Modelling Deposition in the Nasal Cavity

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Overview

- Nasal products are combination products, with complex interaction between the formulation and device
- Most formulations are aqueous solutions or suspensions, but propellant and powder products have been developed and marketed
- For both local and systemic treatments, regional deposition in the nasal airways is an important consideration

https://en.wikipedia.org/wiki/Nasal_spray (modified)

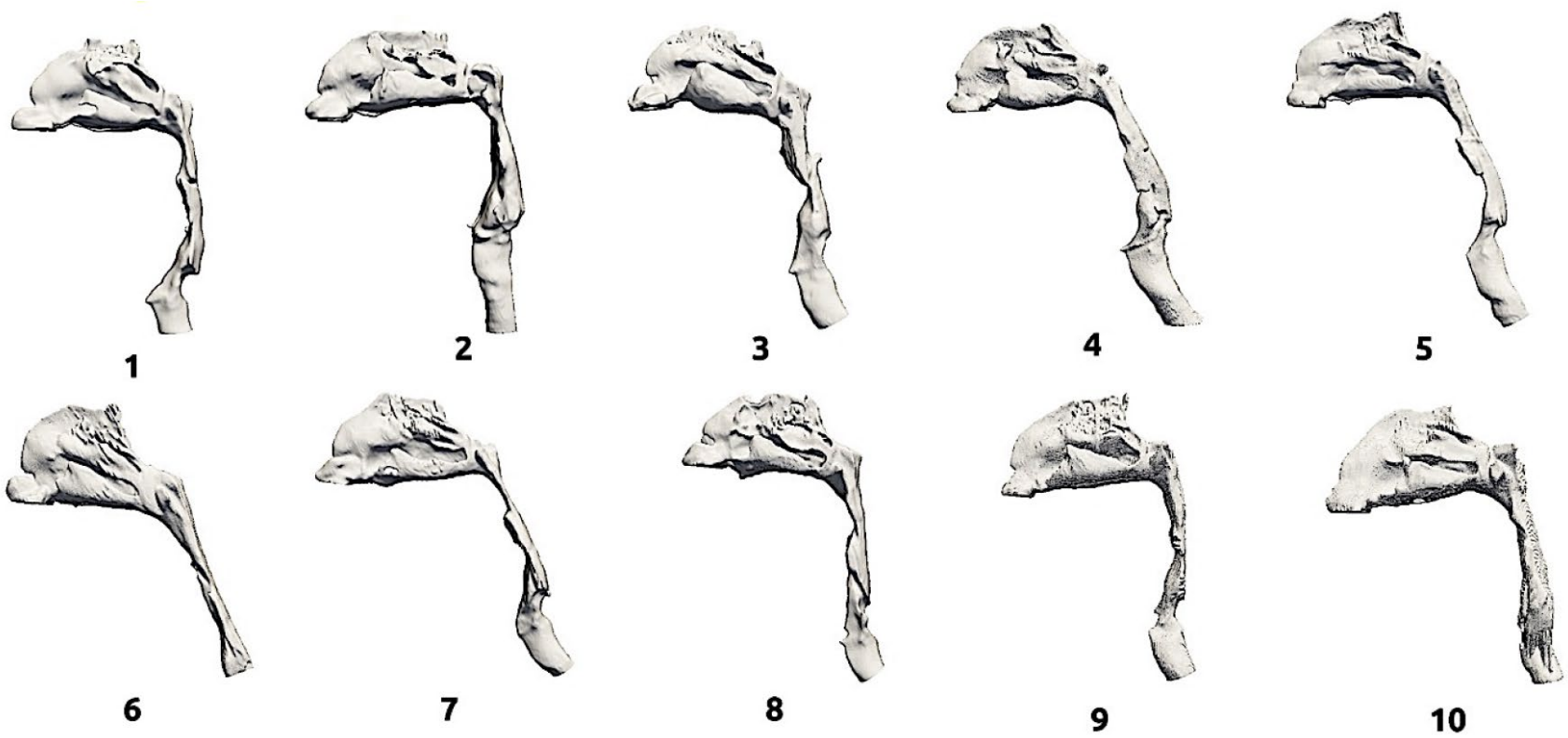
Established *In Vitro* Tests

- FDA Guidance: Nasal Spray and Inhalation Solution, Suspension and Spray Drug Products – CMC Documentation

- Recommended test parameters include:
  - Pump Delivery (Shot Weight)
  - **Spray Content Uniformity** (including priming/repriming, orientation, resting time)
  - **Spray Pattern and Plume Geometry**
  - **Droplet Size Distribution** (D_{10}, D_{50}, D_{90}, span, % droplets < 10 µm)
  - Particle Size Distribution (suspensions)
  - Net Content; Formulation pH, Osmolality, Viscosity
  - Weight Loss, Leachables, Microbial Limits, PM

Nasal Geometries

- Nasal geometries derived from medical imaging have been explored for modeling nasal deposition and/or as inlets for impactor measurements

