

The Computational Simulation of Electrophoretic Focusing and Navigation for Intranasal Target Drug Delivery with Comsol

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Abstract: Direct nose-to-brain drug delivery circumvents the blood-brain-barrier and has multiple advantages over intravenous delivery. However, its application is limited by the extremely low delivery efficiency to the olfactory region where drugs can more efficiently enter the brain. This study evaluated the feasibility and effectiveness of targeted drug delivery with electrophoretic forces in a 2D human nose model. Comsol modules of AC/DC Electromagnetics, CFD, and Particle tracing modules were used to simulate the effect of electric field arrangements, particle release position, and particle charge on the delivery efficiency. It was observed that applying electrophoretic forces significantly enhanced the dosage to the olfactory region. Electrophoretic-guided delivery achieved olfactory dosages of two orders higher than that without electrophoretic forces. Results of this pilot study hereof have implications for the development of effective intranasal drug delivery devices that target at olfactory epitheliums.

Keywords: Comsol, CFD, AC/DC, Particle Tracing, Olfactory deposition, direct nose-brain delivery, medical devices, electrophoretic guidance, nasal drug delivery.

1. Introduction

Intranasal olfactory drug delivery provides a noninvasive practical method of bypassing the BBB and directly delivers the medications to the brain and spinal cord. However, device designed for olfactory delivery has not yet been found. The limitations of conventional nasal devices are obvious; only a very small fraction of therapeutic agents deposit in the olfactory region and enter the brain. Previous studies (1, 2) have shown that less than 1% of nasal-inhaled particles could reach the olfactory nerves which are secluded in the upmost part of the nasal cavity (Fig. 1a). Therefore, it is critical to search for more effective methods to deliver drugs to the olfactory region.

The limitation of conventional inhalation drug delivery devices depend solely on the aerodynamics of the inhaled flow to direct therapeutic aerosols to the target site. The three major forces acting on the particles are particle inertia, drag force, and gravity. There is no control on the trajectories of these particles once they have been released from the inhaler devices such as a nebulizer, powder inhaler, or pressurized metered-dosed inhaler. Accordingly, how far a particle travels, or where it ends up primarily depends on its initial velocity and the nasal airway structure. Due to the lack of control, a significant amount of medication is wasted in the upper airway and doesn't reach to the targeted receptor tissues.

Electrophoretic force on charged nanoparticles can be dominate, which makes it possible to remotely control inhaled aerosols. The smaller the size of the particles, the more they are influenced by the electromagnetic force because of the negligible effect of other forces (3). It is hypothesized that with an appropriate external electric field, charged nanoparticles can be precisely guided via electrophoretic forces and maneuvered through the nasal passages without loss into the airway walls. The required electric field can be achieved by carefully arranging multiple electrodes with different electric potentials around the nose.

In this study, we will 1) develop a computational fluid dynamics (CFD) model of electrophoretic-guided drug delivery; and 2) numerically evaluate the efficiency of the electrophoretic-guided drug delivery in a two-dimensional nose model both with Comsol.

2. Problem Description

2.1 Image-based nasal airway model

Head MRI scans of a healthy non-smoking 53-year-old male (weight 73 kg and height 173 cm) were used in this study to construct the nasal airway model (Fig. 1b). The multi-slice MRI scans were first segmented using MIMICS (Materialise, Ann Arbor, MI) into 3-D model, which was further converted to a set of contours

that define the airway of interest. Based on these contours, an internal surface geometry was constructed in Gambit (Fig. 1c). The resulting model is intended to faithfully represent the anatomy of the nasal airway with only minor surface smoothing.

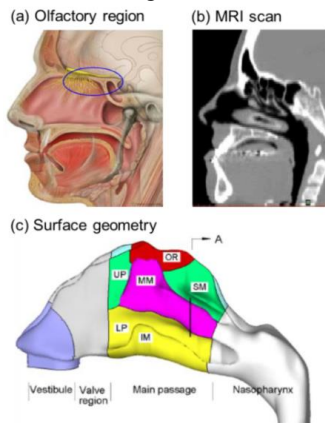


Figure 1. Nasal airway physiology: (a) anatomy; (b) MRI scan; and (c) surface model geometry.

