Nonlinear Control of a Hybrid Pneumo-Hydraulic Mock Circuit of the Cardiovascular System

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ABSTRACT

Objective: Hybrid cardiovascular mock circuits (HMC), designed for dynamic testing of Ventricular Assist Devices (VAD), offer physiologic accuracy by sequestering model complexity *in silico* and ease of construction by reducing number of model elements *in vitro*. Despite superior response time and precision, pneumatic actuation is avoided in HMCs due to nonlinear dynamics and noise. We tested the hypothesis that a HMC consisting of a variable elastance-driven numerical circuit coupled to a pneumo-hydraulic physical circuit can be controlled without linearizing system dynamics. ***Methods:*** Reference left ventricular and aortic pressures generated *in* silico were tracked, respectively, in *in vitro* preload and afterload reservoirs by controlling non-linear pneumatic dynamics using the Lyapunov stability criterion. A centrifugal pump, the speed (i.e. flow) of which was adjusted using PID control, was interposed between the reservoirs and mimicked the VAD under evaluation. The flow of a recirculating gear pump was controlled by the backstepping method to equalize reservoir fluid volumes by rejecting pressure and flow disturbances. Sensor noise was reduced with discrete-time Kalman filtering. ***Results:*** Our results showed that normal, failing and assisted cardiovascular physiologies were numerically simulated and tracked at physical VAD terminals with high accuracy. Reservoir volumes remained stable at various combinations of heart rate, pressure, and VAD flow. ***Conclusion:*** The HMC described here offers a stable performance testing platform for VAD prototypes. ***Significance****:* This is the first proof that hybrid systems using pneumatic actuation at hydraulic interfaces can optimally be regulated with nonlinear controllers to achieve precise reference tracking and robust disturbance rejection.

Index Terms- Hybrid Cardiovascular Mock Circuit, Ventricular Assist Device, Pneumo-Hydraulic System, Kalman Filtering, Lyapunov Stability, Backstepping

I. INTRODUCTION

Advances in implantable medical device technology lead to continuous improvements in the safety, efficacy, and durability of prostheses for the use of the interventional clinician. These devices are made available to the market only after being subjected to thorough performance evaluation at multiple levels of pre-clinical testing platforms, such as numerical (mathematical) analogues, benchtop mock circuits and *in vivo* models of physiological systems [1]. Mechanical Circulatory Assist (MCA) systems, in particular, require special attention in this regard due to the critical nature of both their potential benefits and complications [2].

Performance testing of MCA systems, such as ventricular assist devices (VADs), is conducted on analogue circuits that recreate the characteristic flow and pressure waveforms of the healthy and/or pathological physiology of the cardiovascular system (CVS). Numerical analogues of the CVS are electrical circuits, in which capacitive elements simulate blood-containing compartments and resistive and inertial elements represent, respectively, the viscous friction and mass of the blood inside arterial and venous vasculature [3]. Analogue circuitry may also be exploited to study physiologic subsystems, such as chemo- and baroreflexes or other neural pathways and to understand underlying feedback mechanisms [4].

The design of numerical CVS analogues must be accurate enough to duplicate the desired hemodynamics *in silico*, yet simple enough to be constructed faithfully on-the-bench and operated with ease. A simple physical model can be constructed using constant pressure fluid reservoirs with the VAD interposed in-between, pumping fluid from low to high pressure site. This may allow the determination of the pump's steady-state pressure-flow-speed characteristics, but overlooks the effects of the presence of more complex hemodynamic phenomena, such as ventricular contractility and arterial pulsatility, ventriculo-arterial coupling, heart rate variations, volume overloading of the ventricles, etc. The complexity level of the circuit may be increased with the addition of variable-pressure pumps [5] or reservoirs and other capacitive components, one-way valves, and resistances;

however the addition of each circuit element increases the difficulty of simultaneously controlling pressures, flows and volumes everywhere in the assembly. Also, it is impractical if not counter-productive to adjust the values of capacitances (reservoir cross-sectional areas) and impedances (tubing lengths and diameters) on a case-specific basis.

To circumvent these difficulties, test platforms are modified by incorporating both the numerical and physical versions of the CVS model in a hybrid structure, in which data reciprocates between *in silico* and *in vitro* media through an electro-hydraulic interface [6], [7], [8]. The purpose here is to integrate the accuracy of the *in silico* analogue, the complexity of which can be adjusted almost liberally per the physio(patho)logy of interest, with the ease of construction of the *in vitro* platform, where the physical prototype of the device under investigation is simply connected to the hydraulic inlet and outlet. Voltage values corresponding to desired inlet/outlet pressures of the pump are generated within the numerical part and transferred as references to be tracked in the hardware. In turn, the actual flow corresponding to that pressure differential (and to the pump speed) is measured in the hardware and converted into electric current at the interface. To close the information loop, the current is fed between the ventricular and arterial capacitances of the numeric circuit, where the corresponding voltage values (i.e. reference pressures) are re-calculated and sent to back the interface. The Hardware-in-the-Loop configuration of a hybrid mock circuit (HMC) allows for increasing the complexity of the numeric model by adding further capacitances and resistances and/or dynamically changing system parameters to mimic real-time changes in the physiologic state while the *in vitro* section remains unchanged or minimally adjusted according to the type of hardware under investigation. These advantages notwithstanding, hybrid circuitry faces the challenge of achieving compatibility between the signal transmission dynamics within each domain. Small time-steps must be used to increase the accuracy of the solver on the numerical side, which are difficult to match with the relatively large sampling period imposed by actuator inertia and/or measurement noise limitations on the hardware side [9].

Most HMCs are designed to operate on mechanical or hydraulic power, both of which offer the advantages of system stability and control speed but suffer from actuator response delays due to inherent inertial resistances [10], [11]. The use of pneumatic systems, on the other hand, has been restricted to driving membrane pumps that simulate the heartbeat [7] and seldom elsewhere in the circuit chiefly because of the nonlinearities associated with the compressibility of the air. Apart from the difficulties linked to pneumatic controller design, irregular reservoir compliances cause process variations and wave reflections lead to sensor underdamping and amplification of measurement noise [12].

However, pneumatic systems afford reliability, affordability, safety and structural simplicity as well as speed of response [13]. Signal delays may be reduced simply by keeping short the distance separating the actuator from the controller and the sensor from the source of the signal. It may even be possible to eliminate the signal measurement delays through system order reduction [14]. Various control schemes such as gain scheduling [15], order reduction [16] and sliding-mode control [17] are proposed for pneumatic systems with nonlinear dynamics and signal transport delays. The latter method involves a Lyapunov-based feedback linearization scheme, whereby local stability is guaranteed by constructing a scalar positive-definite energy function of a system state whose time derivative if forced to be negative semi-definite, driving the system asymptotically to a stable equilibrium point [18]. This is attractive in the present context since, if a quadratic form of the error is defined as the energy function, the nonlinearities in system dynamics can be left untreated without introducing linearization errors.

The work presented in this paper is original in the sense that it is designed specifically to test the hypothesis that the inherently non-linear pneumo-hydraulic dynamics of a hybrid CVS simulator's physical moiety can be controlled by linearizing only the tracking errors. The Materials and Methods section is organized to describe the 3 main objectives of the work. 1) To design a 7-reservoir numeric analogue of the CVS driven by ventricular time-varying pressure-volume relationships, fully capable of reproducing normal, failing and mechanically-assisted cardiac physiologies: The numeric circuit generates the reference pressures of the left ventricle and aorta, which are transferred via an electro-hydraulic interface to the *in vitro* part of the hybrid circuit (**Sections II-1.a-c**). 2) To construct the hybrid circuit's physical component, which recreates the reference pressures at the VAD terminals and transmits the resulting flow signal to the numeric part, thus closing the feedback loop: This includes a preload and an afterload reservoir, the VAD to be tested, a recirculation pump and pressure and flow sensors. The structure of the physical part and the dynamics of the model were described separately for the hydraulic system (**Sections II-2.a-c**) and for the pneumatic system (**Sections II-2.d, e**). 3) To configure the pressure and flow control strategies for the pneumatic and hydraulic parts of the physical circuit: Briefly, reservoirs are prevented from emptying or overflowing by making the flow of the recirculation pump track the flow variations of the VAD and reject the disturbance caused by the reservoir total pressure variations (**Section II-3.a**). In turn, reservoir total pressures are made to track their respective reference by controlling their respective pneumatic pressure (**Sections II-3.b**). The organization of the Results and Discussion section follows the same logical progression as the Materials and Methods section. We conclude that our findings represent a simple yet dependable testing platform of VAD performance, combining the accuracy (higher model order) and versatility (instant parameter change) of hybrid circuitry with the speed of pneumatic actuation, affording robust control and precise reference tracking.

II. METHODS

The HMC was designed and constructed by interfacing a 7-reservoir electrical analogue (Numerical Model) of the cardiovascular system with a 2-reservoir *in vitro* system (Physical Model) composed of hydraulic & pneumatic components (**Fig. 1**). The dynamic equations of the numeric, hydraulic and pneumatic sections of the system were determined separately. The hydraulic component is controlled by an integrator backstepping algorithm and the pneumatic component is driven by a Lyapunov-based error linearization controller.

