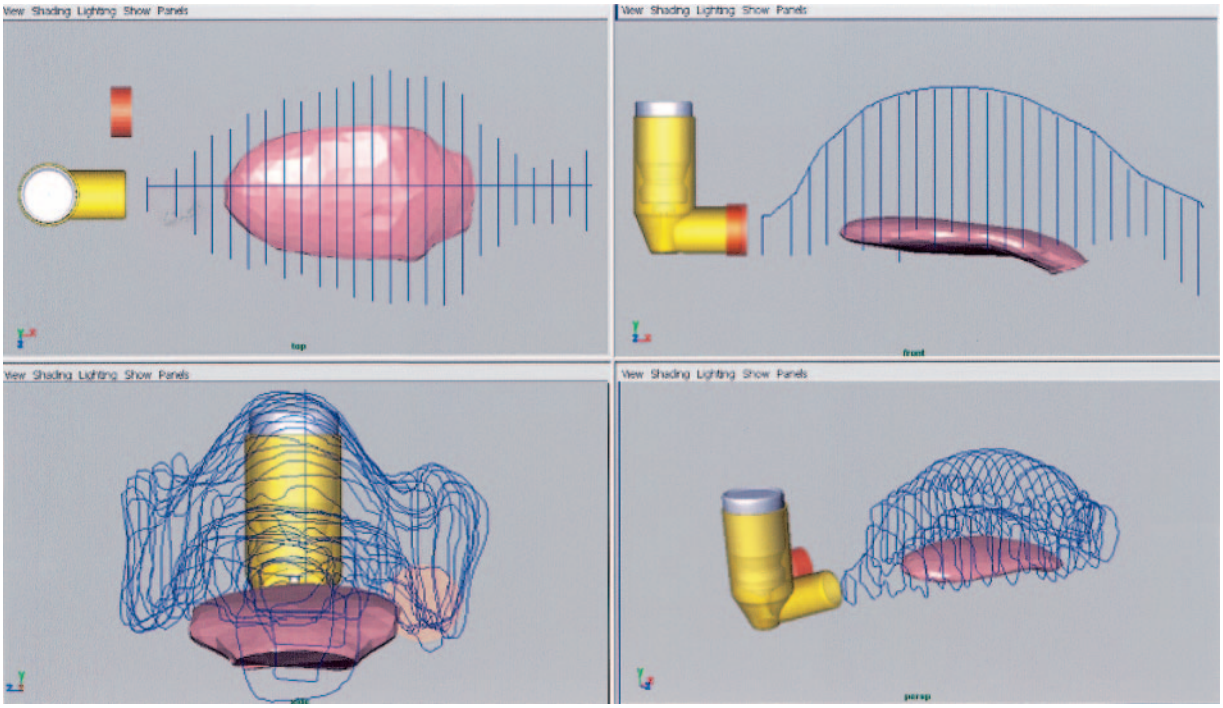

Fig. 10. Position of the tongue within computer-generated oral compartments, relative to a metered-dose inhaler. Top left: Top view of the tongue within the schematic of the mouth. Top right: Side view. Bottom left: View of the tongue and metered-dose inhaler from the back of the mouth. Bottom right: Perspective within the wire frame network.

ticle located in the flow and also increases the turbulence (depending on inhaler design). These 2 processes may substantially influence entrainment and dispersion of drug particles. Device resistance determines turbulence within the inhaler and also the inspiratory effort required to generate equal airflow through the device. Increasing device resistance generally increases the turbulence of the airstream but also increases the force required to generate the same flow rate through the device. Thus, the effect of device factors may be important for DPI formulation performance.

Different inhaler devices have different design features that contribute to unique airflow pathways and airflow resistance. Typically, a device will have flow restrictions that focus airflow onto the powder to be dispersed and/or generate turbulent flow to increase aerosolization performance (see Fig. 17).[24,25] These restrictive flow pathways result in "device resistance" that is related to pressure difference and volumetric flow rate through the following expression:

$$R = \frac{\Delta P^{0.5}}{\dot{Q}} \quad (1)$$

where R is the specific flow resistance, $\dot{Q}$ is the flow rate, and ΔP is the pressure drop across the device.[19] A wide range of device resistance values exist for commercially available DPIs. In vitro and in vivo studies have been performed showing intra-device and inter-device dispersion variability that depends on the flow rate through the specific inhaler device, which is discussed below.

Effects. Inconsistency of dose emission during inhalation due to variations in inspiratory flow rate can be overcome by dose titration for short-acting β agonists, according to the patient's response. However, for inhaled long-acting β agonists, corticosteroids, and drugs with narrow therapeutic indices, this is not a viable alternative. Several studies have shown altered clinical response from DPIs, depending on inspiratory flow.[26,27] This is not surprising, given the variability observed in patient inspiratory flow-rate profiles when inhaling through DPIs.[28] In vitro dispersion studies have been widely reported. For example, in a study of a combination product, variability of dose emission characteristics from each inhaler and between inhalers at each flow rate (28.3 L/min, 60 L/min, and 90 L/min) was found.[29] In addition, aerodynamic particle size characterizations revealed that mean fine-particle doses also changed at different flow rates. Similar in vitro dispersion dependence on flow has been reported by others.[30,31]

In vivo studies have also shown flow-rate dependence with passive inhaler devices[32,33]. The influence of this variability on performance is discussed below.

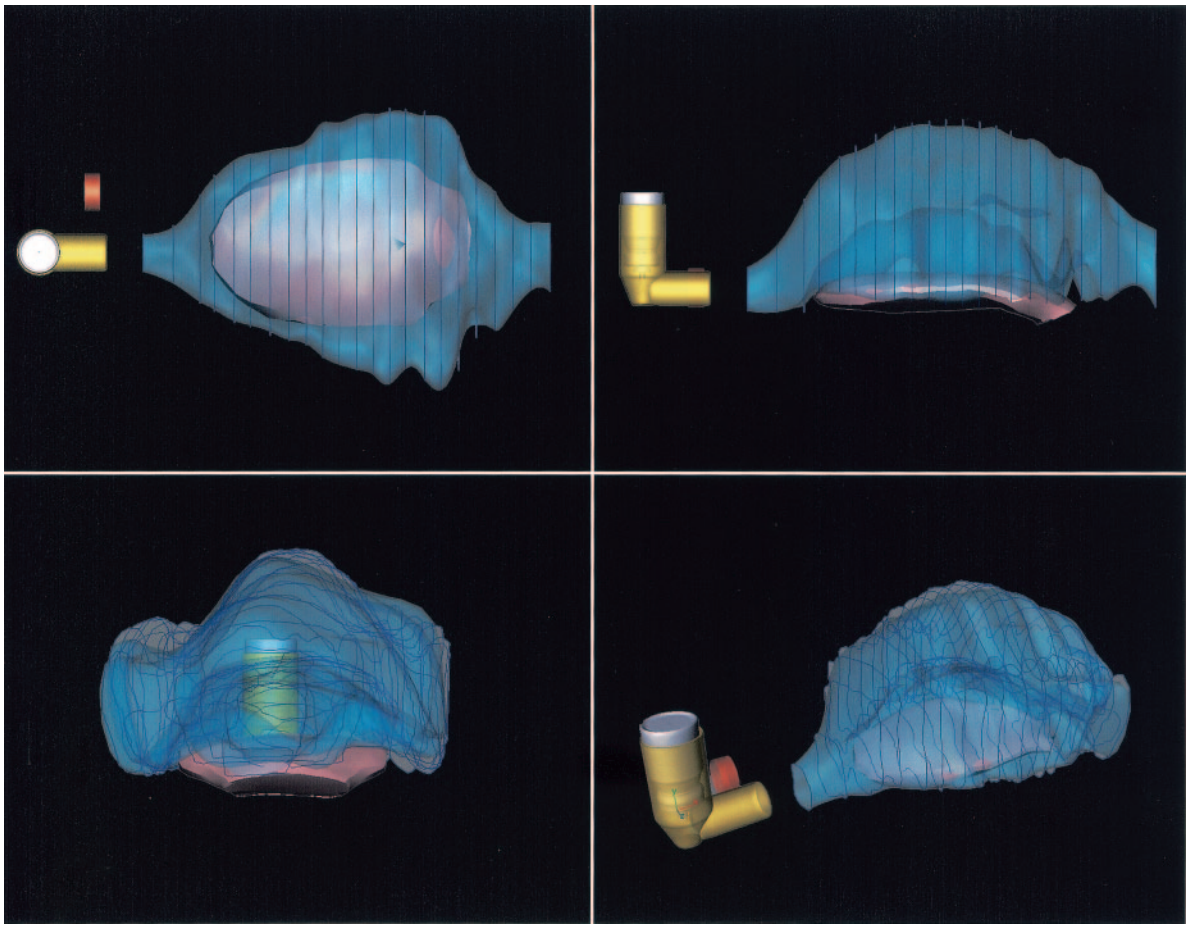

Fig. 11. Position of the tongue within the 3-dimensional nonuniform rational B-spline (NURBS) generated surface of the oral compartment. The 4 panels correspond to the panels in Figure 10. For clinical relevance a metered-dose inhaler is shown.

