# Master's Thesis Summary:
# *A 0D-1D global, closed-loop model of the cardiovascular system*

Stefano Costa

## Motivations

Understanding the complex interactions between the heart and the arterial and venous networks in both physiological and pathological scenarios remains a significant challenge in cardiovascular research. Computational models show promise as effective tools for exploring these complexities; however, addressing methodological challenges is essential for a comprehensive study (Morris et al. 2016).

The aim of this thesis is to couple two cardiovascular models with distinct characteristics to enable an in-depth study of the interplay between the heart and the vascular system. A first step towards this implementation has been proposed in (Heusinkveld et al. 2019), yielding promising results. However, the model in that work carries significant limitations: convective acceleration is neglected, cerebral and coronary vessels are not included in the vessel network, venous valves are not incorporated, and blood vessels are assumed to be non-linear elastic tubes. The aim of this project is to use a more accurate model for the systemic circulation (the ADAVN model) to achieve results that more closely resemble realistic anatomical and functional situations.

The CircAdapt model (Lumens et al. 2009) is a 0D cardiovascular model, developed at the Maastricht University and implemented at the Medical University of Graz, and it is used for the simulation of the heart function. The ADAVN model (L. O. Müller et al. 2023), a 1D anatomically detailed cardiovascular model developed at the University of Trento in collaboration with Hemolab, LNCC (Brazil), is employed for the vascular network. These models were selected for their distinctive features, including CircAdapt's ability to provide fast simulations of heart function under various pathological conditions and ADAVN's capacity to offer detailed, anatomically precise simulations of the vascular network.

## Investigation Methods

Descriptions of the models used follow.

The ADAVN model employs one-dimensional blood flow equations to model the evolution of lumen area A, flow rate q, and pressure p in the space-time domain. The one-dimensional blood flow model employed is characterized as an advection-diffusion-reaction system, described by the following equations (L. O. Müller et al. 2023):

$$\begin{cases} \partial_t A + \partial_x q = 0, & \text{Mass conservation} \\ \partial_t q + \partial_x \left(\frac{q^2}{A}\right) + \frac{A}{\rho}\partial_x p = -\frac{f}{\rho}, & \text{Momentum balance} \end{cases}$$

where $f(x,t) = 8\pi\mu\frac{q}{A}$ represents the friction force per unit length, $\mu$ is the fluid viscosity and $\rho$ is the fluid density.

To differentiate the mechanical behaviour between arteries and veins, which vary due to anatomical characteristics, distinct tube laws are applied for arteries (Blanco et al. 2014) and veins (Eleuterio Francisco Toro et al. 2022). Additionally, mass and energy conservation are enforced at bifurcations/junctions between arteries/veins. The coupling conditions in the ADAVN model extend beyond basic wave relations at junction points, employing generalized Riemann invariants to preserve conserved quantities in hyperbolic systems. These invariants facilitate

effective coupling of one-dimensional vascular domains to peripheral circulation models and ensure the conservation of mass and energy at critical points such as the right atrium and the aortic valve (L. Müller et al. 2015).

The one-dimensional blood flow model is hyperbolized to form a system of first-order partial differential equations suitable for biomedical applications (Montecinos et al. 2014). This system is discretized using a second-order finite volume scheme with explicit local time stepping, ensuring high-order accuracy (L. Müller et al. 2015)(Lucas O. Müller et al. 2015). The numerical methods include the ADER framework and the Dumbser-Enaux-Toro method for solving the generalized Riemann problem (E. F. Toro 2020)(Dumbser et al. 2008).

Time steps are synchronized across the network to maintain stability and are kept constant unless local flow conditions dictate adjustments. Additionally, ordinary differential equations for lumped parameter models, such as those for valves and systemic resistors, are integrated using an explicit Euler method.

The CircAdapt model represents the entire cardiovascular system as a concatenation of modules: a tube module representing the systemic and pulmonary arteries and veins; a chamber module modeling actively contracting chambers (left and right atria and ventricles), where myofiber mechanics and contraction is described by a sarcomere module; inter-ventricular mechanical interaction is modeled through the septum; a valve module representing the aortic, mitral, pulmonary, and tricuspid valves; a module representing systemic and pulmonary microvasculature; and a module accounting for effects of the pericardium. The modules are connected by flows over valves and venous-atrial inlets (Augustin et al. 2021).