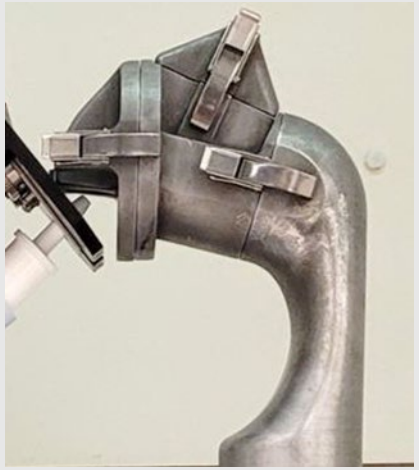


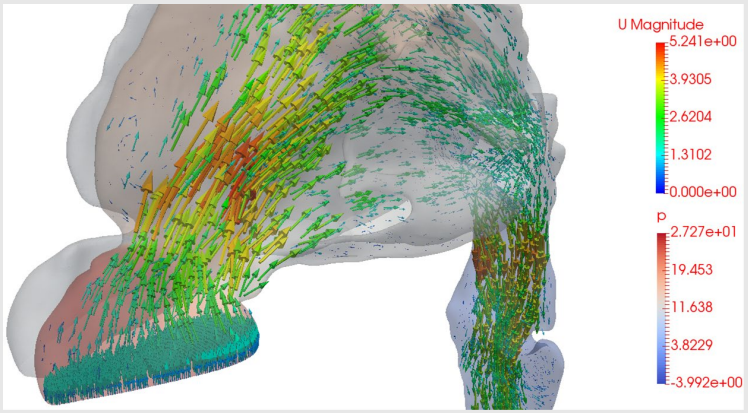
Kiaee et al. Computers in Biology and Medicine, 107:206-217, 2019

Modelling Nasal Deposition

- *In vitro* and *in silico* techniques are complementary

In Vitro	*In Silico*
• Limited parameter space (available test products; resources) • Deposition evaluated over discrete regions of interest • Well suited to characterization and comparison of existing and/or prototype products • Challenging to ensure real-world use conditions are emulated • Movement of deposited drug can occur (spreading, dripping, bounce, resuspension)	• 'Limitless' parameter space to explore • Continuous map of motion and deposition • Well suited to design, optimization, sensitivity studies • Challenging to define initial/boundary conditions for specific drug-device products (size distribution, velocity distribution, spray angle, etc.) • Typically do not include post-deposition motion





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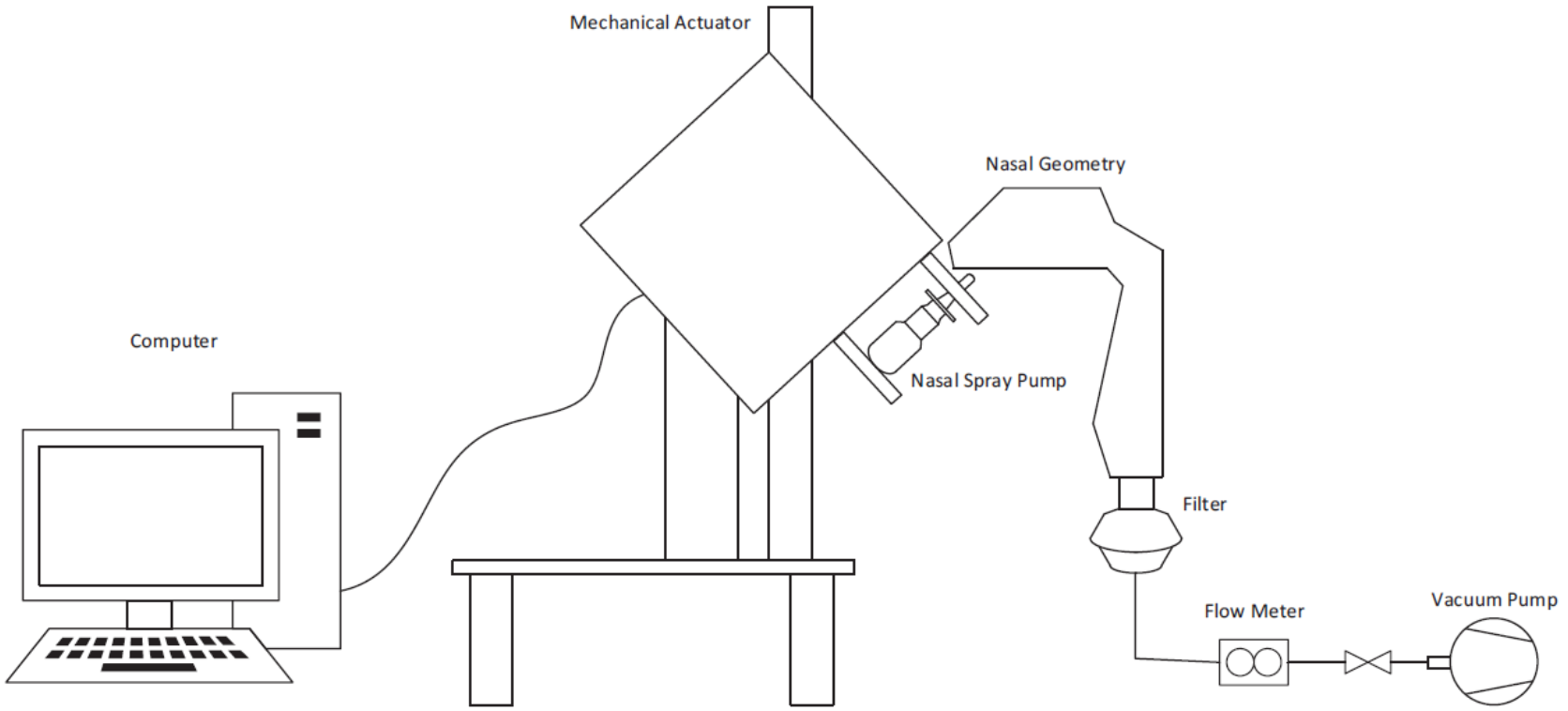
In Vitro Testing with Nasal Geometries

- Chen at al. (2020): sectioned geometries used for *in vitro* testing



Chen et al. Int J Pharm. 582: 119241, 2020.

