AngioSupport

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AngioSupport

a novel and quantitative tool allowing clinical decision making for cardiac teams to plan coronary interventions

Ir. B. G. van Willigen, 2019/053

Supervisors:
Dr. Ir. I. M. M. Lammerts
Dr. Ir. J. M. A. Stijnen

LifeTec Group™
AngioSupport

a novel and quantitative tool allowing clinical decision making for cardiac teams to plan coronary interventions.

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06-09-2019

The work described in this report is executed in accordance with the TU/e Code of Scientific Conduct

Confidential: No

One year project presented to Eindhoven University of Technology towards the degree of Professional Doctorate in Engineering in Qualified Medical Engineer
Public summary

Every year, about 735,000 Americans suffer from Coronary Artery Disease (CAD); one of the leading causes of death in the United States. The Invasive Coronary Angiography (ICA) and the invasive Flow Fractional Reserve (FFR) are the ‘gold standard’ to assess CAD. The patients with a stenose, resulting to $\text{FFR} \leq 0.8$, are assumed to have a significant stenose resulting in ischemia of the myocardium. Those patients receive treatment: either a Percutaneous Coronary Intervention (PCI) or a Coronary Artery Bypass Graft (CABG). The decision between PCI or CABG is based on the experience of the cardiac team, which consist of at least one intervention cardiologist and one cardiac surgeon. For about 20% of these patients discussed during the cardiac team meeting, the effect of PCI or CABG is hard to predict and the defined treatment plan will therefore vary between cardiac teams. Clinicians have no quantitative measurement that supports them with treatment planning for this specific group of patients. Therefore, this report represents a new product AngioSupport: a patient-specific model-based interactive tool to provide clinicians predictions of the post-operative FFR to plan coronary interventions and to support them in clinical decision making during a cardiac team meeting.

AngioSupport consists of three parts:

1) The segmentation of ICA images to generate the centreline and radii of the coronary arteries.
2) The physiological model that computes the blood pressure and flow throughout the coronary arteries.
3) The interface to allow clinicians to perform coronary interventions.

With a prototype of this new AngioSupport, a proof-of-concept has been shown that in principle could lead to a product that is able to support treatment planning for patients with challenging CAD (difficult vasculature, multiple stenoses, or diffuse disease) by allowing complicated interventions (multiple stents, jump-grafts, Y-grafts, and combinations of PCI and CABG).

This new prototype can treat one single occlusion, hence allows the clinician to place one stent (via PCI) or to perform a CABG connected to one location. Demo's and presentations of the prototype have been given to receive feedback and to grow a reputation. The media messages and activities resulted in a user-friendly design and acceptance of AngioSupport as concluded from the conducted user survey. Although the backend (physiological model) of AngioSupport is not properly verified, the verification was good enough to gain trust of the clinicians that the pre-FFR and post-FFR could accurately be predicted. Finally, an first validation test has been performed of the complete prototype of AngioSupport, i.e. the interface at the frontend and the physiological model at the backend.

In summary, the further development of AngioSupport needs a long way to reach its full potential. Nevertheless, this proof-of-concept lifted confidence that it is technical possible to develop the product and that the product will be accepted by clinicians to support clinical decision making as well as an educational tool.
Declaration concerning the TU/e Code of Scientific Conduct for the PDEng thesis

I have read the TU/e Code of Scientific Conduct.

I hereby declare that my PDEng thesis has been carried out in accordance with the rules of the TU/e Code of Scientific Conduct.

Date
08-08-2019

Name
Bettine van Willigen

Signature

---

1 See: https://www.tue.nl/en/our-university/about-the-university/organization/integrity/scientific-integrity/
The Netherlands Code of Conduct for Scientific Integrity, endorsed by 6 umbrella organizations, including the VSNU, can be found here also. More information about scientific integrity is published on the websites of TU/e and VSNU.
Contents
1 Introduction .................................................................................................................. 7
  1.1 Coronary Artery Disease (CAD) .......................................................................... 7
  1.2 Invasive Coronary Angiography (ICA) .............................................................. 7
  1.3 Fractional Flow Reserve (FFR) ............................................................................ 8
  1.4 Invasive FFR in combination with ICA ............................................................. 8
  1.5 Coronary interventions ....................................................................................... 9
  1.6 Clinical decision making .................................................................................... 9
  1.7 Design of a new clinical decision support tool ............................................... 9
2 Project definition ....................................................................................................... 11
  2.1 Aim ..................................................................................................................... 11
  2.2 Project approach ................................................................................................. 11
  2.3 Project organization ............................................................................................ 11
    2.3.1 Planning ....................................................................................................... 13
    2.3.2 Risk analysis ............................................................................................... 13
  2.4 Deliverables .......................................................................................................... 15
3 Definition phase ......................................................................................................... 16
  3.1 Functional requirements ..................................................................................... 16
  3.2 Legislation and regulation .................................................................................. 16
  3.3 Finance ............................................................................................................... 17
  3.4 Technical requirements ...................................................................................... 17
    3.4.1 Segmentation ............................................................................................... 17
    3.4.2 Physiological model .................................................................................... 18
    3.4.3 Interface ..................................................................................................... 18
4 Design concepts .......................................................................................................... 19
  4.1 Concepts of segmentation ................................................................................... 19
    4.1.1 Starting component ..................................................................................... 19
    4.1.2 Patient data .................................................................................................. 20
  4.2 Concepts of physiological model ....................................................................... 21
    4.2.1 Starting component ..................................................................................... 21
    4.2.2 Concept 1 .................................................................................................... 22
    4.2.3 Concept 2: Systemic geometry .................................................................. 22
    4.2.4 Concept 3: Steady inflow .......................................................................... 23
    4.2.5 Concept 4: Sensitivity analysis .................................................................. 23
    4.2.6 Concept 5: Tuning pre-FFR to mFFR ....................................................... 24
    4.2.7 Concept 6: Flow distribution .................................................................... 25
    4.2.8 Concept 7: Stenose element .................................................................... 26
Appendices overview

Table 1.1 shows an overview of all appendices. The project managers wrote and reviewed all technical appendices. The implementation of the method is performed by both project managers.

<table>
<thead>
<tr>
<th>#</th>
<th>Appendix</th>
<th>Written</th>
<th>Reviewed</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Stakeholder analysis</td>
<td>Bettine van Willigen</td>
<td>-</td>
<td>54</td>
</tr>
<tr>
<td>B</td>
<td>Planning</td>
<td>Bettine van Willigen</td>
<td>-</td>
<td>56</td>
</tr>
<tr>
<td>C</td>
<td>Risk analysis</td>
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<td>Tim van den Boom</td>
<td>57</td>
</tr>
<tr>
<td>D</td>
<td>One-fiber heart element</td>
<td>Bettine van Willigen</td>
<td>Tim van den Boom</td>
<td>60</td>
</tr>
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<td>E</td>
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<td>Tim van den Boom</td>
<td>65</td>
</tr>
<tr>
<td>F</td>
<td>Systemic Windkessel element</td>
<td>Bettine van Willigen</td>
<td>Tim van den Boom</td>
<td>68</td>
</tr>
<tr>
<td>G</td>
<td>Coronary Line Element</td>
<td>Bettine van Willigen</td>
<td>Tim van den Boom</td>
<td>69</td>
</tr>
<tr>
<td>H</td>
<td>Coronary Windkessel Element</td>
<td>Tim van den Boom</td>
<td>Bettine van Willigen</td>
<td>70</td>
</tr>
<tr>
<td>I</td>
<td>Stenosis Element</td>
<td>Tim van den Boom</td>
<td>Bettine van Willigen</td>
<td>72</td>
</tr>
<tr>
<td>J</td>
<td>Solution Procedure Model</td>
<td>Tim van den Boom</td>
<td>Bettine van Willigen</td>
<td>76</td>
</tr>
<tr>
<td>K</td>
<td>Procedure Segmentation</td>
<td>Tim van den Boom</td>
<td>Bettine van Willigen</td>
<td>79</td>
</tr>
<tr>
<td>L</td>
<td>Aanvraag nWMO</td>
<td>Bettine van Willigen and Tim van den Boom</td>
<td>Bettine van Willigen and Tim van den Boom</td>
<td>83</td>
</tr>
<tr>
<td>M</td>
<td>Validation Systemic Model</td>
<td>Tim van den Boom</td>
<td>Bettine van Willigen</td>
<td>89</td>
</tr>
<tr>
<td>N</td>
<td>Validation Coronary Model</td>
<td>Tim van den Boom</td>
<td>Bettine van Willigen</td>
<td>92</td>
</tr>
<tr>
<td>O</td>
<td>Adapting Systemic Geometry</td>
<td>Tim van den Boom</td>
<td>Bettine van Willigen</td>
<td>96</td>
</tr>
<tr>
<td>P</td>
<td>Inflow</td>
<td>Bettine van Willigen</td>
<td>Tim van den Boom</td>
<td>109</td>
</tr>
<tr>
<td>Q</td>
<td>Sensitivity Analysis</td>
<td>Bettine van Willigen</td>
<td>Tim van den Boom</td>
<td>111</td>
</tr>
<tr>
<td>R</td>
<td>Coronary flow</td>
<td>Bettine van Willigen</td>
<td>Tim van den Boom</td>
<td>115</td>
</tr>
<tr>
<td>S</td>
<td>Activities</td>
<td>Bettine van Willigen</td>
<td>-</td>
<td>117</td>
</tr>
<tr>
<td>T</td>
<td>Decision diagram; Medical devices</td>
<td>-</td>
<td>-</td>
<td>118</td>
</tr>
<tr>
<td>U</td>
<td>User Survey</td>
<td>-</td>
<td>-</td>
<td>119</td>
</tr>
<tr>
<td>V</td>
<td>1D method Kroon</td>
<td>Tim van den Boom</td>
<td>Bettine van Willigen</td>
<td>121</td>
</tr>
</tbody>
</table>

*Table 1.1: Overview of appendices.*
1 Introduction

1.1 Coronary Artery Disease (CAD)
Every year about 735,000 Americans suffer from Coronary Artery Disease (CAD); one of the leading causes of death in the United States (Mozaffarian et al., 2015). Therefore, diagnosis and treatment should be convenient and accurate with costs as low as possible. Currently, a patient with chest pain (angina pectoris) will be first established as being either non-acute or acute when arriving at a hospital. For acute patients it is crucial to restore the blood flow immediately due to 7.5% increased risk of 1-year mortality for each 30-minute delay of revascularisation (De Luca Giuseppe et al., 2004). Non-acute patients will be evaluated based on non-invasive stress tests. These patients will then be diagnosed as low or medium-to-high risk patients. Low risk patients receive medical therapy, such as blood thinners, while medium-to-high risk patients will be assessed with Invasive Coronary Angiography (ICA) (Figure 1.4). During ICA, contrast fluid is injected in the coronary arteries in order to visualize the vessels with an x-ray machine resulting in a 2D image, a coronary angiogram (Figure 1.1).

![Figure 1.1: Coronary angiogram](image)

1.2 Invasive Coronary Angiography (ICA)
For decades, ICA was the ‘gold standard’ to determine the appropriate treatment for CAD by revealing the location and anatomy of an occlusion, called stenosis. Despite the subjective visual interpretation of the clinician to interpret the ICA, the diameter reduction defined by ICA is a decent indication for revascularization for single vessel stenosis. However, for diffuse coronary disease (Bruyne et al., 2001) or multiple stenosis (Tonino et al., 2009), ICA is unreliable for the diagnosis, because the hemodynamics is unpredictable based on the anatomy of the stenosis. This results in unnecessary revascularization of patients (Kern et al., 1995).

![Figure 1.2: Pressure wire through coronary artery to compute invasive FFR.](image)
1.3 Fractional Flow Reserve (FFR)

To improve the diagnostic method, Pijls et al. developed a new method to determine the impact of the stenosis by measuring invasively the myocardial Fractional Flow Reserve (FFR) (Pijls et al., 1996). This fraction defines the hyperemic flow with a stenosis ($Q_{s}^{hyp}$) relative to the hyperemic flow without disease ($Q_{max}^{hyp}$) based on the ratio of the mean pressure distal to the stenosis ($P_{d}$) and the mean aortic pressure ($P_{a}$) ($FFR = \frac{Q_{s}^{hyp}}{Q_{max}^{hyp}} = \frac{P_{d}}{P_{a}}$). Earlier work of Pijls et al. shows the theoretical background of this simplified relation between the flow and pressure ratio (Pijls et al., 1993).

![Figure 1.3: An increased pressure gradient is shown between rest (lower left) and hyperemic state (lower right). Figure is adapted from (Wilson, 1996) and adjusted.](image)

1.4 Invasive FFR in combination with ICA

The invasive FFR is used in combination with ICA by inserting a pressure wire in the desired coronary artery to measure the $P_{d}$. The hyperemic state is induced by vasodilators, which provides for the maximal possible opening of the vessels, which in turn creates the maximal amount of blood flow. This reveals the pressure gradient that identifies the impact of the stenosis in contrast to the rest state, where vessels may compensate for the stenosis resulting in an underestimation of the pressure gradient and severity of the stenosis. Figure 1.3 shows the difference between the pressure gradient resulting of a stenosis in rest (lower left) and hyperemic (lower right) state. The FFR in combination with ICA improves the diagnosis of multi-vessel and diffuse disease, because the $P_{d}$ covers all changes in the vessel diameter distal to the stenosis (Bruyne et al., 1996). Furthermore, the use of the mean pressures to compute the FFR makes the method more robust to changes of pressure (Bruyne et al., 1996). Moreover, clinical studies show that invasive FFR in combination with ICA gives a better treatment plan for CAD than ICA alone (De Bruyne et al., 2012; Pijls et al., 2007, 2010; Tonino et al., 2009). As a result, FFR with ICA has become the new ‘gold standard’ to assess CAD. However, 30% of the patients who are diagnosed with FFR and ICA do not need an
intervention, meaning this patient group underwent an unnecessary invasive procedure. In addition, peripheral hospitals are only able to perform ICA, so medium-to-high risk patients with a diameter reduction will be sent to a specialized hospital and redo the ICA with FFR (Figure 1.4).

1.5 Coronary interventions

The patients with a stenose resulting to FFR ≤ 0.8 are assumed to have a significant stenose resulting in ischemia of the myocardium (Pijls et al., 2007). Those patients receive treatment either a Percutaneous Coronary Intervention (PCI) or Coronary Artery Bypass Graft (CABG). During a PCI, a stent is deployed by inflating a balloon catheter on place of stenose, which is localized with ICA. The PCI is the fastest method to restore blood flow and therefore often used for acute patients as well. Furthermore, it is a non-surgical procedure and patients are discharged from the hospital the same day. However, in some lesions the rate of in-stent stenose can be up to 59% (Bennett, 2003), which requires repeated revascularization. In contrast to PCI, CABG is a surgical procedure where typically the Left Internal Mammary Artery (LIMA) or great saphenous vein will be sutured after the stenose to literally bypass the stenose. This surgery takes around 6h and the patient must stay for approximately a week in the hospital. However, after complete recovery, the CABG is a life-long solution. The abovementioned characteristics of PCI and CABG are summarized in Table 1.1.

<table>
<thead>
<tr>
<th></th>
<th>PCI</th>
<th>CABG</th>
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<tr>
<td>Time procedure</td>
<td>&lt; 1h</td>
<td>~6h</td>
</tr>
<tr>
<td>Stay at hospital</td>
<td>~2h</td>
<td>1w</td>
</tr>
<tr>
<td>Long-term</td>
<td>re-stenose</td>
<td>Life-long solution</td>
</tr>
</tbody>
</table>

Table 1.1: Most important characteristics of PCI and CABG.

1.6 Clinical decision making

Currently, the decision between PCI or CABG is based on the experience of the cardiac team, which consist of at least one intervention cardiologist and one cardiac surgeon. They consider the age of the patient, number, location (e.g. near bifurcation or left main vessel), length of stenose, and diameter of the vessel to define a treatment plan. For patients with focal stenoses, treatment planning is often straightforward and consists of PCI immediately performed after the diagnoses and therefore is not discussed during the cardiac team meeting in contrast to patients with complex vasculature, multiple stenoses, or diffuse disease: for those patients, treatment planning is challenging (Figure 1.4). For about 20% of the patients discussed during the cardiac team meeting, the effect of PCI or CABG is hard to predict and the defined treatment plan will therefore vary between cardiac teams.

1.7 Design of a new clinical decision support tool

In summary, clinicians have no quantitative measurement that supports them with treatment planning. Furthermore, a patient may encounter inconvenience during diagnosis and treatment of CAD due to multiple ICA’s, unnecessary invasive procedures, and repeated revascularization. This product report represents AngioSupport: an interactive tool to provide clinicians of the FFR predicted after a coronary intervention to plan and to support clinical decision making during a cardiac team meeting (Figure 1.4).

---

1 Information is based on common practice in Catharina Hospital Eindhoven and Sheffield Teaching Hospital and obtained by personal communication with F.N. (Frans) van de Vosse (oid).

2 Information is based on common practice (about 3 challenging patients of 15 per day) in Catharina Hospital Eindhoven and obtained by personal communication with Dr. W.A.L. (Pim) Tonino.
Figure 1.4: Flowchart for non-acute patients with Angina pectoris (confirmed by J. Zelis, MSc. cardiologist in training) with AngioSupport included.
2 Project definition
In this design project, a prototype of an interactive tool has been developed, implemented, and a first validation test is performed to show a proof-of-concept meant to support the cardiac team (during their meeting) to define a treatment plan for the medium-to-high risk non-acute patients with challenging CAD (Figure 1.4). The interactive tool that shows the effects of a coronary intervention (PCI or CABG) on blood flow and pressure and compares it with the current state of the patient and other possible interventions by computing the pre-operative FFR (pre-FFR) and post-operative FFR (post-FFR). The prototype is called AngioSupport.

2.1 Aim
The aim of AngioSupport is to give clinicians patient specific quantitative information of the effects of potential coronary interventions (PCI or CABG), virtually performed by the clinicians themselves to reduce repeated revascularization and healthcare costs. Moreover, it should improve the patient experience and their quality of life.

2.2 Project approach
The first step in the development of AngioSupport (definition) was to collect existing models that meet the functional requirements (Chapter 3.1). After defining the basic components of AngioSupport, AngioSupport has been designed and improved by the cyclic method: Plan-Do-Check-Act (PDCA). Every concept started with formulating a goal and plan (plan), performing the plan (do), testing the results against the technical requirements (check), and analyzing the implementation (act). This cycle continued until the technical requirements (Chapter 3.4) were met, which results in the final design. The final design has been verified on literature and patient data. In addition, a first order validation has been performed based on a user survey after an implementation of the prototype. Figure 2.1 represents the project approach.

2.3 Project organization
AngioSupport has been developed by two project managers (Bettine van Willigen and Tim van den Boom). The project is divided into three parts as can been seen in Figure 2.3; the backend (physiological model led by Tim van den Boom), preprocessing of the data (segmentation led by both project managers), and the frontend (interface led by Bettine van Willigen). The project managers are responsible for their own team and joining in each other's. A good communication between stakeholders and project managers is important to have an efficient and successful development process. Therefore, the impact of the stakeholders is identified and assessed. By clarifying the stakeholders needs, interests, and capabilities, the opportunities and threats has been identified to achieve the optimal project outcome. The following paragraphs describe the stakeholders and Figure 2.3 represents the organization of the stakeholders. A complete stakeholder analysis is available in Appendix A. Figure 2.2
summarizes the interest and power of the stakeholders with communication plan (Appendix A, Table A.2).

![Interest vs. power model of the stakeholders](image)

During the development of AngioSupport, the following institutes should be considered:

1) **LifeTec Group (LTG)**, where AngioSupport has been developed by the project managers Bettine van Willigen and Tim van den Boom. Marco Stijnen is the executive of AngioSupport. Communication between the project managers and the executive has been at LTG during meetings, emails or just in the hallway. LTG would like to have a proof-of-concept at 31th of August 2019 when the funding of CompBioMed is finished. This proof-of-concept has been used to identify the business market for numerical simulations for hemodynamics as LTG wants to start a division for such simulations. The project managers had biweekly meetings to remain Marco updated about the development of AngioSupport.

2) **CompBioMed (CBM)**, a European organisation, which aims to build a virtual human usable for clinicians to bring research developments to the end-user. To achieve this goal, they finance small to medium sized enterprises including LTG. AngioSupport has been part of the development of the virtual human. CBM would like to have a proof-of-concept of AngioSupport at 31th of August 2019. The project team informed CBM (Mariano Vazquez) every half year to give an update of developments of AngioSupport. Furthermore, CBM organizes conferences, annual all-hands meetings, and workshops to attend for the development team. Finally, the communication has been mostly by email, conference calls, and during the annual all-hands meetings.

3) **Eindhoven University of Technology (TU/e)** supplied mathematical models to describe fluid dynamics. The TU/e would like to have a structured mathematical model written in Python that potentially can be used by students. Contact has been with Frans van de Vosse and Wouter Huberts and mostly occurred by email and scheduled meetings for support during the development of the mathematical model. Furthermore, they were present at the 3-monthly meetings for updates.

4) **The clinicians of the Catharina Hospital Eindhoven (CZE)** are the user group of AngioSupport with Pim Tonino (intervention cardiologist) as Senior User. Pim Tonino supplied patient data to verify AngioSupport and gave feedback during the 3-monthly meetings. Furthermore, Pim Tonino has data to verify AngioSupport. By success of AngioSupport, Pim Tonino likes to publish a paper about the application.
5) **Pie Medical Imaging (PMI)** supplied the software for segmentation of the coronary angiograms to generate a 3D patient-specific geometry. The contact person has been Tristan Slots and the project managers had mostly contact by email and meetings at PMI every half year. By success of AngioSupport, they may like to have AngioSupport as addition to CAAS (their coronary segmentation tool).

![Figure 2.3: Stakeholder organization](image)

2.4 **Risk analysis**

During the project, a risk assessment was done every month determining the probability (P) and the severity (S) of a risk. Both values (P and S) are scaled from 1 to 10 and a risk is assumed critical when P*S > 40 (red). Figure 2.4 shows the trend of the risk values for every month. Appendix C shows the entire risk analysis. The highest risks during the development of the prototype were the following:

1. The end-users do not trust AngioSupport to support clinical decisions, because clinicians may not trust simulations in general. If this is the case, clinicians will most likely not use AngioSupport. The project managers classified this risk with a probability of 8 and a severity of 8, so a risk of 64. This is the only risk greater than 40 (red) and plays a role during the entire development until the user survey was conducted.

2. Other high risks (P*S=40) include the segmentation of ICA images. It started with the risk of not finding the proper segmentation tool. After the tool was chosen, the new risk was that the tool is not useful for AngioSupport. Thereafter, the risk ended in that segmentation will not be automated. The latter is transferred to the next developer(s).
3. The final two high risks (P*S=40) are about the verification of the physiological model and the validation of AngioSupport. The patient data could be not sufficient enough to demonstrate a trustworthy prototype or the user survey would conclude of an inadequate interface. Convincing clinicians about the usefulness of AngioSupport during the cardiac meeting would be more challenging, when those risks would have been true.

Figure 2.4: The sum of the priority (P) times severity (S) of monthly risk assessment

2.5 Planning

The planning was made based for the following milestones: 1) the definition phase, 2) segmentation of ICA images, 3) development of the physiologic model, 4) choice of patient specific parameters, 5) development of the interface, 6) allowance of virtual interventions, 7) verification, 8) implementation, and 9) first order validation in the hospital. The initial and final planning are visualized in Appendix B (Table B.1 and Table B2, respectively). The delay in achieving the milestones was due to the delay in receiving the patient data (Table 2.1). Therefore, the segmentation, defining patient specific data, the verification, and the implementation were on hold until the data was received. In addition, the interface was finished a month later due to its dependency of the development of virtual interventions. Finally, the first order validation of AngioSupport was achieved a month earlier, because the last month was reserved for documentation and the presentation.

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<tr>
<td>Validation</td>
<td>01-09-2019</td>
<td>01-08-2019</td>
<td>Documentation</td>
</tr>
<tr>
<td>Final Review</td>
<td>06-09-2019</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 2.1: Milestones and their expected and actual date of achieving.
2.6 Deliverables

At the end of the project, a prototype of AngioSupport has been delivered, with which a proof-of-concept has been obtained. This report has been released with outcomes of the user survey, the verification of the mathematical physiological model, and necessary improvements. At the start of this project, it has been agreed with all stakeholders that the release of a proof-of-concept with a prototype that can be used by clinicians had priority over the accuracy of the computed FFR. Furthermore, the prototype has been verified on single lesions. Coronary interventions consist of single PCI or CABG from the Left Internal Mammary Artery (LIMA). The proof-of-concept should in principle lead to a product that is able to support treatment planning for patients with challenging CAD, for example difficult vasculature, multiple stenoses, or diffuse disease. Therefore, AngioSupport should in future eventually allow complicated interventions, such as multiple stents, jump-grafts, Y-grafts, and combinations of PCI and CABG. A list of deliverables is as follows:

D.1. Design documentation of AngioSupport
D.2. Prototype of AngioSupport
D.3. Outcomes of a first user survey with the prototype
D.4. Verification of the mathematical physiological model
D.5. Verification of the prototype
D.6. Documentation with the necessary improvements to reach the final product

As mentioned, the delivered prototype is not yet the final product. The verification, implementation, and validation steps are just enough to make clinicians enthusiastic about the AngioSupport, to convince clinicians about its usefulness, and to gain trust of the clinicians that the final product could be technically possible and completely verified and validated.
3 Definition phase
The orientation phase was during the first two months of the project (March and April of 2018). During this phase, the project managers talked to Pim Tonino and Niels Verberkmoes (cardiac surgeon) to define a detailed project aim including the functional specifications (Chapter 3.1). Furthermore, information was obtained about law and regulations of medical devices (Chapter 3.2) and the finance of the project (Chapter 3.3). Considering the above-mentioned points, the technical requirements (Chapter 3.4) were made.

