

3D/1D COMPUTED FRACTIONAL FLOW RESERVE COMPARISON IN CORONARY ARTERY DISEASE

by

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This dissertation by **Minglang Yin** is accepted in its present form
by the School of Engineering as satisfying the
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ABSTRACT

Fractional Flow Reserve (FFR) has become the gold standard for diagnosing coronary artery disease (CAD) since Gould et al. [11] claimed so whilst the most traditional way to measure FFR is invasive coronary angiography (ICA). Such modality is invasive and expensive-costing according to DEFER (Deferral Versus Performance of PTCA in Patients Without Documented Ischemia) study [29], half of the patient underwent ICA has no ischemia risk at all. Thus non-invasive, cheap and reliable ways to alternate such operation is demanding and significant and FFR_{CFD} is a promising candidate. By discretizing reconstructed coronary geometry from computed tomography angiography (CTA) and imposing circuit analogy coronary boundary condition, a finite element fluid solver or spectral element solver could reveal the velocity and pressure field inside coronary artery tree and hence FFR could be non-invasive acquired. Nonetheless, the computational cost to perform such method is prohibitive for most of the medical research centers or hospitals, greatly limiting the potential beneficiaries. The motivation of this work is to validate the accuracy of a one-dimensional (1D) reduced-order model of three-dimensional (3D) full order Navier-Stokes equations where the former one could be performed on a personal computer within a couple of minutes. The results show an agreement between high and low fidelity FFR from 3D and 1D pressure and velocity, demonstrating that the 1D solver could be used as a alternative to the 3D solver at fraction of the cost. Moreover, a sensitivity study is shown by varying parameters within a proper physiological range. Robustness of 1D solver has shown assuming proper outflow boundary conditions. This work also provides evidence that the 1D solver can be used reliably and efficiently in the clinical setting for FFR predictions.

For my parents, Li-hong and Lai-qun.

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CHAPTER 1

INTRODUCTION

Ischemic heart attack, also known as coronary artery disease (CAD), ranks top in causes of death globally, and claims millions of patients lives every year. Inside the stenotic coronary artery, plaque made of fat or cholesterol builds up inside vessel wall and causes one or several progressive narrowing of the coronary arteries. Blood flow through these narrowing lumen could cause a sudden pressure drop, which might impede the oxygen-carrying from upstream oxygenated blood to downstream cardiac tissue. And eventually, with the culmination of plaque or atherosclerosis, ischemic heart attack could be triggered under certain circumstances such as exercising or hyperemia, causing a large scale of dysfunction of myocardial tissue in the downstream [11]. Traditionally, implanting a drug-eluting stent to bridge the stenosis part and coronary bypass grafting are two of effective ways to a patient with severe stenosis [37]. However, the relation between stenosis diameter and ischemia was unclear and complex: from experimental data [38], as early as 40% narrowing could cause ischemia [48] while only 40% of patients exhibited ischemia among the patients with 70% stenosis [38].

Nowadays, measuring fractional flow reserve (FFR) on coronary artery disease patient has been shown to be the gold standard to assess functional severity [27], as it is defined as the ratio of maximum blood flow distal to a stenotic lesion, P_d , to normal maximum flow in the same vessel, P_n . Usually it is calculated by $FFR = \frac{P_d}{P_n}$ with ischemia defined as $FFR \leq 0.80$ [24]. There are certain advantages for FFR over other techniques like intravascular ultrasound or CTA because FFR takes into account collateral flow and would not overestimate or underestimate narrowing [28]. The traditional technique to acquire FFR in vivo is invasive; a long thin catheter with a pressure sensor is inserted into the femoral artery on the thigh or the radial artery on the wrist, typically with the sensor on the tip of

the guide wire. And it will be directed toward the stenosed vessel in coronary arteries by angiography. As such the mean distal pressure around the stenosis and normal pressure upstream are measured and recorded separately averaged during several cardiac cycles by a pullback. Based on measured FFR should a doctor decide to implant a drug-eluting stent in the stenosed coronary vessel.

The recent development of computed tomography(CT) and imaging reconstruction technology enable several of non-invasive ways to visualize stenoses lesion, and computed tomography angiography(CTA) is one of them. CTA is a non-invasive method for constructing the 3D structure to visualize CAD, and based on simple evaluation could an experienced cardiologist calculate FFR manually. The methodology of other non-invasive methods has a similar visual-based process. What foreseeable from an Engineering perspective of view is that the manually calculated results are not accurate enough due to the complex nature of fluid dynamics, irregular artery shape and nonlinear coupling between different physiologic homeostatic parameters of each patient. The fact as previous studies [20][24] have shown that only a minority of stenosed coronary arteries cause ischemia given high-graded stenosed arteries from CTA results. And this weak relation between ischemia and lumen diameter may encourage unnecessary ICA given that the invasive and expensive treatment it is.

But that was not a death sentence for non-invasive measurements: as for the future of non-invasive coronary angiography would be more accurate or even an acceptable alternative to the invasive approach, Achenbach et al [1] early in 2001 had made this prediction: "...with the impressive recent advances, the issue should be not if, but when and for which patients."

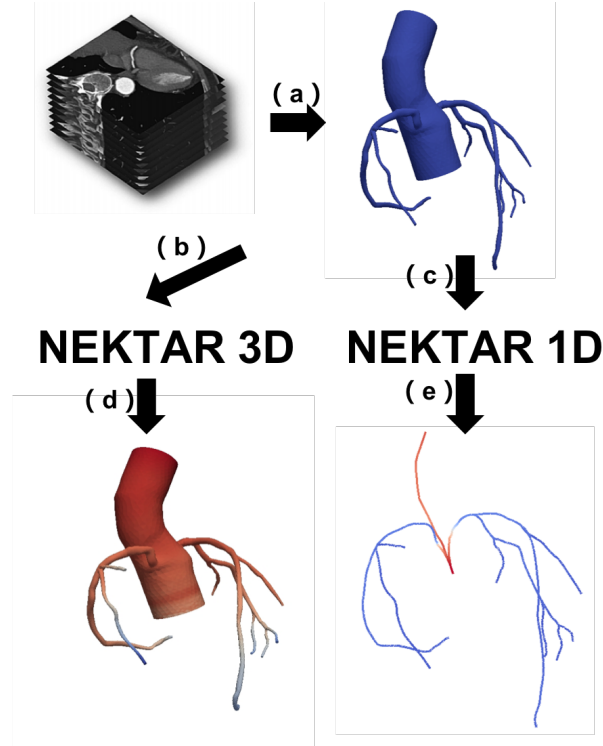


Figure 1.1. Schematic framework of FFR_{CFD} . (a)Reconstruct 3D geometry from CT scan. (b)Smooth and discretize 3D geometry. (c)Extract centerline from reconstructed model. (d)Impose boundary conditions and conduct NEKTAR 3D simulation. (e)Impose boundary conditions and connectivity of each centerline to NEKTAR 1D.

Thanks to the recent development of modern computational fluid dynamics(CFD) and parallel computing, they endow vitality to this non-invasive methods. Combined with imaging structure from CTA, CFD solver could render a 3D flow field simulation with velocity and pressure within every element and wherein the FFR is calculated [46]. The process of which is called FFR_{CFD} and it is shown in Fig. 1.1. This methodology has been proved has high diagnostic accuracy and discrimination for the significance of CAD compared with invasive FFR measurement [24][22]. Moreover, such service and diagnostic analysis are firstly available by HeartFlow Inc, and the US Food and Drug Administration has approved FFR_{CFD} for clinical usage [43].

Numerical solution of blood flow inside blood vessels is widely studied for seeking to understand vascular hemodynamics: Taylor et al. [47] shows the first Engineering software to construct smoothed vascular geometry, perform finite element analysis on the

flow field and visualize the key features from the data. To simulate the coronary circulation, a circuit analogy coronary lumped network was developed by [18], considering the blood flow through arteries, arterials, micro-vascular and veins. Chapter 2 gives a more detailed review of the coronary boundary condition; under some specific vascular conditions, the instability of simulation originated from the flow at outlet boundary is not fully developed. References [23][5][23] described several numerical ways to provide more stability; Sengupta et al. [36] investigated the pressure and velocity of a Kawasaki patient-specific coronary artery tree. Taylor et al. [45][44] and Marsden [19] provide several detailed reviews of CFD application in the field of biomedical engineering including the comparison with invasive FFR and patient-specific modeling.

From a practical perspective, however, solving full-order Navier-Stokes equations require a large amount of computational resources which greatly limits its availability in clinical diagnosis: to simulate one patient-specific coronary artery needs hundreds of cores server for at least a day, and this will grow fast if the fluid-structure model is considered. So recently, seeking a fast reduced-order model for fast diagnosing has been received more attention. The earliest reduced-order modeling on blood flow in arteries can be traced back to Euler [7] who derives the nonlinear differential equation for inviscid flow. This model assumes negligible lateral flow and hence Navier-Stokes equations collapse into a 1D nonlinear partial-differential system. Young [55] and Riemann [31] incorporate wave propagation nature of arterial blood flow and the latter introduced the method of characteristics which is a general analytic tool for the wave system. A detailed literature is provided by Sherwin [40][39]. Numerically, Fernandez et al. [8] and Milivsic et al. [21] provide a local-in-time existence, uniqueness and convergence of classical solutions for 1D coupled problem. With respect to commercial market, an one-dimensional FFR analysis is developed by Siemens Healthineers, but is not yet clinically used. In terms of computational time, solving reduced-order model greatly reduce the demanding computational resources, making on-site computing available. Chapter 3 discusses the computational time for both 1D and 3D model.

However, the assumption made on 1D might not very well hold on the vessel with

stenoses or aneurysms wherein the inner vessel of a diseased vessel, such as atherosclerosis or CAD has one or several of rapid local contractions: complex flow phenomena might corrupt computed velocity and pressure herein lowering the credibility of FFR. So a modified stenosis model should be introduced to compensate this non-linear effect. In literature, Young [53][54] has derived an empirical pressure drop equation over the stenosis area from a hydraulic experiment. The empirical equation determines pressure drop depending on stenosis severity and shape. Details are discussed in Chapter 2.

Moreover, further simplification has been made on 1D model and traditionally is used as describing downstream micro-vascular effect at the outlet due to weak non-linearity of the system, and this simplified model is also known as "windkessel model". Womersley [51] firstly linearized the two-dimensional flow in a straight elastic tube by Fourier transform and since then, this frequency analysis has become the standard technique for analyzing waves in vessels or an arterial system. This linear model is usually coupled with 1D or 3D solver at the end of outlets to mimic the microvascular effect in downstream [49].

The numerical accuracy of the CFD solver does have a crucial role in seeking an accurate FFR value in a stenosed vessel. However, in patient-specific modeling, FFR calculation does not solely depend on it, but also other factors such as approximated geometry, boundary condition values, patient-specific physiological conditions etc. Any perturbation in the candidates above may cause a large impact in the final results. So quantifying the uncertainty and their impacts are the way to study the credibility and sensitivity of the mathematical model. Although a clinical experiment has shown such numerical method has a high sensitivity and accuracy, sensitivity analysis can be also mathematically examined. Literature like [34][35] have investigated such uncertainty by using 3D solver: by varying a set of parameters such as resistance, lumen diameter, boundary conditions etc., the studies show that the minimum lumen diameter takes the dominance followed by resistance, viscosity and lesion length.

The influence of CFD has a wide impact on biomedical engineering community not just on non-invasive FFR prediction. Introducing CFD to modern medicine, especially

hemodynamics, provides an inter-disciplinary modality to quantitatively study bio-fluids in vivo. Assessment of changes in flow and pressure of post-therapeutic interventions, artery bypass graft [42] would be more accurate thanks to applying CFD simulation on after-operation geometry. It also provides a non-invasive measuring way to assess blood flow such as cerebral aneurysm [26], intracranial system [12], which could provide significant assisting information on clinical diagnosing and evaluating. Additionally, a more detailed wall shear stress (WSS) can be calculated from CFD simulation which renders a local WSS distribution. Combining transporting equations enables CFD to explore more application in clinical medicine, oxygen transport, drug delivery.

The 1D and 3D model application in non-invasive FFR prediction have been proposed for years, yet there is not a very comprehensive research provides a validation of the accuracy of the 1D model in coronary FFR prediction and sensitivity analysis. In this research, the comparison between NEKTAR 3D (3D spectral element solver) and NEKTAR 1D (1D Discontinuous Galerkin solver) is listed. It shows a overall good agreement between 1D and 3D model with coronary artery boundary condition. This result provides a possibility to commercially employ 1D model. Also, the pressure drop, or namely FFR, has been studied on a simple stenosed tube and a coronary artery geometry. However, what comes with the reduction in time to perform reduced-order model are lost in field information, and most importantly, the increasing uncertainty. To investigate the robustness of the 1D model under parameter perturbation, an uncertainty quantification study was shown in Chapter 4, and most importantly, shows the influence of each parameter or their combination to predicted pressure and flow-rate.

The remainder of the paper is arranged as following structure: Chapter 2 reviews the governing equations of blood flow in 3D, 1D and 0D forms. Chapter 3 shows the pressure and flow-rate comparison of 3D model and 1D model, and all parameters are listed. Uncertainty quantification in the 1D model is investigated in Chapter 4. Final conclusion and suggestion for future are made in Chapter 5.