Ambient Relative Humidity

When dry powders are exposed to ambient atmospheres, adsorption of water molecules may occur on particle surfaces. The degree of adsorption depends on the partial pressure of water vapor, temperature, and the affinity of the particles for water molecules.[34] The presence of an adsorbed water layer modifies the interactions between individual particles. The influence of adsorbed moisture on particle adhesion is not straightforward, and is expected to depend on the thickness of the adsorbed layer, surface roughness, surface chemistry, contact geometry, and any dissolution and intra-particle absorption or chemical changes that might arise because of the presence of water.

The importance of the effect of nanometer-scale layers of liquid on particles several scales larger has been reported.[35,36] These nanometer-scale liquid layers represent liquid content that was 40 times less than the minimum moisture content of previous studies and corresponded to a liquid coating thickness of < 50 nm. The response of the powder material to these liquid levels was an enormous increase in the angle of repose, indicating important increases in inter-particulate forces. In these studies the typical volume of a liquid bridge was approximately 3×10^{-17} m^3 for the maximum liquid coating thickness, implying that 99.9% of the liquid does not contribute to the adhesive force, possibly because of the surface roughness.[35,36] Although these studies were performed in granular media that are larger than typical particles encountered in DPI formulations, the influence of liquid bridges is no less important.

In addition to the effects of liquid bridging within DPI formulations, relative humidity may also substantially influence molecular structure on the surface of particles. The presence of amorphous material on the surface of a micronized particle may lead to instability of the powder. For example, small changes in humidity and/or temperature can increase the mobility of the amorphous regions and cause re-crystallization and potential particle fusion.[37,38]

From a regulatory standpoint, a DPI must be shown to deliver individual doses reproducibly throughout its shelf life, in temperatures and relative humidities that represent

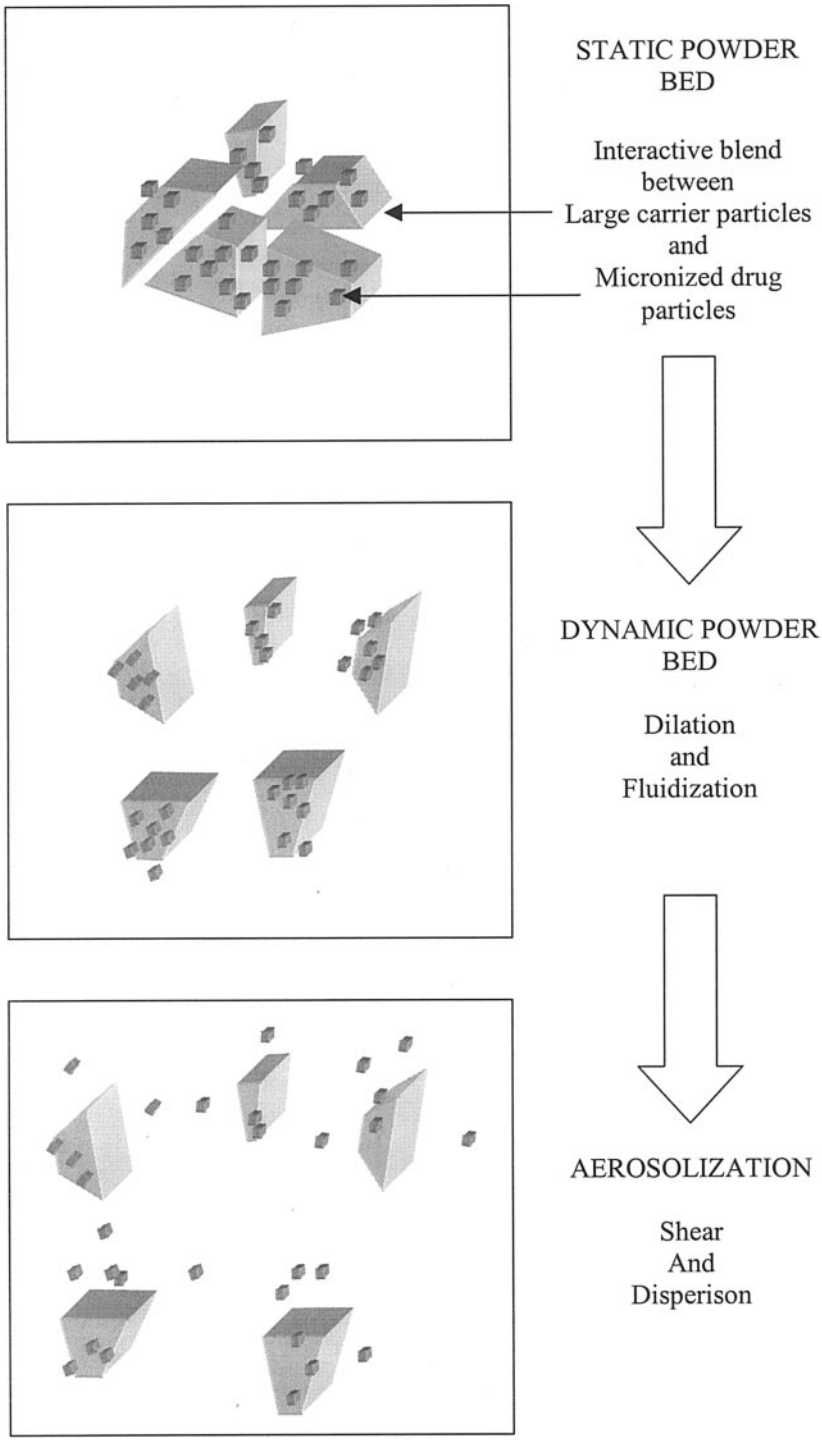

Fig. 12. Schematic of powder aerosol production: a 3-phase process involves the properties of the static powder bed, fluidization, and deaggregation and dispersion.

commonly experienced environmental conditions. Particle size distributions from each inhaler must also be stable over the product's lifetime and the product proven to be manufactured reproducibly. Thus, given the propensity of moisture to cause important changes in particle-particle interactions and the nature of the surfaces of particles, control over relative humidity is critical at all stages of product development and manufacture. To ensure minimal mois-

