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#### EXECUTIVE SUMMARY OF THE THESIS

## Reduced Fluid-structure interaction and non-Newtonian models of blood flows for simulating the aortic valve

LAUREA MAGISTRALE IN MATHEMATICAL ENGINEERING - INGEGNERIA MATEMATICA

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## 1. Introduction

Cardiovascular diseases are one of the major causes of death: 17.9 million people died because of this kind of diseases in 2019, representing the 32% of global deaths. As medicine progresses, computational fluid dynamics simulations of blood flow are becoming of increasing interest towards a better understanding of cardiovascular diseases [4]. Within the cardiovascular system, the aortic valve is one of the most investigated components. In this context the goal of this thesis is twofold. First, it aims at filling the gap in the literature regarding the use of a non-Newtonian model in proximity of a physiological trileaflet valve. Second, different from what can be found in the literature, it employs a reduced model, with momentum balance of the leaflets as 0D equation, for the treatment of the fluid-structure interaction problem between blood and the valve. This method could drastically improve the computational performance of the simulation with respect to other popular approaches used in the literature, which require a full 3D representation of the valve geometry and of its mechanics solver, while retaining a physical meaning for the parameters of the 0D equations. In order to effectively use this model to

represent physiological and pathological cases, an important work in the understanding of the model and in the tuning of the different parameters was performed.

## 2. Mathematical models and numerical methods

To model the fluid-structure interaction problem between blood and the valve we adopt the Resistive Immersed Implicit Surface (RIIS) method [2] coupled with a lumped parameter momentum balance 0D equation for the valve [3]. In the RIIS method the immersed surface  $\Gamma$  is implicitly described at each time  $t$  by a single level-set function as  $\Gamma_t = \{\mathbf{x} \in \Omega : \varphi_t(\mathbf{x}) = 0\}$ . Then, after defining a smooth Dirac function to approximate the “Dirac distribution”

$$\delta_{t,\varepsilon}(\mathbf{x}) = \begin{cases} \frac{1+\cos(\pi\varphi_t(\mathbf{x})/\varepsilon)}{2\varepsilon} & \text{if } |\varphi_t(\mathbf{x})| \leq \varepsilon \\ 0 & \text{if } |\varphi_t(\mathbf{x})| > \varepsilon \end{cases}$$

where the half-thickness of the immersed surface  $\varepsilon$  is the smoothing parameter; the RIIS method consists in enriching the Navier-Stokes equations with a penalization term in the momentum conservation equation with support the immersed surface  $\Gamma$ . The RIIS formulation used to describe the blood flow through the aortic valve

domain  $\Omega$  reads:

Find the velocity  $\mathbf{u}$  and the pressure  $p$  such that:

$$\begin{cases} \rho \frac{\partial \mathbf{u}}{\partial t} - \nabla \cdot \sigma + \rho(\mathbf{u} \cdot \nabla) \mathbf{u} \\ + \nabla p + \delta_{t,\varepsilon} \frac{R}{\varepsilon} (\mathbf{u} - \mathbf{u}_\Gamma) = \mathbf{f} & \text{in } \Omega \times (t_0, T), \\ \nabla \cdot \mathbf{u} = 0 & \text{in } \Omega \times (t_0, T), \\ \mathbf{u} = \mathbf{0} & \text{on } \Sigma_{\text{wall}} \times (t_0, T), \\ \sigma \mathbf{n} = p_{\text{in}} \mathbf{n} & \text{on } \Sigma_{\text{in}} \times (t_0, T), \\ \sigma \mathbf{n} = p_{\text{out}} \mathbf{n} & \text{on } \Sigma_{\text{out}} \times (t_0, T), \\ \mathbf{u}(\mathbf{x}, 0) = \mathbf{u}_0(\mathbf{x}) & \text{in } \Omega \times \{t_0\} \end{cases}$$

