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Characterization of Left Ventricular Hemodynamics in a Pulse Duplicator through Phase Plane Analysis

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Abstract: In vitro simulators give the chance to mimic specific human physiological/unphysiological conditions to test medical devices, accelerating innovation cycles, and rapidly exploring new effective solutions. Specifically, in this work, we consider a Pulse Duplicator in use at the Healing Research Laboratory, at the University of Padova, Italy. It allows assessing the performance of prosthetic heart valves under simulated cardiac conditions by generating a controlled pulsatile flow obtained by setting specific system characteristics such as the peripheral resistance and the compliance. In order to conduct effective prosthetic heart valve tests, the Pulse Duplicator has to be manually tuned to provide suitable hemodynamics waveforms (i.e. flow and pressure waves). To assist this time-consuming and not trivial task, we present a Phase Plane Analysis of a particular signal (i.e., the left ventricular pressure) in order to capture additional hemodynamic characteristics of clinical interest that can serve system tuning purposes.

Keywords: Cardiovascular System, Pulse Duplicator, Left Ventricular Hemodynamics, Phase Plane Analysis.

1. INTRODUCTION

The diseases of cardiovascular system are the most common causes of death and rising health care costs, Roth et al. (2020). In particular, valvular heart diseases have become an increasing problem in the ageing society. A diseased heart valve is a mechanical problem that can not be fixed with drugs alone, and surgery is often necessary to repair or replace the damaged valve, e.g. by means of prosthetic heart valves. A number of methods are used to test this kind of devices for verifying that they perform according to their intended use. For example, cardiovascular engineering exploits in vitro tests to demonstrate the safety, efficacy, and quality of prosthetic heart valves. In particular, the ISO 5840 family of standards offers guidelines for the test apparatus aimed to replicate the target operating conditions in humans, Nolan (1994). An example of this kind of hydraulic-mechanic apparatus is given by a Pulse Duplicator (PD) that reproduces physiological pressure and flow waveforms in the left ventricle and ascending aorta, Burriesci et al. (2016); Di Micco et al. (2022). In this context, one typically exploits a lumped-parameter approach to model the pathophysiological conditions of flows and pressures in cardiovascular circulation, providing the aggregation of system effects such as peripheral resistance (resistance to flow), arterial compliance (expansion of volume under pressure), and atrial supply (feed capacity). In the case of complex systems, assuming that the whole system's behaviour can be reduced to the sum of its pieces is erroneous. This is especially true in the case of PDs, where the components are highly interdependent and interact in a variety of ways.

In this paper, we consider a PD in use at the Healing Research Laboratory (HeR Lab), at the University of Padova, Italy. This test apparatus exhibits high modularity and customizability. The PD includes elastic and rigid tubes, air tanks, chambers, taps, and silicone parts. The flow of the mock circulatory loop progresses serially through separate devices, with each simulating a parameter of the circulatory system. Some parts of this hydraulic mock-up can be easily modified or substituted either from the functional or geometrical point of view, e.g. one can test different aortic prosthetic devices in a deformable arch, i.e. a silicone replica of the physiological anatomic district.

One could say that biological and human systems, and surely even the in vitro workbenches that aim at their replication, are complex systems, Frei and Di Marzo Serugendo (2011). In this scenario, the PD provides the chance to simulate a wide range of pathological and physiological conditions also thanks to the use of a computer-controlled piston, that forces the fluid through the test valve, and a pressure and flow monitoring system. In this way, one understands how variations of cardiac flow rate and blood pressure (i.e. the hemodynamic parameters) influence the hemodynamic performance of the prosthetic elements.

To conduct effective experimental prosthetic heart valve tests, one has to simulate the human systemic circulation under certain physiological conditions. To this aim, the PD

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takes advantage of the presence of both a control unit and the human expert intervention. In particular, the number of heart contractions per minute (i.e. heart rate) and the volume of blood being pumped by the heart per unit time (i.e. cardiac output), is controlled by an electronic control unit (ECU) that acts on a linear electromagnetic motor. Besides, a human expert visually inspects the shape of hemodynamic waveforms, which are available in real-time on the PD monitoring system (e.g. the left ventricular pressure or the aortic pressure), and checks the values of certain significant features like their maximum, minimum, spread, etc.; then, the human operator, through a trial and error procedure, tunes some PD parameters, such as the compliance volume, taps closing degree, and the bellow position reference to obtain a suitable PD operating condition guaranteeing the desired shape of hemodynamic waveforms.