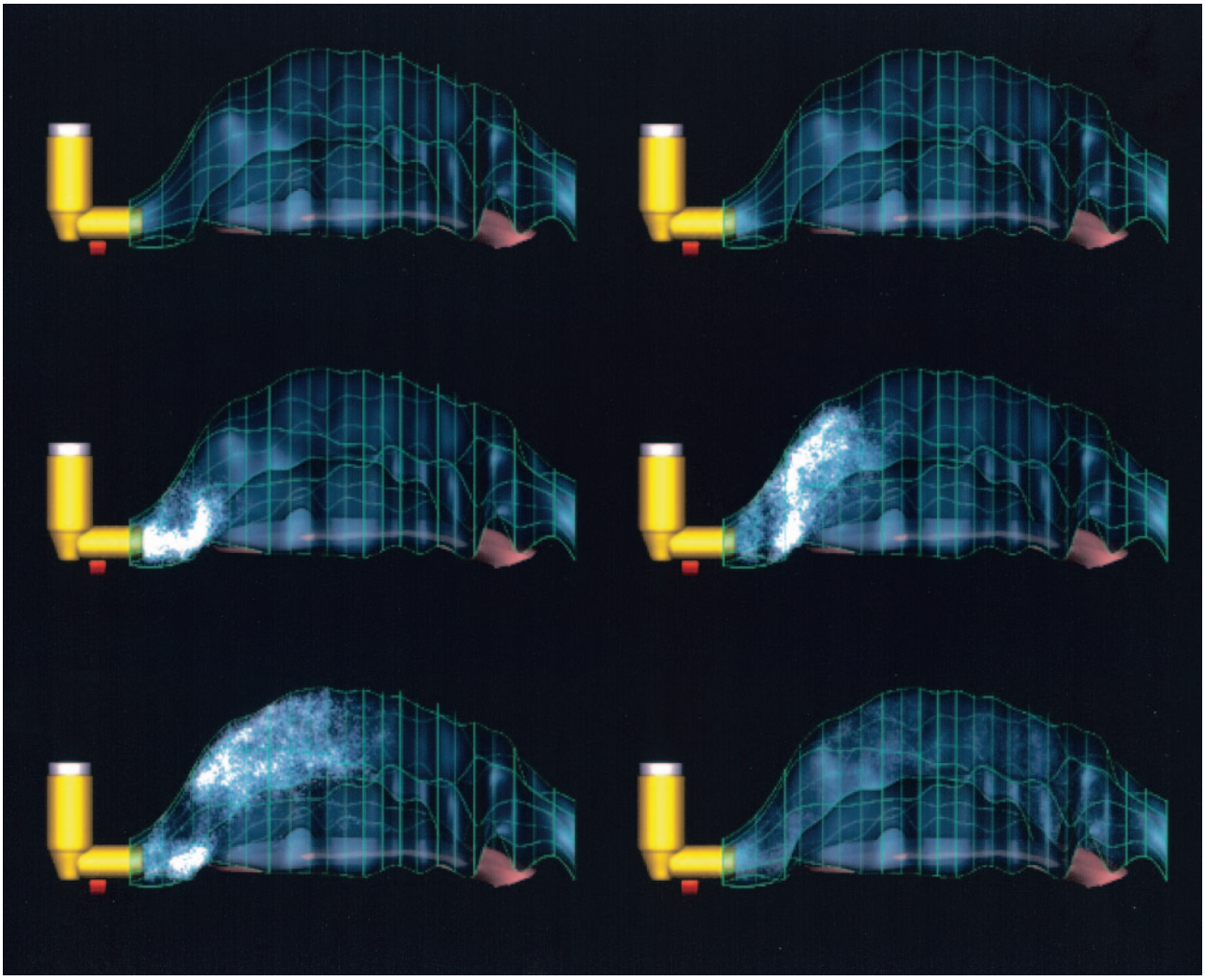

Fig. 13. Side views of drug particles in transit through the oral cavity. The illustrations should be read left to right, top to bottom.

ture influence during normal use by patients, packing technology is also critical to the performance of DPI formulations.

DISCUSSION

In Silico Modeling

To begin this section, we shall naturally address the theoretical (eg, CFD) work presented in our contribution to this conference. However, we recognize the reality of the situation—namely that such efforts may be, in fact, difficult for others to integrate into the medical arena, for a variety of reasons (eg, hardware and software costs, lack of computer personnel, and hospital priorities). Therefore, for practical purposes we shall also, in courtesy, present empirical formulae that are available to estimate particle losses in the upper respiratory tract.

Analytical

The model presented in this work has provided a foundation for physiologically realistic simulations of morphology, airflow, and particle deposition in the mouth. The model has important and timely applications to MDI and DPI aerosols, for 2 straightforward, and intimately related, reasons. First of all, it can be employed to determine particle deposition (ie, losses) during drug administration. The aforementioned aerosol losses will be a function of 3 families of variables: oral morphologies, aerosol characteristics, and breathing conditions. Second, after the particle-filtering efficiencies of the oral passages are accounted for, the model can be used to determine the doses delivered to thoracic airways. The salient point being, of course, that inhaled particles cannot be introduced to human lungs without first penetrating the proximal (ie, upstream) regions. Therefore, a model that describes factors that affect in-

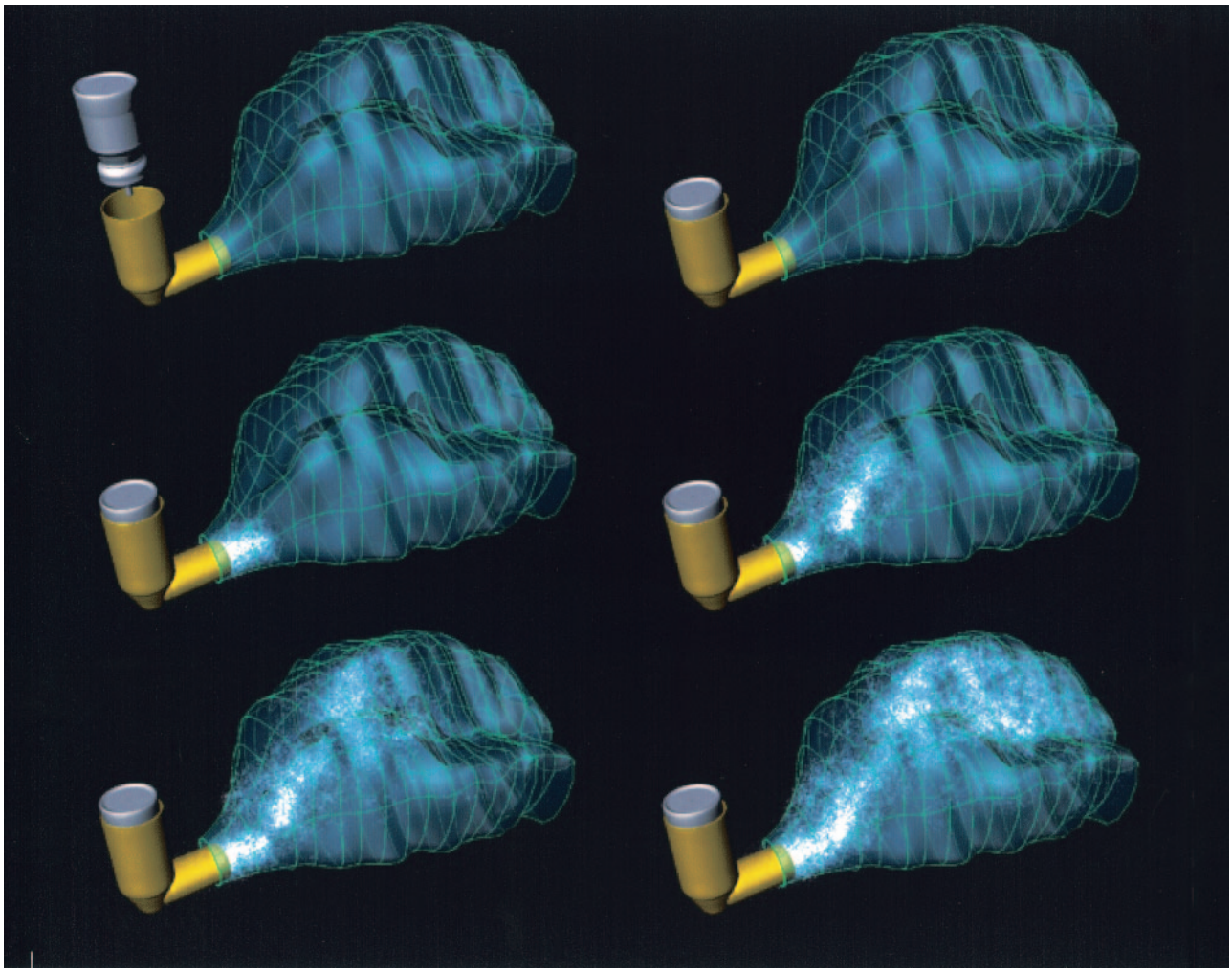

Fig. 14. Perspectives of drug particles in transit through the oral cavity. The illustrations should be read left to right, top to bottom.

haled drugs in the oral, pharyngeal and laryngeal passages is of seminal importance to the delivery of MDI and DPI aerosols.

