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

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Abstract

The intestine is a muscular, tubular organ within the digestive system responsible for the final stages of food processing. The cyclic material transport generates a shear stress on the intestinal lining known as epithelium. Recently, the application of shear stress on epithelial cells has been shown to affect cellular processes such as proliferation, differentiation, and mucus secretion. Despite the extensive research on biological regulation and functional pathways, and biomechanical analyses identifying mechanical events, the mechanical role of mucus and the effect of shear stress in these processes are not fully understood. Our approach is based on a ternary-phase field and a fluid-solid interaction method to represent the basic biomechanical microenvironment of the intestine. We used experimental data on intraluminal pressure, mucosal and fecal rheology, and epithelial geometrical characteristics to predict the shear distribution in healthy and inflamed (UC) intestinal conditions. Our model provides important insights into the time-space mosaic of mechanical forces, as well as how mucus thickness affects the spatial shear stress distribution. Our results suggest that increasing thickness results in a lower shear stress delivery, and its absence causes an order of magnitude higher shear stress on the epithelium. Further, we observe a significant reduction in fecal output in the UC model due to velocity reduction, indicating the lubricative effect of mucus. Our model allows studying the effect of various properties such as viscosity, density, and geometry to investigate possible mechanistic aspects of various intestinal processes in homeostasis and disease.

Keywords: Human intestine, intestinal mucus, shear stress, ternary-phase field, computational fluid dynamics.

Introduction

The human adult intestinal system consists of 7 meters of small and 2 meters of large intestine. Coordinated contractions and relaxations of intestinal muscles allow material transport and mixing. The surface of the intestine is lined with epithelium which is a single layer of specialized cells that absorb nutrients, form mucus that protects against pathogens, and secrete hormones. Intestinal mucus is a gel-like substance that lines the surface of the intestinal epithelium, playing a critical role in protecting the intestine from mechanical forces and pathogens [1]. The mucus is mainly composed of water, proteins, lipids, and mucins and large glycoproteins that give the mucus its shear-thinning properties. In the small intestine, mucus is relatively thin to allow better transport and enhance absorption of nutrients. Large intestinal mucus presents a bilayer structure with a loose viscosity top layer and a firmly attached high viscosity layer. The top layer coats the luminal contents, generating a lubricative effect that eases material transport whereas the underlying layer protects the tissue from mechanical forces and blocks pathogens. During an injury or chronic inflammatory response, the mucus layer is often damaged, causing continuous inflammation and failure to protect against mechanical forces. Although recent studies highlight the roles of mechanobiology and tissue functions in regeneration and immune activation, the mechanical role of mucus is often disregarded [2]. Here, we develop a computational fluid dynamics model of a healthy and UC human large intestinal microenvironment to study the fecal output efficiency and shear stress transfer to the epithelium. Our results indicate that the reduction of mucosal thickness causes increased shear stress transfer and reduced fecal velocity. Moreover, our UC model where mucus is absent, exhibited an order of magnitude higher shear stress and lower velocity than the healthy model. Our results are consistent with clinical observations where patients with inflammatory bowel disease (IBD) often present reduced bowel motility. We anticipate that the change in the mechanical microenvironment may have a role in tissue repair mechanisms and the establishment of homeostasis. For instance, it has been previously shown that shear stress promotes intestinal cell proliferation and differentiation. Furthermore, we believe that our model could be used for studying drug delivery applications and optimization studies.

Governing Equations

COMSOL Multiphysics 6.0 was used to model the human colonic microenvironment. The mucosal models consisted of laminar flow, ternary-phase field, solid mechanics and fluid-structure interaction interfaces. The UC model, on the other hand, consisted of laminar flow, solid mechanics and fluid-structure interaction interfaces. The material properties of the components are given in Tables 1 and 2.

