Turbulence Descriptors in Arterial Flows

Patient-Specific
Computational
Hemodynamics

Magnus Andersson

Linköping Studies in Science and Technology
Dissertation No. 2129

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Patient-Specific Computational Hemodynamics

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Linköping, 2021

Cover: (*Front*) Turbulent flow field in an malformed aorta, colored by its magnitude (volume rendering) and anisotropic characteristics (cross-sections). (*Back*) Self-similar structures (fractals) are often visible in nature, where repeating hierarchy patterns over different scales are analog in rivers and arterial networks.

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To my partner Linn
and to our children
Joline and Jordan

"Yesterday is history. Tomorrow is a mystery, but today is a gift! That is why it is called the present."

Master Oogway

Preface

"Sorry to interrupt you folks, but we're just had a report of some turbulence ahead, so please stay in your seats a little while"

The Far Side by Gary Larson

Indeed, the turbulence research towards this dissertation (carried out at the Division of Applied Thermodynamics and Fluid Mechanics and the Department of Management and Engineering, Sweden) has been a bumpy ride, and the flight time a little bit longer than expected. First, I would like to express gratitude to my main advisor Matts Karlsson, for all inspiring conversations and navigation guidance along this sometimes damp and misty voyage. I also wish to thank the co-advisors Jonas Lantz and Tino Ebbens for providing valuable insights and necessary resources when needed. Special acknowledgment goes to my colleagues at the division for engaging in constructive discussions related to both research and department duties. Not least of all, I am sincerely grateful for the endless support from my family, providing enough fuel to keep me airborne.

Thank you!

Linköping, March 2021

Magnus Andersson

Abstract

At this very moment, there are literally millions of people who suffer from various types of cardiovascular diseases (CVDs), many of whom will experience reduced quality of life or premature life expectancy. The detailed underlying pathogenic processes behind many of these disorders are not well understood, but were abnormal dynamics of the blood flow (hemodynamics) are believed to play an important role, especially atypical flow-mediated frictional forces on the intraluminal wall (i.e. the wall shear stress, WSS). Under normal physiological conditions, the flow is relatively stable and regular (smooth and laminar), which helps to maintain critical vascular functions. When these flows encounter various unfavorable anatomical obstructions, the flow can become highly unstable and irregular (turbulent), giving rise to abnormal fluctuating hemodynamic forces, which increase the bloodstream pressure losses, can damage the cells within the blood, as well as impair essential structural and functional regulatory mechanisms. Over a prolonged time, these disturbed flow conditions may promote severe pathological responses and are therefore essential to foresee as early as possible.

Clinical measurements of blood flow characteristics are often performed non-invasively by modalities such as ultrasound and magnetic resonance imaging (MRI). High-fidelity MRI techniques may be used to attain a general view of the overall large-scale flow features in the heart and larger vessels but cannot be used for estimating small-scale flow variations nor capture the WSS characteristics. Since the era of modern computers, fluid motion can now also be predicted by computational fluid dynamics (CFD) simulations, which can provide discrete mathematical approximations of the flow field with much higher details (resolution) and accuracy compared to other modalities. CFD simulations rely on the same fundamental principles as weather forecasts, the physical laws of fluid motion, and thus can not only be used to assess the current flow state but also to predict (foresee) important outcome scenarios in e.g. intervention planning. To enable blood flow simulations within certain cardiovascular segments, these CFD models are usually reconstructed from MRI-based anatomical and flow image-data. Today, patient-specific computational hemodynamics are essentially only performed within the research field, where much emphasis is dedicated towards understanding normal/abnormal blood flow physiology, developing better individual-based diagnostics/treatments, and evaluating the results reliability/generality in order to approach clinical applicability.

In this thesis, advanced CFD methods were adopted to simulate realistic patient-specific turbulent hemodynamics in constricted arteries reconstructed from MRI data. The main focus was to investigate novel, comprehensive ways to characterize these abnormal flow conditions, in the pursuit of better clinical decision-making tools; from more in-depth analyses of various turbulence-related tensor characteristics to descriptors that evaluate the hemodynamics more globally in the domain. Results from the studies in this thesis suggest that these turbulence descriptors can be useful to: *i*) target cardiovascular sites prone to specific turbulence charac-

teristics, both in the bulk flow and on the intraluminal wall, *ii*) provide a more extensive view of the general flow severity within malformed vascular regions, and *iii*) evaluated and potentially improve cardiovascular modeling strategies and MRI-measured turbulence data.

The benefit of these descriptors is that they all, in principle, can be measured by different MRI procedures, making them more accessible from a clinical perspective. Although the significance of these suggested flow-mediated phenotypes has not yet been evaluated clinically, this work opens many doors of opportunities for making more thorough and longitudinal patient-specific studies, including large cohorts of patients with various CVDs susceptible to turbulent-like conditions, as well as performing more in-depth CFD-MRI validation analyzes.

Populärvetenskaplig sammanfattning

Just nu finns det bokstavligen miljontals människor som lider av olika typer av hjärt- och kärlsjukdomar, av vilka många kommer att uppleva nedsatt livskvalitet samt förkortad livslängd. De underliggande patogena orsakerna bakom dessa åkommor är fortfarande inte väl förstådda, men där onormal blodflödesdynamik (hemodynamik) tros spela en viktig roll, särskilt oregelbundna friktionskrafter på kärlväggens insida (väggskjuvspänningen). Under normala fysiologiska förhållanden är blodflödet relativt stabilt och regelbundet (laminärt), vilket hjälper till att bibehålla kritiska kärlfunktioner. När dessa flöden stöter på olika ogynnsamma anatomiska hinder kan flödet bli mycket instabilt och oregelbundet (turbulent) och ge upphov till onormala fluktuerande flödeskrafter vilket resulterar i förhöjda tryckförluster i blodomloppet, försämring av väsentliga strukturella och funktionella regleringsmekanismer i kärlen, samt stundvis skador på diverse blodkroppar och ge upphov till blodproppar. Över en längre tidsperiod kan dessa abnormala flödesförhållanden främja allvarliga patologiska förändringar och är därför viktiga att kartlägga så tidigt som möjligt.

Kliniska mätningar av blodflödesdynamik utförs ofta icke-invasivt av modaliteter som ultraljud och magnetisk resonanstomografi (MRI). Avancerade MRI-tekniker kan användas för att återskapa en allmän bild av de storskaliga flödesstrukturerna i hjärtat och de större kärlen men är inte lämpad för att uppskatta småskaliga flödesvariationer samt väggskjuvspänningens karaktär i detalj. Sedan introduktionen av moderna datorer så kan numera flödesmönster även estimeras av strömnings simuleringar (beräkningsströmningsdynamik), en metod som på engelska kallas "computational fluid dynamics" eller CFD, vilket ger en diskret matematisk approximation av flödesfältet med mycket högre spatiell och temporal detaljnivå (upplösning) och noggrannhet jämfört med andra modaliteter. CFD simuleringar vilar på samma grundläggande principer som väderprognoser, de fysiska lagarna som beskriver hur ett strömningsfält beter sig, och kan således inte bara användas för att bedöma det aktuella flödestillståndet utan också för att försöka förutsäga utfallsscenarier vid exempelvis olika kirurgiska interventioner. För att möjliggöra blodflödes simuleringar inom vissa kardiovaskulära segment så rekonstrueras vanligtvis CFD-modeller från MRI-baserade anatomisk- och flödsbilddata. Idag är patientspecifika blodflödesberäkningar i huvudsak en forskningsdisciplin, där mycket vikt läggs vid att förstå normal/onormal blodflödesfysiologi, utveckla bättre individbaserad diagnostik/behandlingar och utvärdera resultatets tillförlitlighet/generalitet för att närma sig klinisk tillämpbarhet.

I denna avhandling användes avancerade CFD simuleringar för att beräkna realistiska turbulenta flödesförhållanden i patientspecifika förträngda blodkärlsmodeller återskapade från MRI mätningar. Huvudfokus var att undersöka nya, omfattande sätt att karakterisera dessa onormala blodflöden i strävan efter bättre kliniska beslutsverktyg, från mer fördjupade analyser av olika turbulensrelaterade tensoregenskaper till deskriptorer som utvärderar blodflödesdynamiken mer globalt i domänen. Resultat från studierna i denna avhandling antyder att dessa turbulensrelat-

erade deskriptorer kan vara användbara för att: *i*) karlägga kardiovaskulära regioner exponerad av olika turbulent karakteristik, både i friströmen samt på kärlväggen, *ii*) ge en mer omfattande bild av flödes abnormalitet inom missbildade kärlregioner, och *iii*) utvärdera och potentiellt förbättra kardiovaskulära modelleringsstrategier samt MRI mätningar av turbulens.

Fördelen med dessa flödesdeskriptorer är att de alla, principiellt, kan mätas med olika MRI-tekniker, vilket gör dem mer tillgängliga ur ett kliniskt perspektiv. Även om värdet av dessa föreslagna analysmetoder ännu inte har utvärderats kliniskt, öppnar detta arbete många dörrar för möjligheter att göra mer grundliga och longitudinella patientspecifika studier, inklusive stora kohorter av patienter med olika kardiovaskulär sjukdomar som förorsakar liknande turbulenta flödesförhållanden, samt utför mer fördjupade CFD-MRI valideringsanalyser.

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List of papers

This thesis is based on the following five papers, which will be referred to by their Roman numerals:

- I. **Quantitative assessment of turbulence and flow eccentricity in an aortic coarctation: impact of virtual interventions**, Magnus Andersson, Jonas Lantz, Tino Ebbers, Matts Karlsson, *Cardiovascular Engineering and Technology*, 2015, vol. 6, no. 3, pp. 281–293, doi: 10.1007/s13239-015-0218-x.[†]
- II. **Multidirectional WSS disturbances in stenotic turbulent flows: A pre- and post-intervention study in an aortic coarctation**, Magnus Andersson, Jonas Lantz, Tino Ebbers, Matts Karlsson, *Journal of Biomechanics*, 2017, vol. 51, pp. 8–16, doi: 10.1016/j.jbiomech.2016.11.064.
- III. **Characterization and estimation of turbulence-related wall shear stress in patient-specific pulsatile blood flow**, Magnus Andersson, Tino Ebbers, Matts Karlsson, *Journal of Biomechanics*, 2019, vol. 85, pp. 108–117, doi: 10.1016/j.jbiomech.2019.01.016.
- IV. **Characterization of anisotropic turbulence behavior in pulsatile blood flow**, Magnus Andersson, Matts Karlsson, *Biomechanics and Modeling in Mechanobiology*, 2020, 16 p., doi: 10.1007/s10237-020-01396-3.
- V. **Model verification and error sensitivity of turbulence-related tensor characteristics in pulsatile blood flow simulations**, Magnus Andersson, Matts Karlsson, *Fluids*, 2020, vol. 6, no. 1, 15 p., doi: 0.3390/fluids6010011.[‡]

Note: The appended papers have been reformatted to fit the layout of the dissertation.

[†]Note, the appended paper is the erratum version of the original article, doi: 10.1007/s13239-015-0243-9.

[‡]Published in Fluids as part of the Special Issue "Turbulence in Blood Flow".

"When I meet God, I am going to ask him two questions: Why relativity? And why turbulence? I really believe he will have an answer for the first"

Werner K. Heisenberg

Abbreviations

2D PC-MRI	Two-Dimensional cine Phase-Contrast Magnetic Resonance Imaging
4D Flow MRI	Three-Dimensional cine Phase-Contrast Magnetic Resonance Imaging
AAo	Ascending Aorta
AIM	Anisotropy Invariant Map
AVF	Arteriovenous Fistula
BCA	Brachiocephalic Artery
BCs	Boundary Conditions
CFD	Computational Fluid Dynamics
CFL	Courant-Friedrichs-Levy
CoA	Coarctation of the Aorta
CO	Cardiac Output
CT	Computed Tomography
CV	Control Volume
CVDs	Cardiovascular Diseases
DAo	Descending Aorta
DNS	Direct Numerical Simulations
DTI	Diffusion Tensor Imaging
ECs	Endothelial Cells
EFD	Early Flow Deceleration
FD	Finite Difference Method
FEM	Finite Element Method
FSI	Fluid-Structure Interaction
FVM	Finite Volume Method
ICOSA6	Six-Directional Icosahedron
IH	Intimal Hyperplasia
IVSD	Intra-Voxel Standard Deviation
KE	Kinetic Energy
LBM	Lattice Boltzmann Methods
LCCA	Left Common Carotid Artery
LDL	Low-Density Lipoproteins
LFD	Late Flow Deceleration
LES	Large Eddy Simulations
LSA	Left Subclavian Artery
MC	Million Cells
MRI	Magnetic Resonance Imaging
OSI	Oscillatory Shear Index

POD	Proper Orthogonal Decomposition
RANS	Reynolds-Averaged Navier Stokes
RBCs	Red Blood Cells
RMS	Root-Mean-Square
RMSD	Root-Mean-Square Deviation
ROI	Region-Of-Interest
RT	Residence-Time
SAS	Scale-Adaptive Simulations
SEM	Spectral Element Method
SGS	Sub-Grid-Scale
SM	Supplementary Materials
SMCs	Smooth Muscle Cells
SST	Shear-Stress-Transport
STL	Stereolithography
TAWSS	Time-Averaged Wall Shear Stress
transWSS	Transverse Wall Shear Stress
tWSS	Turbulence-Related Wall Shear Stress
URANS	Unsteady Reynolds-Averaged Navier Stokes
UQ	Uncertainty Quantification
VVUQ	Verification Validation and Uncertainty Quantification
WALE	Wall-Adapting Local Eddy-Viscosity
WSS	Wall Shear Stress

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Part I

Introductory chapters

"Either we're going to create simulations that are indistinguishable from reality or civilization will cease to exist, those are the two options."

Elon Musk

Introduction

1.1 Background

Over a human life span, the heart pumps roughly 5 liters of blood into the cardiovascular circulatory system every minute to maintain the physiological functionalities (homeostasis) of organs, tissue, and cells. Despite these great capabilities, optimized by evolution, this system is susceptible to a wide range of different heart and vascular disorders. In fact, cardiovascular diseases (CVDs) are to-date the most common cause of death both in Sweden and worldwide [197] (Fig. 1a), with $\sim 85\%$ mortalities due to heart attacks or strokes alone, where a majority can be associated to low- to middle-income countries and the elderly population (Fig. 1b). According to the World Health Organization [154], a large portion of the premature deaths, e.g. the 3 million younger than 60 years old, could have been prevented by various measures such as improved diagnostics and intervention procedures. In 2019, Sweden hospitalized around 55 thousand women and 74 thousand men with CVD diagnosis, which is a steadily decline in inpatient care compared to ten years ago [176]. Unlike globally, the number of deaths from CVDs in Sweden has gradually decreased over the past decades (Fig. 1b), which is also true for Western Europe [197]. According to the latest statistics in Sweden, the annual CVDs death rates have continued to decline by $\sim 10\%$ [175], and now account for $\sim 33\%$ of all deaths for both men and women. The main reasons for this enhanced life expectancy can be associated with improved life style (e.g. better food intake, physical activity, reduced tobacco use, and lowered blood pressure), access to better prevention measures (better drug therapy against e.g. high blood pressure and blood fats, and risk assessments) and enhanced clinical treatments [177]. There exist many different types of CVDs associated with the heart and blood vessels caused by various underlying pathogenic processes, many of which today still are not well understood. Collectively, these disorders can be categorized into:

- *Ischemic/coronary heart disease*. Disorder of the vessels supplying the heart muscle, which if blocked can cause an acute heart attack.
- *Cerebrovascular disease*. Disorder of the blood vessels supplying the brain, which if blocked can cause an acute stroke.
- *Rheumatic heart disease*. Inflammatory diseases (by streptococcal infection) causing permanent damage to the heart valves.
- *Congenital disease*. Structural heart and vessel abnormalities apparent at birth.
- *Deep vein thrombosis*. Blood clots in a vein that can cause pain or swelling, or in the worst case dislodge and form a lung clot (pulmonary embolism) or even stroke.

Figure 1: (a) The global percentage of death by cause in 2017 (of the 56 million), including Sweden for the two leading death rates (cardiovascular diseases, CVDs, and various cancers). The map illustrates the death rates from CVDs across the world, indicating a strong East-to-West divide associated with low-to-high income/developed countries. (b) The annual number of deaths by CVDs (including 70 years or older) and cancers worldwide and in Sweden between 1990 to 2017. The data and images were adapted from [Our World in Data](#) [197].

There are also other heart-related diseases, such as cardiomyopathies (heart muscle disorder) and cardiac arrhythmias (electrical impulse disorder). Pathogenesis related to heart attacks, strokes, or large arteries is usually a slow-developing process occurring over several decades, e.g. by gradual plaque buildup within the vessel wall (atherosclerosis). Less common CVDs are associated with different congenital disorders, e.g. malformations of the heart structure/valves and arterial regions. In general, disturbed dynamics of blood flow (hemodynamics) are here believed to play an important role in the susceptibility and progression of many of these CVDs, however, where the causality often is unclear. Under normal physiological conditions, the flow is generally relatively stable and regular (smooth and laminar), which is essential to maintain vascular integrity and functionality [46]. However, if the flow attains more disturbed characteristics (e.g. caused by unfavorable anatomical obstructions, lesions, or intervention implants), critical structural and functional regulatory mechanisms may be impaired, which under sustained conditions may promote pathological responses [41, 44, 124].

In the medical community, "*disturbed hemodynamics*" is often a loosely used term attributed to pathological abnormal flow conditions such as unsteady but laminar flow variations, transitional or turbulent type of flow regimes. Although, recent studies suggest that even apparent physiological flows may exhibit turbulence characteristics [88, 204]. Nevertheless, due to the cyclic nature of the main flow in larger arteries, these pathological flow regimes are typically altered between and within different cardiac phases, making the characterization of the local flow conditions hard but important to target possible disease-prone regions. Unlike laminar or transitional flows, turbulent hemodynamics promotes a highly unstable and chaotic flow environment, with random and irregular pressure and velocity fluctuations in space and time owing to the wide spectrum of (three-dimensional) rotating/interacting flow structures (eddies). Turbulence gives rise to substantial bloodstream pressure losses and elevated fluid stresses that may cause high blood pressure (hypertension) and direct blood cell damage [246]. Along the intraluminal surface, near-wall turbulence induces heterogeneous frictional force variations (i.e. wall shear stress, WSS) of moderate-to-high frequencies, which are believed to downregulate protective stimulus against atherosclerosis, thrombus formation, and vascular wall remodeling [46, 152]. However, the nature of these pathogenic flow mechanisms (flow-phenotypes) is still not well understood [19, 20, 40], where much focus have been directed towards finding new relevant flow descriptors to narrow this gap.

In clinical practice, the most common non-invasive measurement modalities to study cardiovascular flows are doppler ultrasound techniques and magnetic resonance imaging (MRI). Flow measurements using ultrasound is a cheap, accessible, versatile, and a fast technique but can generally only provide a rough estimate of the local velocity field, where quantitative measures usually are susceptible to considerable uncertainties. Today, MRI measurements are the state-of-the-art imaging modality for study patient-specific hemodynamics [58, 150], and provides a reasonably picture of the general flow characteristics in the heart chambers and larger vessels. However, due to the inherent limiting factors of MRI (e.g. spatial and temporal resolution), these methods are not reliable for studying small-scale flow variations nor flow-mediated wall effects.

Flow predictions can also be assessed by mathematical models, governed by the physical laws of fluid motion, through computer-based numerical simulations called computational fluid dynamics (CFD). Equivalent to numerical weather predictions (forecasts), CFD calculates the flow variables at discrete points on a three-dimensional grid of desirable resolution in space and time and is essentially only limited by computational resources and quality of the input data.

Numerical solutions have traditionally been used for solving engineering fluid flow problems but have since a couple of decades ago gained increased traction for predicting patient-specific blood flow patterns [231, 222, 232, 104]. One of the significant upsides with CFD, unlike measurements, is the possibility of predicting specific outcomes (“what-if-scenarios”) such as the flow changes after specific anatomical interventions (virtual surgical planning).

After years of advancement, clinical collaborations, and use of modern technologies (e.g. data-driven cardiovascular flow modeling, supercomputing science, uncertainty assessments), CFD now starts to be a serious tool for better understanding of blood flow physiology and development of better tools for personalized therapeutic decision-making [104, 228, 106, 11]. These patient-specific CFD models are usually decoded from MRI images containing anatomical and flow information, often referred to as image-based CFD. The models are accompanied by many assumptions/uncertainties related to the modeling inputs and simulation procedure, which needs to be taken into account when judging the reliability/generalizability of the output results and before making inroads into clinical use [224, 23, 104, 106]. These inaccuracies can be substantial and are typically estimated by specific verification, validation, and uncertainty quantification (VVUQ) procedures. Therefore, cardiovascular computational hemodynamics should not be viewed as a competitive instrument to MRI-based flow measurements but rather regarded as a complementary tool that could be used to strengthen all measurement modalities by cross-disciplinary studies. In the end, the clinical choice presumably lands on the most reliable and cost-effective method, which may well be a hybrid approach between several techniques.

1.2 Aims

This thesis focused on producing realistic patient-specific arterial turbulent flow conditions through advanced image-based CFD simulations in order to study new, more complete, and effective ways to characterize turbulence-related hemodynamics. These blood flow descriptors were considered in different malformed human aortas diagnosed with aortic coarctation (CoA), a substantial (congenital) narrowing of the aortic wall that give rise to some of the most elevated turbulent intensities in the vascular system. The implication of this work, however, is that these descriptors hopefully can promote a more universal use for characterizing turbulence-related hemodynamics, independent of cardiovascular site.

The specific aims of this thesis were to:

- demonstrate novel and comprehensive ways to characterize realistic patient-specific turbulent flow conditions, towards better understanding of these suggested flow-phenotypes at the vascular macrocirculation.
- propose novel hemodynamic descriptors that, in principle, can be estimated by non-invasive MRI measurement, as well as provide effective ways to facilitate case comparison, in the pursuit of better clinical decision-making tools.
- Shed some light on how some of the proposed turbulence-related descriptors can be used for verification and validation processes in patient-specific CFD modeling.

1.3 Outline

This thesis is divided into two parts, the introductory chapters (Part I) or "kappa", which provides a comprehensive summary of the appended papers (attached in Part II). In Part I, Ch. 1 will introduce the various topics and problem formulation associated with the thesis, followed by the general aims. In Ch. 2 a thorough description of cardiovascular blood flow will be given, starting with the main physiological state, blood rheology, and hemodynamics characterization. The chapter will end by addressing common flow-mediated pathological effects (CVDs and blood damage), with focus on turbulent hemodynamics, as well as a short review of medical modalities commonly used for blood flow measurements. In Ch. 3 the general concepts of CFD will be introduced and followed by explaining/motivating all the key step underlying the patient-specific CFD models related to the papers. The chapter continue by covering the basics of general turbulence modeling and reasoning behind the strategies adopted throughout this thesis. Last, the concepts of model VVUQ will be briefly discussed. In Ch. 4 all relevant theory and key results of the thesis will be summarized and discussed. In Ch. 5 the general conclusion will be remarked. In Ch. 6 an outlook on potential future progress of the current work will be presented. Finally, in Ch. 7 a brief summary of each appended paper will be given, including the different author contributions.

Cardiovascular blood flow

In 1628 William Harvey published the first complete description of the general functionality of the cardiovascular¹ system, which included, at the time controversial proposals that blood circulates in the arteries and veins, owing to the mechanical forces of the heart, and that these vessels are structurally connected at the peripheral tissue bed and in the lungs². [3] Centuries later, we now know much more about this sophisticated blood transporting system and its central role in regulating and maintaining the physiological functionalities, but also its pathological downsides associated with cardiovascular diseases.

This chapter will start with a basic introduction of the physiological state of the cardiovascular system, including blood properties and insight into the characteristics of the general blood flow dynamics. Next, the role between flow-mediated pathological effects will be addressed, including cardiovascular diseases and blood trauma. Lastly, some conventional medical hemodynamics measurement modalities will be reviewed.

2.1 Physiological state

The human cardiovascular network is essentially a heterogeneous hose system that carries the blood volume through a closed loop of arteries and veins every minute (Fig. 2). If stretched out, end-to-end, the total length of the vascular tree would reach about 100 000 km, which is more than twice the circumference of our planet. Some of the main functions of the cardiovascular system are to:

- absorb oxygen and nutrients from the lungs and guts, respectively, and transport them to the tissue, organs, and cells.
- absorb carbon dioxide and other waste products of the metabolism produced by cells (urea and lactic acid) and remove them via the lungs and kidneys.
- carry the body immune system by circulating white blood cells to detected pathogens.
- prevent and stop bleeding (hemostasis), by circulation and aggregation of blood platelets.

¹Cardiovascular stems from the word heart (from ancient Greek *kardía*) and blood vessel (from Modern Latin *vasculāris* or Latin *vasculum*).

²Prior to the 17th century, the belief was that the cardiovascular system was separated by two open-ended networks, arteries and veins, where the blood source came from the liver and somehow diffused throughout the body by centrifugal forces and an ebb and flow-like regulation mechanism. Here, the blood and air were simply depleted in accordance with the tissue and organ demands, while the rest being diffused back into the veins by invisible pores.

- regulate heat throughout the body (thermoregulation), by increasing or reducing the heat loss in hot and cold surroundings, respectively.

Figure 2: Schematic view of the human cardiovascular circulation system, showing oxygenated (arteries, red) and oxygen-depleted (veins, blue) blood sites.

The circulation network can be divided into two separate parts, the systemic and pulmonary circulations. The pulmonary system can be viewed as the heart-to-lung loop for reoxygenizing incoming venous blood, while the systemic side represents the loop supporting all body components with oxygen and the return of deoxygenated blood to the heart.

The driving mechanism for circulating the blood is a sustained pressure difference³ over separate cardiovascular regions, which is regulated by the pumping heart and passive/active response of the vascular system over the cardiac cycle (Fig. 3 and 4). During systole, the heart's left and right ventricle wall contracts in sync and push reoxygenated and deoxygenated blood into the ascending aorta and pulmonary trunk, respectively. In the following cardiac phase (diastole), each ventricle relaxes, and the outflows (and backflow) are stopped by shutting the aorta and pulmonary valve, respectively, whereafter the ventricles are filled up from the atria blood pools. Once a favorable ventricle pressure is reached, the atrioventricular valves close

³Sometimes inadequately refer to as the "pressure gradient", which is the point-specific rate of change of the pressure with respect to a spatial direction.

Figure 3: Schematic representation of normal blood flow rate and pressure variations in the ascending aorta during one cardiac cycle. During systole, the mitral valve (blue) closes the left atrium (LA), and the left ventricle (LV) contracts. Once the aortic valve cannot sustain the increase LV pressure, the aortic valve (green) opens, and the flow is ejected into the aorta until the pressure is recovered again and the valve closes. During diastole, the mitral valve opens, followed by LV filling. Throughout the cardiac cycle, continuous blood flow is upheld by the larger compliant arteries stretch-recoil process and resistance regulation of the smaller peripheral vessels. These mechanisms are also related to the notable phase shift between the flow and pressure peaks. Anatomy insets were adaptive from [142] with permission from Oxford University Press.

between the chambers, and the cardiac cycle repeats. This unique synchronicity between the left and right sides of the heart makes sure that there is a stable mass balance in the cardiovascular system, i.e. no blood accumulation is expected at specific sites under normal physiological conditions. The cardiac output (CO, i.e. the stroke volume per systolic contraction) during rest is normally around 5 L min^{-1} for adults, while during peak exercise can increase to over 35 L min^{-1} for trained athletes [185].

On the arterial side of the systemic circulation, the blood will be transported to the more distal parts of the vascular tree; through the smaller arteries, arterioles, and finally down to the micro-sized capillary bed (a tenth of the thickness of a human hair) to supply cells with oxygen and nutrients. At this junction, the blood will move over to the vein side (via the capillary-venules connection), while removing carbon dioxide and waste products, and towards the right side of the heart via larger and larger veins. Despite a massive difference in cross-sectional size (diameter), the fractal nature of the vascular structure (due to self-similar branching) leads to a vast increase in total cross-sectional area at the smallest vessel ranges due to the huge increase in numbers⁴ [210].

Flow and pressure are oscillatory at the largest arteries (aorta-to-muscular arteries) due to the pulsatile nature of the proximal heart and low resistance of these vessels, with normal sustained pressure variations in the ascending aorta around 80 to 120 mmHg between the diastole and systole phases⁵. These characteristics are, however, efficiently dampen at the smaller vessels (Fig. 4, arterioles) to ensure steady blood perfusion at the peripheral tissue level, which is related to the arterial wall functionality. The general load-carrying structure of all arterial walls is similar, with a layer-like composition of collagen and elastin fibers and smooth muscle cells (SMCs). The aorta and larger arteries, however, contain a higher degree of elastin, making them more flexible compared to other vessels, therefore often referred to as the "elastic arteries". The smaller muscular arteries and arterioles, on the other hand, have a relatively thicker wall and entails more SMCs that help to regulate local resistance and so also the local amount of blood supply by slowly contract (vasoconstriction) or relax (vasodilation) these muscles [210]. During systole, the elastic arteries will stretch and accumulate energy, owing to the precapillary resistance, thereby acting as a momentary reservoir of the ejected blood volume (Fig. 3). In fact, around 50% of the cardiac output will temporarily be stored by this vessel dilatation effect [142]. Once the cardiac ejection ceases, these arteries will recoil as the pressure falls during diastole, which will result in a smooth continuous discharge of blood flow through the remaining cycle. This vessel compliance⁶ also facilitates dampening of the pulse pressure⁷, providing a cushioning effect on the peak pressure waveform (Fig. 3) by inducing a phase-lag between forward-moving and backward (reflecting) pressure waves in the vascular system⁸ [246]. This phenomenon is called the "Windkessel effect" and help to protect the heart from high-pressure peaks, and usually worsen due to for example age-related arterial stiffening.

⁴Number of arteries are ~ 160 , while arterioles $\sim 10^7$ and capillaries $\sim 10^{10}$.

