Development of a CFD Model for Mucociliary Clearance in the Nasal Cavity

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Abstract

Intranasal drug delivery has attracted significant attention because of the opportunity to deliver systemic drugs directly to the blood stream. However, the mucociliary clearance poses a challenge in gaining high efficacy of intranasal drug delivery because cilia continuously carry the mucus blanket towards the laryngeal region. To better understand mucus flow behaviour on the human nasal cavity wall, we present computational model development, and evaluation of mucus motion on a realistic nasal cavity model reconstructed from CT-scans. The model development involved two approaches based on the actual nasal cavity geometry namely: (i) unwrapped-surface model in 2D domain and (ii) 3D-shell model. Conservation equations of fluid motion were applied to the domains, where a mucus production source term was used to initiate the mucus motion. The analysis included mucus flow patterns, virtual saccharin tests and quantitative velocity magnitude analysis, which demonstrated that the 3D-shell model results provided better agreement with experimental data. The unwrapped-surface model also suffered from mesh-deformations during the unwrapping stage and this led to higher mucus velocity compared to experimental data. Therefore, the 3D-shell model was recommended for future mucus flow simulations. As a first step towards mucus motion modelling this study provides important information that accurately simulates a mucus velocity field on a human nasal cavity wall, for assessment of toxicology and efficacy of intranasal drug delivery.

Keywords: Nasal Cavity, Mucus, CFD, Surface-unwrapping
1. Introduction

The highly vascularized nasal mucosa makes the nasal cavity a viable route for local and systemic drug delivery. In-vitro (Shah et al., 2014) and computational studies (Dong et al., 2018a, b; Ge et al., 2012; Tong et al., 2016) have investigated sprayed particle deposition distributions on nasal surfaces, which showed that the delivered drug particles had low efficacy primarily due to high deposition occurring in the anterior nasal cavity (vestibule). This region is covered with squamous epithelium that doesn’t absorb the drug. To optimize nasal administration, it is necessary to understand the role nasal mucociliary clearance plays in the transport and diffusion of deposited drug particles, and this is related to the velocity field of the mucus layer on the nasal cavity surface.

For fast-action drugs, the mucociliary clearance effect helps to identify the eventual translocated position after initial deposition, relative to the therapeutic absorption time. However, for many drug formulations, the challenge is ensuring drug absorption times are faster than the clearance time. Recent work by Rygg and Longest (2016) evaluated a nasal clearance model for corticosteroid mometasone furoate. Additionally, Schipper et al. (1991) discussed strategies to increase absorption times of poorly permeating drugs that includes the class of peptides and proteins which has potential for nasal insulin therapy.

A standard method to quantify mucociliary clearance rate is the Saccharin test, where a saccharin particle is placed 1cm behind the anterior end of the inferior-turbinate and the time is recorded until the patient perceives a sweet taste from the saccharin. The average mucociliary clearance time for a healthy adult is 7-20 min (Corbo et al., 1989; Gizurarson, 2015; Pires et al., 2009; Yergin et al., 1978), and is affected by individual nasal geometries. In a study of 249 healthy non-smokers (134 male and 115 female subjects) (Plaza Valia et al., 2008), the mean and standard deviation for mucociliary clearance time was 17.17 minutes (SD of 8.43); median
was 16 minutes (interquartile range of 12-20 minutes). The upper and lower limits were 6 and 36 minutes, respectively where only 6 subjects had a nasal mucociliary clearance time longer than 36 minutes.

Studies have measured the mucus velocity field using radioactive particles, which reported an average mucus velocity of 5mm/min for a healthy adult (Illum, 2003; Mistry et al., 2009). The mucus velocity was unevenly distributed, and its variation depended on location. While, very low mucus velocity (1-2mm/h) was observed at the vestibule region (anterior nose), higher velocities were found (8-10mm/min) in the posterior nasal cavity (Gizurarson, 2015; Lale et al., 1998; Rusznak et al., 1994).

Since the mucus layer is an extremely thin structure (~10 μm) compared to the nasal cavity (~10 cm), it is impractical to generate a computational mesh and conduct simulations as a film-like domain attached to the 3D nasal cavity wall. Rygg and Longest (2016) proposed a method of transforming the nasal cavity wall to a 2D surface-based model and conducted CFD (Computational Fluid Dynamics) simulations on the flat domain where the flat domain transverse length was equivalent to the nasal cavity cross-sectional perimeter. Mucus was introduced uniformly into the computational domain over the surface, which transported the mucus blanket towards the nasopharynx outlet.