Table 1. *Mucosal parameters (Carreau Fluid)*

Component/ Parameter	Loose mucus	Firmly attached mucus
Zero shear rate viscosity [Pa s]	0.1	21
Infinite shear rate viscosity [Pa s]	0	0.1
Power index (n)	0.375	0.375
Relaxation time (λ) [s]	0.001	15
Density [kg m-3]	1000	1400

Table 2. *Fecal parameters (Power Law Fluid)*

Fecal parameters	
Fluid consistency coefficient (m) [Pa s]	482
Flow behaviour index (n)	0.31
Density [kg m^{-3}]	1060

In all models, the fecal flow was simulated using a distribution equation which was imposed on the inlet boundary (see Fig. 1):

$$P(t) = P_{max} e^{-\frac{(t-t_0)^2}{(2Dt)^2}} \quad (1)$$

where *P(t)* is the pressure, P_{max} is the peak pressure value adapted from clinical studies, and *Dt* is the standard deviation. The pressure applied to the inlet generates a hypothetical peristalsis-like fecal push in the system.

Using the laminar flow interface, the luminal flow is described as:

$$\rho \nabla \cdot \boldsymbol{u}_{fluid} = 0 \quad (2)$$

$$\rho \frac{\partial \boldsymbol{u}_{fluid}}{\partial t} + \rho(\boldsymbol{u}_{fluid} \cdot \nabla)\boldsymbol{u}_{fluid} = \nabla \cdot \left[-p\boldsymbol{I} + \mu\left(\nabla \boldsymbol{u}_{fluid} + \nabla \boldsymbol{u}_{fluid}{}^{T} - \frac{2}{3}\mu(\nabla \cdot \boldsymbol{u}_{fluid})\boldsymbol{I}\right)\right] + \boldsymbol{F_{st}} + \boldsymbol{F} \quad (3)$$

where ρ is the density of the fluid [kg m^{-3}]; $\boldsymbol{u}_{fluid}$ is the fluid velocity vector [m s^{-1}]; t is the time [s]; p is pressure [Pa]; $\boldsymbol{I}$ is the identity matrix; μ is the dynamic viscosity of the fluid [Pa s]; T transpose of the velocity gradient tensor; $\boldsymbol{F_{st}}$ is the surface tension force, and $\boldsymbol{F}$ is the external force acting on the fluid.

Both mucus layers were considered to be shear-thinning non-Newtonian fluids. The Carreau model was used to describe the apparent viscosity $\mu_{app,i}\,(i)$ as a function of the strain rate $\dot{\gamma}$ for as follows:

$$\mu_{app,i} = \mu_{\infty,i} + (\mu_{0,i} - \mu_{\infty,i})[(1 + \lambda\dot{\gamma})^2]^{\frac{n-1}{2}} \quad (4)$$

where $\mu_{\infty,i}$ is the viscosity of phase i at infinite shear, $\mu_{0,i}$ is the viscosity of phase i at zero shear, λ is the characteristic time constant, $\dot{\gamma}$ is shear rate, and n is the power index.

The behaviour of the fecal phase was described through the following:

$$\mu_{app,FC} = m\left(\frac{\dot{\gamma}}{\dot{\gamma}_{ref}}\right)^{n-1} \quad (5)$$

where *m* and *n* were adapted from Woolley *et al*., which were fluid consistency coefficient and flow behaviour index respectively and calculated using rheological data of human faeces and as n<1 results in inaccuracies in the equation, a lower limit for $\dot{\gamma}$ was set as $\dot{\gamma}_{ref}$ [3].

The ternary-phase field model solves the following Cahn-Hilliard equations to track phase volume fractions in the system, assuming the phases are immiscible:

$$\frac{\partial \phi_i}{\partial t} + \nabla \cdot (\boldsymbol{u}\phi_i) = \nabla \cdot \left(\frac{M_0}{\xi_i}\nabla \eta_i\right) \quad (6)$$

$$\eta_i = \frac{4\xi_\Gamma}{\varepsilon}\sum_{j \neq i}\left(\frac{1}{\xi_j}\left(\frac{\partial F_e}{\partial \phi_i} - \frac{\partial F_e}{\partial \phi_j}\right)\right) - \frac{3}{4}\varepsilon\xi_i\nabla^2\phi_i \quad (7)$$

ϕ_i is the phase field variable and i indicates the phase volume fraction varying from 0 to 1; $\boldsymbol{u}$ is the fluid velocity vector; M_0 is the mobility parameter [m^3 s^{-1}]; ξ_i is the capillary parameter; η_i is the chemical potential; F_e is the free energy of the system and ε is the interface thickness.