3.1 Functional requirements
About 15 patients per day with challenging CAD are assessed by the cardiac team to define, within minutes (per patient), a treatment plan consisting of either PCI or CABG. In average, for about 20% of those patients, the effect of PCI or CABG is difficult to predict. AngioSupport has been developed to support the cardiac team (during their meeting) to discuss these challenging cases by giving quantitative information about the flow and pressure after potential coronary interventions (PCI and CABG). This is possible by allowing the cardiac team to perform coronary interventions virtually and to compare those interventions interactively with the help of AngioSupport. Furthermore, to make AngioSupport applicable for the cardiac team meeting and patient specific, it should use the patient data available in the current procedure, such as ICA. In other words, the functional requirements of AngioSupport are (Figure 3.1):

- F.1. Visual detection of coronary arteries based on ICA
- F.2. Computation of blood pressure and flow throughout the coronary arteries
- F.3. Simulation of coronary interventions (PCI and CABG)

The difference between the functional requirements of the prototype and the final product is functional requirement F.3. This report describes a prototype being capable of treating one single occlusion, hence allowing the clinician to place one stent (via PCI) or to perform a CABG connected to one location. The final product will be capable in treating challenging CAD, which could possibly require multiple stents and/or a bypass connected to multiple locations (y-graft or jump graft).

3.2 Legislation and regulation
The project managers spoke to Annette Josefine van Raamsdonk about legislation and regulation. She advised to consider AngioSupport a tool for education and training for now as it is a proof-of-concept. Therefore, AngioSupport will be in first instance not a medical device and CE marking is not necessary yet. Nevertheless, the legislation and regulation for AngioSupport has been determined for the final purpose of AngioSupport to be a diagnostic tool. A qualification (medical device or not) and classification has been described in Chapter 5.5.
3.3 Finance
The project has been financed by CBM till 31 August 2019. This finance is enough to hire two PDEng students (Bettine van Willigen and Tim van den Boom) and cover traveling costs to conferences. AngioSupport has been developed with open source programming languages; therefore, material costs are negligible.

3.4 Technical requirements
Before defining the technical requirements, a flowchart of AngioSupport was created to visualize the realization of the functional requirements (Figure 3.2). As can be seen in Figure 3.2, AngioSupport is divided in three main components:

1. The **segmentation** of the coronary arteries based on ICA to fit in the current procedure (green).
2. The **physiological model** to compute the blood flow and pressure throughout the coronary arteries (blue).
3. The **interface** allowing clinicians to perform coronary interventions (orange). Based on this flowchart, the technical requirements are specified and described per component in the following paragraphs.

![Figure 3.2: Flowchart of AngioSupport](image)

<table>
<thead>
<tr>
<th>Technical requirements</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Segmentation of ICA images</td>
<td>Both project managers agree that the segmentation corresponds with ICA images by visual inspection.</td>
</tr>
<tr>
<td>Generate centerline with radii</td>
<td>Both project managers agree that the coordinates of the centerline and radii generate similar geometry as on ICA images.</td>
</tr>
<tr>
<td>Generate input file for simulations</td>
<td>The file can be used as input for the physiological model that is used in simulations to predict the outcome of interventions</td>
</tr>
</tbody>
</table>

*Table 3.1: Technical requirements of the segmentation*
### 3.4.2 Physiological model

With the physiological model the pressure and flow throughout the coronary arteries will be computed (Functional Requirement, F.2); this leads to several technical requirements:

1. It is not the aim of this proof-of-concept to have a high accuracy. However, it is necessary to have a high enough accuracy to convince clinicians about the usefulness of AngioSupport. Therefore, there has been chosen that the accuracy (ACC) should be at least 70%. Furthermore, computation of the FFR should be within 10s.
2. The model should be flexible in updating input files in order to perform coronary interventions (Figure 3.2).
3. The model should allow coronary interventions. Table 3.2 shows the technical requirements with acceptance criteria for the physiological model.

<table>
<thead>
<tr>
<th>Technical requirements</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verification</td>
<td>ACC of 70%</td>
</tr>
<tr>
<td></td>
<td>Computation time within 10s.</td>
</tr>
<tr>
<td>Flexibility</td>
<td>Input file can be updated</td>
</tr>
<tr>
<td>Operability</td>
<td>Allowance to perform PCI</td>
</tr>
<tr>
<td></td>
<td>Allowance to Perform CABG</td>
</tr>
</tbody>
</table>

Table 3.2: Technical requirements of the physiological model

### 3.4.3 Interface

In order to predict and compare the coronary interventions (PCI and CABG) (Functional Requirements, F.3 and F.4), the interface should meet multiple requirements:

1. First, the clinician should be able to select the desired patient and subsequently start the simulation to compute the blood pressure and flow.
2. The results of the simulation are visualized (with color-coding inside the coronary arteries) and stored for comparison.
3. Furthermore, the interface allows the performance of coronary interventions and generates input files suitable for the physiological model. These interventions can be performed by clinicians without the help of engineers.
4. The results of the interventions are visualized and stored as well.
5. Finally, the interface enables comparison of the results generated from PCI, CABG, and pre-operative. Table 3.3 shows the technical requirements with acceptance criteria of the interface.

<table>
<thead>
<tr>
<th>Technical requirements</th>
<th>Acceptance criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>User can load ICA images of desired patient</td>
<td>Technically possible (yes or no)</td>
</tr>
<tr>
<td></td>
<td>User survey: score of ≥ 4</td>
</tr>
<tr>
<td>The physiological model can be started using pre-operative data</td>
<td>Technically possible (yes or no)</td>
</tr>
<tr>
<td>Visualize results physiological model with colors inside the coronary arteries</td>
<td>Colors corresponding the FFR values with values &gt;0.8 in blue and values &lt;0.75 in red.</td>
</tr>
<tr>
<td>Results of simulation are stored</td>
<td>Technically possible (yes or no)</td>
</tr>
<tr>
<td>User can perform PCI</td>
<td>Technically possible (yes or no)</td>
</tr>
<tr>
<td></td>
<td>User survey: score of ≥ 4</td>
</tr>
<tr>
<td>User can perform CABG</td>
<td>Technically possible (yes or no)</td>
</tr>
<tr>
<td></td>
<td>User survey: score of 4</td>
</tr>
<tr>
<td>Generates input files after interventions</td>
<td>The input file can be used by the physiological model (yes or no)</td>
</tr>
<tr>
<td>The physiological model can be started using post-operative data</td>
<td>Technically possible (yes or no)</td>
</tr>
<tr>
<td>Interventions and pre-operative results can be compared</td>
<td>Technically possible (yes or no)</td>
</tr>
<tr>
<td></td>
<td>User survey: score of 4</td>
</tr>
</tbody>
</table>

Table 3.3: Technical requirements of the interface
4 Design concepts

The aim of CBM is to use platforms, software, and models that already exist to prevent “inventing the wheel again” and focus on “getting research to the end-user”. Hence, these starting components have been improved based on an iterative process (Figure 2.1) until the acceptance criteria (Chapter 3.4) are met. As reminder, the segmentation (Chapter 4.1) should result in a centerline and radii as input for the physiological model. The physiological model (Chapter 4.2) computes the blood pressure and flow pre- and post-operative. The interface (Chapter 4.3) allows clinicians to run the physiological model and perform and compare interventions. The following paragraphs describe the iterative loops of the PDCA for every part separated; starting with the initial components in the first loop. Thereafter, additions, subtractions, and extensions are performed on these existing methods iteratively resulting in different concepts and to meet the predefined requirements (Chapter 3.4).

4.1 Concepts of segmentation

4.1.1 Starting component

AngioSupport should be patient specific and fit in the current clinical procedure (of a cardiac team of) the Netherlands. Therefore, the segmentation should be performed based on measured ICA images. Research has been done to find a suitable segmentation tool for AngioSupport. The most familiar segmentation software tools are VMTK, SimVascular, Medis Suite XA (medis), CathWorks, and CAAS (PMI). VMTK and SimVascular are open source software tools, which is very convenient for the development of AngioSupport. However, the segmentation of 2D DICOM files (such as ICA images) is not feasible with those tools. CathWorks is an Israeli company segmenting the entire coronary tree, but communication with this company was not successful. Medis Suite XA and CAAS are originated from the same company; therefore, their segmentation technique is based on the same method. CAAS has been chosen to perform the segmentation of ICA, because TU/e and CZE have already good contacts with PMI (Figure 4.1). Table 4.1 summarizes the above mentioned.

<table>
<thead>
<tr>
<th>Software</th>
<th>Open source or not</th>
<th>Segmentation images</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>VMTK</td>
<td>Open Source</td>
<td>3D DICOM</td>
<td>-</td>
</tr>
<tr>
<td>SimVascular</td>
<td>Open Source</td>
<td>3D DICOM</td>
<td>-</td>
</tr>
<tr>
<td>Medis Suite XA</td>
<td>Not open source</td>
<td>2D/3D DICOM</td>
<td>-</td>
</tr>
<tr>
<td>CathWorks</td>
<td>Not open source</td>
<td>2D/3D DICOM</td>
<td>No communication</td>
</tr>
<tr>
<td>CAAS</td>
<td>Not open source</td>
<td>2D/3D DICOM</td>
<td>Good contacts with TU/e and CZE</td>
</tr>
</tbody>
</table>

Table 4.1: Segmentation tools

CAAS generates a 3D image when two single plane angiograms are segmented under an angle of at least 30°. The 3D image results in an output file with the coordinates of the centerline and corresponding radii. However, the software segments only one vessel at a time, not the entire coronary tree. Therefore, a procedure has been developed (by both project managers) to segment the vessels one by one, then connect them to each other, and finally extract the coordinates of the centerline and radii. The procedure is written in Appendix K.
### Technical requirements

<table>
<thead>
<tr>
<th>Technical requirements</th>
<th>Acceptance criteria</th>
<th>Implemented</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Segmentation of ICA images</strong></td>
<td>Both project managers agree that the segmentation corresponds with ICA images by visual inspection.</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Generate centerline with radii</strong></td>
<td>Both project managers agree that the coordinates of the centerline and radii generate similar geometry as on ICA images.</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Generate input file for simulations</strong></td>
<td>The file can be used as input for the physiological model that is used in simulations to predict the outcome of interventions</td>
<td>Yes</td>
</tr>
</tbody>
</table>

*Table 4.2: Technical requirements of the segmentation*

All technical criteria have been met: the segmentation corresponds with the ICA images as well as the generated coordinates of the centerline and radii (judged by visual inspection of both project managers). However, the software requires many manual operations to get these results due to the required reference points of each vessel. Furthermore, the segmentation is currently a stand-alone software tool as well as the software that connects the vessels. Therefore, the ICA images must be preprocessed by an expert to generate an input file with coordinates of the centerline and radii that can be used by AngioSupport. Despite these drawbacks, it has been chosen to continue with CAAS, because the aim of the proof-of-concept was to gauge the opinion of the cardiac team. After the possibility of general acceptance of AngioSupport, optimization and automatization of the segmentation will be priority.

![CAAS: Software of Pie Medical Imaging to segment the coronary arteries from two ICA images.](image)

**Figure 4.1:** CAAS; Software of Pie Medical Imaging to segment the coronary arteries from two ICA images.

#### 4.1.2 Patient data

To tune and verify AngioSupport, data have been requested at CZE consisting of a set ICA images before and after PCI with mFFR. The request (nWMO aanvraag) can be found in Appendix L. The received dataset consisted of data from 10 patients (anomized). However, this dataset did not result in a proper segmentation of the vessels due to movement of the patient table, tortuous vessels, overlapping vessels, or lack of information about the pixel size of the x-ray machine.

Hence, a second dataset was requested with the same ‘nWMO aanvraag’. This dataset contained data from 75 patients with ICA images from peripheral hospital in Weert and CZE with pre-FFR values. This dataset was selected for PMI. From these data set, the project
managers managed to segment the entire left side of the coronary tree of 10 patients. PMI managed to segment one vessel of about 25 patients. Therefore, segmentation of the entire left side of the coronary tree of 10 patients is acceptable. This set will be used to tune and verify AngioSupport.

4.2 Concepts of physiological model
The physiological model underwent PDCA cycles to meet the acceptance criteria of Table 3.2 resulting in the following concepts. The results has been generated by a computer with an Intel CORE i7 7th Gen processor.

4.2.1 Starting component
As mentioned, the original physiological model is obtained from the TU/e (van der Horst et al., 2013). This model has been rewritten from SEPRAN to Python 3.6. SEPRAN is an outdated programming language and not designed to create standalone software. For the sustainability of the software, the physiological model has been rewritten in the open source language Python 3.6, which allows interoperability between different platforms and standards.

The next paragraph gives an overview of the physiological model (Figure 4.2). The reader can find a detailed description of the model in Appendix V.

The physiological model of AngioSupport consists of several elements:

1. The one-fiber heart element generates the inflow of the coronary arteries and computes the intramyocardial pressure influencing the coronary windkessel elements (Appendix D).
2. The systemic line elements represent together the systemic vasculature obtained from literature (Appendix E).
3. The systemic windkessel elements describe the resistance and compliance of the peripheral vasculature (Appendix F).
4. The coronary line elements represent the larger vessels of the coronary arteries obtained from a patient specific ICA images (Appendix G).
5. The coronary windkessel elements describe the resistance and compliance of the coronary microcirculation (Appendix H).
6. And the stenosis element describes the pressure drop over the stenosis (Appendix I).
For each element, the reader is referred to the corresponding appendix for an explanation of the mathematical model. The physiological model including all these components can be solved using the solution procedure as proposed by Kroon et al. (Kroon et al., 2012), which is explained in Appendix J, and will result in blood pressure and flow throughout the systemic and coronary geometry.

4.2.2 Concept 1

To verify the implementation of the numerical model in Python, the results (blood flow and pressure) of Horst et al. has been reproduced (Appendix N). Furthermore, a systemic geometry has been defined from literature as this geometry cannot be obtained patient specific, because it is not visible on the ICA images. A reduced version of an anatomically detailed arterial vasculature developed for 1-D blood flow simulations (Blanco et al., 2014) has been used. This reduced version, referred as ADAN56, has been used in the benchmark study of Boileau et al. (Boileau et al., 2015) and the implementation has been verified on the results of this study (Appendix M).

<table>
<thead>
<tr>
<th>Technical requirements</th>
<th>Acceptance criteria</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verification</td>
<td>Accuracy of 70%</td>
<td>Realistic, not verified</td>
</tr>
<tr>
<td></td>
<td>Computation time within 10s.</td>
<td>429 sec</td>
</tr>
<tr>
<td>Flexibility</td>
<td>Geometry should be easy to change</td>
<td>Yes</td>
</tr>
<tr>
<td>Operability</td>
<td>Allowance to perform PCI</td>
<td>Yes, generates new input file</td>
</tr>
<tr>
<td></td>
<td>Allowance to Perform CABG</td>
<td>No LIMA</td>
</tr>
</tbody>
</table>

Table 4.3: The acceptance criteria and the state of concept 1.

For the first concept, a simplified coronary geometry and ADAN56 has been used as input. The simulation resulted in a physiological realistic pre-FFR values (between 0 and 1 and the FFR is decreasing from proximal to distal). The values could not be verified due to the lack of invasive measured FFR (mFFR). The computation time was about 25 min. Furthermore, the systemic geometry of this concept did not contain the Left Internal Mammary Artery (LIMA). Therefore, this concept is not able to perform a CABG. The PCI can be performed by generating a new input file as described in the flowchart of Figure 3.2. This input file consists of new radii values on the location defined by the clinician by placing virtually a stent. Table 4.3 summarizes the acceptance criteria and the state of this concept.

4.2.3 Concept 2: Systemic geometry

To allow CABG procedures, the LIMA has been added to the ADAN56 geometry. In addition, the systemic geometry has been truncated just after the left subclavian artery to reduce the number of nodes from 78 to 11, while allowing CABG to reduce the computational time. The physiological model allows CABG by generating a new input file connecting the LIMA to the coronary geometry. To check the new adaptations to the ADAN56 geometry, the same coronary geometry has been used as in Concept 1. After testing, the computational time has been reduced from 429s. to 300s, but did not meet the desirable 10s (Table 4.4). Appendix O elaborates on the changes of the ADAN56 geometry.

<table>
<thead>
<tr>
<th>Technical requirements</th>
<th>Acceptance criteria</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verification</td>
<td>Accuracy of 70%</td>
<td>Realistic, not verified</td>
</tr>
<tr>
<td></td>
<td>Computation time within 10s.</td>
<td>300 s.</td>
</tr>
<tr>
<td>Flexibility</td>
<td>Geometry should be easy to change</td>
<td>Yes</td>
</tr>
<tr>
<td>Operability</td>
<td>Allowance to perform PCI</td>
<td>Yes, generating new input file</td>
</tr>
<tr>
<td></td>
<td>Allowance to Perform CABG</td>
<td>Yes, contains LIMA and generates new input file</td>
</tr>
</tbody>
</table>

Table 4.4: The acceptance criteria and the state of concept 2.
4.2.4 Concept 3: Steady inflow
The purpose of AngioSupport is to be used during cardiac team meetings. A computation time of 300 sec. is not acceptable for supporting clinical decisions. Therefore, reducing the computational time is of paramount importance. In order to mimic a cardiac cycle, the model uses the one-fiber heart model. This model needs 1000 time steps to generate a pressure and flow curve for one cardiac cycle. However, the output of the model is the FFR computed with mean pressures. Therefore, a steady inflow may be a good approximation and reduces a cardiac cycle to one time step and therefore the computational time. Appendix P shows that the results of the model with steady and pulsatile inflow can be assumed to be equal. After implementing steady inflow, the computation time reduced from 300 s. to 2.27s., which is within the acceptance criteria of <10s.

The computational time per simulation is now acceptable (Table 4.5). Subsequently, the pre-FFR has been compared on a dataset of 10 patients of which their coronary geometry was segmented with CAAS (Chapter 4.1). Considering the cut-off value of 0.8, the accuracy $(\text{ACC} = \frac{TP+TN}{TP+TN+FP+FN})$, the sensitivity $(\text{TPR} = \frac{TP}{TP+FN})$, and specificity $(\text{TNR} = \frac{TN}{TN+FP})$ of this concepts has been 60.0%, 83.3%, and 25.0%, respectively (Figure 4.3). In other words, this concept has been underestimating the FFR, so considers healthy people as sick.

<table>
<thead>
<tr>
<th>Technical requirements</th>
<th>Acceptance criteria</th>
<th>State</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verification</td>
<td>Accuracy of 70%</td>
<td>Accuracy of 60%</td>
</tr>
<tr>
<td></td>
<td>Computation time within 10s.</td>
<td>2.27 sec</td>
</tr>
<tr>
<td>Flexibility</td>
<td>Geometry should be easy to change</td>
<td>Yes</td>
</tr>
<tr>
<td>Operability</td>
<td>Allowance to perform PCI</td>
<td>Yes, generating new input file</td>
</tr>
<tr>
<td></td>
<td>Allowance to Perform CABG</td>
<td>Yes, contains LIMA and generates new input file</td>
</tr>
</tbody>
</table>

Table 4.5: The acceptance criteria and the state of concept 3.

4.2.5 Concept 4: Sensitivity analysis
The verification of Concept 3 did not meet the acceptance criteria of an accuracy of 70%. Therefore, a sensitivity analysis has been performed to identify the most influential parameters on the pre-FFR. Appendix Q explains the sensitivity analysis in detail. As can been seen in Figure Q.2 and Q.3, the mean aortic pressure $(P_{\text{mean}})$ is the most important parameter. The patient data contains the systolic $(P_{\text{syst}})$ and diastolic $(P_{\text{dia}})$ aortic pressure, so the mean aortic pressure is known $(P_{\text{mean}} = \frac{P_{\text{syst}}+2P_{\text{dia}}}{3})$. Therefore, the $P_{\text{mean}}$ can be fixed and has been used as input boundary of the coronary arteries instead of the steady inflow. Using the $P_{\text{mean}}$ as
input and fixed on the measured value, the pre-FFR values have been increased in general (Figure 4.4) compared to concept 3 (Figure 4.3).

![Figure 4.4: Verification pre-FFR of physiological model concept 4 with \( p_{mean} \) as input boundary condition and fixed on its measured value.]

The accuracy, sensitivity, and specificity of the model is now 30.0%, 0.0%, and 75.0%, respectively. Table 4.6 summarized the above-mentioned findings.

<table>
<thead>
<tr>
<th>Technical requirements</th>
<th>Acceptance criteria</th>
<th>Current state</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verification</td>
<td>ACC of 70%</td>
<td>ACC of 30%</td>
</tr>
<tr>
<td></td>
<td>Computation time within 10s.</td>
<td>2.27 sec</td>
</tr>
<tr>
<td>Flexibility</td>
<td>Geometry should be easy to change</td>
<td>Yes</td>
</tr>
<tr>
<td>Operability</td>
<td>Allowance to perform PCT</td>
<td>Yes, by changing input file</td>
</tr>
<tr>
<td></td>
<td>Allowance to Perform CABG</td>
<td>Yes, contains LIMA</td>
</tr>
</tbody>
</table>

*Table 4.6: The acceptance criteria and the current state of concept 4.*

4.2.6 Concept 5: Tuning pre-FFR to mFFR

The pre-FFR of Concept 4 does not meet the acceptance criteria (Figure 4.4). Therefore, another sensitivity analysis has been performed with \( p_{mean} \) fixed on the measured value. As can be seen in Figure Q.4 and Q.5, the flow at rest \( (Q_{cor}) \) and hyperemia factor \( (f_{hyp}) \) are the most important parameters. However, the \( Q_{cor} \) and \( f_{hyp} \) are not measured values. Therefore, pre-FFR has been tuned on the mFFR by changing \( Q_{cor} \) within a realistic range \( (Q_{cor} = [25, 275] \) \). Appendix R explains the method to tune the pre-FFR to mFFR.

![Figure 4.5: Tuning the \( Q_{cor} \) to match the pre-FFR with the mFFR within realistic range.]

24
The expectation was that the pre-FFR would be exactly the same as the mFFR. However, this was not the case as can be seen in Figure 4.5. The cases with a mismatched pre-FFR with mFFR have a $Q_{cor}$ of 275 mL/min, which is the upper boundary of the realistic range. These cases required probably a higher $Q_{cor}$ to match the mFFR; therefore, those cases were unable to tune. The hypothesis was that the flow has not been distributed correctly over the different vessels. This hypothesis has been evaluated during the development of the next concept.

4.2.7 Concept 6: Flow distribution
The flow distribution of concept 5 has been based on the radii of the end of every vessel. The ratio between these radii determined the fraction of flow to this vessel (flow distribution bottom up). In this case, the effect of a potential occlusion was taken into account. However, tempered vessels could end up with less flow than expected. For example, despite the longer branch of the LAD, the flow is significantly less in the LAD as in the LCX (Figure 4.6, left) due to the smaller terminal radius of the LAD. A new flow distribution method has been tested that starts at the top and defines the flow fractions at every bifurcation downwards based on the proximal radius of every branch (flow distribution, top down). As can be seen in Figure 4.6, the LAD and LCX have approximately the same flow and the side branches have less flow as expected. The reader is referred to Appendix R.2 for further details.
Figure 4.7: Tuning the pre-FFR on the mFFR by tuning the flow at rest within realistic range using top-down flow distribution method.

Figure 4.7 shows the results of the top-down flow distribution method. As can been seen in the figure, the results have been improved compared with concept 5 (Figure 4.5). However, the ACC, TPR, and TNR is 60%, 50%, and 100%, respectively, which still does not meet the acceptance criteria (Table 4.6).

4.2.8 Concept 7: Stenose element
The overestimation of the pre-FFR (Figure 4.7) could be caused by the stenose detection. The stenose detection detects a stenose, if there is a radius reduction of 25% compared with the assumed healthy radius (Appendix I.2). The stenose element replaces only that part, while the beginning and the end of the stenose actually starts and ends at an assumed healthy radius. Figure 4.9 shows a schematic view to explain the issues. It shows a stenotic vessel (solid blue) with the assumed healthy radius (dashed green). The stenose detection detects the stenose (dashed red) and will replace that part with a stenose element resulting in the solid red line. To solve this problem, the stenose detection is adapted, such that the stenose starts and ends at an assumed healthy radius. After the adjustments, the stenoses are not only longer, but the detection algorithm recognizes two stenoses close to each other as one (red circles) as expected (Figure 4.10).
Despite the expectation, the results improve barely. Nevertheless, the ACC has been increased to 70% (Figure 4.8). The TPR and TNR are 50% and 100%, respectively. The acceptance criteria are met (Table 4.7). Therefore, this concept will be implemented in the final design.