Maya Unlimited has proven to be a versatile and user-friendly software environment for the reconstruction of the human oral region considered in this work. We believe the software has the potential to facilitate the rapid creation of anatomically realistic models of other respiratory system structures as well, from medical images. In our laboratory the oral model has been integrated with existing models of the extrathoracic region (ie, nasal, pharyngeal, and laryngeal passages) and lung airways to create a morphological model of the entire respiratory system.

Animation tools within Maya Unlimited provide a good first approximation of 3D fluid motion within oral passages, when compared to subsequent CFD analyses using Fluent. Hence, we feel that Maya Unlimited has great potential for use in the medical arena, because it requires neither advanced technical training nor substantial peripheral (eg, hardware) support required for scientifically traditional (ie, more rigorous) CFD analyses. We emphasize that we do not advocate that the more scholastic and comprehensive software be neglected. We are merely encouraging others to recognize the benefits offered by less rigorous software in the real world, especially in the clinical arena, where the emphasis is properly placed on the timely treatment of patients with the best available techniques.

It must be noted that the efforts described above are quite different from the earlier modeling of Martonen[39] and others, as reported in the open literature. In such works the deposition patterns of inhaled aerosolized drugs were based on prescribed flow patterns within the human respiratory system. That is, based on scientific observations, airstreams were classified as being either turbulent or laminar, and if laminar, certain velocity profiles (ie, uniform,

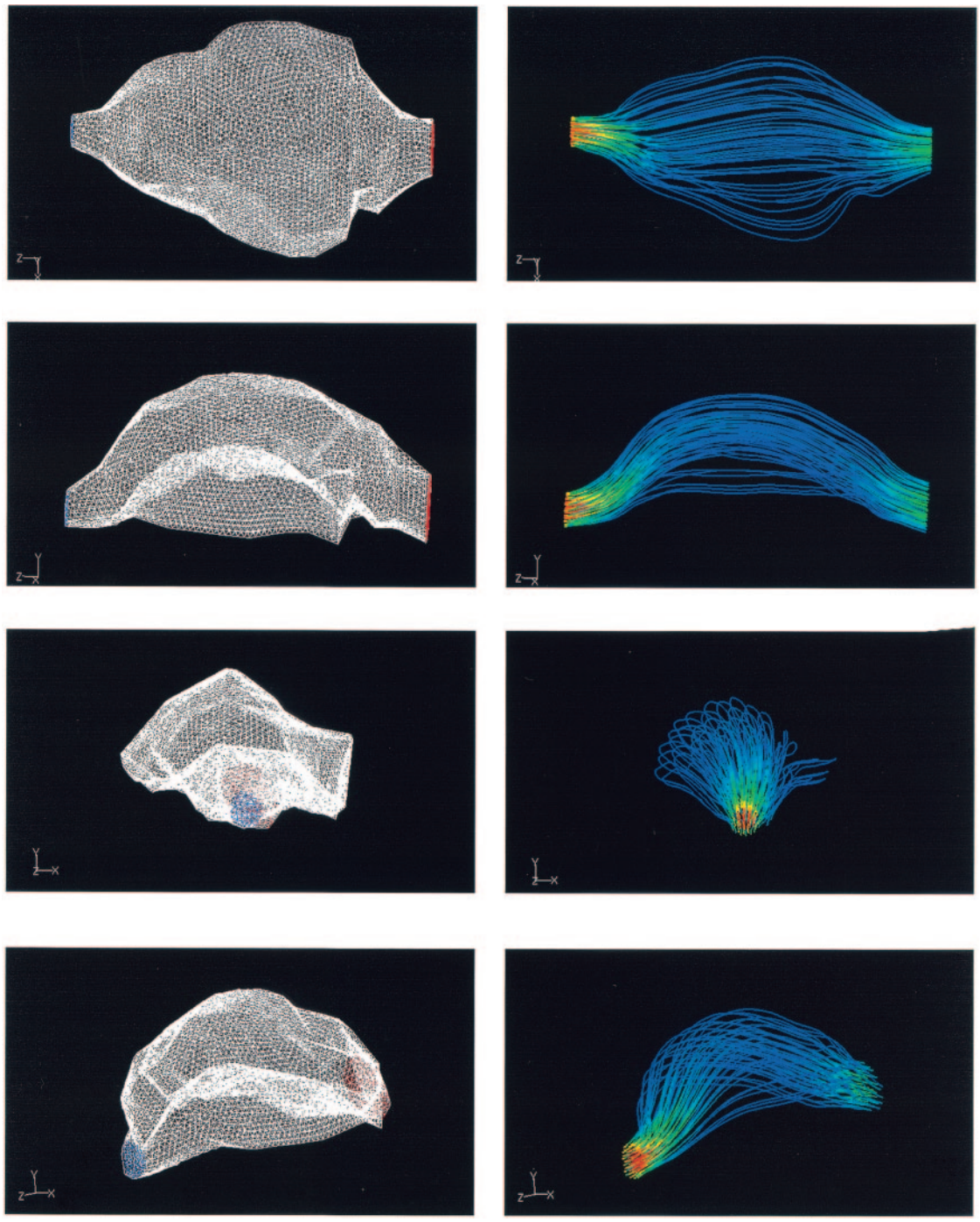

Fig. 15. Computational fluid dynamics (CFD) simulations created with Fluent software. Left column, top to bottom: The grid networks employed for computational purposes within the mouth are shown for top view, side view, front view, and perspective view. Right column, top to bottom: The streamlines of particles for the respective orientations.

developing, or parabolic) were assigned for use in particle-deposition computations. With the availability of CFD software (eg, Fluent), newer models can be based on the calculation of, rather than the assumption of, flow conditions. Indeed, such CFD models are the backbone of current modeling work in our laboratory. It should be acknowledged, however, that the older models have certain advantages, being faster, not requiring CFD software, and operating on simpler (eg, laptop) hardware platforms. Therefore, the older models may, in fact, have characteristics that clinicians find highly desirable for immediate implementation in hospital environments.