The epithelium was modelled as the solid domain which can be expressed as:

$$\rho \frac{\partial^2 \boldsymbol{u}_{solid}}{\partial t^2} = \nabla \cdot (\boldsymbol{FS})^T + \boldsymbol{F_v} \quad (8)$$

where $\boldsymbol{u}_{solid}$ is the displacement in the solid body; ρ is the epithelium´s density; $\boldsymbol{S}$ is the second Piola-Kirchhoff stress tensor; $\boldsymbol{F}$ is the deformation gradient and $\boldsymbol{F_v}$ is the body force.

The deformation gradient can be expressed as the gradient of displacement vector $\boldsymbol{u_{solid}}$

$$\boldsymbol{F} = (\boldsymbol{I} + \nabla \boldsymbol{u}_{solid}) \quad (9)$$

The fluid flow condition that is described by the Navier-Stokes equations provides a solution for the velocity field $\boldsymbol{u}_{fluid}$. The total force exerted on the fluid-solid boundary is given by:

$$\boldsymbol{f} = \mathrm{n} \cdot \left\{ -p\boldsymbol{I} + \mu \left(\nabla \boldsymbol{u}_{fluid} + \nabla \boldsymbol{u}_{fluid}{}^T - \frac{2}{3}\mu (\nabla \cdot \boldsymbol{u}_{fluid}) \boldsymbol{I} \right) \right\} \quad (10)$$

Where p is the pressure; μ is the dynamic viscosity; n is the outward normal to the boundary; and $\boldsymbol{I}$ is the identity matrix, and the fluid velocity is coupled to the solid displacement rate as:

$$\frac{\partial \boldsymbol{u}_{solid}}{\partial t} = \boldsymbol{u}_{fluid} \quad (11)$$

A fully coupled solver used with time stepping is determined automatically using a backward differentiation formula.

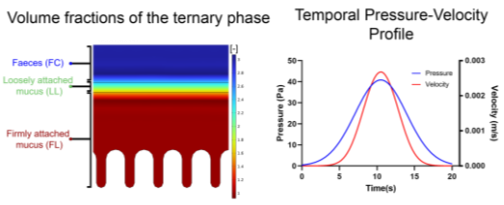

Figure 1. *Volume fractions of the epithelial components in the ternary-phase field and pressure-velocity relationship of the fecal flow.*

Finally, hydrodynamic shear stress was calculated as the product of shear rate and fluid viscosity as follows:

$$\tau = \mu \dot{\gamma} \quad (12)$$

Results

The system exhibits typical laminar flow, with lower velocities near the walls and peak velocity at the center of the channel. The average Reynolds number in the mucus models was $4.13 \cdot 10^{-6}$, while in the UC model, it was $5.23 \cdot 10^{-8}$. In the UC model, the luminal velocity at the center of the channel reached $2.71 \cdot 10^{-5}$ m/s at peak pressure, compared to $1.4 \cdot 10^{-3}$, $1.6 \cdot 10^{-3}$, $2.3 \cdot 10^{-3}$, $2.5 \cdot 10^{-3}$, and $2.6 \cdot 10^{-3}$ m/s for 100, 200, 400, 600, and 800 µm mucus layers, respectively. On average, the mucus models exhibited velocities two orders of magnitude higher than the UC model. This suggests that we capture a key behaviour of intestinal mucus where it functions as a lubricant, facilitating the movement of feces in the colon. The simulated net velocity values were consistent with in vivo measurements of colonic content velocity, around $4.7 \cdot 10^{-3}$ m/s, as measured by MRI [4].