⁵1 mmHg = 133.32 Pa (or 75 mmHg $\approx$ 10 kPa).

⁶The increase in volume with respect increase in transmural pressure.

⁷The pulse pressure is defined by the difference between max (systolic) and min (diastolic) blood pressure (SBP and DBP, respectively). Hypertension is, for example, characterized by elevated SBP, combined with normal or low DBP.

⁸In a rigid pipe the pressure pulse wave velocity is exceptionally high, resulting in minor phase shift between forward and reflecting waves, causing high pressures by the superimposed peaks.

Figure 4: Schematic representation of the systemic circulation with respect to the vessel diameter, average blood flow velocity (speed), total vascular cross-sectional area, blood pressure, and peak Reynolds number (Re), which in the ascending aorta typically can be in the range of 4000 to 9000 (see Sec. 2.3.1). The Re data was derived from [138]. The remaining graphs were reconstructed from [26] licensed under CC BY-SA 4.0.

2.2 Blood

The human blood is nonhomogeneous and composed of deformable cellular elements (and proteins and ions) suspended in a viscous fluid medium called plasma, which corresponds to $\sim 7\%$ of the bodyweight [15]. Under normal conditions, the plasma takes up around 55% of the blood volume. These cells are the red blood cells (RBCs, or erythrocytes), white cells (leukocytes), and platelets (thrombocytes). The RBCs occupies near half of the blood volume (~ 40 to 45% , i.e. the hematocrit level), while the remaining elements only a tiny fraction⁹. The plasma fluid is essentially a mix of water (~ 90 to 95%) and a variety of other elements (proteins, electrolytes, hormones, enzymes, nitrogen). RBCs are semisolids and elastic, with biconcave disc-like shapes (~ 1 to $2.5 \mu\text{m}$ thickness variability and $8 \mu\text{m}$ in diameter), and are produced in the bone marrow with a life expectancy around 120 days¹⁰. They carry the important hemoglobin protein that governs oxygen uptake.

Figure 5: Illustrative behavior of human blood rheology. At reduced cardiac flow rate (Diastole, low shear rate), red blood cells (RBCs) will tend to aggregate, resulting in a non-linear increase of the apparent viscosity. At an increased cardiac flow rate (Systole, high shear rate), RBCs will tend to deform and align with the flow, resulting in viscosity reduction that appears more shear-insensitive (Newtonian).

The viscosity of a fluid is associated with its thickness, or its ability to resist deformation in a moving fluid, owing to the frictional interaction of the molecules within the fluid (its easy to move through the air, while harder through water, and a struggle through honey). Blood plasma can be considered as a Newtonian fluid¹¹, i.e. constant viscosity with $\sim 30\%$ thicker properties compared to water (Fig. 5). Blood as a whole, however, is a multiphase medium, with near half the ratio occupied by RBCs, and can therefore not merely be considered as a homogeneous fluid with constant viscosity. In fact, the viscosity of whole blood (also referred to as “effective” or

⁹Roughly 6 million RBCs, 10 thousand white cells, and 300 thousand platelets can be found in one 1 mm^3 of blood in small vessels [214].

¹⁰Corresponding roughly to 170 thousand cardiovascular loops (one loop per minute).

¹¹A Newtonian fluid like water will strain (deform) linearly over time (shear strain rate, or velocity gradient) in relation to applied shear stresses, where the viscosity determines the degree of this response, i.e. the scalar constant of proportionality between the fluid viscous shear stresses and shear strain rate.

“apparent” viscosity) behaves more like a non-Newtonian viscoelastic fluid, which is primarily attributed to the deformability, aggregation, and elastic energy uptake/release of the suspended RBCs. The rheology properties of blood have shown to mostly depend on the cell concentration (hematocrit), flow shear rate ($\dot{\gamma}$, units in s^{-1}), and vessel diameter [15]. Of these, the hematocrit has likely the most profound effect on blood viscosity, where a 1% hematocrit increase has shown to increase the viscosity by 4% at intermediate-to-high shear rates [21]. Excess of RBCs (~ 60 to 70%), such as during leukemia or boosting by blood doping, induce higher systemic blood pressure owing to the increased viscous vascular resistance, while an RBCs deficiency (anemia), such as blood loss insult, reduce the flow resistance, and lead to elevated cardiac output in order to maintain organ supply [214].

Blood has shear-thinning behavior (Fig. 5), meaning that blood gets thinner (lowered viscosity) in fast-moving flows, and vice versa, which is a result of how the RBCs are dispositioned in the bloodstream. During low shear rates ($\sim \dot{\gamma} < 10 \text{ s}^{-1}$), the RBCs are undeformed (relaxed) and will tend to cling together (aggregate) in favorable energy states, and form so-called “rouleaux” patches (stacks of RBCs) that are dispersed across the vessel domain. This viscoelastic behavior will induce substantial flow resistance and, thus, higher viscosity. At intermediate shear rates ($\sim 10 < \dot{\gamma} < 100 \text{ s}^{-1}$), the RBCs will start to disaggregate and deform, allowing for shorter rouleaux lengths and intercellular plasma flow, which results in less flow-induced drag. During higher shear rates ($\sim 100 \text{ s}^{-1} < \dot{\gamma}$), the RBCs will deform even more along the main flow directionality and form separate cell-to-plasma layers that tend to accumulate more towards the center part of the vessel [214]. This viscoelastic response will favor less flow resistance and hence lower the apparent viscosity. For further flow increase, the blood viscosity will reach a plateau (asymptote) and behave more like a Newtonian fluid. Compared to water, the relative blood viscosity¹² at higher shear rate is ~ 3 to 5 (i.e. around 3 to 5 times higher than water), while being ~ 20 to 100 (i.e. extremely viscous) for very stagnant flow conditions ($\sim 0.1 < \dot{\gamma} < 1 \text{ s}^{-1}$). [21] Blood is also a thixotropic fluid, meaning that the aggregation/disaggregation of RBCs is time-dependent when exposed to a sudden decrease/increase in local shear rates [105, 52]. This phenomenon seems to be most profound for the rouleaux formation process, while the disaggregation is much faster [198]. Due to the pulsating nature of the flow in larger arteries, the blood viscosity is often assumed to be thinner during systole and much thicker during diastole. However, the aggregation timescales during these conditions are not clear, but experiments have indicated latencies in the range of seconds to minutes; suggesting that the flow pulsations ($\sim 1 \text{ s}$) to have marginal effects on normal blood rheology [76, 198]. Although, for low and lasting shear rate conditions, for example expected in slow-moving secondary flow regions triggered by cardiovascular malformations, RBCs aggregation may be more prevalent.

In spite, fluid flows in large arteries are commonly assumed to be Newtonian, using a constant low-viscosity value of 3 to 4 mPa s at 45% hematocrit level, due to the overall high mean shear rates [32]. For vessels with a diameter $\sim 200 \mu\text{m}$ (arterioles-to-venules), the flow has little pulsatility while the blood inhomogeneity is more profound, which reduces the viscosity¹³ and hence the resistance to flow [15].

¹²That is, the whole blood viscosity divided by the water viscosity at 20°C (1 mPa s). Plasma has a relative viscosity ~ 1.3 .

¹³Called the Fahraeus-Lindqvist effect.

2.3 Hemodynamics

The dynamics of blood flow is like all fluid motion¹⁴ governed by fundamental physical principles or conservation laws:

1. *Conservation of mass.* Mass cannot be created nor destroyed. The net mass flux in a closed system should be zero.
2. *Conservation of momentum*¹⁵. Implied by Newton's second law of motion. The rate of change of momentum of a body is due to the net force applied on it. When the latter is zero, the momentum is constant (i.e. no body acceleration).
3. *Conservation of energy.* Implied by the first law of thermodynamics. The change in net energy flux (due to heat and work) in a isolated system is equal to the rate of change of the system internal energy.

Fluids cannot resist deformation, unlike solids, except slightly from viscosity, and will continuously change shape due to any non-zero fluid forces. The motion mechanics of a solid object is easy to see and define, but how to visualize and track a squishy moving fluid like blood? A sophisticated way is to treat a fluid as a tiny volume (infinitely small fluid element/particle, or continuous mass) large enough such that the molecular scales cease to be relevant (i.e. represented by a huge amount of molecules). From this so-called continuum viewpoint, using the physical principles above, the governing equations of fluid flow can be defined, called the Navier-Stokes (N-S) equations. The solution to these partial differential equations can provide an accurate description the flow field at any point in space and time, given proper initial and boundary conditions. Unfortunately, due to the equations highly nonlinear (chaotic) nature, exact solutions only exist for particular simplified problems, while finding exact solutions for more general three-dimensional cases are yet to be proven and remain one of the most significant unsolved problems in physics today. Nevertheless, numerical approximations of the N-S equations (i.e. divide time/space into discrete intervals/regions) have proven to be very useful for predicting a wealth of complex scientific and engineering flow problems. These numerical methods are known as computational fluid dynamics and have been the cornerstone in the current thesis (Sec. 3.1).

Assuming that a liquid can be described as incompressible (constant fluid density) and isothermal (i.e. temperature and pressure levels have a minor effect on the fluid density), with Newtonian-like properties (i.e. fluid shear stresses are proportional to the product of strain rates and viscosity) the differential form of the N-S equations in Cartesian coordinates can be expressed as¹⁶:

¹⁴The description of the flow of fluids (gases and liquids in motion) is called *fluid dynamics*, in contrast to *fluid statics* that concerns fluids at rest.

¹⁵Momentum is the product of mass (or density) and velocity, i.e. a vector quantity.

¹⁶Assuming that the control volume now is an infinitely small element fixed in space, with the fluid moving through it.

$$\nabla \cdot \mathbf{u} = 0 \quad (1)$$

$$\underbrace{\frac{\partial \mathbf{u}}{\partial t}}_{\text{transient term}} + \underbrace{\mathbf{u} \cdot \nabla \mathbf{u}}_{\text{convective term}} = \underbrace{-\frac{1}{\rho} \nabla p}_{\text{pressure gradient}} + \underbrace{\frac{\mu}{\rho} \nabla^2 \mathbf{u}}_{\text{viscous term}} + \underbrace{\mathbf{S}}_{\text{source term}} \quad (2)$$

where $\mathbf{u} = \mathbf{u}(x, y, z, t)$ is the velocity vector, p the static pressure, ρ the constant fluid density, μ the dynamic viscosity, t the time, $\nabla = (\partial/\partial x, \partial/\partial y, \partial/\partial z)$ the gradient operator and $\nabla^2 = \nabla \cdot \nabla$ the Laplacian operator. In CFD modeling of blood flow, it is common to either assume the viscosity to be constant or described by a shear rate dependent function ($\mu = \mu(\dot{\gamma})$). Equation 1 is the *Continuity equation* and ensures mass balance between mass flux in and out from the fluid element. Equation 2 is the *Momentum equations* (i.e. three equations, one for each spatial direction), derived from the Newtons second law applied to a small fluid element¹⁷. The left-hand-side correspond to the rate of change of fluid momentum, i.e. fluid acceleration due to local temporal and spatial velocity variations (transient and convective term, respectively). This change in momentum is dictated by the right-hand-side, which entails the sum of all stresses (force per unit area) acting on the fluid volume. Forces affecting the fluid element can be *i*) surface forces: local pressure gradients and viscous stresses, and *ii*) body forces: such as gravity and/or centrifugal forces. Body forces are normally not considered relevant for describing blood flow. Accordingly, we notice that the entire flow fields in Newtonian liquids (with constant density and viscosity) are merely governed by gradients (derivatives) of pressure and velocity components.

2.3.1 Flow regimes

There are numerous ways fluid flow can be characterized in real-world flow applications. In hemodynamics, however, the flow conditions are typically described as being:

- *Steady or unsteady*. Steady-state (stationary) conditions concern flows that are time-insensitive (i.e. no temporal gradient in Eq. 2). Hence, monitoring points of e.g. velocity and pressure will not change over time. Unsteady (transient) conditions are here referred to as pulsatile flows, where the applied pressure gradients enforce cyclic flow variations over a non-zero mean flow.
- *Laminar, transitional or turbulent*. The latter is sometimes classified as conditionally turbulent or fully turbulent flow. Disturbed flow is also a common term used in the biofluid community and can imply conditions that are non-laminar (e.g. transitional and/or turbulent-like), or laminar but with secondary flow features (shear-layer oscillations, Dean vortices, etc.).
- *Single-phase or multiphase flow*. That is, if the blood flow is treated as a continuous fluid (with Newtonian or non-Newtonian properties) or as a multiphase suspension, e.g. plasma as

¹⁷Here on the form $m\mathbf{a} = \mathbf{F}$, where m is the fluid mass, $\mathbf{a}$ the acceleration vector (rate of change of the velocity), and $\mathbf{F}$ the net force vector acting on the control volume. The mass term in Eq. 2 are represented by the density (mass per unit volume).

the primary fluid with dispersed elements as the secondary phase, such RBCs (i.e. two-phase flow).

Real vascular flows always exhibit some level of perturbations (unsteadiness). However, in smaller vessels ($\sim$ arterioles, Fig. 4) most of the transient pulsatile flow variations are removed owing to the Windkessel effect, making a steady flow assumption more valid. Sometimes, steady-like conditions may be warranted even in intermediate-sized arteries [250]. In the larger central arteries, however, the flow is clearly oscillating (Fig. 3 and 4) due to the pumping heart and distal vascular response. Flows at these sites are, therefore, generally treated as unsteady.

If the fluid velocity is sufficiently slow to allow for smooth and regular motion, it is categorized as being laminar. If visualized by careful ink injection, clear, non-mixing fluid layers would appear along the direction of the flow (Fig. 6, streamlines). Generally, laminar flows are often associated with steady conditions but can also exhibit unsteady/disturbed features as long as the mixing of adjacent fluid layers is suppressed. Turbulence, on the other hand, is more challenging to define explicitly. Using a clinical analogy, if turbulence were equivalent to a disease, the syndrome of this flow regime would usually be associated with the following symptoms:

- Highly unsteady and chaotic, with random/irregular flow fluctuations in space and time.
- Three-dimensional flow characteristics, i.e. rotational structures (eddies) over a wide spectrum of spatial and temporal scales.
- Strong vorticity. Turbulent eddies extract energy from the main flow via vortex stretching, creating smaller and smaller eddies.
- Elevated diffusivity (mixing) of mass, momentum, and heat.
- Elevated pressure losses due to enhanced viscous dissipation of kinetic energy into heat.

The state between the laminar and developed turbulent flow regime is called transitional flows, where the flow locally can move back and forwards between a laminar and turbulent state. If the flow rate would slowly be ramped up, the fluid would sooner or later start to transition to turbulence (Fig. 6a), where small local flow instabilities eventually would prevail, followed by rapid turbulence development. At this stage, any injected ink would be highly dispersed owing to the wide range of eddies mixing the flow. On the other hand, if the main flow momentum is gradually attenuated, the turbulence energy source will be weakened, and the flow will gradually start to relaminarize.

A frequently used parameter to distinguish between these flow regimes is the Reynolds number:¹⁸

$$Re = \frac{\rho UL}{\mu} = \frac{\text{convective inertia forces}}{\text{viscous friction forces}} \quad (3)$$

where ρ and μ are the fluid density and dynamic viscosity, respectively, U and L are associated with the representable (characteristic) velocity and length scales in the flow, respectively. In

¹⁸First introduced by Osborne Reynolds in 1883, who observed a critical change in flow characteristics when conducting different pipe flow experiments that were consistent with the Reynolds number.

Figure 6: Schematic representation of different flow regimes inside idealized arterial vessels. **(a)** In a straight vessel, the flow will sooner or later transition from laminar to turbulence as the flow rate is gradually increased. The transitional process is generally very complex, unpredictable, and case sensitive, but eventually will be initiated by small turbulent-like puffs (bursts) followed by more substantial chaotic flow instabilities (random fluctuations). The temporal mean velocity profile (gray line) in developed laminar flows is parabolic while being more blunter in turbulence. Elevated turbulent conditions also increase the pressure losses in the system, which promotes higher perfusion pressure. **(b)** In a constricted vessel, turbulence may develop by the flow disruption of the sudden geometry expansion (adverse pressure gradient), where significant shear-layer instabilities within the jet may promote turbulence development.

vascular flows, L is often assumed to be the vessel diameter and U the cross-sectional average (mean) axial velocity. This dimensionless quantity measures the ratio of inertial forces to viscous forces in the flow, i.e. the fluid ability to resist change in motion. For different flow applications, the Reynolds number will reach different critical upper thresholds (i.e. the critical Reynolds number), from where the flow will start to transition to turbulence. The fluid viscosity (the fluids frictional resistance to shear forces) has a tendency to damp flow instabilities and hence why very viscous fluid like hydraulic oil tends to be laminar under normal operating flow rate conditions. However, there may be a stage when the inertia forces start to dominate the flow. The importance of these properties can be shown by normalizing the incompressible N-S equation (ignoring the body forces) to its non-dimensional form [190], using the characteristic length and velocity scales described above¹⁹:

$$\nabla^* \cdot \mathbf{u}^* = 0 \quad (4)$$

$$\frac{\partial \mathbf{u}^*}{\partial t^*} + \mathbf{u}^* \cdot \nabla^* \mathbf{u}^* = -\nabla^* p^* + \frac{1}{Re} (\nabla^*)^2 \mathbf{u}^* \quad (5)$$

Noticeably, the only appearing term is the Reynolds number, which directly regulates the viscous forces. Indeed, a high Reynolds number will scale down the viscous contribution, making the flow more susceptible to flow instabilities. From this transformation, it is also evident that fluid flows with the same Reynolds numbers will have the same scaled flow fields. Hence, if the flow through a pipe with twice the diameter as another pipe but with halved mean velocity, the flow characteristics in both cases would be the same. Experiments have shown that fully developed flow in a smooth circular pipe is maintained laminar up to $Re \sim 2000$ in constant-density Newtonian fluids [207].

A consistent critical Reynolds number is hard to find in realistic physiological flows due to the complex non-rigid shaped vessels, non-Newtonian fluid properties, and pulsatile conditions. In fact, even in idealized flows (pipes and channels) this phenomenon is still not fully understood [36, 95]. Under normal blood flow conditions, i.e. vessel shape and cardiac output, the flow in large arteries are generally assumed to be overall laminar [246]. These flows can, however, easily transition to turbulence when facing a severe flow obstruction, such as sudden vessel tapering (stenosis) (Fig. 6b), as low as a Re of a few hundred [220, 246]. In pulsatile flows, turbulence development is normally delayed as the flow is accelerated in systole [229], while the transition to turbulence is expected first after maximum flow rate, during the early stage of the flow deceleration phase of the cardiac cycle if the Re is sufficiently high [252]. In fact, in pulsatile flows through straight tubes, the transition onset have shown to occur first at peak $Re \sim 6000$ (mean $Re \sim 3000$) [181]. In the proximal ascending aorta, turbulent-like conditions have even been observed for peak $Re \sim 4000$ to 9000 for healthy adults at normal cardiac outputs [88, 216, 218], owing to the jet flow disturbances induced by the aortic valve. However, these "normal" turbulent conditions are often much weaker (an order of magnitude lower) than turbulence promoted by aortic valve stenosis [218] and will usually diminish before reaching the arc of the aorta. From Fig. 4, it is clear that it is only the larger elastic arteries that have a sufficiently high Reynolds number to enable turbulence. Further downstream the arterial tree,

¹⁹ $\mathbf{u}^* = \mathbf{u}/U$, $t^* = t/(L/U)$, $p^* = p/(\rho U^2)$ and $\nabla^* = L \nabla$.

the viscous effect dominates, owing to the large decrease in vessel diameter and mean velocity, and hence the flow will stay laminar.

Figure 7: Schematic view of the larger central arteries with examples of regions that occasionally are susceptible to turbulent-like flow conditions due to various cardiovascular structure abnormalities.

The most common causes of turbulence development in arteries are associated with unfavorable anatomical obstructions such as sudden vessel narrowing (i.e. stenosis, e.g. lesion-related or congenital) and enlargement (i.e. aneurysms, e.g. abdominal aortic aneurysm), dysfunctional cardiac valves (i.e. valvular disease, e.g. aortic stenosis), sharp bends and bifurcations (e.g. severe aortic arc kinking or arteriovenous fistula), and intervention-related implants (e.g. grafts, stents and mechanical heart valves). Some of these turbulence-prone sites are depicted in Fig. 7. Weaker turbulent-like conditions have also been observed inside the heart chambers [201, 262, 71], intracranial aneurysms [67, 237], pulmonary artery [219], and distal to coronary artery stenosis [54, 253]. The latter condition may reduce the blood supply to the heart muscle, which under severe cases could lead to myocardial infarction.

There are also several other important factors that may impact the unsteady turbulence behavior in realistic vascular flows:

- *Pulsating characteristics.* In arteries, the difference in frequency as well as velocity amplitude²⁰ of the imposed cardiac pulse have different impact on the local flow characteristics. The pulsatile nature of blood flow is commonly characterized by the dimensionless Womersley number α , which describes the ratio between the pulse-related transient inertia forces and fluid viscous shear forces [255, 250]. In vascular flows, the Womersley number is given by:

$$\alpha = R \left(\frac{\rho\omega}{\mu} \right)^{1/2} = \frac{\text{transient inertia forces}}{\text{viscous friction forces}} \quad (6)$$

where ρ and μ are the fluid density and dynamic viscosity, respectively, R the vessel radius, and $\omega = 2\pi f$ with f representing the frequency of the cardiac cycle (~ 1 Hz, or 60 beats per minute). If ρ , μ , and ω are assumed to have relatively small variability in the vascular system under normal conditions, α is mostly dictated by the vessel cross-sectional dimension, which reduces vastly down to the capillary bed (Fig. 4). The Womersley number in the ascending aorta (Fig. 2) ~ 20 , descending aorta ~ 12 , carotid artery ~ 5 , and femoral artery ~ 3 , while being several order of magnitude lower in the smaller vessels (arterioles ~ 0.01). In general, flows with small α values ($\alpha \lesssim 3$) have minor pulsatility and can be deemed quasi-steady [250]. These slow temporal variations allow the flow to develop during each cardiac cycle and, if sufficiently undisturbed, attain a parabolic-like axial velocity profile. If, however, the α value is sufficiently large ($10 \lesssim \alpha$), the oscillatory inertia forces dominate the viscous effects. Here, the velocity profile will attain a flatter plug-like profile that will oscillate about the pulsatile mean flow. The nature of the pulsation may also influence the turbulence transition threshold. In pipe flows, the critical Re have shown to be decreased for $\alpha \lesssim 3$ and in fact increased for $4 \lesssim \alpha \lesssim 10$ [229, 236]. For higher Womersley number ($10 \lesssim \alpha$), however, the pulsatile effects appear to have minor influence, where the turbulence transition mainly is governed by the size of the Reynolds number [257] (akin to steady flows). The degree of turbulence development during pulsatile blood flows is also affected by the Reynolds and Womersley number [65], however, not enough to be considered fully developed. Here, weaker turbulence disturbances can prevail during the diastolic phase but usually relaminarize completely as the flow is ramped up again during systole. As such, turbulence hemodynamics is sometimes classified as being conditionally turbulent [252].

- *Vessel viscoelasticity.* The larger arteries ability to dilate generally has a diminishing effect on the turbulence levels owing to the temporary reduction in Reynolds number [246], which might delay or even suppress the turbulence development in sensitive cases. Also, considering anatomical and hemorheology factors of real vascular flows, this effect is likely very site-specific. For example, in aortic blood flow, age-related vessel dilation and reduced compliance have shown to enhance turbulence in the proximal ascending aorta compared to healthy subjects [88], while the opposite effect was observed in the descending aorta. Furthermore, turbulence-related flow instabilities contain a relatively wide range of frequencies (wavenumbers), which may interact with the viscoelastic vessel wall and surrounding soft tissue [148]. This interchange is not well understood but might promote additional turbulence dissipation.

²⁰The pulsation amplitude is defined as $A = U_o/U_m$, where U_o and U_m is the oscillatory and mean axial velocity, respectively.

- *Hemorheology.* The high concentration and deformability of RBCs will not only induce non-Newtonian blood characteristics under varying shear strain rates (Sec. 2.2), but may also have a dampening effect on the turbulence development [246, 8]. From a whole blood perspective (homogeneous single-phase fluid) in laminar flows, this is induced by the increase in viscosity, e.g. from reduced shear rates and/or hematological disorders²¹. In turbulent flows, RBCs can act as a barrier, where part of the energy carried by the smaller turbulence eddies would be absorbed by the cell's elasticity and the interaction between them, rather than only via viscous dissipation through the plasma [8]. However, in real turbulence hemodynamics, these effects are still not well understood due to measurement and modeling challenges at these microscales. This cell-to-eddy interplay is presumably also dependent on the nature of the turbulent flow.
- *Secondary flows.* There are many different secondary flow patterns that may play an important role in the initiation, distribution, or attenuation of turbulent flow features. Counter-rotating Dean vortices, e.g. formed in the aortic arch and arterial bifurcations/branching, may promote hairpin vortical structures that e.g. influence near-wall turbulent region [27]. Helical flows promote rotational flow stability that may dampen or delay turbulence development in e.g. the ascending and thoracic aorta [167]. The development or characteristics of local turbulence may also be affected by abnormal upstream flow conditions, e.g. flow disturbances caused by aortic valve stenosis or bicuspid aortic valves (BAV).

2.3.2 Endothelium and near-wall flow

The innermost layer of the arterial wall (from the heart to the capillaries) consists of a single monolayer of endothelial cells (ECs), with direct contact with the flowing blood. This permeable lining, called the endothelium, plays an essential role in maintaining vascular integrity and functionality, where the ECs can adapt (in numbers, shape, and arrangement) to meet local demands [4, 46]. The ECs controls the diffusion of essential materials, fluids, and cells between the bloodstream and surrounding tissue. Some of the key functionalities are:

- Regulation of vascular inner diameter (vascular caliber), to balance the blood pressure.
- Recruitment of white blood cells during wall infection (inflammation inhibitor).
- Promote stimulus against cell growth (proliferation), platelet activation, and blood coagulation (thrombosis).
- Prevent and stop bleeding (hemostasis) after vessel injury.
- To regulate blood pressure by balancing local vessel constriction and dilation (i.e. the vascular tone).
- Creation of new blood vessels from pre-existing (angiogenesis), e.g. to regions with impaired oxygen supply.

Structural and functional regulation of the vessel wall is governed by highly flow-sensitive receptors (molecular sensors) on the ECs, which commutes the hemodynamic forces acting

²¹Hematological disorders could be due to abnormally high cell concentration or cells that are less deformable.

on the cell surface into specific biochemical signals to its surroundings and/or indirectly by activating signal pathways inside the cells (the so-called mechanotransduction pathway) [45]. This vascular response can be fast under physiological flow variations via SMCs relaxation (vasodilation). However, if the new flow conditions are more sustained, the vessels can undergo slow wall-remodeling adaptations [46, 78], where, for example, prevailing increase in flow rate will result in a lumen increase, and vice versa.

As the fluid flow approach the intraluminal wall, a gradual slowdown will occur due to the frictional forces between the fluid and wall molecules and eventually come to full rest at the wall. Indeed, at this point, all velocity components must be zero relative to the surface (the no-slip condition). Due to viscous effects, the near-wall flow also needs to gradually slow down, leading to large local velocity gradients (shear rates) compared to further out in the bulk flow. This near-wall region is commonly referred to as the boundary layer. In pulsatile pipe flow, the boundary layer thickness is inversely proportional to the Womersley number [207]. Thus, in turbulence pulsatile flows with high Womersley number ($10 < \alpha$), the near-wall shear waves induced by the viscous effects will not propagate far into the main flow, but instead be confined to the inner-most region called the viscous sub-layer [95]. These velocity profiles will therefore generally be blunter (plug shaped) compared to flows with much smaller Womersley numbers (with parabolic-like velocity profiles), which results in larger velocity gradients in the vicinity of the wall. Under normal physiological conditions, the flow in the viscous sub-layer can be viewed as Newtonian as this region mainly consist of plasma fluid.

Figure 8: Schematic view of near-wall turbulent flow over the endothelium. The velocity gradients with respect to the wall-normal direction and fluid viscosity induce a frictional force on the arterial surface, called the wall shear stress (WSS or τ). The WSS is a two-component vector $\tau = (\tau_x, \tau_z)$ parallel to the wall and can be decomposed into a mean ($\bar{\tau}$) and fluctuating (τ') part owing to the near-wall flow disturbances. Note, this drawing is not according to scale.

The main force sensed by the endothelium, and deforms the cells²², is the wall tangential

²²ECs deform similarly to a viscoelastic body up to a certain shear stress limit, whereafter the elastic properties are lost (behaving more like a viscous object) and the cells become much more sensitive to shear-induced deformation, and under severe shear stress exposure, even detach from the endothelium. [72]

frictional force along the flow direction, often referred to as the wall shear stress (WSS). Consider a point $\mathbf{x}(x, y, z, t) = \mathbf{x}(x_0, y_0, z_0, t_1)$ on the ECs surface (Fig. 8), then the WSS vector $\boldsymbol{\tau}$ can be defined as:

$$\boldsymbol{\tau} = \mu \frac{\partial \mathbf{u}}{\partial y} \Big|_{y_0=0} \quad (7)$$

where $\partial \mathbf{u} / \partial y$ is the velocity gradients in the wall-normal direction (i.e. $\partial u / \partial y$ and $\partial w / \partial y$) and μ the dynamic viscosity. Due to the unsteady nature of pulsatile flows, the instantaneous near-wall velocity and thus the WSS directionality will have a transient behavior. However, under physiological laminar conditions, without major near-wall disturbances, the ECs will stretch and aligned with the dominant mean WSS magnitude ($\|\boldsymbol{\tau}\| \sim 1$ to 7 Pa in arteries [41]), typically in the axial direction of the flow (Fig. 8, τ_x). However, if the flow conditions are sufficiently disturbed to cause abnormal spatial and temporal changes in the WSS behavior, some of these important ECs functionalities may be compromised.