In this paper we applied the surface unwrapping technique proposed in Inthavong et al. (2014), which was used to map out wall shear stress, and particle deposition patterns on the intricate nasal cavity wall, onto a flat 2D-domain domain (Dong et al., 2016; Shang et al., 2017; Shang et al., 2015; Tong et al., 2016). This method extended the work by Rygg and Longest (2016) where topological features were preserved and contiguous connection between anatomical regions were retained, to account for mucus flow from the maxillary sinus into the nasal cavity.

In this study, two models for CFD simulations of mucus motion were developed:
i. **unwrapped-surface model**: where the mucus velocity field was calculated from a surface mesh applied onto the 2D unwrapped nasal cavity wall;

ii. **3D-shell surface model**: where the mucus velocity field was calculated using a surface mesh attached to the 3D nasal cavity wall

Both models compared mucus velocities at different anatomical regions with experimental measurements. The comparison was aimed at answering whether the mucus uniformly introduced into the computational domain over the boundary surfaces was acceptable for predicting mucus motion.

### 2. Method

**Mucus layer properties**

The mucus is composed of two distinct layers (Figure 1) with total thickness of 5-15 μm (Gizurarson, 2015; Mistry et al., 2009; Ugwoke et al., 2005). The upper layer is a 0.5-5 μm thick gel and consists of about 3% of an overlapping mucin network. The remainder is 90-95% water with electrolytes, serum proteins, immunoglobins, and lipids (Verdugo, 1990). Despite this composition, experimental studies showed that the mucus viscosity was as high as 10,000 times of water (Mestecky et al., 2005) due to the overlapping adhesive mucin fibres. No vertical convection occurs in the gel layer and the mucus velocity is constant along the gel layer depth.

The lower layer is the periciliary layer, which is about 7-10 μm thick (Quraishi et al., 1998). It coordinates rhythmic cilia beat that propels the gel layer towards the nasopharynx. Mucus is secreted from goblet cells and is injected into the periciliary layer before being transported into the upper gel layer. There is velocity gradient, which gradually increases in the periciliary layer from bottom to top. It is widely acknowledged that the upper gel layer constitutes the moving region of the mucociliary clearance. However, there is controversy about the transport rate of
mucus in the lower periciliary layer. The traditional hypotonic-defensin hypothesis and ciliary
stroke analysis consider the periciliary layer to be stationary when compared to the upper gel
layer (Blake and Sleigh, 1974; Fulford and Blake, 1986; King et al., 1993; Satir and Sleigh,
1990; Sleigh, 1977), whereas alternative hypothesis state the transport rate of periciliary fluid
is similar to the transport rate of mucus in the upper gel layer (Matsui et al., 1998). As a proof-
of-concept work, the upper gel layer was only considered and the mucus density was set to
1,000 $kg \cdot m^{-3}$. The optimal value for mucus viscosity was 12 $Pa \cdot s$ suggested by Puchelle
et al. (1987)'s experimental study.

Nasal cavity division based on mucus producing regions

An anatomical nasal cavity model was reconstructed from CT-scan data of a 48-year old
healthy Asian male, used in previous papers (Dong et al., 2018b; Shang et al., 2018; Shang et
al., 2015). Figure 2(a, i) shows the 3D model viewed from the right-chamber-side, and from
the top.

The model was divided into anatomical regions based on major mucus producing regions. At
the entrance of the nose is the vestibule region, which is non-ciliated (Marttin et al., 1998), and
this extends to approximately the anterior third of the nasal cavity (Mygind and Dahl, 1998).
Following this is the respiratory epithelium, which is the major lining of the human nasal cavity
that involves mucociliary clearance. The respiratory epithelium contains both non-ciliated, and
ciliated columnar cells, goblet cells, and basal cells. Cilia starts occurring just behind the front
edge of the inferior turbinate, and ciliated cell density generally increased in the antero-
posterior direction, while there were few regions of non-ciliated epithelial cells (Halama et al.,
1990). Thus, the cell distribution in the nasal cavity is non-uniform.