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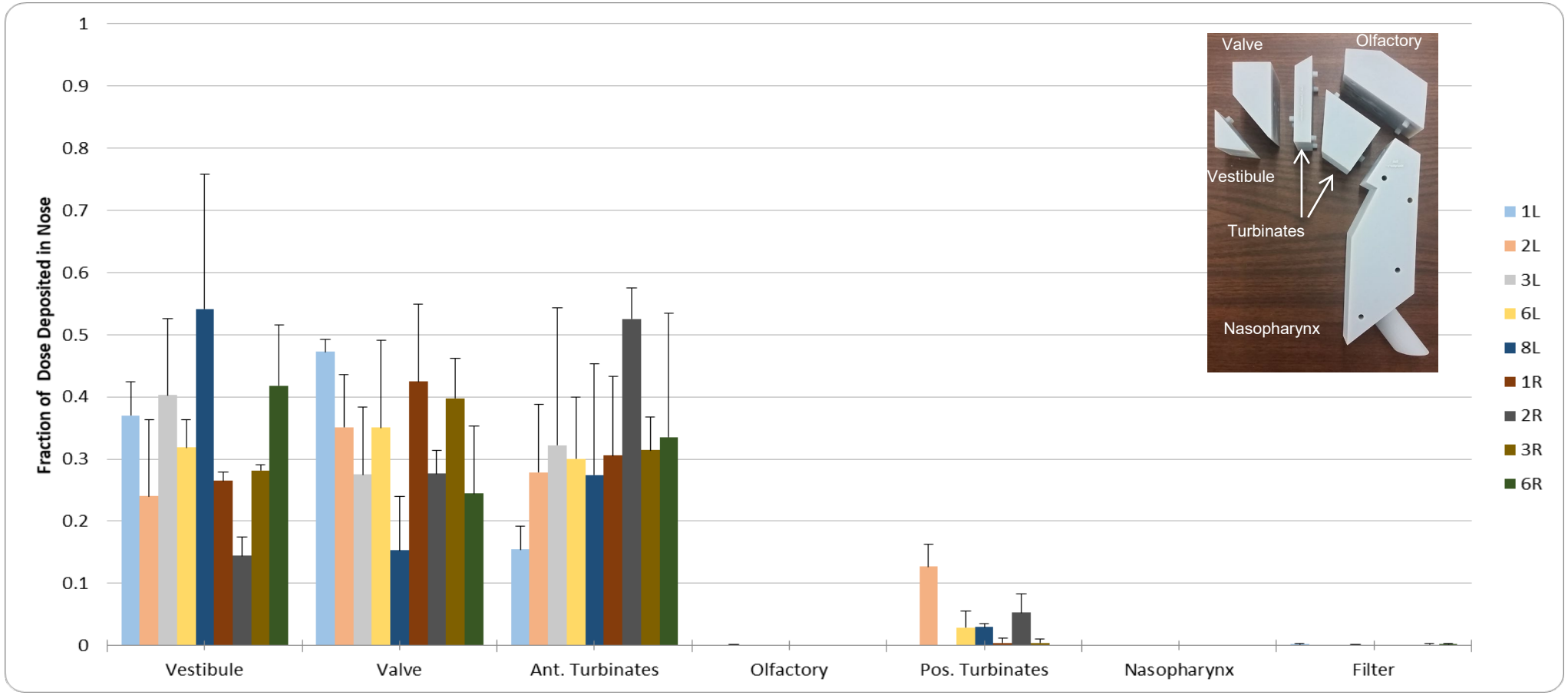
In Vitro Testing with Nasal Geometries

- Notable variation between individual geometries



Regional Deposition: NasalCrom; 7.5 l/min; **60 degree orientation**

Chen et al. Int J Pharm. 582: 119241, 2020.

