Digital twin of analogue man

Valorisation addendum

To combat cardiovascular disease and enable patients at risk to age in a healthier way, roughly two strategies can be distinguished. The first strategy consists of the identification of the cellular mechanisms responsible for cardiovascular disease followed by the development of new drugs acting on these cellular mechanisms to halt or even regress the disease ('the biologist's approach'). The second strategy consists of the earlier detection of cardiac and vascular problems by developing diagnostic technologies that characterise the mechanical performance of the heart and vessels ('the engineer's approach').

This thesis advocates the use of computational models that embody human cardiovascular physiology to achieve better characterisation of heart failure and arterial stiffness mechanisms. Ideally, computational models are so realistic that they can be regarded as **'digital twins'** of actual patients. The path towards such a digital twin comprises of both model development steps (**Chapters** 3 and 5) as well as model corroboration steps (**Chapters** 4, 6, and 7), in which the utility of the model is put to the test. Although an ultra-realistic digital twin of human cardiovascular physiology is not available yet, we contribute substantially to the development of a digital twin. It is therefore of no surprise that the present thesis readily contains significant valorisation potential: First, valorisation of the knowledge obtained in this research may advance society and the academic field as primary target groups. The second valorisation aspect represents economic exploration by transferring knowledge into new products or services through business development.

Below, I provide a discussion on both valorisation aspects.

Target groups

Pathological changes to the heart and blood vessels impact local cardiac and vascular tissue properties and influence their function. In patients, this harmful process can progress silently for years but will eventually become apparent. Therefore, assessment of tissue properties can benefit timely diagnosis of pathologies precluding cardiovascular disease. However, clinically applicable measurements alone are often insufficient to assess tissue properties. The combination of mechanistic computational models with a well-selected set of clinical measurements may allow for estimation of tissue properties, using an inverse approach, in which the model is 'tuned' to the measurements. In this thesis, we showed that an inverse approach to routine data has real potential in detecting diastolic dysfunction, a precursor of heart failure (**Chapter** 6).

Currently, assessment of left ventricular filling pressure in patients relies on a clinical algorithm that is based on three echocardiographic indices. Such an algorithm can discriminate between (four) grades of diastolic dysfunction (i.e. with increasing severity; no-, grade I-, grade II- and grade III diastolic dysfunction) [1], each of them reflecting a category of filling pressure, ranging from low to elevated [2]. However, in the absence of one echocardiographic index and conflicting results of the remaining two indices, the clinical algorithm contains a grey zone in which filling pressure is classified as indeterminate. The model-based method introduced in **Chapter 6**, –providing actual estimations of filling pressure and diastolic compliance– could be used alongside or concurrently with the existing clinical algorithm. Such methodology comes at hand when confronted with patients in which the clinical algorithm cannot determine filling pressure.

An inverse method may also be used for characterisation of vascular wall tissue. For this purpose, we did not use the circulatory computational model, but rather a more detailed model describing local arterial wall mechanics that incorporated distinct features of collagen and elastin. The method allows identification of the wall constituent that contributes the most to the increase in stiffness of a patient's arteries. As such, these models may be of use in the design of new vascular drugs (**Chapter 7**).

Parallel to providing personalised estimates, the developed computational models are useful for hypothesis testing. In **Chapter 4**, our model study challenges a widespread interpretive model in which augmentation index is deemed and promoted as an index for arterial properties. Already, an increasing number of human studies show that augmentation index might also be influenced by ventricular function and thus cannot serve as a distinct marker of arterial stiffness or wave reflection magnitude. Our study provided yet another important piece of evidence that the augmentation index does not solely reflect arterial stiffness.

While the research version of the circulatory computational model we used is implemented in a scientific programming environment (MATLAB, The Mathworks, Natick, USA), a stripped-down version of the model is also available on-line as a user-friendly 'CircAdapt simulator'. This simulator is actively used for teaching cardiovascular physiology in the (bio-)medical curricula at Maastricht University and many other universities. Currently, the simulator is capable of describing a catalogue of cardiac pathologies, including cardiogenic shock, pulmonary arterial hypertension, and valvular defects. Integration of the vascular module (**Chapter 3**) that models pressure and flow phenomena in the systemic arterial and venous circulations, further extends this catalogue. The present work paves the way for simulation-based education with even more (vascular) types of pathology. Examples of pathologies as well as their recommended clinical assessment methods include, e.g. 1) arterial stiffening; quantifiable using carotid-to-femoral pulse wave velocity, and 2) peripheral arterial disease; assessable using the brachial-ankle index, respectively.

Utilisation of knowledge for the development of products or businesses

First, the circulatory computational model is of interest to medical device and (health) technology companies. For example, Samsung and Apple have shown interest in developing wearables (e.g. smartwatches) to be used for continuous measurement of the arterial pulse waveform. Samsung's approach uses a smartwatch to measure the photoplethysmogram (PPG) at the location of the radial artery [3]. Specific features of the wrist-measured PPG waveform are hypothesised to be indicative of vascular conditions such as arteriosclerosis, but also of psychological conditions, including mental stress. Both arteriosclerosis and mental stress are known risk factors of cardiovascular disease [4]. Information from continuous monitoring of arteriosclerosis and mental stress could thus be used to identify patients at risk of cardiovascular disease. Computational models like ours are very well suited to (pre-)test and select sets of PPG features that are sensitive for (changes in) arterial and mental health.

Second, the developed methodologies for determining on the one hand left ventricular diastolic indices and on the other hand, arterial wall constituent properties are already well-suited to be integrated as separate cardiac- or vascular workflows in ultrasound machines. When selecting either of the workflows, the corresponding computational model should be initiated, for example as a third-party application, and the user should be guided to perform the measurements that are required to complete or augment the analysis. These computational model approaches to the interpretation of echocardiographic-, and blood pressure data are of interest to companies, such as Microlife Corporation, IMEC, Pie Medical Imaging, and Philips Medical Systems. Partnerships with these companies can be beneficial in two ways. First, third-party integration projects will generate revenue for the Department of Biomedical Engineering, which can be allocated to the hiring of staff or investments in computational resources. Second, partnerships could also include setting up new research and development projects, thereby providing opportunities to further develop our algorithms (e.g. using machine learning methods based on large clinical data sets).

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