2.4 Flow-mediated pathological effects

Blood flow disturbances, owing to disturbed, nonlaminar, transitional, or turbulent-like conditions, may contribute to a variety of pathophysiological effects, locally as well as on a broader scale in the cardiovascular system [246, 41, 46]. These abnormal flow phenotypes²³ are frequently observed at, for example, various anatomical, lesion, and intervention-related sites (Fig. 7), while their role as a pathological determinant is less understood. In this section, a summary of some of the most common detrimental factors will be given.

2.4.1 Cardiovascular diseases

There are many birth disorders (congenital/genetic diseases) or later acquired CVDs that may promote or are partly initiated/developed by disturbed hemodynamics, or a combination of both. One of the most common is aortic valve diseases, described by dysfunctional heart valves that do not fully open (aortic valve stenosis) and/or close sufficiently (aortic valve regurgitation), and are disorders that often are associated with the elderly population. Aortic valve disease, in turn, stimulates other diseases such as aortic aneurysm (dilatation of the ascending aorta), aortic dissection (small wall tear resulting in intraluminal blood flow through a fake lumen), as well as flow-mediated damage to the blood elements. Another disease example is coarctation of the aorta (Fig. 9), which is a congenital heart disease described by a vessel narrowing defect usually positioned in the distal aortic arc or proximal descending aorta (Fig. 7). A coarctation malformation is rare condition (3 to 4 cases per 10000 birth) and can be an isolated obstruction, include severely malformed nearby vessels (hypoplastic aortic arc and post-stenotic dilatation) and collateral vessel formation²⁴, as well as be accompanied with several heart defects (e.g. BAV, aortic/mitral valve stenosis/regurgitation, atrial/ventricular septal defects, left ventricular

²³Flow phenotypes are referred to specific flow characteristics that can be associated to the initiation and/or progression of cardiovascular diseases.

²⁴Collateral vessels are abnormal and formed to bypass the narrowed area to increase the blood perfusion to the abdomen and lower limbs.

hypertrophy). Examples of a non-congenital disease are atherosclerosis (a vessel narrowing disorder due to intraluminal inflammation and plaque buildup), and aneurysms (an outward bulging of the vessel wall), which are the first and second most common vascular diseases along the aorta, respectively [153].

Figure 9: Schematic representation of a postductal aortic coarctation. During fetus development, blood bypass the dysfunctional lung-loop through a blood vessel, called the ductus arteriosus, connecting the pulmonary artery to the proximal descending aorta. Within three weeks after birth, this shunt is normally closed, leaving a leftover ligament. On rare occasions, however, the degradation of this muscular artery ligament can induce pathological contraction and tissue remodeling of the attached aortic wall region, which eventually may lead to a substantial narrowing of the lumen, clinically known as a coarctation of the aorta.

Pressure loss and hypertension. To supply the production of turbulence requires energy, which is extracted from the main flow. However, the majority of this energy is eventually lost as thermal heat in the plasma fluid, which is an irreversible process and hence will result in additional viscous losses²⁵. These losses will lead to reduced transport efficiency in the bloodstream (Fig. 6), as the heart needs to work harder to maintain proper flow rates, causing elevated blood pressure upstream the turbulent site and abnormal low pressure further downstream. Aortic coarctation is an example of an arterial region associated with major pressure losses [81, 59], which if left untreated could lead to arterial hypertension (i.e. blood pressure $> 140/90$ mmHg) followed by a wide range of cardiovascular complications such as coronary artery disease, structural remodeling of the aorta (aortic stiffening, aneurysm, and dissection formation) and the heart (left ventricle hypertrophy) [179, 235].

In the large elastic arteries, sustained hypertension will result in increased lumen diameter and wall thickness (vascular mass) (Fig. 10), while vice versa in the smaller arteriole vessels. In adults, a marker of CoA severity is often based on the pressure difference across the constricted region²⁶ [56], where a difference of 20 mmHg or higher usually denote a need for intervention [153]. CoA treatment can either be done by open surgical resection (first performed by

²⁵In laminar flows there is also viscous losses, e.g. due to friction between the fluid and wall as well as between adjacent fluid layers for non-zero velocity gradients.

²⁶Either non-invasively by the legs-to-arms systolic pressure difference, or invasively by the peak-to-peak trans-catheter pressure difference over the coarctation site.

a Swedish surgeon in 1944 [123]) or endovascular management. The latter procedure is the most common and minimally invasive approach, where a catheter-guided balloon is used to inflate the narrowed region (called balloon angioplasty). This procedure can be complemented by adding a stent to avoid possible vessel recoil (i.e. transcatheter stent implantation). However, despite removing the severity of the obstruction, these treated CoA patients are often susceptible to high blood pressure (and antihypertensive medications) due to irreversible long-term impairment of the vascular structure (increased stiffness and aortic arc malformation) and ECs dysfunctionality [230].

Endothelial cell impairment/dysfunctionality. Undisturbed, laminar shear stress plays a crucial role in regulating vascular physiology (Sec. 2.3.2). When these conditions are distorted by flow disturbances, which promotes a multidirectional WSS environment of spatial and time-varying magnitude (Fig. 8 and 12), the ECs functionality can be compromised and impair essential mechanotransduction pathways in the vessel structure [39, 41, 45]. In one of the earliest studies on ECs hemodynamic response [72], high WSS levels under turbulent conditions were associated with acute ECs deterioration (cell deformation, damage, breakdown, and loss), contrary to a endothelium subjected to smooth laminar shear rates. In a later study [47], similar ECs effects (including disorientation, morphology changes, and raised cell turnover rate) were also found for considerably lower shear stress levels in turbulent flows, compared to the laminar counterparts; signifying that endothelial impairment and dysfunctionality appeared to be more coupled to the unsteady nature of the near-wall flow (magnitude, frequency, and orientation), rather than just the WSS magnitude itself. Other studies have also attributed ECs impairment/dysfunctionality to large variability in WSS gradients (i.e. large variations over short spatial and temporal scales) [51, 50], typically ascribed by near-wall turbulence, which encourage ECs migration away from the exposed zone, cell division (increased DNA synthesis), as well as atypical intercellular communication modifications. Disturbed flows have also been shown to have a negative impact on e.g. ECs-induced vasorelaxation, inflammatory response, endothelial repair, and vascular permeability (including low-density lipoproteins, LDL), factors which can promote atherosclerosis, thrombosis, and/or adverse wall remodeling [45, 41, 39]. In recent years, a deeper understanding of the pathophysiological mechanisms of disturbed flows on ECs functionality and cardiovascular disease have been developed, albeit still far from well understood due to the sheer complexity of the near-wall flow characteristics (e.g. low and oscillatory vs. highly disturbed, turbulent-like shear stresses) as well as other factors such as high blood pressure, age, sex, and other underlying pathological conditions.

Vascular remodeling. Can be described as cellular adjustments (cell growth, death, migration, and extracellular matrix production/degradation) of the vessel structure (Fig. 10), due to an interplay between vasoactive substances and hemodynamic forces, which change the vascular caliber/thickness during persistent/recurrent alteration of the flow conditions (or sudden injury) [78]. Examples of remodeling-related cardiovascular disorders are aneurysms, post-stenotic dilatation, restenosis, atherosclerosis, systemic arterial hypertension, and malformations associated to bypass grafts, stents, arteriovenous fistula (AVF) [78, 246]. These maladaptive responses are common under disturbed flow conditions and are stimulated by multiple events that can be largely coupled to the dysfunctionality of the endothelium, which gradually weakens the arteries structural integrity.

Figure 10: Schematic view of various vascular wall remodeling disorders. Modified from [193] licensed under [CC BY 3.0](#).

Initiation and progression of outward wall remodeling, such as aneurysm and post-stenotic dilatation, have been associated with a wide range of disturbed near-wall flow characteristics. The most common aneurysm formation sites include the larger brain arteries (part of the circle of Willis, called a cerebral or intracranial aneurysm) and along the aorta (Fig. 7). Aneurysms are triggered by a structural breakdown of the connective tissue within the arterial wall [202], followed by growth and remodeling process in order to withstand the new hemodynamic forces. This is a complex, and very site-specific chain of events²⁷ that is believed to be highly stimulated by ECs pathological regulatory response as well as direct damage to the endothelial lining. If the flow-mediated degradation/breakdown is balanced with the growth/repair mechanisms, the aneurysm is said to be stable; if not, the aneurysm will continue to grow and potentially rupture, which could be fatal [155]. Aneurysm pathogenesis related to altered blood flow characteristics are currently one of the largest research areas within the biofluid community, where for example substantial alterations of pressure and fluid shear stresses governed by turbulent-like instabilities are believed to accelerate the degenerative vascular changes [66, 246]. In aortic aneurysms, the spindle-shaped/fusiform widening (of least 50% in diameter) and high Reynolds number ($Re \sim 2000$ to 5000) will typically favor turbulence development as the flow suddenly decelerates in the dilated area [137, 119]. On the other hand, in the intracranial arteries, aneurysms are spherically-shaped/saccular on the vessel side or positioned in a bifurcation junction, with a considerably lower Reynolds number ($Re \sim 500$). These flows are therefore generally viewed as being laminar, although several studies have found evidence of transitional and turbulent-like characteristics at these sites, particularly for bifurcating aneurysm (e.g. [66, 217, 237, 238]). A recent study also found signs of weak turbulent-like patterns in the upstream vessels [239], which was hypothesized to plausibly play a vital role in the initiation and rupture risks of intracranial aneurysms. Post-stenotic dilatation is a well-known pathological phenomenon that occurs immediately downstream sudden flow constrictions such as aortic/pulmonary valvular

²⁷Not only regarding different flow conditions (Reynolds number and shape: saccular or fusiform) but also details in the vascular structure composition, where for example intracranial and the large aorta vessels varies slightly.

stenosis and aortic coarctations, which can involve severalfold diameter increase with respect to healthy vessels [199], and is likely a precondition to aortic dissection and rupture [251]. The main route leading to this disease state is generally believed to be caused by turbulence-related stresses (velocity and pressure fluctuations) and underlying pathological conditions of the arterial wall [53, 246]; however, the pathogenetic path of post-stenotic aortic dilatation, including ascending aorta aneurysm, still is a somewhat controversial topic where many factors have been suggested [100, 251].

Disturbed, turbulent-like hemodynamics have also been associated with vascular narrowing remodeling due to intimal hyperplasia (IH), i.e. proliferation/migration of SMCs into the intima wall layer, which thickens the wall and increases the stenotic severity (Fig. 10). Intimal hyperplasia remodeling due to non-laminar WSS disturbances is frequently observed in the vicinity of arterial bypasses and arteriovenous grafts [93, 160], at the junction or proximal vein in AVF fistulas [213, 29], and plays a significant role in restenosis/recoarctation formation after angioplasty/stenting intervention as a response to the arterial trauma (endothelium injury) [22].

The initiation and development mechanisms of atherosclerosis (i.e. atherogenesis), which is a slow lumen narrowing process (time scale of decades)²⁸ due to plaque²⁹ build-up within the arterial wall (Fig. 11), dependent on multiple factors such as inflammation and abnormal hemodynamic changes [39, 41, 246]. As the plaque lesion grows, the protected layer (fibrous cap) may rupture³⁰ followed by an inflammatory response that can form blood clots (thrombus) that restrict or entirely blocked the local blood (oxygen) supply, leading to organ failure; the most well-known being heart attack owing to coronary artery disease.

Figure 11: Schematic view of the progression of atherosclerosis and possible complications. Adapted from "Wikipedia", provided by N. Patchett, and licensed under CC BY-SA 4.0.

Arteries with atherosclerosis disease remodel over time and become thicker and stiffer. While the pathogenetic details of this disease are not clear, plaque formation has been linked to non-uniformed WSS variations in regions with secondary or disturbed near-wall flows (laminar as well as non-laminar), especially in the vicinity of vessel bifurcation, branching junctions, and sharp bends where the blood residence time is longer (i.e. slow-moving flows) [124]. These flow disturbances encourage ECs dysfunctionality and impairment that tend to downregulate important atheroprotective mechanisms such as vascular tone adaptation and endothelial re-

²⁸Atherosclerosis typically starts to develop at the middle age, while ischemic organ symptoms due to impaired oxygen supply typically occur decades later.

²⁹Arterial plaques are essentially a composition of fat, cholesterol and calcium.

³⁰Plaques are often categorized as either being stable or unstable.

pair, and upregulate atheroprone processes such as wall inflammation, elevated LDL influx, and white blood cells attachment/infiltration [45]. Here, turbulent-like flows are mainly believed to accelerate plaque growth and sensitivity to rupture risks [55, 246, 124], owing to the elevation of WSS and pressure fluctuations and spatial gradients; flow conditions that often get more severe as the vessel becomes more occluded. Although, a recent study have proposed that turbulence also can act as a initiator for atherosclerosis formation [248].

Figure 12: Schematic representation of different flow characteristics/regimes along a malformed aorta (hypoplastic arc and coarctation), with imposed flow streamlines, and expected cardiac velocity signals (black pulsatile profiles, blue font) as well as WSS patterns (red font). In the ascending aorta and branching vessels, the unsteady flow is laminar with a smooth flow signal. Due to the severe kink of the aortic arc and vessel narrowing, turbulent-like flow is developed, which is recognized by a highly disturbed flow signal. Towards the abdominal aorta, the turbulence dissipates, followed by flow relaminarization.

Atherosclerosis can occasionally be formed in the abdominal aorta, femoral arteries, and in the branching region of the carotid arteries [39]. Atherosclerotic carotid artery stenosis is typically formed along the outer wall (opposite of the separation region, where the flow is most disturbed) of the internal carotid artery supplying the brain. Despite the disease relatively

common prevalence in the general population [1], especially in elderly patients, the underlying pathogenetic mechanisms are unclear, partly as the conditions often are asymptomatic prior to the trauma. In fact, if a lesion ruptures, leaking downstream traveling thrombus material may block part of the brain vessels, which could lead to ischemic stroke. An abundance of hemodynamic attributes has been associated with atherosclerotic development over the years, where disturbed low WSS (<1 Pa) has been identified as an important factor. While it is well established that unidirectional and high WSS protects against atherosclerosis, the role of these disturbed flow-phenotypes (including other factors) is still not well understood and therefore a significant research area. For instance, in complex-shaped vessels, the near-wall flow patterns, and hence WSS characteristics, can be very different (e.g. unidirectional, multidirectional, or oscillatory/bidirectional transient behavior with varying magnitude), e.g. along a malformed aorta (Fig. 12).

2.4.2 Blood damage

Blood flow that promotes high shear strain rates (or fluid shear stresses), such as turbulent flows, is known to mediate damage to the suspended cells within the blood, such as injury to RBCs (hemolysis), activation or rupture of platelets, blood clots formation (thrombosis), arterial blockage (embolism), white blood cell dysfunctionality, and coagulation cascade impairment [70]. Hemolytic activity may release a range of different contents (such as hemoglobin) into the fluid plasma that may promote several clinical complications [205]. Severely damaged (ruptured) RBCs may also lose their deformability and consequently be removed by the filtering organs [64].

Flow-mediated blood trauma can be expected in cardiovascular regions where the local blood flow is accelerated suddenly, e.g. due to severe vessel malformations (stenoses, including unfavorable branching), valvular stenoses, aortic valve prostheses, and through medical assist devices such as blood pumps. These risks are further elevated in turbulent flow regions and in the vicinity of surfaces (due to cell-to-wall interaction), where the cells generally are exposed to higher shear forces [109, 80]. These underlying mechanisms between the fluid viscous forces and degree of damage are not well understood [64, 8, 168], where e.g. the rate of hemolysis appears to be dictated by the nature of the fluid stress-field, which cannot be easily described by single stress-related parameters. One of the main goals of this thesis was to develop more in-depth stress-related flow descriptors (see Sec. 4.2 and Paper IV), which may help to improve blood damage risk assessments.

2.5 Medical measurement modalities

The first indirect measurements of turbulent-like hemodynamics, in the form of heart murmurs, were most likely done in 1816 by Laennec and his invention of the stethoscope [91], which later became the standard for cardiac disease diagnosis. In the 1960s, the first invasive blood flow measurements of flow profiles and disturbances were performed in living humans, using instruments such as hot-film probes, while a decade later progressing to non-invasive pulsed Doppler techniques [246]. Today Doppler echocardiography and MRI are the primary medical measurement modalities to study hemodynamics.

Doppler echocardiography can estimate a one-direction velocity component along the trajectory of the ultrasound probe (beam), which can be visualized graphically (spectral Doppler) or as a 2D colorized image (Color Doppler), or a combination of both (duplex ultrasonography). Here, the local velocity data is decoded from the phase shifts (Doppler effect) of the ultrasonic waves induced by the moving medium (blood or tissue) with respect to the probe receiving the signal. This method is often used in clinical settings to attain rough estimates of general blood flow characteristics, such as peak velocities and anatomical information of the larger vessels. From these parameters, crude approximations of the cross-sectional mean velocities (flow rates) and pressure drops can be derived, which often require erroneous assumptions regarding the local flow conditions (e.g. fully develop flow). The characteristics in spectral Doppler techniques can also be used to detect regions susceptible to turbulent-like flow conditions, e.g. by probing passed a constricted blood vessel. Doppler echocardiography is often the first-line diagnostic tool used to investigate possible impaired (superficial) blood flow regions, where surrogate markers such as the degree of stenosis and peak-systolic velocity typically are used for severity assessment [82]. Compared to MRI, Doppler echocardiography are a cheap, fast, accessible, and versatile modality, but at the same time, limited to specific aggregated flow information. Also, the reliability of these measurements is highly dependent on the operator skills (e.g. controlling the beam-to-flow angle) as well as having a limiting field-of-view.

Magnetic resonance imaging is nowadays the best high-fidelity measurement modality to study hemodynamics in the heart and macro-sized vessels [150, 58], sometimes referred to as CMR (cardiovascular magnetic resonance). Clinically, various MRI techniques are frequently used to detected traumatic brain injuries [209]. Unlike computed tomography (CT), MRI scans do not involve hazardous ionizing radiation but instead rely on strong magnetic fields, magnetic gradients, and radio waves to control the nuclear spin directionality of the hydrogen atoms within the body. By applying sophisticated pulse sequences of radiofrequency spin excitation followed by modulation of the magnetic field gradients in different directions, the contrast between various hydrogen-rich mediums (stationary or moving) can be reconstructed both in space and time owing to the specific nucleus relaxation properties within. MRI-based flow data are susceptible to different errors/uncertainties associated with e.g. the acquisition procedure itself, non-stationary properties of the measured object, and contamination effects due to the surroundings. Some of these induced errors can mostly be corrected for, while other effects are more complicated and limited to the method itself.

The most common and clinically utilized technique is two-dimensional (2D) cine phase-contrast MRI (or 2D PC-MRI), which estimates a single velocity component normal to a 2D slice (through-plane) (Fig. 13a). Measurement using 2D PC-MRI still is the clinical golden-standard for flow rate quantification [58], e.g. to assess collateral, regurgitating, and shunt flows. MRI-derived through-plane velocity profiles are also the most popular choice for reconstructing inflow and outflow boundary conditions for patient-specific CFD modeling [232], and indeed was also adopted for the models in this thesis (Sec. 3.2.3). This 2D velocity mapping typically has an isotropic in-plane voxel resolution ~ 0.5 to 1.5 mm, with a temporal resolution of 40 frames per cardiac cycle. However, this method depend on a much larger through-plane voxel size (slice-thickness), which e.g. tends to add inaccuracies in sections with substantially varying flow conditions.

To attain a more comprehensive description of the hemodynamics, it is now also possible to measure all spatiotemporal varying velocity components ($3D + \text{time} = 4D$) in the large car-

Figure 13: MRI measurement modalities. **(a)** Time-resolved velocity profiles measured by 2D PC-MRI across section A–A in the ascending aorta, shown at maximum flow acceleration (I), peak flow (II), and maximum flow deceleration (III). Adapted with permission from [126]. **(b)** Pathline visualization of a 4D Flow MRI velocity field (colored by its speed) through the left atrium, ventricle, and ascending aorta during systole.

diovascular structures; a method often referred to as 4D Flow MRI or 4D Flow CMR. This is possible by a sophisticated four-point (4P) acquisition framework, where volumetric velocity information can be extracted by considering the phase-shift between a reference scan (without velocity encoding) and three scans adopting (bipolar) velocity encoding gradients in the mutual coordinate axes. 4D Flow MRI data can be used for a variation of flow quantification options as well as visualization of complex blood flow patterns (Fig. 13b) but compared to 2D PC-MRI also is accompanied with a relatively low spatial resolution (~ 1.5 to 3 mm) and is locally often less accurate. However, flow quantification derived from 4D Flow MRI tends to be more mass conserving as the entire volume is measure once, unlike multiple flow rate estimates by 2D PC-MRI that often requires several time-separated acquisitions. Flow measurements using MRI are, unlike ultrasound techniques, only estimating the phase-averaged (mean) flow properties, as the acquisition procedure ensembles the data tagged to different phases over many cardiac cycle realizations. In addition, the MRI data is also time-averaged over the applied velocity encoding gradients as well as spatially averaged over the voxel volume. For 2D PC-MRI, accurate data may be attained within a few minutes, while 4D Flow MRI measurements typically have an acquisition time over hundreds of heartbeats, taking up 25 min [58], hence making these methods less attractive in clinical practice.

In turbulent flow regions, the fluctuating velocity field will affect the alignment of the nucleus spin directions, which manifests as a intra-voxel velocity distribution and signal loss during a 4D Flow MRI measurement. By assuming the shape of this distribution (usually Gaussian), the intra-voxel velocity standard deviation (IVSD), or variance, can be estimated from the same 4P flow encoding scheme but instead from the magnitude differences in the data [61]. The IVSD in the three main coordinate axes can be used to predict the turbulence strength (or turbulence kinetic energy, TKE) within each voxel [60]. This acquisition scheme has recently been extended by velocity encoding along six non-collinear axes according to the vertices of an icosahedron (referred to as ICOSA6) to also acquire the three covariance quantities, enabling the reconstruct of the complete second-order symmetric tensor (a 3×3 matrix) of the statistical

turbulence stresses [92, 112], called the Reynolds stress tensor. The ICOSA6 sequence originates from MRI-based diffusion tensor imaging (DTI) [209], where six encoding directions have shown to be optimal [94]. Compared to the conventional 4P method, the ICOSA6 4D Flow MRI method requires three additional velocity encoding acquisitions, essentially adding 75% more scan time. However, a recent study has demonstrated that these schemes can be pushed down to around 10 min using sophisticated data under-sampling [247], a time-frame that may be more practical in a clinical setting.

Measurements using 4D Flow MRI are still mostly in the clinical research phase but have shown plenty of potential for cardiac and vascular flow-mediated disease assessments as well as general hemodynamics understanding [102]. To-date many different MRI-based hemodynamics descriptors and surrogate markers have been derived with the attempt to improve clinical therapeutic decisions-making, such as quantifying static flow region in aneurysms [265], abnormal aortic valve flow displacement (flow eccentricity) [103], turbulence-induce wall effects [264], intraventricular and vascular TKE assessment [262, 128], and for improving turbulence-related pressure losses as well as blood damage predictions [59, 87, 86]. 4D Flow MRI data have also gained popularity for improving patient-specific numerical modeling inputs, such as inflow velocity profiles [79, 166], intraluminal wall motion [127], and have occasionally been used for validation procedures (e.g. [130, 12]).

Patient-specific CFD

Prior to Isaac Newton and the introduction of calculus (differentiation and integration) in the 17th century, fluid dynamics was merely studied through experiments. With the addition of the new laws of motion mechanics, however, the first crude theoretical approximations of fluid motion could be solved. In the middle of the 19th century, the Navier-Stokes equations were presented (Eq. 1 and 2), which provided the first accurate theoretical description of general fluid flow motion. This insight improved the, at the time, simple theoretical/empirical models, but the equation's practical utility for more complex problems were limited. However, with the ongoing development of high-speed digital computers and numerical algorithms in the middle of the 20th century, numerical approximations of more realistic physical flow problems could be obtained, and the field of computational fluid dynamics, or CFD, was born. Still, it was not until the 1990s that the computer performance (speed, storage, memory, etc.) became sufficient to solve more practical scientific as well as engineering fluid flow problems, since CFD simulations typically required repetitive iterations of millions of numerical operations due to the high degrees-of-freedom (which in essence would be impossible with desk calculators). In simple terms, CFD can be viewed as the analysis of fluid flow systems (mass transfer, pressure and velocity fields, etc.) by means of computer-based numerical simulations of the governing differential equations, or as John D. Anderson Jr. (1995) stated:

"fluid dynamics is the art of replacing the integrals or the partial derivatives (as the case may be) in these equations with discretized algebraic forms, which in turn are solved to obtain numbers for the flow field values at discrete points in time and/or space"

Thus, in contrast to continuous field functions, i.e. analytical/exact solutions (or closed-form mathematical expression) of the differential equation that gives an infinite continuum of values in the investigated domain (which even for simple 3D flow problems is yet to be solved), CFD only provides discrete solutions of the flow field at a limited resolution. With extra constitutive equations, CFD also allows for additional analysis of e.g. heat transfer, transport of various agents, chemical reactions, multiphase mixing/phase transfer, and fluid-solid interaction.

The earliest CFD codes were primarily for research purposes but have in the recent decades expanded into a wide range of applications in different fields such as aerospace, automotive, biomedical, environment, electronics, chemical processing, hydrology and oceanography, meteorology, marine, oil and gas, hydrodynamics, thermal management, construction/architecture wind farms and thus virtually everything that involves fluid motion. Unlike experimental investigation, CFD simulations provide superior (complete) details of the flow variables, are usually less expensive (and faster), allow for extensive parametric studies (e.g. important for optimization), can be applied at any scale (geometry size), and can easily be used to study "what-if-scenarios" (failures, etc.). However, CFD methods are also accompanied by many downsides

related to the accuracy and reliability associated with the errors/uncertainties in the modeling procedure and input parameters. The output result inaccuracies, therefore, typically need to be quantified within the CFD model itself (i.e. model verification) and against real-world (or trustworthy) data (i.e. model validation). Therefore, it is rational to view this relatively new discipline as a complementary tool. Presumably, there will always be a need for some level of experimental evaluation/validation procedures even in the future, as multidisciplinary simulations of a complete system with all its complexities (e.g. entire aircraft or entire vascular system) would either be too computationally expensive and/or impossible to model entirely. CFD simulations are, thus, always constrained to some system boundary (domain-of-interest) as well as the necessity of including various physical simplifications/assumptions compared to the real-world application.

The first attempts to perform CFD modeling of patient-specific blood flow occurred in the late 1990s (e.g. [121, 143, 158, 231]), by cross-pollination between medical imaging and CFD techniques. Image-based CFD, or computational hemodynamics as the field sometimes is called, essentially extracts patient-specific anatomy and flow information from a single or a mix of measurement modalities (e.g. MRI, CT, ultrasound, etc.), which is used in a series of pre-processing steps to construct the computational model.

This chapter will start by introducing the conventional steps involved in CFD modeling. The following chapter will address the framework associated with the patient-specific CFD models used in this thesis. Last, some important procedures on how to evaluate the general quality of numerical simulations will be explained.

3.1 General CFD methodology

In the core of every CFD program lies a large set of numerical algorithms that are programmed to find an approximated solution to the governing flow equations on a discretized domain, given proper prescribed conditions. A CFD practitioner typically needs to walk through three main steps, i.e. pre-processing, solver, and post-processing, when analyzing fluid flow problems, and is often facilitated by a graphic-user-interface.

3.1.1 Pre-processing

The pre-processing part concerns all the preparatory steps needed to define the computational settings of the CFD model. Here, the first steps are to create (limit) the physical domain of the fluid flow region for the CFD calculations, i.e. the computational domain. This typically involves creating a representable CAD-geometry from scratch or adjusting/simplifying (trimming, extending, smoothing, etc.) a preexisting one. The next step is to create a mesh, i.e. dividing the fluid domain into a large number of cells (a grid of elements, or mesh) at which the fluid flow variables are solved. In general, higher cell density will result in a more accurate flow solution but also demands more computational resources. The mesh can be constructed manually or automatically scripted using an applicable meshing software, where different cell types (e.g. structured hexahedral or unstructured tetrahedral cells) may be chosen depending on the particular flow case at hand. Mesh generation is one of the most important craftsmanship within CFD, where factors like cell density and quality will play an essential role in determin-

ing the accuracy of the fluid flow solution, which typically are evaluated using mesh verification procedures (Sec. 3.4). In general, extremely small isotropic cells would be ideal for resolving all flow details; however, for common flow problems, this approach would lead to unrealistically high computational costs even for supercomputers. Therefore, it is common practice to apply a heterogeneous mesh distribution, using the finest cell densities only in the direction of rapid flow variations (i.e. large gradients), including flow-feature-driven (adaptive) cell refinement/coarsening to streamline the mesh efficiency further [7].

After meshing, the model needs to be assigned with proper physics, e.g. the fluid material properties (density, viscosity, etc.), and whether the flow, for example, should be treated as steady or transient, laminar or turbulent, Newtonian or non-Newtonian, and if thermal effects are essential. If the flow is known to be turbulent, most CFD codes resort to additional models that approximate the impact from (all or parts of) the turbulent motion onto the main flow (i.e. turbulence models). At the final stage, the computational domain also needs well-defined physical boundary conditions (BCs) and initial conditions, which are the driving mechanism for the flow solution within the fluid domain. In essence, a CFD solution can be viewed as an extrapolation of the BCs into the interior cells of the domain; similar to numerical predictions of weather forecasts that fundamentally are dictated by measured data applied to the external boundaries of the computational domain (only here the mesh cells are in the scale of kilometers). Also, in a piping system, all bounding surfaces (or related mesh cells) need to be assigned with proper physical representations, such as the location and conditions of the wall (stationary, no-slip, etc.), inflow (mass flow rate, etc.), and outflow regions (static pressure, etc.). These boundary conditions need to be incorporated in a more simplistic form compared to the real physical state, often due to low resolution (or lack of) experimental flow data at these locations, including possible limited implementation capabilities in the used CFD program. Therefore, it is common praxis to position these boundary conditions far away from the investigated region-of-interest (ROI).

