MOCK CIRCULATORY LOOPS USED FOR TESTING CARDIAC ASSIST DEVICES: A REVIEW OF COMPUTATIONAL AND EXPERIMENTAL MODELS

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ABSTRACT

Heart failure is a major health risk, and with limited availability of donor organs, there is an increasing need for developing cardiac assist devices (CADs). Mock circulatory loops (MCL) are an important in-vitro test platform for CAD's performance assessment and optimization. The MCL is a lumped parameter model constructed out of hydraulic and mechanical components aiming to simulate the native cardiovascular system (CVS) as closely as possible. Further development merged MCLs and numerical circulatory models to improve flexibility and accuracy of the system; commonly known as hybrid MCLs. 128 MCLs were identified in a literature research until 25 September 2020. It was found that the complexity of the MCLs rose over the years, recent MCLs are not only capable of mimicking the healthy and pathological conditions, but also implemented cerebral, renal and coronary circulations, and autoregulatory responses. Moreover, the development of anatomical models made flow visualisation studies possible. Mechanical MCLs showed excellent controllability and repeatability, however, often the CVS was overly simplified or lacked autoregulatory responses. In numerical MCLs the CVS is represented with a higher order of lumped parameters compared to mechanical test rigs, however, complex physiological aspects are often simplified. In hybrid MCLs complex physiological aspects are implemented in the hydraulic part of the system, whilst the numerical model represents parts of the CVS that are too difficult to represent by mechanical components per se. This review aims to describe the advances, limitations and future directions of the three types of MCLs.

INTRODUCTION

As of April 2020, in the UK solely, 340 patients are on the active heart transplant list, while only 172 transplants are available.[1] Cardiac Assist Devices (CADs) are an alternative solution to heart failure patients.[2] Implantable Ventricular Assist Devices (VADs) are used as a bridge-to-transplant or permanent support for severe heart failure patients with cardiogenic shock and multiple organ dysfunctions [3] and have substantially improved survival–rates for patients who are awaiting heart transplantation.[4] Due to recent technical advances of VADs, destination therapy became a genuine long-term solution for heart failure patients.[5] However, serious adverse events remain high after VAD implementation: between 2015-2019 causes of death in patients with VAD support were, for example, due to multisystem organ failure (16.4%), neurologic dysfunction (15.6%) and heart failure (12.5%).[2] Thus, ongoing research is needed to enhance VADs as a solution to the increasing donor shortage.

The Mock Circulatory Loop (MCL) plays a key role in the design, development and in vitro assessment of VADs and other CADs (e.g. vascular stents, heart valves, and Intra-Aortic Balloon Pumps (IABP)). In vitro studies are preferred over in vivo studies when quantitative investigation and adoption of specific, controlled, physiological parameters are needed. Moreover, in vitro studies do not require ethical approval and are much more cost-effective than animal studies. Therefore, MCLs are widely used prior to in vivo studies. The MCL aims to mimic the structure and function of the native cardiovascular system (CVS) by providing a realistic test-bench for performance assessment. It simulates hemodynamic parameters like heart rate, ventricle contractility, peripheral resistance, arterial compliance, and fluid inertance under healthy and various degrees of pathological conditions. These parameters are adapted to obtain physiological pressure and flow waveforms. MCLs are employed to study, for example, the fluid balance between the systemic and pulmonary circulation of an adult patient [6], the timing of IABP inflation [7], the unloading effect of a rotary blood pump [8] and to study the hemodynamics of artificial heart valves [9], extracorporeal life support [10] or biventricular assist devices.[11]

Three different types of MCLs exist: firstly, the mechanical MCLs (M-MCLs), which simulates the CVS using mechanical and hydraulic components. M-MCLs were the first type of MCLs developed, see Figure 1. M-MCLs represent the ventricles with hydraulic pumps, the arterial compliance by water and air-filled, reservoirs (or flexible tubes), and the resistance is simulated by obstructions of the flow path. M-MCLs can test various CADs and pathological conditions. However, the fixed design limits the range of applications.

Numerical models of the CVS develop in parallel to M-MCLs, in which the CVS is described with mathematical expressions. Numerical MCLs (N-MCL), that are reviewed in this paper are lumped parameter models. They have absolute reproducibility, controllability and are more flexible than M-MCLs. However, they neglect or simplify physiological aspects and complex properties of the CVS (e.g. wave travel and turbulence).

Merging N-MCLs and M-MCLs defines a third group of MCLs: hybrid MCLs (H-MCLs).[12] In an H-MCL the numerical and mechanical parts run alongside and communicate with each other in real-time using a numerical-hydraulic interface. The H-MCL can describe cardiovascular characteristics using computer algorithms that are too difficult to represent with mechanical components and provides a hydraulic platform to connect the physical prototypes of CADs. Within the next few years, H-MCLs are likely to become an essential test-bench for CADs development.

[insert Fig. 1]

Baturalp and Ertas[13] recently conducted a review of the driving system of MCLs. Furthermore, Shi et al. presented a comprehensive review of the build-up [14] and general structure [15] of MCLs. The focus of these reviews was on M-MCLs. Our review presents an overview of the three types of MCLs and will provide insights into the technological advances and features of the MCLs over the years.

The first section presents a brief overview of the cardiovascular system. The second section explains computational modelling. The next section of the review outlines the methodology of the literature search. The main body of this review then describes the development of the three different types of MCLs. The conclusion draws on the limitation of the current systems and gives an outlook on the future directions of MCLs.

THE CARDIOVASCULAR SYSTEM

The MCL aims to replicate the function and structure of the native CVS as closely as possible. Briefly, the CVS comprises of the heart, the systemic vessels that carry the blood to peripheral organs, and the pulmonary vessels, that carry the blood to the lungs where it gets oxygenated. The contraction of the heart produces a pressure and flow wave that propagates along the arterial tree. The left and right side of the heart that supply the systemic and pulmonary circulation respectively, are a pulsatile pump composed of two chambers: the ventricles, the main pumping force, and the atrium, which provides the ventricle with blood. The left and right ventricles must overcome the systemic vascular resistance (SVR), and the pulmonary vascular resistance (PVR), respectively, to push blood through the aorta into the arterial bed.