CHAPTER 2

MATHEMATICAL FORMULATION

Blood flow in large arteries or arterials could be modeled by full-order incompressible Navier-Stokes equations. So this process could be modeled in computational fluid dynamics (CFD) as a internal flow problem with imposed velocity profile at inlet and modified boundary conditions at outlets. Moreover, other than over full-order 3D Navier-Stokes equations, several assumptions are made so that Navier-Stokes collapses into several reduced-order models, 1D model and 0D model, which will be discussed in this chapter. 1D model with several of minutes cost would be proper for clinical FFR screening, while for those patients with more severe stenosis, a full-scale 3D model is more suitable to get a more detailed and higher fidelity description.

1D reduced-order Fluid-Structural Interaction (FSI) model is typically used to describe blood flow in small arteries or arterials where Re ranges from around 10 to 500. 0D circuit analogous model, the windkessel model, is usually used to mimic the impact from downstream micro-vascular structure. In coronary bed, blood flows from arterials to capillaries, and then collected by veins and right atrium. A more involved system is needed to account for such complex effect.

The chapter is organized as follows. In section 2.1, 2.2 and 2.3, we briefly discuss the mathematical formulation of 3D formulation of 3D, 1D, 0D model and several of boundary conditions. And in section 2.4, we will discuss stenosis model.

2.1 3D blood flow models

Blood flow in large arterials in cardiovascular system can be treated as incompressible,

viscous, Newtonian flow with Re goes up to $\mathbf{O}(10^3)$. Hence the 3D Navier-Stokes equations can properly describe the flow condition in coronary arteries and others cases where the assumptions are still well-held. Typically, the lumen diameter change during a cardiac cycle is measured to be 5% to 10 % in most of arteries. But computing FSI model could drastically increase the computational demand, so out of simplification, here the vessel walls are assumed to be fix.

Here I provide an mathematical overview for the blood flow in arterials and arteries. The subsection will be arranged as followed. Section 2.1.1 gives mathematical layout of blood flow in vessel, with 2.1.2 reviewing the Dirichlet boundary condition at inlet and womersley boundary condition.

2.1.1 Mathematical formulation

Consider a domain with Ω with its boundary Γ , to seek the velocity u and the pressure p which satisfy the condition below:

$$\rho(u_{,t} + (u \cdot \nabla)u) = \nabla \cdot \sigma + f, \quad (x, t) \in \Omega \times (0, T), \quad (2.1)$$

$$\nabla \cdot u = 0, \quad (x, t) \in \Omega \times (0, T), \quad (2.2)$$

where stress tensor σ and initial condition is given as

$$\sigma = -pI + \mu(\nabla u + \nabla u^T), \quad (2.3)$$

$$u(x, 0) = u_0(x), \quad x \in \Omega \subset R^3, \quad (2.4)$$

$$u = g; \quad (x, t) \in \Gamma_g \times (0, T), \quad (2.5)$$

u is velocity vector, x is location vector. Density ρ is assume to be constant in Ω . Γ_g denotes the boundary of Ω where given pulsatile womersley velocity profile is imposed at inlet and corresponding Windkessel boundary conditions are imposed at each outlet.

Spectral/ hp method is employed to discretize spatial domain Ω where:

$$\Omega = \Omega_1 \cup \Omega_2 \dots \cup \Omega_i \cup \dots \Omega_{N_{el}}, \text{ where } i = 1, 2, \dots, N_{el}, \quad (2.6)$$

continuous domain Ω is discretized into a set of contiguous non-overlapping elements Ω_i . Within each element, velocity u and pressure p is decomposed into a linear combination of a set of piecewise continuous orthogonal polynomials and its corresponding modal amplitude.

$$u = \sum_{el}^N \sum_i^p u_i^{el} \phi_i^{el}, \quad (2.7)$$

Let's define the residual of Navier-Stokes as:

$$L(u) = \rho(u_t + (u \cdot \nabla)u) - \nabla \cdot \sigma - f = 0, \quad (2.8)$$

Define inner product of the residual of Navier-Stokes as:

$$(L(u), \phi)_\omega = 0, \quad (2.9)$$

For Galerkin method, ϕ is the same as the basis function in u .

For more detailed information the reader is referred to read [16]. A high-order splitting method is used to renew the pressure term inside the stress tensor [17]. Error analysis to spectral element method can refer to [10] written by Gottlieb.

A Womersley velocity profile is imposed on the inlet area. The velocity profile is determined by Womersley number α , which expresses the fraction of transient inertial force and viscous force. It is denoted as $\alpha = L\sqrt{\frac{\omega}{\nu}}$, where L is characteristic length, and ω and ν are angular velocity and kinematic viscosity. The larger it is, the more flat the velocity profile will be, meaning that the inertial force is dominant. Practically, cross-section shape of human arteries have a high possibility of being irregular shape, and typically, inlets of the system needs to be extend as cross-section become a regular circle. More details can be found in [50].

At outlets, a lumped parameters network is connected with the outlets of coronary arteries which represents the influence of downstream blood flow to cut-off area pressure.

Coupled 0D lumped network is connected with 3D solver at each outlets.

2.2 1D Mathematical formulation

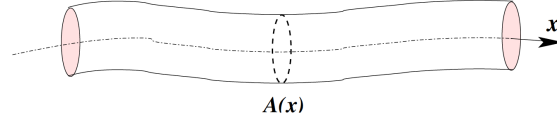


Figure 2.1. One-dimensional model.

Consider a vessel of length l with a centerline described by and cross sectional area A denoted by $A(x, t)$ as indicated in Fig. 2.1. For the 1D system for Newtonian incompressible flow in an impermeable, elastic domain Ω . Assume that no velocity in other than axial direction and vessels are slightly tapered. The Navier-Stokes equations collapse into a continuity equation and a single axial momentum balance equation in one direction. The governing equations are written as:

$$\frac{\partial \mathbf{U}}{\partial t} + \frac{\partial \mathbf{F}(\mathbf{U})}{\partial x} = \mathbf{S}(\mathbf{U}), \quad (2.10)$$

where

$$\mathbf{U} = \begin{bmatrix} U_1 \\ U_2 \end{bmatrix} = \begin{bmatrix} A \\ u \end{bmatrix}, \mathbf{F} = \begin{bmatrix} F_1 \\ F_2 \end{bmatrix} = \begin{bmatrix} uA \\ \frac{u^2}{2} + \frac{p}{\rho} \end{bmatrix}, \mathbf{S} = \begin{bmatrix} S_1 \\ S_2 \end{bmatrix} = \begin{bmatrix} 0 \\ -\frac{1}{\rho}(Kr \frac{u}{A} - s) \end{bmatrix}, \quad (2.11)$$

where x is the axial coordinate along the vessel. $A(x, t)$, $p(x, t)$ and $u(x, t)$ are defined as the average velocity A and pressure p over the cross-section area u . Density is denoted by ρ and Kr is positive which represents the viscous resistance flow per unit length of the tube and s accounts for the tapering effect from stenosis. They are denoted respectively by

$$Kr = \frac{2\alpha\nu\pi}{\rho(\alpha-1)}; s = -\frac{\partial p}{\partial A} \frac{\partial A}{\partial x}, \quad (2.12)$$

For inviscid flow, $\alpha = 0$; for non-Newtonian flow, $\alpha = 1.1$; for Newtonian flow, $\alpha = 2$.

The algebraic form we will adopt later in this paper assumes a thin wall tube where each section is independent of the others. Using Laplaces law leads to a pressure area relationship of the form:

$$p = p_{ext} + \beta(\sqrt{A} - \sqrt{A_0}), \quad (2.13)$$

where β is defined as

$$\beta(x) = \frac{\sqrt{\pi}h_0E}{(1-\nu^2)A_0}, \quad (2.14)$$

where ν is Poisson ratio (typically taken to be $\frac{1}{2}$ for biological tissue) and h_0 and A_0 are vessel thickness and initial cross sectional area. E indicates the Young's modulus. P_{ext} is the constant external pressure.

Typically for the arterial or artery, The relation between E and β follows the empirical formulation [25]:

$$\frac{Eh}{r_0} = k_1 \exp k_2 r_0 + k_3, \quad (2.15)$$

where k_1, k_2 and k_3 are given as:

$$k_1 = 2.00 \times 10^7 g * s^{-2} * cm^{-1}, k_2 = -22.53 cm^{-1}, k_3 = 8.65 \times 10^5 g * s^{-2} * cm^{-1}, \quad (2.16)$$

Above are primitive equations of 1D flow. Recall that assumptions: (a) Our first modeling simplification will be to assume that the local curvature is everywhere small enough so that the axial direction can be described by a Cartesian coordinate x as shown in Fig. 2.1 so that the problem can be defined in one-dimension. (b) Second modeling assumption is that the structural arterial properties are constant at a section. (c) Length is independent of time. (d) Impermeable means there is no flux through the side wall.

Since the nature of the system is Riemann problem, the equations can be reformulated as decoupled Riemann variables with respect to its wave speed and eigenvalues.

$$\frac{\partial \mathbf{W}}{\partial t} + \Lambda \frac{\partial \mathbf{W}}{\partial x} = S_w, \quad (2.17)$$

$$\mathbf{W} = \begin{bmatrix} W_f \\ W_b \end{bmatrix}, \Lambda = \begin{bmatrix} \lambda_f & 0 \\ 0 & \lambda_b \end{bmatrix}, \mathbf{S} = \begin{bmatrix} S_1 \\ S_2 \end{bmatrix} = \begin{bmatrix} 0 \\ -\frac{1}{\rho}(Kr \frac{u}{A} - s) \end{bmatrix}, \quad (2.18)$$

where $W_{f,b} = u \pm 4(c - c_0)$ are the characteristic Riemann invariants of the system where we assume $u_0(x, t) = u(x, 0) = 0$ and $A(x, 0) = A_0$. These formulation is originally obtained by [9]. Λ has two real eigenvalues $\lambda_{f,b} = u \pm c$, c is the local wave speed denoted as

$$c = \sqrt{\frac{\beta}{2\rho A_0}} A^{\frac{1}{4}}, \quad (2.19)$$

typically $\lambda_1 = u + c > 0$ and $\lambda_2 = u - c < 0$.

2.2.2 Connection

The above equations holds for a single vessel with no bifurcation, but the 1D model can be extended to the handle the arterial tree by imposing proper physical constraints at the interfaces as shown in Fig. 2.2. Given the initial area and velocity at the ending and beginning point of corresponding vessels, we need to determine the values of the variables in all of them at next time step. Note that the discontinuity of β and initial cross sectional area A at junction point.

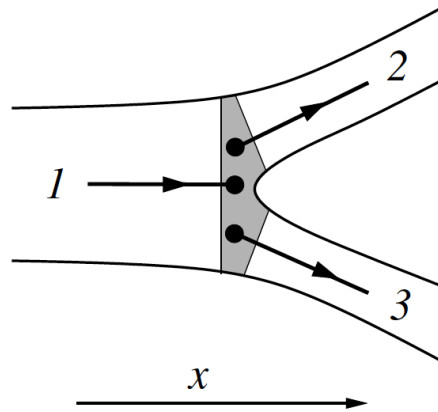


Figure 2.2. Vessel 1 is the parent vessel, where 2 and 3 are daughter vessels.

Under physiological conditions, the law of conservation of mass and continuity of total pressure are still held at the bifurcation. These requirements provide three physical

constraints:

$$A_1 u_1 = A_2 u_2 + A_3 u_3, \quad (2.20)$$

$$p_1 + \frac{1}{2} \rho u^2 = p_2 + \frac{1}{2} \rho u_2^2, \quad (2.21)$$

$$p_1 + \frac{1}{2} \rho u^2 = p_3 + \frac{1}{2} \rho u_3^2, \quad (2.22)$$

There are six unknowns and three equations, we need three more equations to close the system. Recall that the nature of hyperbolic PDE dictates the characteristic variables in each vessels are the same. In other words, from the definition of characteristic variables we have:

$$u_1 + 4(c_1 - c_0^1) = W_1^1, \quad (2.23)$$

$$u_2 + 4(c_2 - c_0^2) = W_2^2, \quad (2.24)$$

$$u_3 + 4(c_3 - c_0^3) = W_2^3, \quad (2.25)$$

where c_0^1, c_0^2, c_0^3 denotes the wave speed evaluated using equilibrium area A_0 . Hence this system is closed and one could use proper numerical method to solve it at every time step.

Merging junction as shown in Fig. 2.3 is common structure in veins and arterials in the circulation systems. Clinically, studying merging vessel is significant, one of the reasons is that the arterials bypass grafting where an alternative channel is surgically introduced due to local-pathological lesion such as atherosclerosis, stenosis or other diseases which affect the normal function, flow rate or pressure of the local region.

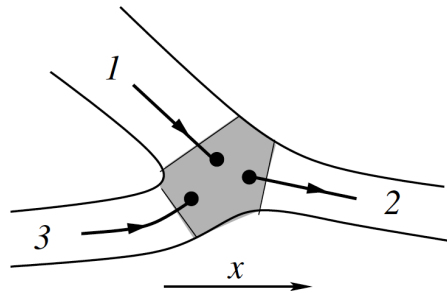


Figure 2.3. Vessel 1 and 3 merge into vessel 2.