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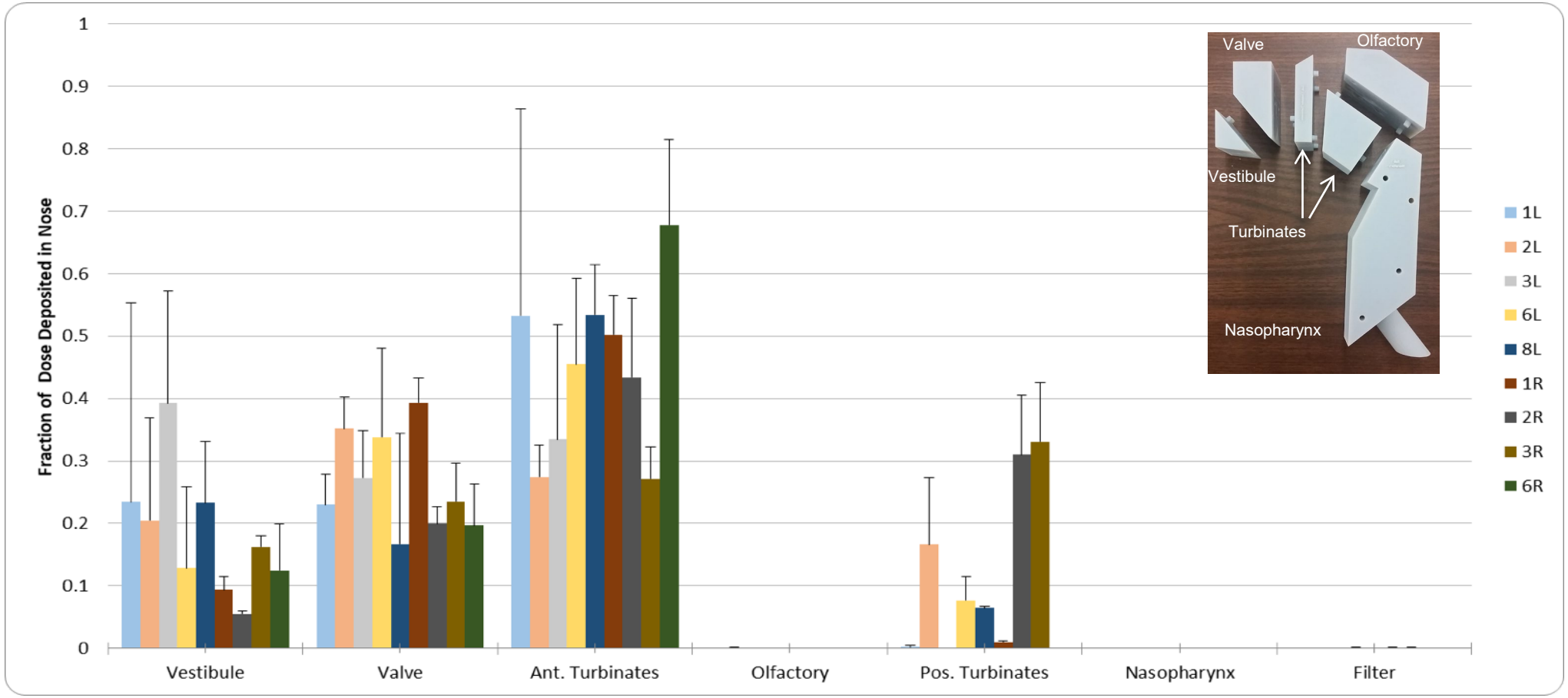
In Vitro Testing with Nasal Geometries

- Broad trends in regional deposition are observable



Regional Deposition: NasalCrom; 7.5 l/min; **45 degree orientation**

Chen et al. Int J Pharm. 582: 119241, 2020.

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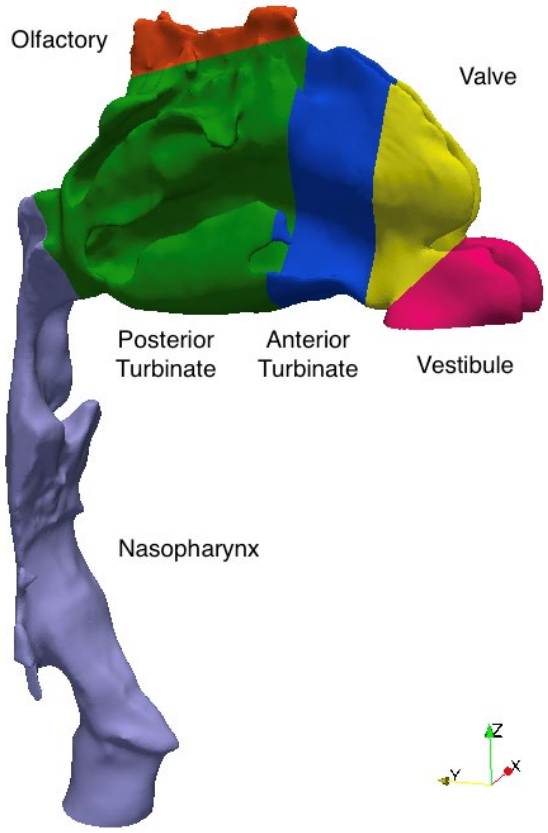
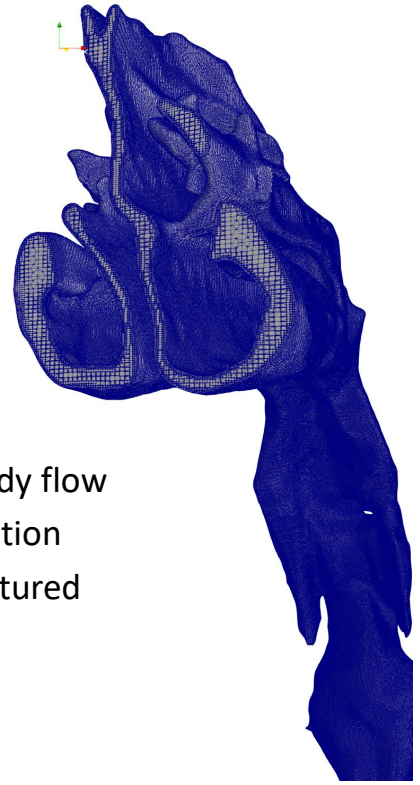
In Silico Study with Nasal Geometries

- Kiaee et al. (2018) used computational fluid dynamics (CFD) simulations to create a database of regional deposition in realistic geometries



OpenFOAM software

- Newtonian fluid; laminar, steady flow
- Second order spatial discretization
- Hexagonal-dominated unstructured mesh (1 to 4 million cells)



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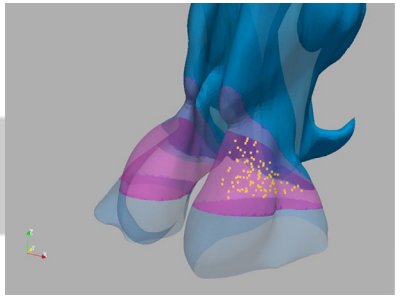
Kiaee et al. Int J Num Methods Biomed Eng. 34:e2968, 2018.