3.1.2 CFD solver

It is through the CFD solver the numerical solution is obtained and for large-scale computations typically implemented on a high-performance supercomputer. Here, a discretized version of the governing flow equations, along with extra transport equations (such a turbulence models), are solved in each cell (called a control volume, CV) in the domain through algebraic expressions. For incompressible flow, we have four equations (the continuity equation and three momentum equations) and four unknown variables (three velocity components and pressure); thus, the system can be solved. The far most common discretization technique within the CFD community is called the finite volume method (FVM), which applies volume integration over each CV, and respectively term in the N-S equations (Eq. 1 and 2)¹. Here, the computational nodes (points) sits in the center of the CV, i.e. where the flow variables are stored, and thus represent the volume-averaged value.

For gradients (derivatives), such as convection and diffusion term, the volume integration

¹Besides the FVM, other discretization methods can be used to solve the governing flow equations, such as the FEM (finite element method), FD (finite difference method), and the SEM (spectral element method), including non-continuum CFD approaches like the LBMs (lattice Boltzmann methods) where the kinetics of fictive particles on a lattice is solved to mimic the fluid motion.

can be transformed to surface integrals over the CV faces using Gauss's divergence theorem. The face values (i.e. spatial gradients or fluxes) are approximated by different interpolation schemes using neighboring nodal values and are techniques that play an important role for the solution accuracy².

Thus, the cell-centered transport (of momentum, energy, etc.) due to convection and diffusion is estimated as a summation of all fluxes over the CV faces surrounding the node. The remaining terms in the integrated equations are treated as sources/sinks. A favorable advantage with the FVM is that net flux over the CV is always balanced, i.e. mass, momentum, and energy are always locally conserved, independent of cell type and size. When applied to every mesh cell of the computational domain, with the addition of enforced boundary conditions along the domain borders, a system of linear algebraic equations can be established, one for each mesh cell. By assigning proper initial conditions to each cell³ this huge set of equations can be solved for the unknown variables iteratively until the flow field does not longer change at every cell location and fulfills the discretized equations (mass and momentum, etc.) to a specified tolerance. The latter is known as iterative solution convergence and is typically estimated from the residuals of the approximated equations, i.e. the imbalance between the left and right-hand-side of the governing equations (one residual per solved equation). In addition, this convergence can also be complemented by monitoring specific flow-related parameters. Proper iterative solution convergence is typically needed for result reliability.

The FVM generally uses two types of solution procedures, called segregated or coupled method. The CFD solver associated with the current thesis employ the coupled procedure⁴, meaning that the flow equations are solved simultaneously (for u , v , w , p), in each cell as a single system, and repeated for all cells in the domain. The calculation sequence is then continued by solving any additional flow-dependent transport (scalar) equations. Hereafter, the process is repeated over many iterations, using the old flow solution from the previous iteration as the new input, and so on until the solution hopefully convergence.

For unsteady flows, the time derivative term in Eq. 2 is non-zero, and the fluid flow solution needs to progress in time. In most CFD codes, the time-stepping approach uses an implicit discretization technique, which in contrast to explicit-type procedures⁵ are unconditionally stable, i.e. the time-step size will generally not induce solution instability issues, such as solution wiggles, divergence or solver failure, during the calculations. However, from a solution accuracy perspective, it is still important to specify a time-step size that fits the temporal variations in the flow field, such as turbulent fluctuations. In order to capture these timescales, the time-

²The solution accuracy is highly affected by the formal order of accuracy of the adopted discretization schemes. First-order accurate schemes (such as the Upwind scheme) are e.g. known to be very dissipative (adding false diffusion) and consequently may dampen important flow characteristics. For general purpose CFD simulations, second-order or higher discretization schemes are therefore recommended.

³A CFD simulation need to start from something, i.e. all dependent flow variable needs a value in each cell. This can be done automatically by an ad-hoc field, or e.g. using a previously obtained CFD solution.

⁴The segregated solver, however, is the most common technique, where the governing equation is solved one by one, separately for all cells. Due to the uncoupling nature of this procedure, additional solution methods (equations) are needed to conserve local mass flux balance (via pressure-velocity coupling algorithms).

⁵An explicit numerical solver approximated the current solution field solely based on older (previous) solution fields and is therefore limited to very small time-steps to avoid solution instabilities. An implicit solver, however, continuously update the solution variables in the neighboring cells within the time-step, thereby avoiding these stability issues.

step size must be less than it takes for the wave of information to travel between two adjacent mesh-cell, which is typically estimated by the so-called Courant-Friedrichs-Lewy (CFL) criteria (Sec. 3.2.5 and Eq. 9). A too-large time-step may also lead to wrong overall flow predictions. Time-stepping procedures can also be advanced using constant or varying (adaptive) time-step size, depending on the nature of the flow. Unsteady flow problems are much more computationally expensive than steady flows, as iterative convergence needs to be met at every time-step, where CFD simulations can easily involve tens or even hundreds of thousands of time-steps before certain flow-related statistics (e.g. temporal mean and variance) are well converged.

3.1.3 Post-processing

Simulation data can often be displayed using high-fidelity software graphics to highlight specific physical characteristics, e.g. scatter graphs (X-Y plots), streamlines, vectors, coherent flow structures, and contours plots. As a result of these often colorful outputs, CFD is sometimes used as a synonym for "Colorful Display", while within the biofluid community, sometimes entitled "Colors For Doctors" [221]. Post-processing is the art of extracting and transforming raw data to demonstrate/facilitate the similarity and differences of the results using appropriate techniques incorporated in figures, tables, animations, etc., which could be done both quantitatively and qualitatively. For more straightforward processing and rendering assessments, user-friendly commercial programs are often sufficient, while for more advanced post-processing, open-source packages such as Paraview (Sandia National Labs, Kitware Inc., Los Alamos National Labs) may be preferable.

3.2 The patient-specific CFD models

This section will provide some general insights behind the rationale of the patient-specific CFD modeling methods related to the papers within this thesis, which generally were based on state-of-the-art practices within the computational hemodynamics community (e.g. [32, 232, 225]), commercial software guidelines, as well as in-house experience.

In all studies, the input data have been acquired from the same patient, a 63-year-old female diagnosed with aortic coarctation restenosis (Fig. 14a), including a malformed (hypoplastic) aortic arc and post-stenotic dilatation. This recurrent narrowed region was widened using catheter-guided balloon angioplasty to relieve the extra resistance to flow. Both MRI measurements and catheter-based pressures were obtained just before the intervention, and after a two-year follow-up assessment, hereafter also referred to as the pre-op and follow-up case, respectively. The cross-sectional percentage narrowing (degree of stenosis) was 65% before the intervention and 50% at follow-up; thus, a substantial recurrent CoA still prevailed after treatment (Fig. 14b). However, despite the small vessel dilatation, the peak systolic pressure drop was reduced from 22 mmHg pre-op to 8 mmHg at follow-up, categorizing these CoAs as severe and mild, respectively [153]. This substantial pressure recovery in the follow-up case could be explained by the significant reduction in measured turbulence intensity levels [128].

Figure 14: Maximum intensity projection MR angiogram with the extracted computational domain, (a) before intervention (pre-op) and (b) after two-year follow-up. Abbreviations are: ascending aorta (AAo), brachiocephalic artery (BCA), left common carotid artery (LCCA), left subclavian artery (LSA), coarctation of the aorta (CoA) and descending aorta (DAo). The imposed centerlines highlight the local intraluminal mean diameter. Adapted from [5].

3.2.1 Image-based geometry and flow conditions

For the reconstruction of the patient-specific computational domain, including necessary BCs, three main steps were required (Fig. 15): *i*) MRI acquisition, where the patient-specific image data was obtained, *ii*) image analyzes, where the physical bounds of the artery and flow conditions were extracted using sophisticated segmentation algorithms, and *iii*) necessary adjustments to improve/ease the meshing processes and BCs representation.

The anatomical and fluid flow data were acquired from a clinical 1.5 T MRI scanner (Philips Achieva, Philips Medical Systems, Best, the Netherlands), both within and expiration breath-hold during resting conditions. Pulse-averaged images (angiograms) were reconstructed from contrast-enhanced magnetic resonance angiography (MRA), obtained by a gradient-echo sequence with a spatial resolution of $0.88 \times 0.88 \times 4 \text{ mm}^3$ pre-op and $0.88 \times 0.88 \times 2 \text{ mm}^3$ at follow-up. Thus, the follow-up MRA data had a twofold higher voxel density in the out-of-plane direction. The angiograms did not entail any vessel movement (e.g. compliance, translation/rotation of the aorta). Blood flow measurements were obtained through a cross-sectional plane (perpendicular to the main flow direction) that intersected the proximal ascending aorta as well as descending aorta using 2C PC-MRI. The in-plane spatial resolution was $1.56 \times 1.56 \text{ mm}^2$, or roughly 20×20 voxels across the AAo cross-section, while the temporal resolution was reconstructed to 40 time-frames per cardiac cycle. These acquisitions were controlled by retrospective gating to a vector cardiogram. In-house correction algorithms were used to adjust noise related to background contaminations (eddy currents and Maxwell effects). More MRI acquisition details can be found in the Supplementary Materials (SM) of Paper III.

A freely available medical image analysis software called [Segment](#) [97] was used to reconstruct the multi-slice MRI image stack to a 3D surface of the vascular geometry (a process known as segmentation), as well as extraction of the 2D flow conditions. In the segmentation analysis, the intensity of the image's pixels is associated with different material properties, which can be fine-tuned by filters (non-linear speed functions) to improve the contrast between the blood flow region (lumen) and surrounding tissue. Through a semi-automatic segmentation algorithm, using a gradient-based level set tracking technique, a 3D surface region can be iter-

actively grown out from one or more seed-points placed within the blood volume to the edge of the lumen, where it stops as the intensity gradients maximize.

Figure 15: Schematic view of the reconstructed image-based patient-specific geometry and flow conditions. The anatomical and flow image-data was obtained from magnetic resonance angiography and 2D PC-MRI, respectively. Different segmentation techniques were thereafter used to extract the three-dimensional physical lumen region (red) as well as the in-plane-average pulsatile flow rate across the AAo and DAo P-P intersection and region-of-interest (green curve). The output stereolithography (STL) surfaces were adjusted to attain a well-defined computational domain. The MRI scanner image was adapted from “Wikipedia”, provided by Blausen Medical Communications, Inc., and licensed under [CC BY-SA 3.0](#).

The output is a stereolithography (STL) reconstruction of the arterial surface, represented by tens of thousands of small anisotropic-shaped triangles. While this approach can capture complex topological features, the technique can also give a relatively rough surface finish due to the limited MRI resolution, particularly in the out-of-plane direction where the voxels are most stretched. A volume-preserving (Gaussian) smoothing filter was applied to allow for a more representable surface finish, attempting to minimize the voxel-related patterns. The smoothing level was determined based on a trade-off between removing these unwanted wall features and preserving important flow-dictating topological characteristics (e.g. curvatures, stenosis shape, etc.). In a patient-specific CFD study of eight healthy aortas [194], the used semi-automatic segmentation approach showed good agreement against a presumable, more exact but also more time-consuming manual segmentation strategy.

Another, more commonly used open-source tool for image-based segmentation is the Vascular Modeling Toolkit (**VMTK**), which rely on a less operator-dependent level set method and sophisticated smoothing algorithms that can preserve important geometrical features [7]. Here, the 3D surface can be derived by wrapping maximum fitted spheres along the vessel’s center-lines, defined from an intraluminal Voronoi diagram, which reconstructs the lumen boundary by smooth tube-like structures with well-defined intersections. These features may be attractive to minimize surface artifacts related to highly anisotropic MRI voxels.

The Segment tool used in this thesis also enabled the extraction of vessel flow profiles from the 2D PC-MRI data and quantification of conventional parameters, such as volume flow rate, cardiac output, and peak velocities. Here, a different semi-automatic method was used to find the cross-sectional ROI within the 2D slice (Fig. 15, e.g. AAO and green curve), providing both time-resolved vessel flow profiles and the cross-sectional-averaged net flow rates. In this thesis, the latter option was used. The cardiac output was 5.0 L min^{-1} pre-op and increased to 5.6 L min^{-1} at follow-up, while the pre-stenotic Reynolds number and Womersley number in the DAO was similar in both cases (temporal-mean $Re \approx 950$, and peak $Re \approx 3500$, $\alpha \approx 26$, also see SM in Paper III).

Prior to the meshing stage, segmented geometries need certain adjustments, such as removing undesirable vessels, trimming/truncating the inlet/outlet areas in order to impose the boundary conditions. Here, it can also be relevant to artificially extend certain vessels that have been inadequately captured by the MRI measurements to avoid complex flow features (e.g. backflow) close to these boundaries. Boundary conditions are also assigned under various assumptions that may affect the near-boundary flow accuracy and should, therefore, preferably be positioned at a safe distance away from the investigated flow ROI. In this thesis, all inflow and outflow areas were trimmed and assigned with a flat wall-normal surface, using the geometry adaptation interface in ANSYS ICEM CFD (ANSYS Inc, Canonsburg, PA, USA) and vessel centerlines extracted from the VMTK. The poorly resolved LCCA segment was smoothly extended several diameters along the outlet normal direction. For simplicity, the LSA segment was also removed in both CoA models, assuming the flow rate out of this vessel to be small enough not to have any major impact on the distal flow characteristics. Furthermore, considering the small size of this vessel ($\sim 4 \text{ mm}$ in diameter), MRI-based flow and geometry data will be highly inaccurate, which arguably may add more uncertainties into the CFD model.

3.2.2 Meshing procedure

In order to solve the governing flow equations, the computational domain needs to be divided (discretized) into small volumes (cells, elements), which is done using suitable meshing procedures. In all studies related to this thesis, the computational mesh was constructed with hexahedral elements using an O-grid blocking meshing approach within ANSYS ICEM CFD. This meshing strategy provides a regular node connectivity pattern between efficiently packed cells (Fig. 16b), sometimes called a structured mesh. Compared to its counterpart, an unstructured mesh with irregular node connectivity (such as tetrahedron cells), hex meshes generally produce higher-quality cells with better resolution per given volume. However, unstructured mesh strategies can be made more efficient by e.g. using flow-aware cell-refinement adaption techniques.

In essence, the hex meshing process begins by splitting the domain into several blocks (core and near-wall blocks in an O-grid structure), where the edges of each block are assigned with a grid point distribution that represents the element corners (vertices). A desirable mesh distribution can be constructed by adapting the number of O-grid blocks, grid density, and adjusting the edge angles. In these studies, around 100 blocks were utilized to guide the mesh resolution of the aortic segments. For complex geometries, this manual work can be difficult and very time consuming (and sometimes impractical) in order to optimize the block distribution, mesh density, and quality of the elements; all of which are important considerations to capture essential

flow details, minimize numerical diffusion (smearing of the results), reduce the computational costs, and improve the robustness/stability of the simulations. The high workload, or lack of automatization of these structured meshing procedures, make these strategies less attractive for extensive case studies, where unstructured meshing methods may be more practical.

In the CoA models, extra mesh density was focused on regions where large flow variations (high solution gradients) were to be expected, such as in near-wall, separating, transitional, and turbulence flow regions (proximal/distal to the stenosis). To resolve the near-wall flow details in the viscous sublayer, the so-called non-dimensional y -plus unit was kept below unity, and the wall-normal cell growth rate kept low. Generally, the maximum growth rate between grid points was limited to 1.2 in the domain, but lower spacing was occasionally used in more complex flow regions. To evaluate mesh-induced solution errors (Sec. 3.4), two different mesh densities were compared for the pre-op case. The coarsest mesh consisted of around 3 million cells (MC), with 52 cells resolving the circumference⁶. For the more resolved case, an additional 2.5 MC were added, with a circumferential resolution of 70 cells⁷. Using the ICEM Quality statistics (see Paper III, SM, p. 6), 99% of the cells had a quality above 0.75, where 1 is considered ideal, suggesting a high-quality mesh. In perspective, a Quality above 0.1 to 0.2 is generally recommended prior to any simulation, but higher may be warranted depending on the flow case, but at the same time could be very challenging to attain. A similar mesh quality was attained for all CFD models.

3.2.3 Boundary conditions

There are various ways that BCs can be imposed for patient-specific CFD modeling, where several assumptions need to be considered in comparison to the real *in vivo*⁸ conditions. In the computational hemodynamics community, there exist general [232] as well as vessel-specific [32, 225] guidelines on BCs implementation; however, the choices are also largely dependent on the type and availability of measurement data, ROI, computational resources, and purpose of the study. The upcoming sections will summarize the BCs assumptions used for the CoA models, namely the wall, inlet and outlet conditions (Fig. 16a). More details can be found in the SM of Paper I–III.

Rigid Wall. The discretized wall was modeled as a rigid, impenetrable boundary with a no-slip condition (i.e. the fluid come to rest at the wall), hence the motion of the vessels was not included, which is common praxis for general patient-specific CFD modeling [223]. Realistic wall dynamics can, however, be important to consider at certain vascular regions where the coupling to the flow is believed to play a vital role [131, 195]. A non-compliant wall also inherently limits the possibility of studying realistic pressure and flow waveforms, as no phase shift can exist between different arterial sites due to the incompressible fluid. This assumption can also be justified by reviewing the 2D PC-MRI data, which indicated small in-plane wall motion and cross-sectional area change at several locations across the DAo (including the CoA

⁶In Paper II, a 1 MC mesh was also evaluated (see SM, p. 5), but was not consider further due to the model substantial underestimation of the turbulence levels compared to the more refined cases.

⁷Referred to as 5.5 MC in Paper I, 5 MC in Paper II, and 6 MC in Paper III–V.

⁸*In vivo* is Latin for "within the living" and are herein used to described the true (real) processes occurring inside a living human.

region); suggesting the wall dynamics to play a minor role in the flow predictions in this case. Indeed, this rigidity (arterial stiffening) is a common long-term symptom among CoA patients [89] and a general feature observed during aging.

Figure 16: Schematic representation of the applied (a) boundary conditions and (b) the computational mesh (3 million cells). The AAo inflow was set by the MRI-based pulsatile flow rate, assuming a flat profile, while a square law controlled the outflows in the aortic arc vessels. The wall was assumed rigid using a no-slip condition. At the DAo outlet, a zero-pressure condition was assigned. The mesh was constructed by high-quality hexahedral cells using an O-grid structuring approach, where different cell densities were used for the different papers herein (see table). In the used CFD solver (ANSYS CFX), the flow variables are stored in the eight corner-nodes (vertices) of the hexahedron cell and correspond to cell-center values computed from a reconstructed control volume around each node using a dual mesh solver approach.

In aorta, the largest vessel movement is situated in the AAo, with relatively large radial and translating/rotation due to the movement of the attached heart. These wall dynamics can be incorporated by prescribing the surface mesh motion derived from 4D Flow MRI data [127], which do not require much extra computational overhead but can be practically challenging to perform, partly due to the low-resolution input data. Another way is to model the wall motion using fluid-structure interaction (FSI), e.g. by a arbitrary Lagrangian-Eulerian method where the transmural pressure regulates the displacement of the vessel wall, and vice versa in a fully coupled system of equations that is solve iteratively every time-step. The upside is that FSI methods can be used to simulate "what-if scenarios", while the prescribed wall

motion is more limited and can essentially only assess the current hemodynamics state, but at the same time also is very computational expensive due to the additional large degree-of-freedom, especially for more high-fidelity CFD simulations related to turbulent flows. As the pressure wave dynamics govern the local wall motion, FSI methods also need more complex outlet boundary conditions (so-called reduced-order models, e.g. 1D vascular networks and/or lumped Windkessel models) that attempt to mimic the pressure response from the truncated distal vascular tree. However, many of these modeling steps require gross/generic assumptions, including ad-hoc input parameters, which may contribute to substantial solution uncertainties.

Inlet and outlet conditions. Under a rigid wall assumption, the driving mechanism for transporting the blood can only come from the inflow and outflow BCs, unlike a compliant vessel where the residual wall-stresses assist during flow ejection (Sec. 2.1). For internal flow problems, maybe the most common and robust BC combinations are to apply a velocity (flow rate) at the inlet and static pressure at the outlet. Indeed, for multiple outflows, like the aorta, at least one outlet needs to be assigned with a reference pressure for the CFD model to be well-posed.

For patient-specific CFD, inlets are typically imposed with a time-varying Dirichlet-type BCs (i.e. specified velocity values) for pulsatile simulations, either as a *i*) velocity profile interpolated directly from the MRI measurements (including all velocity components) or approximates as a uniform profile (flat or plug shaped), or fully developed profile (parabolic or Womersley shaped), or in a more simplistic way as a *ii*) cross-sectional averaged flow rate condition represented by a plug-shaped (completely flat) inlet velocity distribution, which is a common assumption in the AAo [232]. The latter inflow option was used in all CFD studies in this thesis, with the pulsatile flow rate derived from the 2D PC-MRI measurements. For simplicity, the diastolic part of the cardiac cycle was replaced by a low constant flow rate, which was believed to enhance the computational efficiency without having a notable impact on the predicted flow characteristics. Some studies have shown that more realistic inlet conditions (including secondary flow features and even valve morphology) are important to capture local flow features [79, 249]; however, in our cases, we believe this impact to be small in the downstream domain-of-interest. Here, it is more rational to assume that the "memory" of the inlet condition essentially will be lost at this point, owing to the substantial geometrical-driven flow changes prior to the post-stenotic region, including any imposed inlet turbulence intensities typically accompanied with these diseases. For example, in patient-specific carotid artery CFD modeling an entrance length of more than three vessel diameters have shown to have minor impact on the more distal flow predictions [99].

At the DAo outlet, a conventional used (zero) static pressure condition was assigned, where the absolute level is irrelevant as incompressible flows only are dictated by the local pressure gradient (Eq. 2). In the bifurcating vessels of the aortic arc, no 2D PC-MRI measurements were available. Therefore, the BCA and LCCA outflows were determined by an empirical relationship [263], which scales the AAo inlet flow rate based on a squared ratio between the parent and bifurcating vessel diameter. With this square law, 36% and 7% of the AAo flow rate was divided into the BCA and LCCA outlets, respectively. The remaining flow rate corresponded well with the MRI-measured peak flow rate in the DAo. However, as the mass flow is instantaneously conserved in this rigid segment, the natural compliance-induced mismatch between the inlet and outlet flow waveforms (as noted in the MRI data) cannot be reproduced under these assumptions. There are ad-hoc ways to adjust for some of these issues, e.g. by

making corrections based on measured flow difference between parent and bifurcating vessel [227]; however, it is not clear that these changes invoke more realistic physiological conditions as long as the CFD model is assumed to be rigid [223]. The arc outflow BCs were implemented as time-varying uniformed velocity distribution normal to the surface, which is a robust way to minimize solution convergence issues related to possible complex flow features close to these outlets. This assumption is obviously not a good representation of the real local flow conditions in the vicinity of these outlet regions, as the condition assume fully developed flow. On the other hand, it avoids additional computational costs accompanied by further extending these segments. The main purpose with these outflows was to provide realistic flow characteristics (especially the Reynolds number) towards the DAo and CoA region.

3.2.4 Blood model

As note previously (Sec. 2.2), blood has shear-thinning, viscoelastic and thixotropic properties. It is often assumed, but still debated, that flow in larger arteries primarily is driven by high shear rates (typically above 100 s^{-1}), or low constant viscosity, and therefore can be regarded as a Newtonian fluid [223]. However, real blood flow is susceptible to a wide range of shear rates due to its pulsatile nature and possible secondary flow features (e.g. separation and recirculation regions), which presumably would markedly increase the blood viscosity as the local shear rate declines rapidly.

For the unforeseeable further, the modeling of blood rheological needs to be considered under simplistic assumptions compared to the actual response, which roughly would involve simulating trillions of moving and interacting RBCs in large artery segments⁹, which would be impractical with today's computational capabilities. There are many ways that blood can be modeled using various constitutive equations [259]. The most straightforward and most commonly used approach, also used in this thesis, is to consider the fluid as a homogenous mixture (continuum), where the apparent blood viscosity is determined by the local shear rate using empirical functions. These relations have been derived from a variety of experiments of bulk blood rheology under simple flow assumptions and specific shear rates. Additional models have been proposed to also incorporated the effect from RBCs concentration levels in the flow field [254]. Also, other more complex rheology models have been developed, such as multiphase models, including viscoelastic effects, or mesh-free particle-based methods (such as LBM); however, thus far only used for flow simulations in smaller arteries.

In all investigations, the apparent blood viscosity μ were governed by the non-Newtonian Carreau model [37, 42] (Fig. 17)¹⁰:

$$\mu(\mathbf{x}, t) = \mu_{\infty} + (\mu_0 - \mu_{\infty}) \left[1 + (\gamma\dot{\lambda})^2 \right]^{(n-1)/2} \quad (8)$$

where $\dot{\gamma}(\mathbf{x}, t)$ is the computed shear rate, $\lambda = 3.313$ the relaxation time, $n = 0.3568$ the power law index, $\mu_0 = 0.56 \text{ Pa s}$ and $\mu_{\infty} = 0.00345 \text{ Pa s}$ the viscosity asymptote for the low and high shear rates, respectively. This shear rate dependent viscosity models is one of the most widely

⁹RBCs consists of 4 to 6 million per mm^3 for men, which roughly would correspond to half a trillion cells in the aortic computational domain used in this thesis.

¹⁰Note, there is a typographical error (plus and minus sign) in the Carreau model equation presented in the SM of Paper I.

Figure 17: Apparent blood viscosity $\mu(\mathbf{x}, t)$ as a function of shear rate $\dot{\gamma}(\mathbf{x}, t)$ for the Carreau non-Newtonian model (Eq. 8) versus the popular high shear rate Newtonian assumption.

used within the computational hemodynamics community and have shown good agreement against experimental rheology data [42, 110]. As noticed in Fig. 17, the Carreau model mimics the Newtonian behavior of blood roughly above $\dot{\gamma} > 100 \text{ s}^{-1}$.

There are several studies that have indicated the importance of including shear-thinning non-Newtonian characteristics into patient-specific CFD modeling (e.g. [192, 163, 240, 141, 110, 117]), where noticeable impact on the near-wall and turbulence-transition flow characteristics have been observed compared to a standard Newtonian assumption. However, some studies have also suggested the non-Newtonian contribution to be small compared to other modeling uncertainties [134, 223, 115]. Strain-dependent viscosity models also ignore the thixotropic characteristics of real blood and instead assume that the RBCs aggregate instantaneously at lower shear rates, leading to a general overestimation of the non-Newtonian behavior (viscosity thickening) throughout the cardiac cycle [223]. This potential drawback was recently highlighted in several patient-specific aortic aneurysm CFD models [10], where the blood flow residence-time (RT) was incorporated into the viscosity model. Findings showed that only a few fluid regions were susceptible to a combination of both low shear and enough RT to promote RBCs aggregation. The rheology analyzes within the current thesis showed slight turbulence dampening effects owing to the added viscosity; however, without any substantial impact on the general flow characteristics (see SM, Paper I–III). These findings suggest that a Newtonian regime most likely would have been sufficient in the investigated flow cases. Nevertheless, for future studies it may be warranted to include more “flow-aware” rheology models, such as tracking RBCs concentrations [254] and flow stasis [10], including patient-specific hematocrit levels.

3.2.5 CFD solver and solution strategy

The CFD solver used for all computations in this thesis was ANSYS CFX (ANSYS Inc, Canonsburg, PA, USA), a fully coupled, implicit, element-based FVM solver commercially used for flow simulations of general-purpose engineering problems. The software choice was foremost based on general in-house experience, available licenses, previous use for patient-specific CFD

simulations, and coupling to more advanced post-processing procedures. However, the utilized CFD framework in this thesis is not unique to the current solver but could be applied to most of the commonly used CFD programs within the community, such as ANSYS Fluent, STAR-CCM+, or OpenFOAM. The numerical approach for the spatial and temporal discretization of the specific terms in the governing equations largely depend on the type of intended CFD simulations, which often comes with "best practice" modeling guidelines. These recommendations were, in general, followed in the thesis CFD studies and will briefly be presented hereafter.

For the large eddy simulations (Sec. 3.3.2), the non-linear convective term was spatially discretized by a second-order central difference scheme, while hexahedral finite-element shape functions approximated the diffusion and pressure gradient terms. In CFX, these functions are generally used to calculate any variable variations within the mesh cell (from the nodes), such as gradients at integration points and geometrical attributes. As the system of equations here is solved in a coupled manner, no explicit staggered velocity-pressure coupling scheme is needed. However, in certain scenarios, these co-located grid methods may induce pressure-velocity decoupling due to the central difference scheme, which manifests as checkerboard pressure patterns in the flow field and thus contribute to local mass-conservation imbalances. To minimize these effects, the commonly used Rhie-Chow interpolation scheme was adopted [196], which counteract these issues by including higher-order pressure derivatives into the continuity equation. For the URANS simulations (Sec. 3.3.2), the convective term was approximated by the so-called High-Resolution scheme, a hybrid discretization scheme that is essentially second-order accurate and ensures bounded flow properties (i.e. avoiding unphysical overshoots/undershoots).

