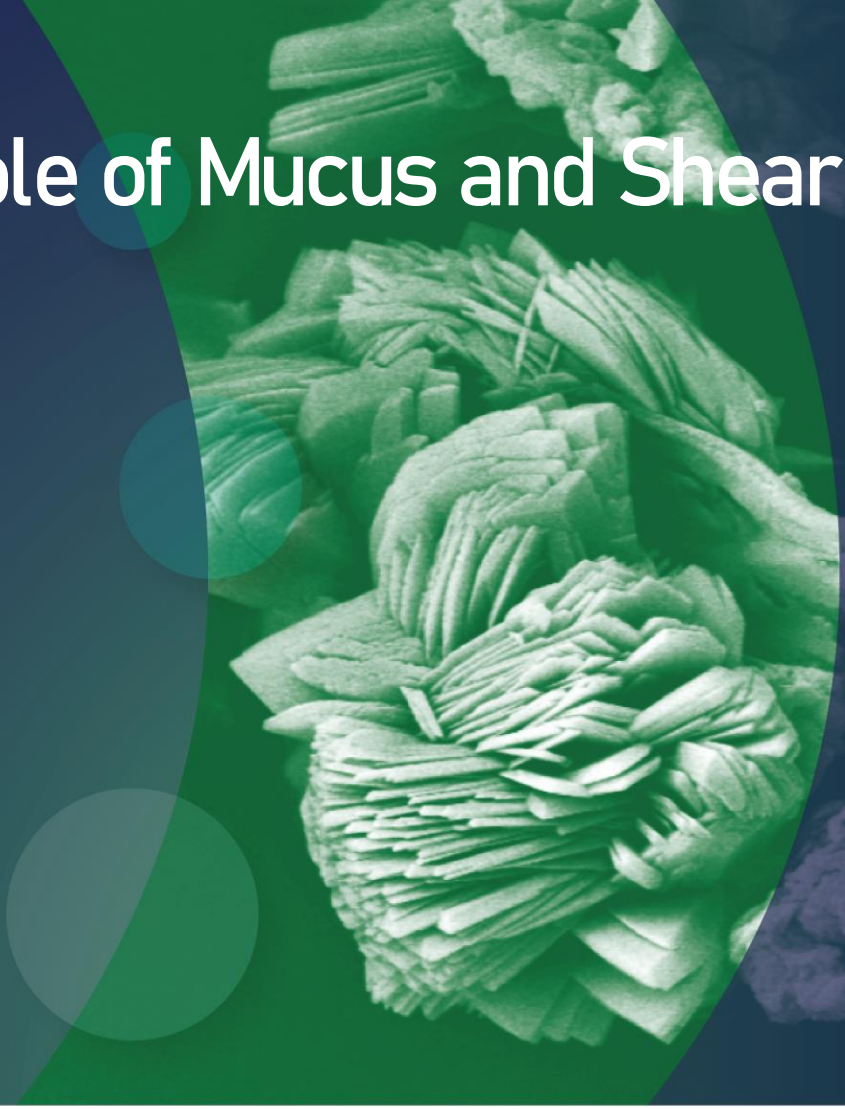
A Multifaceted Model Exploring the Role of Mucus and Shear Stress in Intestine

Ibrahim Erbay

Understanding Biology Through COMSOL



COMSOL Conference, Florence, 2024

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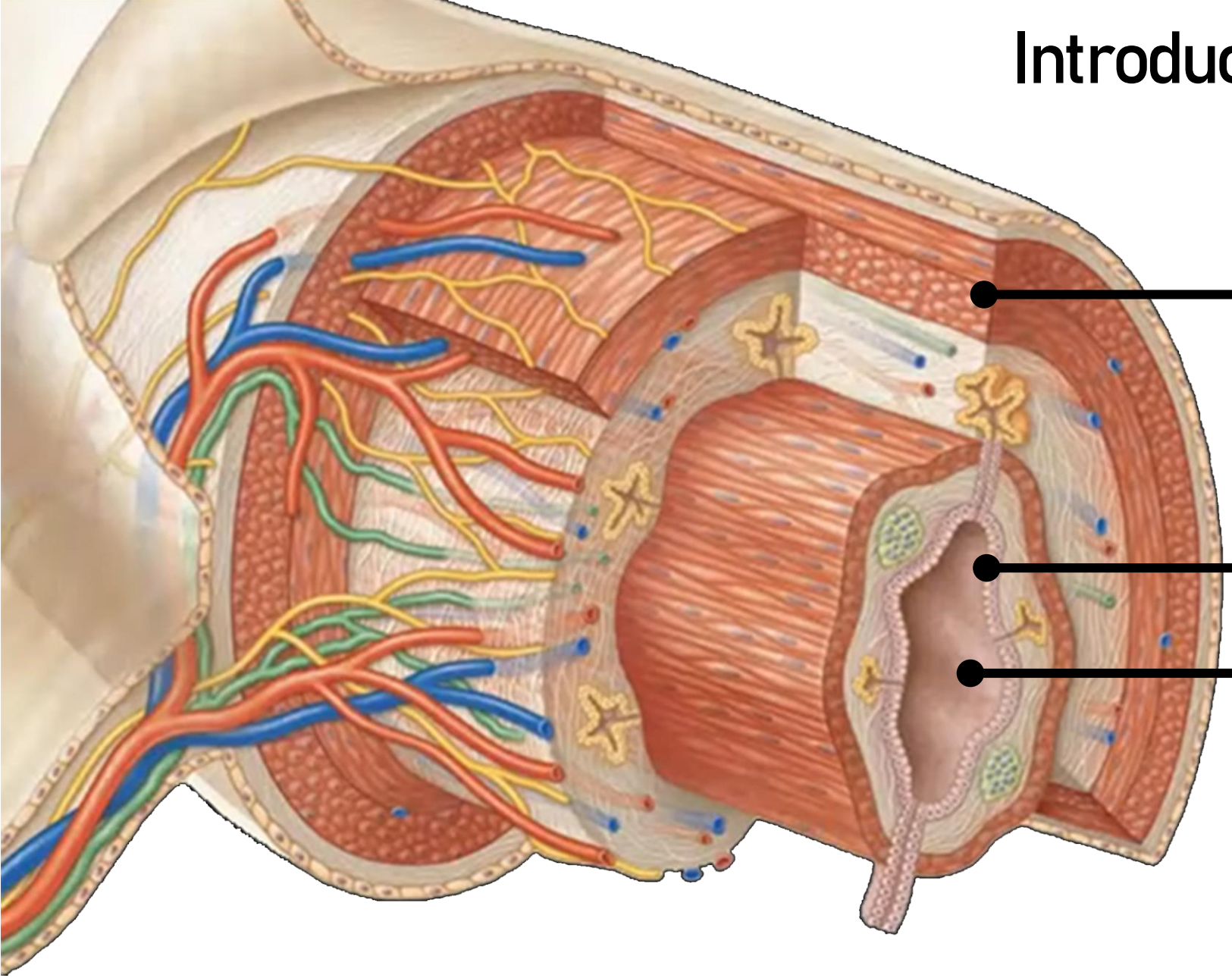
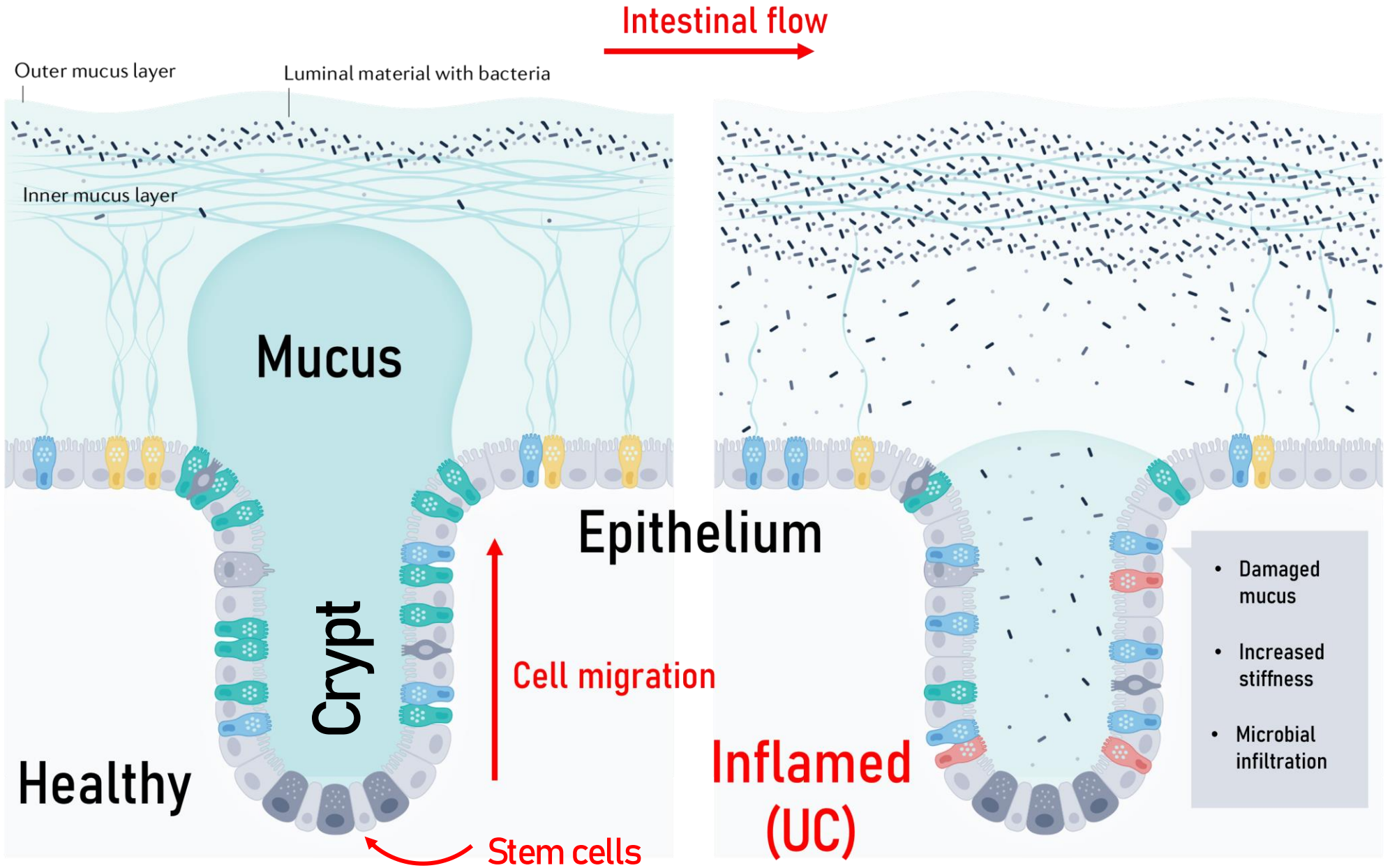
Engineering Underpinning Medicine