where  $\rho$  is the density of blood,  $\sigma$  is the stress tensor,  $R$  is the resistance of the RIIS term, acting as a penalty parameter, and  $\mathbf{u}_\Gamma$  is the velocity of the immersed surface.  $p_{\text{in}}, p_{\text{out}}$  are the pressure values imposed at the inflow and outflow boundaries  $\Sigma_{\text{in}}, \Sigma_{\text{out}}$ , respectively, while the boundary  $\Sigma_{\text{wall}}$  represents the aortic wall. In order to describe the configuration and the velocity of the valve  $\Gamma$ , represented by  $\varphi_t$  and  $\mathbf{u}_\Gamma$ , a structural model is required for the deformation of the surface  $\Gamma_t$ . We denote by  $\mathbf{d}_\Gamma$  the displacement of the leaflet with respect to its reference configuration, and we assume that this term can be written as  $\mathbf{d}_\Gamma(t, \hat{\mathbf{x}}) = c(t)\mathbf{g}(\hat{\mathbf{x}})$ , where  $\hat{\mathbf{x}}$  denotes a point of the reference configuration, that is the closed configuration of the valve. Then the structural model for the movement of the valve is given by a 0D equation derived from a local force balance on the leaflets that can be formulated as follows:

$$\begin{cases} \ddot{c} + \beta \dot{c} + \eta(c, \mathbf{f}) = 0 & t \in (t_0, T), \\ c(t_0) = 0 \end{cases}$$

where  $\eta(c, \mathbf{f})$  depends on the opening coefficient  $c$ , and on  $\mathbf{f}$  which is the external force exerted on the valve due to the surrounding fluid. The RIIS model and the 0D equation are then coupled as follows: the fluid-to-valve stress  $\mathbf{f}$  is computed from the fluid model, while the 0D model provides the valve position and velocity.

The FSI model is complemented with a non-Newtonian model for blood rheology. Indeed, while the Newtonian rheology is by far the most adopted in literature for this type of simulations, blood is a fluid composed of many elements that exhibits complex rheological properties, and for this reason, the usage of a non-Newtonian model is more accurate for many types of applications. In order to include the non-Newtonian nature

of blood in the model, one needs a constitutive equation for the stress tensor  $\sigma$  that incorporates the relation between the viscosity and the shear rate of the fluid. The constitutive equation, assuming blood as a “generalized Newtonian fluids”, can be expressed as  $\sigma = -p\mathbf{I} + 2\mu(\hat{\gamma})\boldsymbol{\varepsilon}(\mathbf{u})$ , where  $\boldsymbol{\varepsilon}(\mathbf{u}) = \frac{1}{2}(\nabla \mathbf{u} + (\nabla \mathbf{u})^T)$  is the strain rate tensor and  $\hat{\gamma}$  is the scalar strain rate, defined as  $\hat{\gamma} = \sqrt{2 \operatorname{tr}(\boldsymbol{\varepsilon}(\mathbf{u})^2)}$ . For the relationship  $\mu(\hat{\gamma})$  we adopt the Carreau model, one of the most used in the context of blood simulations, which reads as:

$$\mu(\hat{\gamma}) = \mu_\infty + (\mu_0 - \mu_\infty) [1 + (\lambda \hat{\gamma})^2]^{\frac{n-1}{2}}$$

where

$\mu_\infty [\text{Pa} \cdot \text{s}]$	$\mu_0 [\text{Pa} \cdot \text{s}]$	$n [.]$	$\lambda [\text{s}]$
$3.45 \times 10^{-3}$	$5.6 \times 10^{-2}$	0.3568	3.313

are values well established in the literature,

Regarding the numerical scheme of the complete model, we introduce a tetrahedral mesh  $\mathcal{T}_h$  of  $\Omega$  for the space discretization, and we define a set of times  $\{t_k\}_{k=0}^N$  such that  $0 = t_0 < t_1 < \dots < t_N = T$  and  $t_{k+1} - t_k = \Delta t \forall k \geq 0$  for the time discretization. For the approximation of the fluid problem, we adopt a semi-implicit BDF-FE scheme of order  $s$ , with the same polynomial degree  $r$  for both discretized FE-space of velocities and pressure, and a SUPG-PSPG stabilization with VMS-inspired coefficients. The non-linearity introduced in the viscosity term by the non-Newtonian model is treated semi-implicitly. Instead, for what concerns the valve’s kinematics, the discrete leaflet velocity is computed from a first-order approximation based on the opening coefficient  $c$ . Concerning the variables that characterize the geometry of the valve, a FE description is used. Finally, for the solution of the Ordinary Differential Equation to find the opening coefficient  $c$ , we adopt an explicit Runge-Kutta method of the fourth order.