2.2 Electrophoretic delivery protocol

A simple device of such delivery protocol will consist of components with the following four functions: (a) aerosol generation (inhaler), (b) particle charging, (c) particle focusing, and (d) particle navigation (Fig. 2). More elaborate devices can add supports to stabilize the device relative to human head. Particles are to be generated using available inhaler devices such as a nebulizer, pMDI, and dry powder inhaler (4). The particles then pass through a charging chamber and acquire a given number of charges (usually positively charges) (5). The positively charged particles subsequently enter the focusing chamber that has multiple slits (6). The first slit has a high positive voltage and the last one has zero voltage. As the particles pass through the slits, the inward repulsive force drives the aerosol into a finely focused beam; meanwhile the forward repulsive force accelerates the particle beam to a certain exit speed (or inlet speed into the nostrils). The advantage of knowing the nasal inlet speed is that the particle trajectory can be predetermined for a given release point. Yet another advantage is that the speed of an aerosol could be much higher than the inhaled air speed so that it does not rely on inhalation maneuvers, making it suitable for seniors or patients with respiration difficulties. Once entering the nasal cavity, the particles are

subjected to the electrophoretic force and begin to deviate from their original trajectories in a controlled manner (i.e., particle guidance). A precise control of the path deviations will guide the particles to the targeted olfactory receptor with minimal loss to the nasal valves and turbinates.

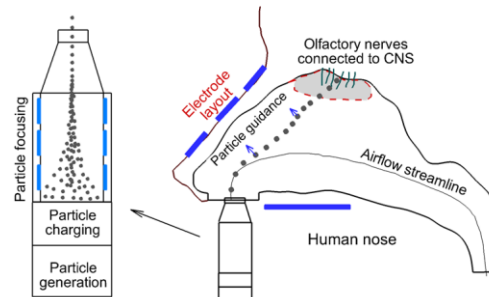


Figure 2. Diagram of electrophoretic guided drug delivery.

3. Use of COMSOL Multiphysics

To solve the metaphysics involved in this study, Comsol (Burlington, MA) was used to simulate the relevant multiphysics that include airflow, electric force, and particle tracing. The modules of AC/DC Electromagnetics, CFD, and Particle tracing modules were used. The inhalation flow rate was assumed steady and under quiet breathing condition. The particle diameter is $0.5 \mu\text{m}$ and electric charge number is 5000. To test the electrophoretic intranasal delivery protocol, four electrodes were arranged around the nose. The electric potentials were set to -3 V , -8 V , -12 V , and 0 V , respectively. Convergence of the flow field solution was assumed when the global mass residual was reduced by four orders of magnitude and the residual-reduction-rates for both mass and momentum were sufficiently small. The computational mesh was generated in Comsol in multi-domains with a physics-controlled manner. The nasal airway was discretized based on fluid physics, and the remaining domains (electrodes and open space) were based on general physics. To resolve the possible steep gradients of flow variables in the near-wall region, body-fitted mesh was also utilized. In light of the high complexity of the nose morphology, corner mesh refinement was implemented throughout the model geometry.

4. Results

The feasibility of electrophoretic focusing and guidance was first tested in a quadrupole geometry (Fig. 3), in which the trajectory of charged particles can be manipulated by varying the electrode arrangements. In this application, the applied voltage was 12 V and the particle size was $0.5 \mu\text{m}$ with 5,000 elementary charges. The inlet velocity of the airflow and charged particles was 0.1 m/s. The electric field and particle trajectories in the quadrupole geometry are shown in Fig. 3 for three test cases with different electrode layouts. In the first trial, we tested the sensitivity of charged nanoparticles to the electrophoretic guidance by varying the electric fields in both direction and strength. In doing so, eight groups of electrodes were arranged along the curve so that different voltage combinations can be specified. In Fig. 3a, the two opposite electrodes had the same voltage (12 V or -12 V). Similarly, a zero electric field was achieved along the curved centerline. The particles were concentrated within this field and at the same time were guided toward the exit, maneuvering through the curvatures by overcoming the inertial force.