Introduction: Organization of the human intestine



Introduction: Intestine in Health and Disease

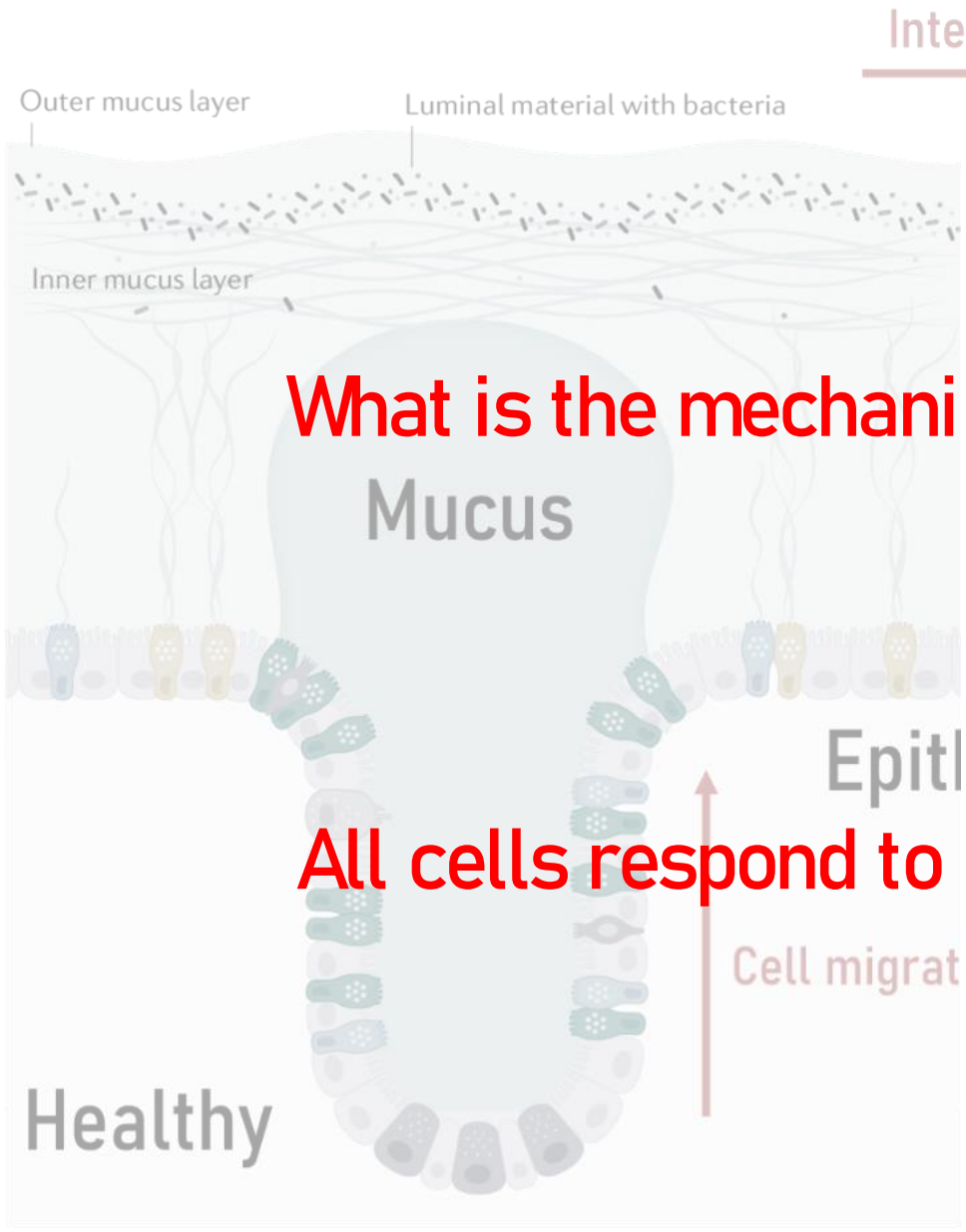


~10^{11} cells/day

Highly mechanical process

Deformed mucus leads to inflammation

Introduction: Intestine in Health and Disease



RESEARCH ARTICLE

ADVANCED SCIENCE
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Modulation of Gut Barrier Functions in Ulcerative Colitis by Hyaluronic Acid System