Similar as convergent vessel, merging vessel governed by the same physical laws which is conservation of mass and continuity of total pressure at merging point and mathematical property where the characteristic variables are the same. Under the same laws, we could modify the constraints on divergent vessel as :

$$A_1 u_1 + A_3 u_3 = A_2 u_2, \quad (2.26)$$

$$p_1 + \frac{1}{2} \rho u^2 = p_2 + \frac{1}{2} \rho u_2^2, \quad (2.27)$$

$$p_1 + \frac{1}{2} \rho u^2 = p_3 + \frac{1}{2} \rho u_3^2, \quad (2.28)$$

$$u_1 + 4(c_1 - c_0^1) = W_1^1, \quad (2.29)$$

$$u_2 - 4(c_2 - c_0^2) = W_2^2, \quad (2.30)$$

$$u_3 + 4(c_3 - c_0^3) = W_1^3, \quad (2.31)$$

Newton-Raphson method is used to numerically solve this system.

2.2.3 Numerical method

As mentioned in previous section, here we have a nonlinear hyperbolic system with piece-wise continuous initial condition. The main numerical challenge hinges on the way to accurately characterize wave propagation without much dispersion and dissipation error. Luckily, there is no abrupt discontinuity for pressure under physiological condition, high-order Discontinuous Galerkin method is suitable to be deployed to solve this system. Here I follow the numerical discretization in [40]. Decomposed by Legendre polynomial L_p and integrate by part can we get:

$$J_e \frac{\partial \hat{U}_{i,e}^p}{\partial t} = - \int_{\Omega_e} J_e F(\hat{U})_p \frac{\partial L_p}{\partial x} d\xi + L_p J_e [F(\hat{U})_i^u]_{x_e^L}^{x_e^R} + J_e \int_{\Omega_e} L_p S_i d\xi, p = 0, \dots, P, i = 1, 2, \quad (2.32)$$

where J_e is the Jacobian, P is the highest polynomial order.

This is the semi-explicit form we have to solve the system.

$$\frac{\partial \hat{U}_{i,e}^p}{\partial t} = f \left(\hat{U}_{i,e}^p \right), \quad (2.33)$$

$$f \left(\hat{U}_{i,e}^p \right) = - \int_{\Omega_e} L_p \frac{\partial F(\hat{U})_i}{\partial x} d\xi - L_p \left[F(\hat{U})_i^u \right]_{x_e^L}^{x_e^R} + \int_{\Omega_e} L_p S_i d\xi, \quad (2.34)$$

To be complete, we choose second order Adams-Bashforth scheme to update each variable:

$$\left(\hat{U}_{i,e}^p \right)^{n+1} = \left(\hat{U}_{i,e}^p \right)^n + \frac{3\Delta t}{2} f \left(\left(\hat{U}_{i,e}^p \right)^n \right) - \frac{\Delta t}{2} f \left(\left(\hat{U}_{i,e}^p \right)^{n-1} \right), \quad (2.35)$$

2.3 0D formulation

This section we review a simplified 1D system, namely 0D or Windkessel, to simulate micro-vascular blood flow. It is widely used in simulating micro-vascular vessel in downstream.

2.3.1 Mathematical formulation

Assume there is no source term and rewrite nonlinear equations 2.10 as:

$$C_{1D} \frac{\partial p}{\partial t} + \frac{\partial q}{\partial x} = 0, \quad (2.36)$$

$$L_{1D} \frac{\partial q}{\partial t} + \frac{\partial p}{\partial x} = -R_{1D} q, \quad (2.37)$$

$$p = \frac{a}{C_{1D}}, \quad (2.38)$$

where

$$R_{1D} = \frac{2(\gamma+2)\pi\mu}{A_0^2}, L_{1D} = \frac{\rho}{A_0}, C_{1D} = \frac{A_0}{\rho c_0^2}, \quad (2.39)$$

Further simplification can be derived by integrating over an arterial domain with length l

$$C_{0D} \frac{d\hat{p}}{dt} + q_{out} - q_{in} = 0, \quad (2.40)$$

$$L_{0D} \frac{d\hat{q}}{dt} + R_{0D} \hat{q} + p_{out} - p_{in} = 0, \quad (2.41)$$

where $q_{in}(t) = q(0, t)$, $q_{out}(t) = q(l, t)$, $p_{in}(t) = p(0, t)$, and $p_{out}(t) = p(l, t)$

$$\hat{p}(t) = \frac{1}{l} \int p dx, \hat{q}(t) = \frac{1}{l} \int q dx \quad (2.42)$$

are the mean pressure and flow-rate. The equivalent electric transmission analogy is shown in Fig. 2.4, where the flow-rate and pressure are analogous to electric current and potential, respectively. In this sense, the counterpart of Ohm's law $U = IR_{cir}$ in hemodynamics is $p = qR_b$ where the resistance is defined as $R_b = \frac{p}{q}$. Similarly, L_{0D} can be related to an inductance and C_{0D} to capacitance. In this sense, physiological variables are endowed with physical meaning in electric engineering, the analysis and simplification in electric engineering can be introduced to characterize dynamics in blood flow.

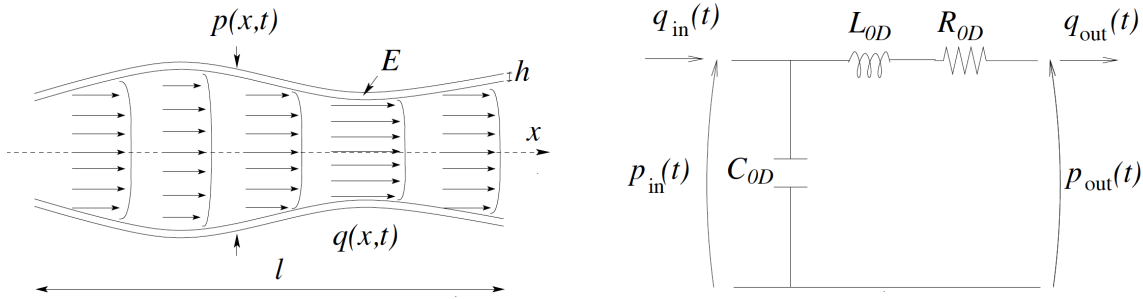


Figure 2.4. 1D vessel and its simplified circuit analogy: RCLR system [2]

2.3.2 Boundary Condition

Further simplification from 1D to 0D can greatly reduce the computational time and resource however, inevitably, more detailed information on dynamics of vessels will be smeared out as well. 0D model could only shows the inlet and outlet pressure and flow-rate. However, this model is suitable to be used with respect to mimic the downstream effect. Here listed the used boundary condition in simulating coronary blood flow.

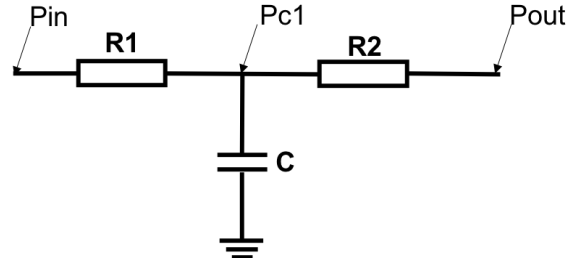


Figure 2.5. RCR aortic boundary condition

Typically, RCR is placed at the end of ascending aorta. Equations 2.40 and 2.41 are used to describe the RCR system:

$$C \frac{dp_{c1}}{dt} + q_{out} - q_{in} = 0, \quad (2.43)$$

$$p_{in} - R_1 q_{in} = p_{c1} = R_2 q_{out} + p_{out}, \quad (2.44)$$

Coronary system, due to its special structure, needs to be described by a more involved 0D system composed with 4 resistors and 2 capacitors. In coronary circulation, oxygenated blood is pumped out from left ventricle and about 4% of it is directed into the left and right coronary arteries and arterials. Then the oxygen and nutrients in oxygenated blood are exchanged in microvasculature vessels and capillaries in myocardial muscle. The de-oxygenated blood is gathered by cardiac veins at different scales and finally recirculated by coronary sinus and flows back to right atrium. The coronary circulation could be expressed by this flowchart.

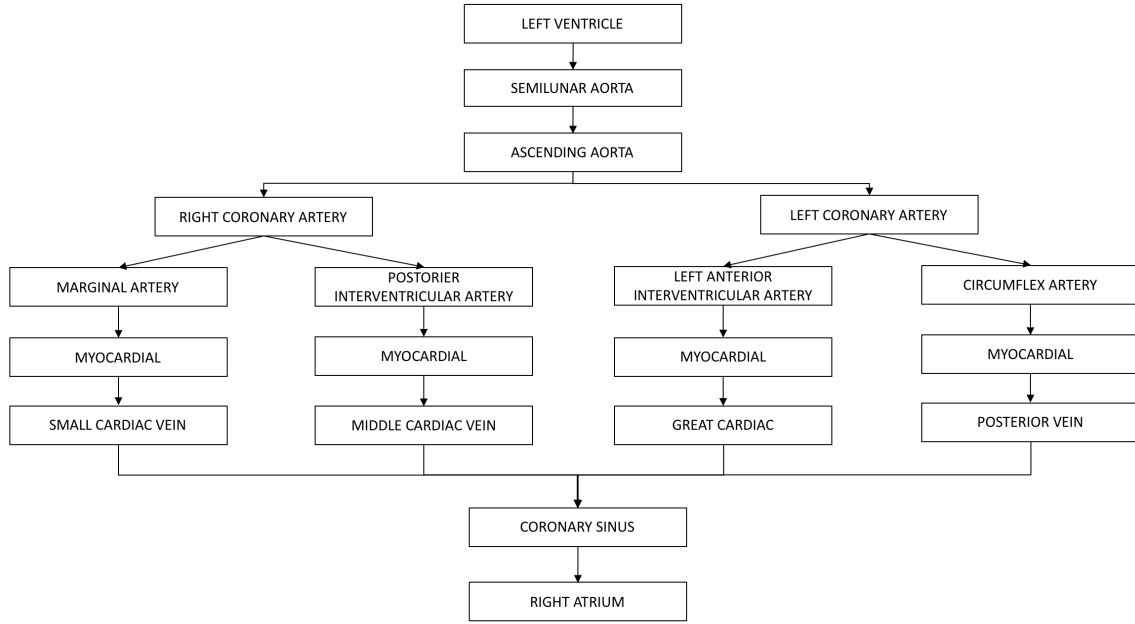


Figure 2.6. Coronary artery blood flow cascade. Blood flows from left ventricle to 4 main branches, and then collected by veins to right atrium.

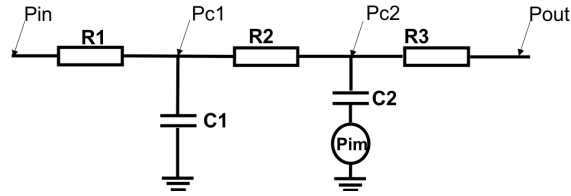


Figure 2.7. Circuit analogy of downstream coronary artery system.

$$q_{in} = \frac{P(A^*) - P_{c1}}{R_1}, \quad (2.45)$$

$$q_{in} = C_1 \frac{\partial P_{c1}}{\partial t} + q_{c2}, \quad (2.46)$$

$$P_{c1} = q_{c2} R_2 + P_{c2}, \quad (2.47)$$

$$q_{c2} = q_{out} + C_2 \frac{\partial P_{im}}{\partial t}, \quad (2.48)$$

$$P_{c2} = q_{out} R_3 + P_{out}, \quad (2.49)$$

In the analogy above, R_1, R_2, R_3 respectively represent the resistance from cut-off coronary arteries, micro-circulation, micro-vascular and venous resistance, and C_1 and C_2 are

capacitance from coronary artery and intra-myocardial tissue. P_{im} is the intra-myocardial pressure.

2.4 Stenosis model

For a full-order Navier-Stokes, there is no specific assumption made on shape of vessel, and the equation can accurately describe the pressure drop over the stenosed part. However, an important geometrical assumption in 1D simulation, where primarily, the axial change in vessel diameter is assumed to be zero or small enough to be neglected, might not be held since the sudden contraction of the diameter might trigger vortices or even turbulent flow downstream. In other words, the radial velocity components are no longer negligible and according to hydraulic mechanics, a certain amount of pressure will be lost during fluid flows across this necking area. 1D model assumption may fail when there is a sudden contraction along the vessel. So, to compensate this pressure drop, an additional term is introduced and will be discussed in this chapter. with a focus on the local velocity field and the wall shear stress.