FIGURE 1

1. Numerical Model:

The *in silico* part of the HMC was designed to provide ease of modification of the cardiovascular system parameters, such as blood reservoir compliances and vascular resistances and, particularly, the time-varying elastances of the left and right ventricles.

a. Design of the Numerical Model:

The circuit was simplified by lumping together systemic arteries, arterioles and capillaries in the aortic compartment and systemic veins, venules and capillaries in the venous compartment. Left and right atria, lungs, and elastic arteries and veins are modeled as capacitive elements (reservoirs) with constant compliance (C), while left and right ventricles are modeled as reservoirs with variable elastance [e(t) = 1/C(t)]. Cardiac valves were modeled as diodes and vascular and valvular resistances were modeled as resistive (R) elements. Dependent variables of the dynamic model were chosen as pressures (P), flows (Q) and volumes (V) (**Fig. 1**). The values for the CVS parameters were adjusted so that the numerical model output matched the physiology of normal or dilated cardiomyopathy (**Table 1**) [19], [20], [21], [22].

b. Dynamics of the Numerical Model:

Reservoir volumes (V) were chosen as state variables and total circuit volume was constrained to an adjustable constant (V_T). State dynamics were calculated using Voltage-Pressure analogy, where capacitor electric charges and currents are analogous to hydraulic reservoir volumes and volumetric flow rates, respectively. This allowed expressing reservoir pressures(P_n) by the capacitance equation ($\mathbf{Eq. 1a}$), capacitance inflows (Q_{n-1}) and outflows (Q_n) by Ohm's Law ($\mathbf{Eq. 1b}$), and net capacitance flows ($q_n = \dot{V}_n$) by Kirchhoff's Current Law($\mathbf{Eq. 1c}$); resulting in the dynamics for the n^th reservoir ($\mathbf{Eq. 1d}$):

$$P_n = e_n V_n \tag{1a}$$

$$Q_n = g_{n+1}(P_n - P_{n+1}) \tag{1b}$$

$$q_n = Q_{n-1} - Q_n \tag{1c}$$

$$\dot{V}_n = e_{n-1} g_{n-1} V_{n-1} - e_n (g_{n-1} + g_{n+1}) V_V + e_{n+1} g_{n+1} V_{n+1} \tag{1d}$$

In the **Eq. Set 1,** the symbol g (admittance) stands for the inverse of arterial and valvular viscous resistances, R. In the case of right and left ventricular reservoirs, **Eq. 1d** was modified by the addition of the zero-pressure volumes,$V_{0,RV}$ and $V_{0,LV}$, respectively (**Eqs. 2a, b**). The volumetric filling rates of the left ventricular and aortic reservoirs were corrected by the subtraction and addition, respectively, of the VAD flow rate, Q_{VAD} ($\mathbf{Eqs. 2b, c}$). Finally, **Eq. 2d** was used to model unidirectional flow across the cardiac valves.

$$\dot{V}_{RV} = e_{RA} g_{RA} V_{RA} - e_{RV}(t)(g_{RA} + g_{RV} e_{RV})(V_{RV} - V_{RV0}) + e_P g_{RV} V_P \tag{2a}$$

$$\dot{V}_{LV} = e_{LA} g_{LA} V_{LA} - e_{LV}(t)(g_{LA} + g_{LV} e_{LV})(V_{LV} - V_{LV0}) + e_A g_{LV} V_A - Q_{VAD} \tag{2b}$$

$$\dot{V}_A = e_{LV} g_{LV} V_{LV} - e_A (g_{LV} + g_A) V_A + e_V g_A V_V - e_{LV} g_{LV} V_{LV0} + Q_{VAD} \tag{2c}$$

$$Q_{valve} = max[0, g_{valve}(P_{n+1} - P_{n-1})] \tag{2d}$$

State variable dynamics were expressed in state-space format as

$$\dot{\boldsymbol{V}} = \boldsymbol{G_1}\boldsymbol{E_1}\boldsymbol{V} + \boldsymbol{G_2}\boldsymbol{E_2}\mathbf{U} \tag{3a}$$

where

$$\boldsymbol{V} = [V_{RA} \quad V_{RV} \quad V_P \quad V_{LA} \quad V_{LV} \quad V_A \quad V_V]^T \tag{3b}$$

$$\boldsymbol{E_1} = -diag[e_{RA} \quad e_{RV}(t) \quad e_P \quad e_{LA} \quad e_{LV}(t) \quad e_A \quad e_V] \tag{3c}$$

$$\boldsymbol{E_2} = diag[e_{LV} \quad e_{RV} \quad 1 \quad 1\,] \tag{3d}$$

$$\boldsymbol{U} = [V_{LV0} \quad V_{RV0} \quad P_m \quad Q_{VAD}]^T \tag{3e}$$

$$\boldsymbol{G_1} = \begin{bmatrix} g_V + g_{RA} & -g_{RA} & 0 & 0 & 0 & 0 & -g_V \\ -g_{RA} & g_{RA} + g_{RV} & -g_{RV} & 0 & 0 & 0 & 0 \\ 0 & -g_{RV} & g_{RV} + g_P & -g_P & 0 & 0 & 0 \\ 0 & 0 & -g_P & g_P + g_{LA} & -g_{LA} & 0 & 0 \\ 0 & 0 & 0 & -g_{LA} & g_{LA} + g_{LV} & -g_{LV} & 0 \\ 0 & 0 & 0 & 0 & -g_{LV} & g_{LV} + g_A & -g_A \\ -g_V & 0 & 0 & 0 & 0 & -g_A & g_A + g_V \end{bmatrix} \tag{3f}$$

$$\boldsymbol{G_2} = \begin{bmatrix} 0 & -g_{RA} & g_V & 0 \\ 0 & g_{RA} + g_{RV} & 0 & 0 \\ 0 & -g_{RV} & 0 & 0 \\ -g_{LA} & 0 & 0 & 0 \\ g_{LA} + g_{LV} & 0 & 0 & -1 \\ -g_{LV} & 0 & g_A & 1 \\ 0 & 0 & -(g_A + g_V) & 0 \end{bmatrix} \tag{3g}$$

In Eq. 3e, the periodic function $P_m$was introduced to simulate the pressure exerted by the skeletal muscle pump on the peripheral veins during exercise.

c. Ventricular Elastances

The empiric formula of Simaan et al. [23] was modified by curve-fitting to reproduce the human end-diastolic pressure-volume relationship (EDPVR) [24], which was then inserted in the model of Sagawa [25] to generate left and right ventricles' time-varying elastances

$$e_{LV}(t) = [e_{max} - e_{min}(V_{LV})]e_n(t) + e_{min}(V_{LV}) \qquad (4a)$$

$$e_{RV}(t) = \begin{cases} (1-\varphi)e_{min,rv} + \varphi e_{max,rv} & 0 \le mod(t,T) < t_{ce} \\ e_{min,rv} & otherwise \end{cases} \qquad (4b)$$

where

$$e_n = \frac{461.5\ t_n^{1.5}}{126.3 + 333.3t_n^{1.9} + 0.38t_n^{37}\ + t_n^{38.9}} \qquad (4c)$$

$$t_n = mod(t,T)/(\ 0.35\frac{60}{HR}) \qquad (4d)$$

$$e_{min}(V_{LV}) = 0.2641\left[e^{\frac{V_{LV}-149.4}{79.4913}} - 1\right] + 0.1235 \qquad (4e)$$

$$e_{min}(V_{RV}) = 0.0375\left[e^{\frac{V_{RV}-100}{26.4831}} + 1\right] \qquad (4f)$$

$$\varphi = 0.9\sin\left[\frac{\pi}{t_{ce}}mod(t,T)\right] - 0.25\sin\left[\frac{2\pi}{t_{ce}}mod(t,T)\right] \qquad (4g)$$

$$t_{ce} = k_0 + k_1 T \qquad (4h)$$

$$k_0 = (-0.0042 * \mathrm{HR}^2\ -\ 0.0417 * \mathrm{HR}\ +\ 257.5) * 10^{-3} \qquad (4i)$$

$$k_1 = (0.0158 * \mathrm{HR}^2\ -\ 5.0417 * \mathrm{HR}\ +\ 445.5) * 10^{-3} \qquad (4j)$$

2. Physical Model:

The *in vitro* part of the HMC consisted of pneumatic and hydraulic systems, interfacing inside 2 acrylic reservoirs (0.05 m dia, 0.63 m height) (**Fig. 2**). The calculation of the dynamical equations and the design of the controllers were accomplished separately for the hydraulic and pneumatic systems.

FIGURE 2

a. Design of the Hydraulic System

The overall purpose of the hydraulic system is to determine the dynamic parameters of the VAD prototype and to test its performance under varying combinations of pump flow, pressure head (pressure difference at pump terminals) and radial speed values. This entails maintaining the fluid levels in the pre- and afterload reservoirs relatively constant throughout, lest the reservoirs empty or overboard after a while. For this reason, a 17 mm-dia, 15L/min-max flow gear pump (UP12/OIL, 24V/7.5A, Marco S.P.A, Brescia, Italy) with adjustable speed (or resistance to flow) was used to move the fluid from the high-pressure afterload reservoir to the low-pressure preload reservoir. Return flow from the preload to the afterload reservoir was through a 24V/1A/22W centrifugal pump with 1.27 cm threaded I/O dia (Model ZYW680, KOSECo, Seoul, South Korea) used as surrogate for the LVAD under evaluation (which was referred to as “VAD” from here on). Flows generated by the gear pump and VAD were measured with electromagnetic probes (0.2-50 L/min18-30 Volts, SM7000, IFM Electronics, Essen, Germany) connected to the reservoirs with 3/4” x 1/8” dia PVC tubing (Bıçakçılar, Istanbul, TR). Connections to both pumps were with 1/2” x 3/32” dia PVC tubing (Bıçakçılar, Istanbul, TR).