### 3. Validation of the non-Newtonian model

As part of the thesis work, the non-Newtonian model was implemented, on top of the previously existing Navier-Stokes solver, in life<sup>x</sup> [1]: a high-performance library for the solution of multi-physics and multiscale problems, mainly for cardiac applications. The model was tested

on a simple geometry, a cylindrical domain, and results were compared with [5], where the same problem is solved in the same domain but using a semi-analytical approach.

	Reference	life <sup>x</sup>
Newtonian flux (m <sup>3</sup> /s)	$6.30 \cdot 10^{-5}$	$5.72 \cdot 10^{-5}$
Carreau flux (m <sup>3</sup> /s)	$5.98 \cdot 10^{-5}$	$5.43 \cdot 10^{-5}$
Ratio flux	5.08%	5.03%
Newtonian WSS (Pa)	9.3	9.31
Carreau WSS (Pa)	9.3	9.26

**Table 1:** Comparison with the reference results in the steady case for  $R = 3.1$  mm.

As we can see from one of the various comparisons performed, shown in Table 1, the results obtained with the implemented model are in accordance with the reference, especially for what concerns the difference between Newtonian and non-Newtonian flows.

## 4. Simulating the aortic valve

The most important results of the thesis were obtained applying the mathematical and numerical models shown in Chapter 2 on a realistic domain in the proximity of the valve.

### 4.1. Numerical setting

Both the geometry of the domain  $\Omega$  and of the closed valve leaflets  $\hat{\Gamma}$  are taken from the Zygote Heart Model, an accurate model of the physiological heart derived from CT-scan acquisitions. For simplicity the left ventricle was replaced with a flow extension: this was done in order to simplify the geometry of the problem, and to facilitate the imposition of the boundary condition at the inlet, as in [3]. A proper opening field  $\mathbf{g}$  was introduced on the leaflets, so that the surface  $\Gamma_{\text{open}}$  corresponding to an opening coefficient  $c = 1$ , represents the physiological open valve configuration with an orifice area of  $3.02 \text{ cm}^2$ . This value is in the physiological range for healthy adults ( $3.9 \pm 1.2 \text{ cm}^2$ ). The mesh was generated tailored towards the application to the Navier-Stokes-RIIS model: a fine mesh in the area corresponding to the aortic was imposed, in order to better capture the complex behavior of the flow and the valve around that area. Details on the mesh size and the degrees of freedom of the problem can be found in Table 2.

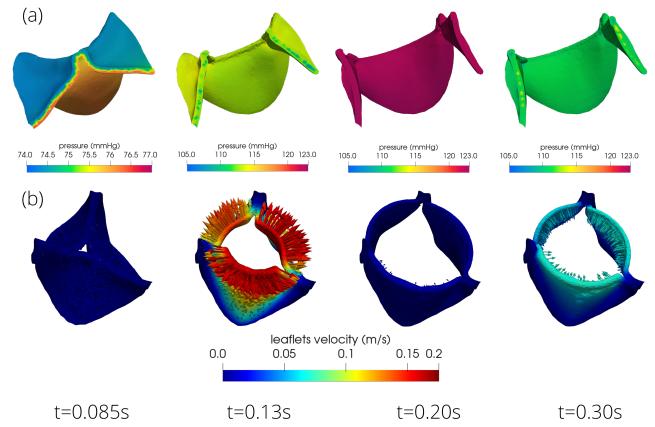
Number of cells	962 549	
DOFs	velocity	468 378
$\mathbb{P}1 - \mathbb{P}1$	pressure	156 126
	total	624 504
$h_{\max}$	$5.50 \cdot 10^{-3}$ m	
$h_{\min}$	$3.38 \cdot 10^{-4}$ m	
$h_{\text{mean}}$	$7.98 \cdot 10^{-4}$ m	

**Table 2:** Mesh size and number of degrees of freedom.

As boundary conditions, we imply time-dependent normal stress both in inlet and outlet, while we prescribe a no-slip condition on the wall.  $p_{\text{in}}$  and  $p_{\text{out}}$  are pressures obtained from a lumped circulation model, after proper calibration in order to be consistent with physiological pressures as reported in Wiggers diagrams. We simulated a whole systole using a time step  $\Delta t = 1 \cdot 10^{-4}$  s.