Here we follow the formulation derived by Young et al. in [53][54][6]. The pressure drop over the stenosis could be expressed as:

$$\Delta P = \frac{\eta K_v}{2\pi a_0^3} q + \frac{\rho K_t}{2A_0^2} \left(\frac{A_0}{A_s} - 1 \right)^2 |q|q + \frac{\rho K_u L_s}{A_0} \frac{\partial q}{\partial t}, \quad (2.50)$$

Here, a_0 and A_0 are radius and cross sectional area of healthy vessel lumen vessel. A_s and L_s represent cross-sectional area and length of the stenosis. K_u , K_v and K_t can be expressed as:

$$K_v = 16 \frac{L_s}{a_0} \left(\frac{A_0}{A_s} \right)^2, K_t = 1.52, K_u = 1.2, \quad (2.51)$$

CHAPTER 3

3D/1D RESULTS

The main goal of this chapter is to validate the NEKTAR 1D accuracy in predicting pressure and flow-rate in coronary artery system by comparing the high-fidelity results from NEKTAR 3D simulation. This chapter is divided into three sections: section 3.1 to section 3.3 show the 3D simulation and 1D results on their centerlines on different geometries, which are a stenotic tube, a healthy coronary artery tree and a coronary system with a stenosis on LAD, respectively. And some suggestions are discussed in the last part to provide further evidence to 1D and 3D simulation. Spectral element solver NEKTAR 3D and Discontinuous Galerkin solver NEKTAR 1D are used to investigate blood flow in the system in high and low fidelity method in which both of them are introduced in Chapter 2. What worthy to mention is that the coronary artery system reconstructed from CTA, so does the other organ or vessel, is usually highly irregular and quite rough on the surface, which dramatically increase the difficulty stabilizing of the simulation and extracting the centerlines out of it. One viable way to resolve this is to dissect the whole vessel into segmentation and employ some algorithms to smooth it out. More details can be found in [4]. After generating a smoothed 3D geometry, 1D centerline of each coronary artery and aorta can be extracted. In this research, an open source software, VMTK, is used to extract centerline of the geometry and based on which the centerlines 1D simulations are performed. The algorithm to extract centerline can be found in [3]. For simplicity, the smoothed coronary artery geometry is downloaded from open source repository SimVascular. The coronary system and its centerline are shown in Fig. 3.1.

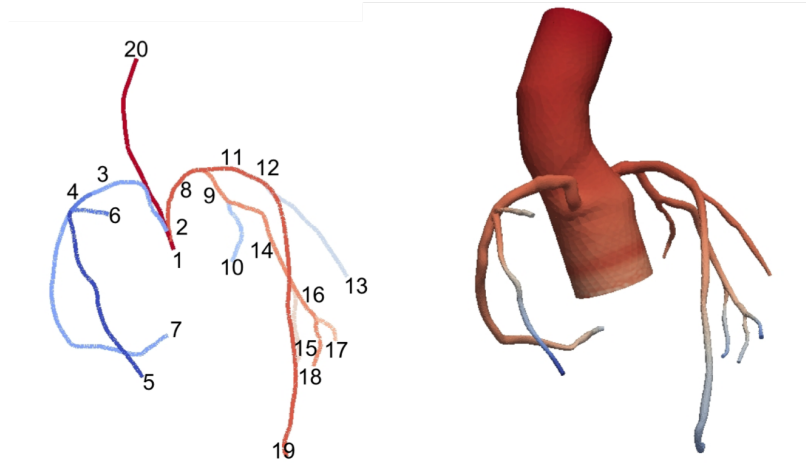


Figure 3.1. Geometric layout from 3D coronary system (right) and its centerline (left).

3.1 Stenosis tube

The goal of this first numerical test is to validate the stenosis model formulated and developed by Young[53][54] in 1973. This model is implemented in NEKTAR 1D as it is used in calculating pressure drop over specific stenosis. In the first test, the pressure drop in a straight tube with a 50% stenosis is studied and calculated by both NAKTAR 1D and 3D. The diameter at the inlet is 4mm and the total length of the tube is 4cm, and it is shown in Fig 3.2. A pulsatile flow-rate profile with unit of cc/s is imposed at the inlet and the outlet is connected with a RC system. Here the value of resistance is set as 4.2×10^9 . The Reynolds number is around 200, same as that in most arteries. Following the findings of Grinberg et al.[14], the value of capacitance is empirically set as $C = 0.18/R$. 29564 elements in total compose the 3D geometry and 3 elements compose the 1D centerline from VMTK. The kinematic viscosity is set as $3.773 \cdot 10^{-6} m^2 \cdot s^{-1}$ and $\beta_{scale} = 0.029$. The 1D simulation over four cardiac cycles took only 10 minutes on a single i7 processor, whereas the 3D simulation required about 8h per cardiac cycle on 256 cores on STAMPEDE 2.

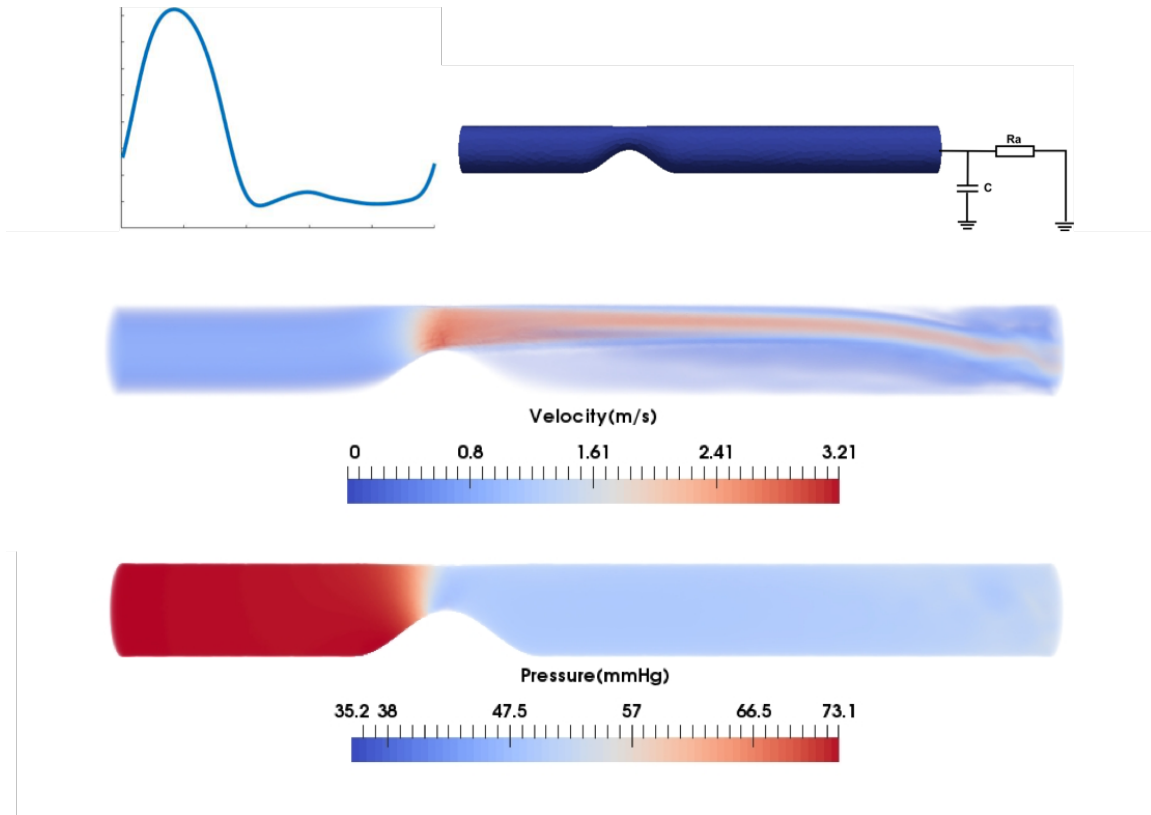


Figure 3.2. Stenosis tube and its diastolic velocity and pressure

Figure 3.2 shows the total velocity and pressure distribution at systolic. It is clear that there exists a over 50% pressure around the bottleneck of this tube and then it recovers about 20 mmHg in the downstream. And the wake induced by asymmetric contraction also extends to the outlet. The pressure is averaged on the outlet surface. In figure 3.3, inlet and outlet pressure calculated from 3D and 1D is plotted. A very good agreement between 1D and 3D pressure at outlet is shown. The L_{inf} error within a heart cycle is less than 1 mmHg. 1D solver with stenosis model could predict a pressure over stenosis with a satisfied accuracy in a straight tube, and this provides the possibility to predict FFR in a more complex geometry. Since there is only one outlet for this tube, the comparison between flow-rate is trivial.

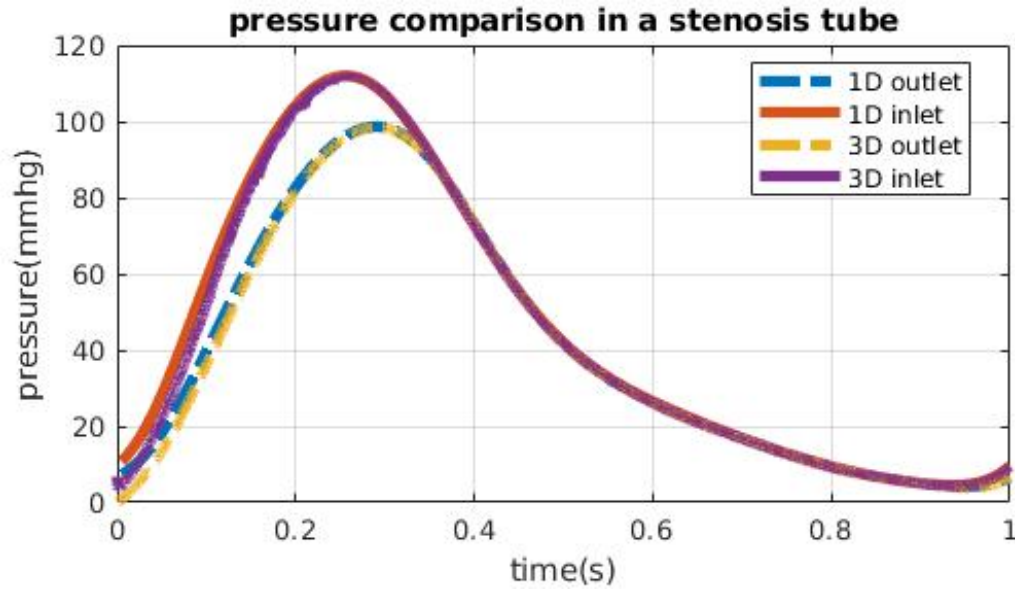


Figure 3.3. 3D/1D Pressure comparison at outlet within one heart cycle

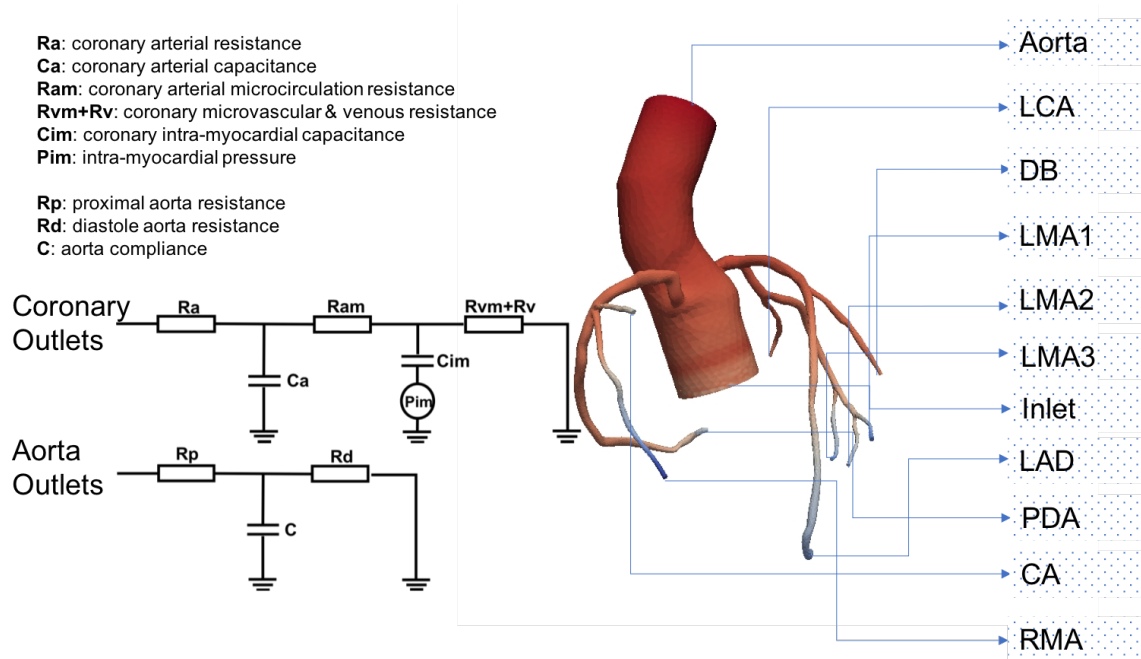


Figure 3.4. Coronary artery tree and corresponding boundary conditions. LCA : left circumflex artery. DB : diagonal branch. LMA1, 2, 3 : left marginal artery 1, 2, 3. LAD : left anterior descending artery. PDA : posterior descending artery. CA : conus artery. RMA : right marginal artery.

3.2 Coronary arteries system

In the second test we consider a healthy coronary system with a single aorta outlet and 9 coronary outlets; 3 of them are on the right hand side, while the rest of them are on the left hand side. Figure 3.4 shows the geometry layout of coronary artery system. The blood would be pumped in from the left ventricle, and 96% of them will provide oxygenated blood to the whole body from aortic outlet with around 4% of blood flows into left and right coronary arteries. RCR boundary condition is connected at the aortic outlet and coronary boundary condition is connected at the coronary outlets.