FIGURE 3

To organize and control the electrical and electronic components of the HMC, an electrical box was designed (**Fig. 3**). A total of 72 BNC Connectors were placed on one side of the box to establish connection with MicroLabBox. On the opposite side of the box, 72 other Mike Connectors were mounted to communicate with various sensors, air valves, gear pump, and motors. Multiple power supplies that source the control boards were connected to a current leakage relay to protect the components in case of a power surge. Next to the relay were located valve boards connected to the inlet and outlet air valves of the reservoirs and the motor driver boards used in controlling the Gear Pump. Sensor boards, which connect pressure and flow sensors to the dSPACE MicroLabBox, were clustered in the bottom right corner of the box. Pulse-width modulation (PWM) of the input voltage was used to drive the gear pump at the desired speed. The pressure differential, ΔP_t, across the gear pump and the PWM duty cycle (%) were recorded as the input while the pump flow rate (Q_{GP}) was recorded as the output of the gear pump.

b. Dynamics of the Hydraulic System

The hydraulic volume difference, ΔV_h, between the preload and afterload tanks (**Fig. 2**) and its dynamics were defined as

$$\Delta V_h = V_{h,after} - V_{h,pre} \tag{6a}$$

$$\dot{V}_{h,after} = Q_{vad} - Q_{gp} \quad \text{and} \quad \dot{V}_{h,pre} = Q_{gp} - Q_{vad} \tag{6b}$$

$$\Delta\dot{V}_h = 2\left(Q_{vad} - Q_{gp}\right) \tag{6f}$$

where $\dot{V}_{pre,h}$and $\dot{V}_{after,h}$ are the rate of change of the hydraulic volumes in the preload and afterload resevoirs, respectively, and $Q_{gp}$and Q_{vad} represent the flow rates generated by the gear pump and the VAD, respectively.

c. Design of the Pneumatic System:

The pneumatic section included a 0.75 kW/220 Volt, 8-bar air compressor (KULETAŞ, Adana, Turkey.), a 3/4 HP/220-240 Volt vacuum pump (VP260 VacuumChambers.eu, Ignatki-Osiedle , Poland) and a Polypropylene pressure reduction tank (0.095 m dia, 0.1 m height, **Fig. 2**). Gas mass flow from the compressor into the pressure reduction tank and from the tank into the reservoirs, and gas mass flow out of the reservoirs into the vacuum pump was controlled by pneumatic solenoid proportional valves (PVQ30 series, SMC Pneumatics, Inc., CA, USA). Reservoir gas and total pressures were measured with $0\sim0.1$-MPa, $0\sim10$-Vsensors (BCT 22-1B, Atek, Kocaeli, TR) placed, respectively, on top and bottom of each reservoir. Pressure and flow data were collected at 10 kHz sampling frequency into a data acquisition system (MicroLabBox, dSPACE, Paderborn, Germany) and analyzed with Matlab (Matlab R2019a, MathWorks Inc., Natick, Massachusetts).

d. Dynamics of the Pneumatic System:

The analogy between pneumatic and hydraulic systems was established by defining gas mass (m_p) and fluid volume (V_h) as independent variables, gas mass flow rate $\left(\dot{m}_p\right)$ and fluid volumetric flow rate $\left(\dot{V}_h = Q\right)$ as dependent motion variables and pneumatic & hydraulic pressures as dependent effort variables (**Fig. 4**).

FIGURE 4

Applying Ohm's Law, gas mass flow rates from the compressor to the reservoir ($\dot{m}_{in}$) and from the reservoir to the vacuum tank ($\dot{m}_{out}$) were calculated as

$$\dot{m}_{in} = g_{in}\left(P_{in} - P_p\right) \qquad (7a)$$

$$\dot{m}_{out} = g_{out}\left(P_p - P_{out}\right) \qquad (7b)$$

where P_{in} and P_{out} are the pneumatic pressures in the pressure reduction and vacuum tanks, respectively, P_p is the pneumatic pressure in the reservoir and g_{in} and g_{out} are conduit admittances (R^{-1}). Using the principle of conservation of mass, the rate of change of gas mass inside the reservoir was related to gas mass flow rate in and out of the reservoir.

$$\dot{m}_p = \dot{m}_{in} - \dot{m}_{out} \qquad (8)$$

Substituting **Eqs. 7a**, **b** into **Eq. 8**

$$\dot{m}_p = g_{in}P_{in} - (g_{in} + g_{out})P_p + g_{out}P_{out} \qquad (9)$$

The mass of gas inside the reservoir was related to reservoir pneumatic pressure using the variable pneumatic capacitance (c_p) of the reservoir. From electrical analogy [$q(Coulomb) = c_e(Farad) * V(Volt)$] and from Ideal Gas Law $\left(P_pV_p = m_pRT\right)$, where V_p is the volume of air in the reservoir, and R and T stand for the gas constant (287 J/kg/ ^oK) and for the gas temperature in ^oK (assumed constant at room temperature), respectively:

$$m_p = c_pP_p \qquad (10)$$

$$c_p = \frac{V_p}{RT} \tag{11}$$

Taking the derivative of **Eq. 10** and applying the chain rule

$$\dot{m}_p = \frac{1}{RT}\left(V_p\dot{P}_p + P_p\dot{V}_p\right) \tag{12}$$

Combining **Eqs. 9** and **12** and rearranging, the dynamics of pneumatic reservoir pressure was obtained

$$\dot{P}_p = \frac{1}{V_p}\left\{RT\left[g_{in}P_{in} - (g_{in} + g_{out})P_p + g_{out}P_{out}\right] - P_p\dot{V}_p\right\} \tag{13}$$

Since total pressure (P_T) and volume in each reservoir is the sum of their pneumatic and hydraulic components, i.e.

$$P_T = P_p + P_h \tag{14a}$$

$$V_T = V_p + V_h \tag{14b}$$

and since the total reservoir volumes are constant

$$\dot{V}_p = -\dot{V}_h \tag{15}$$

Eq. 13 becomes

$$\dot{P}_T = \frac{1}{V_p}\left\{RT\left[g_{in}P_{in} - (g_{in} + g_{out})P_p + g_{out}P_{out}\right] + P_p\dot{V}_h\right\} + \dot{P}_h \tag{16}$$

Calculating $\dot{P}_h$ from the derivative of the capacitance equation (**Eq. 1a**) and $\dot{V}_h$ from Kirchhoff's Current Law (**Eq. 1c**), the dynamics of total reservoir pressure was expressed as

$$\dot{P}_T = e_h RT\,\frac{g_{in}\left(P_{in} - P_p\right) - g_{out}\left(P_p - P_{out}\right)}{e_h V_T - P_h} + e_h\,\frac{\left(P_p + e_h V_T - P_h\right)}{e_h V_T - P_h}\left(Q_{in} - Q_{out}\right) \tag{17}$$

Inspection of **Eq. 17** shows that, by adjusting the admittance of gas inflow and outflow valves, it was possible to control the total pressure inside each reservoir. Note that all other quantities are either constant or continuously measured and recorded.

3. Control of the Physical Model

The pneumatic and hydraulic parts of the physical model were controlled separately. The control of the overall HMC was achieved by combining the pneumatic and hydraulic controllers in parallel arrangement (**Fig. 5**).

FIGURE 5

a. Control of the Hydraulic System:

The aim of the control strategy for the hydraulic system was primarily to keep the fluid volume in the two reservoirs equal ($\Delta V_h = \Delta V_{h,after} - \Delta V_{h,pre}$ =0). Towards this aim, gear pump flow (Q_{gp}) was adjusted using an integral backstepping controller (**Fig. 5**), which calculated the reference input voltage $(v_{in,ref})$. The error in each variable was defined as

$$\varepsilon_V = \Delta V_{h,ref} - \Delta V_h \qquad (18a)$$

$$\varepsilon_Q = Q_{gp,ref} - Q_{gp} \qquad (18b)$$

The first task was to determine $Q_{gp,ref}$ that would drive ε_V to zero. Simplifying the dynamical equations of the gear pump given in[12]

$$Q_{gp} = \alpha_Q \omega \qquad (19a)$$

$$\dot{\omega} = \frac{k_v}{J} v_{in} - \frac{\alpha_P}{J} \Delta P_{gp} \qquad (19b)$$

where $\Delta P_{gp} = P_{T,pre} - P_{T,after}$. The set of **Eqs. 20** was derived from **Eq. 19a**

$$Q_{gp,ref} = \alpha_Q \omega_{ref} \qquad (20a)$$

$$\varepsilon_Q = \alpha_Q(\omega_{ref} - \omega) = \alpha_Q \varepsilon_\omega \qquad (20b)$$