<table>
<thead>
<tr>
<th>Technical requirements</th>
<th>Acceptance criteria</th>
<th>Current state</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Verification</strong></td>
<td>ACC of 70%</td>
<td>ACC of 70%</td>
</tr>
<tr>
<td></td>
<td>Computation time within 10s.</td>
<td>2.27 sec</td>
</tr>
<tr>
<td><strong>Flexibility</strong></td>
<td>Geometry should be easy to change</td>
<td>Yes</td>
</tr>
<tr>
<td><strong>Operability</strong></td>
<td>Allowance to perform PCI</td>
<td>Yes, by changing input file</td>
</tr>
<tr>
<td></td>
<td>Allowance to Perform CABG</td>
<td>Yes, contains LIMA</td>
</tr>
</tbody>
</table>

*Table 4.7: The acceptance criteria and the current state of concept 7 and final concept.*

4.3 Concepts of interface

The interface has been developed from scratch. Like the process of the concepts of the physiological model, the interface has been developed iteratively with PDCA cycles. The start of every PDCA cycle has been based on the feedback of clinicians received during progress meetings or during given demos of AngioSupport in hospitals. Appendix S summarizes all performed media activities.
4.3.1 Starting component
The interface of AngioSupport was developed with Electron\(^1\). Electron is an open source library to build applications with HTML, CSS, and JavaScript. It makes developing apps easy, because of its automatic updates, native menus and notifications, crash reporting, debugging, and windows installers. Furthermore, electron is used by many famous applications, such as WhatsApp, Skype, WordPress, and Slack resulting in many online instructions for solving encountered problems. In short, Electron contains a good basis to develop a cross-platform desktop application (Figure 4.11).

![Hello World!](image)

Figure 4.11: Electron basis for developing applications

The following chapters describe the development different concepts of the segmentation (Chapter 4.1), the physiological model (Chapter 4.2), and interface (Chapter 4.3) by adjusting the existing methods iteratively to meet the predefined requirements (Chapter 3.4).

4.3.2 Concept 1: Initiate
The purpose of the initiation of the interface was to become familiar with Electron, Javascript, CSS, and HTML. The first concept allowed loading a .csv file containing a dummy geometry and visualized the geometry with dummy FFR values, which were visible when hovering over the geometry (Figure 4.12). Table 4.8 shows the implemented technical requirements.

<table>
<thead>
<tr>
<th>Technical requirements</th>
<th>Implemented</th>
</tr>
</thead>
<tbody>
<tr>
<td>User can load coronary angiograms of desired patient</td>
<td>✓ .csv files</td>
</tr>
<tr>
<td>The physiological model can be started using pre-operative data</td>
<td>✓</td>
</tr>
<tr>
<td>Visualize results physiological model with colours inside the coronary arteries</td>
<td>✓ Visualizes the geometry and FFR, but not with colours</td>
</tr>
<tr>
<td>Results of simulation are stored</td>
<td>X</td>
</tr>
<tr>
<td>User can perform PCI</td>
<td>X</td>
</tr>
<tr>
<td>User can perform CABG</td>
<td>X</td>
</tr>
<tr>
<td>Generates input files after interventions</td>
<td>X</td>
</tr>
<tr>
<td>The physiological model can be started using post-operative data</td>
<td>X</td>
</tr>
<tr>
<td>Interventions and pre-operative results can be compared</td>
<td>X</td>
</tr>
</tbody>
</table>

Table 4.8: The table shows which technical requirements are implemented of the interface, concept 1.

---

1 https://electronjs.org/
During progress meeting 1, the following feedback was given by the stakeholders to make the goals of AngioSupport clearer:

“Visualize the current workflow and identify the place where ITSCI\(^1\) would fit in this workflow.”

4.3.3 Concept 2: Progress meeting 1 [08-06-‘18]

After the received feedback of progress meeting 1, two flowcharts were generated; one flowchart to visualize the current workflow including AngioSupport (Figure 1.4) and another flowchart of the interface itself (Figure 3.2). Based on these graphs, the development of the interface continued and resulted in a workflow with six pages:

1. A welcome screen
2. A page to load data
3. A page to start the physiological model
4. A page to compare results (Figure 4.13, right)
5. A page to perform PCI
6. A page to perform CABG

The home page of concept 2 is shown in Figure 4.13 (left). This concept allowed performing the PCI only. Therefore, comparison of interventions was not possible. The implemented technical requirements are summarized in Table 4.9: The table shows which technical requirements are implemented of the interface, concept 2. Table 4.9.

<table>
<thead>
<tr>
<th>Technical requirements</th>
<th>Implemented</th>
</tr>
</thead>
<tbody>
<tr>
<td>User can load coronary angiograms of desired patient</td>
<td>✓ .csv files</td>
</tr>
<tr>
<td>The physiological model can be started using pre-operative data</td>
<td>✓</td>
</tr>
<tr>
<td>Visualize results physiological model with colours inside the coronary arteries</td>
<td>✓</td>
</tr>
<tr>
<td>Results of simulation are stored</td>
<td>✓</td>
</tr>
<tr>
<td>User can perform PCI</td>
<td>✓</td>
</tr>
<tr>
<td>User can perform CABG</td>
<td>X</td>
</tr>
<tr>
<td>Generates input files after interventions</td>
<td>✓</td>
</tr>
<tr>
<td>The physiological model can be started using post-operative data</td>
<td>✓</td>
</tr>
<tr>
<td>Interventions and pre-operative results can be compared</td>
<td>X</td>
</tr>
</tbody>
</table>

Table 4.9: The table shows which technical requirements are implemented of the interface, concept 2.

\(^{1}\) Interactive Tool to Support Coronary Interventions; previous name of AngioSupport
During progress meeting 2, the following feedback was given by the stakeholders:

"Presence of the project managers during the cardiac team meetings at the CZE would be profitable for the development."

![Home page of Interface of concept 2 (left) and an overview of all pages of the interface (right)](image)

**Figure 4.13: Home page of Interface of concept 2 (left) and an overview of all pages of the interface (right)**

### 4.3.4 Concept 3: Progress meeting 2

The project managers joined cardiac team meetings in CZE, which resulted in Concept 3. This concept met the functional requirements for the interface (predicting and comparing coronary interventions; Chapter 3.4.3). This concept allowed performing a CABG and comparing results of different interventions. Figure 4.14 shows the simulation page of concept 3.

![Simulation page of concept 3](image)

**Figure 4.14: Simulation page of concept 3.**
During progress meeting 3, the following feedback was given by Dr. Pim Tonino based on virtually performing a PCI. In this concept, the diameter and length should be chosen of the stent. Subsequently, the location of the center of the stent should be chosen. The following was suggested:

“Preferably, clinicians would like to choose first the start and end point of the stent. Subsequently, the proximal and distal diameter as well as the length should be given by AngioSupport, such that clinicians can choose the proper stent based on this information.”

Furthermore:

“It would be helpful for clinicians, if the chance on in-stent stenose is predicted by AngioSupport.”

<table>
<thead>
<tr>
<th>Technical requirements</th>
<th>Implemented</th>
</tr>
</thead>
<tbody>
<tr>
<td>User can load coronary angiograms of desired patient</td>
<td>✓ .csv and .json files</td>
</tr>
<tr>
<td>The physiological model can be started using pre-operative data</td>
<td>✓</td>
</tr>
<tr>
<td>Visualize results physiological model with colours inside the coronary arteries</td>
<td>✓</td>
</tr>
<tr>
<td>Results of simulation are stored</td>
<td>✓</td>
</tr>
<tr>
<td>User can perform PCI</td>
<td>✓</td>
</tr>
<tr>
<td>User can perform CABG</td>
<td>✓</td>
</tr>
<tr>
<td>Generates input files after interventions</td>
<td>✓</td>
</tr>
<tr>
<td>The physiological model can be started using post-operative data</td>
<td>✓</td>
</tr>
<tr>
<td>Interventions and pre-operative results can be compared</td>
<td>✓</td>
</tr>
</tbody>
</table>

Table 4.10: The table shows which technical requirements are implemented of the interface, concept 3.

4.3.5 Concept 4: Progress meeting 3 [30-11-'18]
Figure 4.15 shows a screenshot of the interface to perform a PCI of concept 3 (left) and concept 4 (right). Besides the change in layout (to standardize all the pages by having a side bar at the left side and to increase the professional look), the manner to choose a stent has been adapted. In concept 3, first the stent with diameter and length should be chosen (Figure 4.15, left, grey area) and subsequently the location of the center of the stent in the coronary geometry. In concept 4, first the location of the start and end point of the stent have to be chosen in coronary geometry first (Figure 4.15, right, first green buttons). Then, proximal and distal diameter and length will be displayed (Figure 4.15, right, first three white lines). Subsequently, the clinician can choose the diameter and length of the stent (Figure 4.15, right, second three white lines).

To gain information of in-stent restenose, the project managers talked to Dr. Pim Tonino. This meeting revealed the following factors that increase the chance on restenose:

1. Location of the stenose closer to the left main or bifurcation,
2. longer lesions,
3. small-diameter vessel,
4. higher age,
5. diabetic,
6. and multivessel disease.
Although, by predicting the chance of re-stenose of the virtually performed PCI’s this would improve the clinical decision making of AngioSupport, the development of this prediction model would consume too much time. Therefore, it has not been feasible in this project.

Figure 4.15: Performing a PCI with AngioSupport concept 3 (left) and AngioSupport concept 4 (right).

The interface met at this point all the technical requirements (Table 3.3, user survey will be held during the validation). Nevertheless, there were some suggestions for “nice to have features” that would improve clinical decision making.

1. A graph that shows the length and diameter of the vessel.
2. Reveal the stenoses that the model detects and show the stenose percentage when hovering over the geometry.
3. Show the diameter when hovering over.

4.3.6 Concept 5: Progress meeting 4 [08-02-'19]
To implement above mentioned features, buttons has been created to change the visualization between FFR (Figure 4.16B) and stenose severity (Figure 4.16C). These buttons are shown in every page after the results are computed (simulation, results, PCI, and CABG page). Before the simulation (load data page), the diameter is shown when hovering over the geometry (Figure 4.16A). Furthermore, clicking on a vessel creates a distance – diameter graph (Figure 4.17). This graph shows the diameter over the length of the vessel starting from the ostium. The graph is mirrored over the length to represent the vessel better. Finally, AngioSupport was presented at BME (BioMedical Engineering) research day and won the first price of best poster and pitch (Appendix S).

The following citation represents the overall reaction at progress meeting 5:

“There should be more focus on the interface to get cardiologists excited about AngioSupport.”
4.3.7 Concept 6: Progress meeting 5

[09-04-’19]

In order to focus more on the interface, the project managers have been given demos to cardiologists in training of CZE (Jo Zelis, Mohamed El Farissi, and Daniëlle Keulards), to the (former and current) head of cardiology of Amsterdam UMC (Bas de Mol and José Henriques, respectively), Associate professor of the biomedical department and cardiologist of ErasmusMC (Frank Gijssen and Joost Daemen, respectively) (Appendix S). The following feedback was given:

1. The width of the vessel was given in radius; however, clinicians work with diameters. Therefore, values in diameters are preferred.
2. Flow is an important parameter to check the FFR. For instance, myocardial resistance may result in low flow resulting in a high FFR, while a stenose could be present. Based
on this feedback, an extra button has been implemented to show the flow as result (Figure 4.16D).

3. Besides the FFR as an important feature for clinical decision making, the clinicians were also enthusiastic about the 3D image, stenose recognition, and diameter visualization, because ICA images are 2D images and perception of 3D is difficult.

In addition, the project managers finally received a workplace at the R&D department of the cardiology in CZE. To get everyone familiar with AngioSupport, a presentation was given to the entire department (Appendix S). Enthusiastic responses and curiosity rose out of the public about AngioSupport.

Together with the stakeholders, a design stop for the interface was decided during Progress meeting 6. The focus shifted to verification, implementation and validation of AngioSupport.

Figure 4.17: Graph to show the diameter over the length of a vessel with 0 at the ostium.

4.3.8 Concept 7: Progress meeting 6 [12-07-`19]

A presentation has been given in Oxford at the all-hands meeting (AHM) of CBM (Appendix S). After the presentation, Alfons Hoekstra (Prof. at AMC) started an interesting discussion with the project managers with the question: “When is AngioSupport validated?” He asked questions like: “Is AngioSupport validated when a high accuracy of the FFR is reached?” Validation of AngioSupport was not in the scope of this project. However, it will be recommended to the next developer(s) to think about these questions.

After progress meeting 6, the focus shifted to the verification, implementation, and validation of AngioSupport. During the validation, the interface has been evaluated with the help of a user survey. This user survey clarified the user-friendliness of AngioSupport. The user-survey (Appendix U) has first been tested on an independent employee of LTG (BS) to identify small problems.
5 Final design and implementation

The design has been iteratively developed as described in the previous chapters. An abstract about AngioSupport accepted for an oral presentation at CompBioMed conference 2019 can be find in Appendix W. In this chapter, the final design of the prototype of AngioSupport is summarized. Furthermore, the legislation and regulations for AngioSupport, as well as a Business Case has been described.

5.1 Pre-processing

The final design consists of the physiological model and the interface as the backend and the frontend of AngioSupport, respectively. In order to use AngioSupport, the input data (ICA images) should first be pre-processed. The pre-processing consists of:

1. the segmentation of single coronary arteries using CAAS
2. and the connection of the segmented coronary arteries (Appendix K).

Both the segmentation and attachment of the arteries are manual acts, which should be performed by a trained biomedical engineer before the cardiac team meeting. Furthermore, the clinicians should receive instructions about how to perform ICA to create most optimal images, such as no table movement, two images ≤ 30° separated, and as little as possible overlapping of the vessels.

5.2 Backend

The backend of AngioSupport computes the pre- and post-FFR. In order to do this correctly, the following data are necessary:

- the centerline and radii of the patient specific coronary geometry obtained from ICA;
- the measured aortic pressure as input for the physiological model;
- the mFFR to determine the flow.

5.3 Frontend

The frontend of AngioSupport allows clinicians to analyze the patient, to perform interventions, and to compare the interventions. For a professional look of the interface, the menu bar is black and a constant factor throughout the pages of AngioSupport. In addition, clicking to a next page results in an extra link, such that it is possible to go to previous pages. AngioSupport consists of the following six pages:

1) the home page,
2) the load page,
3) the simulation page,
4) the result page,
5) the PCI page,
6) the CABG page.

See Figure 5.1. These 6 pages are explained in the following paragraphs.

5.4 Final design of the interface

The Home page

This page contains the AngioSupport logo. The load page appears by pressing the ‘continue’ button.

The load page

This page enables clinicians to load the patient data. AngioSupport allows only .xlsx, .csv, and .json files. Therefore, DICOM files should first be pre-processed. After loading the patient
geometry, the aortic pressure and mFFR with location should be manually entered by the clinician, which then appears in the geometry. Furthermore, the diameter appears when hovering over the geometry with the mouse. The ‘continue’ button can be pressed to go to the simulation page.

**The simulation page**

When the simulation page appears, immediately the physiological model starts to compute the pressure and flow throughout the coronary arteries. When the simulation is finished, the colors of the pre-FFR appear. The values of the pre-FFR are visible when hovering over the geometry. Subsequently, the user can press the ‘flow’ or ‘stenose’ button, which shows the flow (Figure 5.1, left simulation page) or stenose severity (Figure 5.1, right simulation page) in the coronary geometry. The values of both the flow and stenose severity are visible when hovering over the geometry. Clicking on the geometry results in a diameter-distance and pre-FFR-distance graph (Figure 5.1, middle simulation page right side). Pressing the ‘continue’ button results in the result page.

**The result page**

On this page, all intervention results can be compared. In the center, the pre-operative results are visible. At the left and right side of the pre-operative results, shows the results of the PCI and CABG interventions, respectively. The blue buttons allow the user to perform a PCI or CABG. When performed, this page will appear again and simulation of the last performed intervention starts automatically. The results will be saved in a folder underneath the load bar and can be shown in all times. This way, the old results can be visualized again.

**The PCI page**

After clicking on the ‘PCI’ button on the simulation page, the user ends up in the PCI page. By pressing ‘begin stent’, the user can choose the starting point of the stent. Thereafter, the user should press the button ‘end stent’ to choose the end point of the stent. The proximal and distal diameter and the length will be given. The stent diameter is automatically chosen as proximal diameter, but can be adapted by the user. After selecting the location of the stent and the diameter, the user can press ‘place stent’, which results in the adaptation of the diameter in the geometry. Thereafter, pressing the ‘continue’ button results in appearance of the result page.

**The CABG page**

After clicking on the CABG button on the simulation page, the user ends up in the CABG page. The user can immediately select the end point of the LIMA in the geometry. The ‘continue’ button leads the user back to the simulation page.

5.5 Legislation and Regulation

The legislation and regulation for AngioSupport has been determined for the final purpose of AngioSupport to be a diagnostic tool.

5.5.1 Qualification

The qualification has been done with the decision diagram in the ‘Medical Devices: Guidance Document’ (MEDDEV 2.1/6) and is included in Appendix T. Following the steps of Figure 1 of that diagram, AngioSupport is qualified as follows:

1. AngioSupport is a software, because it processes angiogram DICOM images (input data) and computes flow and pressure based on these images (output data).
2. AngioSupport is stand-alone software, because it is not incorporated in a medical device.
3. AngioSupport performs segmentation on the DICOM images and computes flow and pressure based on 1D wave propagation model using Navier-Stokes equations. Therefore, it performs actions different from communication, storage, archive, and simple search.

4. The computed flow and pressure define the severity of the possible stenosis in the coronary arteries. Based on those findings, the clinician can virtually insert a stent in the coronary artery or perform a bypass surgery to predict the effect of the intervention beforehand, which is beneficial for the patient.

5. The final purpose of AngioSupport is to provide clinicians with recommendations for diagnosis and treatment, which agrees with art. 1.2a of Dir. 93/42 EEC. In conclusion, **AngioSupport is a medical device**.

5.5.2 Classification

A stand-alone software is considered to be an active device. Furthermore, AngioSupport is intended for diagnosis, which classifies AngioSupport to Class 2a.
Figure 5.1: Final interface
6 Business case
The following chapter describes the business case of AngioSupport.

6.1.1 The industry
In 2010, an average of 54 CABGs were performed in the Netherlands for every 100,000 inhabitants (Head et al., 2017) and a total of 35,000 PCIs were performed in 2010 (Daemen, 2012). Following prices as stated from Martini Ziekenhuis Groningen, these procedures cost €13,000 and €4,500 for CABG and PCI, respectively. This results in total costs of CABGs of approximately €78 million and PCIs of approximately €158 million\(^1\). Approximately two thirds of patients who require revascularisation have multi-vessel disease and two thirds of this group have an anatomy that is treatable with percutaneous or open heart procedures (Casey and Faxon, 2004). These patients are discussed during the heart team meeting, which consists of a thoracic surgeon and an interventional cardiologist. Together they decide treatment for each patient, based on the coronary angiogram, possible FFR measurement and patient data. Possible choices consist of either CABG, PCI or drug treatment.

6.1.2 The mission
The decision between PCI or CABG is currently based on studying coronary angiograms and the experience of the cardiac team. However, in case of multiple occlusions, diffuse coronary disease or complicated vasculature, choices in the position, length or diameter for a CABG or PCI is challenging. Therefore, a clinical decision support tool which predicts the result of the planned coronary intervention could greatly help in planning coronary interventions.

6.1.3 Achieved milestones
- Scientific research completed
- Physiological model verified on literature data
- First prototype proof-of-concept delivered

\(^1\) https://www.martiniziekenhuis.nl/Documents/Kosten/Passanten%20tarieven%201-2014.pdf
Recommendations for further development

6.1.4 The Market

Table 6.1 shows an overview of all virtual FFR models. Most tools have a run time that exceeds the 10s. (HeartFlow, VIRTU-1, FFRQCA, CathWorks); therefore, those tools cannot be used during the cardiac team meeting. In addition, many tools are only suitable for single lesion; therefore, it is not possible to see the influence of an intervention on multiple vessels. When AngioSupport improves its accuracy, AngioSupport will be the best suited for the cardiac team to see the influence of coronary interventions.
<table>
<thead>
<tr>
<th>Virtual model</th>
<th>FFR developed in</th>
<th>Imaging tool</th>
<th>CFD simulations</th>
<th>Extra requirements</th>
<th>diagnostic accuracy</th>
<th>Single- or multivessel</th>
<th>Approximate run time</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>HeartFlow</td>
<td>California (US)</td>
<td>CT</td>
<td>3D CFD</td>
<td>Myocardial mass</td>
<td>86%</td>
<td>Multi</td>
<td>Remote core computation</td>
<td>(Koo et al., 2011)</td>
</tr>
<tr>
<td>VIRTU-1</td>
<td>Sheffield (UK)</td>
<td>ICA</td>
<td>3D CFD</td>
<td>-</td>
<td>97%</td>
<td>Single</td>
<td>12-24 h</td>
<td>(Morris et al., 2015)</td>
</tr>
<tr>
<td>FFR$_{DCA}$</td>
<td>Leiden (NL)</td>
<td>ICA</td>
<td>Steady-state 3D</td>
<td>contrast velocity</td>
<td>88%</td>
<td>Single</td>
<td>5 min</td>
<td>(Tu et al., 2014)</td>
</tr>
<tr>
<td>CAAS</td>
<td>Maastricht (NL)</td>
<td>ICA</td>
<td>Geometry based</td>
<td>MAP</td>
<td>95%</td>
<td>Single</td>
<td>1 sec</td>
<td>(Majedjedi et al., 2019)</td>
</tr>
<tr>
<td>Medis</td>
<td>Leiden (NL)</td>
<td>ICA</td>
<td>Geometry based</td>
<td>contrast velocity</td>
<td>94%</td>
<td>Single</td>
<td>unknown</td>
<td>(Hwang et al., 2019)</td>
</tr>
<tr>
<td>CathWorks</td>
<td>Kfar-Saba (IS)</td>
<td>ICA</td>
<td>Geometry based</td>
<td>Mean arterial pressure</td>
<td>92%</td>
<td>Multi</td>
<td>2-3 minutes</td>
<td>(Fearon William F. et al., 2019)</td>
</tr>
<tr>
<td>AngioSupport</td>
<td>Eindhoven (NL)</td>
<td>ICA</td>
<td>1D CFD</td>
<td>Mean arterial pressure mFFR</td>
<td>70%</td>
<td>Multi</td>
<td>4 sec</td>
<td></td>
</tr>
</tbody>
</table>

Table 6.1: Overview of software tools simulating vFFR. Data derived on the basis of best interpretation of the published data.
7 Verification
The complete designed prototype of AngioSupport consists of:

1. segmentation,
2. physiological model,
3. and interface.

In Tables 4.1 and Table 4.9, it is shown that the technical requirements of the segmentation and the interface have been met as well as the technical requirements of the physiological model (Figure 4.8 and Table 4.7). The latter verification does, however, only applies on the dataset of 10 patients, because this dataset has been used for tuning as well as for verifying. Furthermore, only the pre-FFR is verified for these patients. Nevertheless, this (in general insufficient) verification yielded in realistic demo’s for clinicians and their trust that high accuracy of the pre-FFR and post-FFR could be managed. This will be elaborated in the next chapter, which describes the validation of this first prototype of AngioSupport, with the help of a conducted user survey.

8 First order validation
As first order validation test (of the user interface and the physiological model), the prototype of AngioSupport has been used by 10 end users (clinicians of the department of Cardiology at CZE). The project managers had executed the segmentation/pre-processing part by themselves. Subsequently, clinicians had been invited one by one at the R&D cardiology research office. First, one of the project managers gave a demo; thereafter, the clinician could use AngioSupport by her/himself, while the other project manager asked her/him some questions. This user survey was divided in three parts:

1. the user friendliness of every page,
2. general questions about AngioSupport at whole,
3. and open questions.

The average of all questions about the user friendliness scores > 4 (out of 5)(see Appendix U for details); therefore, the prototype of the interface has been verified with respect to the technical requirements (Table 3.3). The general questions asked about the purpose of AngioSupport resulted in the following:

1. In general, the interface of AngioSupport is user-friendly (4.1/5)
2. and gives more insight in the patient (4.1/5).
3. The interviewed clinicians think that AngioSupport can be used as education for trainee clinicians (4.1/5)
4. and their opinions are scattered about the use of AngioSupport to explain the treatment plan to patients.
5. In addition, in decreasing agreement, the clinicians think that AngioSupport can support (4.6/5), improve (3.5/5), and replace clinicians (1.2/5) by clinical decision making.

Four open questions were asked:

1. What feature do you miss in AngioSupport?
2. Would you use AngioSupport?
3. Would you trust simulation in general?
4. Any other remarks?
In the following paragraphs the most frequent answers are mentioned. For complete answers, the reader is referred to Appendix U.