We follow Kim et al. [18] to calculate the boundary condition on coronary outlets. $R_{aor} = P_{mean}/Q$ where R_{aor} is the total aorta resistance. A typical healthy heart pressure is around $125000 \text{ dynes}/\text{cm}^2$ and Q is around 80ml/s . $R_p/R_d = 0.09$ and C sets as $10^{-3}\text{cm}^5/\text{dynes}$. To select coronary boundary values, one needs to estimate total coronary resistance which is related to the amount of flow into coronary arteries. We assume that 4% of blood will supply the coronary which means the total coronary resistance is 24 times that of total aorta resistance; $R_{cor,tot} = 24 * R_{aor}$. And for each of the outlet, the resistance when at rest would be divided following $R_{cor,i} = \sum_j \sqrt[2.6]{A_j} / \sqrt[2.6]{A_j} * R_{cor,tot}$, $R_a = 0.32R_{cor,i}$, $R_{am} = 0.52R_{cor,i}$, $R_{v,am} = 0.16 * R_{cor,i}$. Following such criteria to select parameters can we get a list of parameters as followed in Fig. 3.5. Under hyperemic condition, we set $R_{cor,tot} = 5.33 * R_{aor}$, and hyperemic boundary condition is used in the third numerical test when a stenosis is added on LAD.

As a distinguished feature at coronary outlet, the pressure and flow-rate is affected by the intra-myocardial pressure imposed on coronary boundary. This accounts for the impact from different heart phases during a single heart beat. The impact from intra-myocardial pressure vary with the location of coronary arteries, namely the impact would be empirically amplified by 1.5 times in left coronary arteries and would be decreased by 0.5 on the right. Intra-myocardial pressure and inlet flow-rate are shown in Figure 3.6. To discretize the all 3D domain, 49366 elements are meshed to compose the coronary system. In 1D centerlines, 20 domain with up to 36 elements made up the 1D centerline.

Quadrature order within each element is 4. 3D simulation takes about 12h to calculate 1 heart cycles is on 512 cores, and 1D takes around half an hour on a i7 core laptop.

<i>Domain</i>	<i>Area($10^{-6}m^2$)</i>	<i>Length(m)</i>	$\beta(10^6)$	<i>R_tot(rest)</i>	<i>R_tot(hyp)</i>	<i>C_tot(rest)</i>	<i>C_tot(hyp)</i>
1	732.81	0.0031	8.0896				
2	706.41	0.0041	10.115				
3	11.81	0.0502	648.72				
4	12.89	0.0076	570.86				
5	6.80	0.0682	1603.7	354	78.6	2.72	2.72
6	7.00	0.0302	1523.7	260	57.9	3.44	3.44
7	10.80	0.1112	743.18	198	44.1	4.24	4.24
8	15.29	0.0322	449.81				
9	15.29	0.0188	449.81				
10	4.99	0.0348	2792.6	580	129	2.68	2.68
11	16.58	0.0113	404.31				
12	11.41	0.018	683.31				
13	7.92	0.0483	1232.5	597	133	2.62	2.62
14	9.14	0.0519	968.68				
15	3.90	0.0383	4376.5	765	170	2.16	2.16
16	4.38	0.0182	3531.1				
17	3.12	0.0217	6560	319	71.0	4.23	4.23
18	2.76	0.0257	8156.9	469	104	3.15	3.15
19	8.06	0.1211	1195.2	196	43.5	6.18	6.18
20	586.11	0.0682	10.115	1.56	1.56	1000	1000

Figure 3.5. Measurements for the coronary artery

Moreover, to further validate both of 3D and 1D solver, an open source software "Sim-Vascular" is employed to perform the blood flow simulation on the same geometry. It is a linear finite element solver with coronary artery flow section implemented in it. A finer mesh is utilized with 301387 elements to compose the coronary system to make sure the final result is convergent. However, the computational cost to run the software is only about 4 hours per heart cycle on a i7 core laptop.

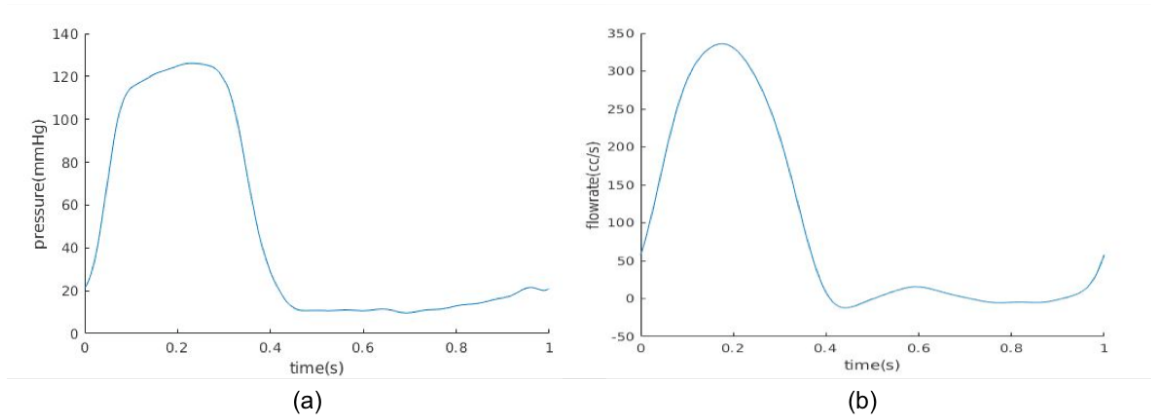


Figure 3.6. (a)intra-myocardial pressure and (b)aorta flow-rate inlet.

Fig. 3.7 compares the pressure and flow-rate from aorta outlet. NEKTAR 1D and 3D correspond well to each other in both systolic and diastolic process with average mean pressure 91 and 93 mmHg, consistent to the assumption we made to calculate total aorta pressure. There is no evident discrepancy in flow-rate at aorta.

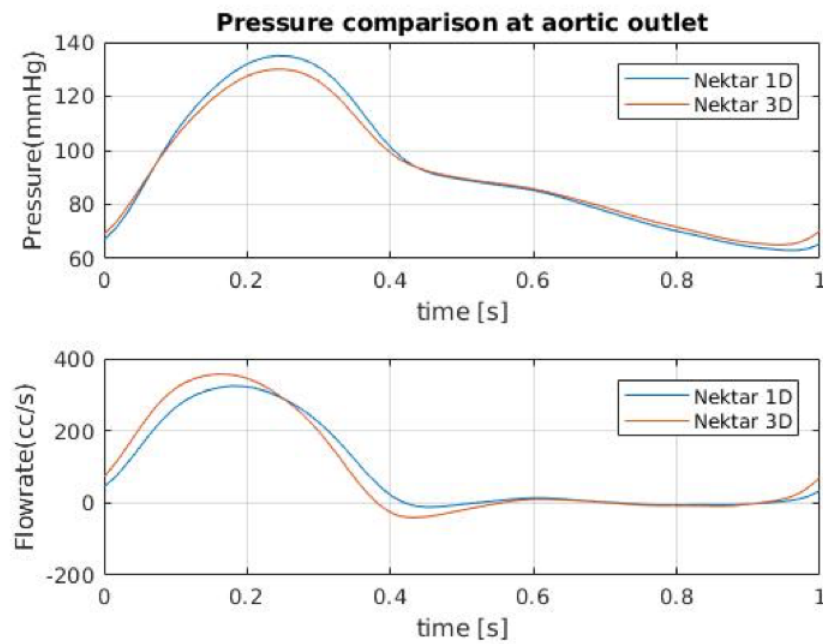


Figure 3.7. 3D/1D Pressure and flow-rate comparison at aortic outlet.

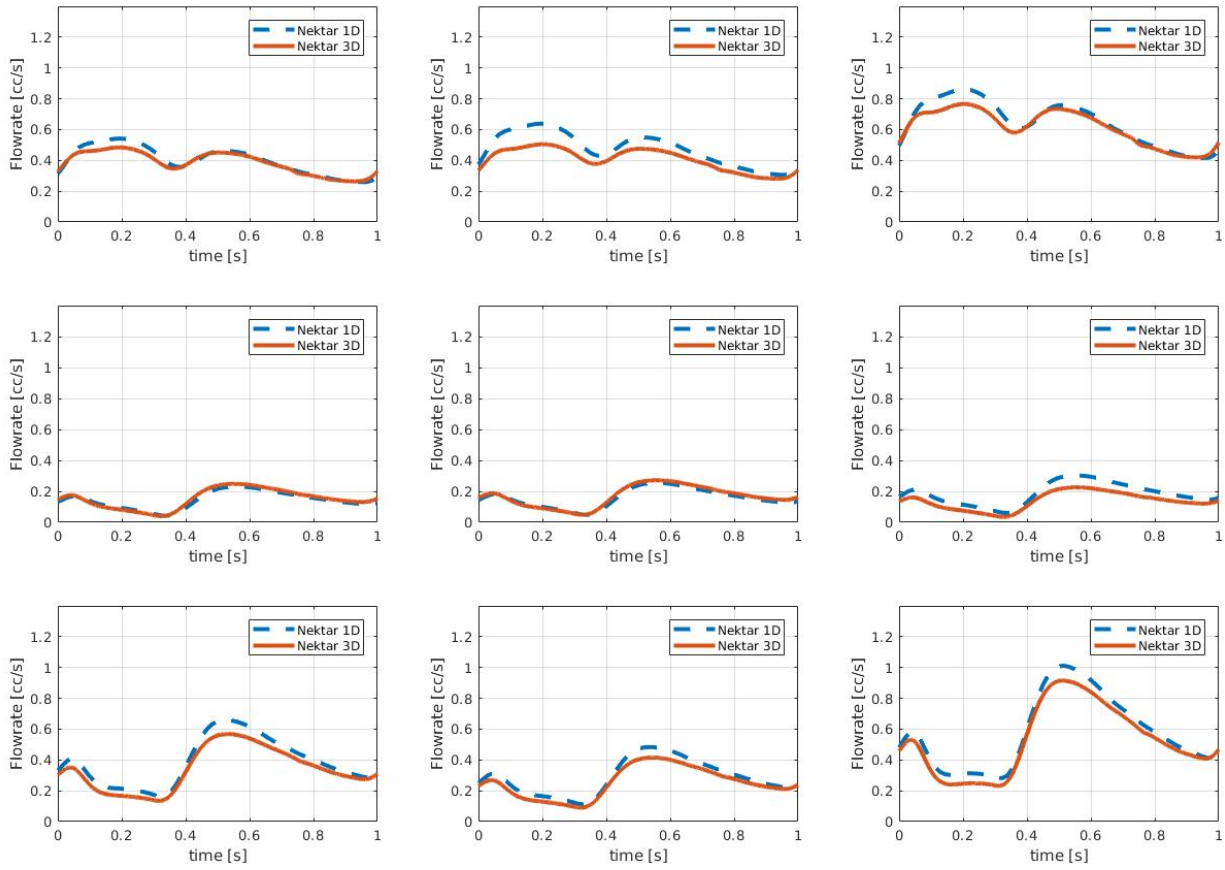


Figure 3.8. Flow-rate comparison between NEKTAR 3D/1D. Top three are right coronary outlets; vessel 5, 6, 7. Figures in middle are vessel 10, 13, 15, 17, 18, 19, respectively. Vessel numbers correspond to that in Fig. 3.1.

Figures in 3.8 and 3.9 show a general good agreement in both pressure and flow-rate comparison. In Fig. 3.8, all of the flow-rate figures show a similar profile within a heart beat. In particular, the top three plot the flow-rate at right coronary outlets where an evident double-peak happens caused by a small distal-originating suction wave. The differences in elastance and pressure generated between right and left ventricles cause this discrepancy [15]. The middle and bottom figures show a lagging peak for the flow-rate in all of the left coronary arteries. The flow-peak arrives about 0.2s later than the flow-rate peak at aorta inlet. In Fig. 3.9, pressure profile at every coronary outlet also has a good agreement. And from the mean value comparison in Fig. 3.10 and 3.11 can we see the

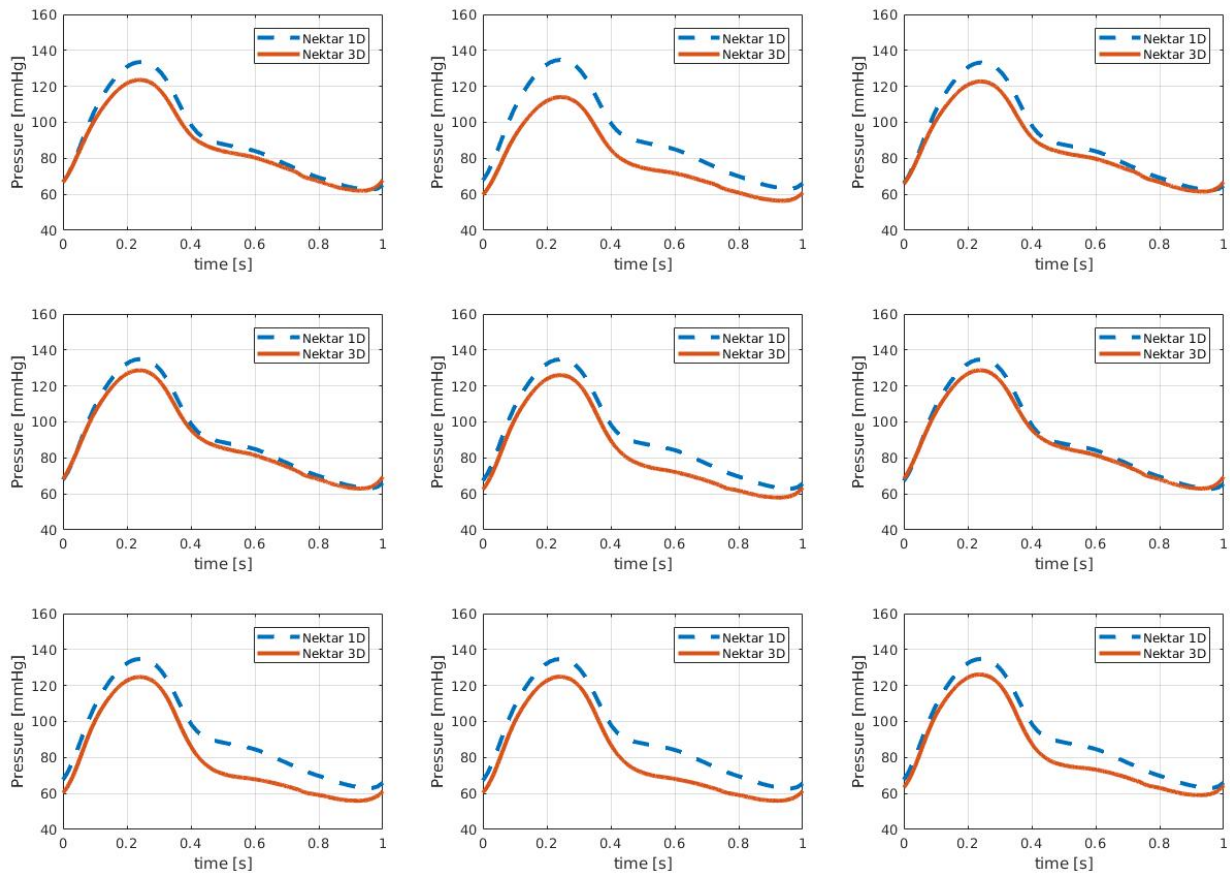


Figure 3.9. Pressure comparison between NEKTAR 3D/1D and SimVascular. Top three are right coronary outlets; vessel 5, 6, 7. Figures in middle are vessel 10, 13, 15, 17, 18, 19, respectively.