The transient term was approximate by a second-order backward Euler scheme, which is a robust, implicit, and second-order accurate in time. Here, the temporal resolution was governed by the CFL number:

$$\text{CFL} = \frac{U \Delta t}{\Delta x} \quad (9)$$

where U is the fluid velocity, Δt the time-step size, and Δx the mesh cell size. A general rule-of-thumb is to keep the CFL number close to unity to ensure that the flow information does not travel further than the cell length-scale over one time-step. However, depending on the nature of the flow, higher CFL criteria may still capture the essential transient flow details while also reducing the computational costs (as shown in this thesis). To also minimize the number of time-steps required per cardiac cycle, a CFL-based adaptive time-stepping approach was adopted to march the pulsatile CFD simulations forward in time. This was initially done using the built-in adaptive scheme within CFX and bound the time-step size limit according to a maximum $\text{CFL} < 1$ or $\text{CFL} < 5$, implying that the local CFL condition will not exceed 1 or 5, respectively, anywhere in the computational domain during the cardiac cycle. The output time-stepping profiles for each simulated case were thereafter slightly adjusted (smoothed) and instead prescribed to make the procedure more cost-efficient. The CFD results showed that, as expected, the time-step size was dictated by the highest axial velocities located in the CoA center, whereas the instantaneous CFL numbers in the post-stenotic regions were overall smaller. In fact, for the maximum $\text{CFL} < 5$ case, the domain averaged CFL number was an order of magnitude lower (0.3 to 0.5). Peak flow sensitivity analyzes for the adaptive 3MC-CFL5 case showed good agreement against the more restrict maximum $\text{CFL} < 1$ criteria as well as against

a constant time-step size (see SM, Paper I–III). The temporal statistics from the different pre-op CFD simulations are given in Tab. 1, showing the time-step output range and differences in required steps per cardiac cycle. By only changing to an adaptive scheme, a threefold cost reduction was obtained.

Table 1: Temporal statistics obtained from the pre-op CFD simulations using different time-stepping approaches (CFL criteria’s, including adaptive or constant time marching). Data display the range of the time-step sizes (Δt , in microseconds μs) and number (#) of time-steps per cycle.

	3MC, maxCFL<5 (Adaptive Δt)	3MC, maxCFL<5 (Constant Δt)	6MC, maxCFL<1 (Adaptive Δt)
Δt range, [min, max]	[162, 2000]	162	[20, 771]
# of Δt per cycle	2000	6200	14 000

The iterative convergence errors for the approximated solution of the momentum and continuity equations within each time-step (i.e. the coefficient loops) were estimated by a root-mean-square (RMS) residual over all grid points in the domain. The convergence target was set to a minimum of 3 coefficient loops, an a RMS residual value below $1e-5$, including a global conservation (imbalance) target $< 1\%$ for each transport equation before progressing to the next time-step. The solution progression was also monitored by various local and global flow quantities. Multiple cardiac cycles were simulated to assess the phase-averaged results. The acquired cycle ranges in each paper are explained in Sec. 4 and its impact on various turbulence descriptors in Sec. 4.4.1. In all cases, however, the first five cycles were omitted to minimize the solution influence from the initial conditions set at the beginning of the simulations. During the simulations, data was saved every 0.01 s, corresponding to 100 equally spaced time-steps per cycle in the pre-op case. This sampling frequency was considered sufficiently dense to capture the general turbulence behavior over the cardiac cycle and was also viewed as a practical upper limit for data storage and post-processing procedures. For instance, a phase averaging procedure of 50 cycles (5000 samples) acquired from the well-resolved (6MC) CFD model involved ~ 0.5 TiB of data per vector variable, which for specific post-processing analysis could take over 24 hours to compute.

3.3 Modeling turbulence

Turbulent flow regions are evident by the much richer frequency content in the time-trace of a velocity/pressure signal compared to laminar and transitional flows (Fig. 6 and 12), which if severe enough, may propagate into the surrounding tissue and manifest as audible detectable murmurs. These seemingly random spatial and temporal flow fluctuations are generated by the interaction of an ensemble of 3D turbulent structures, often called eddies or vortices, which in essence can be viewed as moderately coherent flow region [190]. To understand the fundamental principles on how to model these flows, it makes sense first to provide some insight into the general characteristics/dynamics of turbulence.

Figure 18: **(a)** Schematic illustration of a turbulence energy spectrum. The energy spectrum $E(\kappa)$ (units in $\text{m}^3 \text{s}^{-2}$, i.e. kinetic energy per unit mass) shows the contribution of turbulence kinetic energy from the range of wavenumbers κ (unit in m^{-1} , analog to the inverse of the eddies diameter). Energy cascades from the large energy-containing scales (at low κ) to the less-energetic small-scale turbulence structures (at high κ) where the energy eventually dissipates into heat. The $-5/3$ slope characterizes the universal behavior in the inertial subrange, where the energy is transferred through the cascade without major viscous losses. The overlap between the largest and smallest scales lies around $\kappa \approx 1000$. In turbulence modeling, different amounts of this spectrum are resolved physically, requiring more computational resources. For DNS, all turbulence scales are resolved, while for RANS simulations, the effects from all (steady-state) or most (unsteady) of the scales are modeled. For LES, only the energy-carrying scales are resolved, while the impact from the smaller eddies is modeled. In mixed models, RANS is used in the near-wall region, where the scales are small, while a scale-resolving method is used in the rest of the domain. **(b)** Illustration of different filter widths, $\Delta = L/32$ (small box filter) and $\Delta = L/16$ (large box filter), impact on a homogeneous decaying turbulent flow field in a periodic box of size L^3 computed by DNS, signifying the concept of more or less resolved flow structures. Adapted from "Wikipedia", provided by Charlesreid1, and licensed under [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/).

3.3.1 Turbulence energy spectra and scales

In well-developed turbulence, the flow contains a wide range of eddies with different characteristics (length and time scales) that interact in a complex way. To understand this dynamic process it is sometimes helpful to review the so-called turbulence energy spectrum (Fig. 18a) [190], which provides an overview of the eddies kinetic energy with respect their frequency ($f = 1/T$, where T is the eddy time-scale) or wavenumber ($\kappa = 2\pi/\lambda$, where $\lambda = f/U$ is the eddy wavelength). The largest energy-containing eddies (i.e. the integral length scales) obtain their energy from the mean flow (or mean shear in the near-wall region), with a maximum size (or smallest wavenumbers) roughly comparable to the flow geometry (e.g. vascular diameter, or boundary layer thickness) or other forcing conditions. These large-scale eddies will deform and eventually breakup into smaller and smaller scales (or higher wavenumbers) by a mechanism called "vortex stretching", transferring their energy to smaller and smaller eddies until they finally dissipate into internal energy (heat) by the action of viscosity at the so-called Kolmogorov scales¹¹. This decay-process is also known as the turbulence energy cascade, where the input of energy at the largest scales is equal to the output of energy at the smallest scales (i.e. energy dissipation rate). The width of this energy spectrum is largely regulated by the Reynolds number, with a large-to-small length scale ratio (scale separation) roughly following $Re^{3/4}$ [233]. For higher mean Reynolds numbers, more kinetic energy (inertia) will be fed into the cascade, allowing for even smaller Kolmogorov scales to spawn¹² [190].

At the largest scales, the turbulent structures are highly anisotropic (i.e. the flow fluctuations are not statistically the same in all directions), owing to the strong influence from the boundary conditions, and are the leading cause of turbulent mixing of the flow. However, when moving down the energy cascade, to much smaller scales, the turbulence characteristics will naturally attain a more equilibrium state, meaning that the directional fluctuations will be statistically more evenly distributed and less influenced by the anisotropic bulk flow conditions (i.e. the "memory" of the large-scale flow is effectively lost). Again, assuming that the turbulence is well-developed (i.e. having a sufficiently broad energy spectrum), there is a range of scales where the turbulence behavior is essentially universal (i.e. independent of the mean flow features); the so-called equilibrium range consisting of the inertial subrange and dissipation range. In the former range, the inertia forces overshadow the viscous (i.e. a eddy Reynolds number that still is relatively high), meaning that the energy flux from larger-to-smaller scales is mainly due to inertia effects alone. Studies have shown that this universal behavior in the inertial subrange can be described solely based on the energy dissipation rate ϵ and wave numbers κ , according to the famous $E(\kappa) = C\epsilon^{2/3}\kappa^{-5/3}$ relation (Fig. 18a, -5/3 slope) in the energy spectrum derived by A. Kolmogorov in the 1940s [120]. In the dissipation range, the turbulence characteristics are more isotropic and homogeneous, with a generally steeper energy spectrum controlled by both the viscosity as well as dissipation rate.

In realistic patient-specific blood flow, the pulsatile nature of the flow does not permit fully-

¹¹The local Reynolds number based on the local velocity and length scales of these small eddies will approach unity, and hence will start to be dominated by viscous forces. Also, as the eddies get smaller, their vorticity (rotation rate) increases due to angular momentum conservation, resulting in higher velocity gradients.

¹²Generally, the turbulence kinetic energy is transported from large-to-small scales, i.e. the energy goes one way, also called forward-scatter. However, there are also situations where smaller eddies can transfer parts of their energy to larger structures, i.e. a reverse energy flux that often is referred to as backscatter, which is a phenomenon that is difficult to consider in turbulence modeling.

developed turbulence, not even for the severest constrictions [2], and hence why these flow regimes often are characterized as being transitional, conditionally turbulent, or turbulent-like [252, 29]. However, in vivo measurements of turbulence in real blood flow have shown evidence of relatively wide energy spectrums in the vicinity of the most profound turbulent regions at systole [218, 144], including a noticeable inertial subrange. Also, for homogeneous blood-mimic fluids with similar apparent viscosity behavior, there are several flow-realistic experimental [38, 2, 139] as well as CFD [242, 135, 29, 148] studies that have indicated quite broad frequency contents in the post-stenotic flow regions. These turbulent-like flows, however, do not account for the RBCs viscoelastic nature (accounting for roughly 45% of the volume fraction) that could act as a barrier to dampen any flow structures of comparable size [8], which may limit the size of the smallest possible Kolmogorov eddies and thus shorten the energy cascade in comparison to a homogeneous fluid. This dampening effect is not well understood and could have a noticeable impact on the turbulence behavior in the equilibrium range, but is less likely to substantially influence the energy-containing macro-scales of the flow, which often is of main interest when assessing turbulence hemodynamics.

3.3.2 Turbulence models

There are basically three main approaches that can be adopted for CFD modeling of turbulence [9] (Fig. 18), from extremely computational expensive methods that capture (resolve) all or most of the details of the flow, to more affordable but also crude strategies more suitable for engineering application. A brief summary of these strategies, including the methods adopted in this thesis, will be given in the following section.

Direct numerical simulations (DNS). Within the computational hemodynamics community, DNS are often a loosely used term attributed to any CFD approach that do not deal with any explicit turbulence modeling. However, true DNS solves the unsteady N-S equations (Eq. 1 and Eq. 2) using numerical methods that capture the entire spectrum of turbulence scales, including the small-scale velocity fluctuations, without additional models. The spatial and temporal resolution needed to resolve these flow features roughly scales with $Re^{9/4}$ and $Re^{1/2}$, respectively [233]. Thus, even for moderately high Reynolds number ($Re \sim 10^4$) this would contribute to high computational costs as the mesh typically needs to be represented by billions of discretized points and a time-step size in the order of microseconds [244, 148]. DNS methods also need to rely on high-order, energy-preserving and minimal dissipative discretization schemes to accurately resolve the energy-cascade process, which is difficult to implement for complex geometries. Examples of open-source DNS codes that have been used for blood flow-like applications or patient-specific simulations are Nek5000, a high-order SEM [68] (e.g. [135, 242, 203]) and Oasis, a second-order FEM approach [169] (e.g. [116, 117, 25]).

Large eddy simulations (LES). In this thesis, LES were used to compute the complex flow patterns. Large eddy simulations have been performed on idealized constricted flow configurations (e.g. [161, 74]) as well as patient-specific models (e.g. [128, 148]) showing good agreement against measurements and more resolved DNS data. The rationale of employing LES is to only resolve the largest energy-containing turbulent eddies of the flow, while trying to model the impact from the smaller scales by taking advantage of their more universal behavior. In contrast

to true DNS, this approach avoids the need for extremely fine spatiotemporal resolution, especially for moderate-to-high Reynolds number flows where the turbulence structures are very small, reducing the computational costs drastically. LES methods can be viewed as a low-pass filtering approach on the flow field variables over the computational domain (Fig. 18b), where a spatial filtering operator removes the small-scale flow information over the discretized control volume (mesh cell) according to:

$$\tilde{\phi}(\mathbf{x}, t) = \frac{1}{\Delta^3} \iiint_D \phi(\mathbf{x}', t) dx' dy' dz' \quad (10)$$

where D is the domain, Δ the cutoff length scale (or filter width) determined by the mesh size¹³. In Eq. 10, the commonly used "box filter" has been applied, where any resolved field variable $\tilde{\phi}$ is computed as a volume-average value at each cell-centers, while the flow variations ϕ' below the filter width, called sub-grid length scales, are destroyed. This operation can also be viewed as a decomposition (or sum) of the resolved and unresolved time-dependent variables [136]:

$$\phi(\mathbf{x}, t) = \tilde{\phi}(\mathbf{x}, t) + \phi'(\mathbf{x}, t) \quad (11)$$

If we apply Eq. 10 on the incompressible governing equations (Eq. 1 and Eq. 2), the filtered version becomes (here on tensor notation):

$$\frac{\partial \tilde{u}_i}{\partial x_i} = 0 \quad (12)$$

$$\frac{\partial(\rho \tilde{u}_i)}{\partial t} + \frac{\partial}{\partial x_j} (\rho \tilde{u}_i \tilde{u}_j) = -\frac{\partial \tilde{p}}{\partial x_i} + \mu \frac{\partial}{\partial x_j} \left(\frac{\partial \tilde{u}_i}{\partial x_j} + \frac{\partial \tilde{u}_j}{\partial x_i} \right) \quad (13)$$

where $\tilde{u}_i$ and $\tilde{p}$ is the filtered velocity and pressure field, respectively. The convective term $\rho \tilde{u}_i \tilde{u}_j$ (or apparent stress term, having units in $\text{N m}^{-2} = \text{Pa}$), however, depends on the unfiltered velocity field and thus cannot be solved. One way to decompose this non-linear term is to insert Eq. 11 [190]:

$$\rho \tilde{u}_i \tilde{u}_j = \rho \tilde{u}_i \tilde{u}_j + \tau_{ij}^R \quad (14)$$

which divide the stress tensor into a resolved (first term) and unresolved (second term) part. The latter, referred to as the sub-grid-scale (SGS) or residual stresses tensor, consists of several unclosed terms:

$$\tau_{ij}^R = \underbrace{\tilde{u}_i \tilde{u}_j - \tilde{u}_i \tilde{u}_j}_{\tilde{L}_{ij}} + \underbrace{\tilde{u}_i u'_j + u'_i \tilde{u}_j}_{\tilde{C}_{ij}} + \underbrace{u'_i u'_j}_{\tilde{R}_{ij}} \quad (15)$$

which represent the turbulence contribution of different scales to the SGS stresses owing to the LES filtering procedures. These terms involve the interaction from the resolved stresses (Leonard stresses, $\tilde{L}_{ij}$), between the resolved and the unresolved stresses (cross-stresses, $\tilde{C}_{ij}$) and from the unresolved scales alone (SGS Reynolds stresses, $\tilde{R}_{ij}$). The residual stress tensor

¹³The cutoff length scale is usually estimated as the cubic root of the mesh cell volume and roughly represent the smallest eddy wavelengths that can be preserved by the filter.

is invariant to Galilean transformation¹⁴, but all individual terms generally are not. As such, it is common praxis to abandon this decomposition and view the system as one lumped residual stress tensor that needs to be modeled [187].

For LES modeling, the mesh resolution should be adapted to ensure that the smallest energy-containing scales at least are resolved (typically above 80% of the total kinetic energy) [190], i.e. the filter width should typically be within the inertial sub-range, while the impact from the scales within the dissipative range are modeled. This is done by a so-called SGS model, which has the sole purpose of removing kinetic energy from the resolved scales to attain a realistic energy cascade.

The most common SGS modeling approach is based on the eddy-viscosity hypothesis [9], where the anisotropic residual-stress tensor τ_{ij}^r is taken to be proportional to the local rate-of-strain (deformation) tensor $\tilde{S}_{ij}$ of the resolved flow field:

$$\tau_{ij}^r = \tau_{ij}^R - \frac{1}{3}\delta_{ij}\tau_{kk}^R \approx -\underbrace{\mu_{SGS} \left(\frac{\partial \tilde{u}_i}{\partial x_j} + \frac{\partial \tilde{u}_j}{\partial x_i} \right)}_{2\tilde{S}_{ij}} \quad (16)$$

where the SGS viscosity μ_{SGS} is the constant of proportionality. Here, the contribution from the normal stresses is assumed to be isotropic, i.e. $\tau_{kk}^R/3 = (\tau_{11}^R + \tau_{22}^R + \tau_{33}^R)/3$, and relative small, and therefore not modeled but instead incorporated into a modified filtered static pressure $\tilde{P} = \tilde{p} + \tau_{kk}^R/3$.

The LES momentum equations for constant-density flows, including Eq. 13, Eq. 14 and Eq. 16, now reads:

$$\frac{\partial (\rho \tilde{u}_i)}{\partial t} + \frac{\partial}{\partial x_j} (\rho \tilde{u}_i \tilde{u}_j) = -\frac{\partial \tilde{P}}{\partial x_i} + \frac{\partial}{\partial x_j} \left[(\mu + \mu_{SGS}) \left(\frac{\partial \tilde{u}_i}{\partial x_j} + \frac{\partial \tilde{u}_j}{\partial x_i} \right) \right] \quad (17)$$

In Eq. 17 we can note that the SGS eddy-viscosity model simply mimics the small-scale energy dissipation and diffusion by artificially making the fluid more viscous. However, it is important to emphasize that, unlike the molecular viscosity, the eddy-viscosity is not a fluid property but solely described by the local flow characteristics (i.e. a flow property). How much extra viscosity that is needed depends on the turbulent conditions and the mesh resolution. For a well-resolved LES simulation in turbulent-like vascular flow, the eddy-viscosity ratio (μ_{SGS}/μ) have been reported in the range of 0.5 to 10 [126], indicating that as much as a factor 10 additional viscosity can be added locally by the SGS model. As the mesh is refined, the contribution from the SGS modeling should, in principle, vanish as more small-scales are resolved, being an analog to an DNS approach. It is important to note, however, that commercial LES codes are, unlike true DNS, probably only adequate for predicting up-to second-order moments/statistics [188], such as the Reynolds stresses, to due their lower-order discretization scheme (second-order or lower).

There are many types of SGS models that rely on the eddy-viscosity approach, where the Dynamic Smagorinsky-Lilly model [77], Sigma model [173] and WALE (wall-adapted local eddy-viscosity) model [172] are some of the most well used for LES of blood flow. Based on

¹⁴Galilean invariance implies that the flow variable must not change when the frame of reference is changed, i.e. Newton's laws should hold independently on coordinate transformation.

dimensional analysis, the general form of these models are given by the product of the density, a local length scale $\ell(\mathbf{x}, t) \propto \Delta = \sqrt[3]{V}$ (V = cell volume) and a velocity scale $\vartheta(\mathbf{x}, t) \propto \Delta \widehat{OP}(\mathbf{x}, t)$ [172], according to:

$$\mu_{SGS}(\mathbf{x}, t) = C_m \rho \Delta^2 \widehat{OP}(\mathbf{x}, t) \quad (18)$$

where C_m is an adjustable model coefficient, $\widehat{OP}$ and operator that needs to be defined based on invariants of the filtered velocity gradient tensor $\tilde{g}_{ij} = \partial \tilde{u}_i / \partial x_j$. In this thesis, the SGS viscosity was based on the WALE model, which make use of the fact that turbulent regions are associated to both none-zero local strain rates and rotation rates (or vorticity). In the WALE model, this information is gained by assessing the anisotropic (deviatoric) symmetric part of the squared velocity gradient tensor¹⁵ ($\tilde{g}_{ij}^2 = \tilde{g}_{ik} \tilde{g}_{kj}$), according to:

$$S_{ij}^d = \frac{1}{2} (\tilde{g}_{ij}^2 + \tilde{g}_{ji}^2) - \frac{1}{3} \delta_{ij} \tilde{g}_{kk}^2 \quad (19)$$

It can be shown that the second invariant of this tensor (proportional to $S_{ij}^d S_{ij}^d$) will be sensitive to turbulence structures susceptible to strain and rotation rates alone, or a combination of both (for more details see [172]). The WALE model is defined as:

$$\mu_{SGS} = \rho (C_w \Delta)^2 \frac{(S_{ij}^d S_{ij}^d)^{3/2}}{(\tilde{S}_{ij} \tilde{S}_{ij})^{5/2} + (S_{ij}^d S_{ij}^d)^{5/4}} \quad (20)$$

The nominator $(S_{ij}^d S_{ij}^d)^{3/2}$ is adjusted to return the proper near-wall asymptotic (y^3) eddy-viscous behavior as the flow relaminarize, i.e. μ_{SGS} naturally goes to zero in the vicinity of the no-slip wall without the need of additional, less robust, and ad-hoc procedures (e.g. using damping functions or compute C_m dynamically as required in the Smagorinsky models, which may cause numerical instabilities). The denominator terms in Eq. 20 is used to down-scale the nominator to the correct unit as well as avoid numerical singularities (instabilities), which may arise under pure shear or rotational strain conditions. The coefficient C_w was calibrated to 0.5 using experimental data, which reproduced the best agreement against the time evolution of different energy spectra for freely decaying isotropic homogenous turbulence. Another advantage with the WALE model is that no eddy-viscosity is produced in wall-bounded laminar or pure shear flows, nor disturbed but still laminar flow regions, which generally are attractive features when dealing with laminar-to-turbulent transition processes in pulsatile flows [180]. The Dynamic Smagorisky-Lilly sub-grid model has similar capabilities but needs extra explicit (secondary) filtering procedures at various scales, which may be less suited for complex geometries and adds more computational costs [172]. The Sigma model have shown promising results against under-resolved DNS approaches [148, 125] and can, in essence, be viewed as an enhancement of the WALE model, where a more robust operator ($\widehat{OP}$) have been developed to also be inactive for two-dimensional turbulence or flows undergoing only solid rotations. These latter flow conditions are, however, arguably unlikely to occur in realistic blood flows.

¹⁵For incompressible flows, the velocity gradient tensor can divided into a symmetric part (strain-rate tensor, $\tilde{S}_{ij} = \tilde{S}_{ji}$) and anti-symmetric part (rotation-rate/vorticity tensor, $\tilde{\Omega}_{ij} = -\tilde{\Omega}_{ji}$), i.e. $\tilde{g}_{ij} = \tilde{S}_{ij} + \tilde{\Omega}_{ij}$.

Unsteady Reynolds-Averaged Navier-Stokes (URANS). RANS-based models often focus on the time-averaged flow solution and are by far the most common turbulence modeling approach for high Reynolds number flows within industrial applications. For steady RANS, all turbulence scales associated with the energy spectrum are model, while for unsteady RANS only a small portion of the larger energetic scales may be resolved (Fig. 18). Compared to LES, this modeling strategy generally results in less accurate flow predictions but a significant reduction in computational costs. Unlike steady-state simulations, URANS also includes the transient term in the time-averaged governing equations, which seeks to capture the low wavenumber motion, such as large-scale eddies and strong secondary flow features (e.g. vortex shedding). This method is also more rational to adopt when the flow problem is transient in nature (e.g. pulsatile) or governed by strong unsteady characteristics (e.g. a Kármán vortex street). Unlike LES, RANS methods are based on time filtering. As URANS may resolve some large-scale flow unsteadiness, the dependent flow variables can be decomposed into three parts:

$$\phi(\mathbf{x}, t) = \underbrace{\bar{\phi}(\mathbf{x}) + \bar{\phi}'(\mathbf{x}, t)}_{\bar{\phi}(\mathbf{x}, t)} + \phi''(\mathbf{x}, t) \quad (21)$$

where $\bar{\phi}$ is the time-averaged component, $\bar{\phi}'$ the resolved flow variations around this mean, and ϕ'' the unresolved turbulent fluctuations. The two first terms in Eq. 21 represents the temporal-filtered (resolved) flow field over the time span Δt according to:

$$\bar{\phi}(\mathbf{x}, t) = \frac{1}{\Delta t} \int_{t-\Delta t/2}^{t+\Delta t/2} \phi(\mathbf{x}, t) dt \quad (22)$$

For this assumption to be accurate, the time-step size should be much larger than the rapid small-scale fluctuations (ϕ'') but much shorter than the (resolved) slow-moving large-scale flow variations ($\bar{\phi}'$). These conditions require a wide separation between the resolved and modeled scales (called "scale separation"), which seldom is the case in real flows. By applying the temporal filter (Eq. 22) to the incompressible governing equations (Eq. 1 and Eq. 2) yield an unclosed term associated to the unresolved flow fluctuations called the Reynolds stress tensor $-\rho(u_i''u_j'')$, which is analog to the filtered SGS Reynolds stresses ($\bar{R}_{ij}$) but here much larger. Like LES, this residual stress tensor is usually closed by an eddy-viscosity assumption¹⁶:

$$\tau_{ij}^{R\#} = -\rho(u_i''u_j'') \approx \frac{2}{3}\delta_{ij}k - \mu_t 2\bar{S}_{ij} \quad (23)$$

where $k = (\overline{u_k''u_k''})/2$ is the turbulence kinetic energy, μ_t the turbulence-related eddy-viscosity and $\bar{S}_{ij}$ the mean strain-rate tensor. The final URANS equations (also called Reynolds equations) now reads:

$$\frac{\partial \bar{u}_i}{\partial x_i} = 0 \quad (24)$$

$$\frac{\partial (\rho \bar{u}_i)}{\partial t} + \frac{\partial}{\partial x_j} (\rho \bar{u}_i \bar{u}_j) = -\frac{\partial \bar{P}}{\partial x_i} + \frac{\partial}{\partial x_j} \left[(\mu + \mu_t) \left(\frac{\partial \bar{u}_i}{\partial x_j} + \frac{\partial \bar{u}_j}{\partial x_i} \right) \right] \quad (25)$$

¹⁶There are also more advance methods that are not based on this crude concept, where for example the individual Reynolds stresses are modeled.

The eddy viscosity is here estimated by various turbulence models, such as SST $k - \omega$ model¹⁷ [157], where additional transport equations are used to define the local velocity scale $\vartheta(\mathbf{x}, t) \propto \sqrt{k}$ and length scale $\ell(\mathbf{x}, t) \propto \sqrt{k}/\omega$, which unlike LES is not determined by the filter width (mesh size) but instead represents the energy-dominant turbulence structures. In fact, by comparing the LES and URANS equations, we immediately note that they are the same knowing that no explicit spatial or temporal filtering are used in the WALE nor SST model. Thus, besides the numerical implementation (discretization schemes, etc.), it is, in essence, only the eddy-viscosity that dictates the accuracy of the flow predictions given the same mesh resolution. For RANS-based eddy-viscosity methods, essentially, all large-scale turbulence structures need to be artificially dissipated and diffused (isotropically) by a single turbulence model, which is inaccurate as these eddies are highly anisotropic and not affected by the viscosity. In contrast, LES only models the small-scale turbulence, where the eddy-viscosity assumption is more accurate as these eddies behave more universally (homogenous and isotropic) and are highly influenced by the viscous forces. For URANS models, the eddy-viscosity ratio can easily be in the order of 1000 or larger, and as a result are highly dissipative.

Patient-specific CFD simulations based on RANS-type turbulence modeling strategies are frequently used within the biofluid community as they necessitate very low computational resources compared to more advanced simulation methods. However, these models have shown to have severe dampening effects on the flow instabilities due to their inherent over-dissipative properties. Here, the underlying eddy-viscosity concept can generally not handle the anisotropic flow conditions present in realistic blood flows (pulsatile, transitional, and relaminarizing), resulting in unreliable flow predictions. As such, the use of RANS-based methods for computational hemodynamics has been discouraged in place of more advanced scale-resolving turbulence methods such as LES [222, 200, 260, 232, 75]. URANS can be categorized as a scale-resolving method, which has shown success in predicting external scale separations flows [9]. In *Paper IV*, however, we show that this modeling approach clearly fails to predict the turbulence characteristics when comparing against the well-resolved LES results. There are also other, second-generation URANS models that were not analyzed in this thesis [9], such as Scale-Adaptive Simulations (SAS) or Partially Filtered Navier-Stokes (PANS), or mixed (hybrid) RANS/LES strategies, that may be worth investigating.

3.4 Model VVUQ

A common trait among CFD practitioners are often to put more emphasize on “*what we know*” or “*think we know*” about simulation results, and less on “*what is uncertain*”. Verification, validation, and uncertainty quantification (VVUQ) is a rigorous framework adopted for assessing the credibility of (conceptual) computational analysis [174], starting its journey in the risk assessment community and now grown to become one of the main focus areas within cardiovascular modeling in order to convey uncertainty estimates of hemodynamic descriptors to decision-makers [232, 32, 224, 106, 23, 104]. In essence, model output inaccuracies are a trade-off between the complexity of the model and errors related to the modeling framework (Fig. 19a). For instance, a very simplistic patient-specific model is obviously governed by major assumptions compared to the physiological reality and thus will result in more inaccurate

¹⁷ k is the turbulence kinetic energy (units m^2s^{-2}) and ω the specific rate of dissipation (units s^{-1}).

outputs. On the other hand, a more advanced modeling framework is typically governed by more uncertain inputs, which may be relatively small by themselves, but could interact in the computations and substantially magnify in the output flow solution.

Figure 19: **(a)** Relationship between model output inaccuracy and modeling complexity. When attempting to model a complete multidisciplinary system, the output results will often be dominated by many input uncertainties. Contrary, for a simplistic (decomposed) system, the modeling framework will be the main source of error. The combination of both provides the total output uncertainty, also demonstrating the “sweet spot” of optimal complexity (i.e. minimum uncertainty). Adapted from [106, 69, 90], with permission from Elsevier. **(b)** Mean-value and uncertainty relationship between two parameters obtained from multiple experiments (red markers and error bars) and a numerical model approximation (black curve and shaded area). In this example, the findings suggest that the numerical model have a fairly good ability to predict the physical reality of the system as the uncertainty interval is within the experimental error margin.