Aiming to assist this PD tuning procedure, which has been identified as a challenge, we want to enrich the information extracted from hemodynamic waveforms from the perspective of nonlinear dynamical systems, Kim et al. (1993). In this context, the heart can be viewed as a nonlinear oscillator that generates an output (e.g. the left ventricular pressure) as a function of time, Minorsky and Teichmann (1962). In this paper, the analysis of ventricular hemodynamic is carried out through Phase Plane Analysis (PPA) that is a graphical method for studying the behaviour of nonlinear systems, Strogatz (2018). By exploiting the analysis of phase plane limit cycle attributes one can infer new features of clinical interest (which are not easily detectable when the data are viewed as a function of time as usual) related to hemodynamic waveforms captured by PD monitoring system to assist the PD tuning purposes.

The rest of the paper is organised as follows: Section (2) depicts the PD and its main components; the phase plane analysis is carried-out in Section (3); Section (4) provides a practical example of use of the PPA method, while section (5) provides some conclusive remarks.

2. PULSE DUPLICATOR

PDs main goal is to combine medical, clinical, and engineering knowledge to evaluate technological solutions for better treatment of cardiac pathologies using in vitro simulations, as well as to understand the effects of prosthetic elements (e.g. aortic valves and stents, Rahmani et al. (2012)) in the systemic circulation by evaluating related haemodynamic performances, Burriesci et al. (2016). Modularity and customizability characterize the PD offered at HeR Lab: numerous pieces of the system can be simply changed or modified, either geometrically or functionally, Di Micco et al. (2016). The PD, for example, enables the testing of various aortic prosthetic devices in a silicone replica of the physiological anatomic region, i.e. a deformable arch, as shown in Fig. 1. In this fashion, the PD can simulate the human systemic circulation to see how changes in haemodynamic factors (such as heart flow rate and blood pressure) affect the prosthetic components' haemodynamic performance.

HeR Lab's workbench, in particular, uses a lumped-parameter method to model physiological situations. The flow of the mimic circulatory loop passes through several

(a) On-X prosthetic cardiac valve. (b) Silicone replica or aortic arch.

Fig. 1. Replica of the physiological anatomic aortic arch, and example of prosthetic aortic valve.

devices in series, each imitating a different parameter of the circulatory system, as shown in Fig. 2a. In particular, Fig. 2b shows a bird's eye view of the workbench's functional layout. Arrows indicate the direction of the fluid (in orange the arrows that represent systole while in light blue the ones corresponding to diastole). The primary components of the PD are described below.

2.1 Electromagnetic linear motor and bellow

A metallic bellow is used by the linear motor to move the fluid solution. The entire system functions as a double-direction pump, replicating the contractile function of the left heart (i.e. both systolic and diastolic phases). The position in time of the electromagnetic engine is given by a variable tension imposed to the stator in real-time by the ECU. A variable tension is transferred to the metallic bar with a variable controllable velocity.

2.2 Ventricular Chamber

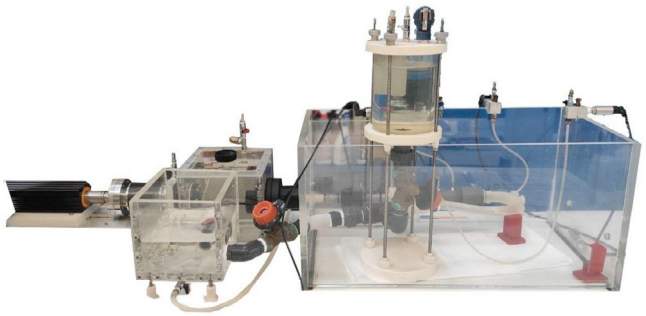
The ventricular chamber, a Plexiglas-enclosed chamber, is directly linked to the bellow. It features two entry holes, one for the bellow and one for the entering mitral flow, as well as one exit hole, which leads to the aortic chamber.

