ParCFD2024
35th International Conference on Parallel Computational Fluid Dynamics
Sep. 02-04, 2024, Bonn, Germany

Computational Modeling of Particles Fate in Nasal Drug Treatments

Silvia Ceccacci[a], Jose Angel Vicente Porres[b], Nerea Rio Grela[c], Hadrien Calmet[a], Abel Gargallo Peiro[a], Clement Rigaut[d], Benoit Haut[a], Guillaume Houzeaux[a] and Ane Beatriz Eguzkitza[a,*]

[a]*Barcelona Supercomputing Center, 1-3 Plaça d'Eusebi Güell, 08034 Barcelona, Spain*
[b]*Universitat Polítecnica de Catalunya, Facultat d'Informatíca de Barcelona, B6 Building Campus Nord, C/Jordi Girona Salgado, 1-3, 08034 Barcelona, Spain*
[c]*Universitat Autónoma de Barcelona, Department of Mathematics, Building C Science Faculty, 08193 Bellaterra, Barcelona, Spain*
[d]*Transfers, Interfaces and Processes Laboratory, Université Libre de Bruxelles, Avenue F.D. Roosevelt, 50, 1050 Bruxelles, Belgium*

ARTICLE INFO[†]

Keywords:
Computational Fluid Dynamics;
Numerical Modeling;
Multi-Scale;
Multi-Physics

ABSTRACT

The present work is one of the three pieces (upper airways, lower conductive and respiratory zones) of a digital twin lung model developed by the *Physical and Numerical Modelling* research group of the CASE department at the Barcelona Supercomputing Center (BSC). In this study, we focus on the upper airways, and we present a computational model to analyze the fate of particles in nasal drug treatments. By integrating fluid dynamics with particle transport algorithms, the computational model, implemented in the in-house code Alya, aims at predicting the particles behavior, from their interactions with the nasal cavity walls considering mucus layer, to their deposition and ultimately their fate once deposited. This work is framed within the project *DREAMS: Particle Deposition Computational Model for ChildREn Airways with Mucus Surface.*

1. Introduction

Inflammatory upper airway diseases, encompassing a range of conditions, such as allergic rhinitis, rhinosinusitis and laryngitis, are estimated to affect around 20% of the global population. The symptoms involve obstruction of the upper airways, resulting in poor breathing capacity, thus inevitably causing poor life quality and high economical costs. Inhalation therapy, including nasal spray treatments, is an attractive approach to treat such respiratory diseases. To improve treatment efficacy, it is crucial to understand the movement of drug particles through the nasal cavity, their interactions with the nasal walls, and their eventual deposition in the Airway Surface Liquid (ASL) layer, which is made of two substrates: mucus layer (highly viscous), and periciliary layer (less viscous). Following deposition, it is important to assess the drug uptake from these particles.

[†]This paper is part of the ParCFD 2024 Proceedings. A recording of the presentation is available on YouTube. The DOI of this document is 10.34734/FZJ-2025-02478 and of the Proceedings 10.34734/FZJ-2025-02175.

*Corresponding author
silvia.ceccacci@bsc.es (S. Ceccacci); jose.angel.vicente@estudiantat.upc.edu (J.A. Vicente Porres); Nerea.Rio@autonoma.cat (N. Rio Grela); hadrien.calmet@bsc.es (H. Calmet); abel.gargallo@bsc.es (A. Gargallo Peiro); clement.rigaut@ulb.be (C. Rigaut); benoit.haut@bsc.es (B. Haut); guillaume.houzeaux@bsc.es (G. Houzeaux); beatriz.eguzkitza@bsc.es (A.B. Eguzkitza)
ORCID(s): 0000-0002-8780-9739 (S. Ceccacci); 0009-0006-4681-4722 (J.A. Vicente Porres); 0009-0008-4329-1668 (N. Rio Grela); 0000-0001-5443-761X (H. Calmet); 0000-0003-3742-2197 (A. Gargallo Peiro); 0000-0003-4999-8601 (C. Rigaut); 0000-0002-3021-0207 (B. Haut); 0000-0002-2592-1426 (G. Houzeaux); 0000-0002-3302-6667 (A.B. Eguzkitza)

2. Particle dynamics modeling

Deposition and uptake processes occur at different time scales. While deposition involves the interaction of drug particles with the nasal surfaces over a short time frame (i.e., seconds), uptake encompasses the gradual absorption of the drug into the ASL, which occurs over a longer period of time (i.e., minutes). By decoupling these processes, we can simulate each phase and provide insights into the effectiveness of nasal drug delivery.