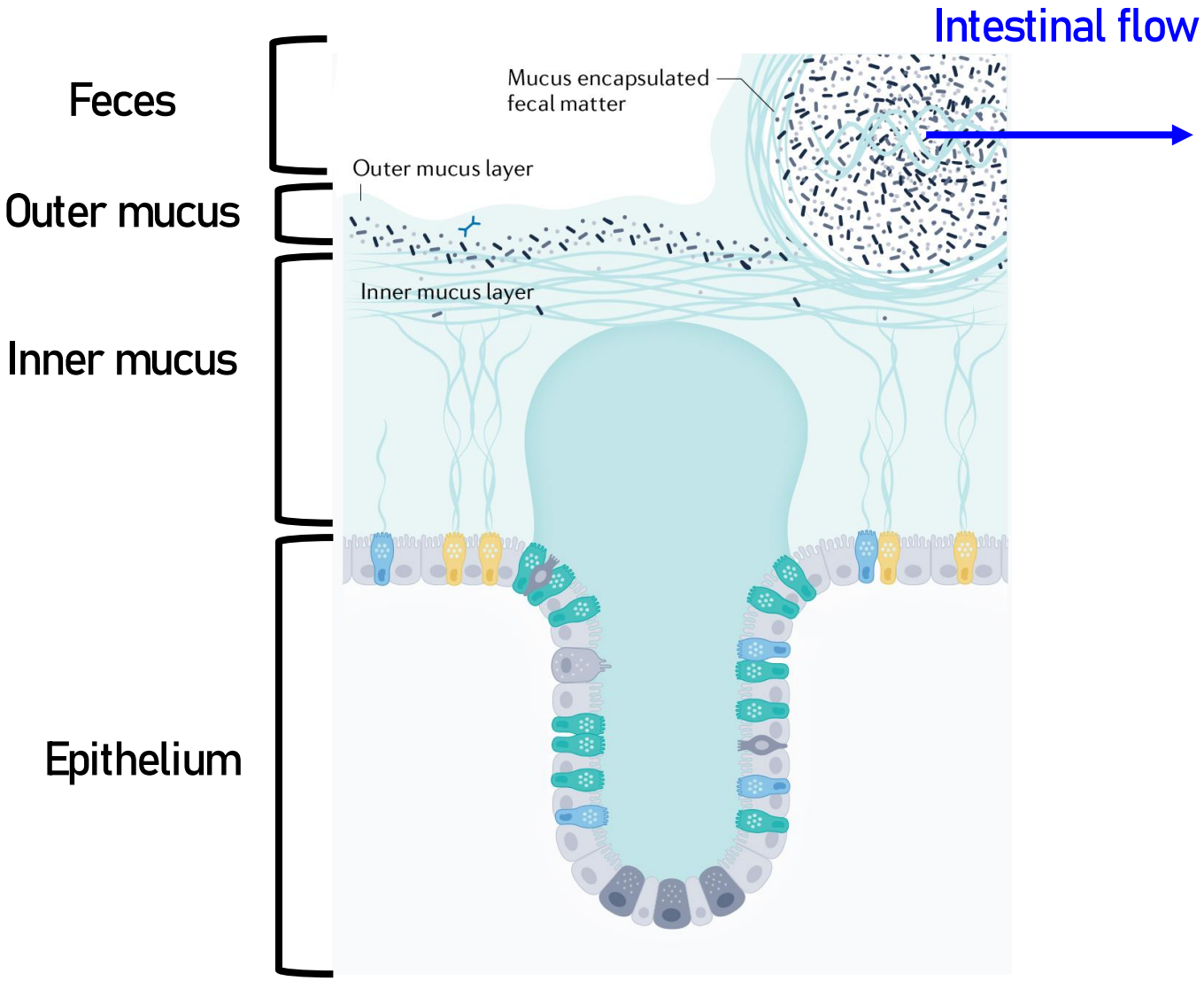
Niranjan G. Kotla, Isma Liza Mohd Isa, Swetha Rasala, Secil Demir, Rajbir Singh, Becca V. Baby, Samantha K. Swamy, Peter Dockery, Venkatakrishna R. Jala, Yury Rochev, and Abhay Pandit**

The active stages of intestinal inflammation and the pathogenesis of ulcerative colitis are associated with superficial mucosal damage and intermittent wounding that leads to epithelial barrier defects and increased permeability. The standard therapeutic interventions for colitis have focused mainly on maintaining the remission levels of the disease. Nonetheless, such treatment strategies (using anti-inflammatory, immunomodulatory agents) do not address colitis' root cause, especially the mucosal damage and dysregulated intestinal barrier functions. Restoration of barrier functionality by mucosal healing or physical barrier protecting strategies shall be considered as an initial event in the disease suppression and progression. Herein, a biphasic hyaluronan (HA) enema suspension, naïve-HA systems that protect the dysregulated gut epithelium by decreasing the inflammation, permeability, and helping in maintaining the epithelial barrier integrity in the dextran sodium sulfate-induced colitis mice model is reported. Furthermore, HA-based system modulates intestinal epithelial junctional proteins and regulatory signaling pathways, resulting in attenuation of inflammation and mucosal protection. The results suggest that HA-based system can be delivered as an enema to act as a barrier protecting system for managing distal colonic inflammatory diseases, including colitis.

intestinal microbiome imbalance[3,4] resulting in gut barrier dysfunction.[5,6] The active stages of intestinal inflammation (in Crohn's and colitis) are linked to decreased transepithelial resistance and increased permeability.[7–9] The elevated levels of reactive oxygen species (ROS) and metalloproteinases cause tissue degradation and necrosis induction.[10,11] Moreover, the inflammatory mediator elements are critical causative factors to mucosal inflammation and enhance overall permeability at the gut wall's ulcerative sites.[12–14] Additionally, patients with IBD have decreased levels of tight junctional proteins (claudins, occludins) and junctional adhesion molecules (cadherins, catenins), leading to increased intestinal permeability resulting in systemic inflammation extraintestinal manifestations.[7,8]

The standard therapeutic interventions for IBD include anti-inflammatory, immunosuppressants, and biological medications, which have focused mainly

