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A mixture model for the dynamic of mucosal barrier

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The main goal of the project is the numerical investigation of a mathematical model describing the mucus barrier of the human gut. We wish to set up a 2D test case demonstrating the ability of the model to recover physiological characteristics of the mucus layer. Several modeling options will be discussed and compared.

1 Biological context

1.1 The gut microbiota

A symbiotic relationship. The main physiological function of the gut is pumping water to maintain the hydration of the whole body. However, secondary functions where identified, often mediated by bacteria hosted by the gut. The human gut is colonized by a complex microbial community, called the gut microbiota. The host develops with its microbiota a symbiotic relationship. The host tolerates those bacterial species that in turn provide several benefits:

- They finalize the digestive process by metabolising components that the host can not assimilate alone (e.g. : fibres...) into assimilable metabolites : up to 10 % of the daily energetic needs are provided by the microbiota.
- They have a direct immune action by avoiding the colonization of pathogens : they can eliminate invading pathogens by dominating them in the competition for food or by active process such as antibiotic secretions.
- They have an indirect beneficial action on the host immune system : they stimulate the immune function during the first stages of life, or they modulate immune process such as inflammation.

The number of bacteria in the gut is about 10 times higher than the amount of human cells in the whole body. The microbiota then gathers several characteristics that lead some biologists to consider it as an organ in its own right.

A scientific hot point. The fast development of DNA sequencing techniques have permitted a huge improvement of the knowledge of microbial community structure and function.

The researcher community now focus on the direct implication of the microbiota in gut diseases (e.g. chronic inflammation) or on ecological issues related to the perturbation of the microbial community structure during biological stress (antibiotherapy, invasion of pathogens...). But more indirect host-microbiota interactions have been discovered such as e.g. the influence of the microbiota composition on allergic disorders, on metabolic disorders related to obesity, or on mental disorders such as mood disorders or autistic disorders. Fundamental research on gut microbiota also interests the food industry for the development of pre and probiotic products. That societal challenges makes the gut microbiota study an important field of microbiology.

1.2 A "first order" immunitary defence against the microbiota : a mucus layer

Despite their benefits, all the bacterial communities represent a potential infection danger for the host. In order to enjoy the goods that the microbiota can provide, the host first have to develop several defensive strategies to protect itself from the negative action of the bacteria. If the host immune system develops complex active mechanisms to manage with its microbiota, a more simpler and passive protective tool also protects the host : an insulating layer of mucus physically separates the microbial populations from the host tissues.

Mucus layer structure and function. The mucus layer is actually composed of two distinct layers with different rheological characteristic. A first viscous layer, 50 μm thick, wraps the epithelial cells (the cells of the gut mucosa) and adheres to the surface of the colonic tissues. An external, thicker (100 μm), more fluid layer covers the first one.

The mucus is mainly composed of mucins, a protein produced in specific epithelial cells : the goblet cells. A specific component of the protein has a brush-like configuration able to capture water, facilitating the formation of the gel-like structure of the mucus. In the outer layer, the mucins have an unfolded configuration that enhance their volume and their ability to fix water. This structural differentiation of inner and outer mucins could promote the rheological discrepancies between mucus layers. An additional mechanism can enforce the viscosity gradient between the external and internal layers. The main physiological function of the gut is absorbing water from the intestinal contents. The active water pumping of the intestinal mucosa dries out the inner layer of mucus, whereas the liquid luminal contents keeps hydrated the outer layer. Furthermore, while the luminal flux erodes the external layer of mucus, the inner layer is continuously renewed by the mucosa, allowing mucus turn over.

A complete review of mucus structure and function can be found in [**?**].

Ecological function of the mucus. Unlike the inner layer, the outer layer can be penetrated by bacteria, allowing them to resist the luminal flow and increase their residence time in the gut. Furthermore, some bacterial species are able to metabolize the mucus, producing metabolites that they, as well as the host, can assimilate. This energetic source counterbalances the energetic cost of mucus production. The outer layer of mucus then represents an ecological niche that influences the global ecological equilibrium of the gut microbiota.

2 Mathematical modeling

The model must represent the mucus turnover : production by the mucosa and elimination by the luminal contents. The model of mucus layer will be considered as valid if its steady state, starting from an initial condition without mucus, is composed of two mucus layers with different rheological characteristics: the inner layer being more viscous than the outer one.