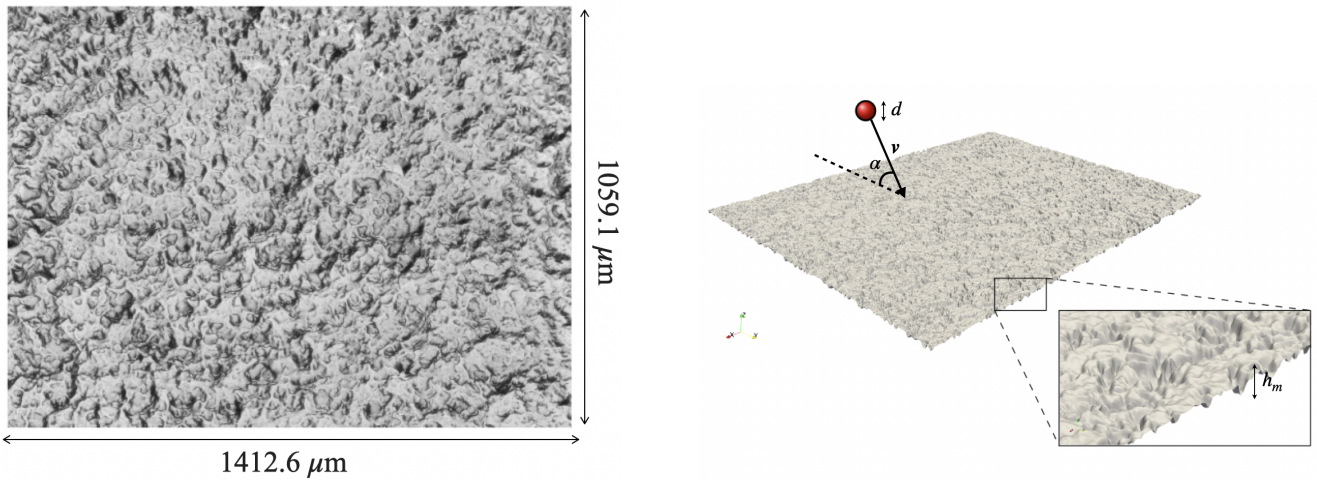
2.1. Particle-wall interaction and deposition model

We propose a computational model for the interaction between solid particles and nasal cavity walls. Unlike conventional approaches that assume a sticking or "deposit-on-touch" condition, our model considers the mucus layer coating the nasal cavity walls. In our approach, a critical collision velocity criterion, based on that proposed by Ohsaki et al. [1], determines whether the particle deposits or rebounds upon colliding with the wall. We define the critical collision velocity as

$$u_{\mathrm{cr}} = \frac{3\pi\mu r_p^2}{2m_p}\left(1+\frac{1}{e}\right)\ln\left(\frac{z}{z_a}\right), \tag{1}$$

