Digital twin of analogue man

Summary

Our cardiovascular system enables transportation of dissolved gases, hormones and other substances to support metabolism, growth, and repair. The system consists of an actively contracting heart, which ejects blood into conducting pulmonary and systemic blood vessels. Usually, the heart's left ventricle and the large arteries are coupled in such a way that the volume and rate of the ejected blood match the impedance of the receiving arteries. This coupling is influenced by changes in cardiac and arterial structure and function, which are interrelated through haemodynamic interactions. Therefore, measurable haemodynamic features are of (clinical-epidemiological) interest as markers of cardiovascular health. However, because such markers reflect changes 'in-between' the interacting heart and arteries, their interpretation may be tricky.

We hypothesised that an integrative description of cardiac and vascular physiology may be better suited to mechanistically explain the interrelationships between cardiac and vascular structure and function. The development and application of a computational modelling platform to assess heart-vessel interaction is the subject of this thesis.

As a first step in the development of our computational modelling platform, we performed a meta-analysis of clinical literature on heart-vessel interaction through treatment-induced changes in arterial properties on the one hand and left ventricular (LV) structure on the other hand (**Chapter 2**). Through meta-analysis, we found that a decrease in arterial stiffness is associated with a reduction in LV mass. Unfortunately, it was not possible to infer any causal relationships between arterial stiffness, blood pressure and LV structure.

To infer causality in heart-vessel interaction, we turned our attention to computational models describing circulatory physiology (**Chapter 3**) and extended the existing CircAdapt model, a well-characterised whole-heart model, with a new transmission line (TL) model that also allows for an accurate examination of wave transmission and reflections in blood vessels. The governing equations of the TL model originate from those derived in the 1880s, describing signal transduction along telegraph wires. We first verified the numerical framework of the TL model by benchmarking against a previously validated pulse wave propagation model. The results showed good agreement regarding pressure and flow waveforms (i.e. relative errors ≤2.9% for pressure, and ≤5.6% for flow). Subsequently, the performance of the combined CircAdapt–TL model was tested in a use-case, simulating carotid artery wave intensity profiles during normotensive as well as hypertensive conditions. The results of this use-case indicate that the domain of applicability of CircAdapt is extended for detailed studies on heart-vessel interaction if the TL model is included.

In **Chapter 4**, we applied the CircAdapt–TL model to scrutinise the validity of the augmentation index (AIx) as a vascular index of increased pulse wave reflections in a stiffer arterial tree. The AIx quantifies a deemed augmentation (i.e. as signalled by an inflection point) of a pressure waveform relative to its peak-to-peak amplitude. In population studies, the AIx increased with age, which is usually interpreted to result from an increase in pulse wave reflections with the age-related stiffening of arteries. We hypothesised that cardiac properties are likely to influence pressure augmentation as well because they too determine the time-course of the arterial pressure waveform. We simulated the isolated and combined influences of myocardial shortening velocity and arterial stiffness on AIx and indeed found that the AIx may depend as much on cardiac as on vascular properties, which goes against the common interpretation of the index.

In the above, our use of models focussed on evaluating hypotheses. A more advanced application would be to predict patient-specific haemodynamic changes and features, which adds the challenge of model personalisation.

Chapter 5 is the first chapter concerning personalisation of computational models. In our previous simulation studies, we prescribed generic vessel geometries for the modelled arterial and veins. Source data describing these geometries came from a collection of independent literature sources. As such, different parts of the modelled vascular tree are based on data from different subjects, differing in age, sex, BMI and other characteristics. Models containing generic descriptions of the human vasculature often appear insufficient for patient-specific predictions. Unfortunately, complete characterisations of blood vessel geometries and properties are usually not available or even attainable in practice. **Chapter 5** presents an adaptation model to complement sparse data on arterial radius and wall thickness, utilising rules for the response to wall stress and shear stress. To test our approach, we acquired vascular MRI and ultrasound data sets of arterial wall thicknesses and radii of central and arm segments in ten healthy subjects. Comparison between adaptation model-predicted and measured geometries demonstrated small differences (bias±2SD of difference equal to 0.2±2.6 mm for arterial radius, and −140±557 μm for wall thickness, respectively). We believe that our methodology is suitable to complete sparse data sets in patient-specific applications.

The subsequent two chapters employed model-based approaches for the patient-specific characterisation of LV or arterial properties, respectively. In **Chapter 6**, we used the CircAdapt–TL model to non-invasively estimate LV end-diastolic pressure (p_{ed}) and compliance (C_{ed}) from routine measurements of brachial artery blood pressure and echocardiographic recordings. We found reasonable agreement between our non-invasive estimates of p_{ed} and C_{ed} and those measured by an invasive catheter.

To improve mechanistic interpretation of clinical arterial stiffness data, inverse modelling approaches may be used to estimate tissue properties from measured vessel geometric and dynamic elastic properties. In **Chapter 7**, we utilised a constitutive model of carotid artery mechanics, describing the stress-strain behaviours of arterial collagen and elastin. As a prerequisite, we performed extensive uncertainty quantification and sensitivity analysis to investigate how measurement

errors propagate into estimation errors. We were able to substantiate that the significant uncertainty with a single set of carotid artery ultrasound and pressure data points can be reduced by increasing the number of repeated acquisitions of cyclic diameter (i.e. distension) and of wall thickness (i.e. intima-media thickness).

This thesis concludes with a general discussion (**Chapter 8**), in which we provide an overall perspective of how the above model developments and personalisation approaches may be further integrated. We envision the role of our developing computational models to facilitate 1) detailed haemodynamic studies, 2) patient-specific estimation of non-measurable characteristics, and 3) *in silico* evaluation of disease progression and treatment scenarios.