2.3 Aortic Chamber

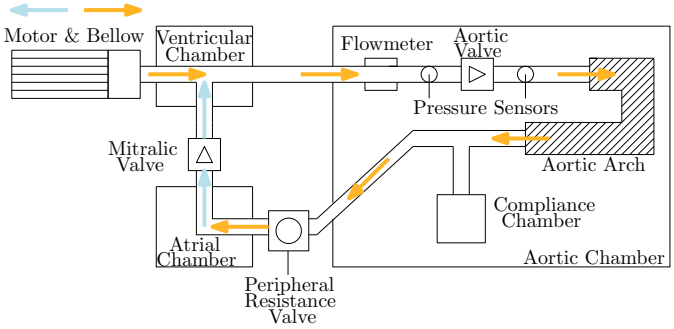
The Aortic Chamber includes the valve housing, two pressure transducers (upstream and downstream of the aortic valve, respectively), and a malleable silicone aortic arch that is a physiological replica of the anatomic area. The Aortic Compliance, the Systemic Compliance Chamber, and the Peripheral Resistance Valve complete the system before the flow enters the Atrial Chamber.

2.4 Atrial Chamber

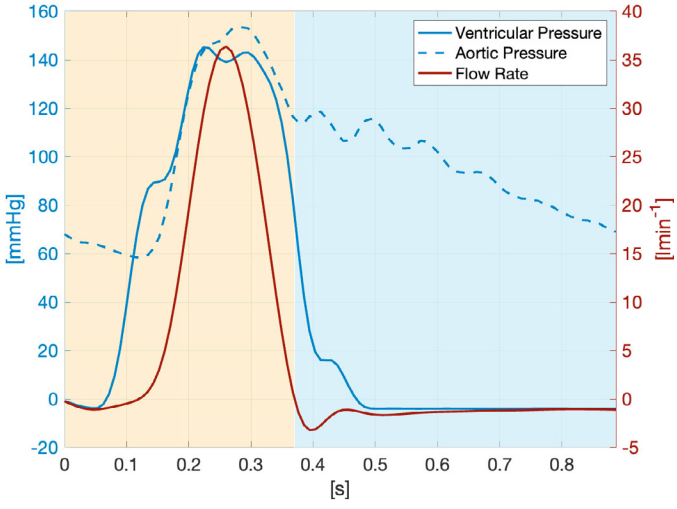
The last circuit component is the atrial chamber, that is a calm tank, in which the oscillatory behaviour of the fluid is softened. It presents two holes for inflow and outflow, at identical height of all the other conduits in the circuit (about 10 cm from zero reference). A constant fluid level is present in the chamber, to mimic the systemic distal pressure reference, of about 10 mmHg.



(a) Workbench available at HeR Lab: it includes rigid and elastic tubes, chambers, air tanks, taps, and silicone parts.



(b) Pulse Duplicator scheme: the lumped parameter model. Orange arrows represent ejection phase while light blue ones correspond to reversal flow phase).



(c) Pressure (in aorta and in ventricle) and flow measured at Cardiac Output (CO) 4.0L min^{-1} and Heart Rate (HR) of 70bpm. The closure of the compliance resistance is 77%, while the peripheral resistance valve closure degree is 60%. The tested aortic valve was On-X of size 25mm. The orange part of the graph is representative of the ejection phase, while the light blue one is representative of the reversal flow phase.

Fig. 2. The Pulse Duplicator at HeR Lab.

2.5 PD Setting Up

To conduct effective in-vitro experiments, the system must simulate the human systemic circulation under certain physiology conditions such as heart rate (the number of heart contractions per minute), cardiac output (the volume of blood pumped by the heart per unit time), aortic pressure (the blood pressure at the root of the aorta) and ventricular pressure.