Mucus is secreted by goblet cells in the respiratory epithelium (Gelman and Meyer, 1979;
Quraishi et al., 1998). It is also secreted within the maxillary sinuses which flow from inside
the sinus and onto the nasal cavity surface via the maxillary ostium (Ballenger and Snow, 2003; Lale et al., 1998; Rusznak et al., 1994). There is a large production of mucus in the maxillary sinus due to the highest density of ciliated cells near the maxillary ostium (Halama et al., 1990).

The left and right vestibule regions (labelled in the Figure 2(a, i)) were separated in the nasal geometry, since they were non-ciliated regions. The frontal sinuses, ethmoid sinuses and sphenoid sinuses were omitted due to limited CT-scanned data resolution. The maxillary sinuses were retained for volume and surface area calculations. In the middle is the main nasal passage, which was divided into seven sub-regions. Table 1 provides the surface area and volume of the main passage and maxillary sinus of the left, and right chambers of the nasal cavity.

A surface-unwrapping technique transformed the 3D surface boundary onto a flat 2D domain (Figure 2(a, ii)). The left and right chambers were separated by the nasopharynx, and the posterior septum wall boundaries. The vestibule was omitted during this step since it neither secretes mucus nor hosts cilia, and the 2D domain is labelled with the vestibule boundary in its place. Although a small portion of mucus enters the vestibule and exits the nostrils, it can be ignored when compared to the amount of mucus produced per day in the nasal cavity of 1-2 litres (Baroody, 2007). Additionally, Rusznak et al. (1994) measured mucus velocity in the anterior nose (vestibule), which was 1-2 mm/h. This is negligibly slow compared to an average velocity of 5 mm/min for the whole nasal cavity and velocity of 8-10 mm/min at the posterior nose. The maxillary sinus geometry was also omitted during the unwrapping process, due to its complex geometry. However, the maxillary ostia were retained to form a boundary allowing a mucus production source term.
Mucus motion model development

We propose two models to reproduce moving mucus and its velocity distribution, Model 1: Mucus motion on the unwrapped-surface and Model 2: Mucus motion on a 3D-shell surface shown schematically in Figure 2b. In Model 1 the mucus velocity was calculated on the unwrapped-surface domain using conservation equations. In Model 2 the mucus velocity was calculated on an outer single-layer shell covering the 3D nasal cavity, using conservation equations. To allow direct comparison of the mucus velocity field, data from the 3D-shell model was projected to its equivalent 2D unwrapped surface. The steady-state continuity equation with a source term was used,

\[ \rho (\nabla \cdot \vec{v}) = \dot{f}_{\text{source}} \]  \hspace{1cm} (1)

where \( \rho \) is density of mucus, \( \dot{f}_{\text{source}} \) is mucus mass generation in the computational domain and \( \vec{v} \) is the mucus velocity. The steady-state momentum equation used was,

\[ \rho (\vec{v} \cdot \nabla) \vec{v} = -\nabla p + \mu \nabla^2 \vec{v} \]  \hspace{1cm} (2)

where \( p \) is the pressure and \( \mu \) is the mucus viscosity.

Mesh generation and CFD setup

In each model, a surface mesh with triangular elements was created in Ansys ICEM 18.2, and then extruded one cell height to represent a thickness of 10 µm. The minimum mesh skewness measured in ICEM were 0.25 for the 3D-shell model and 0.42 for the surface-unwrapped model. A mesh independence test was performed by calculating the average mucus velocity in the inferior meatus, which became stable when the global mesh element size reached 0.6 mm. To guarantee the accuracy, the mesh element size was set to 0.5 mm in this study.
To represent realistic mucus production into the computational domain, a uniform mass source term \(f_{\text{source}}\) was applied (Figure 3). The mass source term was proportional to the nasal cavity surface area, and the representative mucus layer height, \(h\), set to 10µm.

\[
m_{\text{nasal}} = f_{\text{source}} \times A_{\text{nasal surface}} \times h
\]  

Ballenger and Snow (2003) showed a mucus blanket covered the entire maxillary sinus surface area and that it flowed towards the maxillary ostium. At the ostium boundary, the mucus mass flow rate was assumed to be proportional to its maxillary sinus surface area, and proportional to the mucus flow of the nasal cavity surface area, defined as:

\[
m_{\text{ostium}} = f_{\text{source}} \times A_{\text{sinus}} \times h
\]

This means the mucus velocity was derived purely by mass conservation constrained by a constant mucus height and driven by a mass source (mucus generation) which is the \(f_{\text{source}}\) term. No shear stress occurred between nasal wall and mucus, but shear stress does exist inside the flow due to the viscous term in the momentum equation (equation 2).