NEKTAR 1D is consistent to that from NEKTAR 3D. Note that there are some vessels have a quite obvious difference in pressure and flow-rate prediction such as in vessel 6, 13, 17 and 18. The reasons which lead to this discrepancy would be discussed in the last section.

3.3 3D vs 1D stenosis model Result comparisons

In this test we perform 1D simulation on a stenotic coronary artery system to calculate FFR. A 50% stenosis is manually added in LAD where most of stenoses buildup.

Flowrate(cc/s)	NEKTAR 1D	NEKTAR 3D
Vessel 5	0.40	0.39
Vessel 6	0.47	0.41
Vessel 7	0.65	0.62
Vessel 10	0.14	0.15
Vessel 13	0.16	0.17
Vessel 15	0.18	0.14
Vessel 17	0.38	0.33
Vessel 18	0.29	0.25
Vessel 19	0.58	0.53
Aorta	87.09	88.82

Figure 3.10. Comparson of mean flow-rate during a heart cycle.

Pressure(mmHg)	NEKTAR 1D	NEKTAR 3D
Vessel 5	90.96	87.02
Vessel 6	91.90	79.04
Vessel 7	90.71	86.23
Vessel 10	91.89	89.30
Vessel 13	91.50	83.40
Vessel 15	91.45	88.34
Vessel 17	91.68	80.72
Vessel 18	91.43	80.91
Vessel 19	91.74	83.97
Aorta	91.08	93.87

Figure 3.11. Comparson of mean pressure during a heart cycle.

Often, the ischemia could be caused under hyperemic condition which means the increment of flowrate to tissue and decrement of resistance. So we lower the total coronary

resistance by 4.5 times, directing more flows into coronary system without increasing total aortic flow rate. Hyperemic condition is usually caused by exercise, heat or some medicine to soften vessel elasticity. The value of each resistance could be found in Fig. 3.5. And this 1D simulation costs an approximated the same time as that in in last numerical experiment.

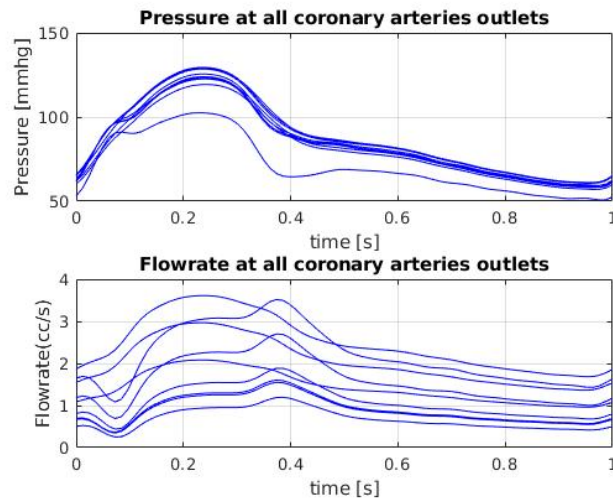


Figure 3.12. Pressure and flow-rate at the outlets of stenotic coronary artery.

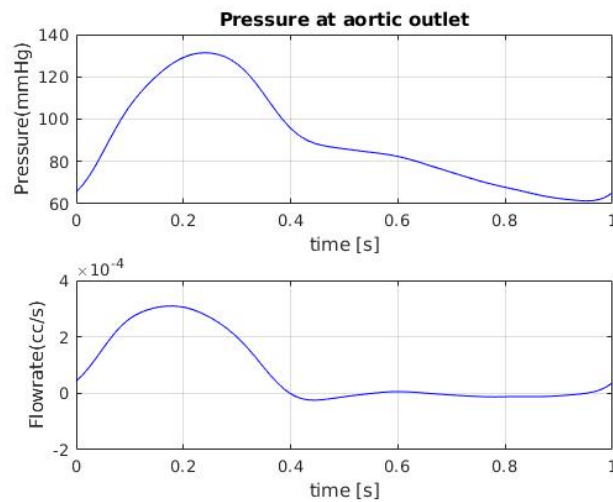


Figure 3.13. Pressure and flow-rate at the aortic outlet of stenotic coronary artery.

The decrement of total resistance at each coronary outlet induce the change in shape of flow-rate. In Fig. 3.12, the two-peak flow-rate profile on the right coronary disappear, replaced by single peak shape. And the flow-rate in left coronary arteries have a earlier flow peak at around the 0.4s during a heart cycle. And absolute flow-rate value in each branch increase 4.5 times accordingly. For the pressure profile, the most distinctive feature comes from the one vessel with stenosis(LAD). Mean pressure in LAD has a 20 mmHg drop in a heart cycle except the first 0.1s in systole. The FFR in LAD is 0.8 for this 50% radius reduction branch where the stenosis could induce sudden ischemia. 3D simulation is running and will be added in the paper which is under preparing.

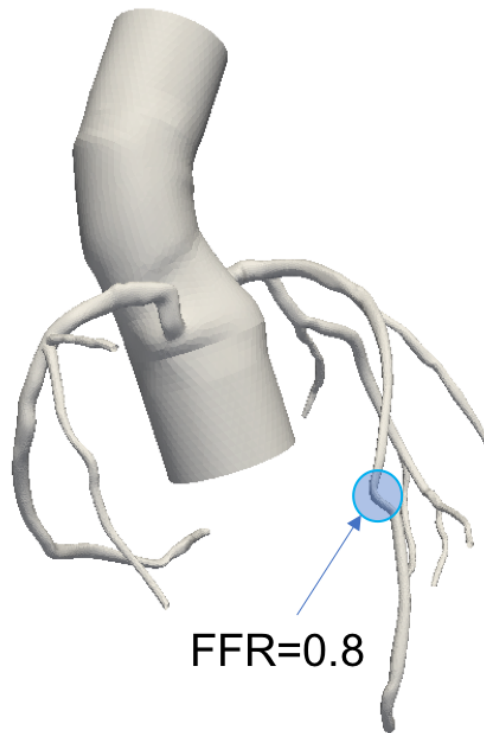


Figure 3.14. Stenotic coronary artery geometry with FFR = 0.8 at hyperemia.

3.4 Conclusion

Overall, results from NEKTAR 1D show a good agreement with the result from 3D where the computational cost is much costly than it is. However, discrepancy between 1D

and 3D results may come from many of reason; in vessel 6, it could be caused by the angle in coronary branches which can not be described by 1D since the all system is made up by a system of straight tube; the quality of centerline in 1D geometry and the number of element to discretize each branch may also introduce error to the final results especially in some rapid contraction area; it could also coming from the energy loss and triggered secondary flow at junction points, which might explain the farther vessels such as 13, 17 and 18 might have such difference. Note that the algorithm to infer parameters for the geometry heavily relies on the outlet facet area, so the discrepancy in cross-sectional area is also another error source.

Due to lacking of clinical data, there is no way to validate the results in this research with real invasively measured FFR. The possible difference with 3D and invasively measured FFR might be caused by many of reason: the turbulence at aorta triggered by the left ventricular valve; the smoothed 3D geometry in numerical computation; fluid-structure interaction effect on both coronary branches and aorta; and other simplified assumption like Newtonian fluid, fixed boundary condition value or mathematical approximation of coronary artery boundary. Further optimization on 3D and 1D is all based on real measured FFR, and it could carried out in future research.

CHAPTER 4

UNCERTAINTY ANALYSIS

4.1 Motivation and background

Numerically solving Navier-Stokes has been using clinically to simulate the blood flow in arteries and arterials to predict the FFR on a stenosed vessel. Following the procedure of calculating non-invasive FFR can we conclude that the main sources of uncertainty arise from (a) anatomic geometry such as lumen dissection, wall thickness or extracting 1D centerline etc. (b) physiological properties like viscosity, elastance or aorta flux etc. (c) mathematical approximation such as rigid wall assumption, Newtonian fluid, boundary condition inference or numerical method.

The predicted FFR or pressure in this patient-specific modeling framework heavily relies on the parameters or data above, and these variables have different impact to the result. So quantifying the uncertainty deviation and identifying the significance for each variables are non-trivial for validating the accuracy and increasing the credibility for the scheme. Previous studies [32][33][34] suggests that geometry has the largest impact on FFR prediction in coronary arteries, and a machine-learning based fast approach for predicting FFR has been utilized to perform "geometric sensitivity". However, the works on perturbations from physiological parameters and boundary condition values to different boundary condition and different location in coronary artery tree has not yet be studied. Moreover, Sankaran et al. [34][33] just study the uncertainty quantification from expensive 3D result or machine learning model, either may suffer from expansive computational cost or model-dependent accuracy. As an ideal alternative, 1D solver, is perfect for studying uncertainty due to the proper trade-off between computational cost and model accuracy. And such numerical experiment for coronary artery tree has not been performed yet. For

simplicity, the main goal of this section is to investigate the quantify the physiological uncertainty of flow rate and pressure deviation in a healthy coronary artery structure under perturbations. Dynamic viscosity, β and effect of intra-myocardial pressure on the outlets, resistances and capacitances are perturbed simultaneously to determine the possible scenario of pressure and flow rate outcomes.

Traditionally, Monte Carlo sampling is a widely adapted method to generate samples from parameter space. Nevertheless, it is suffered from exponential enormous sampling sets when high dimension and slow convergence rate. So we adapt a faster and high-order method, stochastic collocation method (SCM), developed by Xiu and Hesthaven [52] to quantify the deviation of flow-rate and pressure under random parameters input. In this work, 1D reduced-order model is used to investigate such property. Toward this, stochastic collocation method are performed to quantify the certainty and determine the impact of single parameter and its combination with the other parameters to the outcomes. Parameters are sampled by Gaussian quadrature in a proper physiological range. As for analyzing the results, the mean value of pressure and flow-rate result at a specific location and a specific time are calculated by:

$$\bar{f}(x, t) = \sum_{i=1}^N f(x, t, \xi_i) \omega_i \quad (4.1)$$

the standard deviation:

$$\sigma(x, t) = \sqrt{\sum_{i=1}^N (\bar{f}^2 - f(x, t, \xi_i)^2) \omega_i} \quad (4.2)$$

where ξ_i is the sampling vector, N is the number of trails. The results show a small range of deviation for the pressure whilst the flow-rate is more likely to be affected by perturbation. ANOVA [41] is employed to quantify the impact of each parameter under such perturbation. First order index implies the impact from that single parameter while the second order index indicates the impact from those two corresponding parameters. We use this method to investigate the source of uncertainty of the interest variable when the deviation is large.

4.2 Results

To perform the sensitivity study, we use the same coronary artery tree as in chapter 3 with the same coronary boundary condition. There are three sets of simulations performed by NEKTAR 1D to investigate the mean value of pressure and flow-rate to (a) one of left and right coronary arteries (b) the coronary system at rest (c) the coronary system at hyperemia (d) the coronary system at exercise. According to [30][13][18], we choose the kinematic viscosity, mean pressure at the inlet and β_{scale} as shown in table. Gaussian quadrature order is set as 5. Here the assumption is made that it is decoupled between each parameter and each parameter is uniformly distributed in parameter space. Of course, priori distribution or could also be made on sampling but in this study, such assumptions are made for simplicity. We pick the last point in every outlet domain to study the sensitivity of the system.