**What feature do you miss in AngioSupport?**
Four (out of ten) interviewed clinicians would like to see the coronary angiograms next to the coronary geometry generated by AngioSupport to gain more trust in the application. Furthermore, also four clinicians would like to see the post-FFR on the location of the mFFR after the intervention. Currently, the mFFR remains after the intervention and only the color changes to the post-FFR. The clinicians seem to be confused by this as they expect the post-FFR value. Finally, three out of ten clinicians would like to see a connection between the geometry, diameter-distance, and FFR plot at the simulation page, such that the clinicians can see the location of the diameter reduction and/or FFR jump at once.

**Would you use AngioSupport?**
Except for one clinician (who cannot think of a case when he would use AngioSupport), all other clinicians agreed that AngioSupport would be an addition to the cardiac team meeting provided that the software is validated and segmentation would not take too much time.

**Would you trust simulations in general in the hospital?**
Except for one clinician, all clinicians trust simulations when the software is validated, but only as support not as replacement of clinicians.

**Any other remarks:**
Numerous remarks were mentioned, which is a good sign. Clinicians were enthusiastic about AngioSupport and were prepared to think about improvements. Furthermore, many clinicians ended their remarks with complements and expressed their hope on success.

This validation test showed that the prototype meets the functional requirements corresponding to the physiological model (F.1 computation of blood pressure and flow throughout the coronary arteries, Chapter 3.1) and the interface (F.3: simulation of the coronary interventions (PCI and CABG) and F.4: visual comparison of computed results of the interventions, Chapter 3.1). However, the project managers executed the pre-processing; therefore, the first functional requirement (F.1: visual detection of the coronary arteries based on ICA, Chapter 3.1) was not implemented yet. Nevertheless, the output of the segmentation was used by clinicians.
9 Conclusions

During the past 1.5 year, a prototype of a new patient specific model based interactive tool has been developed to provide clinicians quantitative information to plan coronary interventions and support clinical decision making: AngioSupport. In this design project, there was a close cooperation between two project managers: Bettine van Willigen and Tim van den Boom. With the developed prototype, a proof-of-concept has been shown that in principle could lead to a product that is able to support treatment planning for patients with challenging CAD (difficult vasculature, multiple stenoses, or diffuse disease) by allowing complicated interventions (multiple stents, jump-grafts, Y-grafts, and combinations of PCI and CABG). Furthermore, demo’s and presentations have been given to receive feedback and grow a reputation. The media messages and activities (Appendix S) resulted in a user-friendly design and acceptance of AngioSupport (Deliverable D.1, Chapter 2.4) as concluded from the conducted user survey (Chapter 8). Although the backend (physiological model) of AngioSupport is not properly verified, the verification was good enough to gain trust of the clinicians that the pre-FFR and post-FFR could accurately be predicted (Deliverable D.2, Chapter 2.4). Finally, an first order validation test has been performed of the interface at the frontend and the physiological model at the backend (Deliverable D.3, Chapter 2.4). In the following chapter, further recommendations have been given to reach the final product (Deliverable D.4, Chapter 2.4).

In summary, the further development of AngioSupport needs a long way to reach its full potential. Nevertheless, this proof-of-concept lifted confidence that it is technical possible and it will be accepted by clinicians to support clinical decision making and as educational tool.
10 Discussions and recommendations
The following chapter will discuss AngioSupport and lists recommendations (Chapter 10.5), ranked on priority (according to the project managers).

10.1 Segmentation
It has already been mentioned in Chapter 6 (Verification) that the technical requirements of the segmentation prototype are met as shown in Table 4.2. However, pre-processing of the patient data requires a trained biomedical engineer who segments the coronary arteries one by one and attach them to each other before a cardiac meeting. This pre-processing roughly takes 1.5hrs. However, it would be preferable when the clinician can drag and drop the ICA images into AngioSupport and AngioSupport selects the images and frames, segment the coronary arteries, and generates a 3D image automatically. Galassi et al. published a paper to segments coronary arteries automatically from ICA images (Galassi et al., 2018). For further development of AngioSupport, it is suggested to implement an automatic segmentation part in AngioSupport. The automatic segmentation in addition with well instructed clinicians about taking ICA images should allow clinicians to drag and drop the ICA images into AngioSupport and select the images and frames. This would make the biomedical engineers obsolete and the pre-processing time preferably within 5min. Nevertheless, the pre-processing should still take place before the cardiac team meeting.

In addition, the accuracy of the CAAS software should be verified. The interviewed intervention cardiologists all comment that the diameter of the vessels was unexpected small. This could be caused by diffuse disease or inaccurate segmentation of CAAS. In case the next developer will still use CAAS, it is recommended to verify its accuracy.

Moreover, the user survey concluded that intervention cardiologists would like to use AngioSupport during cardiac team meetings and would support clinical decision making. However, the current duration of 1.5 hrs. of pre-processing, is unacceptable; therefore, the tool will be most likely not be used. Hence, optimization and automatization of the segmentation of ICA images is the highest priority for further development of AngioSupport!

10.2 Physiological model
The literature verification of the physiological model showed that the model was well implemented as the results were similar to literature results (Appendix M and N). The model tested on patient data showed an accuracy of the pre-FFR is 70% based on a dataset of 10 patients consisting of the mFFR and ICA images. The model was not verified sufficiently, because of the following reasons:

1. the model was verified and tuned on the same dataset,
2. the number of patients was not large enough,
3. the dataset did not consist of post-FFR values,
4. and the boundary conditions (BCs) of the model are not verified yet.

The next subsection discusses and recommends with respect to the BCs.

10.2.1 Boundary conditions (BCs)
The model consists of 3 BCs (Figure 10.1):
1. the aortic inlet,
2. aortic outlet,
3. and the coronary outlets.
10.2.1.1 The aortic inlet
In the final model, the aortic inlet is the invasively measured mean aortic pressure obtained from invasive measured patient data. The aortic pressure is measured at one time point, while the aortic pressure can change over time due to for instance stress. The sensitivity analysis revealed that aortic pressure has a high influence on the physiological model (Figure Q.3 and Q.4); therefore, it should be investigated what the influence is of the one-time point measurement and compare it to continue pressure measurements of the patient.

![Figure 10.1: Boundary Conditions of the physiological model.](image)

10.2.1.2 The aortic outlet
The aortic outlet is described by a reduced literature based systemic geometry to simulate the flow and pressure in the LIMA. However, the aortic input is the mean pressure; therefore, the systemic geometry has no influence on the coronary geometry. One windkessel describing the systemic geometry would be sufficient to simulate the pressure and flow in the coronary arteries. Furthermore, there is no information about the LIMA, so a population averaged pressure and flow can be subscribed when a CABG is performed. Currently, aortic pressure and flow is subscribed, while actually the FFR in the LIMA is 0.90 (Glineur et al., 2007). In other words, research should be done about the characteristics of the LIMA and subscribe those values when a CABG is performed. In addition, the systemic geometry can be replaced by a windkessel element.

10.2.1.3 The coronary outlets
Finally, the coronary outlets mimic the resistance of the microcirculation distal to the vessel. The resistance is based on four factors (Appendix H):

1. the pressure difference,
2. the total coronary flow at rest,
3. the hyperemia factor,
4. and the flow distribution method.

The coronary outlets are the most uncertain boundary conditions. The pressure difference is the difference between the mean aortic and the venous pressure \( \Delta P = P_{\text{mean}} - P_{\text{ven}} \). The aortic pressure is invasively measured and the venous pressure does not influence the FFR. Therefore, there is assumed that this value is correct. In contrast, the total coronary flow at rest and the hyperemia factor are both unknown. Currently, the total coronary flow is tuned on the mFFR to estimate the resistance distal to the coronary arteries and to avoid the need to measure the flow. The ranges of the coronary flow at rest are used, such that the hyperemia factor is included. However, the assumption is made that the flow distribution is correct in order
to compute the resistances distal to every vessel (Appendix R.2). The results of Figure 4.8 show that this may not be the case, because some patients could not match the pre-FFR with the mFFR. These boundary conditions could be refined by having more patient data. A trainee cardiologist has absolute flow and pullback pressure measurements. Combining these data would result in more accurate resistances at the coronary outlets. In short, more elaborated data should be used to define better boundary conditions.

10.2.2 Further recommendations and improvements of the model
When the boundary conditions are improved and verified, AngioSupport should be verified on a large retrospective dataset (>1000 patients) consisting of pre-FFR and post-FFR data of both PCI and CABG treated patients. If this verification results in ≥ 84% accuracy (accuracy of FFR_{CT} of HeartFlow, (Zarins et al., 2013)), a clinical validation should be performed to compare the clinical outcomes, such as repeated revascularization, patients quality of life and healthcare costs, of patients treated by a cardiac team with and without AngioSupport.

In addition, clinical decision making would improve when prediction of restenose and instent stenose would be added to AngioSupport. Prof. Dr. Ir. A. G. Hoekstra is already developing a model as such. Therefore, cooperation with his research group would be highly required to the next developer of AngioSupport.

Finally, an improvement of AngioSupport would be when it could compute the optimal coronary intervention, such as the optimal length, diameter, and location of (the) stent(s) and the location(s) of the CABG. Subsequently, the optimal CABG and PCI could be compared and the clinician can adjust the optimal intervention based on her/his own insight.

10.3 Interface
The interface scored >4 (out of 5) of overall user-friendliness. However, many tips were given to improve the interface. One clinician responded the following:

“I ask myself the following when I analyze a patient with CAD based on ICA and FFR: Flows there enough blood? Where is the largest pressure jump? And corresponds the pressure jump with an angiographic stenose?”

When the development of the interface focusses on answering these questions as simple as possible and in a blink of an eye, while continue asking for feedback of clinicians, the interface will be continuing improving and reach nearly perfection.

10.4 General
The next developer(s) should figure out the next step to get a CE mark. The privacy of the patient would not be a concern when AngioSupport will be only used in the hospital including the preprocessing of the data and not in contact with the world outside the hospital.

10.5 Summary of Recommendations
1. Optimization and automatization of the segmentation of ICA images (Chapter 10.1)
2. Define and verify boundary conditions for the aortic inlet and outlet and coronary outlets based on a more elaborated dataset with absolute flow and pullback pressure measurements. (Chapter 10.2.1)
3. CE mark (Chapter 10.4)
4. Verification on large dataset (Chapter 10.2.2)
5. Clinical validation (Chapter 10.2.2)
6. Prediction of instent and restenose (Chapter 10.2.2)
7. Computation of the optimal coronary intervention (Chapter 10.2.2)
8. Continue developing the interface by asking feedback of clinicians as often as possible.

47
11 Outlook
At the end of this project, the development of automatization of the segmentation of ICA images is transferred to a master student of the University of Technology in Delft (Nabil el Hasnaoui). His assignment is to develop software to automatize the segmentation for AngioSupport in Amsterdam UMC. Bettine van Willigen will be there the first three months for any support.

Furthermore, an investor showed interest to give support in defining a business plan for AngioSupport.

12 Reflection
The past 1.5 year, I (Bettine van Willigen) worked closely together with Tim van den Boom. The project initially was separated in the interface and the physiological model. However, the collaboration went very well. We could start one project, change to the other’s, and switch back. Therefore, we decided to make one project and divide it in two parts. Nevertheless, at the end I was still responsible for the interface and Tim for the physiological model. The PDEng focusses on managing your own project, taking the lead, communicating, and teamwork. This is exactly what we have done. We discovered that AngioSupport would end up at a higher level when we would be in one project and we showed leadership in our own team. The collaboration went that well that communication and teamwork went naturally between Tim and me. I could not pull this off on my own. I believe we can say: \(1+1=3\).

The collaboration with the stakeholders was sometimes a little bit more difficult, especially with PMI. Using the software and receiving a licence for different versions was not a problem, but PMI gave not complete answers when discussing problems in order to remain their secrets. Out of PMI perspective understandable, but for us difficult and resulting in non-solvable problems, such as retrieving an entire coronary tree with less manual acts and remained questions about the correctness of the segmentation of multiple vessels. Finally, PMI had many questions about our physiological model, such as the methods of our BCs, while they were not permissive in answering ours to remain their company secrets. Looking back, we might agreed too fast to use PMI. It seemed the easy choice, because of their connections with CZE and TU/e. After realising PMI was not very easy to work with, because they must understandably remain their company secrets. It consumed already too much time. Therefore, changing the segmentation tool would not be preferable timewise.

In addition, CBM was difficult for communication. Their aim is to make mathematical models that end up at the end user. However, the companies and institutions we saw at all-hands meetings had very sophisticated models, but the end users were not really in the picture. Promises of collaboration were given, but after the meeting the communication was low. We tried to reach out to people, but after a while our motivation to try to connect went down. We ended up on our own island like the other participants of CBM. Looking back, we should have made more effort to connect with certain participants to improve AngioSupport. We should have created an overview of the participants with their models and how we could be help each other. This way, we could have emailed participants with concrete questions, which could have possible lead to a cooperation. However, we had good contact with Marco Verdiccio of SURFsara. We performed our sensitivity analysis on SURFsara and he helped us with optimizing the code. He was always in for a skype meeting.

In contrast to CBM, communication with our experts Marcel van ’t Veer and Wouter Huberts went very well. We could always plan a meeting with them and they would take the time to listen, think, and advice about our tumbled problems. I was looking forward to those meetings, because I would always end up with more ideas, possibilities, and motivation.
Finally, the project board consisting of Pim Tonino (end user), Marco Stijnen (executive), and Frans van de Vosse (senior supplier) are busy people. Nevertheless, in general they took the time when (progress) meetings were planned. They were all enthusiastic about AngioSupport, which was very motivating. We could catch Marco Stijnen in the hallway of LTG and his door was always open to discuss problems or ideas. Pim Tonino had every Friday off, but took the effort to go to our progress meetings on Fridays. Meetings with Frans van de Vosse should be planned, but when it was planned, he took the time to for us.

In conclusion, I have grown in communication between different groups of people, especially to make connections useful for my project. I had to sell AngioSupport, see the possibilities by connecting with other projects, see problems of other institutions that could possibly be solved by AngioSupport, and learned to listen to the feedback of the end user to transfer this feedback into a feature of AngioSupport. It was a great project where I could be the spider in the middle of a web. Most of all I learned that I like to be this spider and this is what I will be looking for in my next project/job.
13 Abbreviations

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>ACC</td>
<td>Accuracy</td>
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<tr>
<td>ADAN56</td>
<td>Systemic geometry from literature</td>
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<tr>
<td>BC</td>
<td>Boundary Condition</td>
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<tr>
<td>CABG</td>
<td>Coronary Artery Bypass Graft</td>
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<td>CAD</td>
<td>Coronary Artery Disease</td>
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<td>CBM</td>
<td>CompBioMed</td>
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<tr>
<td>CZE</td>
<td>Catharina Hospital Eindhoven</td>
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<td>FFR</td>
<td>Fractional Flow Reserve</td>
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<td>ICA</td>
<td>Invasive Coronary Angiography</td>
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<tr>
<td>mFFR</td>
<td>Invasively measured FFR</td>
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<tr>
<td>LAD</td>
<td>Left Anterior Descending artery</td>
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<td>LIMA</td>
<td>Left Internal Mammary Artery</td>
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<td>LTG</td>
<td>LifeTec Group</td>
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<td>mFFR</td>
<td>Invasive measured FFR</td>
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<td>PCI</td>
<td>Percutaneous Coronary Intervention</td>
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<td>PMI</td>
<td>Pie Medical Imaging</td>
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<td>Post-operative FFR</td>
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<td>Pre-FFR</td>
<td>Pre-operative FFR</td>
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<td>TNR</td>
<td>True Negative Rate or Specificity</td>
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<tr>
<td>TPR</td>
<td>True Positive Rate or Sensitivity</td>
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<tr>
<td>TU/e</td>
<td>University of Technology Eindhoven</td>
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14 References


## Appendix A

### Stakeholder analysis

Written: Ir. B.G. van Willigen
Approved: Dr. Ir. Jan-Jaap Koning

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<th>Name of stakeholder</th>
<th>Organization</th>
<th>Job position</th>
<th>Project position</th>
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<tr>
<td>Marco Stijnen (MS)</td>
<td>LifeTec Group</td>
<td>Head of medtech innovation</td>
<td>Contact at CompBioMed and is involved content-wise</td>
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<tr>
<td>Pim Tonino (PT)</td>
<td>Catharina Hospital</td>
<td>Intervention Cardiologist</td>
<td>Expert on PCI, end-user</td>
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<tr>
<td>Frans van de Vosse (FvdV)</td>
<td>Eindhoven University of Technology</td>
<td>Professor cardiovascular biomechanics</td>
<td>Supplier physiological model</td>
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<tr>
<td>Tristan Slots (TS)</td>
<td>Pie Medical Imaging</td>
<td>Manager product management</td>
<td>Supplier segmentation software</td>
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<tr>
<td>Marcel van ’t Veer (MvV)</td>
<td>Catharina Hospital</td>
<td>Medical engineer</td>
<td>Expert medical devices</td>
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<tr>
<td>Wouter Huberts (WH)</td>
<td>Maastricht University/Eindhoven University of Technology</td>
<td>Assistant professor</td>
<td>Expert 1D wave propagation models and sensitivity analyse</td>
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<tr>
<td>Mariano Vázquez (MV)</td>
<td>CompBioMed</td>
<td>High Performance Computational Mechanics Group Manager</td>
<td>Financial supplier</td>
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</table>

Figure A.1: Identify stakeholders
### APPENDIX A. STAKEHOLDER ANALYSIS

#### Figure A.2: Prioritize stakeholders and assess engagement.

<table>
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<tr>
<th>Name</th>
<th>Power</th>
<th>Interest</th>
<th>Required Attention</th>
<th>Requirements, Expectations and Issues</th>
<th>Current Engagement</th>
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<td>MS</td>
<td>9</td>
<td>7</td>
<td>Manage Closely</td>
<td>Proof-of-concept</td>
<td>advocate</td>
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<td>PT</td>
<td>7</td>
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<td>FvdV</td>
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<td>Mathematical model for Students</td>
<td>supporter</td>
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<td>MvtV</td>
<td>2</td>
<td>6</td>
<td>Keep Informed</td>
<td>Keep informed</td>
<td>neutral</td>
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<tr>
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<td>2</td>
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<td>MV</td>
<td>1</td>
<td>3</td>
<td>Monitor</td>
<td>Potential product for in the clinic</td>
<td>blocker</td>
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#### Figure A.3: Determine desired engagement

<table>
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<th>Name</th>
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<th>Desired project role</th>
<th>Actions desired</th>
<th>Messages needed</th>
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<td>advocate</td>
<td>Review concepts</td>
<td>Meetings</td>
<td>“The product can be commercialized for LifeTec Group”</td>
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<td>PT</td>
<td>supporter</td>
<td>Feedback on interface/Supplier of data</td>
<td>Meetings/Supply of data</td>
<td>“This product can make coronary intervention decisions easier for clinicians”</td>
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<td>FvdV</td>
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<td>Feedback on mathematical model</td>
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<td>TS</td>
<td>supporter</td>
<td>Supplier of segmentation tool</td>
<td>Meetings/supply of segmentation tool</td>
<td>“This product can be an addition to your product”</td>
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<td>Supplier of information</td>
<td>Design discussions</td>
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<tr>
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<td>MV</td>
<td>supporter</td>
<td>Funder of the project</td>
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Appendix B

Planning

Written: Ir. B.G. van Willigen

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Table B.1: Initial planning of the development of AngioSupport

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<td>Interventions</td>
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</tbody>
</table>

Table B.2: Final planning of the development of AngioSupport
## Appendix C

### Risk analysis of the project process

Written: Ir. B.G. van Willigen  
Reviewed: Ir. T. van den Boom  
Approved: Dr. Ir. Jan-Jaap Koning

<table>
<thead>
<tr>
<th>Nr.</th>
<th>Risk</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Functional requirements</td>
<td>cannot be defined within two months</td>
</tr>
<tr>
<td>2</td>
<td>Technical requirements</td>
<td>cannot be defined within two months</td>
</tr>
<tr>
<td>3</td>
<td>Segmentation</td>
<td>No proper segmentation tool</td>
</tr>
<tr>
<td>4</td>
<td>CAAS is not useful for AngioSupport</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>Automatization of segmentation</td>
<td>is not possible</td>
</tr>
<tr>
<td>6</td>
<td>Segmentation cannot be verified</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Physiological Model</td>
<td>Result (FFR) does not make sense</td>
</tr>
<tr>
<td>8</td>
<td>Physiological model is finished</td>
<td>in time</td>
</tr>
<tr>
<td>9</td>
<td>End-users do not trust AngioSupport</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>Parameters</td>
<td>Patient specific parameters could not be defined</td>
</tr>
<tr>
<td>11</td>
<td>Interface</td>
<td>Interface cannot load in patient data</td>
</tr>
<tr>
<td>12</td>
<td>Interface cannot be used by clinicians</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>Interface is not coupled to the physiological model</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>Interventions</td>
<td>PCI not possible</td>
</tr>
<tr>
<td>15</td>
<td>CABG not possible</td>
<td></td>
</tr>
<tr>
<td>16</td>
<td>Verification</td>
<td>No patient data received</td>
</tr>
<tr>
<td>17</td>
<td>Validation</td>
<td>Physiological model cannot be verified</td>
</tr>
<tr>
<td>18</td>
<td>Interface scores bad during the user survey</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td>General</td>
<td>Tim and Bettine are not able to work together anymore</td>
</tr>
<tr>
<td>20</td>
<td>Supervisors are not supporting</td>
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</table>

*Table C.1: Numbering of risks*
### APPENDIX C. RISK ANALYSIS OF THE PROJECT PROCES

<table>
<thead>
<tr>
<th>No.</th>
<th>Cause</th>
<th>Consequence</th>
<th>Category</th>
<th>Probability</th>
<th>Severity</th>
<th>P*S</th>
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<tbody>
<tr>
<td>1</td>
<td>Bad communication between stakeholders</td>
<td>Development of AngioSupport delays</td>
<td>process risk</td>
<td>Moderate (5)</td>
<td>Minor (3)</td>
<td>15</td>
</tr>
<tr>
<td>2</td>
<td>Bad communication between stakeholders</td>
<td>Development of AngioSupport delays</td>
<td>process risk</td>
<td>Moderate (5)</td>
<td>Minor (3)</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>No accessible segmentation tool is suitable for segmenting coronary arteries</td>
<td>No patient specific coronary geometry</td>
<td>quality risk</td>
<td>Moderate (5)</td>
<td>Major (8)</td>
<td>40</td>
</tr>
<tr>
<td>4</td>
<td>CAAS is developed to segment 1 vessel</td>
<td>Entire coronary tree cannot be segmented</td>
<td>quality risk</td>
<td>Moderate (5)</td>
<td>Major (8)</td>
<td>40</td>
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<tr>
<td>5</td>
<td>Many manual acts to generate entire tree from CAAS</td>
<td>Data have to be preprocessed by engineers</td>
<td>technical risk</td>
<td>Likely (8)</td>
<td>Moderate (5)</td>
<td>40</td>
</tr>
<tr>
<td>6</td>
<td>The accuracy of CAAS cannot be verified</td>
<td>The cause of an off result will be unknown</td>
<td>technical risk</td>
<td>Certain (10)</td>
<td>Minor (3)</td>
<td>30</td>
</tr>
<tr>
<td>7</td>
<td>The mathematical formulas are not implemented well</td>
<td>Results will be off</td>
<td>technical risk</td>
<td>Rare (2)</td>
<td>Major (8)</td>
<td>16</td>
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<td>8</td>
<td>Planning</td>
<td>No results</td>
<td>process risk</td>
<td>Rare (2)</td>
<td>Catastrophic (10)</td>
<td>20</td>
</tr>
<tr>
<td>9</td>
<td>Clinicians do not trust models</td>
<td>AngioSupport will not be used</td>
<td>technical risk</td>
<td>ALL</td>
<td>Major (8)</td>
<td>64</td>
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<tr>
<td>10</td>
<td>Not enough data</td>
<td>Boundary conditions are not patient specific</td>
<td>technical risk</td>
<td>Likely (8)</td>
<td>Minor (3)</td>
<td>24</td>
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<tr>
<td>11</td>
<td>Not able to connect with dataset</td>
<td>AngioSupport cannot be used for a patient</td>
<td>technical risk</td>
<td>Unlikely (3)</td>
<td>Major (8)</td>
<td>24</td>
</tr>
<tr>
<td>12</td>
<td>It is not user-friendly</td>
<td>Clinicians will not use AngioSupport</td>
<td>technical risk</td>
<td>Moderate (5)</td>
<td>Moderate (5)</td>
<td>25</td>
</tr>
<tr>
<td>13</td>
<td>Javascript and python cannot connect</td>
<td>Clinicians cannot use AngioSupport</td>
<td>technical risk</td>
<td>Unlikely (3)</td>
<td>Major (8)</td>
<td>24</td>
</tr>
<tr>
<td>14</td>
<td>It is not programmed right</td>
<td>Clinicians cannot perform interventions</td>
<td>technical risk</td>
<td>Unlikely (3)</td>
<td>Major (8)</td>
<td>24</td>
</tr>
<tr>
<td>15</td>
<td>It is not programmed right</td>
<td>Clinicians cannot perform interventions</td>
<td>technical risk</td>
<td>Unlikely (3)</td>
<td>Major (8)</td>
<td>24</td>
</tr>
<tr>
<td>16</td>
<td>Not allowed to receive data from hospital</td>
<td>Not able to test on patient data</td>
<td>quality risk</td>
<td>Unlikely (3)</td>
<td>Moderate (5)</td>
<td>15</td>
</tr>
<tr>
<td>17</td>
<td>Not sufficient data</td>
<td>Proof-of-concept will not be trustworthy</td>
<td>quality risk</td>
<td>Likely (8)</td>
<td>Moderate (5)</td>
<td>40</td>
</tr>
<tr>
<td>18</td>
<td>During development, opinions of clinicians is not in cooperated</td>
<td>AngioSupport will not be used</td>
<td>communication risk</td>
<td>Moderate (5)</td>
<td>Major (8)</td>
<td>40</td>
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<tr>
<td>19</td>
<td>Bettine and Tim end up in a fight</td>
<td>Collaboration between project managers is not good</td>
<td>communication risk</td>
<td>Rare (2)</td>
<td>Major (8)</td>
<td>16</td>
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<tr>
<td>20</td>
<td>Supervisors are not motivated anymore</td>
<td>Bad communication</td>
<td>communication risk</td>
<td>Rare (2)</td>
<td>Major (8)</td>
<td>16</td>
</tr>
</tbody>
</table>