Combining **Eq. 6c** with **Eq.19a** and **20a,b**

$$\Delta \dot{V}_h = 2Q_{vad} - 2\alpha_Q(\omega \pm \omega_{ref}) \qquad (21a)$$

$$\frac{1}{2\alpha_Q}\Delta\dot{V}_h = \frac{1}{\alpha_Q}Q_{vad} + \left(\omega_{ref} - \omega\right) - \omega_{ref} \qquad (21b)$$

$$\omega_{ref} = \frac{1}{\alpha_Q}Q_{vad} + \varepsilon_\omega - \frac{1}{2\alpha_Q}\left(\Delta\dot{V}_h \pm \Delta\dot{V}_{h,ref}\right) \qquad (21c)$$

$$\omega_{ref} = \frac{1}{\alpha_Q}Q_{vad} + \varepsilon_\omega - \frac{1}{2\alpha_Q}\left(\Delta\dot{V}_{h,ref} - \Delta\dot{V}_h\right) + \frac{1}{2\alpha_Q}\Delta\dot{V}_{h,ref} \qquad (21d)$$

Using the derivative of **Eq. 18a** and choosing $\Delta V_{h,ref}$ as constant (preferably zero)

$$\omega_{ref} = \frac{1}{\alpha_Q}Q_{vad} + \left[\varepsilon_\omega - \frac{1}{2\alpha_Q}\dot{\varepsilon}_V\right] \qquad (22)$$

Equating the term in brackets to

$$\varepsilon_\omega - \frac{1}{2\alpha_Q}\dot{\varepsilon}_V = \frac{1}{2\alpha_Q}K_V\varepsilon_V \qquad (23)$$

where K_V is a positive gain, the dynamics of the volume error was linearized

$$\dot{\varepsilon}_V = -K_V\varepsilon_V + 2\alpha_Q\varepsilon_\omega \qquad (24)$$

such that if $\varepsilon_\omega \to 0$, then $\varepsilon_V \to 0$. Defining a positive definite accessory function

$$L_1 = \frac{1}{2}\varepsilon_V^2 \qquad (25a)$$

$$\dot{L}_1 = \varepsilon_V\dot{\varepsilon}_V \qquad (25b)$$

$$\dot{L}_1 = -K_V\varepsilon_V^2 + 2\alpha_Q\varepsilon_\omega\varepsilon_V \qquad (25c)$$

Now, defining the candidate Lyapunov function as

$$L = L_1 + \frac{K_\omega\alpha_Q^2}{2}\varepsilon_\omega^2 \qquad (26a)$$

$$\dot{L} = \dot{L}_1 + K_\omega\alpha_Q^2\varepsilon_\omega\dot{\varepsilon}_\omega \qquad (26b)$$

$$\dot{L} = -K_V\varepsilon_V^2 + 2\alpha_Q\varepsilon_\omega\varepsilon_V + K_\omega\alpha_Q^2\varepsilon_\omega\dot{\varepsilon}_\omega \qquad (26c)$$

where the term $K_\omega \alpha_Q^2$ was added for unit consistency, K_ω being a positive constant with units of square seconds. Taking the derivative of **Eq. 20b** and substituting in **u**

$$\dot{L} = -K_V \varepsilon_V^2 + \varepsilon_\omega \left(2\alpha_Q \varepsilon_V + K_\omega \alpha_Q^2 \dot{\omega}_{ref} - K_\omega \alpha_Q^2 \dot{\omega}\right) \tag{27}$$

Substituting **Eq. 19b** into **Eq. 27**

$$\dot{L} = -K_V \varepsilon_V^2 + \varepsilon_\omega \left[2\alpha_Q \varepsilon_V + K_\omega \alpha_Q^2 \left(\dot{\omega}_{ref} + \frac{\alpha_P}{J} \Delta P_{gp} - \frac{k_v}{J} v_{in}\right)\right] \tag{28}$$

Substituting **Eq. 23** in **Eq. 22**, taking its derivative and replacing for $\dot{\omega}_{ref}$

$$\dot{L} = -K_V \varepsilon_V^2 + \varepsilon_\omega \left[2\alpha_Q \varepsilon_V + K_\omega \alpha_Q^2 \left(\frac{1}{\alpha_Q} \dot{Q}_{vad} + \frac{1}{2\alpha_Q} K_V \dot{\varepsilon}_V + \frac{\alpha_P}{J} \Delta P_{gp} - \frac{k_v}{J} v_{in}\right)\right] \tag{29}$$

If $v_{in}$is selected as

$$v_{in} = \frac{2J}{\alpha_Q k_v K_\omega} \varepsilon_V + \frac{J K_v}{\alpha_Q^2 k_v K_\omega} \varepsilon_\omega + \frac{J K_V}{2\alpha_Q k_v} \dot{\varepsilon}_V + \frac{J}{\alpha_Q k_v} \dot{Q}_{vad} + \frac{\alpha_P}{k_v} \Delta P_{gp} \tag{30}$$

where K_v is a positive constant (units of L^2-sec), then **Eq. 29** takes the form

$$\dot{L} = -K_V \varepsilon_V^2 - K_v \varepsilon_\omega^2 \tag{31}$$

which guarantees asymptotic stability of the origin $\Delta V_h = \Delta V_{h,ref} = 0$. Substituting **Eqs. 18a, 19.a,b** and **20b** in **Eq. 30** and rearranging

$$v_{in} = \frac{J}{k_v \alpha_Q} \left[\dot{Q}_{vad} + \left(\frac{K_v}{2\alpha_Q^2 K_\omega} - K_V\right) \Delta Q + \frac{\alpha_P \alpha_Q}{J} \Delta P_{gp} + \left(2 + \frac{K_v K_V}{2\alpha_Q^2 K_\omega}\right) \Delta V_h\right] \tag{32}$$

where $\dot{Q}_{vad}$ was calculated numerically using the forward Euler method and

$$\Delta Q = \left(Q_{vad} - Q_{gp}\right) \tag{33}$$

$$\Delta V_h = \frac{1}{e_h} \left(P_{h,after} - P_{h,pre}\right) \tag{33}$$

b. Control of the Pneumatic System:

Reference tracking of total pressures (P_T) for the reduction, left ventricle (preload) and aortic (afterload) reservoirs was accomplished by regulating the pneumatic pressures (P_p) inside each reservoir via the gas inlet and outlet valves. The dynamics of the pressure error was defined in terms of total reservoir pressure as

$$\dot{\varepsilon}_P = \dot{P}_{ref,T} - \dot{P}_T \tag{29}$$

and linearized, as in the case of the flow error dynamics, by letting

$$\dot{\varepsilon}_P = -\left(K_{P,in} + K_{P,out}\right)\varepsilon_P, \qquad K_{P,in}, K_{P,out} > 0 \tag{30}$$

The reference for the reduction reservoir pressure $\left(P_{in,ref}\right)$ was kept constant at 1600 Pa, its time derivative, therefore, being zero. The dynamics for the preload reservoir reference pressure ($P_{LV,ref}$) was obtained by substituting **Eqs. 2b** and **4a** in **Eq. 1a** from the numeric model and applying the chain rule for the derivative since the LV elastance is time-varying. The dynamics for the afterload reservoir reference pressure ($P_{AO,ref}$), on the other hand, was obtained by substituting **Eq. 2c** in the derivative of **Eq. 1a** without the chain rule as the aortic reservoir is conceived with a constant elastance in the numeric circuit. After substitution of reference pressure dynamics into **Eq. 29**

$$\dot{\varepsilon}_P = \dot{P}_{ref,T} - g_{in} e_h RT \frac{P_{in} - P_p}{e_h V_T - P_h} + g_{out} e_h RT \frac{P_p - P_{out}}{e_h V_T - P_h} - e_h \frac{P_p + e_h V_T - P_h}{e_h V_T - P_h} (Q_{in} - Q_{out}) \tag{31}$$

and combining **Eq. 30** with **Eq. 31,** the error expression was reduced to

$$\begin{aligned} &\left[\dot{P}_{ref,T} - g_{in} e_h RT \frac{P_{in} - P_p}{e_h V_T - P_h} + K_{P,in}\varepsilon_P\right] \\ &\quad + \left[g_{out} e_h RT \frac{P_p - P_{out}}{e_h V_T - P_h} - e_h \frac{P_p + e_h V_T - P_h}{e_h V_T - P_h}(Q_{in} - Q_{out}) + K_{P,out}\varepsilon_P\right] = 0 \end{aligned} \tag{31}$$

This allowed for the decoupling of the gas inlet and outlet valves so that they could be operated independently from each other during the cardiac cycle. As a result, the control law was determined separately for the admittance of each valve and for each reservoir

$$g_{in} = \frac{e_h V_T - P_h}{e_h RT}\left(\frac{K_{P,in}}{P_{in} - P_p}\varepsilon_P - \frac{\dot{P}_{ref}}{P_{in} - P_p}\right) \qquad (32a)$$

$$g_{out} = \frac{e_h V_T - P_h}{e_h RT}\left[\frac{K_{P,out}}{\left(P_p - P_{out}\right)}\varepsilon_P + e_h \frac{Q_{in} - Q_{out}}{e_h V_T - P_h}\frac{P_p + e_h V_T - P_h}{\left(P_p - P_{out}\right)}\right] \qquad (32b)$$

4. Performance Tests

The parameter set (Table 1) was tuned in accordance with the physiology to be mimicked, which ranged from healthy to advanced LV failure and from resting to mild and moderate physical activity. For each physiology, the pressures, flows and volumes in the virtual and physical reservoirs were recorded and plotted as time series. Left and right ventricular P-V loops were also generated.

a. Numerical Model

The numerical model was first tested in isolation from the physical system. The input value of Q_{vad} was manually set, beginning at zero for the healthy heart and Wiggers diagrams were generated. The duplication of Frank-Starling mechanism was performed by volume infusion (increased V_T) at constant e_{max}. As a surrogate for basal metabolic rate, the heart rate was increased without an attending change in arterial blood pressure or cardiac contractility [26]. To simulate varying levels of physical activity, e_{max} and heart rate were augmented while the skeletal muscle pump was activated and arterial resistance was decreased (baroreflex mechanism). Advancing stages of left ventricular failure were simulated by decreasing e_{max} incrementally. First without mechanical assistance, then with gradually increasing pump flow, the effect VAD support on the vital signs and on the PV loops was observed.

b. Physical Model

As a first step, the operation of pneumatic actuation in the bench-top reservoirs was verified. The parameters of the analogue model were tuned to simulate normal and cardiac failure physiologies. With the value of Q_{vad} set to zero, the signals corresponding to the left ventricular and aortic pressures were transferred via the interface to the nonlinear pneumatic controller, to be used as reference for the reservoir pressures. The VAD flow was irrelevant in this test since it was not fed back to the numerical circuit. The PWM of the VAD was arbitrarily selected manually and the gear pump flow tracked the VAD flow via the backstepping controller. The physical pressure and flow signals were measured, filtered and compared to their respective references. The root mean square error (RMSE) was calculated for each signal to estimate the tracking performance of the controllers. Also, the RMSE between sensor readings and filtered signals was calculated to estimate the performance of the discrete Kalman filter in suppressing the sensor noise.