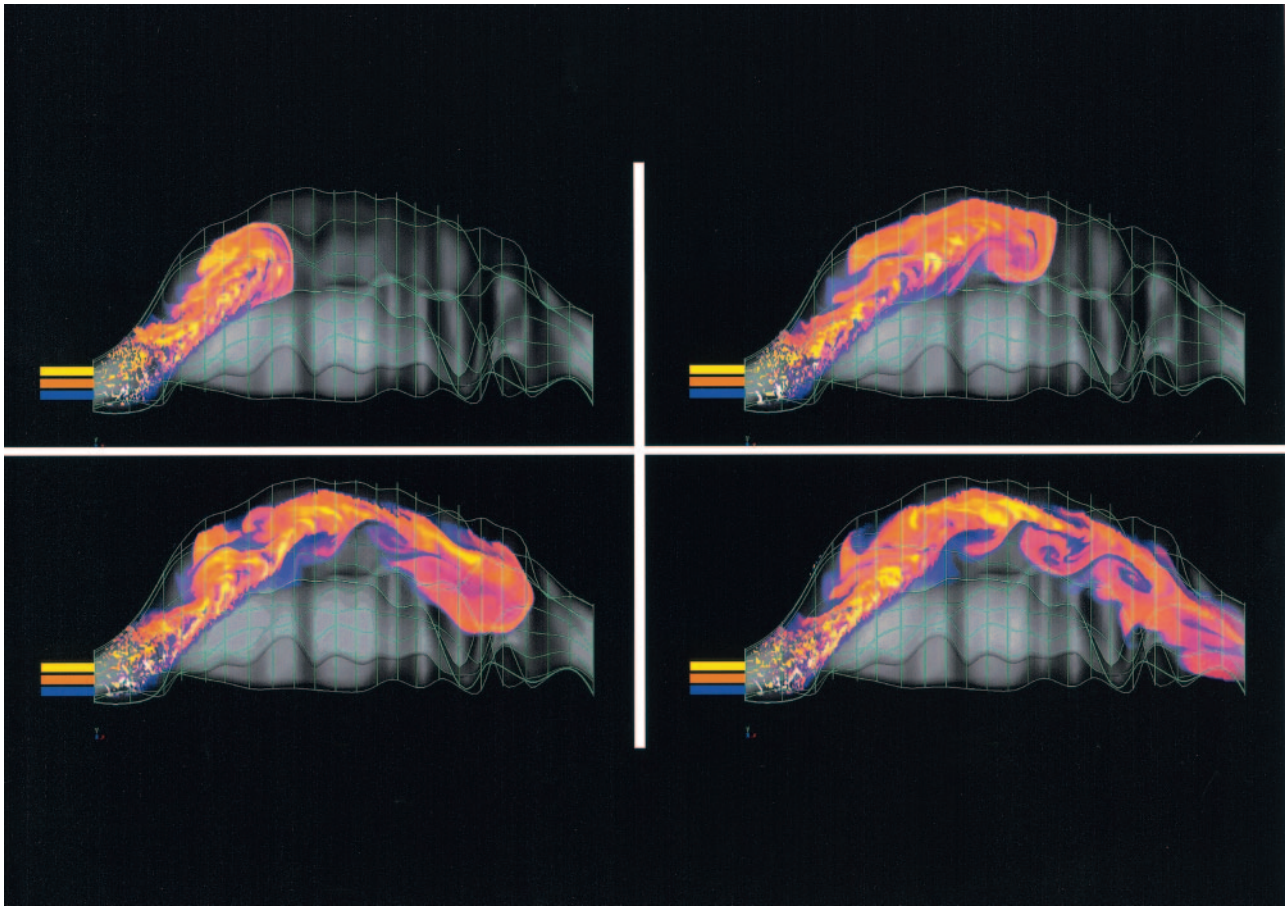

Fig. 16. Three-dimensional computational fluid dynamics (CFD) within the human oral cavity, as mapped with Maya Unlimited software. The tracer colors indicate particles for illustrative purposes.

The results of this study will be integrated with the previous accomplishments of our laboratory, in which 3D morphology, 3D CFD, and 3D particle transport were examined in (1) the nasal, pharyngeal, and laryngeal passages[15] and (2) lungs.[2] The anatomical computer model is shown in Figure 18. In it, the respective components of the respiratory system, previously analyzed separately, are presented in a contiguous format.

Empirical

It has been well recognized that an important fraction of inhaled particle mass may be deposited within the upper respiratory tract and that, therefore, a quantification of drug losses in the head and throat should be incorporated into MDI and DPI protocols. Because of the great complexities of the morphologies of the nasal, oral, pharyngeal, and laryngeal passages, modeling had been rather limited until the arrival of CFD software packages, as considered, for example, in this work. Previously, empirical expressions were derived, as outlined below.

Let the inhaled aerosol mass administered to a patient, as produced by an MDI or DPI, be written as $M_{inhaled}$. Then, the aerosol mass penetrating to the trachea, or entering the lungs, $M_{trachea}$, may be expressed as:

$$M_{trachea} = M_{inhaled} [1 - CE_{mouth}] [1 - CE_{larynx}] \quad (2)$$

where CE_{mouth} and CE_{larynx} represent the collection efficiencies of the mouth and larynx, respectively, as defined in the following text. Following a review of data, empirical formulae presented by Martonen[40] were expressed using an inertial parameter equal to the product of the particle density (ρ, g/cm^3), the square of the particle geometric diameter (d_g, μm), and the volumetric flow rate (Q, cm^3/s). For $\rho d_g^2 Q < 1.67 \times 10^3$, CE_{mouth} was negligible. For $1.67 \times 10^3 \leq \rho d_g^2 Q \leq 10^4$

$$CE_{mouth} = 0.496 + 0.154 \log(\rho d_g^2 Q) \quad (3)$$

and for $\rho d_g^2 Q > 10^4$

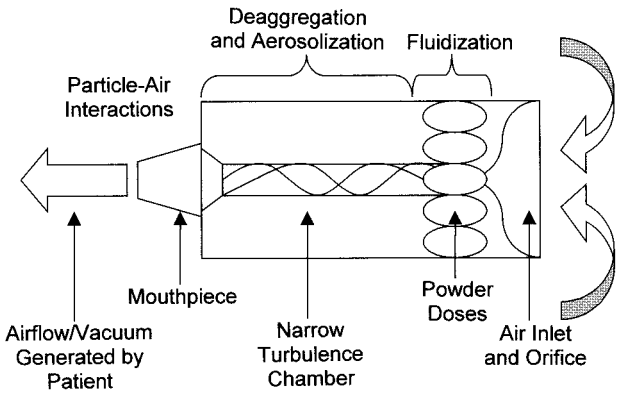

Fig. 17. Schematic of the basic components leading to aerosolization in a passive dry powder inhaler. The patient inspiration through the device mouthpiece generates a pressure differential that gives rise to an airflow through the channels in the device. These channels originate on the opposite side of the device from the patient, and the air may be drawn through an orifice that focuses the incoming air onto the dose of powder to be aerosolized. Fluidization and particle deaggregation occur when the powder is entrained into the air stream and substantial shear is present. Turbulence channels are often included in device designs to improve deaggregation via shear forces.

$$CE_{mouth} = 2.988 + 0.777 \log(\rho d_g^2 Q) \quad (4)$$

By measuring particle deposition within replica laryngeal casts, it was determined that

$$CE_{larynx} = 0.035 + 3.9\ Stk \quad (5)$$

The particle Stokes number is defined as $Stk = \rho D_g^2 W / 18\mu R$, in which W is particle velocity (in cm/s), R is a flow-dependent dimension that characterizes the glottic aperture (in cm), ρ is particle density (in g/cm^3), D_g is particle geometric diameter (in μm), and μ is air viscosity (g/cm·s). Although in use for more than 20 years, the formulae are in good agreement with recent databases and have the advantage of being simple for use in the clinical arena. Recently, the above formulae were adapted for children.[6]

Other empirical models of aerosol deposition in the head and throat have been developed. For instance, in the International Commission on Radiological Protection 1994 radiological protection model, empirical formulae for both nasal and oropharyngeal-laryngeal deposition were formulated.[41] The latter would correspond approximately to our upper respiratory tract. At this juncture we should comment briefly on terminology. Such a combination of the oral, pharyngeal, and laryngeal regions is not uncommon. But in some institutions those respective anatomical components are treated separately, whereas in other laboratories certain components may actually be neglected. This often makes direct comparisons between aerosol-deposition data within airways of the head and throat from different investigators very difficult. The oropharyngeal-laryngeal deposition formulae were derived from data from a number of cited experimental studies. For adults, the deposition was formulated as

$$CE_{URT} = [(1 - \exp(-0.00011 d^{2.8} Q^{0.84} V_T^{-0.28})^2 + (1 - exp(9 d^{0.5} Q^{-0.125})^2]^{0.5} \quad (6)$$

where CE_{URT} is the collection efficiency of the upper respiratory system, d is the particle aerodynamic diameter (in μm), Q is the volumetric flow rate of the air entering the mouth (in mL/s), and V_T is the lung tidal volume (in mL).

A difficulty with empirical formulae is presented by ambiguities in the experimental findings, which are the very basis of the expressions. For example, deposition in the mouth has frequently been measured by rinsing and gargling after inhalation exposures with radiolabeled aerosols. A natural question is, to what extent do the data represent deposition in regions other than the mouth, for example, in the larynx? To address this specific point, Martonen[40] employed replica laryngeal casts. In any event, there is a clear need for an unambiguous way to determine losses in the upper respiratory tract, and in silico modeling using CFD software may provide a viable solution.

In Vitro Investigations

Testing and in Vivo Performance

Techniques. Aerosol deposition in the airways is primarily determined by inertial deposition, sedimentation, and diffusion.[42] The diffusion deposition mechanism (Brownian motion) is most relevant for particles with geometric diameters < 1 μm, and therefore only affects a small fraction of the dose in therapeutic aerosols.[43] Inertial impaction and sedimentation (gravitational) mechanisms are primarily influenced by kinetic and mass properties and can be expressed in terms of particle aerodynamic diameters. As a consequence, in vitro performance evaluations of therapeutic aerosols involve characterizations of aerodynamic particle size distributions. For most regulatory agencies the preferred method of determining aerodynamic particle size distributions is via multi-stage cascade impaction devices.