The process of preparing the PD for simulations in the HeR Lab is somewhat automated: the ECU manipulates inputs (for example, the stator variable voltage of the linear electromagnetic motor) that lead the system to produce specific desired outputs (e.g. heart rate and cardiac output set-points). The operator, on the other hand, manually adjusts various system inputs, such as the Compliance Chamber volume and tap (Peripheral Resistance Valve) closing degrees, to obtain other output characteristics (e.g. mean, maximum, minimum, spread related to the aortic pressure waveform shape), as shown in Fig. 2c. It is worth stressing that, for each different PD hardware setup and desired operative conditions, the above mentioned tuning procedure must be redone.

Table 1. Global hydrodynamic parameters of HER Lab PD (25mm On-X), see Di Micco et al. (2016) for further details.

Working condition	I	II	III	IV
CO L min^{-1}	4	5	6	7
HR bpm	70	70	70	70
AV - OnX size mm	25	25	25	25
Δp mmHg	9.9	11.1	12.1	13.8
Δp max mmHg	29.3	28.2	32.0	35.5
pAO mean mmHg	101.4	100.8	99.1	99.3
pAO min mmHg	69.3	70.8	54.2	47.4
pAO max mmHg	158.6	168.7	179.7	190.6
pLV max mmHg	136.4	133.5	155.4	165.9
SV Pump ml	86.4	104.2	119.2	131.7
SV ml	60.9	75.4	84.0	96.3
CV ml	-3.1	-3.4	-3.4	-5.1
LV ml	-0.1	-0.6	-1.7	-1.1
PF ml	440.4	530.5	604.8	689.7
RF %	5.1	5.6	6.0	4.8
EOA cm^2	2.1	2.5	2.8	3.0

To give an idea of the performance achievable by means of the HeR Lab PD, the global hydrodynamic parameters as measured/calculated at four different working conditions are reported in Table 1. Specifically, information about cardiac output CO, heart rate HR, aortic valve size AV, the pressure drop Δp, the maximum pressure drop Δpmax, the minimum, maximum and mean aortic pressure pAO, maximum left ventricle volume pLVmax, stroke volume SV, closing volume CV, left ventricle volume LV, positive flow PF, regurgitant fraction RF, and effective orifice area EOA are provided. All data refer to On-X valve 25 mm NS. See Di Micco et al. (2016) for further details.

3. PHASE PLANE ANALYSIS OF LEFT VENTRICULAR HEMODYNAMICS

In a clinical environment, PPA is typically performed on left ventricular (LV) pressure wave from cardiac catheterization to obtain measurements of peak systolic and end-diastolic pressures, Yang (1978). In an effort to maximize the amount of useful information extracted from hemodynamic waveforms captured by the sensors in the PD, we exploit characteristics which are typically of clinical interest, Chung and Kovács (2007), to serve our tuning purposes.

In this scenario, hemodynamic assessment can involve the analysis of the LV pressure P, as function of time t, and

its derivative dP/dt. A certain number of points and parameters can be extracted or computed from the pressure P. These points obtained usually include maximum LV pressure P_{max}, minimum LV pressure P_{min}, the positive peak of dP/dt ($\dot{P}_+$), and the negative peak of dP/dt ($\dot{P}_-$), Eucker et al. (2001).

In accordance with the literature, Kim et al. (1993), Winfree and Tyson (1988), we have selected the phase plane as the practical tool to help the human operator to find the desired working point in the PD-specific experimental setting of fixed cardiac output and heart rate. In particular, in this work, the physiological operative conditions are fixed to 70bpm for heart rate, and 4L min^{-1} of cardiac output, guaranteed by the following PD parameters: closure of the compliance tap equal to 77% and peripheral resistance valve closure degree equals 60%.

PPA is performed on periodic or pseudo-periodic functions on a graph that represents the function on the abscissa and its time derivative on the ordinate, Bray and Wikswo (2002). In our application, ventricular pressure P is plotted on the abscissa and its derivative dP/dt on the ordinate. Since the left ventricular pressure is a pseudo-periodic wave, it completes one oscillation for each cardiac cycle, and its phase plane plot form closed trajectories. Those closed curves are usually referred as limit cycles, Chung and Kovács (2007).

The aim of this analysis is to permit an easier recognition of features related to LV function that are not easily detectable when the data are viewed in time, as we are used to (Fig. 3).