Modelling Epithelial Geometry and Intestinal Motility



Poster
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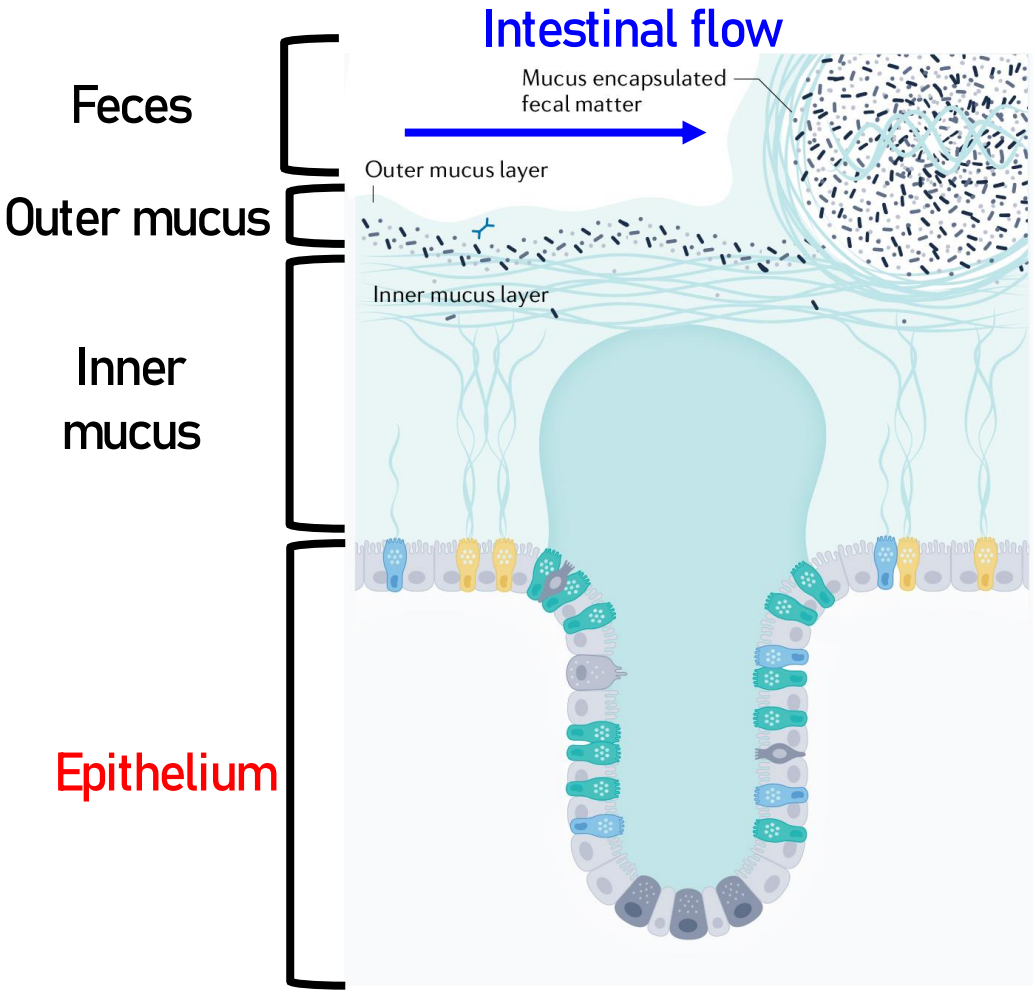
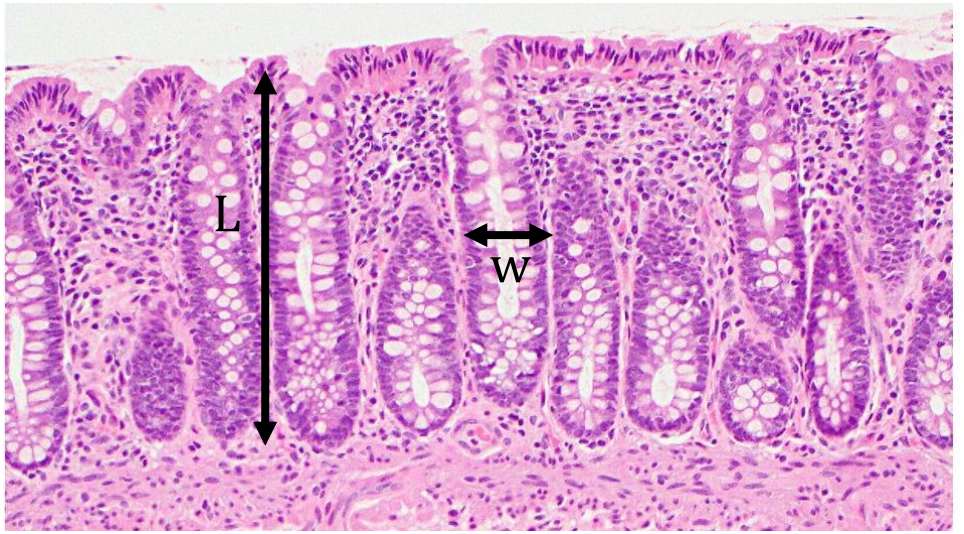
Modelling Epithelial Geometry and Intestinal Motility



Human Colon Histology



Crypt geometry

Webpath Utah

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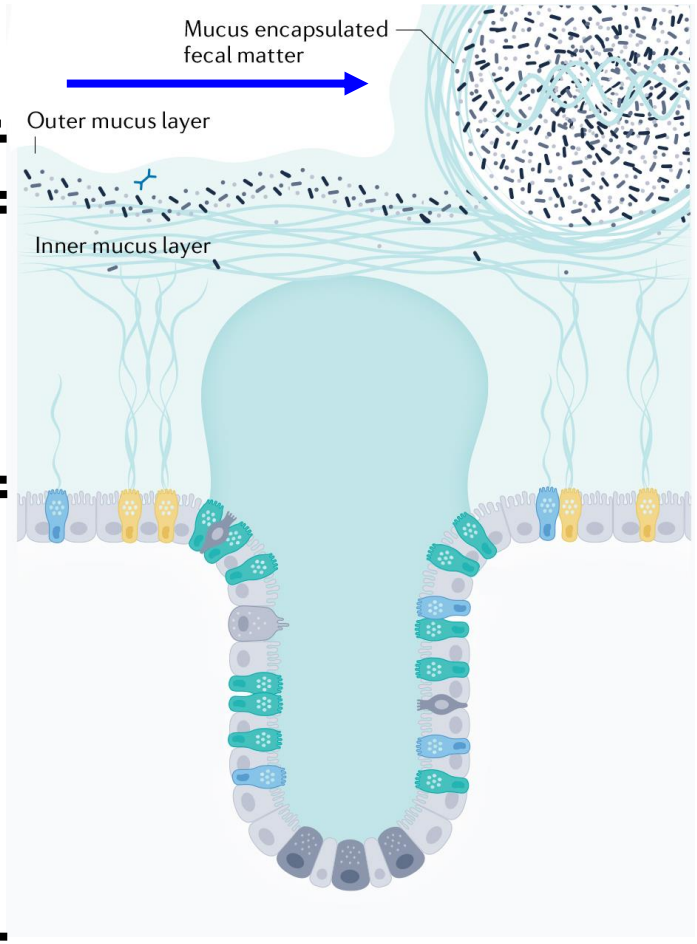
Modelling Epithelial Geometry and Intestinal Motility