As mentioned previously, it is critical for manufacturers to establish that their inhaler products can deliver drug reproducibly, and that the delivered drug is efficacious and safe. In general, in vitro methods such as aerodynamic particle-size analysis are used to demonstrate a product's

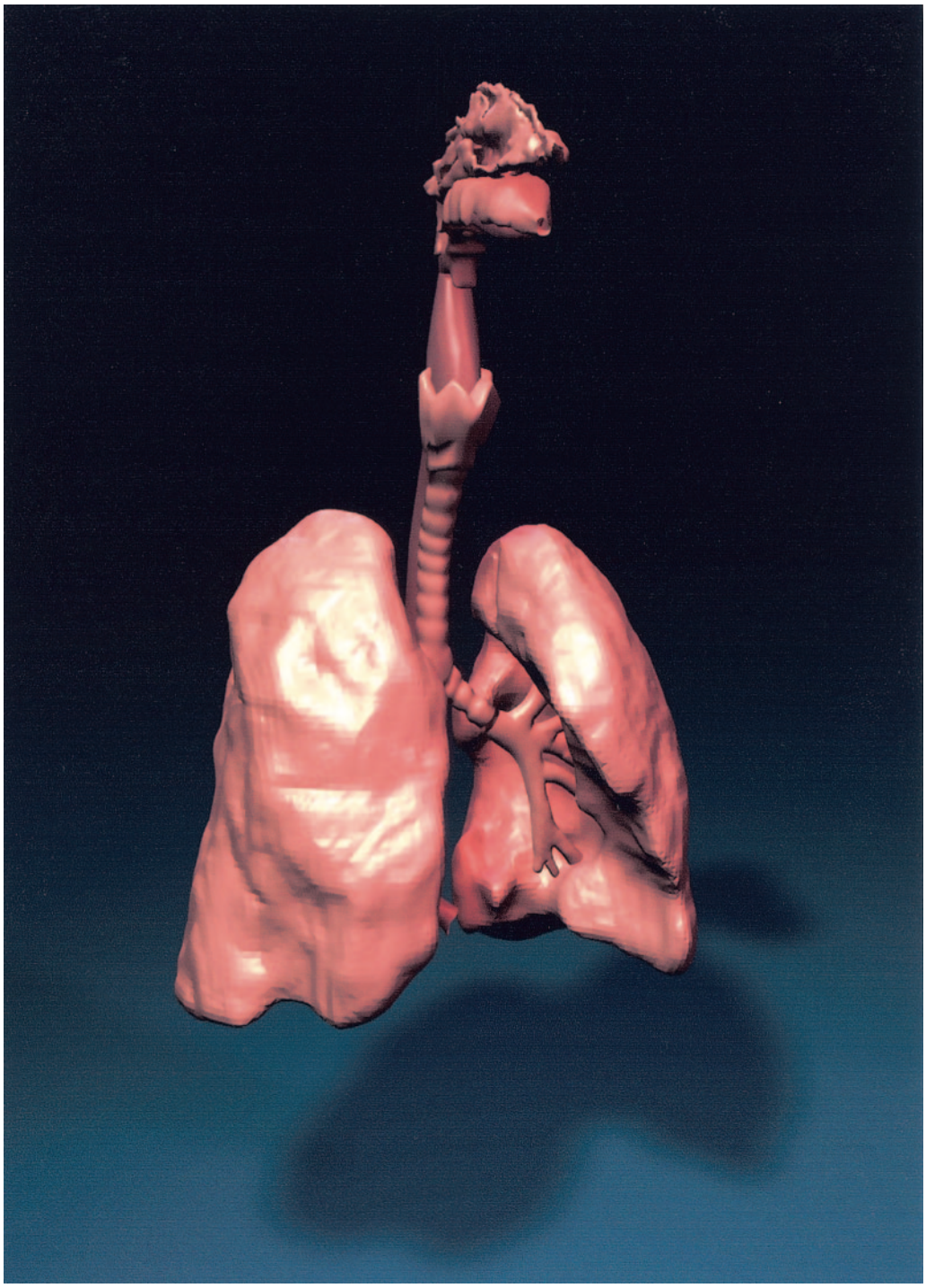

Fig. 18. Three-dimensional computer reconstruction of the entire human respiratory system.

dosing variability characteristics, while in vivo studies are used to establish efficacy and safety.[44]

Correlations. Several comprehensive reviews have investigated the possible correlations between in-vitro-determined particle sizes with in vivo lung deposition and clinical efficacy studies.[44–46] In general, there has been poor agreement between in vitro and in vivo deposition data for a number of reasons. The geometry of in vitro particle-sizing instruments is very much different from anatomical equivalents in human subjects. Specifically, the "throat" inlet port used for cascade impactors does not

reflect the geometry of the oropharynx.[43,47] The fine-particle dose (defined as the amount of drug with an aerodynamic diameter < 5 μm), measured with a cascade impactor, is highly dependent on the geometry of the inlet to the impactor. For example, the fine-particle dose is considerably lower when a cast of a human throat (an "anatomical throat") is used than when a standard glass inlet is used.[48] Also, flow profiles within the cascade impactors do not represent patient inspiratory efforts.[49] Various other influences, including particle bounce, re-entrainment, and pre-separator losses, have also been attributed to errors that result in poor correlations with in vivo studies.[43] Newman et al demonstrated the utility of performing lung-deposition imaging studies to bridge in vitro aerodynamic characterization with in vivo efficacy studies.[44]

Fleming et al systematically compared the results of 2-dimensional and 3D scintigraphy methodologies.[50–53] As a component of that effort, mathematical modeling and computer simulations were performed by Martonen et al[54] and Schroeter et al.[55] The findings of the aforementioned collaborative research indicate that in silico modeling can be a valuable tool in the clinical arena, enabling the airway composition and aerosol deposition within independent voxels of a 3D single-photon-emission computed tomography matrix to be determined.

Variability. Variability in DPI performance measures can originate from a wide range of sources. Generally, these sources can be attributed to either (a) device variability, (b) formulation variability, or (c) variability that arises because of patient use. Variability differences that are observed between in vitro deposition data and in vivo deposition studies are most likely due to patient-related factors, as in vitro methods are sensitive to device and formulation nuances. As discussed previously, passive DPI devices have inherent variability because of differences in dispersion efficiencies at different inspiratory flow rates. The Turbuhaler has widely reported operation mechanism and in vitro variability characteristics.[23,25] Although the Turbuhaler shows relatively high in vitro variability, in vivo variability is less than some devices with low in vitro variability, such as propellant-driven MDIs.[56] These comparisons of variability reflect the interface between patient and device. Variability differences observed between devices sharing similar mechanisms of aerosol dispersion (ie, passive DPIs) will also reflect the patient-device interface but are likely to indicate flow-rate dependence, as discussed previously. Thus, the moderate-to-high airflow resistance designs (eg, Turbohaler [AstraZeneca Pharmaceuticals, Wilmington, Delaware] and Handihaler [Boehringer Ingelheim Pharmaceuticals Inc, Ridgefield, Connecticut]) have generally more efficient delivery than the low resistance systems (Spinhaler [Aventis Pharmaceuticals, Bridgewater, New Jersey]; Diskus and Diskhaler [both from GlaxoSmithKline, Research Triangle Park, North Carolina]), but higher efficiencies may also be associated with steeper dependence of fine-particle dose on airflow rate.[57] Clearly, higher airflow dependence may result in higher deposition variabilities because of inter-patient and intra-patient inconsistencies in inspiratory maneuvers.