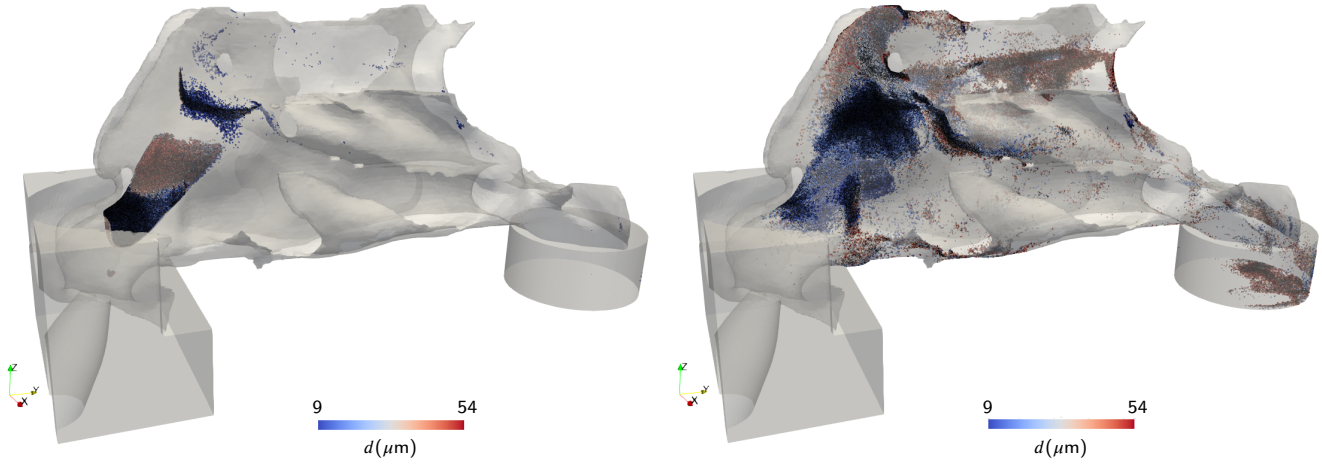
where μ is the mucus viscosity coefficient, r_p is the particle radius, m_p is the particle mass, where ρ_p is the particle density, e is the restitution coefficient, z is the mucus layer thickness, and z_a is the particle surface roughness.

In cases of rebound, the new particle direction is calculated with a statistical model based on the surface roughness



(a) (b)

Figure 1: (a) Microscopic image of the gel coating the 3D nasal cast, simulating mucus layer in the experiments and (b) geometry of the surface roughness obtained from (a), where h_m is the average surface roughness height.

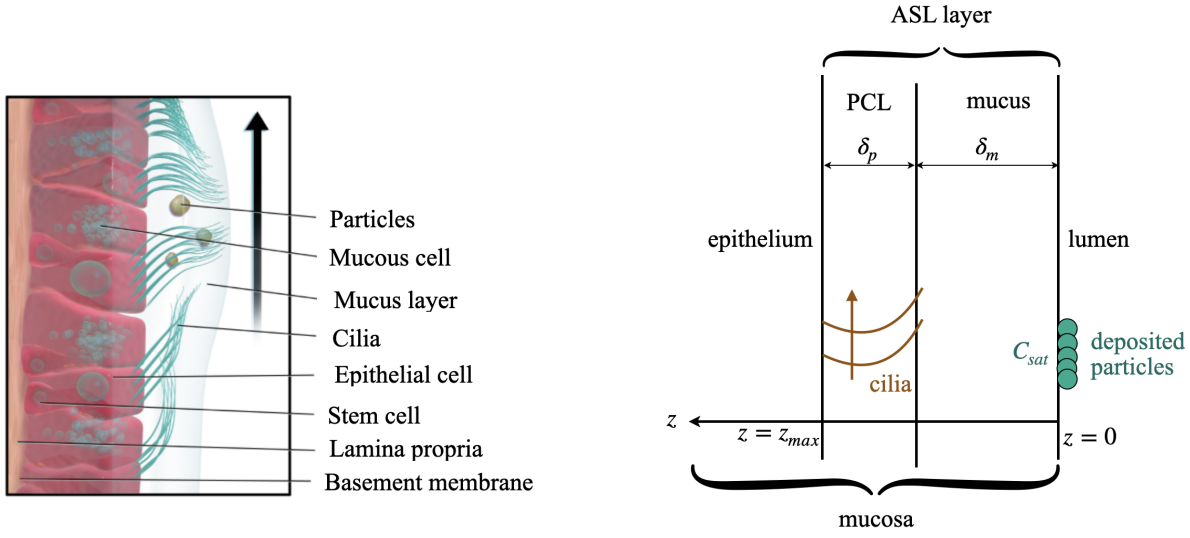


(a) (b)

Figure 2: Deposition maps in a 9-year-old patient nasal geometry, obtained with (a) "deposit-on-touch" condition and (b) particle-wall interaction model, for the flow rate $15L/\text{min}$, where d is the particle diameter (μm).

of the mucus layer [2], illustrated in Fig. 1a. By geometrically characterizing the mucus surface, such model samples the angles of rebound θ and ϕ, in spherical polar coordinates, for a colliding particle of diameter d and angle of attack α (see Fig. 1b). The particle then continues its trajectory within the nasal cavity, gradually losing kinetic energy until it meets the deposition criterion (i.e., $\|\boldsymbol{u}_p\| \leq u_{cr}$, where $\boldsymbol{u}_p$ is the particle velocity), hence it deposits on the ASL layer.