According with the literature, some of these attributes are selected, such as the pressure decay during isovolumic relaxation, the symmetry of $\dot{P}_+$ and $\dot{P}_-$, the relationship between the pressures at which $\dot{P}_+$ and $\dot{P}_-$ occur, the comparison of $\dot{P}_+$ and $\dot{P}_-$ to P_{max}.

In the following analysis, 5 points with physiological significance have been highlighted:

(1) the maximum systolic pressure P_{max};
(2) the negative peak $\dot{P}_-$, occurring during the isovolumic relaxation;
(3) the opening of the mitral;
(4) the minimum diastolic pressure P_{min};
(5) the positive peak $\dot{P}_+$, occurring during the isovolumic contraction.

Fig. 3 shows the relationship between a typical LV pressure over time plot.

By looking at the sensed LV pressure signal of Fig. 3, one can notice some discrepancies with reference to the awaited theoretical standard LV pressure behaviour. Furthermore, given that the PD is a complex non-linear dynamic system, understanding and contrasting the causes of those undesired characteristics is not a trivial task. In particular, the inflexion point between points 5 and 1, the local minimum between 1 and 2, and the shape of inflexion point 3 can be probably caused by the irregular movement of the piston in time; by the presence of a residual air bubble in the ventricular chamber, that can move and modify its shape and volume during the cycle; possible

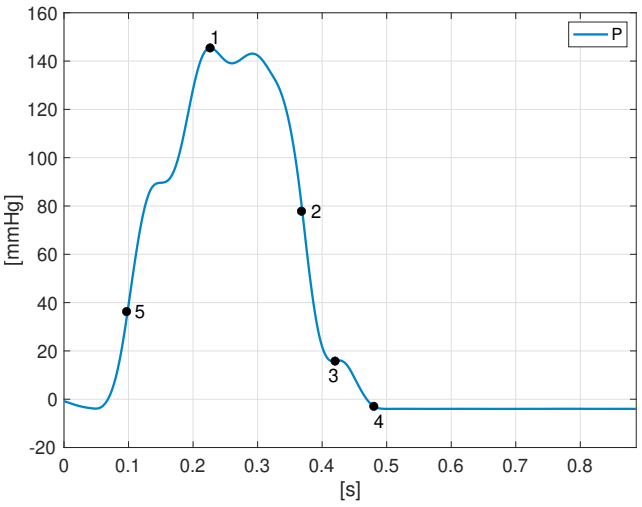


Fig. 3. The LV pressure as function of time.

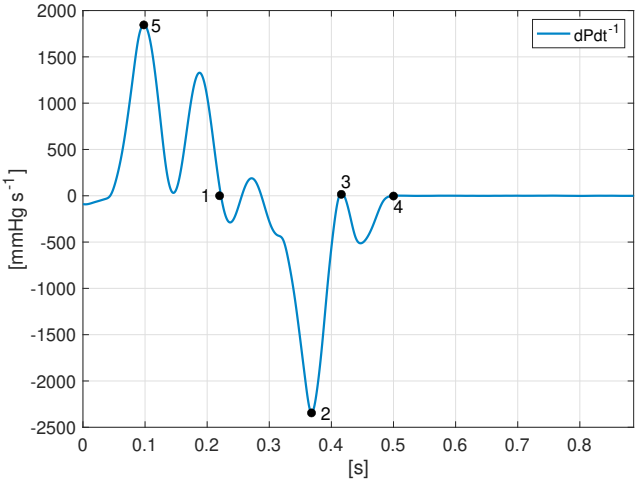


Fig. 4. The LV pressure derivative waveform.