Comparison With MDI Deposition

DPI performance is often assessed relative to MDI performance. Unfortunately, it is hard to rationally assess the relative performance characteristics between devices, even when meta-analysis has been employed.[58] One of the main criticisms of many recent studies is the continued use of chlorofluorocarbon (CFC) based MDIs as the comparator device. This may be necessitated by the unavailability of a CFC-free product but represents a performance comparison with systems that are not state-of-the-art. In addition, many performance studies are focused on bioequivalence measures, in which the intention is to show "no differences" between products.[58]

A Cochrane review recently compared MDIs to other hand-held inhaler devices for the delivery of β_2-agonist bronchodilators for nonacute asthma.[59] Ninety studies were included, and it was concluded that hydrofluoroalkane (HFA) MDIs were as effective as DPIs and CFC MDIs. This outcome might be anticipated from the steep dose-response curves for this class of formulations (ie, all products get a saturated response). Those authors also highlighted the need for improved study design (ie, statistical power, more randomized controlled studies, washout periods, and adequate outcome reporting) in these comparative studies. At this point there appear to be many gaps in clinical understanding of the different performance of each type of device. A similar review for the effectiveness of inhaler devices in asthma and chronic obstructive airways disease demonstrated no evidence to suggest clinical benefit from any other inhaler device over an MDI in corticosteroid delivery.[60]

A recent study comparing patient preference for CFC MDI, HFA MDI, or DPIs, with 100 patients with obstructive airway disease, showed that the HFA MDI and DPI represented acceptable alternatives to CFC MDIs.[61] Fifty-seven patients preferred a DPI over the HFA MDI, but not all DPIs were equally acceptable. The investigators found that replacing the CFC MDI with the patient's preferred alternative device resulted in a more than 3-fold increase in costs.

Active DPIs

Active DPIs are designed, like MDIs, to provide an energy source to disperse the dose more efficiently and reproducibly than the passive dry powder systems described

so far. Active DPIs have been under development for at least 10 years, and currently no such device has been approved for marketing by the Food and Drug Administration.[62] The motivation for development of an active device, where the influence of the patient's inspiratory effort is minimized, stems from the demand for improved reproducibility by regulatory agencies and also the need to deliver compounds with much narrower therapeutic indices. Several examples of these devices are described briefly here. Nektar's PDS (pulmonary delivery system) (Nektar Therapeutics, San Carlos, California) appears likely to reach the market shortly.[57] This device employs a mechanical pump to compress and release a volume of air through a "transjector" into a powder dose contained within a blister package. The dispersed aerosol enters a chamber, from which the patient inhales. Dura Pharmaceuticals (Elan Pharmaceuticals, San Diego, California) has also developed an active system that uses a breath-actuated high-speed motor-impeller to disperse the powder dose. Both systems have been shown to have efficiencies greater than 50% with certain formulations.[57] A third example, from Oriel Therapeutics (Durham, North Carolina), uses powder-specific vibration frequencies from a piezoelectric polymer to disperse the powder for inhalation.[62]

A number of other devices, with similar diversity of mechanisms of dispersion as the three described here, exist. For active devices to become widely accepted, a multitude of factors need to be addressed, including ease of use by different patient populations, acceptance by regulatory agencies, adequate motivation for clinicians to prescribe, and economic costs relative to alternatives.[63] It seems likely that active DPI systems will address the clinical need and patient interface requirements. It remains to be seen whether economic viability can be demonstrated.

Novel Formulations

Alongside the expansion of the DPI market, the science and engineering of dry powder formulations has also grown. Much of the dry powder formulation advancement has been in carrier systems.[64] Carrier particles may have a discrete interactive excipient function, or the particle may be a matrix particle that includes active drug dispersed molecularly or homogeneously within its structure. These 2 types of carriers aim to produce device-independent formulations and patient-independent delivery, respectively, by facilitating drug dispersion or targeting.

Interactive carriers are commonly milled or sieved lactose particles with beneficial aerodynamic characteristics to allow drug to be carried into an airstream, where they can be dispersed and inhaled. Traditionally, interactive carriers have been modulated primarily by controlling particle size. Recent alternative strategies include the addition of ternary components to modulate the interactions between drug and carrier particles,[65] modification of carrier surfaces,[66,67] and particle engineering approaches.[68]

Matrix particle carrier formulations have also received widespread attention. A recent review of these technologies designed for targeted deposition and improved therapeutic outcome has been published.[64] Liposomes,[69] microparticles,[70] nanoparticles,[71] aerodynamically small macroparticles,[72] complexation carriers,[73] and permeation enhancers[74] are the tools that are under development and may be used to counteract inter-patient variability and barriers to disease treatment.

Insulin

There are at least 6 products under development for the treatment of insulin-dependent diabetes with an inhaled aerosol. The current method of administration is via injection, and inhaled administration methods have clear advantages for convenience, compliance, and long-term control of the disease. The most advanced of these development programs seems to be that between Aventis, Pfizer, and Nektar Therapeutics. One inhaled insulin product, Exubera, is an short-acting insulin preparation for the treatment of type 1 and type 2 diabetes. Phase III development of Exubera has been completed. However, because of concerns about the drug's long-term pulmonary safety, filings for regulatory approval in Europe and the United States have been put back several times to allow for more safety data to be obtained.

An approved inhaled insulin product is seen by many as a milestone that would signal the readiness of therapeutic aerosols to be considered a practical delivery strategy for the biotechnology industry. If these predictions are accurate, the market for respiratory drug delivery, and in particular dry powder aerosols, will expand further than previously thought and currently observed. The straightforward and seminal point is that insulin is a protein, and once the efficacy of an aerosolized, inhaled protein is established scientifically and accepted by the medical community and pharmaceutical industry, the associated market will expand dramatically. The most obvious products would include antibiotics and drugs for pain control.

SUMMARY

The efficacy of an inhaled drug obviously depends on its being delivered to appropriate sites to elicit optimum therapeutic effects. We have addressed salient factors that affect the delivery of aerosolized drugs via MDIs and DPIs, including scientific elements (eg, design of devices, formulation of drugs, dispersion of aerosols) and technical points (eg, performance of devices, effects of relative humidity, influences of flow rate and resistance). To promote the targeted delivery of inhaled drugs, we advocate the use

of in silico modeling in the medical arena. That is, modeling should be employed in a complementary manner with aerosol therapy regimens. Models have evolved with the advent of CFD software, which permits drug dosimetry codes to be evermore biologically realistic. Fluent is a valuable, rigorous CFD code that we have found to be extremely useful to simulate conditions in vivo. However, it may be too complicated for common use and integration with aerosol therapy. Maya Unlimited has the potential to be a useful tool in the study of flow and particle deposition in the respiratory system. Specifically, the program can aid in the rapid development of anatomically realistic models of respiratory system structures derived from medical images, and provide a means of generating first approximations of fluid flow and particle motion. We feel that Maya Unlimited would be of use in the development of aerosol therapy protocols and could be employed in a complementary manner in real-time patient treatment. It is our belief that clinicians employing MDIs and DPIs would benefit greatly from consideration of in silico modeling. It is a valuable tool and could be used, in real time, in the medical arena for the targeted delivery of inhaled drugs for the treatment of respiratory diseases per se (eg, asthma) or for systemic delivery (eg, insulin).

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Discussion

Fink: There are big changes in the temperature and humidity conditions as the aerosol moves through the airways and saturation boundaries in the lung, which could dramatically affect aerosol behavior. Does the model account for that?

Martonen: Yes. Because the lung is a warm, humid environment, there is a transition in temperature and relative humidity, and our map of the transition is based on the peer-reviewed literature. Temperature and relative humidity values within the human respiratory system have been measured, and we reviewed the related literature and, to the extent that data are available, mapped temperature and humidity in the nasal, oral, pharyngeal, and lung compartments. It is extremely important to account for the hygroscopic growth of aerosol particles in the lungs. The environment of the entire respiratory system is in the default case of the 3D respiratory system model.

Fink: What's the definition of "in silico"?

Martonen: "In silico" is a counterpart to "in vivo" and "in vitro." We use it to mean "mathematical modeling" and/or "computer simulation" of a biological system. I don't know whose idea it was, but there are numerous uses of the term in the peer-reviewed literature. The reference is to computer silicon chips.

Smaldone: I am curious about the conditions under which the oropharyngeal fluid dynamics were displayed. The MDI sprays particles all over the oropharynx, and some of the particles are carried by the patient's breathing into the lungs. Are those eddies you showed caused by the MDI spray, the patient's breathing, or both? What do the eddies mean for your model?

