Project: designining the release of a new drug

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1 Background

Computational fluid dynamics is tiday a method that is both sufficiently rigorous and efficient to be used for studies of drug delivery in complex physiological structures, like arteries and airways. On the other hand, physical experiments in vitro and in vivo are often expensive and time-consuming. High-performance fluid dynamic has gained increasing attention as a tool in the design process of devices delivering drugs and to reduce significantly the amount of physical experimentation required by conducting virtualized analyses. To understand how drug delivery can be optimized requires simulating idealized vessels in order to understand the principles of mass transport. In this project we will go through an example of such analysis.

A stenotic artery is going to be treated with a new drug that is to be released via a bolus (a thin band with high concentration of drug molecules) injected upstream from the stenosis. The drug has to be as effective as possible, therefore the doctors want to understand under which conditions the drug will be absorbed at best by the single stenosis. In fact, they have the ability to modify the drug diffusivity to obtain the best outcome.

The drug is considered to be a passive scalar, that is, its presence does not influence the underlying flow of blood, the carrier.

The channel is such that:

- the vessel in the unstenotic region has circular cross-section of radius R
- total channel length is $L = 20 * R$
- the bolus is initially centered at $d = L/4$ from the inlet and has width $W = L/20$.
- the stenosis has circular cross-section of radius $G = R/2$, it is at centered at $A = L/2$ away from the inlet and has axial extension $S = L/10$

Let's consider the drug injected in the conduit at initial time in the time-independent, fully developed blood stream. The Taylor-Aris dispersion describes how axial convection, axial diffusion and transverse diffusion combine to control drug transport.

Consider the Poiseuille flow through a healthy cylindrical vessel of length L and radius R. In a straight cylinder, $\bar{u}$is half the maximum speed measured on the cylinder axis.

The mass diffusion coefficient is D and the Peclet number is defined as

$$Pe = \bar{u}R/D$$

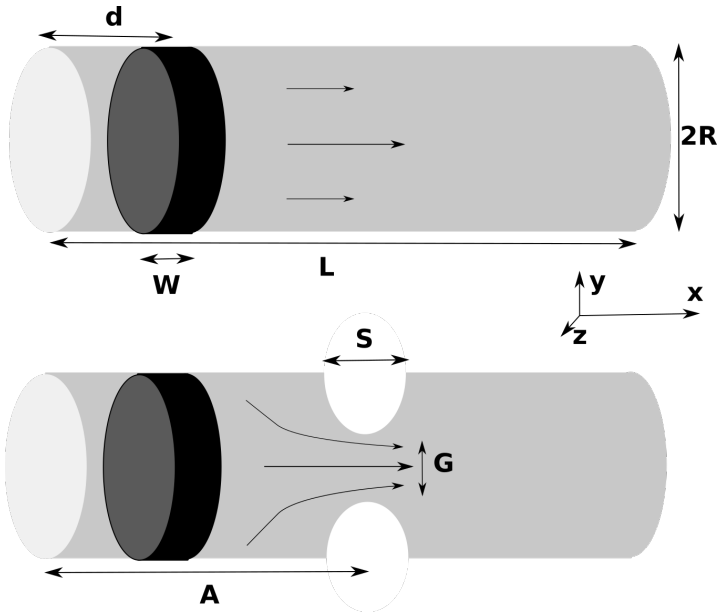

Figure 1: A bolus is released in a stationary flow in a channel of circular section and in absence or presence of a stenosis. The drug bolus has width W. The stenosis is a cylindrical narrowing (step-wise narrowing) of width S and gap G. The channel axis is along the x axis.

Pe characterizes the relative importance of advection versus diffusion while the relative importance of radial diffusion to axial diffusion is controlled by L/R. In addition, the Prandtl number

$$Pr = \nu/D$$

controls the ratio of fluid kinematic viscosity and the bolus diffusivity.

Let's consider the drug concentration $c(x, y, z, t)$ and its cross-sectional average

$$\bar{c}(x,t) = \int dy \int dz c(x,y,z,t)$$

If $Pe \ll L/R$ convection-diffusion can be treated as a two-dimensional problem and ultimately one can write the averaged one-dimensional equation for $\bar{c}$ as:

$$\frac{\partial \bar{c}}{\partial t} + \bar{u}\frac{\partial \bar{c}}{\partial x} = D_{eff}\frac{\partial^2 \bar{c}}{\partial x^2}$$

where the effective diffusivity is:

$$D_{eff} = D\left(1 + \frac{Pe^2}{48}\right)$$

The bolus evolution is given by the cross-sectional average width$\bar{W} = 4\sqrt{ln2D_{eff}t}$. Vice versa, for larger Pe diffusion can be ignored and the bolus width varies in time as $\bar{W} = 2\bar{u}t$.