Feces

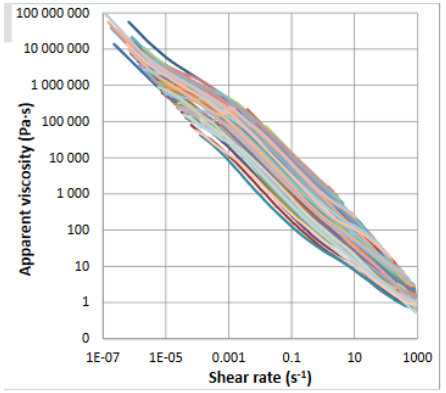
Outer mucus

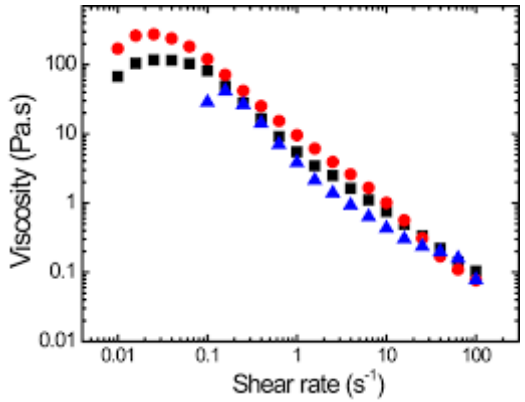
Inner mucus

Epithelium



Human fecal and mucosal rheology





Rheological properties

Woolley et al., 2013

Srinivasan et al., 2022

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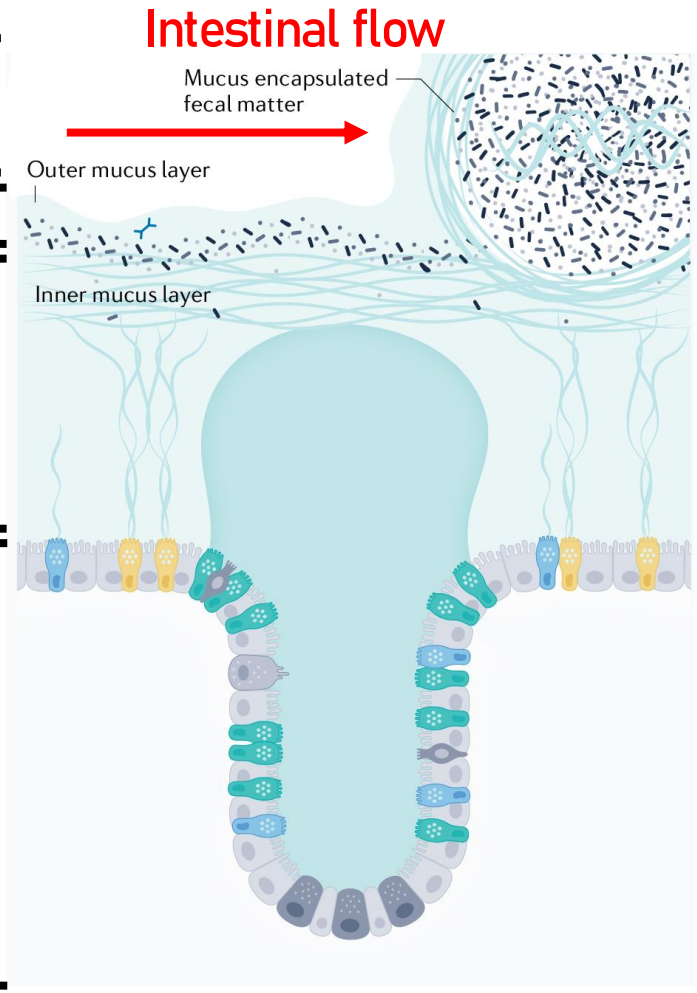
Modelling Epithelial Geometry and Intestinal Motility