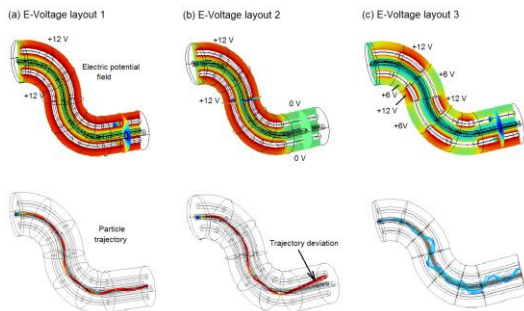


Figure 3. Electric field and particle trajectories within the quadrupole with varying electrode voltage layouts.

In the second trial (Fig. 3b), we removed the voltage from the last two electrode groups to verify the indispensability of electrophoretic forces in particle focusing and navigation. As expected, without electrophoretic forces, particle trajectories departed from the centerline, indicating a break of force balance between the electrophoretic and inertial forces. A careful inspection of Figs. 3a&b further revealed this delicate force balance, which was manifested in the wavelets or fluctuations of particle trajectories along the curved centerline.

The third trial tested the capacity of electrophoretic forces in modifying particle trajectories by adjusting the electrode layout and/or strength (Fig. 3c). In this test, the two opposite electrodes in the same group had different voltages (12 V, 6 V), with the two neighboring groups alternating the voltage arrangement, as shown in Fig. 3c. It was observed that the particle trajectories were indeed modified which largely followed the resultant zero-E field. This is desirable because it provides a promising tool in guiding the drug particles through the convoluted nasal passages and navigating them away from the intruding nasal turbinates. A possible disadvantage of this method is that the level particle focusing might be compromised, as shown by the more erratic and dispersive particle traces in Fig 3c.

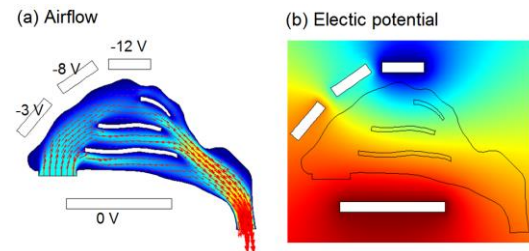


Figure 4. Airflow (a) and electric potential field (b) in the 2-D nose. The red color represents zero volts and the blue color represents negative potential.

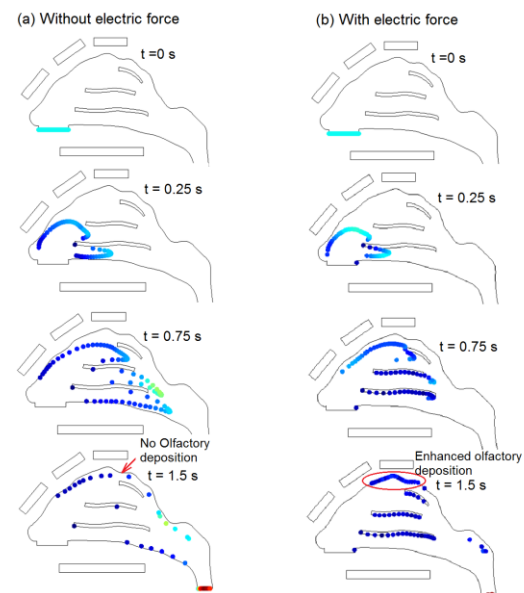


Figure 5. Particle trajectories at different instants after release without and with electric forces.

Figure 4 shows the airflow and electric potential field in the 2-D nose. The E-field is observed to change from nearly 0 V at the nostrils to nearly -12 V at the olfactory region. The small voltage differential (3 V) in the nasal vestibule was to provide a slight driving force toward the upper nasal cavity while at the same time trying to avoid particle collisions with the vestibule. The voltage differential increased to 8 V after the nasal valve region to further guide particles toward the olfactory region.