Axial diffusion tends to increase the effective diffusion while radial diffusion leads to the $W \sim \sqrt{t}$ rather than a linear dependence (as arising if only axial diffusion is acting). While axial diffusion causes bolus broadening, radial diffusion causes the drug to explore both fast-moving and slow-moving parts of the flow.

2 Problem Statement

2.1 Groups

You should work as two groups.

- The first group will simulate the system by modeling blood as an effective medium (without explicit red blood cells). The simulations consists of two values for Peclet $Pe = 1$ and $Pe = 10$ and two for Reynolds $Re = 5$ and $Re = 10$, for a total of four simulations.
- The second group will simulate blood without and with explicit red blood cells, and by choosing $Pe = 10$ and $Re = 1$, for a total of two simulations.

2.2 Protocol

Geometry preparation

To generate the initial geometry you can use the provided script "ShapePainter.py" with given radius, length and stenotic geometric parameters. Beware that the script uses a 3d canvas to create the shape and then marching cubes to generate the surface. Two boxes are used to select inlet and outlet regions. Have a look at ShapePainter.py to control the geometrical features and Paraview to check the consistency.

In the following, all parameters are expressed by using always LBM (not physical) units.
Simulate the evolution of the drug bolus by using the two following protocols.
Protocol 1 (Group 1 only):

1. impose the pulsatile velocity at the inlet and pressure at the outlet and simulate the blood flow and wait until the flow stabilizes
2. release the bolus and analyze its profile $\bar{c}(x, t)$

Protocol 2 (Group 2 only):

1. impose the pulsatile velocity at the inlet and pressure at the outlet and simulate the blood flow made of plasma and red blood cells
2. release the bolus and analyze its profile $\bar{c}(x, t)$

2.3 Parameters

Simulate the three-dimensional system by using the MUPHY code.

- $Pr = 10$
- LBM viscosity $\nu = 0.1$

- inlet velocity
$$u_i(t) = \frac{\bar{u}}{2}\left[\cos(2\pi t/T) + 1\right]$$
with $T = 10^6$ and $\bar{u} = 0.01$
- outlet fixed pressure boundaries for the carrier imposed by using "equilibrium" LBM populations
- Initial concentration in the drug bolus: $c_1 = 1$ and boundary conditions for drug at the inlet and outlet by fixing concentration to $c_0 = 10^{-2}$, imposed by using "equilibrium" LBM populations
- The wall is taken as impenetrable for both the carrier and the drug. No slip boundary conditions are applied for both components
- Simulate about $4 \times T$ steps per case
- Use 256-1024 cores for the various simulations running for a total of 7 days

2.4 Requirements

Deliverables should analyze how much amount of drug persists in the stenotic region by computing the quantity:
$$q(t) = \int_{A-S/2}^{A+S/2} dx \int dy \int dz c(x, y, z, t)$$
which provides a measure of drug efficacy.

- Group 1: analyse how Pe modulates drug efficacy
- Group 2: choose an hematocrit of 30% modulates drug efficacy
- (Group 1+2): Visualize the velocity field at different time instants during the transient. You can use two-dimensional longitudinal cuts and visualize flow streamlines and the LIC modality for visualization in Paraview
- (Group 1+2): Visualize the red blood cells and see how they move and tumble in the stenotic region
- (Group 1+2): Visualize the drug concentration at different time instants. You can use two-dimensional longitudinal cuts of the system and use contour plots.
- (Group 1+2): Report the bolus profile averaged over the cross-section and show how the packed spreads in time

Other things you may want to try are:

- (Group 1+2): Visualize Lagrangian tracer particles in the flow and see how their evolution differs from the advection-diffusion dispersion prediction
- (Group 1+2): You can produce a movie to see how the fluids evolves (for red blood cells you will be provided with a glyph file and instructions).
- (Group 1+2): You can use the Schlierin vizualization, as learned in Module 1, to provide insight in absence and in presence of red blood cells

2.5 Report and Presentation

Each group must turn in a report and give a presentation on their results.

The presentation should be 20 minutes long and should include all necessary background including:

- Problem statement and motivation
- Description of code
- Overview of numerical method used (spatial and temporal discretizations as well as non-linear solvers)
- Parameters of the simulation (how big, what problem, etc)
- Results (including visualizations and findings)
- Discuss critically the trends observed (as a function of Pe and red blood cells) by means of the Taylor-Aris framework
- Conclusions and future work

The report should follow a similar format, but can include more details and mathematics.