The next step was to assess the functioning of the hybrid system while two-way information transfer was allowed at the electrohydraulic interface. First, the Q_{vad} terminal in the numerical circuit was connected to the filtered sensor reading of the VAD in the physical circuit. The analogue model was tuned to simulate the level of desired heart failure, and the resulting pressure references were sent to the physical circuit and duplicated in the reservoirs. The response of the VAD in terms of flow corresponding to the existing pressure differential at the VAD terminals was then sent back to the numerical circuit, closing the loop of information transfer across the interface. Circulatory assistance was established by operating the VAD either on fixed-speed mode, as in the current clinical practice or on fixed-flow mode, using a simple PID controller to reject load (pressure) disturbances. In the meantime, the backstepping controller ensured that the gear pump flow tracked the VAD flow to preserve fluid level balance in the reservoirs.

For all tests, the Wiggers diagram and PV loops were generated in the analogue system and analyzed for conformity to the physiology being simulated.

5. Signal Processing

To characterize sensor noise, the system was operated at constant reservoir pressure and readings of each pressure and flow sensor were obtained separately at a sampling frequency of 10 KHz and recorded as independent time series. The pressure reference setting was incrementally changed and the above procedure was repeated at each setting to collect ensemble data for each sensor. For the flow sensors, the mean of time series, $\bar{x}_{q,ts}$, and the mean of the ensemble data at time index k, $\bar{x}_{q,e}[k]$, were calculated from:

$$\bar{x}_{q,ts} = \frac{1}{N}\sum_{i=1}^{N} x_{ts,i} \qquad (33a)$$

$$\bar{x}_{q,e}[k] = \frac{1}{M}\sum_{i=1}^{M} x_{e,i}[k] \qquad (33b)$$

where N is the length of the time series and M is the total number of pressure reference settings, at which the time series data were collected. Time series averages were compared to ensemble averages for each sensor to determine the ergodicity of the process. Signal variance was obtained from

$$\sigma_{ts}{}^2 = \sum_{i=1}^{N} \frac{\left(x_{ts,i} - \bar{x}_{q,ts}\right)^2}{N-1} \text{ and } \sum\nolimits_{XX} = \frac{1}{N}\sum_{i=1}^{N} \sigma_i^2 \qquad (34)$$

For comparison (and correction, if necessary) the autocorrelation of the mean-adjusted data for each sensor was also determined in Matlab using the formula

$$R_{xx}[\tau] = \mathrm{E}\{\left(x_{ts}[k] - \bar{x}_{q,ts}[k]\right)^T\left(x_{ts}[k-\tau] - \bar{x}_{q,ts}[k-\tau]\right)\} \qquad (35)$$

where the symbol E{.} designates the Expectation Operator. The value of the auto-correlation at 0-lag was taken as the variance of the sensor noise.

$$R_{xx}[0] = \sigma^2\delta[n] \qquad (36)$$

The system was expressed in state-space format

$$\dot{x} = Ax + Bu \tag{37a}$$

$$y = Hx \tag{37b}$$

where the state, x, and output, y, vectors were identical ($H = I$, no state estimation), consisting of the pneumatic and total reservoir pressures (**Eqs. 13** and **17**, respectively) and flows of the 2 pumps in the physical model. Continuous-time dynamic equations of the states were discretized using Forward Euler's $(t \to k\Delta t)$ so that the state progression was predicted as

$$x_{k+1} = x_k + (Ax_k + Bu_k)\Delta t + \mu_k \tag{38a}$$

$$\hat{x}_{k+1} = \hat{x}_k^* + \dot{x}(t)\Delta t \tag{38b}$$

where the non-linear, implicit term $(Ay_k + Bu_k)$ in Eq. A-II.4 is conveniently replaced in Eq. A-II.6 by the dynamics of the variable, the hat over the state vector signifies a prediction, the asterix indicates that the prediction of the previous step is an unbiased, minimum-variance estimate, and the vector μ_k represents the random process $(N/\bar{x} = 0, \sigma_x^2)$ associated with the uncertainty of each state (Process Noise).

The auto-covariance matrices, $\Sigma_{x/k}$ and Q_k, of the process noise were calculated, respectively, from

$$\Sigma_{x/k} = \hat{x}_k^* \hat{x}_k^{*T} \tag{39a}$$

$$Q_k = \mu_k {\mu_k}^T \tag{39b}$$

so that the total variance, $\Sigma_{x/k+1}$, of the state at the prediction step was given by

$$\Sigma_{x/k+1} = \Sigma_{x/k} + Q_k \tag{40}$$

In the next step, the predicted state vector $(\hat{x}_{k+1})$ and its covariance $\left(\Sigma_{x/k+1}\right)$were used as the mean and covariance of the expected measurement vector and this distribution was fused with the actual measurement vector (z_k) and its auto-covariance $(R_k,)$ diagonal matrix of to obtain the updated state estimate. The Kalman coefficient matrix that achieves optimality of the fused distribution was determined from

$$K = \Sigma_{x/k+1} \left(\Sigma_{x/k+1} + R_k\right)^{-1} \quad (41)$$

such that

$$\hat{\Sigma}^*_{x/k+1} = (I - K)\Sigma_{x/k+1} \quad (42a)$$

$$\hat{x}^*_{k+1} = \hat{x}_{k+1} + K(z_k - \hat{x}_{k+1}) \quad (42b$$

III. RESULTS

1. Numerical Model:

a. Design and Dynamics of the Numerical Model:

The temporal evolution of all dynamical system states (nodal pressures, ventricular volumes and ventricular and aortic flows) is shown in **Fig. 6.** The model was observed to faithfully reproduce normal physiologic patterns of the load-dependent cardiac performance indicators at rest and during light (LE), moderate (ME) and peak (PE) exercise [27]. The values of the states remained practically unchanged for various metabolic levels (HR=60, 75, 90 bpm) of the resting physiology. Systolic and diastolic aortic pressures did not rise significantly (143/93 mmHg sys/dia) at maximum exercise, which mimicked the baroreceptor reflex, even when the cardiac output doubled or tripled, which mimicked the Frank-Starling mechanism. All three flows remained equal throughout as expected. The duration of diastole progressively shortened from 680 msec to 430 msec and 240 msec at the increasing heart rates of 60, 90 and 140, respectively [28].

The shape of ventricular PV loops also were in accordance with the expected physiologic responses to increased preload ($\uparrow V_T$,), changes in resting heart rates, and increasing levels of physical activity **(Fig. 7,** respectively from left to right) [29]. The ESPVR was insensitive to changes in preload and beat frequency (left and middle panels, respectively) but responsive to the inotropic state (right panel). Stroke volume (SV) and stroke work (SW, loop inner area) increased significantly after volume infusion reproducing the Frank-Starling mechanism and the after positive inotropy$(\text{increase in } e_{max})$, simulating the effect of load-independent intrinsic cardiac contractility. Neither SV nor SW were significantly affected by changes in heart rate (unchanged end-systolic volume, ESV, and slightly increased end-diastolic volume, EDV).

FIGURE 6

FIGURE 7

The physiologic data produced by the numerical model for both assisted (VAD) and unassisted heart failure scenarios are shown in **Figure 8**. Heart failure was correctly represented as a concurrent deterioration of load-dependent LV performance indicators from normal (0-5 sec) to CO<3.5 L/min, LAP>15 mmHg, MAP<80 mmHg, LVEDP>160 mL and EF$=30\%$ (5-10 sec). With the onset of low grade mechanical assistance$(\mathrm{Q_{VAD}}=3L/min)$, the LV was clearly unloaded $(\mathrm{LVEDV}<140\ \mathrm{mL})$ while the aortic valve kept opening at every beat, but aortic flow did not significantly improve ($\mathrm{Q_{AO}}<4\ L/min,$ 10-15 sec). Arterio-ventricular uncoupling occurred at a VAD setting of 4 L/min with the arterial pressure remaining on the higher end of acceptable levels $(MAP=92\ \mathrm{mmHg}),$ but sufficient peripheral flow was still not achieved, being generated solely by the pump [30]. For a patient with slightly higher resting metabolism (HR=90), the minimum aortic flow of 5 L/min coincided with a higher than recommended MAP of 109 mmHg. With minimal exertion, the aortic valve started to open but LVEDV jumped to 172 mL. At this point, increasing VAD flow to 7 L/min provided sufficient aortic flow at the cost of a risky elevation in the MAP.