The CAD to be studied mainly decides which features of the CVS are important to integrate in the MCL for performance assessment. VADs, biVADs or total artificial hearts (TAHs) require a model of the pulmonary and systemic circulation. The challenge of developing a TAH or VAD is to adequately maintain fluid balance between both circulations. The difficulties arise as part of the left ventricular output returns to, not the right, but left atria via the bronchial arteries, whereas the right ventricular output is completely directed towards the left atrium. Therefore, left ventricular output is higher than the right. Insufficient fluid balance of VADs or TAHs can lead to suction events which can lead to reduced cardiac output. To study the performance of an IABP the implementation of the coronary circulation and its autoregulation is recommended. The coronary flow is highest during diastole, as during systole the ventricle constricts the coronary artery. The IABP aims to increase mean arterial pressure and myocardial perfusion during diastole. It is positioned inside the aorta, and therefore, to study the performance in an MCL a model of the aorta is required.

REGULATORS OF THE BLOOD FLOW IN THE CARDIOVASCULAR SYSTEM

Multiple regulatory mechanisms of the CVS are able to increase cardiac output or redirect blood towards active tissue. The volume of blood flow of the heart is regulated by the heart's intrinsic ability to adapt to increasing volume of inflowing blood, known as the Frank-Starling mechanism. The Frank-Starling mechanism states that the greater the heart muscle is stretched during filling, the greater is the force of contraction and the greater the stroke volume. The Frank-Starling mechanism enhances venous return to the heart, for example, during exercise. Moreover, the heart can compensate for the reduced cardiac output in heart failure patients to maintain sufficient organ perfusion.

The CVS can also regulate blood flow by redirect the blood towards active tissue, for example, when exercising more blood is needed in the skeletal muscles, heart and lungs. The autonomic nervous system plays a key role in the regulation of vascular homeostasis. The heart rate can be changed by the sympathetic and parasympathetic nerves, which respond to a fluctuation in mean arterial pressure. The sympathetic nervous system innervates small arteries, which can constrict arterioles throughout the body. This increases the blood volume in larger arteries and as a result, mean blood pressure. Sympathetic nerves also innervate the veins, controlling the venous reservoir and heart preload. The parasympathetic nerves innervate the heart, they can decrease heart rate and ventricular contractility.

The most well-known nervous response mechanism is the baroreceptor reflexes. The baroreceptors are primarily found in the sinuses of the aorta and the carotid arteries. The baroreceptors respond to a change of stretch in the blood vessel. Increased blood pressure will stretch the baroreceptors more

tightly, initiation action potentials at a higher rate. The sympathetic nerves will, in a response to the increase action potentials, dilate peripheral arterioles and thus reducing the blood pressure. The baroreceptors in the venae cavae and right atrium monitor the blood pressure as the blood returns from the systemic circulation, ensuring that blood ejected by the left ventricle is equal to the blood flow into the right atrium. When blood flows into the right atrium is more rapidly than the ejected blood of the left ventricle, the arterial receptors will increase the cardiac output until homeostasis is achieved. A schematic overview of the reaction of the baroreceptors to a change in mean arterial blood pressure is given in Figure 2. The baroreceptors can detect even the slightest change in pressure, which is especially important when a person stands up after laying down. The falling pressure at the baroreceptor elicits an immediate reflex to compensate for the decrease in pressure in the cerebral circulation and upper body.

[Insert Fig. 2]

COMPUTATIONAL MODELS OF THE CARDIOVASCULAR SYSTEM

The CVS can be modelled computationally from 0D to 3D models depending on the aims and accuracy of the study. In Figure 3, the different dimensional models are represented. 0D models, also known as, lumped parameter models reduce the components of the CVS into electrical elements.[16,17] 1D models of the CVS are able to describe the pulse wave transmission within the vasculature, and can be used to study, for example, the blood flow around stents.[18] 2D models can be used to study the local flow velocity in axisymmetric domain, for example, to study prosthetic valves.[19] With 3D models, complex flow patterns can be studied, however, they are computationally very demanding. [20]

Hales was the first one in 1733 to introduce a conceptual lumped parameter model of the arterial tree. He observed that the variation of pressure in the arterial system is related to the elasticity of large arteries. Weber was the first to compare the elasticity of the arteries with the Windkessel, in which the pulsatile pump is damped by an air chamber. Frank was the first to mathematically describe the arterial response with a so-called two-element Windkessel model, using an electrical resistor and a capacitor to represent the SVR and the total arterial compliance, respectively.[21] Three and four-element Windkessel models were later developed to increase the accuracy of the impedance.[22] Although the Windkessel elements do not simulate a specific vessel, they demonstrate good arterial impedance over a wide range of frequencies of the physiological heart rate.[23]

[insert Fig 3.]

METHODS

The literature is researched for MCLs of the CVS from the earliest possible start date until 25 September 2020 in SCOPUS. The search focusses on English peer-reviewed articles and conference papers.

The following search string: '*Mock Circulatory Loop OR Mock Circulatory System AND Cardiac Assist Device OR Ventricular Assist Device OR Biventricular Assist Device OR Total Artificial Hearts OR Mechanical Heart Valves OR Intra-Aortic Balloon Pump*' identified the start set of papers. Backward reference searching identified other relevant papers, see Figure 4.

[Insert Fig. 4]

This paper solely includes N-MCLs of lumped parameter models. For reasons of space, numerical models that were exclusively used to study wave phenomena and not CADs performance were not addressed in this paper.