### 4.2. Simulation of a healthy valve

We obtained the case of a healthy valve, calibrating the model to reproduce the physiological behavior observed in healthy individuals.



**Figure 1:** Pressure within the leaflets (a) and leaflets velocity  $\mathbf{u}_{\Gamma}$  (b) at four different time steps: before the opening (0.085 s), during the valve opening phase (0.13 s), when the valve is completely open (0.20 s) and during the closing phase (0.30 s).

The evolution of the orifice area is in accordance with the evolution of a physiological valve, that is, it can be divided into three stages: an opening phase, a slow closure with very small changes of the orifice area, and a rapid closure. In particular the duration of the opening phase

in our configuration is of 83 ms, in accordance with the literature that indicates as physiological an opening time of  $76 \pm 30$  ms. The closing phase can be divided into two steps: a slower one of about 45 ms when the orifice area doesn't change much (approximately from 95 to 70 %), and a faster one of about 20 ms (from 70 to 0 %). In total the whole closing process requires about 65 ms, very close to the physiological one of  $42 \pm 16$  ms. This behavior can be observed in Figure 2, where the evolution of the opening coefficient and the orifice area is shown for the three different physiological configurations. As we can see from Figure 1 (b), in the early stages of the simulation, while the valve is still closed, the whole pressure gradient is concentrated in correspondence of the valve and a pressure difference of about 2 to 3 mmHg is developed in this area which causes the beginning of the opening of the valve. Then, the opening is accompanied by a progressive development of the typical jet flow through the aortic orifice (see Figure 3 (a)), and much smaller pressure differences can be observed. Despite this, during this phase, a non-negligible pressure gradient can be observed in the RIIS region, due to the non-zero leaflet velocity  $\mathbf{u}_\Gamma$ . Instead, when the valve reaches its fully open configuration, the pressure is essentially constant in the leaflets volume, since the valve velocity  $\mathbf{u}_\Gamma$  is close to zero during this phase. With the valve fully open at the maximum orifice area, the aortic jet fully develops (see Figure 3). Finally, the closing phase is accompanied by a strong negative pressure gradient. The valve starts its closing, at the beginning with  $\mathbf{u}_\Gamma$  much slower with respect to the opening phase (see Figure 1 (b)).

#### 4.3. Simulation of pathological cases

By varying the parameters of the 0D model, we were able to obtain the two most common pathological cases that can be caused by a dysfunction of the aortic valve: stenosis and regurgitation. From Figure 2 we can see how both the orifice area and the opening coefficient for the stenotic case do not reach the value of complete opening that is reached in both healthy and regurgitant cases: this is the main characteristic of a stenotic valve.

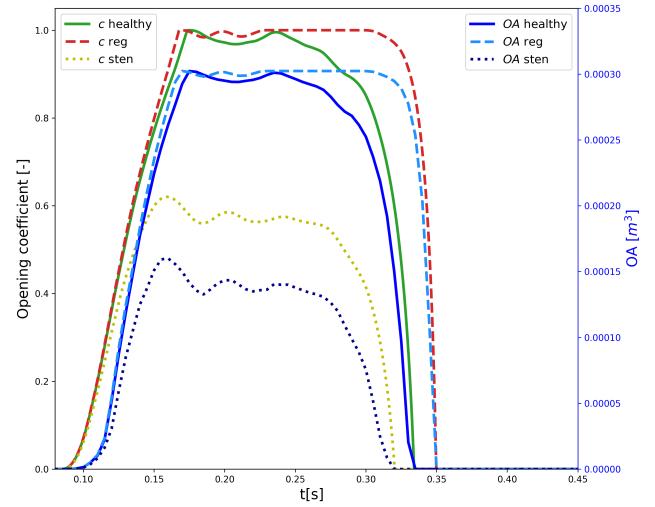


Figure 2: Comparison of the opening coefficient and Orifice Area in the three configurations.