Table C.2: Cause, consequence, category, probability, severity, and priority value
<table>
<thead>
<tr>
<th>Risk response strategy</th>
<th>Owner for this action, accountable for completion</th>
<th>Content of action</th>
<th>Agreed date of completion</th>
<th>Current status of completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Avoid Bettine and Tim</td>
<td>Keep communicating with the stakeholders</td>
<td>1-May-18</td>
<td>Done</td>
</tr>
<tr>
<td>2</td>
<td>Avoid Bettine and Tim</td>
<td>Keep communicating with the stakeholders</td>
<td>1-May-18</td>
<td>Done</td>
</tr>
<tr>
<td>3</td>
<td>Avoid Bettine and Tim</td>
<td>Talk to companies and literature research</td>
<td>30-Jun-18</td>
<td>Done</td>
</tr>
<tr>
<td>4</td>
<td>Mitigate Bettine and Tim</td>
<td>Arrange meetings with PMI to get the best of the software</td>
<td>30-Jun-18</td>
<td>Done</td>
</tr>
<tr>
<td>5</td>
<td>Transfer Bettine and Tim</td>
<td>Arrange meetings with PMI to get the best of the software</td>
<td>30-Jun-18</td>
<td>Done</td>
</tr>
<tr>
<td>6</td>
<td>Transfer Bettine and Tim</td>
<td>Arrange meetings with PMI to get the best of the software</td>
<td>30-Jun-18</td>
<td>Done</td>
</tr>
<tr>
<td>7</td>
<td>Avoid Tim</td>
<td>Arrange meetings with Wouter Huberts</td>
<td>31-Jul-18</td>
<td>Done</td>
</tr>
<tr>
<td>8</td>
<td>Avoid Tim</td>
<td>Arrange meetings with Wouter Huberts</td>
<td>31-Jul-18</td>
<td>Done</td>
</tr>
<tr>
<td>9</td>
<td>Mitigate Tim</td>
<td>Good verification of the model</td>
<td>31-Jul-18</td>
<td>Done</td>
</tr>
<tr>
<td>10</td>
<td>Transfer Bettine</td>
<td>Meetings with Pim to retrieve more data</td>
<td>28-Feb-19</td>
<td>Done</td>
</tr>
<tr>
<td>11</td>
<td>Mitigate Bettine</td>
<td>Investigate needs of software</td>
<td>31-Jul-18</td>
<td>Done</td>
</tr>
<tr>
<td>12</td>
<td>Mitigate Bettine</td>
<td>Hold an elaborate user survey</td>
<td>31-Jul-19</td>
<td>Done</td>
</tr>
<tr>
<td>13</td>
<td>Avoid Bettine</td>
<td>Study the connection between javascript and python</td>
<td>31-Jul-18</td>
<td>Done</td>
</tr>
<tr>
<td>14</td>
<td>Avoid Bettine</td>
<td>Study program languages</td>
<td>31-Jan-19</td>
<td>Done</td>
</tr>
<tr>
<td>15</td>
<td>Avoid Bettine</td>
<td>Study program languages</td>
<td>31-Jan-19</td>
<td>Done</td>
</tr>
<tr>
<td>16</td>
<td>Mitigate Tim</td>
<td>Make nWMO together with Marcel</td>
<td>31-Oct-18</td>
<td>Done</td>
</tr>
<tr>
<td>17</td>
<td>Mitigate Tim</td>
<td>Meetings with Pim to retrieve more data</td>
<td>31-Jul-19</td>
<td>Done</td>
</tr>
<tr>
<td>18</td>
<td>Mitigate Bettine</td>
<td>Give many demo's</td>
<td>31-Jul-19</td>
<td>Done</td>
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<tr>
<td>19</td>
<td>Avoid Tim and Bettine</td>
<td>Communicate well</td>
<td>31-Aug-19</td>
<td>On track</td>
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<tr>
<td>20</td>
<td>Avoid Tim and Bettine</td>
<td>Keep involve supervisors</td>
<td>31-Aug-19</td>
<td>On track</td>
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</table>

Table C.3: Actions and decisions
Appendix D

One-fiber heart element

Written: Ir. B.G. van Willigen
Reviewed: Ir. T. van den Boom
Approved: Dr. Ir. W. Huberts

The contraction of the heart influences, amongst others, the coronary inflow; therefore, varies over time during a cardiac cycle. The contraction of the myocardium results in squeezing the coronary arteries, which leads in a decrease of coronary inflow during systole (Figure D.1) due to reduction in cross-sectional area of the coronary arteries and increase of resistance. In contrast, the myocardium is relaxed during the diastolic phase leading to highest coronary inflow. The one-fiber heart model of Bovendeerd et al. describes an one-fiber heart model to estimate intramyocardial pressure and contraction of the myofibers in the cardiac wall in order to compute the coronary inflow [8]. The left ventricle is modelled as thick-walled sphere with nested spherical shells assuming rotational symmetry and homogeneity of mechanical load and stress based on the model of Arts et al. [1].

Figure D.1: Aortic pressure and coronary flow during one cardiac cycle (adapted from R.E. Klabunde, www.cvphysiology.com).

The stress in the myofibers $\sigma_f$ is modelled with two components: the passive ($\sigma_p$) and active ($\sigma_a$) component:
\[ \sigma_f = \sigma_p(l_s) + \sigma_a(l_s, v_s, t_a), \]  
with \( \sigma_p \) depending on the sacromere length \( l_s \) and \( \sigma_a \) depending on \( l_s \), sacromere shortening velocity \( v_s \), and time elapsed since activation \( t_a \).

The passive stress depends on the scaling parameter \( \sigma_{p0} \), curvature parameter \( c_r \), and fiber stretch \( \lambda_f \), when the sacromere length exceeds the length \( l_{s0} \) of the cavity volume at zero transmural pressure \( V_{lv0} \) \[5\]. This is given by:

\[ \sigma_p(l_s) = \begin{cases} 0 & l_s \leq l_{s0}, \\
\sigma_{p0}(e^{c_r(\lambda_f - 1)} - 1) & l_s > l_{s0}. \end{cases} \]  

The fiber stretch is located at the shell one third of the ventricular wall: \( r_{lv} = \bar{r}_{lv} \). The fiber strain at this location is similar to the fiber strain and incompressibility is assumed. Therefore, \( \lambda_f \) can relates to the ventricular geometry:

\[ \lambda_f = \frac{l_s}{l_{s0}} = \left( \frac{V_{lv} + \frac{1}{3}V_w}{V_{lv0} + \frac{1}{3}V_w} \right)^{\frac{1}{3}} \]  

with the wall and cavity volume of left ventricle \( V_w \) and \( V_{lv} \), respectively.

The active stress is described based on three functions and the contractility \( c \):

\[ \sigma_a(l_s, v_s, t_a) = cg_1(l_s)g_2(t_a)g_3(v_s) \]  
The function \( g_1 \) relates to scaling \( \sigma_{a0} \) and curvature \( c_a \) parameter, when the sacromere length exceeds a certain denoted length \( l_{sa0} \) for which \( \sigma_a \) becomes zero.

\[ g_1(l_s) = \begin{cases} 0 & l_s \leq l_{sa0}, \\
\sigma_{a0} \tanh^2(c_a(l_s - l_{sa0})) & l_s > l_{sa0}. \end{cases} \]  

with \( l_s = \lambda_f l_{sa0} \).

The function \( g_2 \) depends on the activation time and relates to the activation rise and decay time constant \( t_a \) and \( t_d \) during activation:

\[ g_2(t_a) = \begin{cases} 0 & t_a < 0, \\
\tanh^2\left(\frac{t_a}{t_d}\right) & 0 \leq t_a < t_{max}, \\
0 & t_a \geq t_{max}. \end{cases} \]  

with the activation duration \( t_{max} \).

The function \( g_3 \) has a hyperbolic dependency on the sacromere shortening velocity:

\[ g_3(v_s) = \frac{v_{s0} - v_s}{v_{s0} - c_e v_s}, \quad v_s(t) = \frac{dl_s(t)}{dt} \]  

with the unloaded shortening velocity \( v_{s0} \) and the curvature of the hyperbolic relation \( c_v \).

Then, the intramyocardial pressure \( P_{im} \) at \( r_{lv} = \bar{r}_{lv} \) is assumed to be linearly dependent on the radial position in the wall, radial stress \( \sigma_r \), and left ventricular pressure \( P_{lv} \):

\[ P_{im} = P_{im}(\bar{r}_{lv}) = \bar{\sigma}_r + \frac{r_{a,lv} - \bar{r}_{lv}}{r_{a,lv} - r_{l,lv}} P_{lv} \]  

with the inner radius \( r_{l,lv} = (\frac{1}{2}\pi V_{lv})^{1/3} \) and outer radius of the ventricle \( r_{a,lv} = (\frac{1}{2}\pi (V_{lv}+V_w))^{1/3} \), respectively. The \( P_{im} \) results at the limits in:
\[ P_{im}(r) = \begin{cases} \bar{\sigma}_r + P_{lv} & r = r_{i,lv} \\ \bar{\sigma}_r & r = r_{o,lv} \end{cases} \]  \hfill (D.9)

The left ventricular pressure can be described in relation to \( V_{lv}, V_w, \sigma_f, \) and \( \sigma_r, \) because the ventricle is assumed rotational symmetry and homogeneity of mechanical load:

\[ P_{lv} = \frac{1}{3}(\sigma_f - 2\bar{\sigma}_r) \ln \left(1 + \frac{V_w}{V_{lv}}\right) \]  \hfill (D.10)

With the radial stress at location \( r_{lv} = \bar{r}_{lv} \) depending on the scaling and curvature parameters \( \sigma_{r0} \) and \( c_r, \) respectively, when the sacromere length exceeds \( l_{s0}, \)

\[ \sigma_r(l_s) = \begin{cases} 0 & l_s \leq l_{s0} \\ \sigma_{r0}(e^{c_r(\lambda_r - 1)} - 1) & l_s > l_{s0} \end{cases} \]  \hfill (D.11)

with the radial stretch \( \lambda_r \) related to the fiber stretch \( \lambda_f^2. \)

The \( P_{im} \) is connected to the three capacitors of the coronary windkessel (Appendix H) to simulate the pressure of the cardiac contraction on the coronary vessels.

![Figure D.2: Schematic view of the one-fiber model (adapted from [22]).](image)

The flow of through the left side of the heart is simulated with valves as diodes (Figure D.2). The flow over the mitral valve \( (Q_{mv}) \) is determined based on Ohm’s law:

\[ Q_{mv} = \frac{\Delta P_{mv}}{R_{mv}} \]  \hfill (D.12)

with pressure difference over the valve \( \Delta P_{mv} = P_{ven} - P_{lv}, \) and resistance of the valve \( R_{mv}. \) The value of the resistance:

\[ R_{mv} = \begin{cases} R_{mv,o} & \text{if } \Delta P_{mv} \geq 0 \\ R_{mv,c} & \text{if } \Delta P_{mv} < 0 \end{cases} \]  \hfill (D.13)

with the resistance of the valve in open and closed position \( R_{mv,o} \) and \( R_{mv,c}, \) respectively.

The inertia of the valve is considered for the aortic valve \( L_{ao} \) resulting in:

\[ Q_{ao} = \frac{\Delta P_{ao} - L_{ao} \frac{dQ_{ao}}{dt}}{R_{av}} \]  \hfill (D.14)

with the pressure over the aortic valve \( P_{av} = P_{lv} - P_{ao}, \) \( P_{ao} \) is obtained from the previous time step. The aortic valve resistance \( R_{av}. \) The value of the resistance:

\[ R_{av} = \begin{cases} R_{av,o} & \text{if } P_{lv} > P_{ao} \\ R_{av,c} & \text{if } P_{lv} \leq P_{ao} \end{cases} \]  \hfill (D.15)
with the resistance of the valve in open and closed position $R_{av,o}$ and $R_{av,c}$, respectively.

The $Q_{ao}$ is the inflow in the aorta, whereof a fraction goes to the coronary arteries. The Table ?? shows all parameter values used in the on-fiber heart model.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>unit</th>
<th>value</th>
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</thead>
<tbody>
<tr>
<td>$\sigma_{p0}$</td>
<td>[Pa]</td>
<td>0.9e3</td>
</tr>
<tr>
<td>$c_p$</td>
<td>[-]</td>
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</tr>
<tr>
<td>$V_{i0}$</td>
<td>[m$^3$]</td>
<td>60e - 6</td>
</tr>
<tr>
<td>$V_w$</td>
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Table D.1: Parameter values of the one-fiber model.
Appendix E

Systemic Line Element

Written: Ir. B.G. van Willigen
Reviewed: Ir. T. van den Boom
Approved: Dr. Ir. W. Huberts

The ADAN56 topology of Boileau et al. [6] is used as geometry for the systemic circulation. This geometry includes the aortic arch until the tibial fibular trunks (segment of the artery below the knee). This topology is divided into small elements and every element is described based on local mass and momentum balance integrated over the cross-sectional area after applying Reynolds Transport Theorem (RTT) derived of Hughes and Lubliner [11]. The RTT uses both system (sys) and control volume (CV) concepts to describe fluid motion. The system is considered as a certain amount of fluid, while the CV is a fixed place. As can be seen in Figure E.1, at a certain time point (left), the CV (blue) and sys (red) cover the same space. However, at time step later (right), the CV remains, but the system moves. The RTT links the system and the CV.

![Figure E.1: Schematic representation of the system (sys) and control volume (CV) to explain the Reynolds Transport Theorem (RTT).](image)

Equation E.1 shows the general RTT equation with the movement of the extensive property ($B$) of the system, the first right term represents storage of the intensive property ($\beta$) inside the CV, and the second right term represents netto flux (outflow - inflow) of $\beta$ leaving the control surface (CS). The CS is the surface of the CV.

$$
\left. \frac{dB}{dt} \right|_{sys} = \int_{CV} \frac{\partial}{\partial t} \rho \beta dV + \int_{CS} \rho \beta (\vec{u}_{rel} \cdot \hat{n}) dA,
$$

(E.1)

with $\rho$ the density, $V$ the volume, $\vec{u}_{rel}$ the velocity of $\beta$ crossing CS relative to motion of CS, and $A$ the area.
In the following paragraphs, the conservation of mass and momentum using RTT to describe the systemic elements are explained based on Figure E.2 representing an example of a geometry of a vessel along the z-axis. Subsequently, a velocity profile function is used to express the momentum balance in pressure and flow. To simplify the solution, a last equation, a constitutive relation, will be used to describe the linear relation between the pressure and cross sectional area. There is assumed that the flow is incompressible and axi-symmetric (in this case along the z-axis). Furthermore, the fluid (blood) is assumed Newtonian.

Figure E.2: The geometry of part of a vessel along the z-axis bound by cross-sectional surfaces $A_1(z = z_1)$ and $A_2(z = z_2)$ and circumferential surface $S$. The total volume is denoted by the symbol $V$, an arbitrary cross-section perpendicular to the $z$-axis by $A$ and its boundary by $l$. Figure is adapted from Bessems et al.[3].

### E.1 Conservation of mass

The mass balance is derived from Hughes and Lubliner[11] describing the conservation of mass. It represents the storage of inflow and its outflow of volume $V$ (Figure E.2).

$$\frac{\partial A}{\partial t} + \frac{\partial q}{\partial z} + \Psi = 0 \quad (E.2)$$

with $t$ the time, $p$ the pressure, $q$ the volume flow, $z$ the axial coordinate, $\Psi$ the volumetric outflow per unit length to simulate the outflow of side branches. The vessel area compliance $C_0$ with the chosen linear relation around the reference pressure ($p_{ref}$):

$$C_0 = \frac{\partial A}{\partial p} \bigg|_{p=p_{ref}} \quad (E.3)$$

Equation E.3 is substituted in E.2 and $\Psi$ is not incorporated, since an impermeable vessel wall and no side branches is assumed. This will result in:

$$C_0 \frac{\partial p}{\partial t} + \frac{\partial q}{\partial z} = 0 \quad (E.4)$$

### E.2 Conservation of momentum

The momentum balance describes the relationship between pressure, viscous, body, surface, and inertial forces. Assuming that the velocities in x and y direction are negligible compared with the axial velocity $v_z$, the momentum balance results, after integration over $A$, in:

$$\frac{\partial q}{\partial t} + \frac{\partial \gamma}{\partial z} + \frac{A}{\rho} \frac{\partial p}{\partial z} = Af_z + \frac{2\pi a}{\rho} \tau_w + \frac{\eta}{\rho} \frac{\partial^2 q}{\partial z^2} \quad (E.5)$$

with the dynamic viscosity $\eta$, the wall shear stress $\tau_w$, the density of the fluid $\rho$, the vessel radius $a$, and the non-linear convection term, $\gamma$, are expressed as follows:
\[ \gamma = \int_A v_z^2 dA \quad \tau_w = \eta \frac{\partial v_z}{\partial r} \bigg|_{r=a_0} \quad (E.6) \]

Assuming that the pressure depends only on \( z \) and \( t \) and no-slip condition holds equation E.5, no body forces occur \((Af_z) = 0\) and \( \frac{\partial^2 r_z}{\partial r_z^2} < 1 \) results in:

\[ \frac{\partial Q}{\partial t} + \frac{\partial \gamma}{\partial r_z} + A \frac{\partial p}{\partial r_z} = \frac{2\pi r_z}{\rho} \tau_w \quad (E.7) \]

### E.3 Velocity profile function

To solve the conservation of momentum equation, \( \gamma \) and \( \tau_w \) should be expressed in \( p \) and \( q \). The velocity profile approximated based on Navier-Stokes equations for an axisymmetric and fully developed flow in a straight tube is used to estimate \( \gamma \) and \( \tau_w \) [3]:

\[ \frac{\partial v_z}{\partial t} = -\frac{\partial p}{\partial r_z} + \eta \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial v_z}{\partial r} \right) \quad (E.8) \]

Flow through a tube is now influenced by two forces: 1) viscous forces and 2) convection forces. Next to the wall where shear stress is at maximum, viscous forces dominate. In contrast, the viscous forces can be neglected in the core of the tube and convection forces dominate. The area between the core and wall is influenced by both forces and described with Equation E.8. However, there is assumed that this area is assumed to be negligibly small. Therefore, only viscous and convection dominated areas are described:

\[ \frac{\partial p}{\partial r_z} = \begin{cases} -\rho \frac{\partial v_z}{\partial t} & \text{for } 0 \leq r < a_c \\ \eta \frac{1}{r} \frac{\partial}{\partial r} \left( r \frac{\partial v_z}{\partial r} \right) & \text{for } a_c \leq r < a \end{cases} \quad (E.9) \]

with the radius from the core till the viscous layer \( a_c \) and the radius of the vessel \( a \). Applying Bessem et al. assumptions [3], the size of the central core is related to the Wormersly number, \( \alpha \) (see Figure ??):

\[ \frac{a_c}{a} = \max \left[ 0, \left( 1 - \frac{k}{\alpha} \right) \right] \quad (E.10) \]

with \( \alpha = a \sqrt{\frac{\omega}{\eta}} \), where \( \omega \) is estimated on the fundamental frequency.

Figure E.3: The geometry of part of a vessel with local radius \( a \). The present fluid dynamical forces are shown on the left and on the right our approximation, where \( a_c \) is the core radius and \( \delta = a - a_c \) the viscous layer. The solid curve on the left represents an exact velocity profile and the solid curve on the right the approximation according to our method. Figure is adapted from Bessem et al.[3].

Solving Equations E.9 and E.10 for \( v_z \) results in:

\[ v_z = \frac{-\ln \hat{\zeta}}{1 - \zeta_c} v_z - \frac{a^2}{4\eta} \left[ 1 - \zeta_c + \frac{1}{2} (\zeta_c + 1) \ln \hat{\zeta} \frac{\partial p}{\partial r_z} \right] \quad (E.11) \]
APPENDIX E. SYSTEMIC LINE ELEMENT

with the parameters:

\[ \zeta = \left( \frac{x}{a} \right)^2 \]

\[ \zeta_c = \left( \frac{x_c}{a} \right)^2 \]

\[ \hat{\zeta} = \max[\zeta, \zeta_c] \]  

(E.12)

Substituting Equation E.11 in E.6, the wall shear stress can be written as:

\[ \tau_w = -\frac{2\eta}{(1-\zeta)a} q + \frac{a}{4} (1-\zeta) \frac{\partial p}{\partial z} \]  

(E.13)

and with the assumption that viscous forces can be neglected, because of a relatively large core, the non-linear convection term with the assumption that as:

\[ \gamma \approx \frac{2-\zeta_c(1-\ln \zeta_c) q^2}{(1-\zeta_c)^2} \]

(E.14)

When substituting Equations E.13 and E.14 in E.7, the final momentum balance will be:

\[ \frac{\partial Q}{\partial t} + \frac{\partial \gamma}{\partial z} + \frac{A}{\rho} (2-c_p) \frac{\partial p}{\partial z} + \frac{A}{\rho} c_q R_0 q = 0 \]  

(E.15)

with \( c_q = \frac{1}{2}(1-\zeta_c)^{-1}, \quad c_p = 1 + \frac{1}{2}(1-\zeta_c), \) and \( R_0 = \frac{8\eta}{\pi a^2} \)

E.4 Constitutive relation

To linearize the relation between pressure and cross sectional Area, \( A \), solving the mass and momentum balance equations written as RTT will be simplified.

\[ A(z, t) = A(p(z, t), z) = A_0(z) + \int_{p_{ref}}^{p} C_0 dp = A_0(z) + C_0(p - p_{ref}) \]  

(E.16)

Assuming linear, thin walled, elastic material, the area compliance is defined as:

\[ C_0 = \frac{2\pi (1-\mu^2) a^3}{hE} \]  

(E.17)

with the wall thickness \( h \), poisson’s ratio \( \mu \), and the Young Modulus \( E \). Finally, the following solvable set of equations is obtained:

\[ \begin{align*}
C_0 &= \left. \frac{\partial A}{\partial p} \right|_{p=p_{ref}} \\
\frac{\partial Q}{\partial t} + \frac{\partial \gamma}{\partial z} + \frac{A}{\rho} (2-c_p) \frac{\partial p}{\partial z} - \frac{A}{\rho} c_q R_0 q &= 0 \\
A(z, t) &= A_0(z) + C_0(p - p_{ref})
\end{align*} \]  

(E.18)

The solution procedure is explained in Appendix J.
Appendix F

Systemic Windkessel Element

Written: Ir. B.G. van Willigen
Reviewed: Ir. T. van den Boom
Approved: Dr. Ir. W. Huberts

Every end-point of the 1D systemic model is lumped with a three-element Windkessel for systemic vessels. The relation of flow and pressure is written as Westerhof et al. [23]:

\[ C_w \frac{\partial p}{\partial t} + \frac{\Delta p}{R_{\text{tot}}} = q \] (F.1)

with the peripherical compliance of the artery \( C_w \) described with a time constant, \( \tau \), and the peripherical resistance \( R_w \), which is the sum of the impedance \( Z \) and resistance \( R_w \) (Figure F.1): \( C_w = \frac{1}{\tau} \) and \( \tau = 2s \), the pressure \( p \), the flow \( q \), and \( R_{\text{tot}} \) the total resistance compute by the average flow (\( \tilde{q} \)) and average pressure drop (\( \Delta \tilde{p} \)) (see Equation F.2).

\[ R_{\text{tot}} = \frac{\Delta \tilde{p}}{\tilde{q}} \] (F.2)

with \( \Delta \tilde{p} = p_{\text{ao}} - p_{\text{ven}} \), the aortic pressure \( p_{\text{ao}} \) and venous pressure \( p_{\text{ven}} \). A single windkessel is represented in Figure F.1 containing \( R_w \), \( C_w \), and the characteristic resistance, \( Z \). The characteristic resistance \( Z \) is chosen to match the impedance of the terminal vessel the windkessel is connected, which gives:

\[ Z = \sqrt{ \frac{L}{C} } = \sqrt{ \frac{\rho h E}{2\pi a^5(1-\mu^2)} } \] (F.3)

Figure F.1: Three-element windkessel with the wave impedance \( Z \), peripheral resistance, \( R_w \), and peripheral compliance, \( C_w \).
Appendix G

Coronary Line Element

Written: Ir. B.G. van Willigen
Reviewed: Ir. T. van den Boom
Approved: Dr. Ir. W. Huberts

The topology of the coronary circulation described is shown in Figure G.1 is used as geometry for the coronary circulation. This geometry is based on the coronary angiogram of each patient, which is segmented using the procedure in Appendix K. This geometry includes Left Main (LM), LAD, and LCx. This topology is described with the one-dimensional propagation of pressure and flow, like explained in Appendix E.