The effect of mechanical circulatory assistance on the PV loops during rest and minimal exertion is depicted in **Fig. 9.** In the case of heart failure without assistance, the end systolic volume of the left ventricle (LVESV) during rest, mild and medium exertion were right-shifted by approximately 60 mL, 90 mL and 130 mL, respectively [31]. The zero-pressure hypothetical volume,$\mathrm{V_0}$, shifted to the right (from 10 mL to 50 mL), as is often seen in clinical the scenario [32]. During pump support, as the flow rate of the VAD was increased, the PV loops were observed to progressively narrow, indicating that more and more of the cardiac external work was taken over by the pump; the isovolumetric phases of contraction and relaxation disappeared; and the loops shifted to the left, indicating that significant unloading of the left ventricle was taking place. The level of VAD support that first caused LVESV to fall below that of the unsupported ventricle (green loop on the left panel and blue loop on the right panel) was noted to coincide with the same support level, at which the aortic valve first ceased to open and the sharp upper left corner of the loop vanished.

FIGURE 8

FIGURE 9

2. Physical Model:

It should be noted that the VAD flow was held constant (flat line) in the scenarios testing the performance of the isolated numeric circuit, as explained above. This is not realistic in the actual clinical application due to the load sensitivity of continuous flow assist devices. This was corrected when both parts of the hybrid circuit were coupled, as the speed of the VAD was regulated either manually or with a PID controller. The fluctuations of its flow, then, reflected the changing pressures at its inflow and outflow terminals.

a. Performance of the Hydraulic System:

Volume reference tracking performance of the hybrid circuit is shown in **Figure 10**. The top panel reflects the scenario, where the healthy heart at rest (HR= 60 bpm) and during exercise (HR= 90 and 120 bpm) was simulated by the numerical circuit with the value of Q_{vad} set to zero. On the physical side, the VAD duty cycle (PWM, %) was varied manually from 0.6 to 1 for each heart rate setting, and the resulting VAD flow rate was not fed back to the numerical circuit. The bottom panel recordings, on the other hand, shows performance test of the physical system fluid level controller, where the numerical system was operated in heart failure mode, VAD flow was adjusted by the PID controller and fed back to the numerical circuit, and the gear pump's PWM was regulated by the backstepping controller to track the ΔV_h reference (**Fig. 10,** bottom panel). The values of Q_{vad} and Q_{gp} (above tracings in each panel) as well as the value of area-normalized fluid volume error (ΔV_h, below tracing in each panel) between the after- and preload reservoirs were recorded until steady state is reached for each HR-PWM combination. The transient period after each change was observed to be less than 1 sec. and the means of both pumps' flows remain nearly equal at the set levels although their amplitude was different and there was a delay. The mean of the area-normalized ΔV_h signal varied between $-1.57 \text{ cm and } -8.46 \text{ cm}$, but the tracing crossed the zero-line at all times, indicating continuous volume equalization in the reservoirs by the backstepping controller within the relevant frequency (heart rate) range.

FIGURE 10.

b. Performance of the Pneumatic System

The pressure reference-tracking performance of the pneumo-hydraulic controller in the aortic (afterload) and ventricular (preload) reservoirs of the physical circuit was first tested for the normal cardiac physiology at low (resting, HR=60 bpm) and high frequency (moderate exertion, HR=120 bpm) ranges (**Fig. 11,** top panel). At 60 bpm, both pressures were observed to closely follow their reference, particularly during the rapid isovolumic contraction and relaxation phases. A high signal-to-noise ratio was observed with small amplitude ripples in the ejection and filling phases. For the P_{LV} and the P_{AO}, respectively, the root mean square error (RMSE) was calculated as 0.20 mmHg and 0.24 mmHg at HR=60 bpm and as 0.72 mmHg and 0.76 mmHg at HR=120 bpm, indicating successful conditioning of the sensor signal. The deviation of the P_{LV} from its reference in the high frequency region was due to insufficient pressure, P_1, stored in the pressure reduction tank, the volume of which may have to be increased to eliminate the divergence. The test was repeated for low (HR=60 bpm, panel 2nd from top) and high basal metabolic rate (HR=90 bpm, bottom panel) at rest. As mechanical circulatory assistance was initiated at 3 L/min the aortic pulse narrowed and, at 4 L/min, arterio-ventricular dissociation occurred. The second panel from bottom of **Fig. 11** shows the effect of VAD assistance at a higher heart rate (90 bpm), for high (2-4 sec) and low (4-8 sec) basal metabolism. At the same VAD flow of 5 L/min, the aortic valve ceases to close in the case of the resting patient if their metabolic rate is high (2-4 sec) whereas the ventricle of the mildly exercising patent with lower metabolic rate continues to eject (4-6 sec). For the latter case, the valve closes only when higher VAD support (7 L/min) was provided. In the bottom panel, the cardiac output $(Q_{LV}, \text{green tracing})$ is non-zero at a VAD flow rate of 3 L/min (0-3 sec) but disappears as the aortic valve closes permanently, upon increasing VAD flow rate to 4 L/min (3-6 sec). The VAD flow (burgundy tracing), on the other hand, was seen to increase with each ventricular systole, which is to be expected considering the load-sensitivity of continuous flow devices. These findings were in excellent accordance with the numerical model outputs shown in **Figs. 6-9.**

FIGURE 11.

c. Signal Processing

Figure 12 shows the autocorrelation values for the flow sensor measurements, where the peak at zero-lag was assumed to be the variance of the sensor noise used as initial values in the covariance matrix calculation for the measurement update in Kalman filter calculations (**Eqs. 35** and **36**). Upon further tuning by comparison with **Eq. 34**, all process covariance matrices for tank pressures were set to $1.00 * 10^{-6}$, while the covariance measurement matrices for tank pressures were set to 8.00*10^{-2} (P_1, P_{2p}, P_2) and 1.82*10^{-3} (P_{3p}, P_3). Similarly, the process and measurement covariance matrices for the pumps were set, respectively, to 1.00*10^{-6} and 7.5173*10^{-4} (Gear pump) and to 1.00*10^{-6} and 6.3571*10^{-4} (VAD). The difference between the measured and filtered signals, as seen in **Fig. 11** (top 3 panels) and expressed in RMSE values were minimal ($< 0.1\ \%$ of peak pressure values).

FIGURE 12.

IV.DISCUSSION

The concept of a hybrid simulation circuit was first conceived by Pillon et al. in 1992 who proposed it as a “solution, which has both the advantages of the numerical and hydraulic approaches” and, in which “the prosthesis being tested interacts with a numerically simulated cardiovascular model through one or more interface points, […] for instance, the two cannulas of a ventricular assist device.” [33] The method was put to practice as early as 2001 by a joint team from Rome and Warsaw, who used a minimalistic (3-element Windkessel) approach for the analogue CVS model together with a single (atrial) physical reservoir and a gear pump for recirculation in an open-loop configuration (no arterial reservoir or VAD) [34]. The same team later reported the realization of a closed-loop hybrid system incorporating either a mechanically (piston-in-cylinder) operated left ventricle [6] or impedance transformers placed at the hydro-numerical interfaces [35]. The reciprocating type pump, which offers linear system dynamics and ease of control, has been a favorite actuator mechanism for creating inlet and outlet pressures on the physical side of hybrid circuits [5], [36], [37], [38], [39], [40]. Alternative actuators have also been attempted, such as pinch valves that adjust the input/output impedance [41], dynamic cardiac compression for the left ventricle-VAD complex [42], [43], a triple-gear pump system configured to operate as an operational amplifier [44], a pneumatic muscle band that simulates ventricular contractions [45], or voice coil actuators [13], [46], [47].

The use of air pressure in the circuit was initially limited to simulation of passive vascular [48] or active arterial [49] compliances or of active membranes that simulate ventricular elastances [9], [37], [50], [51]. Oschner and his colleagues at ETH (Zurich, CH) was the first to control the pneumatic pressure in a pneumo-hydraulic reservoir in a hybrid circuit in order to simulate left ventricular and aortic pressures [16], [52]. They regulated the reservoir fluid levels using a PI controller with roll-off and anti-reset windup. Pressure reference tracking, on the other hand, was realized by optimally designing the complementary sensitivity of a PI controller with a lead extension according to the bandwidth requirements imposed by the frequency content of the pressure trajectories($15\ Hz \leq \omega_{bc} \leq 32\ \mathrm{Hz}$). To achieve this, they had to linearize the plant, for which they lumped both pneumatic and hydraulic systems in a SISO model and estimated the transfer function of each subsystem. This entailed a high degree of deviation (up to 25 mmHg) between the reference and the output signals, which they were able to reduce (down to 1.79 mmHg) only by compensating for the phase shift (10 msec delay). To avoid the problems associated with the linearization of the pneumatic dynamics, Salesh [53] et al. used constant pneumatic inlet and outlet pressures above the fluid reservoirs while they adjusted the total reservoir pressures by controlling the fluid levels therein. In our design, we used the exact opposite strategy and regulated the pneumatic pressures while keeping the fluid level constant. This allowed us to avoid the physical limitations associated with rapid hydraulic actuation and offered the advantage of faster pneumatic response within a wider bandwidth of load fluctuations, as seen in **Fig 11**, even when the heart rate rose to as high as 140 bpm.