Feces

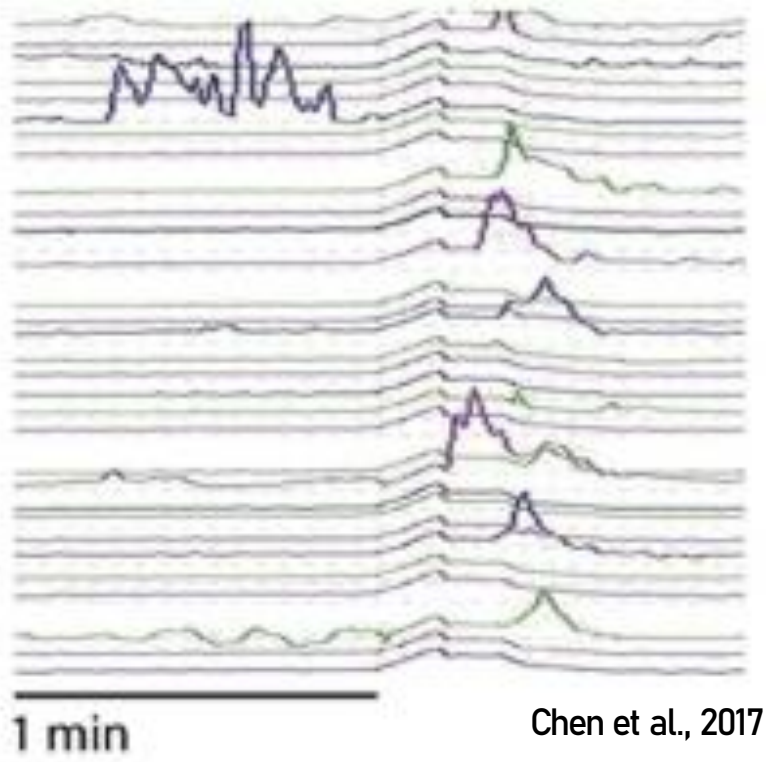
Outer mucus

Inner mucus

Epithelium



Human intestinal pressure waves



Chen et al., 2017

Flow characteristics

$$P(t) = P_{max} e^{-\frac{(t-t_0)^2}{(2Dt)^2}}$$

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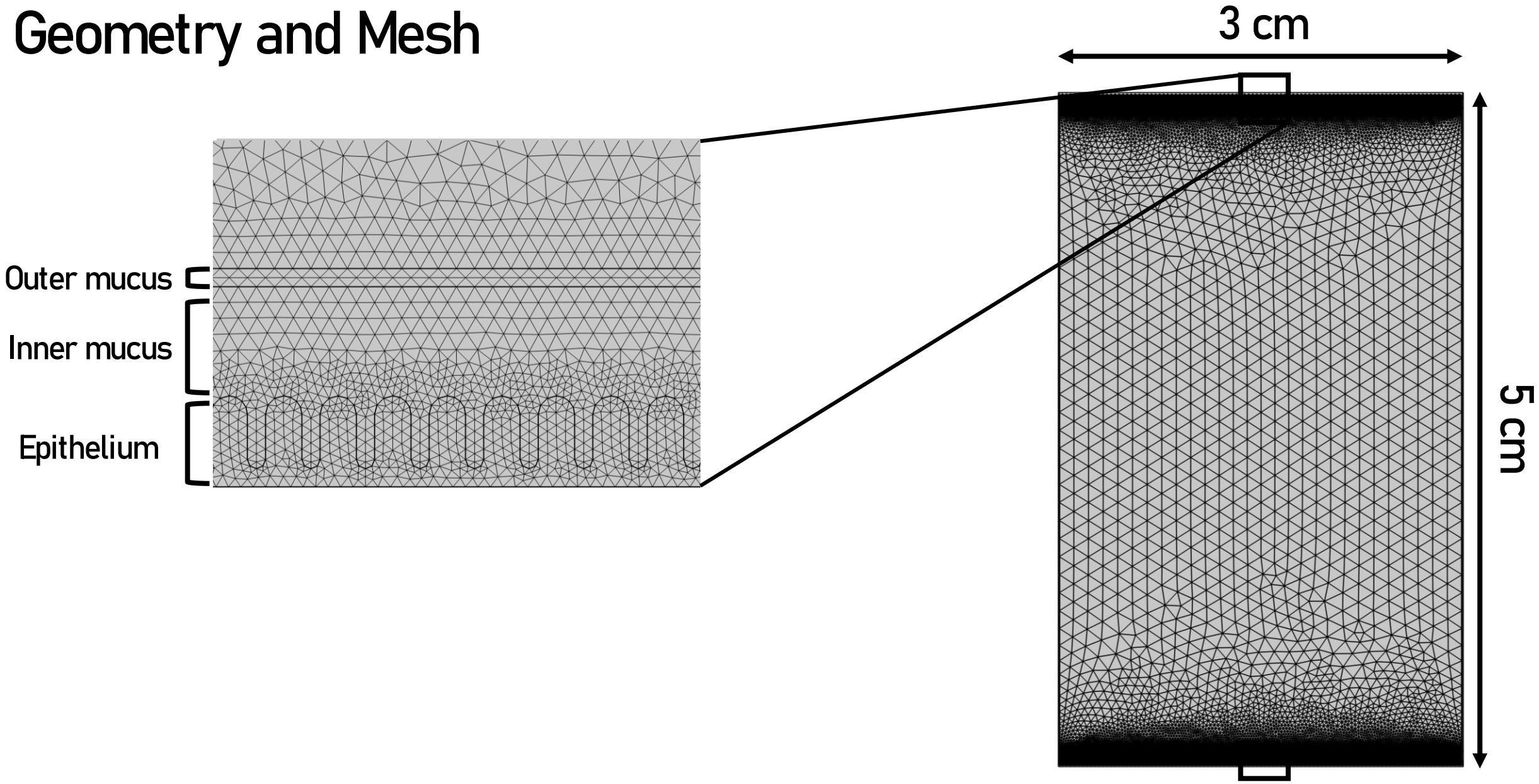
Geometry and Mesh



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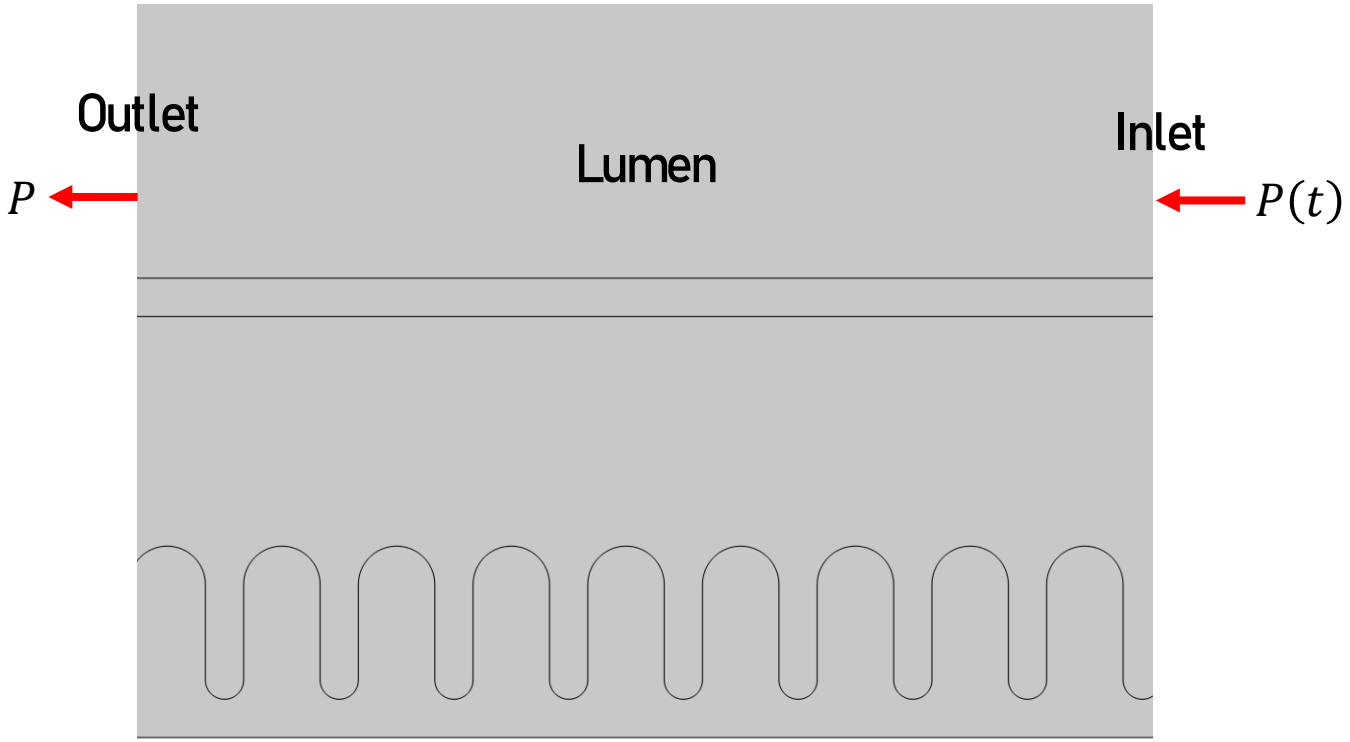
Boundary Conditions and Domains



Structural mechanics

Solid Domain

Epithelium

Laminar flow
Ternary-phase field
Moving mesh

Fluid domain

Feces (Power Law Fluid)
Outer mucus (Carreau Fluid)
Inner mucus (Carreau Fluid)