![Figure G.1: Geometry of the left side of the coronary circulation.](image)

Like solving the systemic circulation, solving pressure and flow for the coronary circulation uses the conservation of mass and momentum using RTT. Subsequently, a velocity profile function is used to express the momentum balance in pressure and flow (for the explanation of the equations, see Appendix E). To simplify the solution, a constitutive relation, will be used. This constitutive law is described by van der Horst et al.[22]. This constitutive relation only needs the radius of the coronary vessel. The Young’s modulus and wall thickness are based on the radius and result from empirical data. This is needed since the segmentation of the coronary angiogram only gives the radius of the vessel.
Appendix H

Coronary Windkessel Element

Each terminal of a coronary vessel ends with a coronary windkessel, working as a lumped parameter model. This coronary windkessel describes the coronary microcirculation, using a lumped 0D element, consisting of 4 resistances and 3 capacitances, as shown in Figure H.1. These resistances are subdivided in $R_{art,c}$, $R_{myo,1}$, $R_{myo,2}$, and $R_{ven,c}$ representing the coronary arterial, the two intramyocardial and venous resistances, respectively. The capacitances are $C_{art,c}$, $C_{myo,c}$, and $C_{ven,c}$ the coronary arterial, intramyocardial and venous compliance, respectively.

![Figure H.1: 7 element coronary windkessel element as described by Bovendeerd et al.](image)

The numerical implementation of these 7 elements are similar to the numerical implementation of a windkessel element, which is explained in Appendix F, and is therefore not further explained in this section. Only the needed parameters for each coronary element are explained ( $R_{art,c}$, $R_{myo,1}$, $R_{myo,2}$, $R_{ven,c}$, $C_{art,c}$, $C_{myo,c}$, and $C_{ven,c}$).

To estimate these parameters, the total peripheral resistance of the coronary vasculature is calculated. Therefore, the mean pressure drop and mean flow in each coronary windkessel needs to be estimated. First, the mean pressure drop $\Delta P$ is calculated with:

$$\Delta P = P_{ao} - P_{ven} \quad \text{(H.1)}$$

with $P_{ao}$ and $P_{ven}$ the mean aortic pressure and venous pressure, respectively. Here, $P_{ao}$ will be measured during the coronary angiography of the patient and $P_{ven}$ is set to 700 Pa [8]. This therefore neglects the pressure drop already present in the 1D coronary vessels. To calculate the total resistance $R_{tot}$, the total flow towards the coronary arteries $Q_{tot}$ is estimated as 5% of total cardiac output. The $R_{tot}$ can than be calculated with:

$$R_{tot} = \frac{\Delta P}{Q_{tot}} \quad \text{(H.2)}$$
Subsequently, the total resistance at the end of each vessel $R_{term,i}$ is computed:

$$R_{term,i} = \frac{\Delta P}{Q_{term,i}}$$  \hspace{1cm} (H.3)

Currently, this terminal mean flow $Q_{term,i}$ is calculated by using the terminal radii at each terminal vessel $r_i$. The total flow to the coronaries is then subdivided over the vessels [16]. First, the fraction of flow $Q_{frac,i}$ to a terminal coronary vessel $i$ is estimated with:

$$Q_{frac,i} = \frac{r_i^3}{\sum_{i} r_i^3}$$  \hspace{1cm} (H.4)

with $n_{terms}$ the total number of terminal vessels. The flow at each terminal vessel is then simply calculated with:

$$Q_{term,i} = Q_{tot}Q_{frac,i}$$  \hspace{1cm} (H.5)

The total terminal windkessel resistance is calculated with H.3. This total terminal resistance is then distributed over the arterial, first myocardial, second myocardial and venous resistances with 25%, 34%, 34% and 7%, respectively [8]. The values for the three coronary capacitances are based on measurements by Spaan et al. [20], which gives estimated that the total capacitance of the three groups are $C_{art} = 0.2 \text{ mm}^3\text{ Pa}^{-1}$, $C_{myo} = 0.53 \text{ mm}^3\text{ Pa}^{-1}$ and $C_{ven} = 0.65 \text{ mm}^3\text{ Pa}^{-1}$. Using the $Q_{frac,i}$, the total capacity is subdivided over the coronary windkessels, with:

$$C_{term,i} = C_{tot}Q_{frac,i}$$  \hspace{1cm} (H.6)

To compute FFR, hyperemia is considered. Therefore, the total resistance of each coronary windkessel has a fourfold reduction and the distribution of the resistance over the arterial, myocardial and venous compartment changes to 42%, 13.5%, 13.5% and 31%, respectively [22, 20, 8].
Appendix I

Stenosis Element

Written: Ir. T. van den Boom
Reviewed: Ir. B. G. van Willigen
Approved: Dr. Ir. W. Huberts

First, the stenosis element is explained and how it is numerically implemented. Then we explain how the model recognizes stenosis elements.

I.1 Modeling of stenosis element

Although the one-dimensional model is a proper model to simulate wave propagation in straight or slightly tapered tubes no correct results are obtained when the local lumen varies too much. In case of a changing geometry, eg. a stenosis or an aneurysm, the radial velocity will no longer be negligibly small compared to the axial velocity. Furthermore, the used velocity profile can no longer be based on the theory of fully developed flow in straight vessels. This means a new pressure flow relation is necessary. Based on two-dimensional simulations on the stenosis geometry visualized in Figure I.1, a relation for the pressure drop over stenosis to the flow and the stenosis geometry was derived by Bessems et al. [3].

\[ a = a_0 - \frac{a_0 - a_s}{2} (1 - \cos\left(2\pi \frac{z - l_s/2}{l_s}\right)) \]  

I.1

Figure I.1: A two-dimensional representation of the stenosis element.

The stenosis geometry is described with the following relation:
APPENDIX I. STENOSIS ELEMENT

where $a_0$ is the proximal radius, $a_s$ is the radius at the neck of the stenosis, $z$ the axial position and $l_s$ is the length of the stenosis. For which at $z = \frac{l_s}{2}$ or $z = -\frac{l_s}{2}$, then \ref{eq:1} results in $a = a_0$ and for $z = 0$, then \ref{eq:1} results in $a = a_s$. The relation for the pressure drop over the stenosis to the flow and the stenosis geometry can be derived based on 3D axisymmetric simulations with the geometry of Figure 1.1 [3]:

\[-\frac{\partial p}{\partial z} = \frac{1}{L_u}K_u L_u \frac{\partial q}{\partial t} + K_v R_s q + \frac{\rho K_t}{2A_0^2} (A_0 - A_s)^2 \left| q_n \right|^2 q + K_c R_s q\]  \hspace{1cm} (I.2)

where viscous loss coefficient $K_v$, the offset coefficient $K_c$, the constant turbulence coefficient $K_t$ and the constant unsteady coefficient $K_u$ are empirically determined by:

\[K_v = 1 + 0.053 \frac{A_s}{A_0} \alpha^2\]  \hspace{1cm} (I.3)

\[K_t = 0.95\]  \hspace{1cm} (I.4)

\[K_c = 0.0018 \alpha^2\]  \hspace{1cm} (I.5)

\[K_u = 1.2\]  \hspace{1cm} (I.6)

With the parameters $R_s$ and $L_u$ described by:

\[R_s = \frac{8\eta}{\pi a_0^4} \int_0^{L_s} \frac{a_0^4}{a_0^4(z)} \, dz, \quad L_u = \frac{\rho}{A_0} \int_0^{L_s} \frac{a_0^2}{a^2(z)} \, dz.\]  \hspace{1cm} (I.7)

Where $\alpha$ is the Womersley number, $A_s$ the cross-sectional area at the maximum constriction in the center of the stenosis area, $A_0$ the proximal cross sectional area and $q$ the time-averaged flow over one cardiac cycle.

The stenosis element can then be described using the balance of momentum and continuity of mass equations, resulting in the following set of equations:

\[\begin{align*}
  c_1 \frac{\partial p}{\partial t} + c_2 \frac{\partial q}{\partial z} &= 0 \\
  \frac{\partial q}{\partial t} + c_4 q + c_5 \frac{\partial p}{\partial z} &= f_2
\end{align*}\]  \hspace{1cm} (I.8)

where:

\[c_1 = C_0\]  \hspace{1cm} (I.9)

\[c_2 = 1\]  \hspace{1cm} (I.10)

\[c_4 = \frac{K_v R_s}{K_u L_u} + \frac{\rho K_t}{K_u L_u A_0^2} (A_0 - A_s)^2 |q_n|\]  \hspace{1cm} (I.11)

\[c_5 = \frac{l_s}{K_u L_u}\]  \hspace{1cm} (I.12)

\[f_2 = \frac{\rho K_t}{2K_u L_u A_0^2} (A_0 - A_s)^2 |q_n| q_n - \frac{K_v R_s}{K_u L_u} q_n\]  \hspace{1cm} (I.13)

which has been linearised using the Newton-Raphson method. This now has the same shape as for the line element in Appendix E and can be solved the same way. For a larger explanation of the stenosis element, the reader is referred to [10] and [13].
I.2 Stenosis Recognition

To replace line elements with a stenosis element, we need to automatically recognize these stenosis in the geometry. This is done by first subdividing the coronary geometry into segments. Each segment is then processed separately to recognize a stenosis. Figure I.2 shows an example of a coronary vasculature of which each segment has a different color. For each segment, the distance and diameter is known, as shown in Figure I.3.

For each segment, a linear fit is created that is assumed as the healthy radius. When the radii is $\leq 75\%$ of the healthy radius, then recognized as a stenosis. This line elements are then replaced with a stenosis element, as shown in Figure I.4.
APPENDIX I. STENOSIS ELEMENT

Figure I.4
Appendix J

Solution Procedure Model

Written: Ir. T. van den Boom
Reviewed: Ir. B. G. van Willigen
Approved: Dr. Ir. W. Huberts

In order to solve the model including 1D line and 0D windkessel elements, the equations are rewritten in the same general form (J.1) by using method of Kroon et al. [14].

\[
K^t_{0D} \frac{d}{dt} p^{t+\Delta t} = \int_{z}^{t} K^t_{0D} d \Delta t + q^{t+\Delta t}. \tag{J.1}
\]

The following paragraphs describe how to rewrite the 1D line elements (Chapter J.1) and 0D windkessels (Chapter J.2) to the general form (J).

J.1 1D Line Element Equations

First of all, the following set of equations:

\[
\begin{align*}
C_0 &= \frac{\partial A}{\partial p} \bigg|_{p=p_{ref}} \\
\frac{\partial q}{\partial t} + \frac{\partial \gamma}{\partial z} + A p (2 - c_p) \frac{\partial p}{\partial z} + A c_q R_0 q &= 0 \\
A(z, t) &= A_0(z) + C_0(p - p_{ref})
\end{align*}
\]  

(J.2)

To describe the linearized version of the 1D balance of mass and momentum equation as given by (J.2), the vessels are divided into non-overlapping two-noded elements. The trapezium rule is then used to spatially integrate the element equations between the nodes. The linearized conservation of mass equation has the form:

\[
C_0 \frac{\partial p}{\partial t} + \frac{\partial q}{\partial z} = 0 \tag{J.3}
\]

Integrating the mass equation within an element results yields:

\[
\int_{e} C_0 (\frac{\partial p}{\partial t}) dz = \frac{\Delta z}{2} (C_{A,1} \frac{\partial p_1}{\partial t} + C_{A,2} \frac{\partial p_2}{\partial t}) \tag{J.4}
\]

\[
\int_{e} \left( \frac{\partial q}{\partial z} \right) dz = (q_2 - q_1) \tag{J.5}
\]
The linearised conservation of mass equation using the Newton-Raphson method on the advection term, it now has the form:

$$\rho \frac{\partial q}{\partial t} + \frac{\partial p^{t+\Delta t}}{\partial z} = -\frac{\partial (q')^2}{\partial t} - \rho \frac{\partial (q')^2}{\partial z}$$

(J.6)

Integration gives:

$$\int_c \frac{\partial p^{t+\Delta t}}{\partial z} dz = (p_2^{t+\Delta t} - p_1^{t+\Delta t})$$

(J.7)

$$\int_c (h') dz = \frac{\Delta z}{2} (h_2' - h_1')$$

(J.8)

with \(h\) the right hand side of (J.6). When using second-order backward differentiation for the time derivatives with time step \(\Delta t\), (J.3) and (J.6) can be written in the form:

$$F_e \tilde{p}_e^{t+\Delta t} + G_e \tilde{q}_e^{t+\Delta t} = h_e,$$

(J.9)

where:

$$F_e = \begin{bmatrix} \frac{3}{2\Delta t^2} \Delta z C_{A,1}^{t-1} & \frac{3}{2\Delta t^2} \Delta z C_{A,2}^{t-1} \end{bmatrix}$$

(J.10)

$$G_e = \begin{bmatrix} -\frac{1}{2\Delta t^2} \rho & -\frac{1}{2\Delta t^2} \rho \end{bmatrix}$$

(J.11)

$$h_e = \begin{bmatrix} 0 \end{bmatrix} + \begin{bmatrix} \frac{\Delta z}{2} \left( \frac{2}{\Delta t^2} C_{A,1}^{t-1} p_1^{t-\Delta t} - \frac{1}{\Delta t^2} C_{A,1}^{t-1} q_1^{t-\Delta t} \right) + \frac{\Delta z}{2} \left( \frac{2}{\Delta t^2} C_{A,2}^{t-1} p_2^{t-\Delta t} - \frac{1}{\Delta t^2} C_{A,2}^{t-1} q_2^{t-\Delta t} \right) \end{bmatrix}$$

(J.12)

After separation of matrix \(G_e\), the 1D element equations finally read:

$$[G_e^{-1} F_e] \tilde{p}_e^{t+\Delta t} = [-G_e^{-1} h_e] + \tilde{q}_e^{t+\Delta t}$$

(J.13)

Which is in the general form of:

$$K_{e,0D} \tilde{p}_e^{t+\Delta t} = f_{e,0D}^{t+\Delta t}.\quad \text{(J.14)}$$

### J.2 0D Windkessel Element Equations

The three elements in Figure F.1 are described by two resistors and one compliance. In matrix form, the equations for these elements become:

$$\begin{bmatrix} \frac{1}{R_1} & 1 \\ -1 & 1 \end{bmatrix} \begin{bmatrix} p_1 \\ p_2 \end{bmatrix} = \begin{bmatrix} q_1 \\ q_2 \end{bmatrix},\quad \text{(J.15)}$$

$$\begin{bmatrix} \frac{1}{R_2} & 1 \\ -1 & 1 \end{bmatrix} \begin{bmatrix} p_2 \\ p_3 \end{bmatrix} = \begin{bmatrix} q_3 \\ q_4 \end{bmatrix},\quad \text{(J.16)}$$

$$\begin{bmatrix} C & -1 \\ -1 & 1 \end{bmatrix} \begin{bmatrix} \frac{\partial p_2}{\partial t} \\ \frac{\partial p_3}{\partial t} \end{bmatrix} = \begin{bmatrix} q_5 \\ q_6 \end{bmatrix} \quad \text{(J.17)}$$

These elements can be assembled to

$$C_e \frac{\partial p}{\partial t} + R_e p_e = q_e,\quad \text{(J.18)}$$

AngioSupport
with:

\[
C_e = \begin{bmatrix}
0 & 0 & 0 & 0 \\
0 & C & -C & 0 \\
0 & 0 & 0 & 0 \\
0 & -C & C & 0
\end{bmatrix},
\] (J.19)

\[
R^e_e = \begin{bmatrix}
\frac{1}{2} & -\frac{1}{2} & 0 & 0 \\
-\frac{1}{2} & \frac{1}{2} + \frac{1}{R} & 0 & -\frac{1}{R} \\
0 & -\frac{1}{R} & 0 & \frac{1}{R} \\
0 & 0 & 0 & 0
\end{bmatrix},
\] (J.20)

where \( p_e = [p_1, p_2, p_3, p_4]^T \) and \( q_e = [q_1, q_2 + q_3 + q_5, q_4, q_6]^T \).

Application of the second order backward differentiation scheme on (J.18) to step forward (\( \Delta t \)) in time results in:

\[
\left( \frac{3}{2\Delta t} C_e + R^e_e \right) p_e^{t+\Delta t} = (C_e(-\frac{2}{\Delta t} p_e^t - \frac{1}{2\Delta t} p_e^{t-\Delta t}) + q_e^{t+\Delta t},
\] (J.21)

which is now cast into the same general form (J).
Appendix K

Procedure segmentation

Written: Ir. T. van den Boom
Reviewed: Ir. B. G. van Willigen

For the procedure to segment coronary arteries, the following is required:

- CAAS 5.11.2
- CAAS 8.1.1
- Code to connect the vessels

First, patients should be selected with CAAS 8.1.1 who satisfy the following criteria:

- The LM, LAD, and LCX should be seen clearly in two coronary angiograms under an angle \( \geq 30^\circ \) (Figure K.3).
- The vessels should not be tortuous
- The vessels should not overlap
- In both images, a clear LM is seen, which is as reference to overlap the coronaries.

This criteria resulted that only 10 coronary angiograms could be segmented of the 75 patients coronary angiograms we received. This corresponds with Pie Medical Imaging, who segmented 25 out 75 patients. The difference for Pie Medical Imaging is that they only segment one single vessel, while we are segmenting the entire left coronary vasculature.

When we have selected a good coronary angiogram, the following steps were taken to create a full vasculature:

Step 1 Find matching images

First, the two movies from two different angles need to be matched. One single image is used from each movie to segment the coronary vessels. In both movies, the frame is selected just before systole. This frame has the highest filling of the left ventricle and coronaries are shown best.

Step 2 Draw contours vessels

In both images, the contours of the coronary vessel is drawn. An example is shown in Figure K.1. In both images, the drawing starts at the Left main and ends in the distal coronary. The drawn edges is automatically done by CAAS, but can then be manually modified. Important for this part is that the right coronary vessel is drawn, because the software will create the vessel even if they don’t match anatomically. The full movie can be used to see how the coronary vessels combine.

Step 3 Centreline and radius

AngioSupport
APPENDIX K. PROCEDURE SEGMENTATION

Figure K.1: example of two chosen images.

The CAAS software will then use the two contour drawing to create the coronary vessel. By placing the two images in the correct angle, a 3D vessel is created, as shown in Figure K.2. This 3D segmentation is made into a .stl file. The software also create a .txt file with the centreline and radius of the vessel. An example of such a text-file is shown in Figure K.3.

Figure K.2: 3D scatter plot of centerline and radius segmented vessel.

Figure K.3: Text file created by Caas software

Step 3 Draw more contours

After first coronary vessel is created, the next vessel is segmented. The current contours are deleted and another coronary vessels is drawn. Important here is to place the Common Image Point at the same position as in the first segmentation, since this is needed to have the same coordinates between coronary segmentations.
Step 4 Connect coronaries

In Figure K.4, the centreline of both segmented vessels is plotted in 3D. When plotting both drawn vessels, the first segment will overlap, since in both images the Left main was drawn. This is now used to recognize where the two vessels separate. This first part is then deleted and the second vessel is connected to the first vessel at the bifurcation.

Figure K.4: Combination of two vessels into one single vasculature.

Step 5 Connect more coronaries

Now more vessels are drawn with CAAS software, and then connected with the procedure described above. Figure K.5, K.6 and K.7 show the completion of the left coronary vasculature segmentation process.

Figure K.5
Appendix L

Aanvraag nWMO

Written: Ir. B.G. van Willigen and Ir. T. van den Boom
Approved: Dr. W. A. L. Tonino

An Interactive Tool to Support Coronary Intervention (ITSCI)

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Protocol: 03-07-2018, Version 1.1

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1. BACKGROUND AND RATIONALE

To assess the physiological significance of intermediate lesions in patients with coronary artery disease (CAD) fractional flow reserve (FFR) has become standard care. Subjective visual judgement of these lesions on coronary angiography, especially in patients with diffuse disease and long segments, has been proven to be inaccurate for physiological assessment [1], [2]. Moreover, many studies have shown that an FFR guided strategy improves outcomes in patients being treated for CAD when compared with angiographic guidance alone [3], [4].

Traditionally, the sole treatment of CAD is Coronary Artery Bypass Surgery (CABG). CABG is safe and efficient compared to medical therapy, with significant improvement in survival rate [6]. However, the need of less invasive interventions led to the implementation of percutaneous coronary intervention (PCI) using bare metal stents. The addition of drug eluting stents resulted in the wide spread use of PCI. The issue of PCI versus CABG has become a topic of debate between interventional cardiologists and cardiac surgeons. The results of 2 large randomized controlled trials comparing PCI with CABG were published with different conclusions [7], [8]. One trial suggested that CABG might be better than PCI in patients with left main CAD, while the other trial concluded that PCI with drug eluting stents is not inferior to CABG in left main CAD patients with low or intermediate complexity scores [9]. Furthermore, the anatomy of coronary arteries and the amount of disease make it difficult to define a treatment based on experience, FFR, and angiography images.

Around 1 million PCI procedures are performed annually in the United States at a cost of approximately $10 billion; the rewards for successfully modeling virtual FFR are therefore considerable [10]. Using computational fluid dynamics, calculations of coronary flow and pressure fields enable the simulation of FFR from anatomic image data. These in silico models allow for the prediction of post-operative FFR (post-FFR) values [10]. Using the coronary angiography to create patient specific vessel networks, these models can assist in planning coronary interventions. An Interactive Tool to Support Coronary Intervention (ITSCI) is an application able to compute pre-operative FFR (pre-FFR) based on coronary angiography and post-FFR of virtually performed coronary intervention(s) (PCI or CABG) by a clinician.
1.2 Rationale for ITSCI

In everyday practice it is often difficult to assess the physiologic severity of lesions in patients with CAD. Therefore, coronary intervention planning can be challenging for patients with CAD. Besides the difficult decision between PCI and CABG, the size of the stent, the location of the stent, or the attachment of the CABG could be hard to determine due to multiple stenosis, diffuse disease, or anatomy. ITSCI gives a prediction of the post-FFR of the virtually performed coronary intervention. Clinicians are able to perform multiple coronary interventions with ITSCI in order to compare different interventions based on post-FFR. This way ITSCI could support clinicians with coronary intervention planning.

2. STUDY OBJECTIVES

2.1 Hypothesis

The hypothesis of this study is that ITSCI can support clinicians with coronary intervention planning, including the decision between percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) and the size and location of the intervention.

2.2 Primary objective of this pilot study

The primary endpoint will be the percentage of patients that ITSCI predict the post-FFR compared with the invasive post-FFR within 0.3 uncertainty.

2.3 Secondary objectives

A secondary endpoint will be comparison between the pre-FFR computed by ITSCI with the invasive FFR.

3. PATIENT ELIGIBILITY

Data from patients must meet all criteria to be enrolled.
3.1 Criteria to comply to study objective

3.1.1 Age ≥ 18 years
3.1.2 Single stenosis in the LAD
3.1.3 Measured invasive FFR pre- and post-operative. The intervention consists of PCI or CABG from the Left Internal Mammary Artery (LIMA)

3.2 Exclusion criteria

3.2.1 Severely calcified lesions
3.2.2 Excessive tortuosity, type C lesions
3.2.3 Complex bifurcation lesions

5. STUDY PROCEDURES

This study has a retrospective design. Anonymous data from 10 patients with a single LAD lesions will be collected, retrospectively from the Catharina Hospital Eindhoven. These patients previously underwent a coronary angiogram before and after an PCI or CABG (with a LIMA). Furthermore, the invasive FFR was measured before (pre-FFR) and after (post-FFR) the treatment. The invasive pre-FFR will be compared with the virtual pre-FFR computed by ITSCI. Subsequently, the coronary intervention will be virtually recreated with ITSCI per patient and corresponding invasive post-FFR will be compared with the virtual post-FFR.

5.3 Follow-up

No follow up will be performed.

5.4 Withdraw and removal of subjects

Not applicable

6 ADVERSE EVENTS

Not applicable
7 STATISTICAL CONSIDERATIONS

7.1 Data analysis
This pilot study will compare the invasive with virtual post-FFR and invasive with virtual pre-FFR, a linear regression will be performed and Bland-Altman plots will be made.
The diagnostic characteristics of virtual pre-FFR will be evaluated against those of invasive pre-FFR by using statistics, including sensitivity, specificity, positive predictive value, negative predictive value, and accuracy, with their corresponding 95% confidence intervals.

8. STUDY MANAGEMENT

8.1 Role of commercial support
This study is an investigator-initiated study with an unrestricted research grant from CompBioMed. The financial supporter will not be granted access to the data during any time of the study, nor will their advice be requested before publication of any of the data. No other companies are involved in this study. Although this is a retrospective study and a non-WMO we will ask the Medical research ethics committee (MEC-U) of our hospital for.

