Article Title: A Hybrid Experimental-Computational Modeling Framework For Cardiovascular Device Testing

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Abstract:

Significant advances in biomedical science often leverage powerful computational and experimental modeling platforms. We present a framework named "PSCOPE" that can capitalize on the strengths of both types of platforms in a single hybrid model. PSCOPE uses an iterative method to couple an in-vitro mock circuit to a lumped-parameter numerical simulation of physiology, obtaining closed-loop feedback between the two. We first compared results of Fontan graft obstruction scenarios modeled using both PSCOPE and an established multiscale computational fluid dynamics method; the normalized root-mean-square error values of important physiologic parameters were between 0.1% ~ 2.1%, confirming the fidelity of the PSCOPE framework. Next, we demonstrate an example application of PSCOPE to model a scenario beyond the current capabilities of multiscale computational methods-- the implantation of a Jarvik 2000 blood pump for cavopulmonary support in the single-ventricle circulation; we found that the commercial Jarvik 2000 controller can be modified to produce a suitable rotor speed for augmenting cardiac output by approximately 20% while maintaining blood pressures within safe ranges. The unified modeling framework enables a testing environment which simultaneously operates a medical device and performs computational simulations of the resulting physiology, providing a tool for physically testing medical devices with simulated physiologic feedback.

Key Terms: hardware-in-the-loop; hybrid; numerical; mock loop; medical device; benchtop; verification; translational;

INTRODUCTION

Current state of numerical and in-vitro methods

Numerical simulations and in-vitro experiments offer potential means for reducing the amount of animal and human testing necessary and expediting the development of medical products. Computational models, depending on the quality and fidelity, provide the opportunity for detailed analysis of important hemodynamic parameters and physiologic changes in the cardiovascular system. Since the 1960s numerical lumped-parameter approaches have been used to model cardiovascular physiology [1-4], finite element models have evolved to simulate 3-dimensional dynamics of moving structures [5, 6], and multiscale models have integrated 3-dimensional dynamics of static geometries with lumped-parameter physiology simulations (Fig 1A) [7, 8]. *In-vitro* mock circulation loops, on the other hand, offer the advantage of directly testing medical devices and investigating physical phenomena that are not fully captured by simplified computational models. However, the ability of mock loops to model the dynamic closed-loop response of the heart remains limited, the challenges including difficulties in achieving realistic end-systolic and end-diastolic pressure-volume characteristics as well as the preload sensitivities of the heart chambers[9-13]. Despite significant advances in computational and *in-vitro* methods for modeling different aspects of the cardiovascular system, the ability to capitalize these advances in a unified high-fidelity framework is still beyond reach.

The hardware-in-the-loop approach

The hardware-in-the-loop (HIL) approach combines an in-vitro experiment with a numerical simulation of physiology, possessing the potential to capitalize on the strengths of both in-vitro and numerical platforms in a hybrid model (Fig 1B). Pillon et al. first suggested the HIL approach for cardiovascular modeling in 1992 [14]. Later, Hanson *et al.*[15] and Alazmani *et al.*[16] each constructed an HIL model containing a ventricle-mimicking actuator setup controlled based on the desired pressures calculated in real-time from a simple numerical lumped-parameter simulation. Nestler *et al.*[17] used a hybrid mock loop to create a feedback environment for testing rotary ventricular assist devices under steady flow conditions. Investigators from the Polish Academy of Sciences and Italian National Council of Research presented several example applications of hybrid mock loops containing experimental domains in the vicinity of the aortic arch[18-21]. Ochsner *et al.*[22] presented a pressure controller design with output-monitoring to provide pressures across the aortic valve as an interface between the experimental and numerical domains of a hybrid framework.

These previous HIL simulations have demonstrated that dependence of the mocked-ventricular pressures on factors such as ventricular preload and contractility can be achieved in a hybrid framework. However, due to the physical limitations of real-time hydraulic actuation as well as of sensor measurements in fluids, such as bandwidth and signal qualities, the HIL approach has not become a practical method for high-fidelity cardiovascular modeling despite its significant potential. The aforementioned implementations of cardiovascular hybrid models have been limited to scenarios where the experimental-numerical interface is near the ventricle

since in these scenarios the high amplitudes of hydraulic signals in the experiment allow for delays and experimental input and output errors to be tolerated without rendering the model unusable.