Coronary Outlet		At Rest & Hyperemia		Exercise	
β_{scale}	$[0.5\beta_{scale}, 1.5\beta_{scale}]$	β_{scale}	$[0.5\beta_{scale}, 1.5\beta_{scale}]$	β_{scale}	$[0.5\beta_{scale}, 1.5\beta_{scale}]$
ν	$[0.00143, 0.00713]$	ν	$[0.00143, 0.00713]$	ν	$[0.00143, 0.00713]$
R_{cor}	$[10^{11}, 10^{12}]$	R_{aor}	$[0.75R_{aor}, 1.25R_{aor}]$	R_{aor}	$[R_{aor}, 1.5R_{aor}]$
C_{cor}	$[10^{-12}, 10^{-11}]$	C_{aor}	$[0.75C_{aor}, 1.25C_{aor}]$	C_{aor}	$[0.5C_{aor}, C_{aor}]$
sf_{left}	$[1, 2]$				
sf_{right}	$[0.25, 0.75]$				

Figure 4.1. The parameters ranges under different physiological condition. $\beta_{scale} = 0.029$, $R_{aor} = 155534 \text{ dynes/cm}^2$ and $C_{aor} = 10^{-3} \text{ cm}^5/\text{dynes}$ in this case.

4.2.1 Sensitivity analysis to coronary outlet

To investigate the sensitivity in different coronary location, one of outlet in both right and left coronary artery are picked to be investigated. As shown in table 2, a global parameter, kinematic viscosity, and four local parameters, namely β_{scale} , impact factor of intra-myocardial pressure, vessel total resistance and capacitance, are perturbed. The rest of parameters are kept the same as those shown in Figure 3.5 in chapter 3 at rest. 781 trails are performed for each side of coronary outlets.

The mean value, the blue line, and standard deviation, the blue dotted lines, at these two outlets are shown in Fig. 4.2. In this figure, it also shows a small deviation around 3% for pressure, meaning the 1D simulation is robust for pressure prediction in healthy geometry given proper approximating physiological parameters and mathematical conditions. However, the uncertainty in parameters has more impact on the flow-rate, partly because of the absolute value of flow-rate is at $O(10^{-6})$. So this implies that coronary pressure would not be affected the perturbation on single branch boundary condition given the rest of the system is fixed.

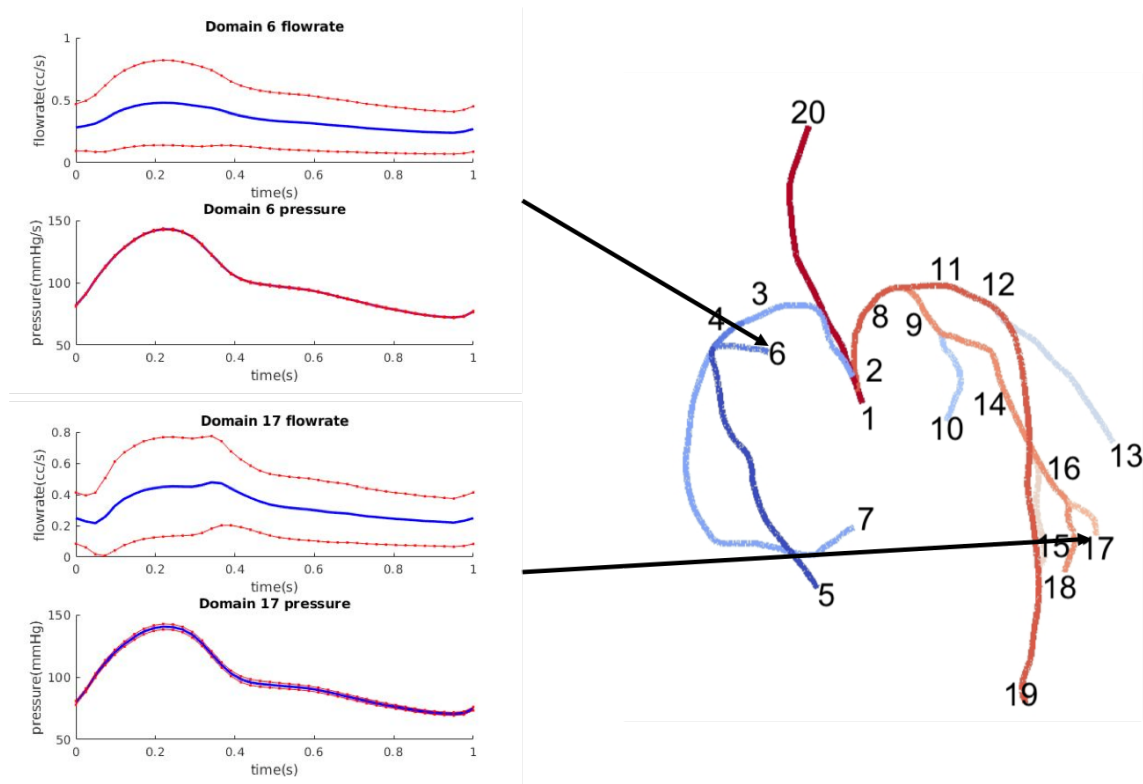


Figure 4.2. Pressure and flow-rate sensitivity in left and right coronary artery outlet.

So we analyze each variable's sensitivity to coronary flow-rate by ANOVA and Fig. 4.3 shows the first and second order Sobol indices. In right coronary artery, intra-myocardial pressure accounts most of the impact while the viscosity has a little impact on the flow-rate profile. However, in right coronary artery, coronary outlet resistance has the largest

impact instead of intra-myocardial pressure. And the combinations between resistance-capacitance and resistance-intra-pressure also contribute to the deviation.

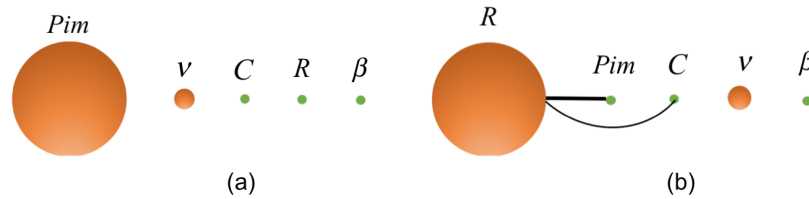


Figure 4.3. Sobol 1st and 2nd indices for (a)right coronary artery and (b)left coronary artery.

[Sobol 1st and 2nd indices for (a)right coronary artery and (b)left coronary artery. Area and connecting lines of and between each parameter indicate the impact of their own and their combination. Green area means first order Sobol index is 0. (c)]

4.2.2 sensitivity analysis to aorta outlet

Pressure and flow-rate of the coronary arteries may vary with the different physiological condition. Here we study the mean value and deviation under rest, hyperemia and exercise condition. Aside with the perturbation in kinematic viscosity and β_{scale} , the total coronary resistance and capacitance are also changed by varying that in aorta within a proper range [18] as shown in figure 4.1. Specifically, the rest and hyperemia condition share a common total aortic resistance however, the ratio of total coronary and aortic resistance is no longer 24 for hyperemia; it is 5.33. The decrement in total coronary resistance divides more flows to both coronary branches and causes more pressure deviation at the end of coronary outlet. As for the exercise condition, the capacitance is increased by 4.5 and period halves besides the drop in total coronary resistance. The rest of parameters are kept the same.

Figure 4.4-6 show the pressure and flow-rate within one standard deviation when at rest, hyperemia and exercise respectively. We could observe a similar pressure and flow-rate profile in chapter 3 under rest and hyperemia. There is an obvious increment in mean pressure and flow-rate when in exercise, corresponding to a higher pressure and a faster heart rate. As shown in all of these figures, the flow-rates tends to have a narrower

deviation band while on the contrary, the deviation in pressure figures are more uniform.

The variable of interest in this scenario is pressure, so ANOVA analysis is conducted to coronary outlet pressure. What interesting is that we observe a very similar Sobol indices in all these three physiological conditions in all of the coronary arteries. In Fig. 4.6, standard deviation in pressure comes from aortic Resistance, capacitance and viscosity and the resistance-capacitance combination. The value of Sobol indices can be found in Appendix A.