The mucus accumulated in the single-layer computational domain, and due to mass conservation, moved towards the nasopharynx outlet. Although in principle the upper mucus (gel) layer is transported by cilia motion, the model relies on the momentum equation to redistribute the mucus flow velocity field similar to (Rygg and Longest, 2016) and (Rygg et al., 2016)’s studies. For each model, the mucus production rate (source term) was determined in such way that the average mucus velocity over the nasal cavity wall reached 5 mm/min (Illum, 2003; Mistry et al., 2009; Pires et al., 2009; Ugwoke et al., 2005). As mucus flow patterns vary between the models, the exact mucus production rates don’t have to be the same. The final mucus production rates were \(f_{\text{source}} = 0.9224 \text{ kg \cdot s}^{-1} \text{ \cdot m}^{-3}\) for the 3D-shell model and \(f_{\text{source}} = 0.8030 \text{ kg \cdot s}^{-1} \text{ \cdot m}^{-3}\) for the surface-unwrapped model.
Given the high viscosity and the low velocity magnitude, the Reynold’s number $Re = \frac{\rho UD}{\mu}$ was below $1e-4$ and the mucus flow was classified as creeping laminar flow. The discretization schemes were second-order, and the SIMPLE coupling was used. Convergence was set by residuals reaching $1e-6$ and the simulations were performed using Ansys-Fluent v18.2. The boundary condition at the nasopharynx exit was set as outflow, and the remaining surfaces were treated as slip wall boundaries, thus no shear effects at the wall.

3. Results

Mucus velocity fields

Mucus velocity fields for the unwrapped-surface and 3D-shell models (Figure 4b) were indicated by unit vectors and velocity magnitude indicated by the colour band. General velocity flow behaviour was similar in both models, where there is a symmetric pattern between the left and right chambers. Mucus accelerated from the anterior to posterior nasal cavity with velocities at the nasopharynx.

In the unwrapped-surface model (Figure 4(b. i)) the contour plot showed a smooth change in velocities from the vestibule boundary steadily increasing to a peak velocity at the nasopharynx. The low velocity regions were concentrated near the vestibule boundary. In the 3D-shell model (Figure 4(b, ii)) low velocity regions were found across all anatomical regions in the main nasal passage except for the septum and nasopharynx. A velocity jump was found near the choana, where the mucus velocity rapidly increased from $\sim 10$ mm/min to $>30$ mm/min. Another noticeable high velocity region was found at the inferior septum boundary, which was the floor of the nasal cavity wall.
Mucus motion differed between the two models. For the unwrapped-surface model, the mucus motion followed the geometry from the vestibule boundary towards the nasopharynx, while for the 3D-shell model there was a radial pattern originating from the maxillary ostium.

**Virtual saccharin test**

In clinical applications, a standard method called the saccharin test is frequently used to check the condition of the mucociliary clearance. A saccharin particle is placed 1 cm behind the antero-inferior turbinate and the elapsed time is recorded until a patient can detect the taste of saccharin. It takes 7-20 min for a healthy adult to perceive the saccharin (Gizurarson, 2015).

We conducted a ‘virtual saccharin test’ by introducing a particle at the anterio-inferior turbinate and calculated its elapsed time as it moved along the mucus velocity field until the nasopharynx exit.