MOCK CIRCULATORY LOOPS: EARLY BEGINNINGS

The M-MCLs adapted lumped parameter modelling into a physical test rig: electrical components were replaced by their hydraulic equivalents. A typical M-MCL set up is illustrated in Figure 5. The compliance of vessels was modelled by Windkessel chambers, a closed water reservoir with a trapped volume of air above the water level [24–26], occasionally using spring capacitors [27,28], or flexible tubes.[29,30] The resistance of arteries was modelled by adding an obstruction in the flow path using, for example, swing check valves [25] or throttles [9], which mimic vasoconstriction. The inertance of the system is dependent on the fluid density and the tube's dimensions.

[Insert Fig. 5]

Preliminary work on M-MCLs was focused on testing artificial heart valves [26,31] and occasionally TAHs.[25,32,33] Donovan et al. developed a compact MCL in which the systemic and pulmonary circulations were simulated using a two-element Windkessel model [25], adopted by many others.[33–37] They were the first ones to attempt implementation of a simplified version of the baroreceptor response; SVR and PVR were automatically set using bellow operated valves.[25]

The abstracted Windkessel models of the CVS in M-MCLs provided an important in vitro test platform for artificial blood pumps and heart valves. However, it does not allow the study of wave propagation, a limitation of using Windkessel modelling. Reul et al. [38] were early pioneers in the development of a hydromechanical model of the arterial systemic circulation with approximated geometry and elastic properties of arteries. Although the model could not be used for CAD's performance assessment, it is a valuable in vitro tool to study haemodynamic properties of the arterial system.

ADVANCES OF THE MOCK CIRCULATORY LOOPS

COMPUTER CONTROLLED DRIVING SYSTEMS

Pneumatic [26,39] and hydraulic [31,40] pumps were used to drive early M-MCLs. To improve the reliability and comparability of M-MCLs, Verdonck et al. [41] developed a computer-controlled in vitro model of the left heart for testing artificial heart valves. The silicon models of the left atrium and ventricle were placed within a water-filled housing, where the amount of pressure was controlled by a feedback system. The system was able to regulate left arterial filling pressure and, arterial and ventricular contraction, relaxation and heart rate. Also Left Ventricular Assist Devices (LVAD) have been used to generate realistic flow conditions controlled by a pneumatic apparatus.[42]

By introducing computer-controlled ventricles in the M-MCL, researchers gained the ability to alter cardiac output which allowed simulation of exercising conditions [43–45] and pathological conditions such as congestive left heart failure [39,46–51], right heart failure [46], valve regurgitation [52,53] and cardiac arrhythmias.[54] Timms et al. [55] used a pneumatic ventricle in an M-MCL to simulate normal and heart failure at rest by adjusting mean arterial pressure, heart rate, contractility, SVR, PVR and arterial compliance. Cardiac output was reduced from 5.15 L/min to 2.7 L/min for healthy and left heart failure patients, respectively. The M-MCL was later used for VADs performance assessment.[56,57] Similar conditions were reproduced by Pantalos et al. who manipulated driveline pressure and SVR resulting in a reduction of cardiac output from 5.0 L/min to 3.0 L/min.[27] Whilst Tsuboko et al. [58] simulated right heart failure by regulating the atrioventricular interaction. Similar heart conditions were simulated in N-MCLs [59], by reducing the compliance of the left ventricle.

FRANK STARLING MECHANISM

The Frank-Starlings mechanism was implemented into MCLs, by using the computer controllable ventricles.[27,60,61] MCLs including Frank-Starling mechanisms describe the interaction of the CADs with the CVS more closely [62], whilst MCLs without preload and afterload response will produce unphysiological results.[63] Early researchers implemented the Frank-Starling mechanism [17,63–66] using the time-varying elastance model of Suga-Sagawa.[67] Baloa et al. [63] were among the firsts to implement this elastance model into an M-MCL. In this model, the elastance of the left ventricle is linearly related

to ventricle volume and pressure. Baloa et al. [63] reported a left ventricular elastance (i.e. the gradient of the end-systolic-pressure-volume curve) in the range of 2.14 mmHg/ml to 2.27 mmHg/mL. Yokoyama et al. [68] reported a linear elastance curve ranging from 1.75 to 0.56 mmHg/ml in their M-MCL, which can simulate healthy and heart failure conditions.

Burkhoff et al. [69] questioned the assumption of the linear end-systolic-pressure-volume relationship in humans and noted that the time-varying elastance model inadequately describes the contractility of the left ventricle under diseased and cardiac support conditions. Furthermore, Vandenberghe et al. showed in an in vivo experiment that the time-varying elastance model insufficiently represented the left ventricle under mechanical support.[70] Moreover, in MCLs using the linear elastance model [63,64,71], the end-systolic-pressure-volume curve crosses the volume axis at a negative value, which suggests a negative unstressed ventricle volume.

Colacino et al. [72] adapted the linear time-varying elastance model to a non-linear elastance variant and proved through a numerical and experimental validation that the non-linear elastance model can simulate the preload and afterload sensitivity of the natural ventricle more closely. Other researchers used a natural logarithmic elastance model [73] and look-up tables.[16]

PHYSICAL ANATOMICAL MODELS

In parallel with the development of the mock ventricles, researchers implemented anatomical models for flow visualisation studies and higher-order Windkessel models of the systemic and pulmonary circulations. Five-element Windkessel models were introduced to simulate both systemic and pulmonary circulations.[74] Anatomical models of arterial beds [7,75] and pulmonary trunks [76] were developed to study haemodynamics of CADs. Patient-specific left ventricles were developed to assess intraventricular balloon pump [77] and for in vitro flow visualisation studies.[78–81] Several studies include anatomical models of the aortic arch [78,82,83], for example, Litwak et al. used an anatomical model of the ascending and descending aorta to study the aortic blood flow of continues flow and pulsatile flow VADs.[84] Geier et al. [82] used an aortic model to study different cannulation types of extracorporeal membrane oxygenation. And Peter et al. [83] developed an anatomical model of the aorta including renal circulation to study wave travel.