Figure 5 shows the snapshots of particle positions at varying instants from their release at the nostrils. The particle profiles with and without electrophoretic forces appear similar initially ($t = 0.25$ s). The deviation becomes apparent thereafter and continues to increase till 1.5 s. Due to the increasing upward electrophoretic force, a majority of the particles impinge on the three nasal conchae (or turbinates), and only a small portion of particles (~14%) reach the olfactory region. In contrast, there is almost no deposition in the olfactory region without electrophoretic guidance.

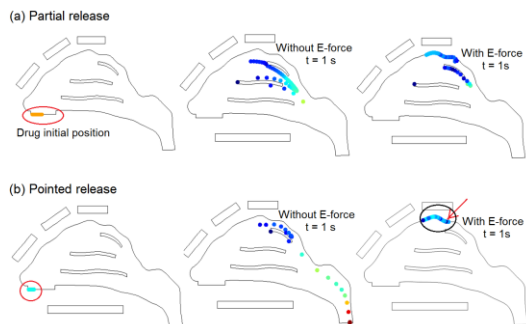


Figure 6. Particle trajectories without and with electric forces: (a) partial release; (b) pointed release.

Notice that the conchae depositions are predominately from particles that are released at the lower half of the nostril, it is natural to conceive that avoiding releasing drug from this region will decrease unwanted depositions in the nasal conchae. Figure 6a shows the scenarios of partial drug release from the upper nostrils only, which significantly reduces the deposition in the middle concha and almost eliminate the deposition in the inferior concha. In the case of electrophoretic guiding, partial release delivers about 45% drugs to the olfactory region, with the reminders (~55%) deposit on the superior concha. In light of the 55% waste, we further

refine the drug release area so that all particles from that area could navigate through the nasal passages and reach the olfactory region. Figure 6b shows the particle dynamics one second after their release from a pointed region at the tip of the nares. Nearly all electrophoretic-driven particles from this region (~95%) deposit on the olfactory region. In contrast, only 0.77% particles from this region end up in the olfactory region, with the rest being inhale into the lung.

5. Conclusions

This study studied the feasibility of targeted drug delivery with electrophoretic forces in a 2-D nose model. The influences of electric fields-, drug-release positions, particle sizes and initial velocities were examined and compared. Specific findings of this study are:

1. It is practical to focus and guide nanoparticles with voltage that is safe to human body (<12 V).
2. With appropriate electrophoretic guidance and selective drug release, significantly improved olfactory dosage could be achieved.
3. Comsol multiphysics plus different modules is an effective and powerful tool in doing this simulation and achieving meaningful results. They are great helps in making others clearly visualize the effect and efficiency of drug delivery with electrophoretic focusing.

6. References

1. Shi H., Kleinstreuer C., Zhang Z. Laminar airflow and nanoparticle or vapor deposition in a human nasal cavity model. *Journal of Biomechanical Engineering*, **128**,697-706 (2006)
2. Si X., Xi J., Kim J., Zhou Y., Zhong H. Modeling of release position and ventilation effects on olfactory aerosol drug delivery. *Respiratory Physiology & Neurobiology*, **186**,22-32 (2013)
3. Xi J., Longest P.W., Anderson P.J. Respiratory Aerosol Dynamics with Applications to Pharmaceutical Drug Delivery. In Fanun M (ed) *Colloids in Drug Delivery*. CRC Press, 501-26 (2010).
4. Geller D.E. Comparing clinical features of the nebulizer, metered-dose inhaler, and dry

powder inhaler. *Respiratory Care*, **50**,1313-21; discussion 21-2 (2005)

5. Covert D., Wiedensohler A., Russell L. Particle charging and transmission efficiencies of aerosol charge neutralizers. *Aerosol Science and Technology*, **27**,206-14 (1997)

6. Zeng Y., von Klitzing R. Scaling of layer spacing of charged particles under slit-pore confinement: an effect of concentration or of effective particle diameter? *Journal of Physics-Condensed Matter*, **24** (2012)