To avoid variations caused by the different locations, the ‘virtual saccharin’ test was performed from three locations A, B and C, which were 0.6 cm, 1.0 cm and 1.4 cm behind the anterior inferior turbinate. The particle trajectories on the unwrapped-surface model and the 3D-shell model are shown in Figure 4c, where the particles travelled along the lateral sides of the nasal cavity wall and moved through the inferior meatus before entering the nasopharynx. The paths were coloured by residence times and Table 2 summarises the clearance times (time taken to travel to nasopharynx) where similar times were achieved between left and right chambers of both models. However, for the unwrapped-surface model the clearance times ranged between 34.9 – 68.3 min, while for the 3D-shell model it was 14.8 – 27.2 min; a difference of 2.5x. In the unwrapped-surface model, the clearance time decreased when the saccharin release point was posteriorly located, while for the 3D-shell model the opposite occurred.
Mucus velocity on a characteristic line

Investigations of mucus motion measured the mucus velocity distribution from anterior to posterior middle turbinate (Gizurarson, 2015; Rusznak et al., 1994). For comparison, the mucus velocity magnitude along a characteristic line (Figure 5a) starting at the anterior inferior turbinate and ending at the nasopharynx was plotted for both models (Figure 5b). Although the line coordinate is defined from the unwrapped geometry, the velocity magnitude values were obtained by transforming the velocities from the 2D geometry domain to the 3D geometry domain to allow direct comparisons with experimental measurements (Gizurarson, 2015; Rusznak et al., 1994).

Figure 5b shows the mucus velocity increasing as it moved towards the nasopharynx. For the unwrapped-surface model, the velocity increased smoothly from nearly 0 mm/min at the nasal valve to 7 mm/min at the posterior inferior turbinate. The velocity remained relatively constant in the posterior middle meatus before increasing to 16 mm/min at the nasopharynx. For the 3D-shell model, the velocity decreased from 3 mm/min to ~1 mm/min and then increased to 3 mm/min in the inferior turbinate region. In the posterior middle meatus, the velocity increased rapidly from 3 mm/min to 11 mm/min, and continued to increase to 38 mm/min at the nasopharynx.

Mucus velocity on a cross-section

Figure 6a shows a vertical cross-section created 6 cm inside the nasal passage to examine mucus velocity distribution along the cross-section perimeter. The perimeter was projected onto the 2D domain of the unwrapped geometry where the starting and end points were the same location that connected the cross-section together. The origin of the perimeter (starting point) was taken at the interface of the inferior meatus and septum. The distance from the origin
follows the depicted arrows in Figure 6a. The velocity magnitude along the perimeter between
the two models are shown for the left (Figure 6b) and right chambers (Figure 6c).

Both models produced similar velocity profiles between the left and right nasal chambers.
However, between the two models, the velocity profiles were very different. The unwrapped-
surface model presented relatively similar velocity along the perimeter, with higher velocities
reaching 7 mm/min at middle meatus and middle turbinate, and lower velocities around 1
mm/min at the inferior meatus, inferior turbinate, olfactory and septum. For the 3D-shell model,
higher velocities were concentrated at the inferior meatus and septum, reaching up to 10.5
mm/min at the interface between them. At other regions, the mucus velocity was much lower
fluctuating between 1-3 mm/min.

4. Discussion
We present computational models for detailed mucus velocity distribution on the nasal cavity
wall. This is a first study to visualise the mucus velocity distributions on the anatomical nasal
regions. In experimental studies, radioactive particles $^{88m}$Tc and $^{111}$I are often used to measure
local mucus velocity (Lale et al., 1998). However, the analysis is hindered by highly
overlapping nasal structures, which obstruct the $\gamma$-camera to accurately detect the location of
the radioactive particles leading to approximate mucus flow patterns.

Negligible mucus velocity (~1-2 mm/h) detected in the anterior part of nose (Rusznak et al.,
1994) confirmed the rationale for removing the vestibule from the models. The reported
velocity in the posterior nose was 8-10 mm/min (Rusznak et al., 1994), which was slighter
larger than the predicted velocity of 7.0-7.3 mm/min from the unwrapped-surface model and
match the simulated velocity 2.7-11.6 mm/min from the 3D-shell model. Quinlan et al.
(1969)’s study described particle movement on the medial surface of the inferior turbinate
moving laterally to the inferior meatus and then posteriorly towards the choana. Velocity fields from both unwrapped-surface and 3D-shell models showed good agreement with this description. Andersen et al. (1971)’ study observed an area in the anterior nasal cavity where the mucus moved forward. This validates the 3D-shell model as forward-moving mucus was found in the anterior region of the maxillary ostium, while the unwrapped-surface model did not. Andersen et al. (1971) also observed abnormal spots in the middle passage where the mucus velocity was extremely slow. This phenomenon matched the low velocity distribution generated by 3D-shell model very well, whereas no such low velocity region was found in the unwrapped-surface model.