2.1 2 phases, 1 velocity/pressure

We start with a simple model involving two phases, with a single velocity and a single pressure:

- $m(t,x)$ = volume fraction of mucus,
- $\ell(t,x)$ = volume fraction of liquid,
- $u(t,x)$ = velocity field
- $p(t,x)$ = pressure field.

The volume fraction obey convection–diffusion equations:

$$\partial_t m + \nabla_x \cdot (um - D_m \nabla_x m) = 0,$$

and

$$\partial_t \ell + \nabla_x \cdot (u\ell - D_\ell \nabla_x \ell) = 0.$$

The idea is that the liquid is mainly driven by convection, except next to the boundary: D_ℓ is thus space-dependent, with small values in the domain, and of order 1 in the vicinity of the wall.

The velocity/pressure pair satisfies

$$-\nabla_x \cdot (\mu(\nabla_x u + \nabla_x u^\intercal)) + \nabla_x p = 0.$$

The viscosity is a function of m, with, say, a sigmoidal profile, with high values when m reaches a certain threshold. The constraint that determines the pressure is given by

$$m + \ell = 1.$$

Thus summing the conservation equations, it casts equivalently as

$$\nabla_x \cdot u = \nabla_x \cdot (D_\ell \nabla_x \ell + D_m \nabla_x m) = \nabla_x \cdot ((D_m - D_\ell)\nabla_x m).$$

We turn to the discussion of the boundary conditions, that drive the dynamics of exchanges between the flows and the boundaries. Mucus and liquid go out and in, respectively, when their volume fraction exceed certain threshold, according to a membrane law. It leads to Robin's like boundary conditions for m and ℓ:

$$(mu - D_m \nabla m) \cdot n = f_m(m) \quad \text{and} \quad (\ell u - D_\ell \nabla \ell) \cdot n = f_\ell(\ell),$$

with $f_m = \theta_m[m - m_\star]_-$ et $f_\ell = -\theta[\ell - \ell_\star]_+$. It follows that the following relation holds on Γ_e

$$\begin{aligned} D_m \nabla(m+\ell)\cdot n &= (m + \frac{D_m}{D_\ell}\ell)u\cdot n - \left(f_m(m) + \frac{D_m}{D_\ell} f_\ell(\ell)\right) \\ &= 0 \end{aligned}$$

It defines the normal component of the velocity

$$u\cdot n = \frac{f_m(m) + \frac{D_m}{D_\ell} f_\ell(\ell)}{m + \frac{D_m}{D_\ell}\ell}.$$

Therefore, denoting $u = (u_x, u_y)$, the Stokes system is complemented with

$$u_x = \frac{f_m(m) + \frac{D_m}{D_\ell} f_\ell(\ell)}{m + \frac{D_m}{D_\ell}\ell} \quad \text{and} \quad u_y = 0$$

2.2 3 phases, 1 velocity/pressure

We can add a volume fraction of bacteria, denoted hereafter $b(t,x)$. It obeys

$$\partial_t b + \nabla_x\cdot(ub - b\nabla_x\Phi) = \nabla_x\cdot(D_b\nabla_x b).$$

In this equation Φ is a chemotactic potential, intended to describe attraction of bacteria by the mucus. Namely, we set

$$\Delta\Phi = m.$$

The potential equation is complemented by Neumann boundary conditions. The constraint becomes

$$m + \ell + b = 1$$

or, equivalently

$$\nabla_x\cdot u = \nabla_x\cdot(D_b\nabla_x b + D_\ell\nabla_x\ell + D_m\nabla_x m + b\nabla_x\Phi).$$

For the boundary conditions on the wall, we suppose that bacteria cannot cross the membrane:

$$D_b\nabla_x b\cdot n = 0,$$

and we use the same conditions as above for m and ℓ.

2.3 2 and 3 phases, 2 velocities

We can write a similar model, but considering two velocities, but still a single pressure:

$$\begin{aligned}
&\partial_t m + \nabla_x\cdot(u_m m - D_m\nabla_x m) = 0,\\
&\partial_t \ell + \nabla_x\cdot(u_\ell \ell - D_\ell\nabla_x \ell) = 0,\\
&-\nabla_x\cdot(\mu_m(\nabla_x u_m + \nabla_x u_m^\intercal)) + m\nabla_x p = 0,\\
&-\nabla_x\cdot(\mu_\ell(\nabla_x u_\ell + \nabla_x u_\ell^\intercal)) + \ell\nabla_x p = 0,\\
&\nabla_x\cdot(mu_m + \ell u_\ell) = \nabla_x\cdot(D_\ell\nabla_x\ell + D_m\nabla_x m) = \nabla_x\cdot((D_m - D_\ell)\nabla_x m),
\end{aligned}$$

endowed with the same b.c. as above.