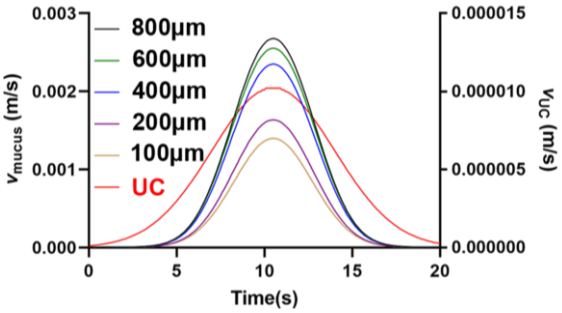

Figure 2. *Temporal velocity comparison of healthy and inflamed (UC) models*

In the UC model, luminal shear at the center of the channel reaches 1.06 Pa after 10 seconds at peak pressure, compared to 6.35, 9.9, 13.9, 14.7, and 19.6 Pa in the mucus models with mucus thicknesses of 100, 200, 400, 600, and 800 µm, respectively. These findings align with velocity data, as higher velocities are associated with increased shear. Further statistical analysis of shear stress variance near crypt structures shows significantly higher values in the UC model compared to mucus models. This suggests that the absence of mucus results in a notable increase in shear stress, while thicker mucus layers reduce shear transfer to crypt structures. These findings are consistent with recent research by Kotla et al., which demonstrated that applying a hydrogel-based physical barrier reduced inflammation in a mouse colitis model by mimicking the protective effects of mucus in shear dissipation and epithelial barrier

restoration [5]. Shear stress trends downward with increasing mucus thickness, with 600 µm showing the lowest values, while 800 µm mirrors the behavior of the 400 µm model at all three measurement sites. Analyzing shear-induced traction on crypts shows that in both UC and mucus models, traction behavior correlates with epithelial cell migration from the crypt base to the top which suggests that the shear may have a role in active cell migration in the intestine. The model suggests that shear stress increases from $0.094 \cdot 10^{-5}$ to $2.47 \cdot 10^{-5}$ Pa at the crypt base to 0.71 and 7.34 Pa at the crypt top in homeostatic and UC models, respectively. These results highlight the protective role of mucus in shielding the epithelium from shear stress, which is known to influence cellular behavior. Consistent with theories of shear-driven intercellular forces, our numerical results support the hypothesis that shear stress regulates cell migration dynamics from the crypt base to the top. This is in line with recent findings by Pérez-González et al., who demonstrated that pressurization and patterned forces drive crypt morphogenesis and epithelial cell migration in intestinal organoids. The observed increase in shear stress from the crypt base to the top may also play a role in processes like cellular differentiation and immune surveillance.

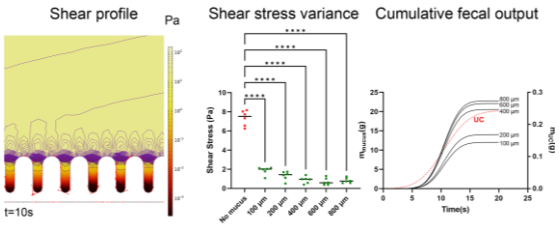

Figure 3. *Shear profile and quantification of results.*

Conclusions

We report a multi-physics model of the colon to investigate the effects of motility-induced shear stress on the colonic crypts and the role of the mucus bilayer. The model incorporates physiologically relevant intraluminal flow conditions, viscoelastic mucus layers, and analyses shear stress at biologically crucial crypt zones, representing unique features compared to existing models. Our findings emphasize the significant interplay between velocity, shear stress, and mucus, which may play a crucial role in both intestinal inflammation and homeostasis. This focus on mucus and shear stress may be critical for developing better microphysiological models, offering unique mechanistic insights into colonic function. Further, utilizing such models may allow studying mucus-drug interactions to optimize therapeutic applications. Ultimately, this model provides a computational tool for investigating the mechanistic framework of both healthy and inflamed intestinal states, expanding our understanding of biological mechanisms and supporting the development of new therapeutic hypotheses.

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Acknowledgements

This work was supported by Science Foundation Ireland 18/EPSRC-CDT/3583 and the Engineering and Physical Sciences Research Council EP/S02347X/1. This work has emanated from research supported in part by a grant from Science Foundation Ireland (SFI) and the European Regional Development Fund (ERDF) under grant number 13/RC/2073_P2.