Martonen: We considered various cases. In Figure 16, aerosol was being emitted into a stationary reservoir, so patient breathing was not affecting the plume. In all these 3D fluid dynamics simulations you have to appropriately define your terms. The control case is that the patient is not inhaling, so I ejected the plume into the mouth and got these particular fluid dynamics patterns. In other simulations I built on that and had the patient inhale to see the simultaneous effects.

Smaldone: Did the mouth then decompress from that plume, or did you just assume that there is no pressure buildup in the mouth?

Martonen: The conditions depended on the particular problem being considered. In Figure 16 there is no pressure built up in the mouth. As you are correctly suggesting, a key factor in the simulations is relative motion, as it affects the shear layer between the ejected aerosol and air in the mouth.

Rubin: Beautiful, nonlinear fluid dynamics.

Martonen: I will be happy to do that work—given the funding.

Rubin: CT is very good at imaging the lungs. When you build your in silico images, do you think you could remap the airway and how it changes in the disease state?

Martonen: I agree. The work at Southampton is done as follows. First, John Fleming at Southampton General Hospital and Joy Conway at Southampton University do MRIs of the left and right lungs—the bounding envelopes. Then, what I used to do was use my branching algorithm for the internal 18–20 million airways, based on either a Horsfield or Weibel morphology. Now we use high-resolution CT to measure the trachea, main and lobar bronchi, and distal generations of segmental and subsegmental bronchi; they give me data as deep as they can go. Southampton sends me the CT data via the Internet, and then comes the tricky part. To the high-resolution CT data, which ends at about generation 7 or 8, we use the computer algorithm to "tack on" an idealized branching network to represent the rest of the lower airways. Using the known volumes of the right lung's 3 lobes and the left lung's 2 lobes, I reconstruct the composite airway network. And the mucus layer is simulated too.

Rubin: So the mucus layer is included in the model?

Martonen: Yes. The mucus layer is present, in the sense that it's got dimensions and it's distributed based on data from the literature. What I didn't mention is that the model also has cilia, and the mucus layer is viscoelastic, modeled with rheological properties, from an engineering perspective. Particles deposited on the mucus layer are moved up and out of the lungs by the cilia. The model's particle-movement rate is based on published data.

MacIntyre: During Gerry Smaldone's presentation I was struck by his picture of aerosolizing cyclosporine to target specific areas of the transplanted lung. Are we close to the time when, if I send you a CT scan and perhaps a ventilation scan or hyperpolarized helium MRI scan, you can tell me what breathing pattern to use and how to position the patient to optimize the aerosol delivery to a transplanted lung? Put another way, with

these scanning techniques can you tell me how the aerosol will respond to various breathing patterns, patient positions, and aerosol characteristics so I can target a transplanted lung or tumor?

Martonen: That's precisely what the in silico model will do. It's merely a matter of time.

Smaldone: I'd like to see one of those patient's data given to you and then, under the conditions under which one of those scans was done, your model come out with the same scan. If you give the model the boundary conditions and breathing pattern, you ought to be able to get down to the nitty-gritty. Those scans are unique for each patient; the combination of forces and events is unique in each patient, so you can't average them all together; you can't smooth them. But if you're going to help Joe Blow and his lungs, you have to really understand the pathophysiology; you ought to be able to predict the data just from basic parameters. I think we're getting close to that.

Martonen: In the Southampton project, John Fleming gets his 3D SPECT data and presents it in a matrix format. They measure the deposition patterns, or quantitate them, and you can see them in color. Then I do my theoretical computations of deposition and assign block values: red, blue, etc. Then we superimpose my theoretical 3D patterns on John's experimental results. Do we get 100% resolution and agreement? I don't know, because when you look at SPECT, or 3D scintigraphy, or voxels, there are critical questions about data interpretation. For instance, how small can a voxel be?

Smaldone: In the cases that Neil is talking about, you have one lung versus the other, or you have a lot of deposition in central airways that you can see, even with planar scintigraphy. Are we at that stage?

Martonen: I can assure you that we are at that stage.

Dhand: But what about looking at individuals? I think this would be a great technique for predicting what would happen in populations. For example, Neil [MacIntyre] has been working on lung transplants: you have a single-lung transplant and you want to see how the deposition of cyclosporine would be affected by X number of parameters.

Smaldone: True, but first we must validate the model. The model must be able to predict the results of scintigraphy scans from real patients with real disease.

Martonen: I concur. I started this presentation with slides from my presentation at the RESPIRATORY CARE Journal Consensus Conference in Bermuda, in 1999.[1] In that manuscript there were comparisons of theoretical predictions with experimental data, such as the Heyder et al database.[2] The model has been validated. In the past few years I have extrapolated, using it to simulate asthma when a physician can describe the location and severity of the disease.[3,4] The point is, in that previous RESPIRATORY CARE paper the model was validated. Now we are simulating disease using a tested model.

But your point is well taken, Gerry; I understand what you and Neil are saying. It doesn't mean that the model should never be tested again, especially when we are looking at diseased lungs. And in the case of asthma, not only is there a physical manifestation of the disease in changing airway caliber, but it affects breathing also. Those conditions actually exist, and the model should always be checked. The key thing is this: there will never be an ultimate mathematical model, because developing a code is an evolutionary process, particularly as computing power and speed increase; we can do things today that we couldn't 6 months ago. The important thing to me is that the modeling is not an abstract pie-in-the-sky thing; the in silico model should be in the clinical arena and have medical relevance. And if I want it to be there, it has to be driven by clinicians who trust it and use it. That's what's important to me.

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Lacke:* It is pretty exciting where that can go. Big imaging companies do 3D CT scanning and such. Have you engaged them to see if they can turn your modeling into something that's compatible with new imaging techniques? Real-time imaging that would allow clinicians to improve therapies would be important. From a manufacturer's perspective, what sort of device could this lead to?

Martonen: No, I have not contacted them. I am waiting for them to contact me.

Lacke: Do they know you're there?

Martonen: I'm here. That's the candid answer. My friends in the audience are laughing because they know I have been doing this for about 20

* Steve Lacke, Cardinal Health, McGaw Park, Illinois.

years now, and we always joke about difficulties in getting companies interested in this. As far as I am concerned, F = ma; always has and always will. Therefore, if you believe in the laws of physics, you can target the delivery of drugs, although there are complications caused by diseases and other factors.

Regarding the second part of your question—the model is a tool. Future medical students will have a white coat, a stethoscope, and a CD with my program on it. Pulmonary medicine is going to be done in real time. The program can help determine the experimental conditions under which tests should be done and aid in interpreting data from PET and SPECT scans, as I am doing with the Southampton staff. We're still actively involved with that project, but from a modeling perspective I have pushed that work as far as I can go right now, primarily based on voxel resolution and associated problems. Plus, I have been working on such issues for years now and I am sort of tired of those mathematical problems. I have switched gears and am working with Tony Hickey now, putting a model head on the model lungs and studying DPIs and MDIs and related problems.

This problem can be either very complex or very simple. I try to keep things simple. I never try to solve anything in 3 dimensions that I haven't solved in 2 dimensions first; I never do turbulent flow before I do laminar flow first. What I want is to target the delivery of inhaled drugs, because I think you can enhance the efficacy of a drug if you can put it where it's needed. If you have a cut on your finger, you put a band-aid on that cut. That's targeted delivery.

Current aerosol techniques deliver large doses to get some drug to the appropriate site, which is analogous to wrapping-up your whole body, like a mummy, to cover a cut on your finger. With targeted delivery we won't have to administer as much drug. As Gerry and others have said today, that never used to be a problem with bronchodilators, because they are relatively safe. But with aerosol chemotherapy and gene therapy and other drugs that are either toxic or expensive, we need targeted delivery, which depends on 3 families of variables: morphology, aerosol characteristics, and ventilation. Ventilation is the key word for patients. DPIs are activated by patient inhalation.

The commonality between in silico and clinical practice is ventilation. The flow rate through the DPI is the flow rate at which the aerosol enters the lungs. If a physician can tell me where the patient has asthma, then we know where we want the aerosol to go, and since we know the DPI produces certain particle sizes, we can calculate deposition patterns in the lungs. Then we can say this is how the DPI should function, and develop a device that acts under those flow conditions to target delivery. That's how it all ties together.