Sarcomere mechanics is characterized by an ordinary differential equation that defines sarcomere active stress, which includes sarcomere contracting length, contractility, and passive stress. Passive stress is considered as the sum of the stress due to cellular structures and the extracellular matrix, respectively (Lumens et al. 2009)(Walmsley et al. 2015).

An actively contracting chamber is modeled as a closed sphere using the volume, length of the contractile element of the sarcomere and contractility as state variables. Changes in midwall volume and area are driven by inflow and outflow of blood (Walmsley et al. 2015).

Cavity pressures and cavity volumes are interconnected as follows: volumes regulate cavity wall areas, which in turn determine strain of the myofibers in the wall. Strain is used to calculate myofiber stress, which drives wall tension in each cardiac wall. Midwall tension $T_c^{\text{mid}}$ and midwall area $A_c^{\text{mid}}$ are connected to fiber stress $\sigma_c^{\text{fib}}$ and strain $E_c^{\text{fib}}$ through the law of conservation of energy. Using the law of Laplace, one can obtain:

$$T_c^{\text{mid}} dA_c^{\text{mid}} = \sigma_c^{\text{fib}} V_c^{\text{wall}} dE_c^{\text{fib}},$$

where $V_c^{\text{wall}}$ is constant wall volume.

Cavity pressures are then found by adding the transmural pressures to the intra-pericardial pressure surrounding the myocardial walls. Consecutively, cavity pressures are used to update flow over valves and thus intra-cavitary volume (Augustin et al. 2021).

The core of the model consists of a system of 26 differential equations related to state variables over time (Arts et al. 2005):

- 8 ODEs: for volume updates, one ODE for each of the four tubes and four cavities.
- 2 ODEs: for midwall volume and radius updates, used for the septum.
- 10 ODEs: for sarcomere contracting length and contractility updates, used for the sarcomeres and the septum.
- 6 ODEs: for flow updates, one ODE for each of the four valves and the two outlets.

The system of 26 ordinary differential equations is solved using the Runge–Kutta–Fehlberg method, as referenced in (Hairer et al. 1993).

The coupling of the two models enables detailed analysis of the interactions between the heart and the circulatory system, with an emphasis on venous return, while maintaining low computational costs. The use of a 1D model for blood flow also allows for efficient analysis of wave propagation phenomena. The coupling is designed to preserve the individual functionalities and characteristics, ensuring seamless communication without interference. The codes of both models are adapted to allow information exchange, and appropriate coupling conditions are imposed to maintain coherence and consistency.

The project has been planned to fit within a six-month schedule. It began with the familiarization with the existing models and a detailed exploration of the numerical discretizations, focusing on how the coupling conditions between arterial, venous circulation, and cardiac model are achieved. Following the initial phase, the CircAdapt and the ADAVN models are currently being modified to enable the exchange of coupling variables and to implement the coupling strategy. The obtained coupled model will then be tested against physiological data from the literature. The project will conclude with the application of the model to simulate selected pathologies, assessing their observability in the arterial and venous systems and evaluating the impact of changes within these systems on the pathologies.

## Expected results

At the conclusion of the project, a 0D-1D global, closed-loop model of the cardiovascular system will be developed. The model's output will be validated against physiological data from the literature.

The validated model will achieve a level of accuracy and detail previously unattainable by the standalone versions of ADAVN or CircAdapt models. This novel model will allow to study the impact of certain cardiac pathologies on hemodynamics, as well as to verify whether such pathologies are observable by hemodynamic variables. In addition, as the CircAdapt model is modular, further improvements (currently under development in Trento under the supervision of Prof. Pezzuto) will be incorporated, allowing the range of pathologies and the capabilities of the simulations to be expanded.

The list of planned simulations, which is not final, includes several scenarios. Firstly, the reference simulation will serve as a benchmark for comparison with scientific literature. Regarding pathologies, the CircAdapt model will be used to simulate various cardiac conditions. Tricuspid regurgitation will be simulated by increasing the tricuspid valve leak, causing retrograde blood flow in the venous system during ventricular systole. This will allow for an investigation into the effects of this condition on venous pressure and return, as well as on the propagation of pressure waves in the venous system. Congestive heart failure will be modeled by reducing ventricular volumes, impairing the heart's ability to pump blood efficiently. This setup will enable an analysis of how cardiac insufficiency affects venous pressure and blood volume.

Further simulations will be done using the multipatch enhancements developed in Trento to study in detail the impact of electrophysiological phenomena. An example of such a simulation involves atrial fibrillation, a condition that can only be studied indirectly and with little precision by standalone models.

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