Furthermore, the verification of previous hybrid models has primarily been by method of comparing results to physiologic data in literature to identify agreement. These comparisons have indicated the potentials of the HIL hybrid framework for creating physiologically realistic models. However, without a precise verification standard, the detriments of actuator response time limitation, feedback signal delay, and measurement noise propagating in an HIL setup are unknown and a rigorous verification of the model fidelity is lacking.

The Physiology Simulation COuPled Experiment (PSCOPE)

In this study, we create the Physiology Simulation COuPled Experiment (PSCOPE) framework to address the aforementioned limitations in previous cardiovascular HIL models. This framework utilizes an iterative method to mitigate the physical limitations in the hydraulic experiment such as signal noises and delays; furthermore, it allows for the direct evaluation of the solution quality, guaranteeing the convergence of the solution below a known residual. The goal of this study is to present 1) the implementation of the PSCOPE framework, 2) quantitative verification of PSCOPE model results compared directly against established multiscale simulation results, and 3) an example application of PSCOPE to model a scenario beyond the current capability of multiscale simulations.

In summary, the PSCOPE's main strength is the ability to experimentally investigate a scenario that is challenging for numerical simulations (i.e. fluid-structure interactions), and fully couple the experimental results with a physiology simulation (which is challenging to produce experimentally).

METHODS

PSCOPE coupling principle

The dynamic interactions between an *in-vitro* experiment and a numerical physiology simulation require the exchange of pressure and flow signals between the two domains in a way that is compatible with the operations of both. The traditional implementation of HIL requires the exchange of information between modeling domains at each time step of the numerical simulation. For cardiovascular numerical models, this time step is often in the range of ~1ms or smaller, meaning employing the traditional real-time sequential signal exchange requires that the response time of the hydraulic experiment be very stringent. In addition, solving the differential equations in the numerical model with fine time steps means that the exchanged information, and therefore the inputs and outputs of the hydraulic experiment, must be extremely precise and noise-free to avoid large errors in the gradient calculations. The PSCOPE framework takes an alternate approach by utilizing an iterative coupling method to achieve the dynamic closed-loop feedback between the two domains while allowing signal conditioning in the hydraulic experiment. We illustrate the concept of this coupling approach

by considering the scenario composed of a rigid experimental domain containing one inlet and one outlet, and a numerical domain representing a simple lumped-parameter circuit (Fig 2A). The numerical domain contains two ordinary differential equations:

$$\frac{dP_1}{dt} = \frac{1}{C_1}\left(\frac{P_i - P_1}{R_1} - Q\right) \qquad (1)$$

$$\frac{dP_2}{dt} = \frac{1}{C_2}\left(Q - \frac{P_2}{R_2}\right) \qquad (2)$$

Q, $P_{subscript}$, $C_{subscript}$, and $R_{subscript}$ represent the flow rate, pressures, capacitance values, and resistance values as indicated in Fig 2A. For any given set of lumped component values, initial values for P_1 and P_2, and a periodic pressure source P_i, this hybrid model has a periodic waveform solution for P_1, P_2, and Q that should satisfy both the governing equations in the numerical model (equations 1 and 2) and the actual measurements across the physical experiment. To implement the information exchange between the domains on a cycle-to-cycle basis, we iteratively improve the entire Q waveform until the correct solution is identified. Based on equations 1 and 2 in the numerical model, a specific Q waveform returns a specific ΔP waveform where $\Delta P=P_1-P_2$, which we refer to as ΔP_{num}. Applying the same Q waveform in the physical experiment and measuring the pressure drop across the region of interest, we obtain another ΔP waveform, referred to as ΔP_{exp}. The Q waveform corresponding to the correct solution of this coupled hybrid model is expected to produce $\Delta P_{num}=\Delta P_{exp}$. By identifying this correct Q waveform, we achieve a direct coupling between the experimental and numerical domains, forming a closed-loop PSCOPE model. In other words, this method matches the boundary conditions between the numerical model and the experiment by ensuring that at the boundary interface, the flow and pressure drop in the experiment match those in the numerical model. This general coupling approach is applicable to PSCOPE models consisting of any complex lumped-parameter circuits.