Model verification techniques quantify the numerical approximation errors, e.g. owing to the discretization (mesh and time-step resolution, numerical schemes, etc.) and iterative convergence procedure. The fundamental idea of this process is to identify these errors for the quantities of interest (e.g. using global or local error norms) and try to reduce them to ensure that the numerical model is solved correctly and accurately in accordance with the mathematical implementation/description in the CFD solver. Thus, the verification process does not deal with the results’ physical correctness and should, therefore, be assessed in the early chain of the model development, prior to validation of the model. A validation process deals with the model agreement against real-world data (e.g. obtained from experiments) or data that presumably is a better representation of reality (e.g. acquired from accurate CFD simulations). Performing proper model validations for complex CFD models is often rigorous due to the high-degree of uncertainties associated with the CFD predictions as well as experimental outputs, which sometimes even is infeasible/impractical to acquire. Therefore, it is often rational to make these assessments on sharable, but less complex fluid flow systems, such as *in vitro* hemodynamic flow benchmarks¹⁸.

Model output uncertainties can be manifested from various sources that result in non-deterministic outcomes. These are often categorized into *i)* recognizable uncertainties (i.e.

¹⁸In *vitro* is Latin for “in glass” and are herein referred to experimental flow studies of idealized (simplified) blood flow conditions.

aleatoric uncertainty) associated with the inherent randomness/variability of the physical systems (or model inputs), and *ii*) unacknowledged uncertainties (i.e. epistemic uncertainty), which is related to the ignorance or limited knowledge of the physical system and related modeling parameters/inputs. For patient-specific cardiovascular modeling, aleatory uncertainties could be related to the variability of the patient's physiological state (e.g. cardiac output, heart rate, hemorheology, and vessel translation due to body movement). Epistemic uncertainties can be associated with lack of, poorly defined, or little knowledge of model inputs (boundary conditions, wall representation, blood model, etc.), limiting understanding of the physical process (e.g. turbulence modeling and fluid-solid interaction effects). Unlike aleatory uncertainties, the impact of epistemic uncertainties is reducible by gaining more modeling knowledge (e.g. more and improved data inputs as well as fine-tuning the numerical models).

A general methodology for uncertainty quantification (UQ) in CFD simulations are so-called forward propagation, which in essence deals with the characterization (probability distribution) and propagation of the most sensitive inputs parameters through ensemble computing to develop a statistical estimation of the distribution of the outputs, e.g. expected (mean) value and variance (Fig. 19b). This non-deterministic simulation approach is thus very computationally expensive, as it is no longer sufficient to perform one single input-to-output CFD prediction. A more simplistic and less costly way, closely related to UQ, is to perform so-called sensitivity analyzes ("what-if" or perturbation studies) to get insight into the output quantities sensitivity to variations of the modeling assumptions and input parameters [174]. In this thesis, these analyzes were used to assess the sensitivity of the CFD results from various modeling assumptions, e.g. a Non-Newtonian vs. Newtonian blood model and a adaptive time-stepping framework (Paper I and II, SM), as well as varying steady inflow rates (Paper IV). Also, the results impact from different mesh densities, time-step sizes, and phase averaging sampling sizes have been analyzed. The key findings of these investigations are summarized in Sec. 4.4.

Turbulence descriptors

This chapter will summarize the most important findings related to the parameters used to describe the patient-specific turbulent flow characteristics (descriptors) evaluated in this thesis. The chapter will, however, start by first establish how turbulent flows are commonly characterized, including some parameters that are often used within the biofluid community to describe abnormal blood flow conditions. In the subsequent sections, the key thesis findings will be highlighted and discussed. For clarity, the investigated turbulence descriptors have been divided into *i*) bulk flow descriptors that are associated with characteristics away from the intraluminal wall, and *ii*) WSS-based descriptors associated with the shear forces acting on the intraluminal wall, including their correlations against the near-wall flow characteristics. In the final section, some of these descriptors will be reviewed from a modeling verification and validation perspective.

4.1 General characterization

There are many ways to characterize well-resolved three-dimensional and time-dependent turbulent flow data. Generally, this huge amount of spatiotemporal information is for convenience often assessed from a statistical point-of-view, providing insights into the averaged behavior of the turbulent flow field. In blood flows, the physical interpretation of the complex transient flow dynamics is regularly made qualitatively by e.g. visualization of vector fields, streamlines, coherent turbulence structures (such as vortex-detection methods, e.g. Q-criterion or Lambda-2 criterion), volume rendering, and tracking of particles/scalars. The distinction of different flow regimes (laminar, transitional and turbulent-like hemodynamics) is often evaluated by point-wise 1D time-races (probes) of the flow variables (velocity, pressure, WSS, etc.), including power-frequency spectra analyzes. These low-order methods can, however, only provide valuable insight into the local nature of the flow (see e.g. Fig. 20) and less into the global context. Moreover, these probes are usually positioned somewhat arbitrarily, before the simulations, without detailed knowledge of the flow. Spectral analyzes of the entire flow field is also possible but less common within the biofluid community (see Ch. 6 for further discussions). In engineering, it is often the application response over time (or time-averaged results) that are of primary interest. This view-point may arguably also be of foremost significance in a clinical setting, where the mean flow characteristics considered over a multitude of cardiac cycles (i.e. phase-averaged results) may provide the most representable hemodynamics picture for therapeutic-decision making. In this thesis, essentially all flow descriptors were derived from a phase averaging perspective.

4.1.1 Phase averaging

In periodic pulsatile flows, turbulent-like behavior can be recognized by substantial cycle-to-cycle flow variations owing to the irregular (random) motion of the turbulent structures (Fig. 20a). From a statistical sense, any flow-related variable $\phi(\mathbf{x}, t)$ (e.g. velocity, pressure or WSS) in these flows can be split into three parts (Fig. 21), also called triple decomposition [107], according to:

$$\phi(\mathbf{x}, t) = \underbrace{\bar{\phi}(\mathbf{x}) + \tilde{\phi}_p(\mathbf{x}, t)}_{\langle \phi \rangle(\mathbf{x}, t)} + \phi'(\mathbf{x}, t) \quad (26)$$

Figure 20: CFD-based time-traces of (a) the velocity magnitude U at different points (P1 to P9) along the centerline of the investigated pre-op aorta in this thesis, and (b) their corresponding phase-averaged results acquired over 30 cardiac cycles. $\langle U \rangle$ represents the phase-averaged velocity magnitude and U_{rms} the root-mean-square (in red), or standard deviation, associated with the degree of local velocity variations (random nature of the flow). Qualitatively, undisturbed laminar flow can be noticed at P1 and P2 in the ascending aorta. Between the kink and CoA region, evident transitional or turbulent-like characteristics can be depicted. Immediately downstream the constriction (P5), the turbulent flow fluctuations appear to be most profound, while gradually starting to weaken further downstream (P6 to P9) as the flow starts to relaminarize.

where $\bar{\phi}$ is the time-averaged value, $\tilde{\phi}_p$ the periodic pulsations from the enforced inflow waveform, and ϕ' the turbulence-related fluctuations.¹ If all cardiac cycles are ensembled into one, called ensemble averaging or phase averaging, it is possible to differentiate between flow disturbances associated to the repeated laminar flow pulsations, which should manifest close to

¹For LES, it is important to note that the flow field represents the time-evolution of the spatially filtered variables, i.e. $\phi(\mathbf{x}, t) = \tilde{\phi}(\mathbf{x}, t)$, but for convenience this extra notation is ignored.

identically at every cycle, and those from turbulent fluctuations (Fig. 20b). The phase-averaged operator can be defined as:

$$\langle \phi \rangle (\mathbf{x}, t) = \frac{1}{N} \sum_{n=0}^{N-1} \phi (\mathbf{x}, t + nT) \quad (27)$$

where N is the number of ensembled cycles and T the time of the constant cycle period. The turbulence-related part can now be computed from Eq. 26. The time-averaged value of the flow variable over the period $[t_0, T_\Phi]$ in the cycle is computed as:

$$\bar{\phi} (\mathbf{x}) = \frac{1}{T_\Phi} \int_{t_0}^{t_0+T_\Phi} \phi (\mathbf{x}, t) dt \quad (28)$$

Figure 21: Schematic presentation of the triple decomposition of a fluctuating velocity signal $u_i(\mathbf{x}, t) = (u_1, u_2, u_3) = (u, v, w)$ in a periodic pulsatile turbulent flow field. This velocity time-trace can be divided into a time-averaged part $\bar{u}_i(\mathbf{x})$, periodic part $\tilde{u}_{p,i}(\mathbf{x}, t)$ linked to the driving inflow waveform, and the part related to the turbulent-like fluctuations $u'_i(\mathbf{x}, t)$.

A statistical estimate of the variations (or variance) of these turbulence-related flow fluctuations around the ensembled mean value can be computed by the phase-averaged cross-correlation between the six independent velocity fluctuations $\langle u'_i u'_j \rangle$ according to:

$$R_{ij} = \begin{bmatrix} R_{11} & R_{12} & R_{13} \\ \vdots & R_{22} & R_{23} \\ \vdots & \cdots & R_{33} \end{bmatrix} = \rho \langle u'_i u'_j \rangle = \frac{\rho}{N} \sum_{n=0}^{N-1} \underbrace{(u_i - \langle u_i \rangle)(u_j - \langle u_j \rangle)}_{u'_i u'_j} \quad (29)$$

where e.g. $R_{23} = \rho \langle u'_2 u'_3 \rangle = \rho \langle v' w' \rangle$ in a Cartesian coordinate frame. If multiplied by the density, these components are called phase-averaged Reynolds stresses, which can be represented in tensor form R_{ij} (a symmetric 3×3 matrix), called the Reynolds stress tensor. As previously mentioned, Reynolds stresses are not real fluid stresses (unlike the viscous stresses) but are second-order moments that reflect on the mean momentum transport due to turbulent velocity fluctuations in various directions; at specific phases within the cardiac cycle. The Reynolds stress tensor consists of six separate stress-terms, the three normal stresses ($i = j$, i.e. the

variances of the velocity components) on the main diagonal and the three off-diagonal shear stresses ($i \neq j$, i.e. the covariances of the velocity components). It should be noted that in purely laminar flows, without cycle-to-cycle flow variations, all Reynolds stress components are by definition zero.

4.1.2 Conventional descriptors

This section will summarize some of the most commonly used parameters adopted for describing abnormal blood flow characteristics. These parameters were either used for flow visualization purposes or for relative comparison against the new flow descriptors investigated in this thesis (see Sec. 4.2).

To distinguish high-flow from low-flow regions in the domain, it is common to render the scalar magnitude of the velocity vector (the velocity magnitude or speed) according to the L^2 norm:

$$U = \|u_i(\mathbf{x}, t)\| = \sqrt{u^2 + v^2 + w^2} \quad (30)$$

The Reynolds stress tensor has traditionally been used to assess different properties of turbulent blood flows, such as the turbulence kinetic energy (TKE, units $\text{Pa} = \text{J m}^{-3}$) derived from the first (principal) tensor invariant (i.e. half the trace R_{kk}):

$$k = \frac{1}{2}\rho R_{kk} = \frac{1}{2}\rho (\langle u^2 \rangle + \langle v^2 \rangle + \langle w^2 \rangle) \quad (31)$$

which provides an estimate of the mean kinetic energy of the turbulent fluctuations. The TKE is analog to the phase-averaged (mean) kinetic energy (KE) of the flow:

$$E_k = \frac{1}{2}\rho (\langle u^2 \rangle + \langle v^2 \rangle + \langle w^2 \rangle) \quad (32)$$

In Paper II, results in the post-stenotic region showed that the KE could be an order of magnitude higher than the TKE.

In pulsatile hemodynamics the overall behavior of the instantaneous wall shear stress $\tau(\mathbf{x}, t)$ (see Eq. 7) is often described by the time-averaged WSS magnitude (TAWSS) and oscillatory shear index (OSI) [96]:

$$\text{TAWSS} = \overline{\|\langle \tau \rangle\|} = \frac{1}{T_\Phi} \int_{t_0}^{t_0+T_\Phi} \|\langle \tau \rangle\| dt \quad (33)$$

$$\text{OSI} = \frac{1}{2} \left(1 - \frac{\|\tau_m\|}{\|\langle \tau \rangle\|} \right) \quad (34)$$

where τ_m represents the time-averaged WSS vector over the period $[t_0, T_\Phi]$, which traditionally is considered over the complete cardiac cycle (i.e. a cycle-averaged quantity). These two parameters have regularly been utilized in disease studies associated to the aorta, carotid arteries, arteriovenous fistulas, aneurysms, and coronary arteries (e.g. [13, 44, 234, 108]). Historically, atherosclerotic lesion formations have been coupled to regions of low TAWSS [35], but later understood to be more related to the oscillatory nature of the near-wall flow [122]. The OSI is based on the so-called low, oscillatory WSS theory and is used to estimate the overall departure

of the WSS vector $\boldsymbol{\tau}$ from the mean direction in unsteady/disturbed but laminar flows. Here the nominator in Eq. 34 will be smaller than the denominator (i.e. the TAWSS) as long as the instantaneous vector is not aligned with the mean direction during the assessed time period. Thus, for very oscillatory near-wall flows, typically found in regions of relatively low TAWSS, the OSI will attain a high value (maximum of 0.5) and vice versa for more fast-moving (non-reversing) unidirectional-dominant near-wall flows. The OSI is a crude estimate of these conditions and can often result in similar values for substantially different local WSS variations. These apparent shortcomings may partly be the reason why this index alone still lacks conclusive evidence as a sufficient blood flow marker for atherosclerosis nor aneurysm pathogenesis [184, 155, 256]. In addition to these original flow-mediated descriptors, plenty of focus have also been dedicated towards WSS-based spatial and temporal gradients, WSS angle deviations, and, more recently, the characterization of the multidirectionality or topological structures of the WSS vector fields.

To assess the cycle-to-cycle WSS variations promoted by near-wall turbulent fluctuations, it is common to compute the square root of the variance [75, 129] (i.e. the root-mean-square (RMS) value) of the phase-averaged WSS fluctuations as:

$$\langle \boldsymbol{\tau}_{rms} \rangle (\mathbf{x}, t) = \sqrt{\frac{1}{N} \sum_{n=0}^{N-1} [\boldsymbol{\tau}(\mathbf{x}, t + nT) - \langle \boldsymbol{\tau} \rangle (\mathbf{x}, t)]^2} \quad (35)$$

A time-averaged scalar-measure of the turbulence-related WSS magnitude (tWSS) is often defined as:

$$\text{tWSS} = \overline{\|\langle \boldsymbol{\tau}_{rms} \rangle\|} = \frac{1}{T_\Phi} \int_{t_0}^{t_0+T_\Phi} \|\langle \boldsymbol{\tau}_{rms} \rangle\| dt \quad (36)$$

The tWSS parameter will only provide a non-zero value for turbulent-like instabilities, analog to the Reynolds stress components, but here associated with phase-wise fluctuating magnitude of the WSS vector.

4.2 Bulk flow descriptors

4.2.1 Tensor descriptors

(Paper III & IV)

Turbulence-related tensors, statistically ensembled from the fluctuating velocity field (and its derivatives), such as the Reynolds stress tensor, can be used to define the regional turbulence characteristics. A general single-point description of the more energy-containing turbulence scales can be described by a set of second-rank tensors [111, 98, 16] according to:

$$R_{ij} + D_{ij} + F_{ij} - (C_{ij} + C_{ji}) = R_{kk} \delta_{ij} \quad (37)$$

The Reynolds stress tensor R_{ij} are, as previously mentioned, related to the relative strength (energy) of the different fluctuating components, often referred to as the "componentality" of the turbulence field. The remaining, so-called structured-based tensors are associated with the

large-scale turbulence morphology (structures), where the dimensionality tensor D_{ij} and circularity tensor F_{ij} represents the anisotropy of the physical length scales and vorticity field, respectively, and the inhomogeneity tensor C_{ij} the degree of turbulence inhomogeneity. Collectively, these tensors provide a good depiction of the structural turbulence information and the evolution of the turbulence stresses. In this thesis, the analyzes were focused on the characterization of the turbulence componentality, but the methods described hereon can also be applied to any of these tensors.

In patient-specific flows, it hard to gain meaningful insight by mere assessments based on the individual components alone in the Reynolds stress tensor, as the fluctuating directions are somewhat arbitrary with respect to the complex vessel morphology. Yet, even for local vessel (cylindrical) coordinates, a more complete picture of the turbulence properties would be difficult to comprehend using single scalar quantities. It is, therefore, common to resort to parameters that are coordinate-insensitive and sometimes dimensionless. This can be done by considering different invariants of the Reynolds stress tensor, such as the magnitude, anisotropy (shape), and orientation of the turbulence stresses.

One way to characterize the turbulence anisotropy is to extract the normalized traceless tensor, called the Reynolds stress anisotropy tensor [146]:

$$b_{ij} = \frac{R_{ij}}{2k} - \frac{\delta_{ij}}{3} \quad (38)$$

where $k = R_{kk}/2$ is the TKE (magnitude). By construction, b_{ij} vanish in pure isotropic turbulent flows. Any symmetric tensor ($b_{ij} = b_{ji}$) can be transformed into only diagonal components, representing the tensor principal eigenvalues λ_i , according to:

$$X_{ik} b_{kl} X_{lj} = a_{ij} \quad (39)$$

where $a_{ij} = \lambda_i \delta_{ij}$ is the diagonal eigenvalue matrix of b_{ij} and X_{ij} the corresponding orthonormal eigenvector matrix consisting of column vectors x_i that are mutually perpendicular ($x_i x_i^T = I$). The diagonalization in Eq. 39 can be reordered to attain a_{ij} on (invariant) canonical form, i.e. non-increase order of the eigenvalues ($\lambda_1 = \lambda_{max} > \lambda_2 = \lambda_{int} > \lambda_3 = \lambda_{min}$). The eigenvectors signify the major, intermediate and minor axis (i.e. the principal coordinate axis) of the turbulent momentum transport, which are scaled according to the size of the corresponding normalized eigenvalues. Here, the direction of the eigenvectors between R_{ij} and a_{ij} are not changed by the decomposition in Eq. 38, while the eigenvalues are scaled according to $\lambda_i = \lambda_i^R / 2k - 1/3$. As velocities are defined by a real vector space, any fluctuating velocity correlations (Reynolds stresses) need to satisfy the following realizability constraints [208]:

$$\begin{aligned} R_{\alpha\beta} &\geq 0, \alpha = \beta, \\ R_{\alpha\beta}^2 &\leq R_{\alpha\alpha} R_{\beta\beta}, \alpha \neq \beta, \\ \det(R_{ij}) &\geq 0 \end{aligned} \quad (40)$$

where the Greek indices $\alpha, \beta = \{1, 2, 3\}$ refers to the tensor components, without Einstein summation ($R_{\alpha\alpha} \neq R_{11} + R_{22} + R_{33}$). The first condition imply that any normal stress ($R_{\alpha\alpha}$) cannot be negative. The second term is due to the Cauchy-Schwarz inequality, inferring that the energy associated with a shear stress term ($R_{\alpha\beta}$) is always bounded by the size of the associated

normal stresses ($R_{\alpha\alpha}$ and $R_{\beta\beta}$). Along with the third condition (i.e. a positive determinant), it follows that R_{ij} needs to be a positive-semidefinite tensor, with only real and non-negative eigenvalues. When these conditions are applied to the anisotropy tensor a_{ij} , the following constraints on the normal ($a_{\alpha\alpha}$) and off-diagonal ($a_{\alpha\beta}$) components can be obtained [16]:

$$\begin{aligned} -1/3 &\leq a_{\alpha\alpha} \leq 2/3, \\ -1/2 &\leq a_{\alpha\beta} \leq 1/2 \end{aligned} \quad (41)$$

For a diagonalized tensor (Eq. 39), the diagonal components are the eigenvalues. Thus, for a_{ij} this means that $-1/3 \leq \lambda_i \leq 2/3$. The anisotropy principal invariants of this second-rank tensor can be defined as:

$$\begin{aligned} \Pi_a &= a_{ij}a_{ji} = 2(\lambda_1^2 + \lambda_1\lambda_2 + \lambda_2^2), \\ \text{III}_a &= a_{ij}a_{jk}a_{ki} = -3\lambda_1\lambda_2(\lambda_1 + \lambda_2) \end{aligned} \quad (42)$$

By cross-plotting the second (Π_a) and third (III_a) invariant (Fig. 22a), the different turbulence states can be demonstrated in a triangular-like region, also called an invariant anisotropy map (AIM) or Lumley triangle after its originator [145]. The borders of the AIM can be derived from the realizability constraints (Eq. 40 and Eq. 41) and represents the limiting region where all physical turbulence states should lie within. Here, Π_a and III_a can be associated with the degree and nature of the turbulence anisotropy, respectively. The fundamental limiting states of the AIM can be characterized by expanding the anisotropy tensor according to the spectral theorem:

$$a_{ij} = \lambda_1 x_1 x_1^T + \lambda_2 x_2 x_2^T + \lambda_3 x_3 x_3^T \quad (43)$$

The number of non-zero R_{ij} eigenvalues ($\lambda_i^R \neq 0$), or a_{ij} eigenvalues $\lambda_i \neq -1/3$, corresponds to the rank of the tensor and reflects on the number of active turbulent fluctuating directions in the principal axis. The three extreme corner-states in the map, with corresponding stress field shapes (Fig. 22a, see glyphs), can be defined as:

- *One-component turbulence (1C)*, represented by $\lambda_i = \{2/3, -1/3, -1/3\}$ and thus only one non-zero eigenvalue. At this extreme state, the turbulence fluctuations have one-directional characteristics.
- *Two-component axisymmetric turbulence (2C)*, represented by two non-zero equal eigenvalues, $\lambda_i = \{1/6, 1/6, -1/3\}$. Here, the turbulence fluctuations manifest symmetrically across a plane.
- *Three-component isotropic turbulence (3C)*, represented by three equal non-zero eigenvalues, $\lambda_i = \{0, 0, 0\}$. This isotropic state is governed by random three-dimensional turbulence fluctuations, hence lacking any preferential direction.

The three borders joining the AIM corners can be described by intermediate states (Fig. 22a), which often are characterized by a turbulence stress field that either is pancake-like (two-component limit), rod-like (axisymmetric expansion), or disk-like (axisymmetric contraction).

A final, special state can be defined for $\text{III}_a = 0$, i.e. the plain-strain condition, where only one anisotropy eigenvalue is zero (or one $\lambda_i^R = 2k/3$), with an exception for the 3C state where all $\lambda_i = 0$. Here, the turbulence momentum exchange only occurs along the two anisotropy principal axis, while the turbulence along the third axis is statistically stationary (isotropic).

Figure 22: Different anisotropy invariant maps of a second-order turbulence-related tensor, where all physically realizable states should be situated within. **(a)** Shown in principal invariant coordinates (II_a , III_a), also called the Lumley triangle, and are governed by a non-linear relationship between the anisotropy eigenvalues. The glyph insets illustrate the characteristic ellipsoid shapes of the tensor field, i.e. the relative size of the three eigenvalues in the principal axis. The corners represent the fundamental limiting states: one-component (1C), two-component axisymmetric (2C) and three-component isotropic (3C) turbulence, confined by intermediate states: axisymmetric expansion (rod-like turbulence), axisymmetric contraction (disk-like turbulence) and the two-component limit (pancake-like turbulence). Across the plain-strain state, at least one principal direction is statistically stationary (isotropic), with turbulence anisotropy only active within a plane. Adapted from [5]. **(b)** Barycentric colormap, based on a linear combination of the eigenvalue-related weights $\{C_{1C}, C_{2C}, C_{3C}\}$ (or limiting states), ranging from $[0, 1]$, with associated red-green-blue color triplets. Adapted from [6] under the [CC BY 4.0](#) license.

A downside with the conventional AIM (Fig. 22a) is the skewed triangular domain, owing to the non-linear relation between the principal invariants and eigenvalues (Eq. 43), which distorts the results within the map, and in effect making interpretations more difficult. Therefore, an equivalent linear representation has been proposed [16], called a barycentric AIM (Fig. 22b). This map can be reconstruct by rewriting Eq. 43 in terms of the known principal anisotropy tensor basis:

$$a_{ij} = C_{1C} \underbrace{\begin{bmatrix} 2/3 & 0 & 0 \\ 0 & -1/3 & 0 \\ 0 & 0 & -1/3 \end{bmatrix}}_{a_{1C}} + C_{2C} \underbrace{\begin{bmatrix} 1/6 & 0 & 0 \\ 0 & 1/6 & 0 \\ 0 & 0 & -1/3 \end{bmatrix}}_{a_{2C}} + C_{3C} \underbrace{\begin{bmatrix} 0 & 0 & 0 \\ 0 & 0 & 0 \\ 0 & 0 & 0 \end{bmatrix}}_{a_{3C}} \quad (44)$$

where $C_{iC} \geq 0$ are the eigenvalue-related weights of a_{ij} in the tensor basis a_{iC} making up the three turbulence corner states. A convex (linear) combination between these tensor basis can be achieved by the following relations:

$$\begin{aligned}
 C_{1C} &= \lambda_1 - \lambda_2, \\
 C_{2C} &= 2(\lambda_2 - \lambda_3), \\
 C_{3C} &= 3\lambda_3 + 1, \\
 C_{1C} + C_{2C} + C_{3C} &= 1
 \end{aligned} \tag{45}$$

This setup naturally put each C_{iC} weight in the range $[0, 1]$, corresponding to the closeness to the respectively limiting corner state. These weights can by themselves be used to assess certain anisotropic characteristics [16], such as an anisotropy index (AI_a) that measures the departure from the isotropic 3C state (or degree of anisotropy)²:

$$AI_a = C_{1C} + C_{2C} \tag{46}$$

A linear AIM representation can now easily be constructed by just allocate the C_{iC} weights into barycentric coordinates (x_B, y_B) on a equilateral triangle:

$$\begin{aligned}
 x_B &= C_{1C}x_{1C} + C_{2C}x_{2C} + C_{3C}x_{3C}, \\
 y_B &= C_{1C}y_{1C} + C_{2C}y_{2C} + C_{3C}y_{3C}
 \end{aligned} \tag{47}$$

where (x_{iC}, y_{iC}) represent the corner vertices.

These AIMs have traditionally be used to map data into the triangular domain, e.g. to characterize the turbulence states along an array or cloud of points extracted from the computational domain. This approach, however, inherently remove the spatial context and making broad-scale physical interpretations harder. To deal with this problem, an intuitive approach is to represent the barycentric AIM as a color triangle (colormap) [62], by assigning color triplets to the weights:

$$[RGB] = C_{1C} [RGB_{1C}] + C_{2C} [RGB_{2C}] + C_{3C} [RGB_{3C}] \tag{48}$$

where RGB_{iC} represents the specific color associated to each corner state. In this thesis, the red-green-blue triad was found to be well suited for the purpose of the studies (Fig. 22b). However, examples of more advanced non-linear color schemes have also been suggested [62], to better contrast between certain features within the map.

In turbulent flows, AIMs have often been used for improved physical interpretations of turbulence (e.g. [111, 43, 62]) or for turbulence modeling development (e.g. [140, 18, 57]), including uncertainty assessments (e.g. [159]), while, thus far not been reported within the biofluid community. Characterization of more complete turbulence-related tensor properties, e.g. associated with the Reynolds stresses or dissipation rates, may provide deeper insights into these potential flow-phenotypes in various patient-specific flows and are descriptors that may be acquired non-invasively by both CFD and MRI turbulence measurements. For MRI-based diffusion tensor imaging, similar tensor characterization techniques are today successfully used to estimate the apparent microstructural properties/changes of the brain tissue [209], which can

²A similar anisotropy index can also be defined directly from the second principal invariant of the anisotropy tensor, i.e. $AI_a = \frac{3}{2}\Pi_a$.

be coupled to the ellipsoid shapes (magnitude and componentality) of the local diffusion tensor field.³

In *Paper IV*, the main objective was to demonstrate different, more broadband ways to characterize phase-averaged turbulence tensor fields in patient-specific flows, focusing on the commonly explored Reynolds stress tensor and turbulence dissipation tensor. This was done by evaluating LES results using the 6MC-CFL1 pre-op CoA model computed over 50 cardiac cycles (Sec. 3.2.5). However, herein, the follow-up CoA results were also included to add some more context, while for brevity only focus on the Reynolds stress characteristics. In both cases, the results were acquired for the 3MC-CFL5 resolution and phase-averaged over 80 cardiac cycles, which have shown decent agreement against the more resolved 6MC-CFL1 model (see *Paper V* and Sec. 3.4).

Figure 23: Patient-specific centerplane velocity flow features and Reynolds stress characteristics before (pre-op) and after the intervention (follow-up), shown shortly after peak systole (PS) in the early flow deceleration phase of the cardiac cycle (inset, solid line, and marker) where the overall turbulence kinetic energy (k , or TKE) levels were substantially elevated (inset, dashed lines, showing the volume integrated cardiac evolution of the TKE in the descending aorta). The left column represents a pulse-instant snapshot of the velocity magnitude, while the remaining columns the phase-averaged results acquired over 80 cardiac cycles using the 3MC-CFL5 models.

³For diffusion tensor imaging, the tensor characteristics are often described by two indices: *i*) mean diffusivity, corresponding to the diffusion magnitude (analog to the TKE), and *ii*) fractional anisotropy, which measures the degree of anisotropy in the range of $[0, 1]$ (analog to the anisotropy index described herein).

Figure 24: Patient-specific centerplane velocity flow features and Reynolds stress characteristics before (pre-op) and after intervention (follow-up), time-averaged over a majority of the early flow deceleration phase of the cardiac cycle (inset, shaded area) where a quasi-steady turbulent jet still prevailed in both cases. Cross-sectional planes of the turbulence states were added normal to the centerline at 0.5D, 1D, 1.5D and 3D downstream the smallest stenotic diameter (D) within the CoA. For reference, the left (L), anterior (A) and posterior (P) sides of the aorta are denoted. Additional details are given in Fig. 23.