The saccharin test is significantly affected by individual variation and was reported as taking 7-20 min for healthy adults (Corbo et al., 1989; Gizurarson, 2015; Pires et al., 2009; Yergin et al., 1978) and should not exceed 36 mins when taking high individual variations into account (Plaza Valia et al., 2008). The ‘virtual saccharin’ test time of 34.9 - 68.3 min predicted by the unwrapped-surface model exceeds the range, even when accounting for individual anatomical variations. The 3D-shell model produced much better agreement with clearance times ranging between 14.8 – 27.2 min. The mucus velocity field generated by the 3D-shell model exhibited a more efficient pattern for mucociliary clearance than in the unwrapped-surface model. The virtual saccharin particles immediately travelled along the floor of the nasal cavity wall after release and joined a region of high mucus velocity flow.

There were large differences in the mucus velocities between unwrapped-surface and 3D-shell models. For each model, the mucus velocity field was generated by the continuity equation with a uniform source term and constrained by the nasal cavity surface. Due to the unwrapping process from 3D domain to the 2D domain, the surface mesh was significantly deformed. Comparisons of regional surface areas between unwrapped-surface and 3D-shell models are listed in Table 3. The area ratio was defined as the ratio of regional area in the 3D domain and
its corresponding area in the 2D domain. The largest and smallest ratios were found at the
nasopharynx and olfactory regions, respectively. As a result, a lower averaged velocity at the
nasopharynx and a higher average velocity at the olfactory region were found for the
unwrapped-surface model, compared to the 3D-shell model. Therefore, we recommend
avoiding simulations of mucus flow on an unwrapped nasal domain. Instead, the 3D-shell
model is more suitable to predict the mucus velocity field on the nasal cavity wall.

For simplicity, the mucus velocity field was calculated without gravity. To estimate its effect,
the gravity acceleration $9.8 \text{ m/s}^2$ was applied to the $-y$ direction of the 3D-shell model
(replicating upright standing position), and the velocity distribution at a cross-section was
compared to that in the original 3D-shell model. The location of the cross-section was identical
to that in Figure 6 and the velocity difference was defined as $(v_{\text{gravity}} - v_{3d-shell})/v_{3d-shell} \times 100\%$. Figure 7 showed that the mucus velocity change caused by gravity was less than 5%
for both chambers, and the peak difference occurred at olfactory regions, with 3.0% for the left
chamber and 4.2% for the right chamber. The gravity has minimal effects on the mucus velocity
field, and is reasonable to be ignored for the majority of mucus motion simulations.

**Conclusion**

Mucociliary clearance is critical to the efficacy of intranasal drug delivery. Mucus motion on
the human nasal cavity wall was simulated using CFD by two approaches, namely unwrapped-
surface model and 3D-shell model. Validation of the models compared overall mucus velocity
patterns, virtual saccharin particle tracking and quantitative mucus velocity magnitude
distributions with existing experimental data. Based on the study, the following conclusions
were drawn:
• Mucus was introduced as a mass source term to initiate mucus flow within the nasal cavity, where the 3D-shell model exhibited higher velocities, particularly near the choana.

• In the main passage region, the 3D-shell model resulted in a radial velocity pattern originating from the maxillary ostium whereas the unwrapped-surface model presented a mucus velocity field with a uniform direction.

• The velocity magnitude distributions on a cross-sectional perimeter illustrated the mucus was concentrated along the floor of the nasal cavity in the 3D-shell model whereas in the unwrapped-surface model, relatively higher velocity was found in the middle meatus and middle turbinate.

• The virtual saccharin test showed that saccharin clearance time in the 3D-shell model had better agreement with experimental data acquired from healthy adults.

Of the two models, the 3D-shell model produced much better and more realistic results that matched existing experimental data compared with the unwrapped-surface model. This lays a solid foundation for future predictions on drug absorption via intranasal drug delivery using the 3D-shell model.
Acknowledgements

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Conflict of Interest

The author declares no conflict of interest.