Privacy All data collected in this study will be treated with strict confidentiality. Only existing data are re-used and will be provided anonymously. Personal identifiable information from the data sets will be removed. The data will be saved for 15 years.
9. REFERENCES


Appendix M

Verification Systemic Model

Written: Ir. T. van den Boom
Reviewed: Ir. B.G. van Willigen
Approved: Dr. Ir. W. Huberts

To verify our self created 1D CFD code, we used a benchmark study by Boileau et al. [6] to compare the results of our model written in Python. The geometry used in this study can be seen in Figure M.1. For an extensive description of the used geometry and choice in boundary conditions, the reader is referred to [6] and [21].

![Figure M.1: The geometry used in the benchmark study](image)

Results are shown of the aortic arch (node 1), the right renal (node 44), the abdominal aorta (node 47) and the right anterior tibial (node 54). The results of the python version (orange) and Boileau et al. [6] (blue) are indistinguishable and therefore the model is assumed validated (Figure M.1).
Figure M.2: The flow (left) and pressure (right) in the aortic arch

Figure M.3: The flow (left) and pressure (right) in the right renal
Figure M.4: The flow (left) and pressure (right) in the abdominal aorta

Figure M.5: The flow (left) and pressure (right) in the right anterior tibial
Appendix N

Verification Coronary Model

Written: Ir. T. van den Boom
Reviewed: Ir. B.G. van Willigen
Approved: Dr. Ir. W. Huberts

To verify the implementation of the coronary model the results of the PhD thesis of van der Horst [22] are reproduced. The geometry used in this study can be seen in Figure N.1. For an extensive description of the used geometry and choice in boundary conditions, the reader is referred to [22].

Figure N.1: The total model consisting of the left ventricle (LV), with the mitral (Mv) and aortic valve (Av), the aorta, and the coronary circulation. The LMCA has a length of 5 mm and splits into the LAD and the LCx, with a length 7.5 cm and 6 cm, respectively. Side branches are modeled at intervals of 1.5 cm. Each coronary segment is represented by the characters a - f. The radius of segment a is 1 mm and Murrays law is used to determine the radius of segments b-f. All a-segments are connected to the three Windkessel elements representing the coronary microvessels. The intramyocardial pressure (pim) acts on the three capacitors that represent the vessel compliance. When a stenosis is modeled, it is incorporated into the c-segment of the LAD. The figures is obtained from [22].
First, Figure N.2 and Figure N.3 show the left ventricular pressure-volume loop (left), left ventricular and aortic pressure (middle), and the flow through aortic and mitral valve of the PhD thesis of van der Horst and our model made in Python, respectively. As can be seen, the results are identical and therefore our Python model is assumed to be correctly implemented in Python.

Figure N.2: The left ventricular pressure-volume loop (left), the left ventricular pressure (-) and aortic (-) pressure (middle), and the flow through the aortic (-) and mitral (-) valve (right) obtained from the PhD thesis of van der Horst [22].

Figure N.3: The left ventricular pressure-volume loop (left), the left ventricular pressure (blue) and aortic (orange) pressure (middle), and the flow through the aortic (blue) and mitral (orange) valve (right) obtained from our Python model.
Second, Figure N.4 and Figure N.5 show the left main and right coronary pressure (left), flow (middle), pressure-flow relation (right) from PhD thesis of van der Horst and from the python model, respectively. The flow of the python model in coronary circulation is not identical to the flow of the model of van der Horst due to the lack of knowledge of the exact parameters used in his model. It showed therefore difficult to replicate the exact results. Nevertheless, the graphs show the same characteristics. Furthermore, the python model will use different boundary conditions when patient specific data will be used. Therefore, we consider the python model validated for the coronary circulation. The differences still seen between our version and the version of van der Horst et al. [22] are assumed not to influence the results of our FFR calculation. But this will be further investigated in the sensitivity analysis in Appendix Q.

Figure N.4: The left main (-) and right (- -) coronary pressure (left), flow (middle), and pressure-flow relation (right) obtained from the PhD thesis of van der Horst [22].

Figure N.5: The left main (blue) and right (orange) coronary pressure (left), flow (middle), and pressure-flow relation (right) obtained from our Python model.
Third, Figure N.6 and Figure N.7 show the pressure over time for a 50% and 70% stenosis both proximal and distal from the stenosis obtained from the PhD thesis of van der Horst and the python model, respectively. Our Python model again has the same global characteristics as in the PhD thesis of van der Horst. The small differences are again due to not being able to fully reproduce the model of van de Horst, since we do not have the originally used data. Nevertheless, the effect of the stenosis has the same result and is able to produce the pathologically expected results when compared in the PhD thesis of van der Horst [22]. The differences still seen between our version and the version of van der Horst et al. [22] are assumed not to influence the results of our FFR calculation. But this will be further investigated in the sensitivity analysis in Appendix Q.

![Figure N.6: The pressure proximal (-) and distal (--) to a stenosis obtained from the PhD thesis of van der Horst [22].](image)

![Figure N.7: The pressure proximal (blue) and distal (orange) to a stenosis obtained from the Python model.](image)
Appendix O

Adapting systemic geometry

Written: Ir. T. van den Boom
Reviewed: Ir. B. G. van Willigen
Approved: Dr. Ir. W. Huberts

The systemic geometry as described in Appendix M is a large systemic geometry as also used in Boileau et al. [6]. Hereafter, we refer to this geometry as ADAN56. ADAN56 consists of the 56 largest arteries and is a reduced version of the anatomically detailed arterial network model developed by Blanco et al. [5]. This geometry is often used also in other studies [6, 5, 4] and is benchmarked with 3D simulations [6]. However, this systemic geometry describes a generic patient and can therefore not yet be used in the current study. There are three problems concerning the ADAN56 geometry:

1. The windkessel parameters used in the ADAN56 are not modelled with a characteristic resistance. Currently, the first windkessel resistance \( Z_0 = \frac{1}{4} R_p \), which does not attenuate high frequency wave reflections as described by Vosse et al.. The total windkessel resistance \( (Z_0 + R_p) \) needs to be rearranged.

2. The geometry does not include a Left Internal Mammary Artery (LIMA). To be able to simulate a CABG by attaching the LIMA to a coronary artery, the LIMA must be added to the ADAN56 geometry.

3. The geometry includes many arteries, such as in the legs and arms, which can be excluded out of the simulations to reduce simulation time. We will investigate how much can be excluded to maintain precision of the numerical predictions and the effect of changing the boundary conditions.

1. Windkessel parameters

The ADAN56 geometry has 31 terminal nodes and subsequently has 31 three-element windkessels. The origin of the parameters for these windkessels are not found in [6], but do have the same ratios, since for each windkessel:

\[
Z_0 = \frac{1}{4} R_p, \tag{O.1}
\]

\[
C = \frac{\tau}{R_T} = \frac{\tau}{Z_0 + R_p}, \tag{O.2}
\]

with \( R_p \) the peripheral resistance, \( C \) the peripheral compliance, \( R_T \) the total resistance of the windkessel and \( \tau \) is a time constant with value 0.2832. This constant \( c_1 \) is taken from [6] and the origin of this value is unknown. However, to attenuate the high frequency non-physiological wave
APPENDIX O. ADAPTING SYSTEMIC GEOMETRY

Figure O.1: The three-element windkessel

Reflections, the characteristic resistance must be calculated with:

\[ Z_0 = \sqrt{\frac{L}{C}} = \sqrt{\frac{\rho h E}{2\pi a^5(1 - \mu^2)}}. \]  

(O.3)

The peripheral resistance is then calculated with:

\[ R_p = R_T - Z_0, \]  

(O.4)

calculate with:

to compare the new windkessel values with the original, both simulations are shown in Figure O.2. For these simulations, only the windkessel parameters are changed. For everything else the same settings were done as in Boileau et al. [6]. The new windkessel elements show minor differences with the original windkessel elements and in

Figure O.2: The original and new windkessel simulations with the pressure and flow in the aortic root and subclavian.

the aortic root mean pressure difference was 0.79 Pa. The new windkessel elements are therefore not of big influence and can be maintained for the further steps.
APPENDIX O. ADAPTING SYSTEMIC GEOMETRY

2. LIMA

the ADAN56 geometry does not have a LIMA. Since this LIMA is often used for bypass surgery and therefore needed in AngioSupport [24], the LIMA must be added to the geometry. However, in paper by Avolio et al. [2] a LIMA is included, which will be added to the ADAN56 geometry. The terminal windkessel parameters for the LIMA are chosen such that the total peripheral resistance and compliance is equal to the Posterior interosseous R (see Boileau et al. [6]). The Posterior interosseous R was used since this vessel has the a total outflow which is in the same order as the LIMA. The parameters for this LIMA is shown in Table O.1. The placement of the LIMA in the ADAN56 geometry can be seen in Figure O.3. The values for $Z_0$, $R_p$ and $C_p$ are taken equal to the

<table>
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</tr>
<tr>
<td>Radius</td>
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</tr>
<tr>
<td>Wall Thickness</td>
<td>0.03 cm</td>
<td></td>
</tr>
<tr>
<td>Youngs Modulus</td>
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</tr>
<tr>
<td>$Z_0$</td>
<td>$2.18 \times 10^9$ Pa</td>
<td></td>
</tr>
<tr>
<td>$R_p$</td>
<td>$2.17 \times 10^{10}$ Pa</td>
<td></td>
</tr>
<tr>
<td>$C_p$</td>
<td>$1.18 \times 10^{-11}$ m$^3$Pa$^{-1}$</td>
<td></td>
</tr>
</tbody>
</table>

Table O.1: parameters of the LIMA.

Adding the LIMA to the ADAN56 geometry reduces the mean pressure in the aortic root and subclavian with 65.1 and 72.4 Pa, respectively. The flow wave in the aortic root stays equal, while the mean flow in the subclavian increases from 4.4 ml/s to 4.9 ml/s. The pressure and flow waveforms are shown in Figure O.4.

These changes in waveforms is all due to the extra outlet at the LIMA, which results in a reduced total peripheral resistance and more outflow towards the subclavian.
Figure O.3: The ADAN56 geometry with a added LIMA

Figure O.4: The ADAN56 geometry with a added LIMA
3. Reducing Geometry Size

To be able to model patient-specific blood flow, an estimation of the model parameters from available clinical data is required, ideally noninvasively. The larger the number of arterial segments in a distributed 1D model, the greater the number of input parameters that need to be estimated. To be able to reduce the needed parameters, the study by Epstein et al. [9] is used. By dividing the peripheral 1D model branches into windkessel models that preserve the total resistance and compliance of the original model. The reduction of the 1D part also allows for a reduced simulation time by reducing the computational domain.

This section shortly describes the method to lump the 1D model branches with the peripheral windkessels, a more elaborate description can be found in [9]. First, to reduce a single vessel, the resistance and compliance of the 1D line element must be estimated. This is done with the mean value Theorem (MVT) by first integrating the linearized 1D equations of E.18 along the z-axis gives:

\[
\int_{0}^{l} \left( C_0 \frac{dp}{dt} + \frac{d}{dz} \right) dq \, dz = 0, \tag{O.5}
\]

\[
\int_{0}^{l} \left( \frac{d}{dz} \right) \left( \frac{q^2}{A} \right) \, dz + \int_{0}^{l} \left( \frac{A}{\rho} (2 - c_p) \frac{dp}{dz} + \frac{A}{\rho} c_q R_0 q \right) \, dz = 0, \tag{O.6}
\]

which result in:

\[
\int_{0}^{l} C_0 \frac{dp}{dt} \, dz + \int_{0}^{l} \left( \frac{d}{dz} \right) dq \, dz = 0, \tag{O.7}
\]

\[
\int_{0}^{l} \left( \frac{d}{dz} \right) \left( \frac{q^2}{A} \right) \, dz + \int_{0}^{l} \left( \frac{A}{\rho} (2 - c_p) \frac{dp}{dz} \right) \, dz + \int_{0}^{l} \left( \frac{A}{\rho} c_q R_0 q \right) \, dz = 0. \tag{O.8}
\]

Within the cardiovascular system, pulse waves propagate rapidly, while arterial lengths can vary between few millimeters up to 10 cm. As a result, pulse wave transit times within a vessel are very small compared with the duration of the cardiac cycle. Thus, at any given time the space averaged values will be close to the point wise ones. We also assume that the fluid inertia terms (which are the first two terms in Equation O.8) are negligible, since peripheral inertia has a minor effect on flow waveforms. Thus, O.7 and O.8 become:

\[
\int_{0}^{l} C_0 \frac{dp_{in}}{dt} \, dz + q_{out} - q_{in} = 0, \tag{O.9}
\]

\[
(p_{out} - p_{in}) \int_{0}^{l} \left( \frac{A}{\rho} (2 - c_p) \right) \, dz + q_{out} \int_{0}^{l} \left( \frac{A}{\rho} c_q R_0 \right) \, dz = 0. \tag{O.10}
\]

These can be rewritten into the general form for a compliance and resistance:

\[
C_v \frac{dp_{in}}{dt} + q_{out} - q_{in} = 0, \tag{O.11}
\]

\[
p_{out} - p_{in} = -R_v q_{out}, \tag{O.12}
\]

with \(C_v\) and \(R_v\) the integrated arterial compliance and resistance, respectively. Which give:

\[
C_v = \int_{0}^{l} C_0 \, dz, \tag{O.13}
\]

\[
R_v = \frac{\int_{0}^{l} c_q R_0 \, dz}{\int_{0}^{l} \left( 2 - c_p \right) \, dz}. \tag{O.14}
\]

Now we can reduce a 1D arterial segment to a two element windkessel model with resistance \(R_v\) and compliance \(C_v\). To close the problem we must also consider the terminal windkessels attached to the 1D line element and lump the three resistances and 2 compliances into one single three
APPENDIX O. ADAPTING SYSTEMIC GEOMETRY

Figure O.5: Reducing a single vessel

The new total resistance and compliance for this lumped windkessel and line element can be calculated by:

\[ R_{\text{new}} = R_p + Z_0 + R_v, \quad (O.15) \]

\[ C_{\text{new}} = \frac{C_v R_p + C_v Z_0 + CR_p + R_v C_v}{R_p + Z_0 + R_v}, \quad (O.16) \]

For an explanation of these equations, the reader is referred to [9]. After calculation of the new total resistance of the new windkessel using Equation O.15, the characteristic resistance \( Z_0 \) and peripheral resistance \( R_p \) are then calculated using O.3 and O.4.

At a bifurcation, two branches need to be lumped together. Firstly, we transform each daughter vessel into two parallel 2 element windkessel elements using the method described in this section and also shown in Figure O.6.

Figure O.6: Reducing a single bifurcation
APPENDIX O. ADAPTING SYSTEMIC GEOMETRY

We can then combine these two 0D models into a single three-element windkessel model, with a new total resistance $R_{\text{new},T}$ and compliance $C_{\text{new}}$. These are calculated with:

$$R_{\text{new},T} = \frac{1}{\frac{1}{R_{1,T}} + \frac{1}{R_{2,T}}},$$

**(O.17)**

$$C_{\text{new}} = C_{1,T} + C_{2,T}.$$  

**(O.18)**

This method is now used to reduce the systemic geometries. The ADAN56 geometry, with the rearranged resistances and added LIMA is used as a ‘golden standard’, to which all reduced geometries will be compared. All simulation settings are based on Boileau et al. [6]. The changes in the aortic root and the LIMA are investigated, since these will function as boundary conditions for the coronary vasculature.

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<td>blood density $\rho$</td>
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<tr>
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<tr>
<td>Hemodynamic tolerance</td>
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<td>-</td>
</tr>
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</table>

Table O.2: simulation settings.
1.

Figure O.7: Reduced geometry

Figure O.8: Pressure and flow wave forms for the aortic root and LIMA.

<table>
<thead>
<tr>
<th></th>
<th>'golden standard'</th>
<th>reduced geometry</th>
</tr>
</thead>
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</tr>
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</tr>
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<td>112.4</td>
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</tr>
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<tr>
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Table O.3: Results
APPENDIX O. ADAPTING SYSTEMIC GEOMETRY

2.

Figure O.9: Reduced geometry

Figure O.10: Pressure and flow wave forms for the aortic root and LIMA.

<table>
<thead>
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<td>112.4</td>
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<td></td>
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<td>0.557</td>
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Table O.4: Results
3.

Figure O.11: Reduced geometry

Figure O.12: Pressure and flow wave forms for the aortic root and LIMA.

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<td></td>
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Table O.5: Results
APPENDIX O. ADAPTING SYSTEMIC GEOMETRY

4.

Figure O.13: Reduced geometry

Figure O.14: Pressure and flow wave forms for the aortic root and LIMA.

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<td>Mean flow [ml/s]</td>
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<tr>
<td>LIMA Mean pressure [kPa]</td>
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Table O.6: Results
APPENDIX O. ADAPTING SYSTEMIC GEOMETRY

5.

Figure O.15: Reduced geometry

Figure O.16: Pressure and flow wave forms for the aortic root and LIMA.

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<tr>
<td>Mean pressure [kPa]</td>
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<tr>
<td>Mean flow [ml/s]</td>
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<td>-</td>
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</table>

Table O.7: Results
Conclusions
The method as described by Epstein et al. [9] to reduce the systemic geometry has been successfully applied to the ADAN56 geometry. Five reductions of the geometry are shown. as shown in the first 2 cases, the effect of multiple reflections sites downstream (i.e. after the first generation of bifurcations) can be lumped into single windkessel sites while maintaining the main shape of the pressure and flow waveforms. This was also the conclusion by Epstein et al. [9], which stated: "The effect of multiple reflection sites downstream vessels of the first generation of bifurcations can be lumped into single reflection sites at the end of these vessels."
The larger change in waveforms occur when the first generation of bifurcation sites are being reduced. Although mean pressure and flow are maintained in the aortic root and LIMA, waveforms have a higher amplitude, which was also found by Epstein et al. [9]. This is due to the lumping of superior mesenteric and renal arteries.
The use of this method to reduce the systemic geometry has great impact on computational cost, with a ten-time reduction in computational time when comparing case 1 to case 5. A sensitivity analysis will be performed to investigate whether the reduction of the systemic geometry has an impact on the sensitivity of calculating the FFR in the coronary arteries.
Appendix P

Inflow

Written: Ir. B.G. van Willigen
Reviewed: Ir. T. van den Boom
Approved: Dr. Ir. W. Huberts

To compare the FFR calculation using steady inflow instead of a pulsatile inflow, the geometry in Figure P is used and the FFR is computed with steady and pulsatile inflow at the points A-K changing the stenose (red circle) from 0% to 95% radius reduction. First the one fibre element was used as inflow at the aortic root and then the mean inflow was used for the steady state. Figure P shows the results in a scatterplot. The difference between the two FFR’s is within 0.02 (standard deviation of the variability of mFFR [12]); therefore, the FFR resulting from pulsatile and steady inflow are assumed equal.

Figure P.1: Scatterplot of the FFR resulting from steady and pulsatile inflow.
Figure P.2: Scatterplot of the FFR resulting from steady and pulsatile inflow.
Appendix Q
Sensitivity Analysis

Written: Ir. B.G. van Willigen
Reviewed: Ir. T. van den Boom
Approved: Dr. Ir. W. Huberts

The Variance Based Sensitivity Analysis (VBSA) attributes the contribution of every uncertain parameter and its interactions to the total output variance[17][19]. Now consider an example of the total variance of a model as a circle with unit area (Figure Q). This total variance can be fractionated proportional to the variance of the individual parameters and their uncertainty ($V_1, V_2, \text{and } V_3$) or to the interactions of these parameters ($V_{12}, V_{13}, V_{23}, \text{and } V_{123}$). A parameter with a large contribution to the variance of the total output is most rewarding to measure as accurately as possible to reduce the total variance of the output (Factor Prioritization), which is expressed with a high main sensitivity index ($S_{M,i}$), referring to $V_1$ in case of Figure Q. A parameter with a small contribution to the total variance of the output, including its interactions, could be fixed in its uncertainty range (Factor Fixing), because the outcome of the output would not depend on this parameter. These are the parameters with a low total sensitivity index ($S_{T,i}$).

For example, $V_3$ could be fixed due to its minor contribution and small interactions ($V_{12}, V_{23}, \text{and } V_{123}$). The main and total sensitivity indices are computed based on the decomposition of the output ($f(x)$) with the input variables defined as $x = \{x_1, x_2, \ldots, x_n\}$ (Q.1). This decomposition is called a high-dimensional model representation (HDMR) [15]. The number of subscripts of the function provides the order of the function, for example $f_{ij}(x_i, x_j)$ is a second order function. Furthermore, $f_0$ is the mean of $f(x)$ and the total number of terms can be computed with $2^n$.

$$Y = f(x) = f_0 + \sum f_1(x_i) + \sum \sum f_{ij}(x_i, x_j) + \ldots + f_{12\ldots n}(x_1, x_2, \ldots, x_n) \quad (Q.1)$$

I. M. Sobol’ was inspired by the HDMR. To enable the computation of the main and total indices, he made this decomposition unique based on two conditions. First, he assumed that the integral over a function of one of its own variable is zero (Q.2).
\[ \int f(x_i)dx_i = 0 \]  
\hspace{1cm} (Q.2)

This results in that all terms of \((Q.1)\) are orthogonal and can be computed individually.

\[ f_0 = E(Y) \]  
\hspace{1cm} (Q.3)

\[ f_i = E(Y|X_i) - E(Y) \]  
\hspace{1cm} (Q.4)

\[ f_{ij} = E(Y|X_i, X_j) - f_i - f_j - E(Y) \]  
\hspace{1cm} (Q.5)

With \(E(Y)\) the unconditional expected value of the output \((Y)\) and \(E(Y|X_i)\) the conditional expected value of the output with known input vector \(X_i = x^1_i, x^2_i, ..., x^N_i\) for parameter \(i\) with \(N\) the number of samples.

The second condition he added, is that \(f(x)\) is squared integrable; therefore, in combination with the first condition, all terms are squared integrable resulting in:

\[ \int f^2(x)dx - f_0^2 = \sum_i \int f^2_i(x_i)dx_i + \sum_{i<j} \int f^2_{ij}(x_i, x_j)dx_i dx_j + \int f^2_{12..n}(x_1, x_2, ..., x_n)dx_{1,2,...,n} \]  
\hspace{1cm} (Q.6)

\[ V(Y) = \sum_i V_i + \sum_i \sum_{ij} V_{ij} + ... + V_{12..k} \]  
\hspace{1cm} (Q.7)

With \(V_i = V(E(Y|X_i))\) and \(V_{ij} = V(E(Y|X_i, X_j)) - V_i - V_j\) the conditional variances. Dividing the terms with the unconditional \(V(Y)\) results in the sensitivity indices with the first order terms as main sensitivity indices:

\[ 1 = \sum_i S_i + \sum_{i<j} S_{ij} + ... + S_{12..k} \]  
\hspace{1cm} (Q.8)

With the main sensitivity index denoted as \(S_i(M,i) = S_i = \frac{V_i}{V(Y)}\). In other words, it defines the effect of one parameter on the output. It considers the interactions, but is not able to define the interactions between the parameters, which makes the purpose Factor Prioritization. The total influence of a parameter \((S_{T,i})\) includes its interactions; therefore, computed with all terms concerning the parameter. For a model with three parameters, the total sensitivity index for the first parameter holds:

\[ S_{T1} = S_1 + S_{12} + S_{13} + S_{123} \]  
\hspace{1cm} (Q.9)

With input \(X_{(i)}\) including all input parameters except of the \(i^{th}\) parameters. The fractions of the variances of the individual parameters and their interactions are summed one. Therefore, \((Q.9)\) results in the total sensitivity index of the \(i^{th}\) parameter. In other words, \(S_{(T,i)}\) measures the influence of the parameter including its interactions. If this value is low, the concerning parameter can be fixed in its uncertainty range (Factor Fixing).