A qualitative depiction of the phase-instant as well as time-averaged patient-specific flow characteristics at the early flow deceleration (EFD) phase in the cardiac cycle can be seen in Fig. 23 and Fig. 24, respectively. In both cases, clear disturbed flow regions could be noticed in association to the flow separation at the aortic kink and eccentric jet formed at the throat of each CoA, which gradually breakdown into smaller streamwise-traveling flow structures. By assessing the magnitude and shape of the Reynolds stress tensor, distinct regions of elevated TKE as well as turbulence anisotropy could be observed, which manifested into a wide range of different stress-states in the barycentric map. For example, in the surrounding jet region, turbulence attained 1C-like characteristics (Fig. 24, cross-sections) while progressively getting more isotropic (3C-like) further downstream in the bulk flow. In the thin layer close to the wall, the turbulence states approach the two-component limit, which agrees with the well-known near-wall turbulence characteristics [140]. It is also interesting to note that, although the TKE levels were much lower in the follow-up case, owing to the milder constriction, the overall degree of anisotropy appeared to be slightly higher (also see Paper III).

By projecting physical points from the turbulent region into the barycentric map itself, these

Figure 25: Barycentric maps with 50k evenly distributed nodal mesh points taken from the turbulence region (vessel inset, black region) before (pre-op) and after (follow-up) intervention, colored by the turbulence kinetic energy (k). The columns represent three different time assessments over the flow deceleration phase: phase-instant snapshot and time-averaged data over the early (EFD) or late (LFD) flow deceleration phase (insets, shaded area). The dashed lines within the maps demonstrate suggested borders of each turbulence stress-state at EFD.

methods also discovered some apparent time-varying stress-state behavior (Fig. 25). While the phase-instant results showed a wide range of states across the entire map, the time-averaged results showed an retraction from the two limiting axisymmetric borders and the 3C corner during the flow deceleration phase, implying that these extreme states only take place under a short time-frame. However, as discussed in Sec. 4.4.1 and Paper V, some of these findings may be related to relatively large phase-averaging errors of the phase-instant turbulence states. These concerns need to be clarified by including much more cardiac cycles in these statistics.

The clinical implications of turbulence-related tensor characterization may be several. MRI measurements of the complete Reynolds stress tensor [92, 112] have been used to enhance non-invasive predictions of pressure losses across stenosis (e.g. [87, 84]), and flow-induced blood damage (e.g. [86]). The robustness and reliability of these predictors rely on accurate tensor-based markers (Sec. 3.4). In fact, single parameters from these tensors have traditionally been used for hemolysis predictions with limited success [64]. As shown in Paper IV, the nature of the large-scale turbulence stresses may give rise to small-scale turbulence anisotropy at the turbulence dissipation range. Here, it is possible that the amplitude, shape, and even orientation of the local stress-field may induce different hazardous viscous force environments sensed by the cells.

4.2.2 Global flow descriptors

(Paper I)

From a clinical perspective, it is arguably more favorable if hemodynamic descriptors can be accurately estimated by non-invasive measurement procedures as well as providing practical ways to facilitate comparison to better aid in the decision-making. In *Paper I*, different qualitative and quantitative descriptors were proposed to assess the overall (global) spatial changes in turbulence magnitude and flow eccentricity patterns for various shaped constrictions. The benefit of these global flow descriptors is that they can be derived from 4D Flow MRI velocity and turbulence data [60].

To attain a broad overview of the turbulence development along the domain, so-called space-time diagrams (or spatiotemporal maps) can be adopted. This approach was utilized in a recent study [128], where spatiotemporal maps of the TKE were evaluated based on centerline data. However, this method was found to be unsuitable for eccentric flow features, where essential flow characteristics easily could be overlooked by the one-dimensional data extraction. In consideration, we chose to instead estimate the cross-sectional-averaged TKE value (k_S), as:

$$k_S(\bar{\mathbf{x}}, t) = \iint_S k(\mathbf{x}, t) dS \quad (49)$$

where $\bar{\mathbf{x}}$ denote the centroid position of the plane (cross-section). Regarding the flow eccentricity, a simple way to obtain an estimate of the highest kinetic energy region within a cross-sectional plane is to compute the KE-weighted mean position, or center of KE (C_{KE}), according to:

$$C_{KE}(\bar{\mathbf{x}}, t) = \frac{\frac{1}{n} \sum_{i=0}^n r_i(\mathbf{x}) E_{k,i}(\mathbf{x}, t)}{\frac{1}{n} \sum_{i=0}^n E_{k,i}(\mathbf{x}, t)} \quad (50)$$

were n represents to the total number of cross-sectional points with the corresponding coordinates r_i . Here, the C_{KE} will be non-zero for all skewed (eccentric) velocity profiles. By normalizing the relation in Eq. 50 with the local mean radius of the lumen, an intuitive descriptor of the local flow eccentricity can be attained along the arterial region.

In Paper I, these flow descriptors were analyzed for the pre-op case and relative to six different virtual interventions of the CoA, where different degrees of concentric as well as eccentric dilation methods were applied with the intention to restore the post-stenotic flow in various ways (see Paper I, SM). Herein, only the results for three interventions (C1, C3, and C5) are shown in relation to the pre-op and follow-up cases (Fig. 26a), including the effect on the near-wall turbulence intensity (Fig. 26b).

In summary, the patterns within these space-time maps could be coupled to the characteristics of the post-stenotic jet, which showed a clear impact on the spread, penetration depth, and local intensity of the turbulence field along the aortic segment. Pre-op, the CoA induced a very eccentric jet immediately downstream the constriction, imposing elevated TKE in the proximal region of the opposing wall. By outer-curvature dilation (C1), the jet eccentricity around peak systole was slightly reduced but also maintained further into the cardiac cycle. Contrarily, with a more concentric dilation approach (C3), the flow eccentricity penetration depth was reduced, along with the near-wall TKE. By dilation more towards the inner-curvature (C6), the turbulent flow became more concentric. For the follow-up case, a mix of characteristics could be seen in relation to these virtual interventions.

Eccentric flow conditions have been associated to vascular remodeling, e.g. downstream BAVs [49, 212, 101] and CoAs [156], while also increase the susceptibility of thromboembolic activity [226]. Restoring these flows to a more physiologically normal state is challenging but may be assisted by improved hemodynamic evaluation tools and virtual intervention procedures, which start to become more frequently explored within the biofluid community (e.g. [211, 81]). The findings in Paper I suggest that the current state-of-the-art dilation interventions by e.g. (uniformed/concentric) balloon angioplasty may not favor the best way to restore normal flow conditions. However, it important to emphasize that these CFD simulations, at best, can hope for accurate outcome predictions immediately after the intervention, while long-term remodeling aspects due to e.g. wall trauma, altered flow and pressure conditions are difficult to foresee.

To attain an even more concise (aggregated) description of the overall turbulence intensity, the TKE data was also integrated over the DAo domain (D):

$$k_D(t) = \iiint_D k(\mathbf{x}, t) dV \quad (51)$$

The volume integrated TKE k_D is analog to collapsing (summing over) the spatial direction in the space-time TKE map, and has previously been used to assess volumetric TKE content over the cardiac cycle [12, 128, 113]. To quantify the total amount of TKE over the cardiac cycle, the k_D parameter can also be integrated over time (here referred to as the total TKE $\overline{k_D}$):

$$\overline{k_D} = \int_0^T k_D(t) dt \quad (52)$$

This parameter can be viewed as aggregating the information in the space-time TKE map into one single scalar value. In Fig. 27 the time-trace of k_D and corresponding $\overline{k_D}$ values are displayed for the CoA cases described herein. The k_D profiles facilitated easy detection of the tur-

Figure 26: (a) Space-time maps showing the evolution of the turbulence kinetic energy (TKE) and flow eccentricity for different virtual CoA interventions (C1, C3 and C5) in relation to the pre-op and follow-up case. The top row shows all CoA segments, where the interventions have been color-coded with the dilation displacement with respect to the pre-op case. The degree of outward dilation, or smallest cross-sectional area increase is denoted by ΔA . Abbreviations are: aortic coarctation (CoA), descending aorta (DAo), maximum acceleration (MA), peak systole (PS) and maximum deceleration (MD). (b) 1 mm intraluminal wall-normal surface offsets colored by the time-averaged TKE.

Figure 27: **(a)** Time-traces of the volume integrated turbulence kinetic energy (TKE) k_D in the post-stenotic region (vessel inset, black region) for the different CoA cases described in Fig. 26. The data was normalized by the pre-op peak value. **(b)** Degree of cross-sectional area increase in relation to the total TKE $\overline{k_D}$, corresponding to the area underneath the k_D profiles in (a).

bulence onset in the volume (however, without the spatial context), which appeared to be similar but slightly delayed for the more dilated constrictions. Here, the total TKE indicated an asymptotic plateau with respect to the degree of dilatation, which suggests that only a limited amount of TKE reduction can be obtained by treating this CoA alone, without considering the upstream vessel malformations as well. Furthermore, a strong correlation was found between the relative changes in peak k_D values and $\overline{k_D}$ (see Paper I, Fig. 5). To date, the severity of a CoA is partly estimated by the peak-to-peak pressure difference over the constriction (Sec. 2.4.1), mainly caused by the turbulence-related viscous energy losses. Several attempts have been made to predict these irreversible pressure drops by MRI-based TKE measurements (e.g. [59, 87, 85]). The finding in Paper I suggest that the peak values alone may be used to assess the overall TKE response and corresponding pressure losses, which may be beneficial as the MRI velocity encoding sensitivity typically is tuned to attain the best measurement accuracies around these elevated flow conditions [58].

4.3 WSS-based descriptors

(Paper II & III)

4.3.1 Turbulence-related WSS characteristics

Traditionally, cycle-averaged descriptors such as the TAWSS and OSI have been used to assess wall region prone to WSS disturbances (low/oscillatory) in unsteady but laminar flows [232]. The OSI have, as previous mentioned, a tendency to overlook various WSS characteristics, as the index cannot differentiate between unidirectional or multidirectional disturbances (Fig. 28a), nor entail any magnitude information. For example, in a recent study, it was shown that both the WSS oscillatory and magnitude characteristics appeared to play an important role in coronary artery disease development and vulnerability [234].

To better account for the multidirectional nature of the temporal WSS patterns, a new parameter called the transverse wall shear stress (transWSS) was recently proposed [183], and defined as:

$$\text{transWSS} = \frac{1}{T_\Phi} \int_{t_0}^{t_0+T_\Phi} \|\langle \boldsymbol{\tau} \rangle \cdot (\mathbf{e}_n \times \mathbf{e}_m)\| dt \quad (53)$$

where the cross-product between the wall-normal unit vector $\mathbf{e}_n$ and the cycle-average WSS unit vector $\mathbf{e}_m = \boldsymbol{\tau}_m / \|\boldsymbol{\tau}_m\|$ represents the transverse (orthogonal) direction. By taking the scalar-product against the phase-instant WSS vector $\langle \boldsymbol{\tau} \rangle(\mathbf{x}, t)$, the transverse portion of the WSS magnitude can be calculated over a desirable period. Thus, by construction, this parameter will only be non-zero for WSS variations that depart from the $\mathbf{e}_m$ directionally, which traditionally have been represented by the dominant (cycle-averaged) flow direction, which often is viewed as the atheroprotective direction due to the ECs alignment (Sec. 2.4.1). Hence, the transWSS is only insensitive to strictly unidirectional near-wall flow disturbances (Fig. 28a).

Figure 28: (a) Schematic illustration of some possible temporal variation patterns of the local WSS vector (black arrows) exhibiting the same TAWSS. These near-wall flow environments may, in theory, give rise to similar (or zero) values for the WSS descriptors described herein (see table inset), despite dissimilar characteristics. (b) Barycentric anisotropy invariant map (also see Fig. 22), with the used $tWSS$ anisotropy index (AI_{wb} , Eq. 57) colormap along the two-component limit, including 2D glyphs exemplifying the relative size of the planar WSS fluctuations in the principal axes.

Since its introduction, the transWSS parameter has been used for studying regions susceptible to atherosclerotic plaques (e.g. [183, 162, 182, 73]) and remodeling in AVF (e.g. [63, 29]). However, these studies have been limited to unsteady laminar-transitional type of flows, while no transWSS investigations have been reported for patient-specific flows with substantial near-wall turbulence. As this flow regime only are conditionally turbulent over the cardiac cycle, the transWSS may be a useful parameter for predicting general WSS disturbances, which unlike the conventional parameters is not limited to purely laminar nor turbulent-like WSS variations (Fig. 28a).

In Paper II, the characteristics of the transWSS parameter were evaluated in both the pre-op and follow-up case, in relation to the conventional WSS parameters described in Sec. 4.1.2.

Figure 29: WSS-based characteristics before (pre-op) and after (follow-up) intervention in the descending aorta. The left column represents a time-instant snapshot showing the complex WSS magnitude patterns, which clearly highlights the impact from the wall-interacting flow structures. The remaining parameters were time-averaged over the most profound turbulent phase in the cardiac cycle (see insets, shaded area). For explanation of the AI_{wb} colormap, see Fig. 28b.

These parameters were time-averaged over the entire cardiac cycle, according to common practice. However, herein results are only presented for the time averaging over the most turbulence intense phase of the cycle (Fig. 29), which is arguably more rational when comparing results against the tWSS descriptor. For brevity, the cycle-averaged OSI results were not included but can be found in Paper II.

Taken collectively, results showed that regions of elevated near-wall turbulence intensity generally appeared to promote high transWSS and tWSS values. Contrary, in transitional-like flow regions manifested by much weaker near-wall turbulence intensity, elevated transWSS co-localized better with low and oscillatory WSS. At first glance, these versatile responses of the transWSS parameter may suggest a more complete way to capture WSS disturbances compared to the conventional parameters (e.g. OSI or tWSS). To assess the actual transient dynamics of the WSS vector over multiple cardiac cycles, so-called rose diagrams were examined at different feature locations of the DAo (Fig. 30). From these plots, it is easy to see that large differences in multidirectional WSS dynamics can result in similar intermediate-to-high transWSS values and overall inconsistency against e.g. the OSI. At locations A1 to A3, the elevated transWSS suggests multidirectional characteristics, whereas the WSS rose diagram clearly indicates unidirectional-dominant behavior. These findings point out an apparent drawback with the transWSS parameter, also previously hypothesized [183], which appeared to be associated with the cycle-averaged WSS topological features [14], in this case, a saddle-type fixed point (Fig. 30, A1 to A3), where the temporal mean WSS directionality τ_m clearly is misrepresented as the flow turns 180° between the systolic and diastolic phase. Considering these profound changes in main WSS directionality (also indicative for location B2 and C1), one may question the validity of using the cycle-averaged direction as the favorable alignment for ECs functionality. While, geometry-derived reference directions also have been suggested [164, 13], finding a rational favorable/unfavorable WSS directionality would still be difficult at these highly disturbed vascular sites. Furthermore, it is also known that ECs exposed to near-wall turbulent flows tend to disorient into a cobblestone patterns (Sec. 2.4.1). Under these circumstances, the transWSS parameter can probably only act as a descriptor of WSS disturbances, where the "transverse" contribution is of less value.

In *Paper III*, a new approach was developed to characterize the magnitude and anisotropy (componentality) of the turbulence-related WSS fluctuations. The clinical implication of these characteristics are yet to be decided but may provide valuable insight into potential flow phenotypes contributing to ECs dysfunction and atherogenesis under these conditions. The central concept of this approach can be realized knowing the fact that all near-wall velocity fluctuations will only act two-dimensionally when approaching a wall. This implies that the principal direction of the tWSS fluctuations only act parallel to the intraluminal wall and can be described by the states across the two-component limit in the AIM (Fig. 28b).

A tensor containing the six-independent phase-averaged cross-correlations between the fluctuating WSS components $\langle \tau'_i \tau'_j \rangle$ (for $i = 1, 2, 3$), analog to the Reynolds stress tensor (Eq. 29), can be defined as:

$$T_{ij} = \langle \tau'_i \tau'_j \rangle = \frac{1}{N} \sum_{n=0}^{N-1} \underbrace{(\tau_i - \langle \tau_i \rangle) (\tau_j - \langle \tau_j \rangle)}_{\tau'_i \tau'_j} \quad (54)$$

Figure 30: Rose diagrams showing the accumulated dynamics of the WSS vector τ over 40 cardiac cycles (400k samples) at different feature locations with respect to the cycle-averaged WSS direction τ_m at 0° (also shown as surface streamlines). The bin radius represents the amount of data in the sampled directions associated with each 10° sector, including a colormap representing the averaged WSS magnitude. The table insets show the corresponding values of the investigated WSS-based descriptors. The feature locations are grouped into: (A) unidirectional-dominant WSS fluctuations proximal to the saddle point, similar (B) intermediate and (C) high transWSS and tWSS values, respectively.

where e.g. $T_{12} = \langle \tau'_1 \tau'_2 \rangle = \langle \tau'_x \tau'_y \rangle$ in Cartesian coordinates. The traceless anisotropy tensor is then given by:

$$w_{ij} = \frac{T_{ij}}{T_{kk}} - \frac{\delta_{ij}}{3} \quad (55)$$

where time-averaging of $\sqrt{T_{kk}}$ is equal to the tWSS magnitude (see Eq. 36). The degree of one-componentality of the tWSS, or tWSS anisotropy index (AI_w), can now be defined from the second (principal) tensor invariant (Π_w) as:

$$AI_w = \underbrace{(w_{ij}w_{ji})}_{\Pi_w} - \frac{1}{3} \quad (56)$$

This index is analog to AI_a for R_{ij} , but instead rescales the second invariant between 0 and 1 (vertically within the Lumley triangle, Fig. 22) between the 2C corner (random oriented tWSS fluctuations, i.e. the axisymmetric isotropic state) and 1C corner (unidirectional tWSS fluctuations, one-component state). In the barycentric AIM, an equivalent tWSS anisotropy index can be acquired, but here instead directly along the two-component limit (Fig. 28b), by simply assessing the size of the C_{1C} anisotropy weight:

$$AI_{wb} = C_{1C} \quad (57)$$

The only difference between these anisotropy indices are the linear distribution of the data, e.g. the plain-strain position for $AI_w = 1/9$ whereas for $AI_{wb} = 1/3$. In Paper III the tWSS anisotropy was described by AI_w , while the results herein are presented using AI_{wb} .

These tWSS descriptors were assessed in both the pre-op and follow-up case. Collectively, results showed that most of the elevated tWSS regions could be characterized by axisymmetric-dominate states (Fig. 29), mainly realized between the 2C corner and the plain-strain state (Fig. 28b, $AI_{wb} \approx [0, 0.33]$). However, also some sizable region of more elevated tWSS anisotropy could be seen in the turbulent region ($AI_{wb} > 0.4$), and especially in some regions of weaker tWSS magnitudes (i.e. in transitional-relaminarizing-like flows), e.g. between the aortic kink and CoA. The general characteristics of the tWSS anisotropy did not change markedly in the follow-up case (except location-wise), despite the significant tWSS magnitude reduction. Also, no consistent relation was found between the tWSS anisotropy indices and the transWSS nor OSI parameter. These findings may be explained by the fact that the tWSS anisotropy does not entail any magnitude information and leave out low-frequency laminar-related WSS variations.

4.3.2 Near-wall flow correlations

In a clinical setting, enabling the interpretations of accurate in vivo measurement of hemodynamic descriptors is arguably preferable over indirect analyzes derived from image-based modeling results, which adds extra layers of complexities into the decision-making due to the additional errors and uncertainties. Over the past decades, several attempts to estimate WSS-based parameters using MRI have been made at various arterial sites in order to target regions susceptible to endothelial and biological dysfunctionalities [191]. However, the accuracy of these MRI-based WSS predictions are poor compared to well-resolved CFD results, with a general

tendency of underestimate the WSS magnitude substantially due to the limited (near-wall) spatial resolution (voxel size) [28, 186], especially in high WSS region where the near-wall velocity gradient is very steep. Thus far, MRI WSS estimations can, therefore, only be evaluated on a relative trend basis [191]. For 4D Flow MRI measurements, turbulence-related quantities are often evaluated using the intravoxel velocity standard deviation (Sec. 2.5), a proxy for the turbulence intensity, which near the lumen wall have been proposed for estimation of turbulent-like WSS disturbances [189, 60]. In a recent study, promising results were found between near-wall TKE and the magnitude of the tWSS, obtained from CFD-based 4D Flow MRI simulations under steady flow conditions [264]. Of late, 4D Flow MRI has also been used to estimate all Reynolds stress components [92, 112], which have shown clinical potential for improving pressure loss and blood damage predictions [87, 86, 84] and, as shown in this thesis, for general turbulence anisotropy characterization (Sec. 4.4.2).

Figure 31: Spearman's rank correlations between WSS-based and near-wall bulk flow descriptors. All correlation where significant ($p > 0.001$) (a) cycle-averaged correlations from Paper II, pre-op and at follow-up (denoted: pre/follow). The KE and TKE parameters were extracted at 0.5 mm wall-normal offset distance. (b) Correlations at different wall-offsets (0.1 to 4 mm), time-averaged over the most profound turbulent phase in the cardiac cycle. For both flow cases a strong correlation can be noticed between tWSS magnitude and TKE at a substantial distance (~ 3 mm) away from the wall, while the anisotropy indices (AI) only shows a substantial correlation in the inner-most wall region of the turbulence anisotropy layer (roughly represented by the shaded gray area).

In Paper II and III, part of the objective was to investigate the correlation between possible MRI-measurable near-wall bulk-flow descriptors and different WSS parameters in a physiologically realistic flow environment, using the pre-op and follow-up CoAs as two representable conditions with substantially different near-wall turbulence intensities (Fig. 26). In Paper II the so-called Spearman's rank correlation was used to determine the strength and direction of the monotonic relationship between two variables, which is given by the correlation coefficient r_s in the range $[-1, 1]$, without regards to its linear or non-linear tendency. Here, the sign of r_s indicates if the correlation has an increasing (positive) or decreasing (negative) monotonicity. One of the key findings in this paper was the very strong correlation ($0.95 < r_s$) between the near-wall TKE (at 0.5 mm wall-offset) and tWSS (Fig. 31a), which was in agreement with the previous MRI study [264].

In *Paper III*, more in-depth investigations were performed by assessing the correlation between the magnitude and anisotropy characteristics of the WSS-related tensor (T_{ij}) and Reynolds stress tensor (R_{ij}) as a function of wall-normal offset distance (Fig. 31b). Here, we also calculated the so-called Pearson's correlation coefficient r , which is analog to the Spearman's correlation but estimates the linear relation between two variables. The trends between the correlation coefficient were, however, shown to be fairly similar. In summary, an overall strong monotonic correlation ($0.9 < r_s$) could be observed over the entire wall-offset range between the tWSS magnitude and near-wall TKE, showing strong linearity ($0.9 < r$) up to roughly 3 mm away from the wall. Between the anisotropy indices (AI_w and AI_a) a strong correlation could only be found in the inner-most wall region (~ 0.1 mm), while being more decorrelated ($r_s \sim 0.5$) halfway into the near-wall "turbulence anisotropy layer". No substantial differences were found between the pre-op and follow-up cases, suggesting these correlations to be fairly consistent.

For aortic 4D Flow MRI, the (isotropic) voxel size is typically in the range of ~ 2 mm [58], which suggest that near-wall TKE may be used for non-invasive assessment of the tWSS magnitude, without substantial wall-induced errors. However, the validity of this proposition needs to be tested using real measurements and over a more extensive set of patient-specific flows. The degree of anisotropy between tWSS and Reynolds stress tensor appeared to only conform well within the sub-millimeter wall-offset range and, therefore, can presumably only be estimated by well-resolved CFD methods or possibly a hybrid CFD-MRI approach.

4.4 Model verification & validation

In Sec. 3.4, the importance of performing proper model verification, validation, and uncertainty quantification was emphasized to estimate the inaccuracies in the output results. This section will summarize some of the key verification and validation findings related to the different CFD modeling strategies adopted throughout this thesis. Uncertainty quantification was beyond the scope of this thesis but may be the target for future studies as it is a crucial step for clinical reliability [224]. Some of these aspects are discussed in the Outlook chapter (Ch. 6).

4.4.1 Verification aspects

(*Paper I to III & V*)

In all papers, the modeling errors related to the spatial and temporal resolution of the CFD model as well as phase averaging sampling size (Sec. 3.2.2 and 3.2.5) were analyzed by different sensitivity studies. In this section, the main findings of these verification studies will be presented and discussed. More details and other sensitivity studies can be found in the papers SM.

In *Paper I to III*, the sensitivity analyzes were (partly or entirely) based on the volume integrated TKE (k_D , Eq. 51), which is an aggregated parameter that shows the pulse-varying amount of turbulence-related energy in the vascular region. With this descriptor, only a minor difference was observed between the coarse (3MC-CFL5) and fine (6MC-CFL1) spatiotemporal resolutions (Fig. 32a), findings which suggest that a majority of the energy-containing

scales were well-resolved. Other results (Paper II, SM) also indicated very similar k_D predictions when adopting a factor five larger time-steps ($CFL < 5$) in comparison to the more conservative (conventional) approach ($CFL < 1$). This contributed to more than a tenfold lowering in computational costs when comparing the 3MC-CFL5 (~ 650 CPUh/cycle) and 6MC-CFL1 (~ 8700 CPUh/cycle) pre-op cases. For the phase averaging results (Fig. 32b), small overall k_D differences could be noticed after 10 cycles and near negligible by including more than 20 cycles. Here, the results from the non-overlapping cycle ranges of equal sample size showed close agreement.

Figure 32: Different sensitivity analyzes of the volume-integrated turbulence kinetic energy k_D across the cardiac cycle in the pre-op case, assessed in the post-stenotic domain (aorta inset, black region). Results were normalized by the peak values of the most well-resolved case in each analysis. (a) Impact from different spatiotemporal resolutions: 3 million cells (MC) with maximum $CFL < 5$ (3MC-CFL5) versus 6 MC with maximum $CFL < 1$ (6MC-CFL1). The phase-averaged results were derived for 50 cardiac cycles. (b) Impact from different doubling phase-averaged sampling sizes, including non-overlapping ranges between 5 to 80 cycles (denoted with * or **). For example, here 10* and 10** represent the first and last 10 cycles, respectively, within the full 80 cycle range.

In Paper V, the sensitivity analyzes were based on the change in Reynolds stress tensor characteristics using a root-mean-square deviation (RMSD) measure to assess the errors associated with the magnitude (Eq. 58) and componentality (Eq. 59) in different regions of the computational domain:

$$k_{rms} = ((\Delta k)^2)^{1/2} = |\Delta k| \quad (58)$$

$$C_{rms} = \left(\frac{1}{3} \sum_{i=1}^3 (\Delta C_{iC})^2 \right)^{1/2} \quad (59)$$

where k is the TKE (Eq. 31), C_{iC} the weights (Eq. 45) of the barycentric AIM, and Δ denoting the cell node change of the quantity between two cases. The C_{rms} metric is an intuitive descriptor that provide an direct sense of the turbulence states percentage variation within the barycentric AIM. Qualitative case comparisons were made along different cross-sectional planes in the turbulent region (for brevity here only shown for one location), at one phase-instant snapshot (Fig. 33) and for the time-averaged results over the EFD phase (Fig. 34). Quantitative

assessments were also made by considering the cross-sectional mean of k_{rms} and C_{rms} over different post-stenotic location (Fig. 35a). Also, for the phase averaging analysis, the mean third quartile⁴ (Q_3) value of k and each C_{iC} weight were evaluated to assess the parameters overestimation/underestimation tendency as a function of included number of cardiac cycles (Fig. 35b).

Take collectively, the largest discrepancies were associated with the phase-instant results, exhibiting considerable errors (above 10%) even at the 40 cycle range for both the TKE and turbulence states. For the time-averaged data, the corresponding errors were well below the 5% margin. These analyzes also showed that the errors associated with the lower cycle ranges could easily outweigh the spatiotemporal errors. Between these descriptors, TKE showed overall lower errors, with fairly small deviations for the EFD time-averaged results already at 10 cycles. However, for the phase-instant TKE, the cross-sectional mean error $\sim 15\%$ between the 40 independent cycle ranges (Fig. 35a, Instant, blue), which is significantly larger compared to the errors estimated from the volume-integrated TKE method (Fig. 32b). By evaluating the phase averaging dependency on the Q_3 values (Fig. 35b), fewer cycles could be coupled to a clear underestimation of the time-averaged TKE, C_{2C} and C_{3C} states, while C_{1C} states, on the other hand, was substantially overestimated. However, at the 40 cycle mark, the Q_3 value of both C_{1C} and TKE were well converged ($\sim \pm 5\%$), whereas the C_{2C} and C_{3C} states still showed major deviations compared to the 80 cycle reference case. These trends can also be indicated in the contour plots (Fig. 33 and 34), where e.g. C_{3C} is clearly underestimated in the core flow region at the lower cycle ranges. In general, these findings demonstrate that the most demanding Reynolds stress characteristics to statistically converged from an phase averaging sense are associated with moderate-to-low turbulence intensities with higher degrees of active fluctuating directions (componentality).

Generally speaking, caution should be taken when selecting a proper model verification framework, where error sensitivity analyzes preferably should be based on the specific parameters of interest to assure better result reliability. For more global flow descriptors, a method such as the volume integrated TKE may be an appropriate turbulence-related metric. However, if more in-depth analyzes of tensor-related quantities (fields) are explored, a more comprehensive verification approach, such as the one described in Paper V, may be more suitable to avoid misleading results and conclusions. For examples, the findings in Paper V suggest that much more than 50 cardiac cycles (as used in Paper IV and usually less in the computational hemodynamics community) are required in order to attain sufficiently low phase averaging errors. For quantitative comparisons, however, it is also important to emphasize that a slight shift in the flow feature positioning (e.g. in jet angle, penetration depth, etc.) between two flow cases will lead to large point-wise deviation errors, while the overall flow characteristics may be fairly similar. Therefore, it is important to also analyze these results qualitatively and contrast the errors against other modeling errors/uncertainties.

⁴The third quartile (also called the upper quartile or 75th percentile) represent the median of the upper half of the data values or the threshold dividing the top 25% from the lower 75% values.

Figure 33: Sensitivity analyses of the phase-instant Reynolds stress characteristics, showcased at one cross-sectional position (inset, 1D) downstream the constriction, showing the contour of turbulence kinetic energy (k), turbulence stress-states and root-mean-square (RMS) deviations. The snapshot was acquired at the early flow deceleration phase (inset, solid line, marker). Different non-overlapping (independent) cycle ranges were compared against each other (denoted $*vs.**$) as well as against the whole data range. For example, $40*vs.40**$ compare the phase-averaged results between the first 40 cycles against the last 40 cycles, whereas for example, the notation $40*vs.80$ compares the first 40 cycles against the complete range ($N = 80$).