In Silico Study with Nasal Geometries

- Parameter space defined to create database (224,000 simulations)



Parameter	Number of Parameter Values Simulated	Range of Values
Particle diameter	5	5 - 40 μm
Spray half cone angle	2	17.5 and 30° from spray cone direction
Spray cone direction	2	Upward (i.e., vertical) and semiupward (aimed at the nasal valve entrance, approximately 75° from vertical)
Particle injection velocity	4	0-20 m/s
Position of injection disk	200	Generated randomly within a defined boundary
Nasal airway geometries	7	Normal airway geometries derived from computed tomography scans
Spray injection side	2	Left and right nostril injection simulated separately

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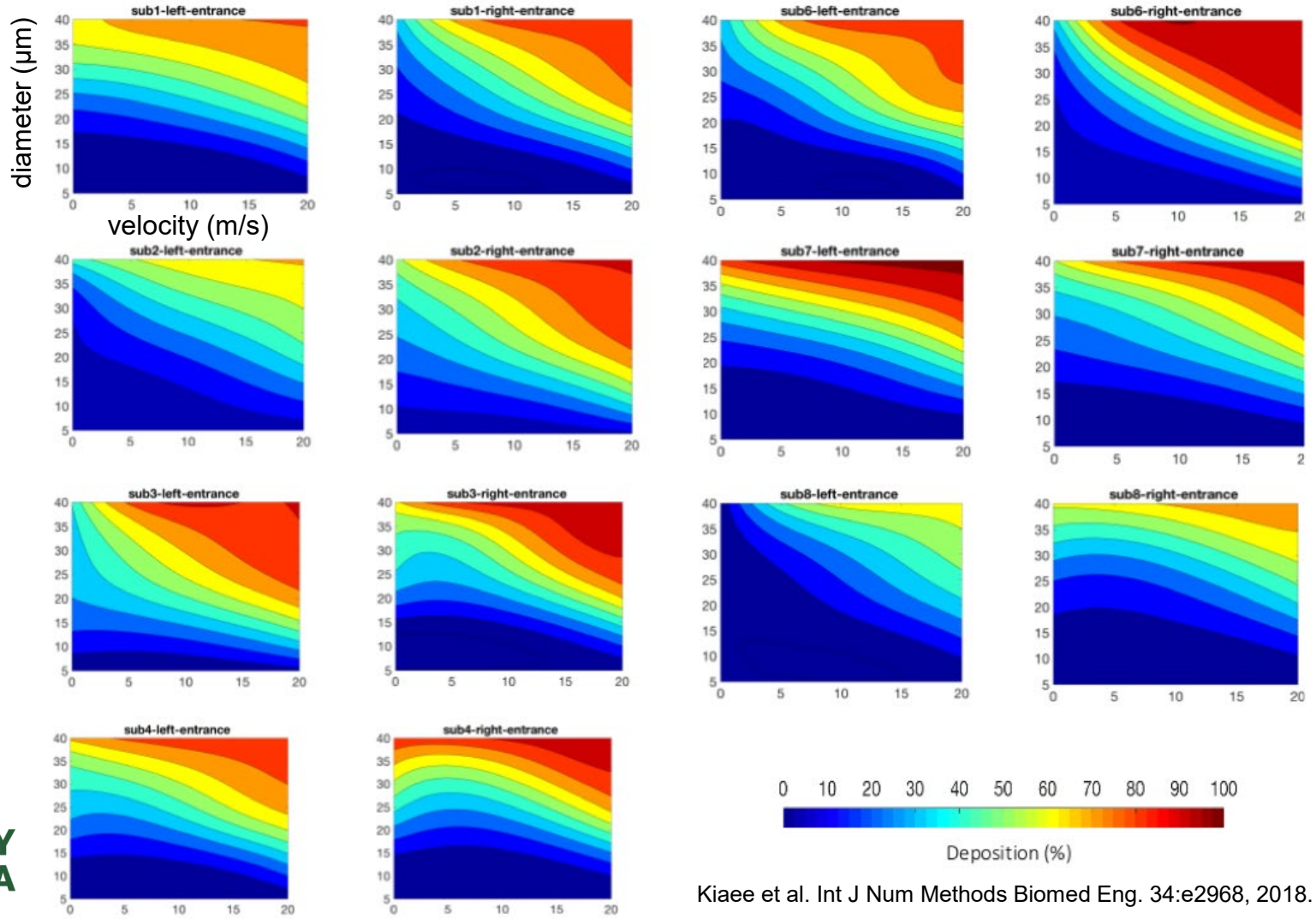
Kiaee et al. Int J Num Methods Biomed Eng. 34:e2968, 2018.