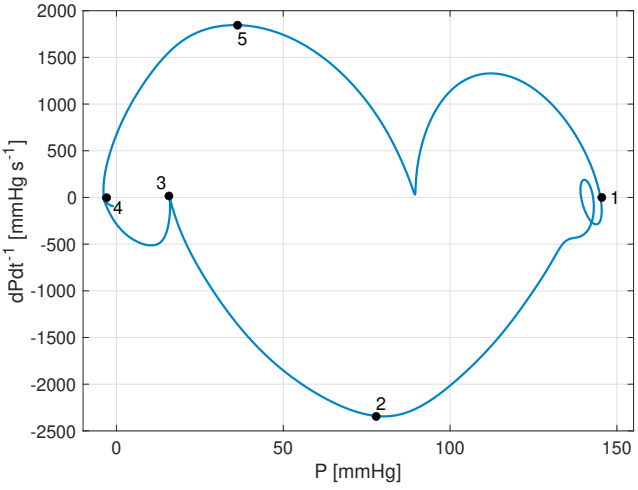


Fig. 5. Phase Plane Analysis: $dPdt^{-1}$ vs $P(t)$.

jerky movements on the prosthetic aortic valve, caused by the fact that it is worn out due to its massive use in the last years of experiments. Regarding the flat line after point 4, it is most likely due to acquisition problems.

As one can notice, in Fig. 3 is not easy to determine the five highlighted points, that are useful for the PD tuning and set-up. By looking simultaneously at the temporal derivative dP/dt, reported in Fig. 4, the position in time of the five points of interest is easier. If we combine the information of P and its temporal derivative, we obtain the LV pressure phase plane plot, depicted in Fig. 5. By looking at this figure, the five points of interest in the cardiac cycle are of much easier detection. In fact, the LV pressure phase plane plot is bounded on the left by P_{min}, on the right by P_{max}, on the top by $\dot{P}_+$, and on the bottom by $\dot{P}_-$. As an example, looking at portion 2–3, a segment of the isovolumic relaxation is now easily distinguishable.

A limitation of the PPA approach is that the progress of time is not explicitly observable in the phase plane. To overcome this restriction, Fig. 6 shows a three-dimensional phase plane/time diagram, with time on the x-axis, LV pressure on the y-axis, and dP/dt on the z-axis. If a cardiac cycle is considered, a spiral-like, three-dimensional plot is projected onto the three orthogonal planes, the standard P over t, dP/dt over t, and dP/dt over P (phase plane plot) can be identified. Using this projection format, the standard characteristics of the LV pressure contour, such as R-R interval, diastole, systole, and isovolumic contraction and relaxation, are easily discerned.

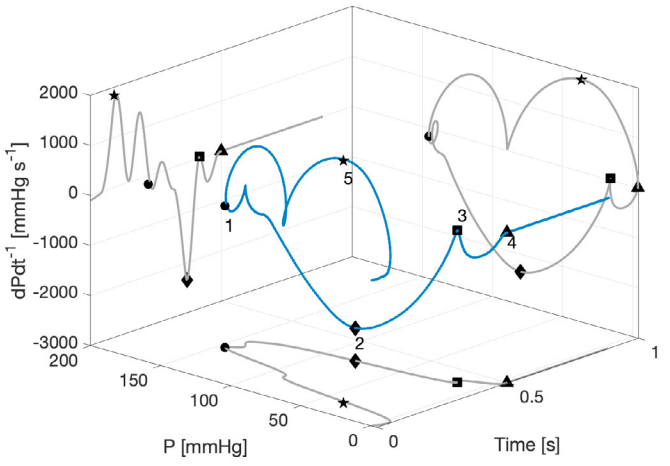


Fig. 6. 3D plot of P and dP/dt over t, and P over dP/dt, i.e. PPA, along with their projections on the planes.

4. PPA AS A TOOL FOR ASSISTING THE PD TUNING TASK

This section shows how the PPA could be used as a tool to assist the tuning of the PD. Let us consider Fig. 7 that depicts an actually PD ventricular pressure waveform (orange-coloured), i.e. the time series, coming from ten consecutive heart beats and a desired pressure waveform (blue-coloured). We want to tune some degrees of freedom of the system such as the compliance volume, taps closing degree, and the bellow position reference to obtain the desired blue-colored pressure waveform characteristics, e.g., in terms of specified values for the reference points 1-5. It is worth noticing that, this may be not so easy by only inspecting pressure data as function of time. Indeed, on the one hand the two signals seem to be very close on the other hand certain characteristics are different.