In summary, this global model is widely used, because it is straight forward to implement and easy to interpret \([18]\). It can be used for Factor Prioritization and Factor Fixing. Furthermore, the sensitivity indices are quantitative. Moreover, Saltelli et al. (2004) states that this method is model free. However, Borgonovo (2007) pointed out that the variance fails for models with a highly skewed output due to its statistical moment dependency as result of quantifying the sensitivity with the variance \([7]\). Therefore, it should be mentioned that the method is model free if the output can be captured with the variance.
Q.1 Results sensitivity analysis

The sensitivity analysis is performed on the physiological model with the aortic pressure $P_{\text{mean}}$, the venous pressure $P_{\text{ven}}$, the coronary rest flow $Q_{\text{cor}}$, the arterial, myocardial, and venous compliance $C_{\text{art}}$, $C_{\text{myo}}$, and $C_{\text{ven}}$, respectively, the hyperemia factor $f_{\text{hyp}}$, the threshold to detect stenose $t_{\text{se}}$, factor to change radius and length of the stenose $f_{\text{rsten}}$ and $f_{\text{lsten}}$, respectively, and distribution of resistance over arterial, two myocardial, and venous resistance $f_{R_{\text{art}}}$, $f_{R_{\text{myo1}}}$, $f_{R_{\text{myo2}}}$, and $f_{R_{\text{ven}}}$, respectively. These parameters are changed within a realistic range (Table Q.1).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Min</th>
<th>Max</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>$P_{\text{mean}}$ [mmHg]</td>
<td>50</td>
<td>140</td>
<td>(Ramanathan and Skinner, 2005)</td>
</tr>
<tr>
<td>$P_{\text{ven}}$ [mmHg]</td>
<td>3</td>
<td>8</td>
<td>(Klingensmith, 2008)</td>
</tr>
<tr>
<td>$Q_{\text{cor}}$ [ml/min]</td>
<td>25</td>
<td>275</td>
<td>(Aasmouse et al., 2007)</td>
</tr>
<tr>
<td>$f_{\text{hyp}}$ [-]</td>
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<td>0.41</td>
<td>(Wilson et al., 1990)</td>
</tr>
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<td>$C_{\text{art}}$ [m$^2$/Pa]</td>
<td>$0.2 \times 10^{-9} \div 0.1$</td>
<td>$0.2 \times 10^{-9} \div 1.9$</td>
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</tr>
<tr>
<td>$C_{\text{myo}}$ [m$^2$/Pa]</td>
<td>$0.53 \times 10^{-9} \div 0.1$</td>
<td>$0.53 \times 10^{-9} \div 1.9$</td>
<td></td>
</tr>
<tr>
<td>$C_{\text{ven}}$ [m$^2$/Pa]</td>
<td>$0.65 \times 10^{-9} \div 0.1$</td>
<td>$0.65 \times 10^{-9} \div 1.9$</td>
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<tr>
<td>$f_{R_{\text{art}}}$ [-]</td>
<td>0.05</td>
<td>0.15</td>
<td>(Fayad Zahi A., et al., 2000)</td>
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<td>$t_{\text{se}}$ [%]</td>
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<td>$f_{\text{rsten}}$ [-]</td>
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<td>1.1</td>
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<td>$f_{\text{lsten}}$ [-]</td>
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<tr>
<td>$f_{R_{\text{ven}}}$ [-]</td>
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Figure Q.2: Parameters ranges

During the first sensitivity analysis, all parameters of Table Q.1 were included. The results showed that $P_{\text{mean}}$ is the most important parameter (Figure Q.1 and Q.1). After the first sensitivity analysis, the $P_{\text{mean}}$ was fixed on the measured value and a new sensitivity analysis was performed. This resulted in $Q_{\text{cor}}$ as most important parameter (Figure Q.1 and Q.1)

Figure Q.3: Main sensitivity indices.
APPENDIX Q. SENSITIVITY ANALYSIS

Figure Q.4: Total sensitivity indices.

Figure Q.5: Main sensitivity indices.

Figure Q.6: Total sensitivity indices.
Appendix R

Coronary flow

Written: Ir. B. G. van Willigen
Reviewed: Ir. T. van den Boom
Approved: Dr. Ir. W. Huberts

R.1 Tuning pre-FFR

The resistance of the myocardium, described by the windkessels, is unknown and cannot be measured. This resistance is computed based on the pressure difference between the aortic and venous pressure ($\Delta P = P_{ao} - P_{ven}$), the coronary flow at rest ($Q^{cor}$), and hyperemia factor ($f_{hyp}$) (R.1). In other words, the myocardial resistance distal to every vessel is described by a $R_i$ based on the flow in the corresponding vessel ($Q^{cor}_i$), $\Delta P$, and $f_{hyp}$. The flow in that vessel is determined by a flow distribution method (chapter R.2). When the $R_i$ is determined for a vessel, the resistance will be distributed over an arterial ($R_{art}$), two myocardial ($R_{myo1}, R_{myo2}$), and venous ($R_{ven}$) resistance $R_i$ (Appendix H). As can be seen in Appendix Q Figure Q.1, the value of these fractions (together a value of one) of $R_{art}$, $R_{myo1}$, $R_{myo2}$, and $R_{ven}$ do not influence the result. Therefore, assuming the correct fractions for these resistances, the correct flow distribution and fixed values for $P_{mean}$ and $P_{ven}$, the $Q^{cor}$ and the $f_{hyp}$ are the only parameters to tune to determine the myocardial resistance. Because $Q^{cor}$ has a great influence on the result (Figure Q.1 and Q.1), $Q^{cor}$ will be tuned to match the pre-FFR with the mFFR.

$$R_i = \frac{\Delta P}{Q^{cor}_i} \times f_{hyp}$$ (R.1)

R.2 Flow distribution method

During this project, two flow distribution methods are used: 1) The bottom-up method and 2) the top-down method. The initial method, bottom-up, determines $Q^{cor}_i$ of every vessel based on the fraction of the radius at the terminal ($r_i$) and the sum of the radii of every terminal both to the power of three (R.2).

$$Q^{cor}_i = \frac{r_i^3}{\sum r_i^3} \times Q^{cor}$$ (R.2)

The top-down method determines the $Q^{cor}_i$ of every vessel based on the fraction between the radii of the proximal of the vessels after a bifurcation. So, the flow in the daughter vessels ($Q^{di}_cor$) are fractional of the parent vessel ($Q^{p}_cor$).
APPENDIX R. CORONARY FLOW

\[ Q_{\text{cor}}^{di} = \frac{r_{di}^3}{r_{d1}^3 + r_{d2}^3} Q_{\text{cor}}^p \]  
(R.3)

An example of the division of flow is shown in Figure R.1. At each bifurcation, this method is used to determine the flow expected to the terminal coronary vessel.

Figure R.1: Explanation of the flow division using the top-down method.
# Appendix S  
## Activities

<table>
<thead>
<tr>
<th>Date</th>
<th>What</th>
<th>Where</th>
<th>Activity</th>
<th>For who?</th>
<th>Note</th>
</tr>
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<td>CVB meeting</td>
<td>TU/e</td>
<td>Presentation</td>
<td>Cardiovascular Biomechanics Group</td>
<td>Presented by both project managers</td>
</tr>
<tr>
<td>13/12/18</td>
<td>MaTe</td>
<td>Philips stadium</td>
<td>Poster presentation</td>
<td>Materials Technology group</td>
<td>Presented by both project managers</td>
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<tr>
<td>09/01/19</td>
<td>GME flyer</td>
<td>Media Flyer</td>
<td>Graduate students</td>
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| 18/01/19   | LGT news item            | Media Item LTG website | Potential clients | https://www.lishtgroup.com/research/micro- 
                                              | simulations-assessment- 
                                              | process/prasers?source= |                                                                       |
| 28/02/19   | Demo                    | LTG           | Demo                      | Cardiologist in training of CZE                | Presented by both project managers                                   |
| 07/03/19   | Demo                    | MCErasmus     | Demo                      | Biomedical engineering department and cardiologists | Presented by both project managers                                   |
| 02/04/19   | BME research day        | TU/e          | Pitch + poster presentation | All biomedical engineering faculty members    | First price, pitch presented by Tim                                   |
| 04/04/19   | Demo                    | Amsterdam UMC | Demo                      | Previous and current head of cardiology        | Presented by both project managers                                   |
| 17/06/19   | LGT news item            | Media Item LTG website | Potential clients | https://www.lishtgroup.com/research/micro- 
                                              | simulations-assessment- 
                                              | process/prasers?source= |                                                                       |
| 29/04/19   | All-Hands Meeting CBM   | Oxford        | Presentation              | All stakeholders of CBM                       | Presented by Bettine                                                  |
| 06/05/19   | Cursor                   | Media Item in 4TU career magazine | All engineering graduates | https://www.4tu.nl/publicat 
                                              | ions-center-special- 
                                              | s/20190019.pdf (page 10) |                                                                       |
| 23/05/19   | Demo                    | CZE           | Presentation for the R&D employees | Bounded by Tim                               | Presented by Tim                                                      |
| 24/05/19   | CBM conference           | -             | 2 abstracts for CBM conference | Academia                                      | Accepted for oral presentation and poster presentation               |
| 24/05/19   | Case description         | Media Item LTG website | Potential clients | https://www.lishtgroup.com/research/micro- 
                                              | simulations-assessment- 
                                              | process/prasers?source= |                                                                       |
| 04/06/19   | Flow at heart meeting   | TU/e          | Presentation              | Group of Frans van de Vosse                   | Presented by Tim                                                      |
| 23/05/19   | CBM conference           | London        | Presentation + Poster presentation | Participants of the conference | Bettine: Oral presentation Tim: poster presentation               |

Table S.1: Activities of AngioSupport
Appendix T

Decision diagram; Medical devices

Figure 1: A decision diagram to assist qualification of software as medical device.
Appendix U

User survey

**Interface gebruiksvriendelijk**

<table>
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<th>3</th>
<th>4</th>
<th>5</th>
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<td>4.9</td>
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<td></td>
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<td>4.8</td>
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Appendix V

1D method Kroon

Written: Ir. T. van den Boom
Reviewed: Ir. B. G. van Willigen
Approved: Dr. M. A. Stijnen

In the following abstract, the method by Kroon et al. [14] is explained and its benefits compared to other models. This model is used for the 1D CFD model in AngioSupport.
Pulse wave propagation modelling with reduced complexity

Van den Boom, T. MSc, Van Willigen, B. G. MSc, Dr. Stijnen, M., Prof. Dr. Van de Vosse, F.N.

LifeTec Group B.V., Eindhoven University of Technology

1. Introduction

One-dimensional (1D) network models have been extensively used to investigate blood pressure and flow wave propagation phenomena in arteries and veins. These so-called pulse wave propagation models allow the assessment of the effects of vascular disease on the pressure and flow waveforms, wave reflections, and the relation between central and peripheral pressures. The ease of use and the relatively low cost make 1D models also attractive for vascular intervention planning (Huberts et al., 2012) or for estimating boundary conditions for higher dimensional models.

These 1D network models consist of connected line elements that locally describe the relation between pressure, area, and flow. These pressure and flow relations are based on the 1D mass and momentum equations (Bessems et al., 2007). At terminal branches, the 1D network is often truncated with 0D windkessel elements or structured outflow trees. These methods vary from each other by using different formulations of the 1D equations and different constitutive laws to relate area and pressure. In addition, they differ with respect to the velocity profile, choice in boundary conditions, the way of coupling at junctions, and the numerical schemes (van de Vosse and Stergiopulos, 2011).

In this study, the numerical scheme as proposed by Kroon et al. is explained, which has a reduced complexity due to only requiring pressure as a state variable (Kroon et al., 2012). The scheme allows for flexible model building, by casting each element in the same form. This study then shows the ease of implementing more complex modelling equations, such as at junctions and stenosis. Finally, the numerical scheme is compared to other 1D numerical schemes.

2. Method

In large arteries, blood pressure $p$ (Pa), blood flow $q$ ($m^3 \cdot s^{-1}$), wall shear stress $\tau_w$ (Pa), and vessel cross sectional area $A$ ($m^2$) are related using the 1D conservation of mass, momentum balance equations and a constitutive law. By assuming no leakage, no gravitational forces and an incompressible Newtonian fluid, the 1D equations can be written as (van de Vosse and Stergiopulos, 2011):

$$\frac{\partial p}{\partial t} + \frac{\partial q}{\partial z} = 0 \quad (1)$$

$$\frac{\partial q}{\partial t} + \frac{\partial}{\partial z} \left( A \frac{q^2}{2} \right) + A \frac{\partial p}{\partial z} = -\rho \frac{\partial \tau_w}{\partial A} \quad (2)$$

with the axial location $z$, $t$ describes time and $\rho$ is the blood density. Wall shear stress $\tau_w$ and the convective term ($\frac{\partial}{\partial z} (\frac{q^2}{2})$) are estimated by assuming a velocity profile. The relationship between pressure and area ($A$), which also accounts for the fluid structure interaction of the system, is described with a constitutive law. This allows the Equations (1) and (2) to be linearized using estimates as described from previous time steps (indicated by symbol $\hat{\cdot}$):

$$\frac{\partial \hat{p}}{\partial t} + \frac{\partial \hat{q}}{\partial z} = 0 \quad (3)$$

$$\frac{\partial \hat{q}}{\partial t} + \frac{\partial}{\partial z} \left( A \frac{\hat{q}^2}{2} \right) + A \frac{\partial \hat{p}}{\partial z} = -\rho \frac{\partial \tau_w}{\partial A} \quad (4)$$

The momentum and mass equation for each element are spatially integrated along the vessel axis using the trapezium rule. Thereafter, to step forward in time, a difference scheme is needed. This model uses a second order backward difference scheme. As shown in Figure 1, each line element has two nodal flows, which are chosen to defined inwards to reduce the complexity of solving the entire system. Finally, at the formulation of the 1D line elements as shown in Figure 1 can be made, where column $\hat{p}_z$ and $\hat{q}_z$ are the nodal pressures and flows, respectively. Matrix $K_e$ is the element matrix and $f_e$ is the element right-hand side. The superscripts $t$ indicates the current
time step and the superscript $t + \Delta t$ the next time step. Therefore, the element vectors $q_e$ and $q_2$ are the unknown variables.

At vessel junctions, three 1D arterial elements are connected. Since flows are defined inwards, continuity of mass is automatically satisfied and no extra coupling equations are needed. This results in a shared node at junctions and a continuity of static pressure. This again shows the flexible coupling between 0D and 1D elements, without the introduction of penalty functions or the computation of Riemann invariants (Kroon et al., 2012). However, when continuity of total pressure is desired, the implementation of a 0D element at junctions is possible. This 0D elements accounts for differences of the dynamic part of the pressure at vessel junctions. It can be shown that, following the approach by Kroon et al., the nonlinear pressure flow equations at junctions can be easily incorporated. Boom et al. shows that this junction element can also account for the extra energy dissipation due to the formation of vortices at the entrance region of junctions (Boom et al., 2018).

Since at a stenosis the velocity components in the radial direction are no longer negligibly small with respect to their axial counterpart and the velocity profiles can no longer be based on the theory of fully developed flow in straight vessels, the 1D line elements are no longer accurate.

\[ K_e^0 \Delta x^2 = q_e^0 + F \]

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\[ K_e^0 \Delta x^2 = q_e^0 + F \]
3. Results

In a benchmark study (Boileau et al., 2015), six numerical schemes that are commonly used for 1D arterial blood flow modelling were compared to investigate the different numerical implementations on the pressure and flow waveforms, while using the same velocity profile, boundary conditions and constitutive law. The numerical schemes considered were locally conservative Galerkin, discontinuous Galerkin, Galerkin least-squares finite element method, finite volume method, MacCormack finite difference method and the method as proposed by Kroon et al. Six benchmark problems were defined (i.e., a reflection free tube, a tube mimicking the common carotid artery, the upper thoracic aorta, an aortic bifurcation, and experimental arterial networks with 37 and 56 of the larger arteries, published as the ADAN56 model). The results showed good agreement among all numerical schemes. It was concluded that the method by Kroon et al. just as accurate in solving the nonlinear 1D equations and to capture the main features of pulse wave propagation (Boileau et al., 2015). Moreover, using this approach an arterial network consisting of 100 line elements and a time step of 1 millisecond is simulated in real time.

When comparing the approach of Kroon et al. to a 3D solution, the numerical scheme showed able to capture the main features of 3D pressure, flow and area waveforms in the arterial bifurcations and large arterial trees. Only when simulating a larger vascular network (ADAN56), discrepancies were shown in the approach of Kroon et al.. This was caused by the coupling at junctions, for which continuity of static pressure was chosen. However, when using the junction element as described in this study, these discrepancies were resolved (Boom et al., 2018).

4. Discussion

A simplified numerical method is shown for time-domain simulation of blood pressure and flow waveforms in the vascular system that couples nonlinear 1D wave propagation models for the blood vessels to 0D windkessel elements for the periphery using pressure as only degree of freedom. By following the inward-directed flow approach as described by Kroon et al. we showed the flexibility of this approach and the relative ease of implementing a new element. By casting every element in the same form as in Figure 1 and defining flow inwards at element level, no extra coupling equations were needed between elements and computational speed, accuracy and efficiency were maintained (Kroon et al., 2012). Moreover, this approach can also easily be used to implement other vascular concepts with nonlinear pressure-flow rate relations, such as a stenosis (Bessems et al., 2007), bifurcating flows (Boom et al., 2018), a heart pump, or the calf muscle pump function. This shows the potential of this 1D approach and ease of coupling with other elements, since no additional coupling equations are needed between elements. This makes this approach also very suitable to coupling with higher dimensional models, i.e. 3D simulations of the aortic arch. While 0D models are often used as boundary conditions, a combined 1D and 0D segment could easily be implemented, using only pressure as a communicating variable. This allows the ability to parameterize the downstream vasculature to patient pathologies, but also show the effects of downstream wave reflections in the 3D simulations.
Appendix W

Abstract AngioSupport

Written: Ir. B. G. van Willigen
Reviewed: Ir. T. van den Boom
Approved: Dr. M. A. Stijnen

This abstract has been written for the CompBioMed Conference 2019 and is accepted for an oral presentation.
AngioSupport: an interactive tool to support coronary intervention
Van Willigen, B.G. MSc1,2, Van den Boom, T. MSc1,2, Dr. Stijnen, M.1, Prof. Van de Vosse, F.N.2
1LifeTec Group B.V., 2Eindhoven University of Technology

1. Introduction
Every year about 735,000 Americans suffer from Coronary Artery Disease (CAD); one of the leading causes of death in the United States; therefore, diagnosis and treatment should be convenient and accurate with costs as low as possible. Currently, medium to high risk stable patients have been assessed based on invasive coronary angiography (ICA). In other words, ICA was the ‘gold standard’ to determine the appropriate treatment (pharmaceutical treatment, percutaneous coronary intervention (PCI), or coronary artery bypass graft (CABG)) for CAD by revealing the location and anatomy of the stenosis. This diagnostic method is based on the research of Gould et al., which demonstrates the relationship between the stenosis (lumen diameter) and ischemia (determined based on myocardial blood flow) during the hyperemic state (Gould et al., 1974). Despite the subjective visual interpretation of the clinician to interpret the ICA, the percentage stenosis defined by ICA is a decent indication for revascularization for single vessel stenosis. However, for diffuse coronary disease or multiple stenosis (Tonino et al., 2009), ICA is unreliable for the diagnosis, because hemodynamics are unpredictable based on the anatomy of the stenosis. This may result in unnecessary revascularization of patients.

To improve the diagnostic method, Pijls et al. developed a new method to determine the impact of the stenosis by measuring invasively the myocardial fractional flow reserve (FFR) (Pijls et al., 1996). This fraction defines the hyperemic flow with a stenosis (Q̇_{hyp}) relative to the hyperemic flow without disease (Q̇_{max}) based on the ratio of the mean pressure distal to the stenosis (P̄_d) and the mean aortic pressure (P̄_a) (FFR = Q̇_{hyp}/Q̇_{max} = P̄_d/P̄_a). The invasive FFR is used in combination with ICA by inserting a pressure wire in the desired coronary artery to measure the P̄_d. The FFR, in combination with ICA, improves the diagnosis of multi-vessel and diffuse disease, because the P̄_a covers all changes in the vessel diameter distal to the stenosis. Furthermore, the use of the mean pressures to compute the FFR makes the method more robust to changes of pressure. In order to verify its diagnostic ability, three clinical studies were performed: 1) Fractional Flow Reserve versus Angiography for Multi-vessel Evaluation (FAME), 2) FAME 2, and 3) DEFER these studies show that invasive FFR in combination with ICA improves the decision between pharmaceutical treatment and PCI for CAD than ICA alone. As a result, FFR with ICA has become the new ‘gold standard’ to assess CAD. However, a part of the patients only requires pharmaceutical treatment while an invasive procedure was already performed. Therefore, multiple companies developed software to assess CAD minimal- or non-invasive.

For assessment of lesions based on coronary ICA, multiple software tools are available to quantify the length and percentage of stenosis by generating 3D construction of the vessel with stenoses. Examples are the software tools of Pie Medical Imaging (CAAS) and Medis (QAngio XA 3D). Although these tools can quantify lesions accurately, a 3D construction of only one vessel can be generated, so assessing multi-vessel lesions is inconvenient. Cathworks and Heartflow generate the entire coronary tree in 3D and computes the FFR virtually based on ICA and compute tomography (CT), respectively. CT is non-conventional to assess CAD; therefore, tools based on ICA is preferred over CT. Nevertheless, both tools have shown a high correlation with invasive FFR and a reduction in invasive treatments. However, for treatment planning it may still be difficult to determine the position, length or diameter for a CABG or PCI based on ICA and FFR due to multiple occlusions, diffuse coronary disease or complicated vasculature.
A tool that can predict the treatment outcome may support the cardiac team that discusses the treatment of multiple patients with CAD, every morning.

An existing tool to predict the FFR after PCI is VIRTUheart. However, the computational time is 95s per case, which is not feasible in a dynamic environment, such as a cardiac team meeting where multiple patients with CAD are discussed and multiple interventions per patient will be analysed within minutes. Furthermore, predicting the outcome of CABG next to PCI would be beneficial to compare PCI with CABG. Therefore, AngioSupport is developed to provide clinicians useful information while using conventional ICA and predicting the outcome of CABG or PCI within seconds to support clinical decision making.

2. Method

AngioSupport is a toolchain consisting of a segmentation tool and a 1D wave propagation model. The segmentation of the coronary arteries is performed by CAAS (Coronary Angiographic Analysis Systems, Pie Medical Imaging) and requires two single plane angiograms with an angle $\geq 30^\circ$ obtained by conventional ICA. The segmented coronaries are combined to create a patient specific full coronary vasculature. An existing 1D wave propagation model of the human vascular system was simplified and extended with the patient coronary system, as developed at the Eindhoven University of Technology (van der Hors et al., 2013). To simulate the pressure and flow propagation, the model is provided with patient specific clinical measures, such as patient length, weight, heart rate and aortic blood pressure, to compute the pre-operative FFR (pre-FFR) throughout the patient’s system. In additions, an interactive interface is developed, such that clinicians can select standard stent sizes and deploy them virtually in the area that seems affected by disease. Alternatively, the CABG option can be simulated by selecting the location of the anastomosis on the coronary tree. To be able to compare coronary interventions with AngioSupport, the post-operative FFR (post-FFR) is calculated throughout the coronaries. In practice, the clinician will only have to load the ICA and, subsequently, perform multiple interventions virtually.

3. Results

The post-FFR is computed within seconds and can be compared between the different interventions (Figure 1). This allows AngioSupport to be used during the cardiac team meetings, where patient treatment plans are determined in a short time span. By allowing clinicians access to the numerical models through the straight-forward AngioSupport user interface, clinicians will have an additional tool to support this difficult, but vital decision. The validation of AngioSupport is currently ongoing in cooperation with multiple hospitals in the Netherlands.
Figure 1 The result of AngioSupport calculations within the middle the pre-operative FFR calculation and left and right the results from a PCI and CABG. The heart team can now directly compare the post-operative FFR and determine a patient-specific treatment.

4. Discussion
An interactive interface for clinicians is developed as front-end for the physiological model developed by van der Horst et al. to compute blood pressure and flow throughout the coronary arteries (van der Horst et al., 2013) to analyse stenoses, compute pre-FFR, perform interventions, and predict post-FFR. AngioSupport aims to support clinicians with treatment planning, especially for multi-vessel and serial stenoses and diffuse diseased vessels. In addition, it could potentially reduce the number of repeat revascularization and stents for patients with multiple stenoses. This contributes to lower medical costs and an increase in convenience of the patient. In order to prove those benefits of AngioSupport, validation of AngioSupport with its assumptions should be performed. These assumptions with upcoming validations are discussed in the following paragraphs.

First, the segmentation of the coronary arteries is performed with CAAS. This software is developed to segment only one vessel, not an entire tree. Therefore, post processing was needed to connect the coronary arteries to each other. In addition, to generate a 3D image, the assumption is made that the vessels are ellipsoid. In order to validate that circular vessels and segmentation of CAAS is accurate enough to compute the FFR (pre- and post-operative) throughout the entire coronary tree, the virtual FFR values should be compared with measured FFR values.

Second, there has been chosen for a steady inflow as boundary condition to reduce computational time in respect to pulsatile inflow. Steady flow is assumed accurate enough to compute the FFR (pre- and post-operative). This is verified by comparing the FFR generated by pulsatile inflow simulated with the model of Bovendeerd et al. (Bovendeerd et al., 2006) and the FFR resulted of steady inflow. Both outcomes are considered equal, because the difference is smaller than 0.02, which is equal to the standard deviation of the repeatability of invasive FFR (Johnson et al., 2015).

Third, to simulation the blood pressure and flow real-time, the simulations are 1D assuming that flow is unidirectional. This is assumed to be accurate for calculation of mean pressures. This can be validated by performing the same simulations with the same boundary conditions with a 3D model and compare those results with the 1D results.
Fourth, AngioSupport consists of a multiple boundary conditions with parameters, which are population based defined. Therefore, a sensitivity analysis is performed to discover the influential parameters to subsequently couple those to patient data to define patient specific parameters. This could be validated against invasive pre- and post-FFR data.

Finally, the clinical relevance of AngioSupport should be proved by a clinical trial where a treatment plan will be defined for a group of patients based on the current procedure and for a patient group based on AngioSupport. For both groups follow-up data will be collected, such as repeated revascularization, number of stents, and end point of death and those data will be compared between the groups.

In summary, current results of AngioSupport looks promising; however, more validation must be performed to confirm its accuracy and clinical relevance.

5. References


Bibliography