Results. The efficacy of the particle-wall collision rebound model was assessed against experimental results using the same nasal cast geometry (from a 9-year-old patient), for the flow rates of $15L/\text{min}$ and $60L/\text{min}$. A parameter study has been carried out to identify the optimal values for the numerical deposition against the experimental one [3]. In Fig. 2, the deposition maps computed with"deposit-on-touch" and particle-wall interaction models, show a substantial difference in the particles distribution. In addition, the proposed model significantly enhances the accuracy of deposition maps, demonstrating a high level of consistency between the computational predictions and experimental observations.



(a) (b)

Figure 3: (a) Illustration of the mucosa in the respiratory tract and (b) schematic diagram for mathematical modeling.

2.2. Dissolution and diffusion models for deposited particles

Once the particles are deposited on the ASL layer, they are subject to dissolution, diffusion and advection processes [4]. The dissolution of drug particles in a liquid medium, through which they will progressively be reducing their mass and size, is described by the Noyes–Whitney equation

$$\frac{dm}{dt} = \frac{-AD_m(C_s - C_b)}{h}, \tag{2}$$

where m is the particle mass, A is the particle surface area, D_m is the diffusion coefficient, h is the mucus layer thickness, C_s is the drug solubility and C_b is the concentration of the dissolved drug in the bulk phase.

The dissolved particles diffuse across both layers of the ASL towards the epithelium, are advected towards the pharynx due to the mucociliary clearance, and are subject to enzymatic degradation. A diagram of the mucosa is illustrated in Fig. 3a (image adapted from Intersurgical[1]). The diffusion-advection-reaction equation is given as

$$\frac{\partial C}{\partial t} + \nabla \cdot (\boldsymbol{u}C) = \nabla \cdot (D_m \nabla C) + \rho(C), \tag{3}$$

where C is the drug concentration, $\boldsymbol{u}$ is velocity of the mucus and $\rho(C)$ is the reaction term, accounting for the enzymatic degradation. Eq. (3) is solved subject to boundary conditions, such that $C(z = 0) = C_{sat}$, where C_{sat} is the saturation concentration, assuming local equilibrium at the lumen-mucus interface, and $C(z = z_{max}) = kC$, where $z_{max} = \delta_m + \delta_p$, and k is the absorbance of the epithelium (see Fig. 3b).

[1] https://au.intersurgical.com/info/filtrationandhumidification

3. Conclusions

Once the particle-wall interaction and diffusion models are implemented separately, the outlook of this work is to couple them to achieve a more comprehensive simulation. In this integrated approach, the concentration of deposited particles will be evaluated at the nodes of the computational mesh at each time step. These particles will then be iteratively dissolved into the ASL layer and advected through the nasal cavity.

References

[1] S. Ohsaki, R. Mitani, S. Fujiwara, H. Nakamura, S. Watano, Effect of Particle–Wall Interaction and Particle Shape on Particle Deposition Behavior in Human Respiratory System, Chemical and Pharmaceutical Bulletin 67 (12) (2019) 1328–1336. doi:10.1248/cpb.c19-00693.

[2] R. Zhang, Y. Li, Y. Liu, Improvement and application of a two-dimensional fractal particle-wall collision model, Powder Technology 411 (2022) 117910. doi:10.1016/j.powtec.2022.117910.

[3] H. Calmet, D. Dosimont, D. Oks, G. Houzeaux, B. V. Almirall, K. Inthavong, Machine learning and sensitivity analysis for predicting nasal drug delivery for targeted deposition, International Journal of Pharmaceutics 642 (2023) 123098. doi:10.1016/j.ijpharm.2023.123098.

[4] S. Chari, K. Sridhar, R. Walenga, C. Kleinstreuer, Computational analysis of a 3D mucociliary clearance model predicting nasal drug uptake, Journal of Aerosol Science 155 (2021) 105757. doi:10.1016/j.jaerosci.2021.105757.