More complete anatomical models of the systemic circulation have been developed by Kolyva et al. [7] and Gehron et al.[10] Kolyva et al. tested an IABP on an M-MCL with an anatomical model of the aorta and twelve of its largest branches.[7,85] Local compliance and resistance were simulated using syringes of varying air volume and capillary tubes of different sizing at the outlet of the branches. Gehron et al. [10] made a life-sized arterial bed of the venous and arterial circulation which allowed visualisation and quantification of flow phenomena of the CVS under extracorporeal life support. In this study the local compliance values could not be changed; however, resistance could be adjusted using variable Hoffman clamps which increased or decreased vessels diameter.

Refinement of the anatomical models of the pulmonary circulation was achieved by Knoops et al. [76], Mueller et al. [86], and D'Souza et al. [87]. Knoops et al. [76] analysed the pulmonary hemodynamics by recreating an anatomical model of the pulmonary trunk with two generations of bifurcations. Their research showed the possibility of recreating patient- and pathology-specific models for haemodynamic investigations. Mueller et al. [86] developed a pulmonary M-MCL with an anatomical model of the right heart to study the effects of CADs on the pulmonary circulation. The M-MCL was able to mimic a healthy pulmonary condition, mild and severe pulmonary hypertension and right heart failure. D'Souza et al. [87] recreated a patient-specific 3D model of the proximal pulmonary artery used as a vascular test device. The model was evaluated in an M-MCL of the pulmonary circulation to evaluate hemodynamics. The pulmonary circulation has been redefined in a computational model by King et al.[88] In this study, a computational Windkessel model was developed to simulate patient-specific pulmonary conditions.

CORONARY, CEREBRAL AND RENAL CIRCULATION MODELS

Another important development of MCL is the implementation of the coronary circulation. Geven et al. [89] were among the firsts to accurately mimic this. The native coronary circulation supplies the heart muscle with blood during diastole, whereas in systole the coronary vessels are compressed due to the high ventricular pressure. The heart can regulate the amount of blood flow into the coronary arteries via vasoconstriction or vasodilation. Geven et al. [89] simulated the coronary vessel with a tube that collapses under ventricular pressure. The autoregulation of the coronary blood flow was presented as a clamp between the myocardial circulation and the coronary artery. Other researchers simulated the coronary circulation using a dynamic resistor in M-MCLs [27] or in N-MCL by connecting left ventricle output with right atrium input.[90,91]

Rezaienia et al. [92,93] implemented the coronary circulation with autoregulatory mechanism and aortic anatomical model in an M-MCL. The M-MCL also included the hemodynamic response of the cerebral autoregulation while operating a mechanical circulatory support device in the descending aorta. The dilation and constriction of the cerebrovascular system and coronary system was mimicked with pinch valves. Similar techniques have been used to simulate the autoregulation of the renal circuit in M-MCL as well.[94]

More recently, Gregory et al. [95] managed to replicate physiological accurate waveforms with an M-MCL that simulates systemic, pulmonary, cerebral and coronary circulations. The hemodynamic response of the M-MCL was validated using impedance cardiography data from healthy humans. The Frank-Starling response of the ventricles and the cerebral and coronary autoregulation were included. Furthermore, Clark et al. [96] introduced the cerebral circulation in an N-MCL and M-MCL to study the effect of thromboembolism and Bozkurt [97] modelled the cerebral circulation including the circle of Willis in an N-MCL.

HYBRID MOCK CIRCULATORY LOOPS

Numerical models of the CVS form the basis of the H-MCL, part of the model is presented by a hydraulic [98] or an electrical section.[99,100] The difficulty in the development of H-MCLs is achieving a fast and accurate numerical-physical interface, i.e. the interaction between the numerical and physical model and the CAD. This interaction is achieved with sensors, actuators and fast responding control systems. In electrical-numerical MCLs, the interface is achieved by voltage-controlled current and voltage generators.[101] Ferrari et al. created a numerical-hydraulic interface using DC motor driven gear pumps; atrial and arterial pressure were acquired from the hydraulic circuit and are used as two input variables for the numerical part.[100] Output flow is computed in the numerical model and sent to a DC motor and servo amplifier to control the flow of the gear pump in the hydraulic circuit. The same interface has been adopted by others.[102] This H-MCL was used to test VADs and IABPs, in which the CADs were connected to a physical arterial tree or aorta.[29,98]

Alternatively, Ochsner used two pressure-controlled reservoirs and a flow probe as a numerical-hydraulic interface to test TAHs.[103] This interface is similar to others, instead, SVR was adjusted to elicit changes in vasculature pressure.[104–106] Recently, Mirzaei et al. [107] studied the coupling of a physical experiment with multiple branches with a lumped parameter computer simulation. The numerical-hydraulic interface has been tested to show its applicability, however, has not been used to study CADs yet. Others have developed an H-MCL to test cardiac compression devices; an apparatus that wraps around the heart to provide beating assistance.[108,109] The physical part of the H-MCL, mechanical ventricles, interacted with a numerical model of the CVS. The contraction of the CAD is measured with a force sensor, which is used as input to the numerical model. The computational model uses the force measurement to calculate the cardiac output and venous return of the heart. The diameter of the simulated ventricles was calculated, from the cardiac output and venous return, and adjusted in the physical system using a swing-arm actuator.