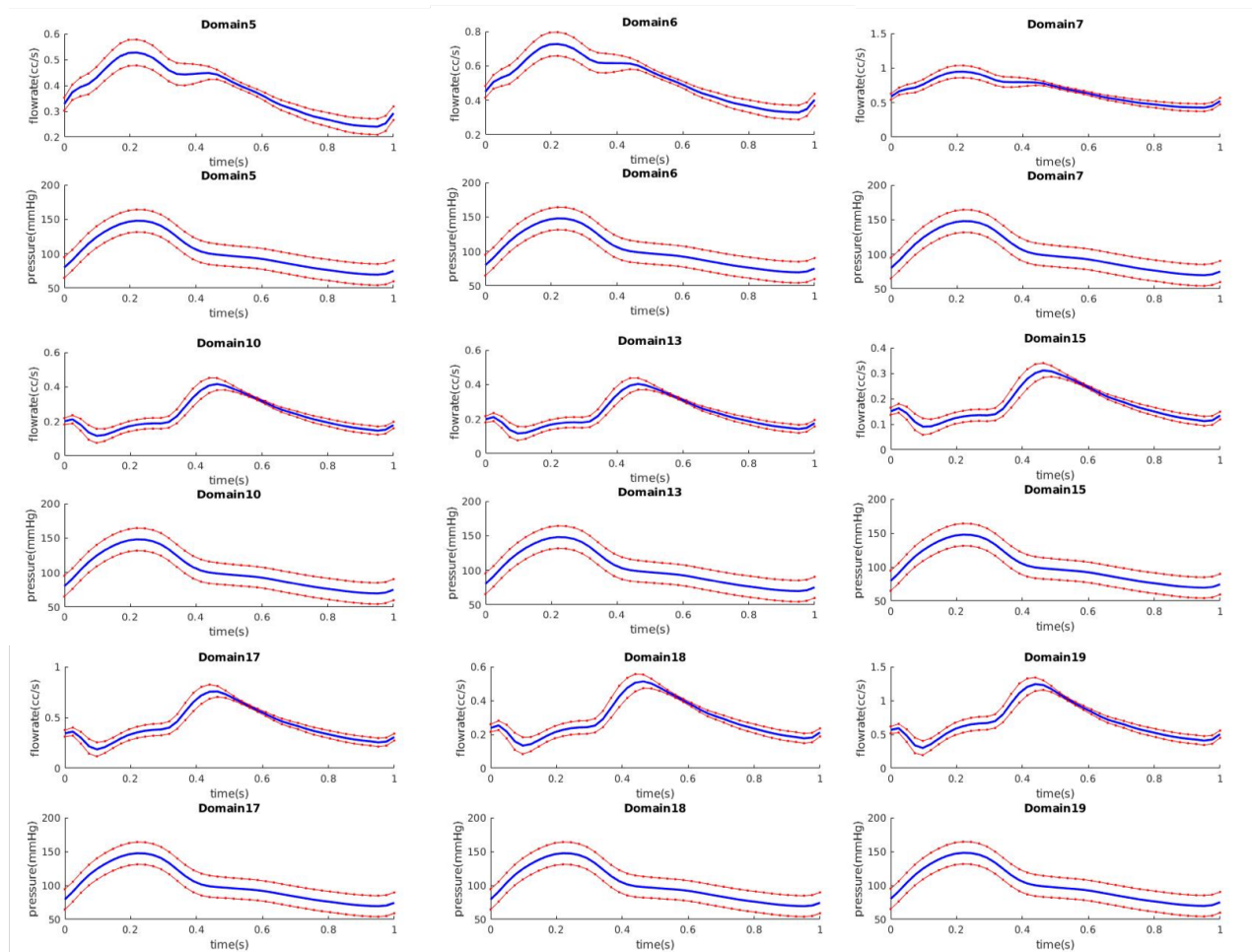


Figure 4.4. Mean pressure and flow-rate at coronary outlets at rest

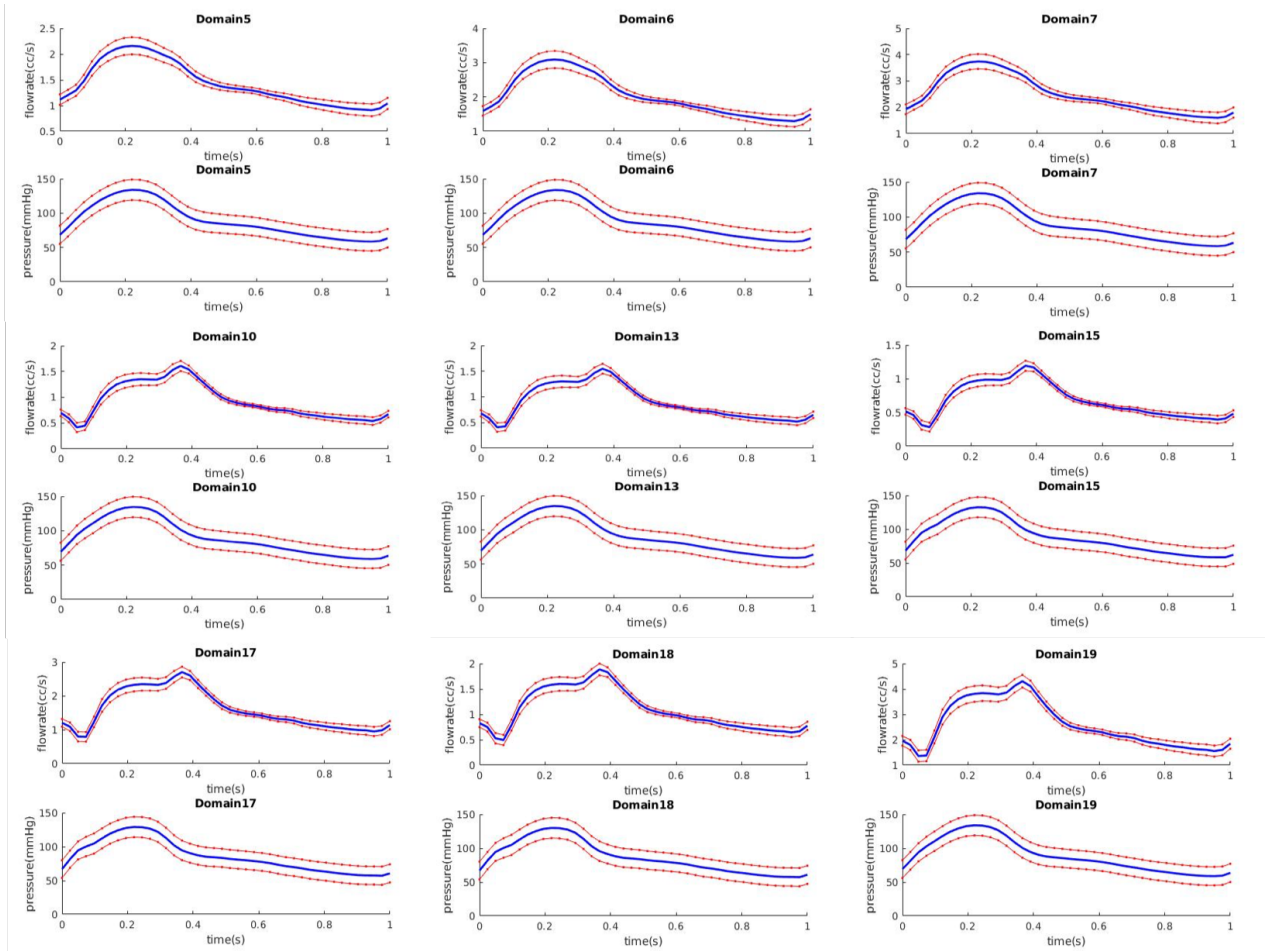


Figure 4.5. Mean pressure and flow-rate at coronary outlets under hyperemia

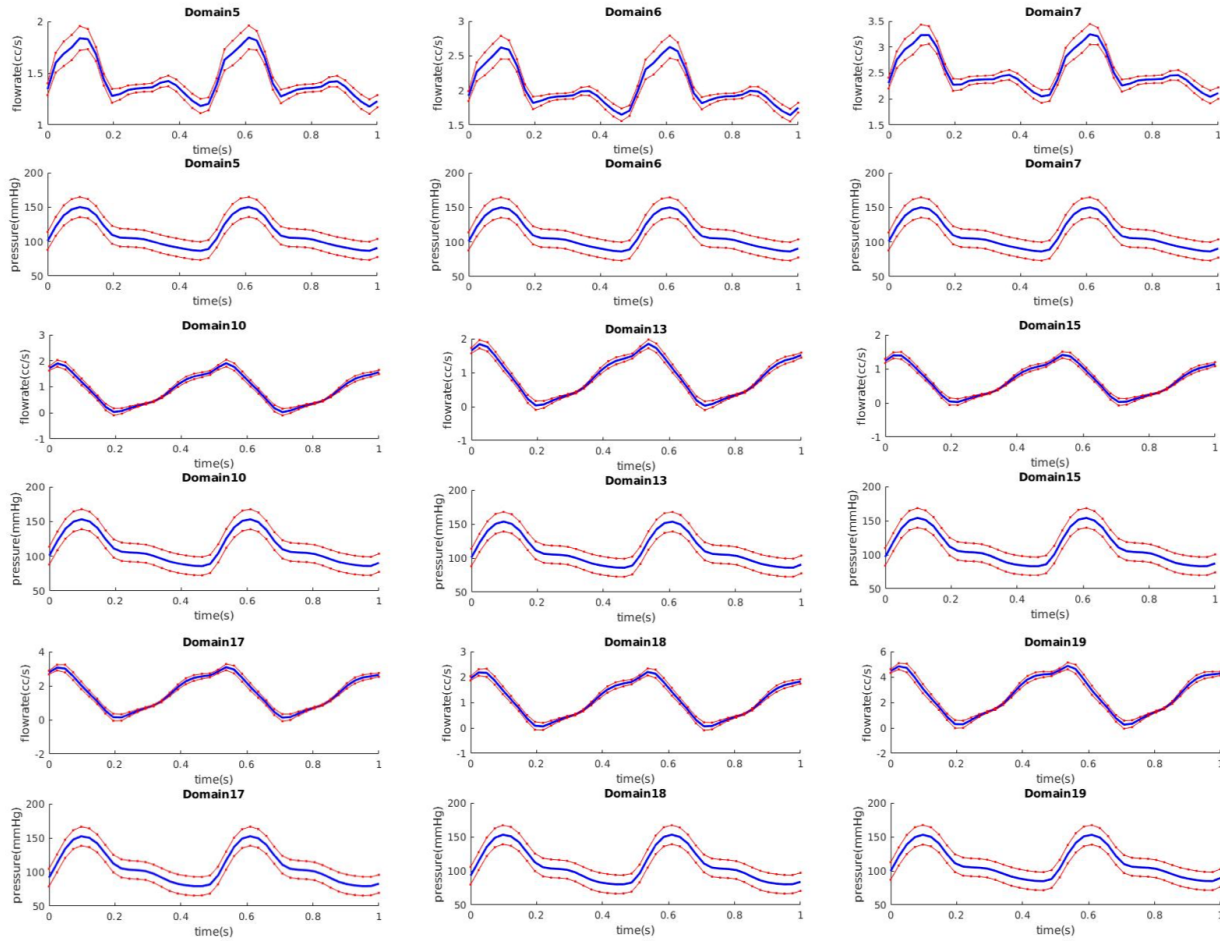


Figure 4.6. Mean pressure and flow-rate at coronary outlets when exercise

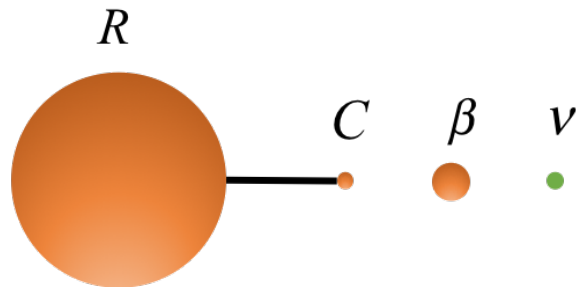


Figure 4.7. Sobol 1st and 2nd indices for pressure in vessel 6.

4.3 Discussion

Looking at the figure 4.4 - 4.6 can we conclude a very similar result: flow-rate are tends to be more robust than pressure in coronary artery under different physiological conditions.

When at rest, flow-rate on both right side (Domain 5,6,7) and left side (rest of the outlets) have an increment ranging from 0.15 to 0.05 cc/s; arteries on the right side tend to have a more obvious increment due to its simpler structure and less branches. There exists more uncertainty at diastolic phase where the pressure is rapidly increased by a stroke of the left ventricle. The standard deviation varies from 0.1 cc/s to around 0.15 cc/s. Then the error band contract with close of the left ventricular valve when the flow-rate start to decrease. Uncertainty when at hyperemia is very similar to that at rest, the difference is the increment is more evident due to the adjustment in total coronary artery resistance. The flow-rate on either side in exercise has a distinguishable difference; right coronary artery flows follow the similar profile development while the left coronary branches have a more evident lagging effect due to the resistance redistribution at the boundary. Meanwhile, the maximum uncertainty on the left coronary arteries is only around 6%, fairly small compared with the perturbation ranges of parameters.

However, the pressure deviation under these three physiological condition is quite uniform and relatively large as shown in figure below(insert fig); the stripe shape error has a 18% standard deviation in average for all of the conditions. Compared with small pressure deviation in single coronary can we conclude that the flow-rate to each coronary artery is more easily to be influenced by aorta flow-rate and the flow ratio to the coronary branches. This shows that some specific systemic parameters such as aorta resistance, inlet flow-rate or the amount of flow to the aorta has been to be carefully chosen because of their impact to the final results. This could provide some useful instruction when it is used in clinical. More quantitative data are provided in Fig.

Noted that these results are just from statistical average, it does not mean that it conforms the results from 1D solver or the all possible result are within the deviation range. Certainly there is an evident mismatch between statistical mean value and calculated result due to the non-uniform parameter distribution, nonlinear effect and complex coupling between boundary condition and the solver. However, it has proven the robustness of the 1D solver we use in predicting downstream pressure.

Domain	Rest		Hyperemia	
	Max STD (%)	Min STD (%)	Max STD (%)	Min STD (%)
Vessel 5	22.14	11.04	23.21	11.10
Vessel 6	22.13	11.04	23.21	11.13
Vessel 7	22.14	11.04	23.21	11.11
Vessel 10	22.10	11.04	23.09	11.06
Vessel 13	22.10	11.04	23.10	11.05
Vessel 15	22.11	11.09	23.30	11.25
Vessel 17	22.12	11.12	23.59	11.63
Vessel 18	22.12	11.12	23.58	11.54
Vessel 19	22.10	11.05	23.10	11.12

Figure 4.8. Maximum and minimum of relative error of standard deviation and mean value of pressure

Domain	Rest		Hyperemia	
	Max STD (%)	Min STD (%)	Max STD (%)	Min STD (%)
Vessel 5	12.88	3.33	13.08	4.29
Vessel 6	12.63	3.37	12.65	3.63
Vessel 7	12.66	3.52	13.15	4.61
Vessel 10	35.25	2.27	21.33	4.01
Vessel 13	34.67	2.29	21.30	4.10
Vessel 15	35.73	2.27	22.81	4.58
Vessel 17	36.56	2.19	17.89	4.47
Vessel 18	36.89	2.15	20.26	4.59
Vessel 19	34.89	2.02	16.25	4.48

Figure 4.9. Maximum and minimum of relative error of standard deviation and mean value of flow-rate

CHAPTER 5

CONCLUSIONS

Introducing CFD into medical imaging enables non-invasive measurement of patient-specific ischemia by FFR_{CFD} . But the computing-intensive feature of current 3D method greatly limits its application to vastly use in market, since performing one time simulation requires hundreds of cores on a parallel server, or even supercomputer. The NEKTAR 1D is a more promising way carry out such computation; the promising potential of 1D solver is not only in the reduction in computational resources and cost, but bring a more economical medical expenditure to CAD patients from cutting off upstream unnecessary cost on purchasing computing sources. In this work, one-dimensional solver for computing coronary flow pressure over stenosis is further completed, and its corresponding auxiliary frameworks, including reconstructing patient-specific 3D geometry, extracting centerlines of corresponding vessels, visualizing computational field are also under developing. This research also studies the accuracy and robustness of 1D solver in computing patient-specific FFR. Although further researches of 1D solver needs to be conducted such as accuracy, sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV), this research proves the possibility to apply 1D in clinical and the value to carry out further test.

However, due to the series of assumption made to derive the 1D equation and non-linearity nature of the governing equation, numerous artifacts may affect the accuracy of such method. Besides parameters such as viscosity, elastance, inflow rate and inferred boundary condition parameters, the reconstructed anatomic geometry could also have a huge impact, so calcification, motion can also deteriorate the accuracy of the method. And for the patient who has different types of vascular disease, FFR_{CFD} values could also undershoot or overshoot those of measuring value.

What numerical results could show is much more than just velocity and pressure; significant quantities such as wall shear stress, coronary flow reserve and oxygen concentration could be acquired by undertaking CFD simulation. Combining with clinical data, more numerical methods such as multi-fidelity computing, model reduction could also be introduced to calculate FFR_{CFD} result with higher fidelity. It can be foreseen that CFD would play a more important role in modern medical science and clinical diagnosis.

APPENDIX A

SOBOL INDICES TABLE

	VESSEL 6 (LEFT)		VESSEL 17 (RIGHT)	
1 st order <u>Sobol</u> indices	β	0.000	β	-0.000
	v	0.001	v	0.017
	R	0.000	R	0.873
	C	0.000	C	-0.001
	Pim	1.014	Pim	0.002
2 nd order <u>Sobol</u> indices	$v + R$	0.002	$R + C$	0.055
	$v + C$	0.002	$R + Pim$	0.050
	$v + Pim$	0.005		

Figure A.1. 1st and 2nd order Sobol indices for right and left coronary artery flowrate. This figure corresponds to the Sobol indices in section 4.2.1. The rest of 2nd order Sobol indices are considered as 0.

1 st order <u>Sobol</u> indices	β	0.050
	v	0.000
	R	0.887
	C	0.010
2 nd order <u>Sobol</u> indices	$R + C$	0.029

Figure A.2. 1st and 2nd order Sobol indices for coronary artery pressure. This figure corresponds to the Sobol indices in section 4.2.2. First and second indices at all of the outlet under all of conditions exhibit a very similar result, with a max deviation within 0.01. For simplicity, we just show the indices from vessel 6 at rest. The rest of 2nd order Sobol indices did not listed are considered as 0.

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