In this context, it could be helpful exploiting the PPA on both the desired pressure waveform along with the position of the reference points (the blue-coloured trajectory in Fig. 8) and the heart-beat time series (the orange-coloured trajectory in Fig. 8). The goal is to make the actual orange-coloured PD pressure trajectory get closer to the desired behaviour, i.e. the blue one. For example, one of the objective is to make the descending part of the ventricular pressure wave (from point 1 to point 3) smooth and, given its slope, to take higher pressure values (i.e. along with the orientation of the dashed arrow in Fig. 8). In order to fulfil this goal, one could change the characteristics of the bellow in terms of shape of the imposed displacement curve.

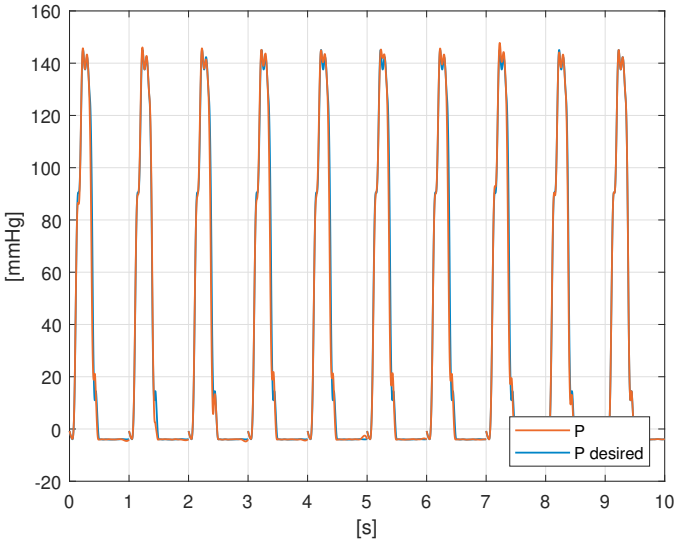


Fig. 7. Two time series of 10 consecutive ventricular pressure waves in time: the desired waveform (blue-colored) and the actual one (orange-coloured). The signals seem very similar.

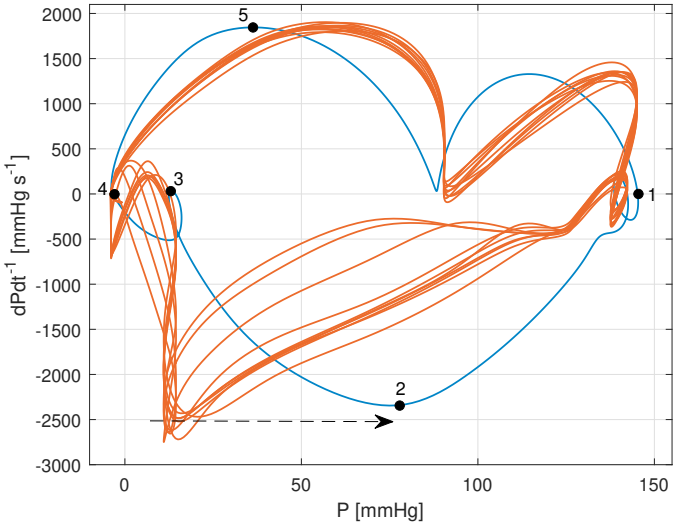


Fig. 8. PPA of the ventricular pressure waves reported in Fig. 7 (orange-coloured), along with the desired trajectory (blue-coloured).

5. CONCLUSIONS

This paper has considered the in-vitro cardiovascular hydrodynamic testing system in use at the Her Lab PD. In an effort to enrich the amount of physiological information inferable from hemodynamic waveforms, the PPA has been used to carry out the investigation of LV hemodynamic data. Specifically the paper has selected the derivative of the LV pressure over the time as independent variable while the dependent variable is the LV pressure. The proposed PPA permits an easier recognition of features related to LV function that are not easily detectable when the data are viewed in time, as we are used to see. For example, these additional features can be profitable used to assist the manual tuning of the PD peripheral resistance and the compliance. Future developments will include the analysis of other mimicking-blood signals like the aortic pressure and the flow rate, and the possibility to control the compliance even of the ventricular chamber, in order to refine the tuning procedure.

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