In Silico Study with Nasal Geometries

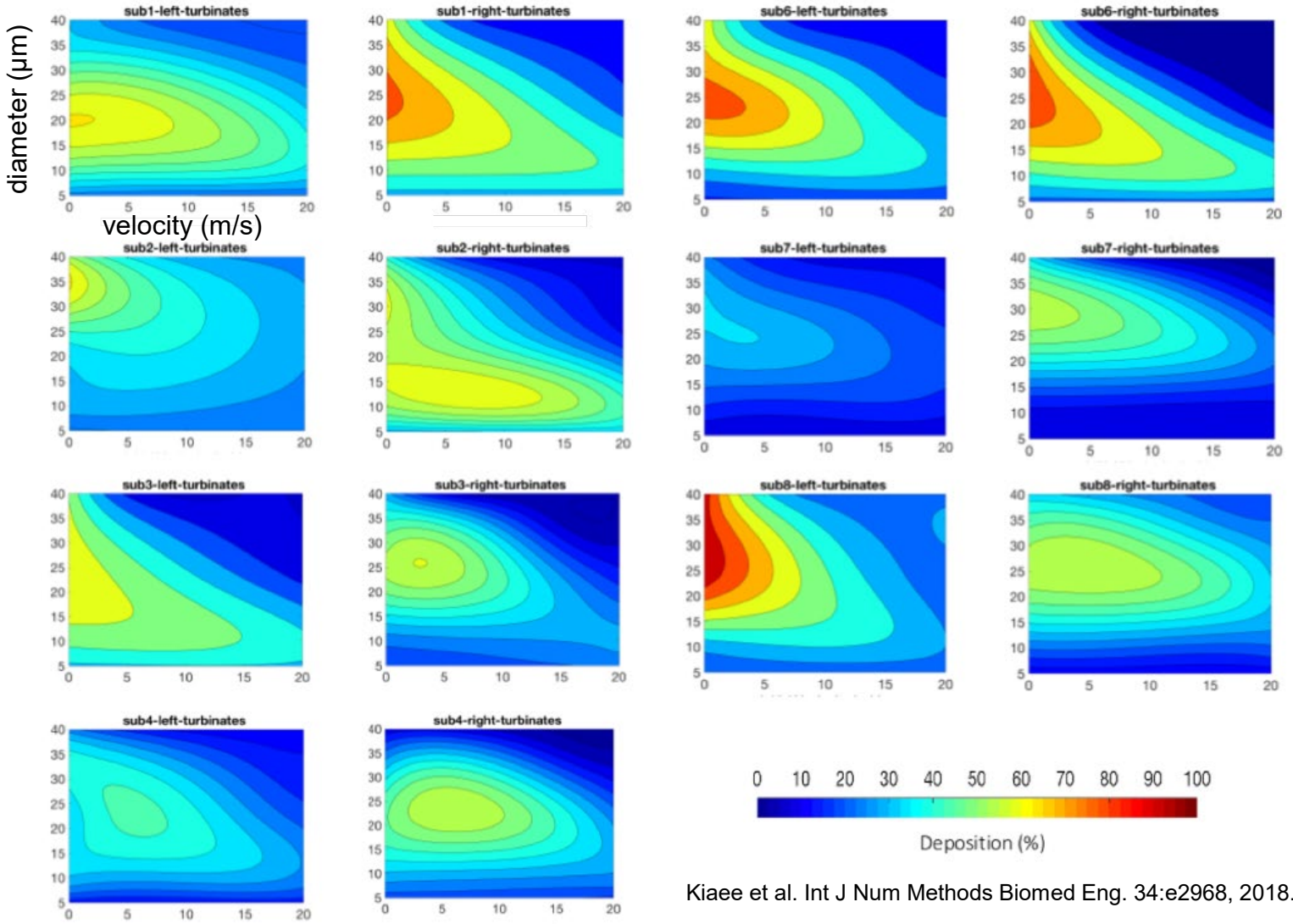
- <u>Vestibule and Valve Deposition</u> (avg. over cone angle, spray direction, injection location):



Kiaee et al. Int J Num Methods Biomed Eng. 34:e2968, 2018.

In Silico Study with Nasal Geometries

- Turbinates Deposition (avg. over cone angle, spray direction, injection location):