Figure 34: Sensitivity analyzes of the time-averaged Reynolds stress characteristics, showcased at one cross-sectional position (inset, 1D) downstream the constriction, showing the contour of turbulence kinetic energy (k), turbulence stress-states and root-mean-square (RMS) deviations. The time averaging was performed over the most profound turbulence phase (early flow deceleration) in the cardiac cycle (see insets, shaded area). For additional details see Fig. 33.

Figure 35: **(a)** Bars showing the phase-instant and time-averaged (EFD) cross-sectional mean RMSD (root-mean-square deviation) of the Reynolds stress characteristics (TKE and stress-states) for the investigated sensitivity analyzes. The TKE deviation was normalized by the combined cross-sections third quartile Q_3 value (58 Pa), which provide a relative error measure against the median of the upper half of the turbulence intensity. The error bars signify the min/max variability over the assessed cross-sections (inset, 0D to 3D). For additional details see Fig. 32, 33, and 34. **(b)** Mean variations (with min/max error bars) of the TKE and AIM weights (C_{iC}) Q_3 values against the phase-averaged sampling sizes. The data was spatiotemporal-averaged over the EFD phase and over all five cross-sections (0D to 3D), and normalized by the corresponding Q_3 value for the most resolved 80 cardiac cycles case.

4.4.2 Validation aspects

(*Paper IV*)

Part of the aim of Paper IV was to validate the Reynolds stress characteristics derived from different (simplified) conventional used modeling strategies, using the LES results as the physiological realistic reference data. The first comparison was against a steady (non-pulsatile) inflow assumption, which sometimes is used to represent a worst-case scenario (e.g. peak flow) due to lack of sufficient BCs and/or motivated by reduced computational costs. Several studies have indicated that steady flow regimes generate substantially different turbulent behavior in pipe constrictions compared to pulsatile conditions (e.g. [241, 242, 149]). In Paper IV, turbulence-related tensor properties were investigated in a more physiological realistic setting. Here, the pulsatile peak and mean flow rates were used as steady inflow conditions. The second strategy was to model the turbulent flow field using a URANS approach (Sec. 3.3.2), where the phase averaging is replaced by only evaluating the results derived from one cardiac cycle, which leads to a substantial reduction in computational costs, data storage, and post-processing steps. To minimize these costs, RANS simulations are, unlike LES, performed on relative coarse mesh densities. In this study, however, we opted to only compare the impact from the turbulence modeling itself by simply replacing the LES WALE subgrid model with the two-equation eddy viscosity formula using the SST model, while keeping the same spatial (mesh) filter width.

In *Paper IV*, the steady inflows showed a general qualitative agreement against the anisotropic stress-states of the time-averaged pulsatile results (Fig. 36). However, the TKE was substantially overestimated at peak flow, while being underestimated for the mean flow conditions. The turbulence states agreement can be explained by the quasi-steady turbulent jet with similar post-stenotic trajectory seen in both cases, whereas the latter disagreement is primarily due to the difference in main flow momentum (Reynolds number). Within the AIM, however, the steady inflow condition entailed a generally broader spectrum of stress-states, with noticeable pattern differences compared to the pulsatile results. Here, the steady flows entailed much more isotropic-dominant stress characteristics, i.e. higher C_{3C} weights, which most likely can be associated with the more well-developed turbulence field in this case, allowing for more isotropization. It is important to note, however, that the time-averaged LES results were, compared to the pulsatile results, acquired for many orders of magnitude more time-steps in order to fully capture the three-dimensional random-oriented fluctuations of these states. By the same token, the EFD pulsatile results is conceivably a better depiction of these stress-states as the data, in essence, have been reconstructed (time-averaged) from 1000 samples (50 cycles $\times$ 20 time-steps) as compared to the phase-instant results which used 50 samples (50 cycles). However, this statement assumes that the flow needs to be quasi-steady over the time-averaged phase, which may be true for this particular flow case, both not in general.

RANS-based methods are the most common turbulence modeling approach within the general CFD community. However, for blood flow predictions involving pulsatile, transitional, and relaminarizing flow characteristics, RANS modeling is not usually recommended due to their poor overall performance [161, 232]. Nevertheless, RANS predictions are still quite common within the computational hemodynamics research field. In *Paper IV*, the RANS results showed poor agreement against the Reynolds stress characteristics obtained by LES (Fig. 36),

Figure 36: Validation of the patient-specific centerplane Reynolds stress characteristics, showing the reference pulsatile LES results (top row), in comparison to the LES using steady inflow conditions (middle row) and pulsatile URANS turbulence modeling (bottom row). The reference LES and URANS results were time-averaged over the early flow deceleration (EFD) phase.

with apparent underestimation of the TKE as well as anisotropic stress-states. Here, the turbulent region was dominated by close-to isotropic characteristics, predominantly in the vicinity of the plain-strain condition. These findings have been reported elsewhere for steady RANS solutions [62], and verifies the model's known inability to cope with turbulence anisotropy; here also confirmed for URANS modeling.

Barycentric anisotropy invariant mapping was also used to evaluate the reliability of Reynolds stress tensor characteristics acquired from ICOSA6 4D Flow MRI measurements [87]. The flow rig consisted of a straight pipe with fully developed laminar inflow forced through a sudden constriction (orifice), with 75% cross-sectional area reduction, which triggered turbulence flow. In this study, two different flow rates were investigated, providing a Re_D of 2058 and 5383 based on the large diameter section. Herein, only the intermediate flow rate ($Re_D = 3346$) is shown.

Figure 37: MRI-based Reynolds stress characteristics downstream a constricted pipe, showing the axial plane contours of velocity magnitude, turbulence kinetic energy (TKE), anisotropy index (Anisotropy, AI_a), and turbulence stress-states. The barycentric AIM shows the highest 25% TKE values (i.e. above the third quartile value), including the nonphysical (unrealizable) voxels that fell outside the triangular domain; also rendered as black voxels over the gray axial plane.

Qualitatively, the MRI-based Reynolds stress characteristics showed general expected TKE as well as stress-state patterns (e.g. anisotropic features along the jet) in the post-orifice region (Fig. 37), in consideration of the coarse spatial resolution. At the same time, extensive regions of unrealizable voxels could be pinpointed in part of the turbulence spot, even associated with the 25% highest TKE values (i.e. above the Q_3 threshold), demarked by the black voxels in Fig. 37. These latter, nonphysical voxels appeared to be co-localized to regions associated with high shear-intensity (shear-layer destabilization), where also the turbulence production presumably is elevated. Within the triangular map, the highest TKE levels were associated with 1C-dominant characteristics and vice versa. These findings seem to be at odds with the general trends predicted by e.g. the patient-specific LES model using a steady inflow condition (Fig. 36, barycentric AIM), which may suggest that some characteristics (voxels) within the AIM to entail inadequate flow physics. However, the reliability of these possible inaccuracies needs to be validated in by more thorough MRI-CFD benchmark studies. The violation of the realizability constraints also suggests that more emphasis should be placed on improving the

MRI measurement techniques and data reconstruction methods.

Conclusions

This thesis has demonstrated some novel and intuitive ways to characterize the phase-wise turbulence blood flow patterns in realistic but periodic patient-specific flows. These cycle-to-cycle turbulence-related flow variations were assessed in the bulk flow as well as on the intraluminal wall; from in-depth analyzes of various tensor characteristics (such as magnitude and anisotropy of Reynolds stresses and turbulence-related WSS) to more global hemodynamic descriptors (such as space-time TKE and flow eccentricity maps, and total TKE over the cycle). The benefit with these descriptors is that they all, at least in principle, can be acquired by non-invasive MRI measurements, hopefully making inroads into clinical practice easier. Also, methods like barycentric anisotropy invariant mapping may assist in the development of more reliable CFD models for turbulence predictions as well as MRI-based turbulence measurements within the biofluid community. The clinical significance of these potential flow-mediated phenotypes has so far not been outlined but might help in targeting disease-prone cardiovascular regions, to better understand endothelial and biological dysfunctionalities and improve blood damage predictions; towards improved individual-based risk assessments and intervention procedures.

All studies within this thesis were based on data from one single patient (disease), from which general conclusions cannot be drawn. However, it is important to note that the emphasis of these studies was aimed towards showing new methods for describing turbulent flow characteristics in complex arterial models reconstructed from medical images, rather than focus on the absolute values/differences of the specific results. Nevertheless, many of the overall trends agreed well with expectations and results found in other studies. However, to assess the generality of these findings, a much larger cohort of patient-specific investigations are encouraged, including different cardiovascular diseases governed by various turbulent-like conditions.

Outlook

The studies related to this thesis entail many modeling limitations and assumptions with respect to the real physiological state (Sec. 2.1), many of which have been addressed in Sec. 3.2 as well as discussed in the appended papers and SM within. Although the current work has been restrained to specific phase-averaged flow descriptors and post-processing techniques, there are many other ways to analyze turbulent flows. Over the past decade, the biofluid community has progressed significantly, showing new and more comprehensive ways to modeling realistic cardiovascular flows and describing flow disturbances. This chapter will outline some of the potential development possibilities related to image-based CFD modeling strategies, hemodynamics descriptors, and other important general aspects.

- *Tensor descriptors.* This thesis focused on the componentality of turbulence, which represents the relative strength of the fluctuating velocity components. However, according to the complete single-point tensor description (Eq. 37), there are also information related to the structure of the turbulent field (e.g. the dimensionality and circulicity tensor), which have shown to be highly affected by e.g. wall irregularities [261] and depart from the turbulence componentality depending on the local flow properties [17]. In Paper IV, we characterized the Reynolds stress and dissipation rate tensor; however, these methods may also be applied to any flow-related (symmetric) positive semi-definite tensor [16], such as the anisotropy strain rate tensor. In this work, we also ignored the orientation of the turbulence, which can be described by the three principal eigenvectors. This information can, for example, be used to visualize the dominant (major eigenvector) directionality of the tensor descriptor along the wall (e.g. by WSS surface vectors/streamlines) or in the bulk flow (e.g. using hyperstreamlines [48]).
- *Spectral analyzes.* An alternative to phase averaging could be to assess the transient flow instabilities through proper orthogonal decomposition (POD) [83, 114], which can identify the energy-containing modes (harmonics of coherent structures) associated with varying flow patterns in laminar-turbulent regimes. To attain high spectral resolution in POD analyzes, more or less the complete time history of the data needs to be saved, which can be storage demanding. However, unlike phase averaging methods, cardiovascular POD analyzes can be adopted using only one representative cardiac cycle, where mode decompositions can be applied to evaluate the turbulent contribution. However, a downside is that POD tends only to capture the energy-dominant flow variations (low modes) while being less sensitive to weaker small-scale instabilities [11]. Nowadays, several extended POD versions exist, such as spectral POD, which can analyze mode-variations both in space and time, and dynamic mode decomposition, which can be used to study the modes associated with specific flow frequencies.

Another commonly used method is to simply apply frequency-based filtering on the pulsatile flow field (e.g. [118, 170, 171]), to distinguish between low-frequency flow variations, carried by the inflow pulsations and secondary flow features, and more high-frequency flow instabilities associated with the turbulence characteristics. This approach is not limited to any flow regime and appears to provide a relatively good picture of the regional flow frequency content, using substantially fewer cardiac cycles than required for phase averaging analyzes. Also, an interesting analysis would be to cross-compare the nature of the turbulence anisotropy and frequency content in various regions of different patient-specific hemodynamics.

- *Boundary conditions.* The image-based CFD models used in this thesis were assigned with the simplest form of BCs (Sec. 3.2.3), i.e. rigid wall, prescribed flat inflow and outflow profiles, and a constant pressure outlet. To favor better flow predictions throughout the entire computational domain, these BCs should preferably be replaced by more realistic conditions, e.g. including axial and in-plane velocity components (secondary flow features) and, if needed, turbulence information. However, to assign representable conditions to mimic the true in vivo conditions are not trivial between MRI-obtained velocity profiles (with coarse spatial resolution, compliance-induced phase-shifts, time-varying lumen area, etc.) and a well-resolved rigid CFD mesh. This low-to-high rank data reconstruction between these two modalities needs to be assessed carefully to attain proper BCs for the purpose of the study [232, 11]. A promising modeling improvement would be to incorporate the measured lumen wall dynamics, which have been successfully implemented in cardiovascular flow simulations using high-resolution CT data [127, 33], as well as for much coarser MRI data [127]. CT-based CFD modeling has the benefit of attaining a well-resolved vessel geometry, which has shown to be the most crucial modeling aspect influencing the flow predictions [147], but lacks any patient-specific flow information. These flow-related BCs can be acquired from additional measurements using MRI or e.g. generated artificially from population statistics. Also, simulations derived from several different modalities make case comparison (validation) more complicated and less robust. MRI-based CFD suffers from poorer geometry representation (often acquired from cycle-averaged angiograms), but on the other hand, entails the flow data. Recent studies, however, have open the door for automatic segmentation and flow quantification techniques of 4D Flow MRI data [31], including the transient wall dynamics [30]. Patient-specific CFD simulations solely encoded from 4D Flow MRI data would ease BCs mapping as well as uncertainties related to the validation process (if the method can reproduce a sufficient wall-representation). Speaking of, in this thesis, the lumen walls were represented by MRI-based STL-surfaces (i.e. a network of small anisotropic triangular elements), which could capture the essential topological features of the malformed aorta; however, also including unwanted surface distortions in the order of the anisotropic MRI resolution. These coarse voxel-related surface features will naturally be captured by a well-resolved CFD method when the mesh size approach the size of the STL triangles, which occasionally can be noticed in the WSS contour patterns in this work. To minimize these undesirable features, the segmented data could instead be reconstructed by an analytical "best-fit" geometrical descriptions, such as lofting/patching between cross-sectional contours [147], or as a union of spheres derived from a Voronoi diagram [7], including parametrization of flow-mediated morphology features [24].

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- *WSS topological skeleton.* Lately, there has been a rising interest in the characteristics of the topological structures of the WSS vector field (e.g. [14, 151], and Fig. 30), i.e., the location and nature of so-called WSS fix points and manifolds, which are an indirect reflection of the near-wall flow characteristics. In a recent study [165], some of these topological features could predict long-term restenosis after carotid disease intervention. An interesting extension of these promising hemodynamic markers would be to distinguish between WSS topological skeleton dictated by low-frequency laminar flow variations and turbulent-like intermediate-to-high frequency fluctuations associated with the tWSS vector. It would also be interesting if MRI measurements would be able to capture any of these near-wall features. However, during highly turbulent near-wall flows, as in the pre-op case, these topological WSS structures are very irregular/unstable (see Fig. 29, instantaneous WSS), presumably lacking any well-defined fix-point region nor manifold characteristics over a majority part of the cardiac cycle.
 - *Uncertainty quantification.* Modeling errors and input uncertainties are controlling the true accuracy of output predictions (Sec. 3.4), which ideally should be reflected by both a mean and variance measure. Therefore, UQ is an essential pre-clinical step, which has received increased attention within the computational hemodynamic community over the past years (e.g. [224, 106, 104, 23]). With this in mind, the hemodynamic descriptors outlined in this thesis should preferably be analyzed against, for example, the most sensitive inputs, which have been proposed to be foremost associated with the inflow conditions [132] and geometry uncertainties [147]. Also, UQ related to the LES subgrid modeling alone [159] would be interesting to examine for cardiovascular flow predictions. Conventional UQ, however, typically requires a huge set of simulations (samples) in order for the results to be statistically valid. Considering the computationally expensive CFD strategies used for computing phase-averaged solutions within this thesis (including the large amount of manual labor in both pre- and post-processing steps), the future focus should be on identifying cost reductions towards the most effective or "bang for the buck" solution strategies. In a newly published study [258], a variance-based sensitivity method was utilized to attribute the uncertainty of the outputs to specific modeling inputs, which required significantly less number of samples than standard UQ methods. This UQ framework used LES on patient-specific aortic aneurysm models and an idealized aortic arc benchmark to assess the output sensitivity to uncertainties in geometry and inflow variations, and modeled subgrid dissipation strength. Among the targeted flow descriptors (TAWSS, OSI, and volume integrated total KE), the geometry uncertainty appeared to have the largest impact in this study.
 - *CFD solver aspects.* The reliability of CFD predictions is highly dependent on choosing proper numerical modeling strategies to solve the discretized governing equations in the computational domain. In this thesis, the energy-carrying turbulent flow field was computed by the commercial CFD solver ANSYS CFX using an FVM-based LES approach (Sec. 3.2.5 and 3.3.2). Commercial solvers are usually implemented with lower-order discretization schemes, second-order or lower, which are known to be fairly dissipative (i.e. in effect adding extra viscosity to the flow) and can inhibit natural flow development in comparison to higher-order methods [25, 203]. Also, these CFD codes are closed, and hence the true (apparent) order of accuracy of the CFD simulation is unknown. For the LES simulations herein, the used spatiotemporal schemes were formally second-order accurate; however, the apparent order of accuracy can only be found via e.g. mesh sensitivity studies using the Richardson's

extrapolation procedure. Commercial CFD solvers are also essentially designed for engineering applications, and less for academic turbulence research, with arguably a higher priority towards delivering converged solutions over accurate ones.

Indeed, over the past decade there have been a growing interest within the biofluid community of using CFD methods that are minimal-dissipative highly-resolved (e.g. [238, 239, 116, 148, 25]) and of higher-order (e.g. [133, 241, 242, 135, 203]) to improve the predictions in transitional-turbulent flows, where conventional low-resolution/order CFD approaches are less favorable. The open-source Nek5000 CFD solver [68], which is a higher-order spectral-element method (SEM) characterized by high computational efficiency and excellent parallel (supercomputing) performance for large-scale turbulent flow simulations. In fact, various flow studies have shown that for a given accuracy and computational resources, the time-to-solution is significantly less for Nek5000 compared to lower-order finite volume solvers (such as OpenFOAM) [215, 34]. The feasibility of using Nek5000 have already been shown for patient-specific modeling [135, 133] and blood-like applications [241, 242, 203]. Patient-specific turbulence simulations using true, fully-resolved DNS on homogeneous blood-mimic fluids are not pragmatic due to the high computational costs nor wise due to the RBCs viscoelastic dampening effects in real blood [8], which most likely narrows the turbulence energy spectra. Therefore, a more rational approach would be to find the "sweet spot" between accuracy and computational efficiency by adopting under-resolved DNS or LES methods. For minimal-dissipative numerical schemes, such as the SEM, the energy drainage by the unresolved subgrid scales needs to be accounted for, which usually is done by a relaxation term equivalent to a low-pass filtering approach. SEM-based LES have shown excellent agreements against fully-resolved DNS results [206, 245], but for substantially lower costs. However, one of the main issues of high-order CFD codes is the mesh constraints, where the computational domain often needs to be represented by high-quality (hexahedral) spectral elements, which can be challenging to reconstruct for complex cardiovascular geometries. However, if this bottleneck can be superseded by more efficient methods, such as improved lumen surface representations and adaptive mesh refinement techniques [178], high-order under-resolved DNS may become an attractive tool for future high-fidelity transitional-turbulent blood flow predictions.

- *Flow visualization.* The presentation of blood flow data should not only be clear and easily accessible but also appealing for the user/audience (technicians or clinicians) to facilitate result interpretations [228]. In this thesis, focus has been put on finding a trade-off between comprehensiveness and clearness of the displayed results, e.g. by decoding the hemodynamic descriptors originated on a 3D surface onto a 2D domain (Paper II and III), mapping turbulence componentality (Paper IV and V) and including intraluminal flow eccentricity polylines (Paper I) into the physical domain. Future visualization strategies may incorporate a more dynamic view, e.g. by showing the evolution of the hemodynamic descriptors in a carousel-type representation [228], including animations. A recent study also extruded a third dimension in the barycentric AIM to contextualize the time evolution of the turbulence characteristics [243]. Interpretations may also be facilitated by visualizing the flow frequency content in different ways [170, 171], as well as topology skeleton visualization on the lumen wall or in the near-wall region.

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- *MRI-CFD validation.* Although 4D Flow MRI is the golden standard for assessing in vivo hemodynamics, the results are spatially and temporally coarse and entailed substantial uncertainties. For patient-specific CFD simulations, additional uncertainties are included, making benchmarking between MRI and CFD difficult. To narrow this gap, more thorough validation procedures are needed, where these input uncertainties are minimized. Here, it would be rational to start with simpler in vitro studies, such as the flow rig assessed in Paper IV, and thereafter progress to more physiologically realistic (pulsatile) flow conditions through idealized vessel shapes. The current benchmark established by the US Food and Drug Administration for validating biomedical CFD codes, the so-called FDA nozzle, is a bad choice due to its design and input uncertainties, resulting in very sensitive outcome predictions [25, 203].

Summary of appended papers

Paper I

Quantitative assessment of turbulence and flow eccentricity in an aortic coarctation: impact of virtual interventions, Magnus Andersson, Jonas Lantz, Tino Ebbers, Matts Karlsson, *Cardiovascular Engineering and Technology*, 2015, vol. 6, no. 3, pp. 281–293, doi: 10.1007/s13239-015-0218-x.[†]

This paper performed image-based CFD simulations to study the turbulence and eccentric flow features in a recurrent aortic coarctation (CoA) and after various (simulated) virtual dilatation procedures aimed to restore the post-stenotic flow differently. All suggested blood flow descriptors can be measured by MRI and, therefore, potentially be used for noninvasive therapeutic decision-making. Space-time maps of the turbulence kinetic energy (TKE) and flow eccentricity could be coupled to the characteristics of the post-stenotic turbulent jets', showing distinctive impact on the flow skewness and distribution patterns of the turbulent field for the different cases. For example, certain eccentric morphology changes of the constriction appeared to favor more concentric downstream flow conditions, which induced less turbulence-to-wall interaction. This study also evaluated flow descriptors that assessed the cyclic evolution of the combined TKE in the vascular domain, including the total amount energy accumulated over the cardiac cycle, as a measure of CoA severity. These descriptors found a asymptotic decay of TKE in response to less degree of constriction, findings which suggest that the flow restoration in terms of turbulence removal, in this case, cannot be fully achieved by treating the CoA alone.

Author Contributions: Andersson, Lantz, and Karlsson conceptualized the study. Andersson designed the methodology, computational models, performed all simulations and post-processing steps and wrote the original draft. Lantz and Karlsson supervised the work and helped with the result interpretations. Karlsson and Ebbers contributed with funding, data, and computational resources. All coauthors assisted with the review of the manuscript.

[†]Note, the appended paper is the erratum version of the original article, doi: 10.1007/s13239-015-0243-9.

Paper II

Multidirectional WSS disturbances in stenotic turbulent flows: A pre- and post-intervention study in an aortic coarctation. Magnus Andersson, Jonas Lantz, Tino Ebbers, Matts Karlsson, *Journal of Biomechanics*, 2017, vol. 51, pp. 8–16, doi: 10.1016/j.jbiomech.2016.11.064.

This paper investigated the response of various WSS-based descriptors, conventionally used or recently introduced to assess WSS disturbances, in two patient-specific CFD models of a aortic coarctation (CoA) before and after intervention. The primary focus was on evaluating the recently proposed transverse WSS (transWSS) descriptor ability to predict multidirectional WSS disturbances under different near-wall flow regimes (laminar, transitional and turbulent) manifested over the cardiac cycle. Qualitatively, the transWSS results signified a quite versatile response, unlike the conventional parameters, capturing wall regions dictated by both transitional and turbulent-like near-wall flow disturbances. However, by more in-depth analyzes of the actual transient WSS dynamics using rose-diagrams, several local inconsistencies could be observed where the tranWSS parameter displayed misleading WSS characteristics. This apparent drawback was associated with the WSS topology structures, where ill-defined cycle-averaged WSS vector directionality were co-localized close to so-called WSS fix-points.

Author Contributions: Andersson, Lantz, and Karlsson conceptualized the study. Andersson designed the methodology, computational models, performed all simulations and post-processing steps and wrote the original draft. Lantz and Karlsson supervised the work and helped with the result interpretations. Karlsson and Ebbers contributed with funding, data, and computational resources. All coauthors assisted with the review of the manuscript.

Paper III

Characterization and estimation of turbulence-related wall shear stress in patient-specific pulsatile blood flow, Magnus Andersson, Tino Ebbers, Matts Karlsson, *Journal of Biomechanics*, 2019, vol. 85, pp. 108–117, doi: 10.1016/j.jbiomech.2019.01.016.

In this paper, a novel approach was showcased to characterize the phase-averaged turbulence-related WSS (tWSS) disturbances in realistic cardiovascular flows. This was done by reconstructing a tensor from the six-independent cross-correlations between the fluctuating WSS components, from which both the magnitude and anisotropy (shape) of the tWSS could be extracted. These WSS descriptors were evaluated in two patient-specific CoA models, before and after intervention, using scale-resolving CFD. Furthermore, we also explored the potential ability to acquire these descriptors from near-wall MRI data by analyzing at which wall-normal offset distance the Reynolds stress tensor (turbulence kinetic energy, TKE, and degree of anisotropy) correlate with the proposed tWSS descriptors. Results showed that regions prone to elevated tWSS magnitude were generally characterized by near isotropic (randomly-oriented) WSS fluctuations, whereas in more transitional-like near-wall flow regions (characterized by weak tWSS magnitude), these fluctuations appeared to be more anisotropic. The near-wall correlations showed a strong linear relationship up to 2–3 mm wall-normal distance between the tWSS and TKE, which may be sufficiently far to allow for accurate MRI turbulence measure-

ments. On the other hand, the tWSS anisotropy characteristics only appeared to correlate well in the inner-most wall region (~ 0.1 mm), suggesting that this descriptor only can be assessed by well-resolved CFD methods.

Author Contributions: Andersson and Karlsson conceptualized the study. Andersson designed the methodology, computational models, performed all simulations and post-processing steps and wrote the original draft. Karlsson supervised the work and helped with the result interpretations. Karlsson and Ebbers contributed with funding, data and computational resources. All coauthors assisted with the review of the manuscript.

Paper IV

Characterization of anisotropic turbulence behavior in pulsatile blood flow, Magnus Andersson, Matts Karlsson, *Biomechanics and Modeling in Mechanobiology*, 2020, 16 p., doi: 10.1007/s10237-020-01396-3.

This paper demonstrated a novel, practical, comprehensive approach to characterize phase-averaged (second-order, symmetric) tensor fields in patient-specific cardiovascular flows and MRI-acquired turbulence data. The relative strength of the turbulence fluctuations (componentality) can be rendered directly in the fluid domain by sophisticated use of the tensor eigenvalues. This so-called barycentric anisotropy invariant mapping was showcased in the turbulent flow field acquired from a patient-specific CoA model using LES, as well as in an in vitro orifice pipe experiment measured by 4D Flow MRI. In addition, we also validated different conventional modeling simplification with respect to the reference LES results. Qualitatively, the Reynolds stresses showed a relatively broad spectrum of different turbulence states throughout the patient-specific turbulent field and early flow deceleration phase. Over the cardiac phase, some of the more extreme anisotropic states only manifested over a limited time period. Similar but generally less anisotropic characteristics were also found for the turbulence dissipation rate tensor. The validation process highlighted some markedly stress-state difference when assuming a steady inflow condition or turbulence modeling by a RANS-based eddy-viscosity approach. The MRI-measured Reynolds stresses displayed overall expected characteristics in the post-orifice region. However, the proposed method also found MRI-voxels with stress-states that were unphysical and/or with conceivably unrealistic characteristics, suggesting that more in-depths MRI-based turbulence measurements and validation frameworks are needed.

Author Contributions: Andersson and Karlsson conceptualized the study. Andersson designed the methodology, computational models, performed all simulations and post-processing steps and wrote the original draft. Karlsson contributed with funding and computational resources. Karlsson supervised the work, helped with the result interpretations, and assisted with the review of the manuscript.

Paper V

Model verification and error sensitivity of turbulence-related tensor characteristics in pulsatile blood flow simulations, Magnus Andersson, Matts Karlsson, *Fluids*, 2020, vol. 6, no. 1, 15 p, doi: 0.3390/fluids6010011.[‡]

This paper used the flow characterization approach introduced in Paper IV to demonstrate a thorough and effective way to assess modeling-induced errors associated with second-ranked tensor invariant quantities, such as its magnitude and anisotropic properties (componentality), in patient-specific computational hemodynamics. This modeling verification framework was showcased in an image-based LES model of a severe aortic coarctation by evaluating the property changes of the Reynolds stress tensor (i.e. the turbulence kinetic energy, TKE, and stress-states) concerning the spatiotemporal resolution and phase averaging sampling size. This study showed that the errors associated with the phase averaging procedure could easily dominate the errors coupled to the spatiotemporal resolution if too few cardiac cycles are simulated. In this case, these tensor characteristics needed considerably more cycles than typically reported within the computational hemodynamics community to be converged sufficiently. Here, the phase-instant results were identified with the largest errors, while the time-averaged results appeared to be more forgiving. Among the invariant quantities, the turbulence componentality was the most sensitive, particularly the more isotropic stress-states associated with moderate-to-low TKE.

Author Contributions: Andersson and Karlsson conceptualized the study. Andersson designed the methodology, computational models, performed all simulations and post-processing steps and wrote the original draft. Karlsson contributed with funding and computational resources. Karlsson supervised the work, helped with the result interpretations, and assisted with the review of the manuscript.

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Part II

Appended papers

"Perhaps one day we will have machines that can cope with approximate task descriptions, but in the meantime, we have to be very prissy about how we tell computers to do things."

Richard P. Feynman

Papers

The papers associated with this thesis have been removed for copyright reasons. For more details about these see:

<http://urn.kb.se/resolve?urn=urn:nbn:se:liu:diva-175193>

An aerial photograph of a river delta, showing a complex network of waterways branching out from a single point. The water is a light grey color, contrasting with the darker, textured land. The branching pattern is reminiscent of a tree or a spider web.

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