Hydraulic dynamics are significantly more susceptible than pneumatic systems to fluid and actuator inertia, which lead to output delays that interfere with reference tracking performance, particularly in the transient phase. In our case, however, rather than the precise equalization of the reservoir volumes at all times, the main concern was to avoid the full drainage of either one of the reservoirs in the long term. Designing our control strategy, therefore, we focused primarily on achieving acceptable robustness against the periodicity of the load disturbance, and on preventing the accumulation of steady state error despite the oversimplifications in modeling the gear pump dynamics. In that regard, the backstepping algorithm accurately handled the voltage-speed-flow-volume cascade rejecting significant load variations; and the Lyapunov stability criterion completely compensated for parameter variations despite significant phase delays. This is visible in **Fig. 10**, where the instantaneous gear pump flow (orange tracing) lags the VAD flow by almost 180^0 and the average flow error gets as high as 330/8 cc/L at 90 bpm(top panel, 30 sec mark); however, the average difference between reservoir fluid levels always crosses the 0-mark despite oscillations. The steady-state volume error, which averages around -2 ± 2 cm at low frequencies reaches a maximum of $8.5\,\mathrm{cm}$, can easily be eliminated with the addition of integral action to the backstepping controller [54]. The noise observed in the volume error signal was caused by the disruptive pressure peaks of the gear pump and can be significantly reduced by inserting an M5 valve between the transducer and the fluid column, which was not in our possession at the time of writing the manuscript.*

The correct representation with the numerical model of a large spectrum of physiologic states (healthy and failing, at rest and during physical activity, with or without circulatory assistance) was important for drawing accurate conclusions regarding the performance of the VAD under investigation. For this reason, the parameters of the computer simulations for normal/failing and resting/activity physiologies were meticulously selected, and the numerical model output was carefully inspected to match published data (**Tables 1 and 2**). The performance of the CVS model was also compared with clinical data from LVAD recipients, whose tolerance to increased levels of exertion had been evaluated while pump flow was being adjusted as needed (**Fig. 8**). It should be noted that, due to the nature of ventricular elastance expressions, e_{LV} and e_{RV}, both the accessory state transition matrix, $\boldsymbol{E_1}$ $(\mathbf{Eq.\,3c})$, and the accessory input matrix, $\boldsymbol{E_2}$ $(\mathbf{Eq.\,3d})$, are usually nonlinear and time-varying in standard CVS models. This makes it rather challenging to simultaneously obtain all representative features of the desired pathophysiology within each model compartment. For example, reducing the $e_{LV,max}$ without changing the e_{RV} in isolated left heart failure may shift the systolic/diastolic duration ratio into an unacceptable range, adjusting the arterial resistance during exercise with a baroreceptor reflex without the necessary alterations in the venous capacitance may result in ventricular asynchrony, or shaping the passive tension curve in a way that is inconsistent with the desired diastolic filling pattern may result in insufficient volume overloading of the failing left ventricle. The multivariate machine learning algorithm used in our study allowed us to fine-tune CVS model parameters so that conformity to a wide range of physiological scenarios was achieved. The CVS model will be expanded in future studies to incorporate the coronary circulation as well, in order to account for the effect of mechanical circulatory assistance on cardiac energetics and myocardial efficiency.

In conclusion, controlling the reservoir pressure dynamics with a nonlinear controller allowed us to significantly minimize the complexity in physical part of the hybrid circuit. The necessary hardware was downsized from multiple gear pumps, voice coil actuators or

* Manufacturer's catalogue, https://www.metrolog.net/files/bct22_en_metrolog.pdf

complicated mechanical contraptions to a single gear pump. By avoiding the use of conventional nested PI controllers known to be greatly affected by actuator inertia and load variations, a simple backstepping algorithm was designed and used to robustly operate the gear pump. On the other hand, the need for linearizing the pneumatic dynamics was completely eliminated by the implementation of a discrete-time Lyapunov-based feedback error linearization controller, which allowed very high precision in tracking the pressure references. The method, which is believed to constitute a first in the mock circulatory loop literature, is believed to constitute a dependable platform for the performance testing of novel circulatory assistance technologies.

Declaration of Competing Interest

None.

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Ethical approval

Not required.

Data statement

Data are available from the corresponding author on request.

Supplementary materials

Supplementary material, particularly a video of the system in operation, can be shared upon request by the reviewers.

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Table 1A

Healthy			
Parameter	Rest HR=60	Medium Exertion HR=120	Peak Exertion HR=140
	Value/Range		
Vascular Admittances $(\boldsymbol{mL.s^{-1}.mmHg^{-1}})$			
$\mathrm{Art_{sys}}$	0.9	1.6	3
$\mathrm{Ven_{sys}}$	70	107.5	171
Pulm	5	10.03	10.07
Valvular Admittances $(\boldsymbol{mL.s^{-1}.mmHg^{-1}})$			
AO	210	320	520
Pulm	210	215	520
Tricuspid	1000	925	800
Mitral	1000	850	600
Elastances $(\boldsymbol{mmHg.mL^{-1}} * 10^{-3})$			
$\mathrm{LV_{max}}$	3,000	5,500	6,700
$\mathrm{LV_{min}}$	1.3-45	40-70	2.3-40
$\mathrm{Art_{sys}}$	700	510	500
$\mathrm{Ven_{sys}}$	2.4	3.5	4.06
$\mathrm{RV_{max}}$	0.5	0.8	1.5
$\mathrm{RV_{min}}$	50-70	60-120	47-128
Pulm	120	110	150
LA	82.5	90	75

Table 1B

HFrEF			
Parameter	Rest HR=60	Mild Exertion HR=90	Peak Exertion HR=120
	Value/Range		
Vascular Admittances $(\boldsymbol{mL.s^{-1}.mmHg^{-1}})$			
$\mathrm{Art_{sys}}$	0.98	1.1	1.36
$\mathrm{Ven_{sys}}$	70	107.5	145.5
Pulm	5	10.03	11.3
Valvular Admittances $(\boldsymbol{mL.s^{-1}.mmHg^{-1}})$			
AO	210	320	437.5
Pulm	50	19.82	29.68
Tricuspid	1000	925	850
Mitral	1000	850	700
Elastances $(\boldsymbol{mmHg.mL^{-1}} * 10^{-3})$			
$\mathrm{LV_{max}}$	1,000	1,100	1,200
$\mathrm{LV_{min}}$	75-93	75-90	80-100
$\mathrm{Art_{sys}}$	1,000	1,500	1,500
$\mathrm{Ven_{sys}}$	4	6	8
$\mathrm{RV_{max}}$	540	800	900
$\mathrm{RV_{min}}$	100-150	190-250	320-360
Pulm	110	90	100
LA	110	100	120

Table 2A

Healthy			
Variable	Normal HR=60	Medium Exertion HR=120	Peak Exertion HR=140
Pressures $(\mathbf{ed/es}, \boldsymbol{mmHg})$			
P_{AO}	80/115	89/120	94/125
P_P	18/24	26/34	31/41
P_{LA}	4&6.7	12&16	9/14
P_{LV}	4&115	12&120	9/125
MAP	87.3	94.6	106.6
Volumes (ed/es, mL)			
V_{LA}	78/110	100/135	127/155
V_{LV}	50/133	29/138	35/165
V_{RV}	60/146	44/155	45/173
Load-dependent LV Performance Indexes			
SV (mL/beat)	83	109	128
CO (L/min)	5	13,080	18,060
SW (J/beat)	7,747	10,311	14,123
EF (%)	62	78	82
Other			
t_d / t_s	0.68/0.36	0.3/0.2	0.24/0.15
τ_A (sec)	1.58	1.25	0.66
$e_{LV,es} / e_a$	3/1.18	5.5/1.1	6.7/1.14

Table 2B

HFrEF			
Variable	Resting HR=60	Mild Exertion HR=90	Peak Exertion HR=120
Pressures $(\mathbf{ed/es}, \boldsymbol{mmHg})$			
P_{AO}	53/90	76/132	94/156
P_P	23/27	25/28	31/34
P_{LA}	15/18	18/21	21/25
P_{LV}	18/90	18/132	21/156
MAP	72	114	135
Volumes (ed/es, mL)			
V_{LA}	72/115	100/145	150/200
V_{LV}	100/157	134/194	180/245
V_{RV}	64/120	58/156	94/142
Load-dependent LV Performance Indexes			
SV (mL/beat)	57	60	65
CO (L/min)	3,4	5,4	7,8
SW (J/beat)	4.104	6.840	16.200
EF (%)	37	30	26
Other			
t_d / t_s	0.68/0.36	0.43/0.25	0.3/0.2
τ_A (sec)	1	1.36	1.11
$e_{LV,es} / e_a$	1/1.6	1.1/2.2	1.2/2.4

FIGURE CAPTIONS and TABLE LEGENDS

Figure 1 Electrical analogue for the hybrid mock circuit (HMC) of the cardiovascular system (CVS) coupled with a continuous-flow ventricular assist device (VAD). The numerical (*in silico*) section (left) communicates with the physical (*in vitro*) section via the electro-hydraulic interface (dSPACE). Analogue signal for VAD flow (Q_{VAD}) is fed into the CVS, where it interacts with the digital node pressures. Digital signals for the resulting left ventricular and aortic pressures (P_{LV}, P_{AO}) are, in turn, fed into the physical environment, where they are re-created at the terminals of VAD (P_{pre}, P_{after}) and affect its flow. The rotational speed of the gear pump is adjusted real-time to meet Q_{VAD} in order to keep constant the level of the fluid in the reservoirs. See text for symbols.