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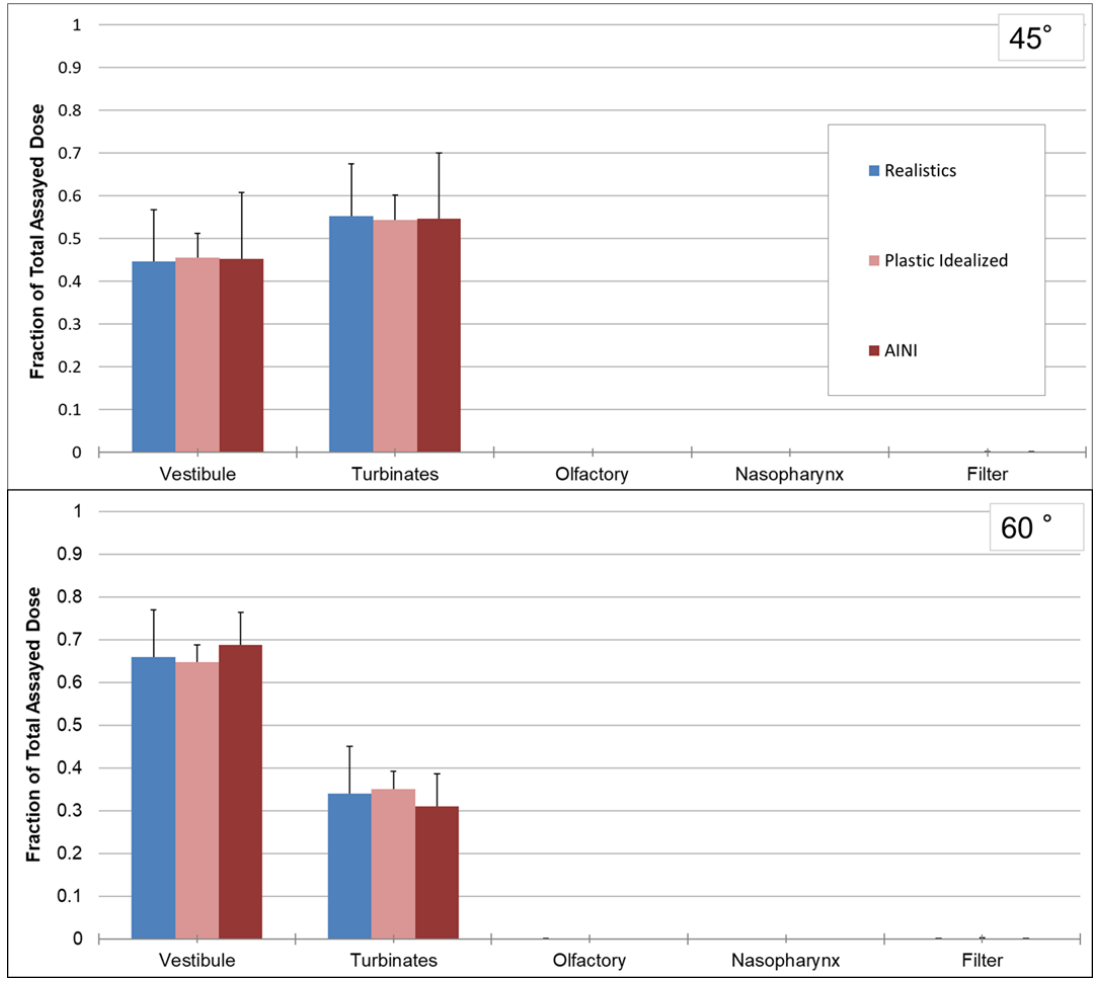
Development of Idealized Nasal Airway

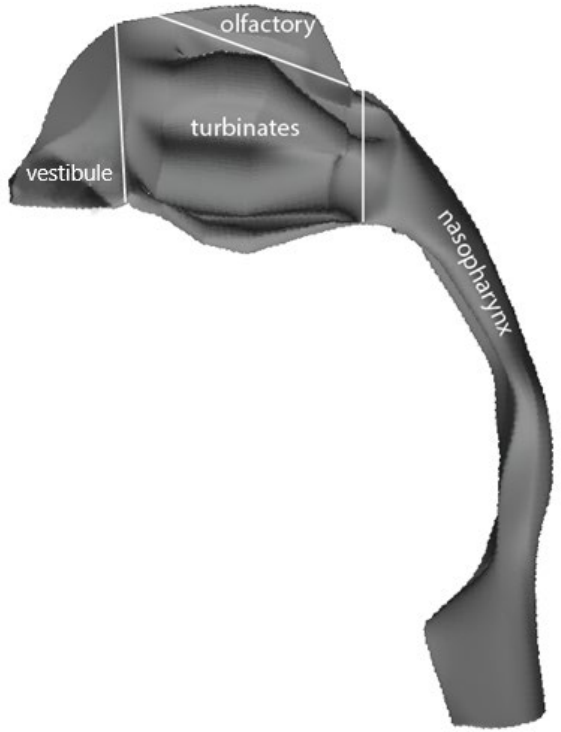
- Goal was to emulate average regional deposition simulated in realistic geometries over large parameter space
- Balance with geometric simplicity to allow robust manufacture
- Geometry was refined parametrically *in silico* to match average deposition in realistic geometries, with validation work completed *in vitro*
- Resulting idealized geometry available as the Alberta Idealized Nasal Inlet (Copley Scientific)