The Frank-Starling mechanism has also been widely adopted in H-MCL using Sagawa's [67] variable elastance model [100] or using a time-varying wall stress function.[108] Ochsner et al. [103] used the non-linear elastance model of Colacino et al. [110]in their H-MCL, while Hanson et al. [108] used a numerical heart model of Urbaszek and Schaldach.[111] H-MCL were also able to simulate pathological states, such as reduced left ventricular elastance [29,101,112,113] and reduced ventricular contractility.[103,108]

BARORECEPTOR RESPONSE

Ochsner et al. [103] evaluated the performance of VADs on an H-MCL with baroreceptor response. The baroreceptor response adapted SVR and PVR when the pressure in the arterial system changed while keeping the heart rate constant. Fresiello et al. [114] studied IABP timing on baroreceptor activity and the VAD's performance [115] with an H-MCL. The baroreceptor response was based on the mathematical description by Ursino [116], change in mean pressure affected heart rate, SVR and venous volume. Cuenca-Navalon et al. used an H-MCL to study TAHs which included a numerical model of the baroreceptor response [117] in which SVR and venous volume were adopted to maintain mean arterial pressure. Heart rate changes and contractility were not included in this model, as the TAH to be tested should be able to replicate these native feedback mechanisms.

The baroreceptor response has been studied in M-MCLs as well. Mushi et al. adopted Ursino's model [118] into a continuous flow M-MCL.[119] The computational model, calculated heart rate, ventricular contractility and SVR from mean arterial pressure. Heart rate and ventricular contractility were changed in the physical model by adapting the speed of the centrifugal pump. SVR was adjusted with a pressure valve.[120] Jansen-Park et al. managed to fully implement the Frank-Starling mechanism and baroreceptor response into an M-MCL.[121] The mean arterial pressure was regulated by changing the heart rate, contractility, SVR and unstressed venous volume. The baroreflex response implemented by Vaes et al. [122] was based on a mathematical model by van Roon et al. [123] in which the baroreceptor response readjusted systemic pressure by changing the heart rate.

Lastly, Bozkurt et al. [124] investigated their newly developed continues flow LVAD using an N-MCL including baroreceptor response and healthy and pathological hemodynamics. Similarly, Bonnemain et al. [125] used an N-MCL including baroreceptor response to study the hemodynamics of a continues flow LVAD on the location of the anastomosis. An overview of MCLs that included the baroreflex mechanism is given in Table 1.

Table 1: Overview of the baroreflex mechanisms implemented in MCL. The table specifies which parameters of the baroreflex mechanism are considered.

		Feedback Mechanism			
First Author	**Type**	**Contractility**	**Resistance**	**Unstressed volume**	**Heart rate**
F.M. Donovan[25]	M-MCL	Not Considered	Considered	Not Considered	Not Considered
X. Ding[126]	N-MCL	Not Considered	Considered	Not Considered	Considered
M. Vaes[122]	M-MCL	Not Considered	Not Considered	Not Considered	Considered
F.M. Colacino[110]	M-MCL	Not Considered	Considered	Not Considered	Not Considered
S. Mushi[119]	M-MCL	Considered	Considered	Not Considered	Considered
S. Bozkurt[124]	N-MCL	Not Considered	Not Considered	Not Considered	Considered
J. Bonnemain[125]	N-MCL	Considered	Considered	Considered	Considered
G. Ochsner[103]	H-MCL	Not Considered	Considered	Considered	Not Considered
E. Cuenca-Navalon[117]	H-MCL	Considered	Considered	Considered	Considered
L. Fresiello[114]	H-MCL	Considered	Considered	Considered	Considered
S. Schampaert[127]	M-MCL	Not Considered	Not Considered	Not Considered	Considered
S.H. Jansen-Park[121]	M-MCL	Considered	Considered	Considered	Considered
A. Petrou[6]	H-MCL	Considered	Considered	Considered	Considered

DISCUSSION AND CONCLUSION

Ever since the development of one of the first MCL [32], their numbers and complexity rapidly rose over the years. MCLs play a key role in the development of a wide range of CADs. The MCLs's repeatability, flexibility and controllability make it a valuable platform to access CADs performance preliminary to in vitro studies. An increasing number of researchers have developed a system which is capable of reproducing a wide variety of patient conditions, including rest [55], exercise [44], different degrees of heart failure [50,128], hypertension [46] and valve insufficiencies.[6] The recent study of Gregory et al. [95] showed the excellent controllability and flexibility of the M-MCL. They studied the hemodynamics of simulated patients in resting, exercise and left heart failure conditions with and without ventricular support. However, the M-MCL lacked implementation of the baroreceptor response. Alternatively, Shi et al. [17] studied the hemodynamics responses of different VADs in their N-MCL, but the numerical representation of the VAD does not allow for the study of complex hemodynamic effects. Thus, the solely hydraulic or computer-based platform does not always provide the flexibility that is required for a full performance assessment of CADs.

Table 2: Comparison table between the different MCLs.

	M-MCL	N-MCL	H-MCL
High flexibility	✗	✓	✓
Compact	✗	✓	✓
Physical prototype	✓	✗	✓
Numerical prototype	✗	✓	✓
High reproducibility	✗	✓	✓
Complex hemodynamic effects	✓	✗	✓

The hybrid platform allows interaction between the physical prototype and the numerical model of the CVS. This gives the advantage to use the hybrid platform over the solely mechanical or computer-based ones, a comparison between the systems is made in Table 2. The H-MCL of Petrou et al. [6] showed the unique versatility of the hybrid platform. The numerical part of the H-MCL can easily be changed from the native CVS to the Fontan circulation. Moreover, the mechanical valves can be removed, which makes the hybrid platform sufficient to study both biVADs and TAHs. However, the numerical models used by Petrou et al. [6] lack validation, due to the absence of relevant clinical data.

The lack of validation is a recurring problem in mock circulatory studies. Often, researchers compare their static hemodynamic magnitudes against a range defined in the literature. For example, Mueller et al. compared their static hemodynamic parameters against a range of literature data from clinical and mock circulatory studies.[86] In another study, the effect of arterial compliance on IABP performance was studied both in an MCL and in patients.[129] However, it is important to evaluate the time response of the MCL as well, to study the performance of CADs during postural changes or exercise.[95] This problem has only recently been recognised and addressed in the study of Gregory et al. [95] who validated their acquired data from an M-MCL against clinical data. However, clinical data of pathological conditions was not available to them, and thus validation has only been done for healthy patients. A complete validation of an MCL is still absent in the available literature.