Figure 2 – Schematic representation (left) and physical structure of the bench-top (*in vitro*) section of the hybrid mock circuit (HMC). The admittance (g) pneumatic solenoid proportional valves are adjusted via a Lyapunov-based controller so that total reservoir pressures (P_{pre}, P_{after}) track their respective reference created in the numerical (*in silico*) section. Pulse width modulation (PWM) of the input voltage is kept constant for the ventricular assist device (VAD), or it is regulated by a PID controller to match the cardiac output generated in the numerical model. The PWM of the gear pump is automatically adjusted by an integral backstepping controller for the gear pump, in order to keep the hydraulic volume difference (ΔV_h) the reservoirs at its reference value of zero.

Figure 3 – Electronic Control Box. 1: BNC Connectors (72 total) connected to MicroLabBox, 2: Current Leakage Relay, 3: Solenoid Valve Control Boards, 4: Gear Pump Motor Driver Boards, 5: Mike Connectors (72 total) communicating with sensors, air valves, gear pump, and motors, 6: Power Supplies, 7: Sensors Data Boards.

Figure 4 - Schematic of the gas flow ($\dot{m}$) and fluid flow (Q) rates in and out of the preload and afterload reservoirs of the physical circuit. Total reservoir pressure (P_T) is the sum of

pneumatic and hydraulic pressures $(P_T = P_p + P_h)$. V: Volume, g: Pneumatic solenoid valve admittance, P_{in}: Compressor pressure, P_{out}: Vacuum pressure.

Figure 5: Control diagram for the physical section of the hybrid mock circuit (top) and the control board (bottom). The input voltage, $\mathrm{PWM_{VAD}}$, or the PID controller, adjusts the rotational speed of the LVAD, which generates flow, Q_{VAD}, against the varying load, ΔP. The integral backstepping controller adjusts the flow rate of the gear pump (Q_{GP}) according to the feedback variable, ΔV_h. The Lyapunov-based controller of the pneumatic system adjusts the admittance (g) of the pneumatic proportional valves so that pressures, $\vec{P}$, in the reservoirs track the reference, $\vec{P}_{ref}$, generated in the CVS **(Eq. Set 1).** Bottom panel shows the user-friendly interactive control board. Physiologic states and controller activation commands are on the upper left quadrant, the controllers are tuned by varying the parameters on the bottom left quadrant, and the numerical and physical model outputs are displayed on the screens at the right. The symbols are described in the text.

Figure 6: The output of the numerical analogue as time series of nodal pressures (P_i, top panel), capacitance volumes ($\mathrm{V_{LV}}, \mathrm{V_{RV}}$, middle panel) and flows ($\mathrm{Q_{LV}}, \mathrm{Q_{RV}}, \mathrm{Q_{AO}}$, bottom panel) for healthy cardiovascular physiology. A 5-sec recording for each condition is shown. N/R: Normal, resting, N/R/V: Normal, resting, volume infusion, LE: Light exercise, ME: Medium exercise, PE: Peak exercise, HR: Heart rate, SV: Stroke volume (mL), CO: Cardiac output, MAP: Mean arterial pressure, SW: Stroke work (mmHg.mL), EF: Ejection fraction (%).

Figure 7. Left ventricular pressure-volume (LVPV) loops for healthy cardiac function, showing the effect of increased basal metabolic rate (increased heart rate at rest, left panel) and increased preload (volume infusion, middle panel) at rest (constant ESPVR), and of increased inotropic and chronotropic states (right panel). PV: Pressure-Volume, ESPVR: End-systolic PV relationship, V_T: Total volume, HR: Heart rate.

Figure 8. The output of the numerical analogue as time series of nodal pressures (P_i, Top panel), capacitance volumes ($\mathrm{V_{LV}}, \mathrm{V_{RV}}$, Middle panel), flows ($\mathrm{Q_{LV}}, \mathrm{Q_{RV}}, \mathrm{Q_{AO}}$, Bottom panel) and numerical values of load-dependent cardiac performance indicators for failing cardiovascular physiology (Table). A 5-sec set is collected for each physiology as indicated on the horizontal axis. N/R: Normal resting, F/R/#: Heart failure/Resting/VAD Flow (L/min), F/ME/#: Heart failure/Mild exercise/VAD Flow (L/min), HR: Heart rate, SV: Stroke volume (mL), CO: Cardiac output, MAP: Mean arterial pressure, SW: Stroke work (mmHg.mL), EF: Ejection fraction (%).

Figure 9: Left ventricular pressure-volume (LVPV) loops, showing the effect of increasing levels of physical exertion (left panel) on a volume-overloaded left ventricle ($e_{max} = 1\ \mathrm{mmHg/mL}$) at heart rates of 60 bpm, 90 bpm and 120 bpm (left panel); and the effect of increasing levels of VAD support (1 L/min-10 L/min at rest ($e_{max} = 1\ \mathrm{mmHg/mL},\ HR = 60\ \mathrm{bpm, middle\ panel}$) and mild exertion ($e_{max} = 1\ \mathrm{mmHg/mL},\ HR = 90\ \mathrm{bpm, right\ panel}$). HFrEF: Heart failure with reduced ejection fraction, VAD: Ventricular assist device, e_{max}: Maximum left ventricular elastance.

Figure 10: Instantaneous pump flow rates and reservoir volume differences showing the load disturbance rejection and reference tracking performance of the backstepping controller in the physical circuit. The tables in the middle show errors. Top panel shows results at each load combination as the healthy heart is simulated at rest (HR= 60 bpm) and during exercise (HR= 90 and 120 bpm). The VAD control input (PWM, % load cycle) is changed manually from 0.6 to 1. The VAD flow rate is not fed back to the numerical circuit. In the bottom panel, the reference VAD flow rate is fixed with the PID controller. If VAD assistance is off, the flow reference is set to the numeric model cardiac output (0-10 and 20-25 sec) and it is not fed back to the numeric model. When the VAD assistance is on, the flow reference is set to the indicated flow rate and is fed back to the numeric circuit (10-20 and 25-35 sec). $\bar{\varepsilon}_V$: Average volume error (**Eq. 6a**), $\bar{\varepsilon}_Q$: Average flow error (**Eq. 18b**).

Figure 11. Pressure reference tracking performance of the nonlinear controller in the hybrid circuit reservoir pressures. The upper panel shows recordings for normal cardiac function at

rest ($e_{max} = 3\ \mathrm{mmHg/mL}$, HR=60 bpm; 0-3 sec) and during moderate physical activity ($e_{max} = 5.4\ \mathrm{mmHg/mL}$, HR=120 bpm; 3-4.7 sec). In the panel second from top, the physiology of heart failure at rest is compared to that of the normal cardiac physiology first without mechanical assistance ($e_{max} = 1\ \mathrm{mmHg/mL}$, HR=60 bpm; 3-6 sec), followed by VAD support at 3 L/min (6-9 sec) and 4 L/min (9-12 sec). The panel second from bottom also shows the VAD effect, first for higher basal metabolism at rest (HR=90 bpm, 2-4 sec), then for lower basal metabolic rate during minimal exertion at VAD flow of 5 L/min (HR=90 bpm, 4-6 sec) and 7 L/min (HR=90 bpm, 6-8 sec). The bottom panel shows the relationship between instantaneous flow rates and pressure waveforms for a ventricle in failure ($e_{max} = 1\ \mathrm{mmHg/mL},\ HR = 60\ \mathrm{bpm}$) under VAD assistance. Here the numerical circuit is operated in heart failure mode, VAD flow is adjusted to the desired values of 3 L/min (0-3 sec) and 4 L/min (3-6 sec) with a PID controller, and is fed back to the numerical circuit.

Figure 12 – Autocorrelation functions for the flow sensors of the VAD (top) and the gear pump (bottom). The peak value of the autocorrelation at zero lag was used as the noise variance in Kalman filter design.

Table 1 Numeric model parameter values assigned for healthy heart (Table 1A, left) and for Heart Failure with Reduced Ejection Fraction (HFrEF, Table 1B, right). HR: Heart rate (bpm), $\mathrm{Art_{sys}}, \mathrm{Ven_{sys}}$: Systemic arteries and veins, Pulm: Lungs, AO: Aorta, $\mathrm{LV_{max}}/\mathrm{LV_{min}}$: Maximum/minimum left ventricle, $\mathrm{RV_{max}}/\mathrm{RV_{min}}$: Maximum/minimum right ventricle, LA: Left atrium.

Table 2 Calculated and observed physiologic variables for healthy heart (Table 2A, left) and for Heart Failure with Reduced Ejection Fraction (HFrEF, Table 2B, right). Pressures and volumes are as explained in Section II.1. Load-dependent performance indexes are as explained in Fig. 6. ed/es: End diastolic/End systolic, $t_d\ /t_s$: Ratio of diastolic to systolic duration, τ_A: Arterial time constant, $e_{LV,es}\ /e_a$: Ratio of end systolic LV elastance to arterial elastance.