Similarly, we wish to consider the system with 3 phases

$$\begin{aligned}
&\partial_t m + \nabla_x \cdot (u_m m - D_m \nabla_x m) = 0,\\
&\partial_t \ell + \nabla_x \cdot (u_\ell \ell - D_\ell \nabla_x \ell) = 0,\\
&\partial_t b + \nabla_x \cdot (\tilde{u} b - b \nabla_x \Phi) = \nabla_x \cdot (D_b \nabla_x b),\\
&-\nabla_x \cdot (\mu_m (\nabla_x u_m + \nabla_x u_m^\intercal)) + m \nabla_x p = 0,\\
&-\nabla_x \cdot (\mu_\ell (\nabla_x u_\ell + \nabla_x u_\ell^\intercal)) + \ell \nabla_x p = 0,\\
&\nabla_x \cdot \tilde{u} = \nabla_x \cdot (D_b \nabla_x b + D_\ell \nabla_x \ell + D_m \nabla_x m + b \nabla_x \Phi),
\end{aligned}$$

where $\tilde{u} = \frac{m}{m+\ell} u_m + \frac{\ell}{m+\ell} u_\ell$.

2.4 Fictitious membrane

Another modelling option consists in describing the mucus domain through a fictitious "color function": $\phi(t,x)$, with $\phi(t,x) = 1$ in the mucus, $\phi(t,x) = 0$ otherwise. The membrane is assumed to have a certain thickness, where ϕ varies from 0 to 1. The membrane dynamics is governed by a Cahn-Hilliard equation

$$\partial_t \phi + \nabla_x \cdot (\phi u) = CH(\phi).$$

The right hand side is given by

$$CH(\phi) = \nabla \cdot \big(a(\phi)\big(f''(\phi)\nabla\phi - \kappa \nabla \Delta \phi\big)\big),$$

with $a(\phi) = a_0 \phi(1-\phi)$. Here f is a certain mixing energy density and the derivation of the equation relies on the property of the energy functional (the chemical energy of mixing)

$$\int \big(f(\phi) + \frac{\kappa}{2} |\nabla \phi|^2\big)\, \mathrm{d}x.$$

Note that f is not necessarily convex. A typical profile for f can be obtained as follows: f reaches a negative minimum at $0 < \phi_\star < 1$, $f(\phi)$ increases to 0 as ϕ decreases to 0, and f admits an inflexion point in $(0, \phi_\star)$. A possible example reads $f(\phi) = c_1 \phi^4 - c_2 \phi^2$. Remark also that $CH(\phi)$ vanishes out of the membrane. Equilbrium profile can be identified, and the thickness of the interface is determined by the parameters of the function f.

The velocity obeys the Stokes equation, with surface tension term, proportional to the curvature of the interface

$$-\nabla_x \cdot (\mu(\nabla_x u + \nabla_x u^\intercal)) + \nabla_x p = ST.$$

For the rhs, we can set

$$\nu \nabla \phi + \epsilon \frac{1-\phi^2}{4} \nabla \frac{\nu}{\rho}$$

with

$$\nu = f'(\phi) - \kappa \Delta \phi,$$

and

$$\rho = 1 + \frac{\epsilon}{2}(\phi - 1).$$

The parameter ϵ is given by $\frac{\bar{\rho}_1 - \bar{\rho}_2}{\bar{\rho}_1}$, with $\bar{\rho}_1$ the mass density of the nucus which is larger than the mass density $\bar{\rho}_2$ of the carrier fluid. We can work with $\epsilon = 0$, $\rho = 1$, and thus $TS = \nu \nabla \phi$ (which

again in non zero only in the thick membrane). The expression of the surface tension can be related to the chemical energy of mixing.

We bear in mind that the viscosity depends on m. For m, s, we still use convection–diffusion equations, but now the diffusion coefficients depend on ϕ. For instance the diffusion coefficients can be of order 1 next to the wall, in the mucus zone when $\phi = 1$, and very small otherwise. It is also possible to make them depend on $\nabla\phi$, bearing in mind that, as we make the interface sharp, is behaves like a Dirac function (more precisely $\nabla\phi$ vanishes in the the domains separated by $\{0 < \phi < 1\}$; in this domain $\nabla\phi \cdot n \simeq |\nabla\phi|$). For this problem, we can use specific numerical tools, developped by S. Minjeaud, with free software developed in `C++`.

References

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