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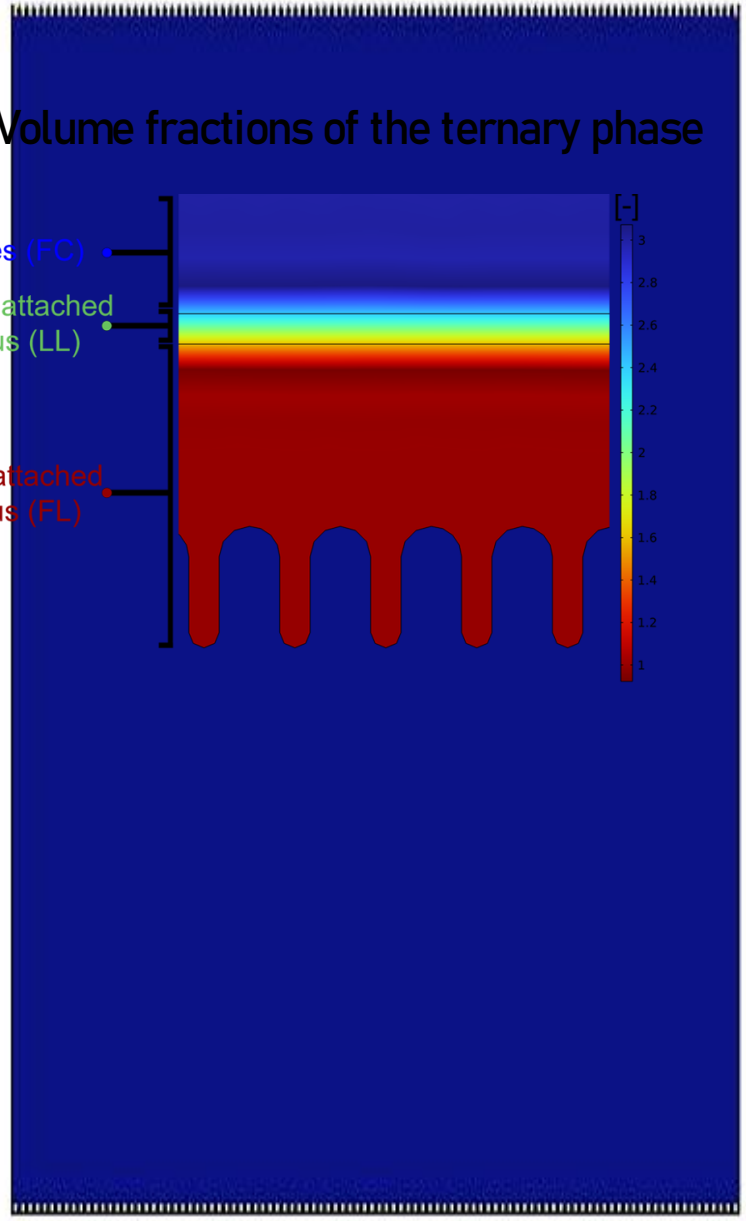
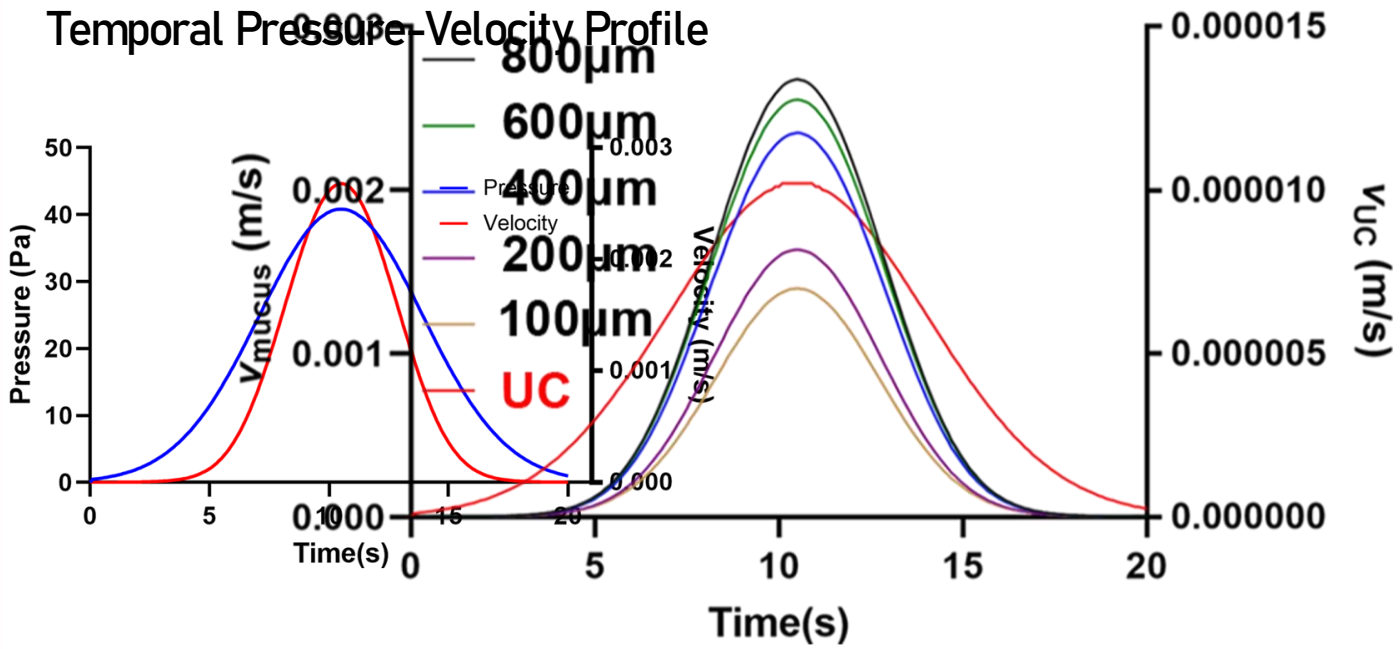
Mucus Increases Flow Velocity