Iterative solution identification

We designed a protocol (Fig 2B) to identify the correct Q waveform solution while minimizing the number of iterations required. To obtain a good initial guess for Q, we first utilize a mathematical surrogate to approximate the behavior of the physical experiment (Fig S1). A series of steady flow tests are conducted in the physical experiment to relate the flow through the experiment and ΔP_{exp}; for a physical experiment with multiple outlets, this is repeated to relate the flow and the ΔP_{exp} between the inlet and each outlet. An appropriate mathematical equation is chosen and fitted to each set of measured flow and ΔP_{exp} data. Temporarily replacing the physical experiment with the mathematical surrogate, the hybrid model converts to a purely numerical model, allowing a computational simulation to be performed to obtain an initial estimate for the Q waveform (Fig 2C "Initial"). Next, an iterative algorithm adjusts the Q waveform repeatedly (Fig 2C) based on the differences between the resulting ΔP_{num} and ΔP_{exp} waveforms (Fig 2D), continually decreasing the residual which is quantified by the normalized root-mean-square error (NRMSE) between ΔP_{exp} and ΔP_{num} (Fig 2E). This iterative method is analogous to the non-linear iterations in a numerical finite

element simulation for the continual improvement of the solution until an acceptable residual is obtained. Specifically, the *Q* waveform is iteratively adjusted according to the following equation:

$$Q_{n+1} = Q_n + Kp(\Delta P_{\exp} - \Delta P_{num}) \qquad (3)$$

Q_n , Q_{n+1} and K_p represent the *Q* waveform of the current iteration, the adjusted *Q* waveform for the next iteration, and the controller gain, respectively. The value of K_p is optimized to avoid oscillations in the *Q* waveform (K_p value too high) or a very slow progression of waveform adjustments between iterations (K_p value too low). To identify the threshold for the optimal K_p value for a specific PSCOPE, we gradually increase K_p until oscillation in the *Q* waveform occurs. This process does not require significant time as the system's response to each K_p value can be observed within just a few iterations. Once a suitable K_p is identified, we iteratively update the *Q* waveform according to equation 3 until the residual plateaus or falls below a user- specified tolerance.

Physiology simulation

The physiology simulations in this study utilize a previously published lumped parameter network (LPN) of the single-ventricle circulation (Fig S2)[23]. The LPN implementation and specific parameter values are detailed in the supplementary materials. The changes in intra-thoracic pressure due to respiration directly affects central venous blood flow, therefore the respiratory cycle in the physiology simulation defines the periodicity of the PSCOPE. Each respiratory cycle contains four cardiac cycles; the word "cycle" in this paper refers to the respiratory cycle unless otherwise specified. On the contrary, the word "iteration" in this paper refers to each time the *Q* waveform is updated to improve the solution.

PSCOPE verification setup

To quantitatively verify the results from PSCOPE, we model a scenario involving a static experimental section such that existing, established computational multiscale methods[24, 25] are capable of simulating and providing the actual model solutions. We examine the scenario involving an obstruction of the Fontan graft in the cavopulmonary pathway, clinically occurring due to deposition of calcium in the conduit and/or somatic growth and subsequent longitudinal torsion of the graft[26]. The Fontan graft obstruction geometry coupled to the physiology simulation are modeled using both PSCOPE and multiscale computational fluid dynamics (CFD) for result comparisons. The PSCOPE model consists of a hydraulic experiment representing a stenosis in the inferior vena cava (IVC) coupled to the LPN physiology model (Fig 3A). Correspondingly, a computational fluid dynamic simulation of the identical stenosis geometry coupled to the same location in the same physiology model (Fig 3B) provides the reference data for verification. Test cases involving stenosis levels (by area reduction) of 60% and 85% and simulated physiologies of 1 and 5 metabolic equivalent (MET) are used to demonstrate the PSCOPE's ability to model different combinations of physical experiments and physiology simulations. The detailed 3D geometries of the 60% and 85% area obstructions used in the

verification experiments are included in the supplemental materials (Fig S3); each geometry has a patent diameter of 19 mm representing an extra-cardiac conduits implemented during the Fontan surgical operation[27] and contains a lengthy portion downstream of the stenosis to capture the complex flow and the dissipation of vortices shed by the stenosis.

To conduct the PSCOPE, we physically reproduce the 3D geometries using a high resolution 3D-printer (Connex 350 PolyJet, Stratasys Inc., MN) and rigid material (VeroClear, Stratasys Inc., MN). We performed flow experiment, data collection, and data processing using each physical phantom as described in the supplemental materials; each flow experiment is coupled to the Fontan physiology simulations representing 1 and 5 MET.