MCLs have been developed with additional subparts of the CVS such as the coronary, carotid and renal circulations.[89,95,115,130] By expanding the MCL, more physiological parameters can be investigated such as renal perfusion, which often leads to complications in patients with LVAD.[131] Moreover, a module

of the coronary circulation would allow evaluation of specific pathologies like myocardial infarction.[89] Some MCLs only consider the left heart and systemic part of the CVS [48,121,132] or the pulmonary circulation [86], however, since a CAD interacts with the entire CVS, it is essential to model the complete circulation. Moreover, it is important to study the fluid balance between the pulmonary and the systemic circulation for physiological and pathological states.[133] The cerebral circulation has solely been modelled in an N-MCL [134] a hydraulic representation of it is up to this date limited to only the carotid arteries. A hydraulic model of the cerebral circulation would provide valuable insight into the interaction between the CAD and the cerebral circulation.

The regulatory mechanisms of the renal and cerebral arteries have only been partly implemented into a few MCLs.[95,135] The renal arteries can constrict afferent arterioles, reducing renal blood flow. The effect of CAD on renal pathology is complex and not yet well understood.[136] An MCL could be used as a tool to understand the hemodynamics of the renal circulation. Furthermore, the brain responds to an increase in carbon dioxide or hydrogen ions, which causes dilation in the cerebral vessels, allowing the waste products to wash out. This autoregulatory mechanism has not been assessed in MCLs yet.

The Frank-Starling mechanism has been implemented in several MCLs [65,115,137,138], however, in some MCLs this mechanism is still absent, resulting in unrealistic representations of the response of the native heart.[10,44,104] Moreover, the linear approximation of the elasticity of the heart seems to be outdated and needs to be replaced with a non-linear variant.[72] The baroreceptor response, which affects heart rate, contractility, venous volume and SVR, has been introduced in MCLs as well.[103,119,121] Most of the MCLs simulating the baroreceptor response kept the heart rate constant [139,140] or only considered the change of HR.[127] Jansen-Park et al. were able to implement the complete baroreceptor response in an M-MCL. The baroreceptor response was evaluated with a bleeding test where 450mL was dispensed from the system. The M-MCL was able to compensate for some of the pressure drops, mean arterial pressure dropped from 90 mmHg to 72.5 mmHg and was increased to 82.5 mmHg. However, it was not able to fully recover to the mean arterial pressure.

For future MCLs, it is imperative to address these limitations of current MCLs. Integrating fully automated compliance chambers [141] and resistance devices [142] allows the implementation of the necessary autoregulation of the CVS. Parts of the CVS that are too difficult to model hydraulically can be implemented into the MCL with a numerical model, obtaining a flexible and cost-effective H-MCL.

FUNDING ACKNOWLEDGEMENT

Femke Capon is financially supported through EPSRC Doctoral Training Programme and magAssist Inc. to Brunel University London.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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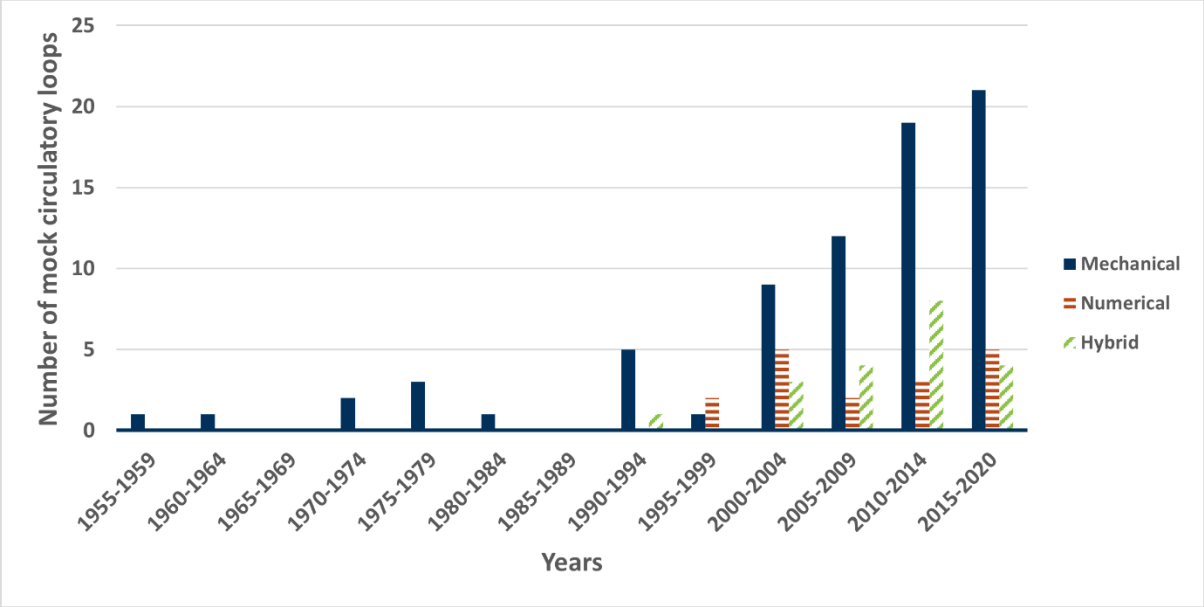

Figure 1: The number of the three types of mock circulatory systems developed over the years.