Two orders of magnitude lower velocity in the inflamed model

Increasing mucus thickness resulted in increased flow velocity

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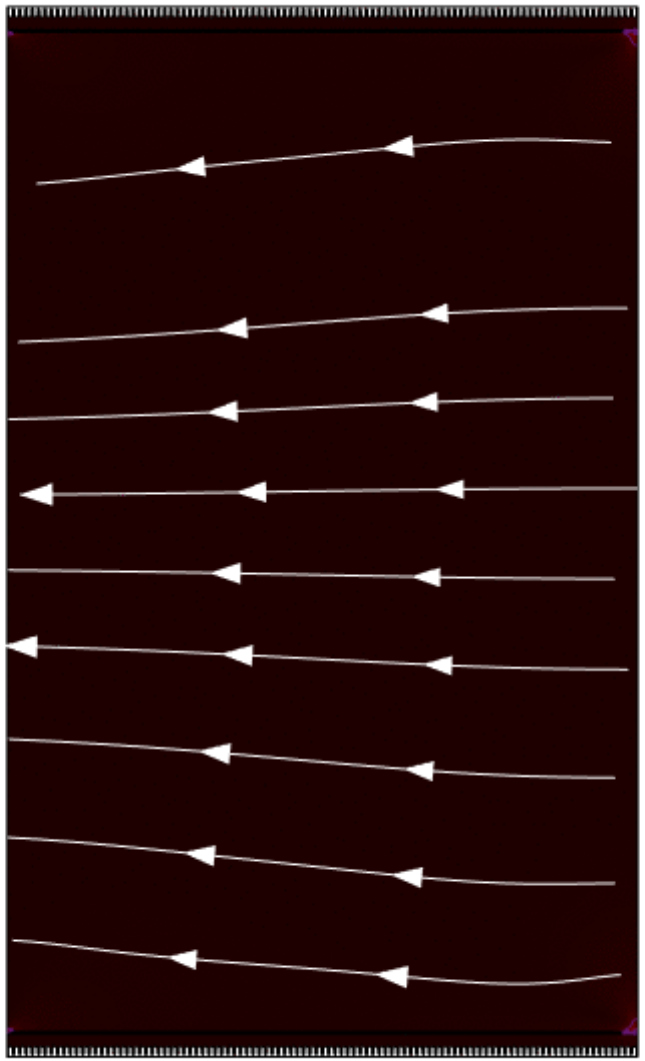
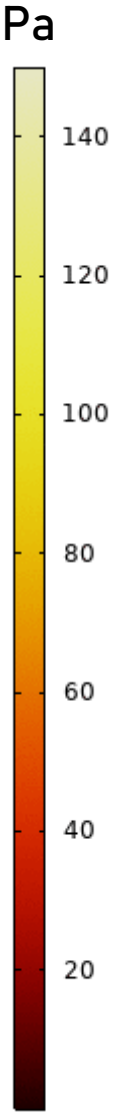
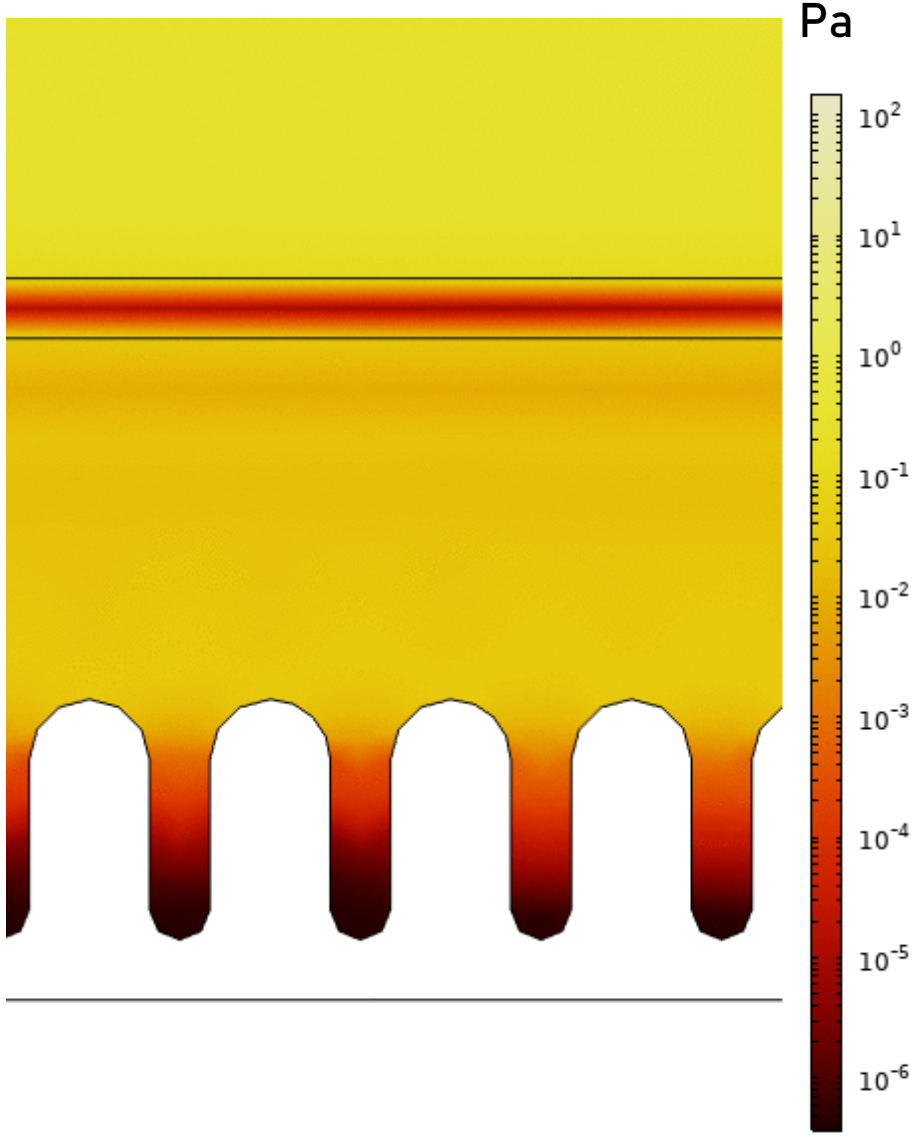
Mucus reduces shear stress applied on the epithelium







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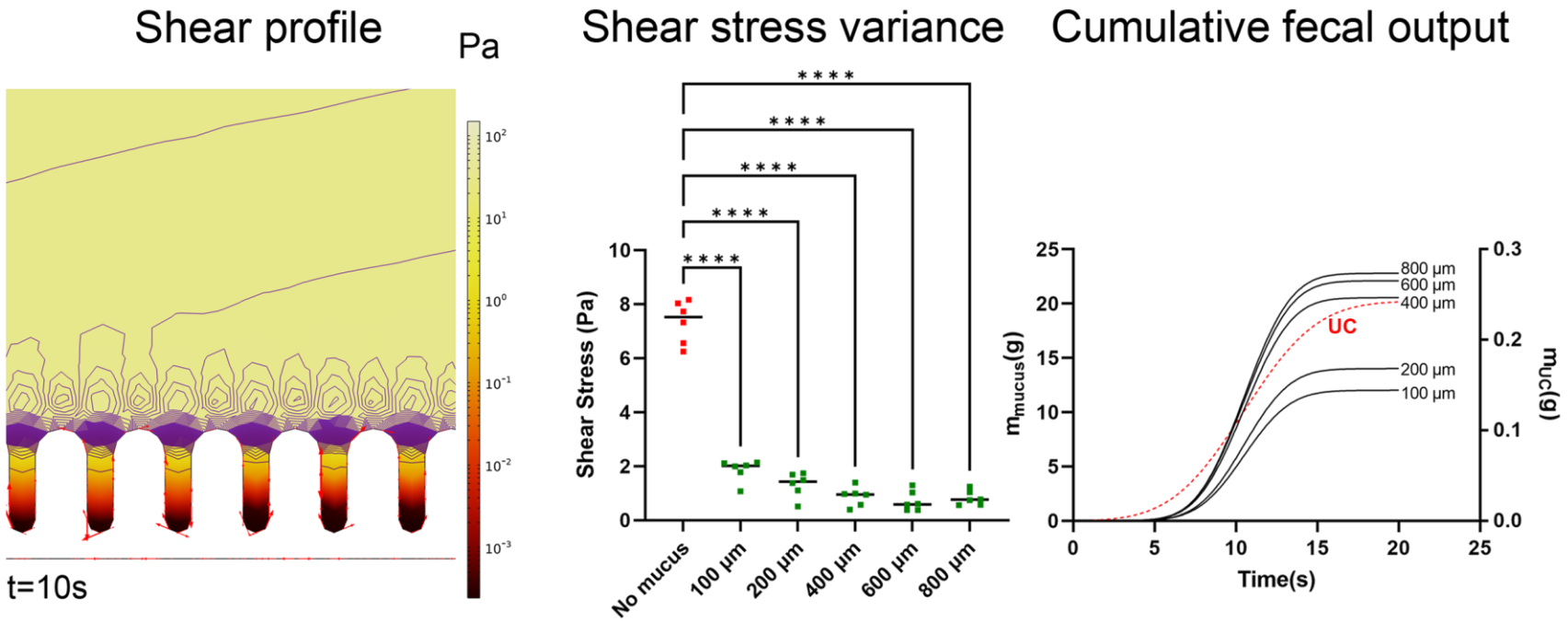
Mucus reduces shear stress applied on the epithelium



Lower shear magnitude on epithelium in mucus models

Increased fecal mass output in mucus models

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Why does this matter?

- Shear stress is known to change cell behaviour in intestine (e.g. division, differentiation, death, mucus secretion and migration)

- We hypothesize that mucus modulates the shear stress transferred to the epithelium and its absence may cause crypt damage via increased mechanical input

- This model could be used for optimizing understanding intestinal biology and drug delivery applications (e.g. nanoparticles)

Acknowledgements

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Dr Alessio Alexiadis

All CURAM and lifETIME CDT members

Thanks for the attention!
Any questions?

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