Images courtesy Copley Scientific

AINI: Comparison with Realistic Geometries

- Experiments done using NasalCrom; 7.5 l/min inhalation; 2 orientations





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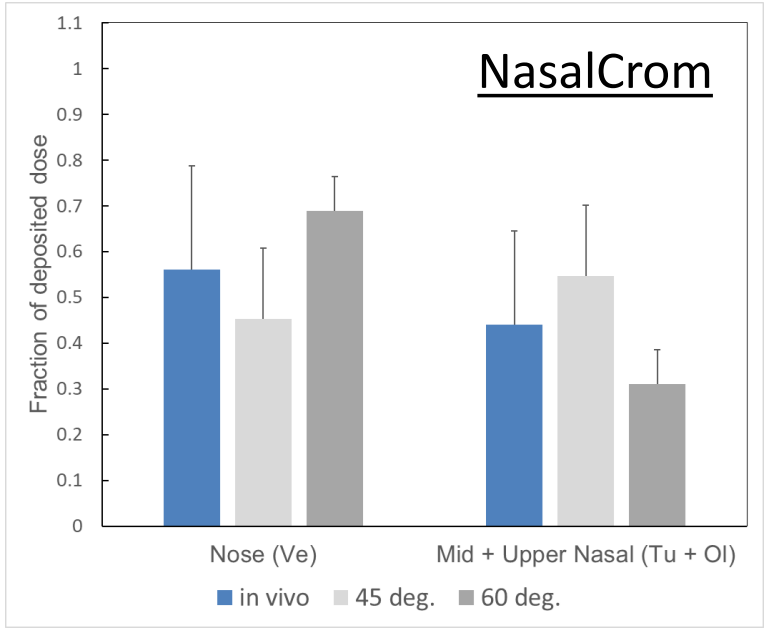
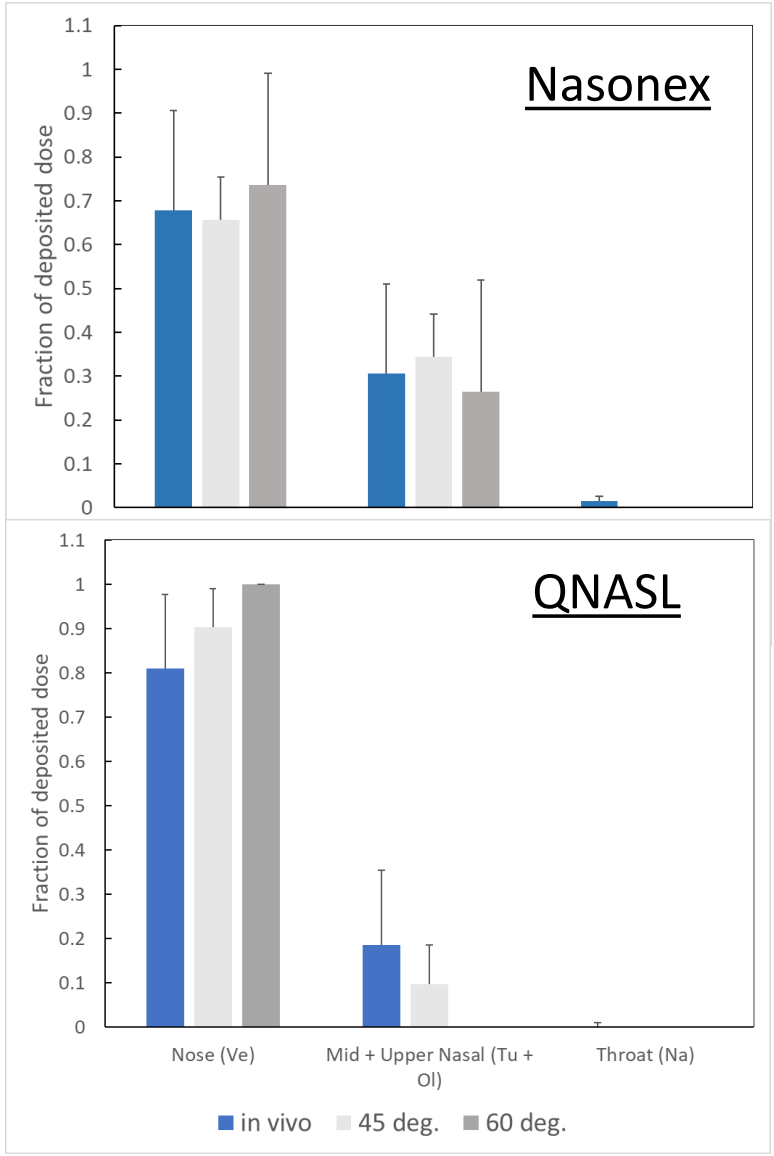
Chen et al. Pharm Res. 39: 3021-3028, 2022

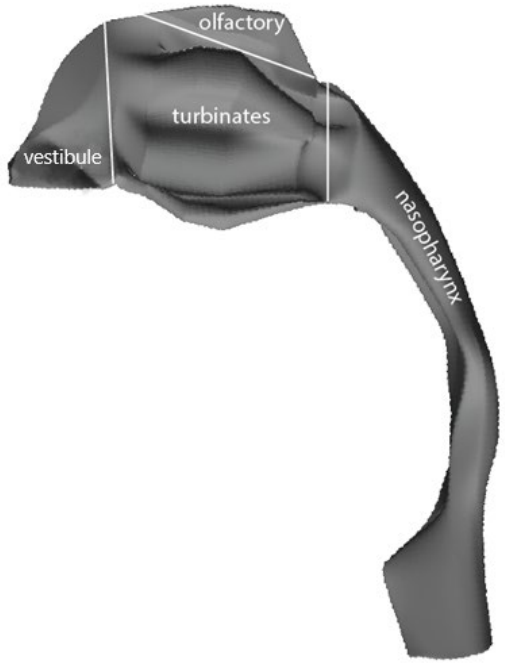
AINI: Comparison with *In Vivo* Data

Al-Ghananeem et al. (2008):



Leach et al. (2015):





Chen et al. Pharm Res. 39: 3021-3028, 2022

Open Questions/Research Needs

- Linking regional deposition to events that follow:
  - spray/wall interaction, liquid spreading, drip
  - clearance, dissolution and absorption
- *In vitro* methods for powders:
  - bounce, resuspension
  - coating surfaces
- What region(s) of the nose should be targeted? What refinement in targeting is needed to optimize therapy?
  - for local delivery, systemic delivery, CNS diseases, vaccines…

Acknowledgements

- Michelle Noga, Radiology & Diagnostic Imaging, University of Alberta

- The AINI geometry was built and supplied for testing by Copley Scientific

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Thank you

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