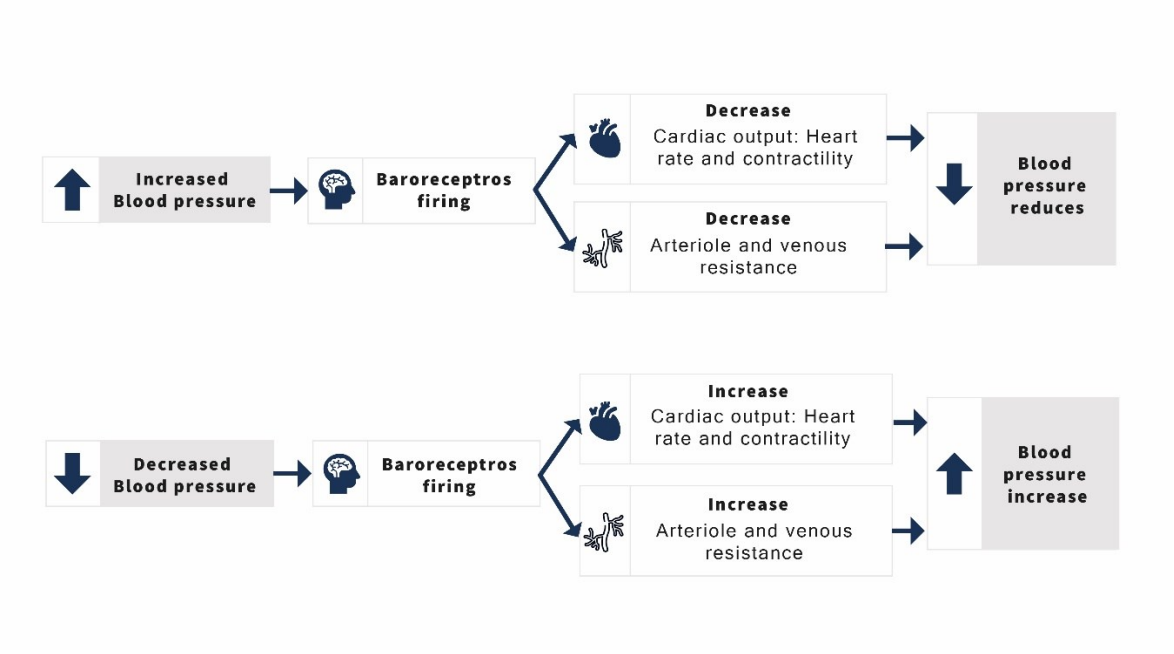

Figure 2: Response of the baroreceptors to a sudden decrease or increase of blood pressure. The baroreceptors can control the cardiac output of the heart and the resistance of the peripheral and systemic arteries.

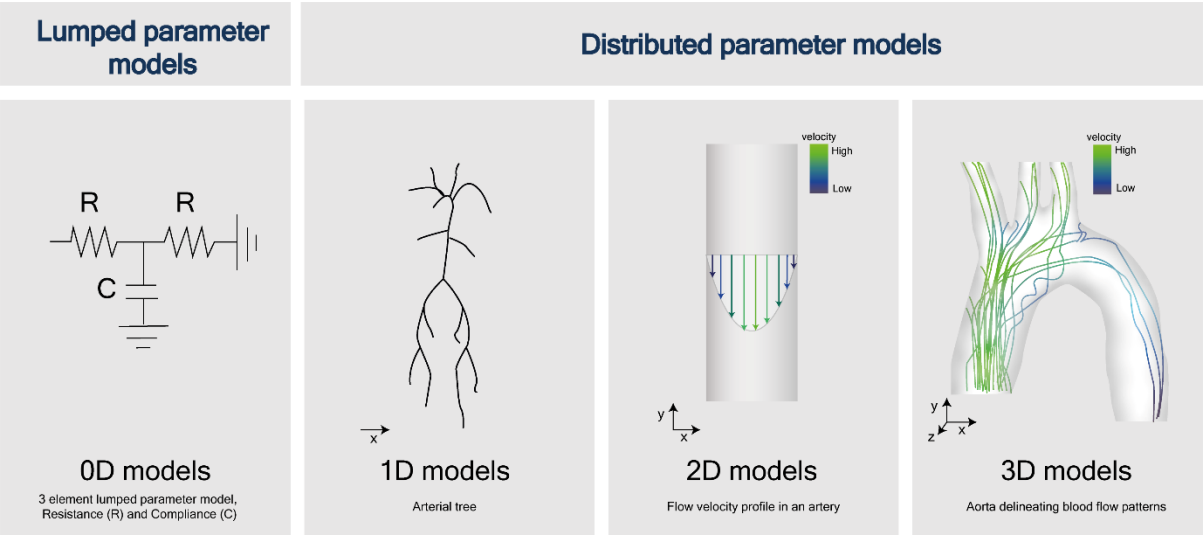

Figure 3: Comparison between lumped parameter model and the distributed parameter models. The focus of numerical models in this review is on lumped parameter models.