The reduced orifice area and the shorter time interval in which flow is allowed through the valve yield a stronger aortic jet with respect to the healthy configuration, as we can see from Figure 3 (b).

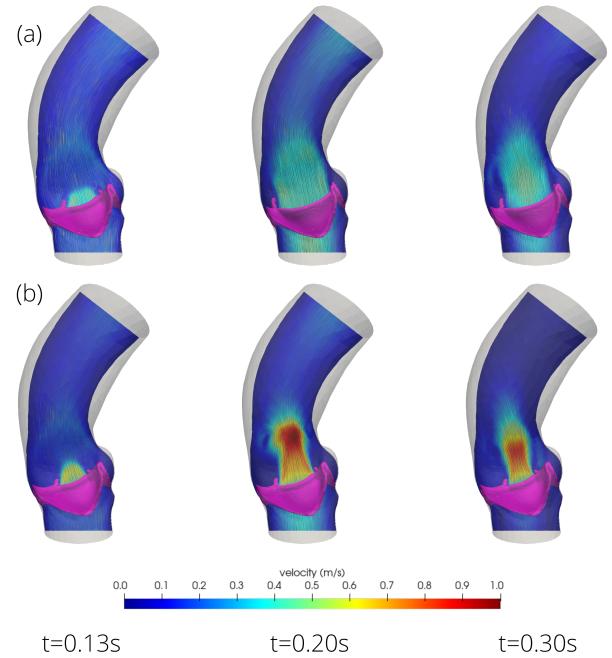


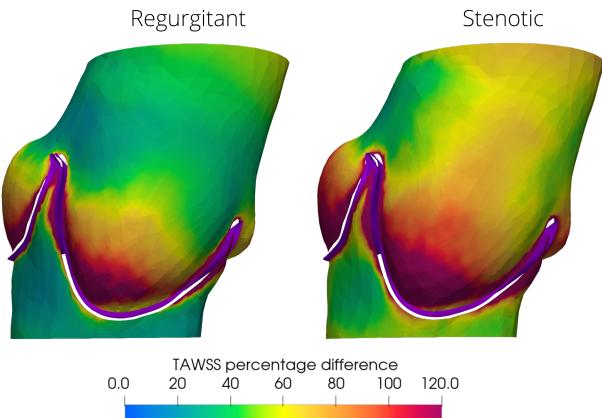
Figure 3: Velocity distribution in healthy (a) and stenotic (b) cases for three different time steps: during the valve opening phase (0.13 s), at maximum valve opening (0.20 s) and during the closing phase (0.30 s).

Concerning the regurgitant case, the delay in the closure of the valve with respect to the

healthy case, which can be observed in Figure 2, causes the pressure jump to increase significantly. The valve begins closing too late, so that a strong backward flux returns into the ventricle: this is the main characteristic of regurgitation. This phenomenon has a strong impact on the dynamic of the blood flow during the closing phase: the backward flow observed is very intense in magnitude and the duration of this phenomenon is quite long: 5 ms.

#### 4.4. Comparison of Newtonian and non-Newtonian models

Finally, the comparison between the Newtonian and non-Newtonian rheology was carried out for the two pathological configurations. Our results confirm that the rheological model has only little influence on quantities such as valve dynamics, transvalvular pressure drop and large-scale flow structure: this is in accordance with what can be found in literature, even if a different type of valve and model are considered. Significant differences, instead, can be observed in more “specific” quantities, such as wall shear stress. In arterial blood flow, the wall shear stress, is defined as  $\mathbf{WSS} = (\mu \frac{\partial u_t}{\partial r})_{r=0}$  where  $u_t$  is the flow velocity parallel to the wall and  $r$  is the distance to the wall. Physically it expresses the force per unit area exerted by the wall on the fluid in a direction on the local tangent plane. Wall shear stress has often great importance in the medical field, for example it has great influence on the formation of plaque in atherosclerosis or in the wall elasticity.



**Figure 4:** Percentage difference between Time-Averaged Wall Shear Stress in regurgitant (left) and stenotic (right) cases.