References


List of Tables

Table 1. Surface area and volume of major components of the nasal cavity.

<table>
<thead>
<tr>
<th>regions</th>
<th>vestibule</th>
<th>left</th>
<th>right</th>
<th>nasopharynx</th>
<th>left</th>
<th>right</th>
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<tbody>
<tr>
<td>Area (mm²)</td>
<td>1627.6</td>
<td>8632.7</td>
<td>8458.3</td>
<td>1641.9</td>
<td>1572.2</td>
<td>1131.8</td>
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<tr>
<td>Volume (mm³)</td>
<td>3317.8</td>
<td>7178.6</td>
<td>11227.5</td>
<td>4682.6</td>
<td>3505.9</td>
<td>2012.3</td>
</tr>
</tbody>
</table>

*volume of main passages calculated for region between the vestibule and nasopharynx regions*
Table 2. Clearance times of ‘virtual saccharin particles’ placed in locations A, B and C in left and right nasal chambers.

<table>
<thead>
<tr>
<th>Nasal chamber</th>
<th>Model</th>
<th>Clearance time (min)</th>
<th></th>
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<tr>
<td></td>
<td></td>
<td>Location A</td>
<td>Location B</td>
<td>Location C</td>
<td>Average</td>
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<td>Left side</td>
<td>Unwrapped-surface</td>
<td>68.3</td>
<td>49.3</td>
<td>37.9</td>
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<td></td>
<td>3D-shell</td>
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<td>27.2</td>
<td>19.7</td>
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<tr>
<td>Right side</td>
<td>Unwrapped-surface</td>
<td>62.6</td>
<td>45.9</td>
<td>34.9</td>
<td>47.8</td>
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<tr>
<td></td>
<td>3D-shell</td>
<td>15.4</td>
<td>17</td>
<td>21.4</td>
<td>17.9</td>
</tr>
</tbody>
</table>
Table 3. Regional surface area in 3D and unwrapped domains.

<table>
<thead>
<tr>
<th>Name of regions</th>
<th>Area mm²</th>
<th></th>
<th>Area Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3D domain</td>
<td>Unwrapped domain</td>
<td></td>
</tr>
<tr>
<td>Olfactory</td>
<td>1890.2</td>
<td>959.3</td>
<td>0.51</td>
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<tr>
<td>Atrium</td>
<td>664.4</td>
<td>545.6</td>
<td>0.82</td>
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<tr>
<td>Middle turbinate+</td>
<td>1951.8</td>
<td>1169.9</td>
<td>0.60</td>
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<tr>
<td>Middle meatus</td>
<td>3306.5</td>
<td>2068.8</td>
<td>0.63</td>
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<td>Inferior turbinate</td>
<td>1763.0</td>
<td>1689.8</td>
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<td>Inferior meatus</td>
<td>3318.2</td>
<td>3755.7</td>
<td>1.13</td>
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<td>Septum</td>
<td>4111.6</td>
<td>5150.3</td>
<td>1.25</td>
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<td>Nasopharynx</td>
<td>1642.0</td>
<td>3326.0</td>
<td>2.03</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>18647.7</td>
<td>18665.4</td>
<td>1.00</td>
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</table>
List of Figures

Figure 1. Nasal mucus composed of two distinct layers with total thickness 5-15 μm: i) upper gel layer consisting of overlapping mucin fibrous network, and ii) lower periciliary layer consists of cilia.
Figure 2. The nasal surface division strategy and surface-wrapping technique used for mucus motion simulation. (a) Nasal cavity divided into multiple regions. The vestibule (grey), and the nasopharynx represent the anterior and posterior regions, respectively. In the middle is the main nasal passage which was divided into seven further sub-regions: vestibule, atrium, middle turbinate, middle meatus, inferior turbinate, inferior meatus, and septum. (b) Schematic of Model 1 (b. i., unwrapped-surface model) where the mucus velocity is calculated directly from the 2D unwrapped surface, and Model 2 (b. ii., 3D-shell model) where a shell around the 3D model is first created, and the mucus velocity is calculated directly from the 3D shell domain, and projected to the 2D unwrapped surface.

*The middle turbinate region also included superior meatus.
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*The middle turbinate region also included superior meatus.
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*The middle turbinate region also included superior meatus.