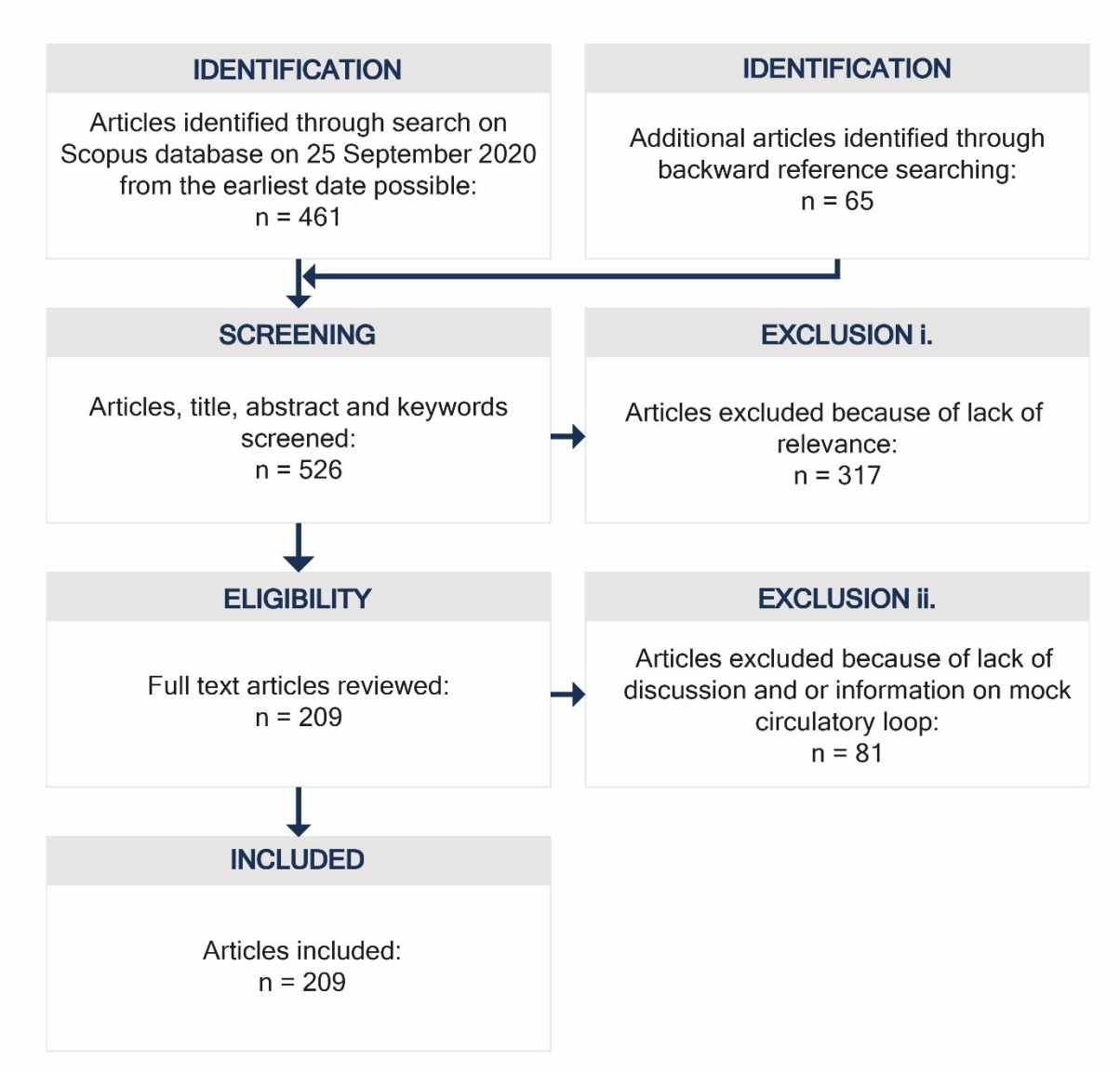

Figure 4: Flowchart of the literature search. A staring set of papers was identified using SCOPUS. Using backwards referencing an additional 65 articles were added. Articles were screened on their title, abstract and keywords. Full-text articles were reviewed and included depending on their relevant information to mock circulatory loops.

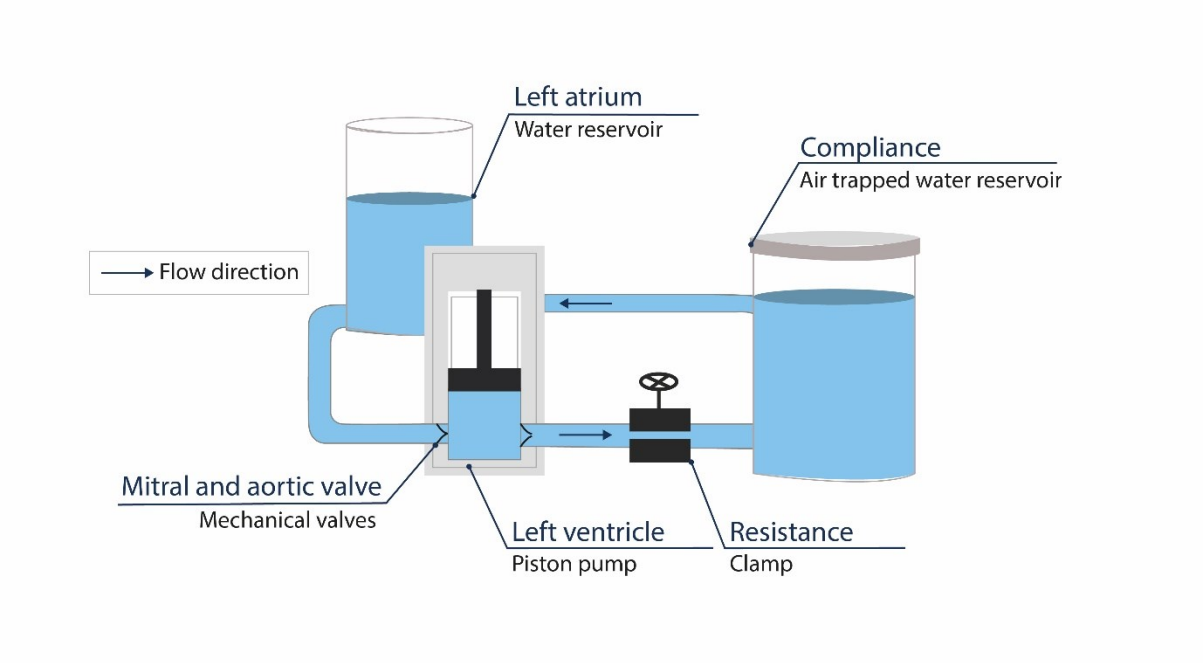

Figure 5: Typical mechanical mock circulatory set-up in which the systemic part of the circulation is simulated with a left ventricle, variable resistance, variable compliance and left atrium.