Significant differences can be observed in this quantity for different time steps and for different areas of the domain. The wall shear stress is always higher in the non-Newtonian case, probably because in this case the viscosity of the fluid is always greater or equal than the Newtonian one (that corresponds to  $\mu_\infty$  of the Carreau model, so the minimum viscosity that can be achieved). A useful indicator to understand the behavior of the shear stress on the vessel wall throughout the whole time period is the Time-Averaged Wall Shear Stress (TAWSS). This quantity can be computed as

$TAWSS = \frac{1}{T} \int_0^T |\mathbf{WSS}(\mathbf{s}, \mathbf{t})| dt$ . To better visualize the difference observed in the TAWSS, we computed the quantity that expresses the percentage difference on TAWSS between the two rheological model as

$$TAWSS_{\text{perc-diff}} = 100 \frac{TAWSS_{\text{NN}} - TAWSS_{\text{New}}}{TAWSS_{\text{New}}}.$$

Figure 4 shows this quantity computed for both pathological configurations, and, as we can see, the difference in TAWSS is significant for both configurations. In the red areas this difference reaches more than 100%. These are typically areas where the value of TAWSS is quite low, and so the quantitative difference may be not as significant as it seems. However, basically in the whole domain, and even in the areas where the TAWSS is higher, we can observe differences that are around 20 ~ 50 %. This means that if one is interested in computing the WSS in the aortic valve domain, the choice of the rheological model is very impactful, and the non-Newtonian nature of blood should not be neglected.

#### 5. Conclusions and further development

In this work, we investigated the mathematical modeling of the aortic valve. The clinical motivation for this work stems from the millions of patients annually diagnosed with pathologies of the aortic valve.

We were able to calibrate the reduced order model, based on momentum balance on the leaflets as 0D equation, to reproduce different physiological scenarios. Indeed, the healthy configuration was proved to be in accordance with most of the physiological parameters measured in the literature during the systole, such as the

duration of the opening and closing phases and transvalvular pressure difference. Moreover, the physiological dynamics of the valve and of blood flow were recovered. In this sense, this could be considered an improvement with respect to [2], where the opening phase was a lot shorter than what is physiologically observed, and to [3] where only the opening stage was investigated. Varying the parameters of the 0D model we were able to obtain configurations which represent the two most common pathological cases caused by malfunctioning of the valve. These configurations show all the important characteristics that can be physiologically observed within these types of diseases.

Moreover, we were able to effectively implement and validate a non-Newtonian model on a high-performance library. This model was then used to investigate the differences that can be observed using different rheological models, in proximity of the aortic valve, for the two pathological cases. Our results confirmed that the rheological model has only little influence on quantities such as valve dynamics, transvalvular pressure drop and large-scale flow structure, in accordance with what can be found in literature. Significant differences, instead, could be observed in the wall shear stress. In particular, considering a Newtonian blood rheology leads to an underestimation of the wall shear stress. We thus conclude that the non-Newtonian rheology of blood must be taken into account whenever wall shear stress is in the focus of the clinical investigation.

The major limitation in this thesis is in the study of the period after the closure of the valve, when, due to geometrical inconsistencies, some reverse flow can be observed when the valve should be closed. This issue could be overcome by manually adjusting the valve and aortic root geometries to improve their consistency. Other limitations are induced by the choice of the model itself. For example, although the reduced 0D model for the valve induces a reduction in the computational time required for the simulation, it should be considered that this can cause a loss in the accuracy of the model with respect to 3D coupling of the valve.

Further developments of this work can be carried out in multiple directions. Concerning the rheology of blood, other types of non-Newtonian

models could be investigated. Then, a wider domain of investigation, for example including the left ventricle, could be analyzed in order to conduct a more complete simulation and observe the differences caused by the non-Newtonian model also in the left ventricle. In order to improve the accuracy of the results, particularly on the wall shear stress, the compliance of the aortic wall could be taken into account. Finally, this computational framework could be applied to a patient-specific geometry and data as in [2]. Indeed, variability among different patients can be captured only by considering the patient-specific aortic geometry and the patient-specific leaflets in the correct position.

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