For the multiscale simulations, each 3D geometry is discretized spatially heterogeneously (with different zones as shown in Fig S3) into a finite element mesh containing linear tetrahedral elements using meshing software (MeshSim, Simmetrix Inc., NY)[28]. The resulting meshes contain a total of 11.1×10^6 and 11.8×10^6 elements for the 85% and 60% stenosis geometries, respectively. Comparing to a previous numerical study investigating stenosis of similar dimensions and Reynolds number[29], the meshes we employ contain numbers of elements that are one order of magnitude higher (Table S1). All of the simulations utilize a time step size of 0.001s. We have included a mesh density and time step size analysis in the supplemental materials. A no-slip boundary condition is applied to the vessel wall of the geometries; pressures from the physiology simulations are coupled to the finite element model at the inlet and outlet faces as Neumann boundary conditions. A Newtonian fluid with density and dynamic viscosity as measured in the PSCOPE experiment is prescribed in the simulations. The 3D solver utilizes a previously validated stabilized finite element method[30-32] to solve the incompressible Navier-Stokes equations. Four and five respiration cycles are simulated for the 1 MET and 5 MET cases, respectively; and results from the last respiration cycle (after stabilized periodicity) are used for analysis. The NRMSE of the pressure drop waveforms across the 3D geometry between the last and second last cycles are <0.6% in all cases, confirming that stable periodicity is achieved.

Example application of PSCOPE

No numerical simulation to date has contained a 3D dynamic model of a blood pump fully coupled in closed-loop with a physiology simulation. We demonstrate the PSCOPE's capability to model such a scenario by investigating the potential use of the Jarvik 2000 (Jarvik Heart, Inc., NY) ventricular assist device implemented in-line in the IVC of single-ventricle circulation for cavopulmonary support[33]. In this investigation, the PSCOPE involves a hydraulic experiment of the Jarvik 2000 device coupled to a computational physiology simulation of single-ventricle circulation (Fig 3C) representing resting condition (1 MET). The supplemental materials detail the physical setup involving the Jarvik device hydraulic experiment.

RESULTS

Verification of the PSCOPE framework

In all cases of the verification experiments, the PSCOPE achieved 1%~6% final residual after 5~10 iterations (Table 1). Various initial guesses for the solution Q waveform converge to the same final solution, although requiring different number of iterations (Fig S4). Results from the multiscale simulation show that under the most severe flow condition (the peak flow time point at 5 MET in the 85% stenosis case), the peak normalized vorticity at the outlet have recovered to similar magnitudes as those at the inlet (Fig 4), suggesting that the length of the 3D geometry downstream of the stenosis is sufficient for capturing the dissipation of vortices shed by the stenosis. Comparing results from the PSCOPE to those from the multiscale simulations, the NRMSE of important physiologic parameters including the IVC flow, pulmonary pressure, and ventricular pressure and volume waveforms range between 0.1% ~ 2.1% in all test cases (Fig 5). The NRMSE of the pressure drop across the 3D geometry (ΔP) is 0.6% ~5.7%, with the 60% stenosis case exhibiting the higher NRMSE due to the signal amplitude being very low; the absolute RMSE of ΔP in the 60% stenosis case are 0.07 mmHg and 0.44 mmHg for 1 and 5 MET, respectively.

Example application in modeling Fontan cavopulmonary support

The PSCOPE reveals the changes in the simulated physiology as the rotor speed setting on the Jarvik 2000 in the hydraulic experiment is physically adjusted (Fig 6A). The simulated cardiac output and pulmonary pressure both increase while the IVC pressure decreases with pump speed. Clinically, venous pressure outside of approximately 0~22mmHg can be considered alarming. While the regular operating RPM range of the Jarvik 2000 produces favorable increases in cardiac output, the pulmonary arterial pressure (equaling the superior vena cava pressure in the Fontan circulation) becomes too high for upper body venous return, and the negative IVC pressure indicates IVC collapse[34]. However, by modifying the off-the-shelf Jarvik controller, we achieved a rotor speed suitable for Fontan cavopulmonary support at approximately 5000 RPM. At this speed, all physiologic pressures stay within safe ranges, and the ventricular preload, systolic pressure, and stroke volume are improved by 14%, 12%, and 16%, respectively, compared to the unsupported scenario as seen from the ventricular pressure-volume loops (Fig 6B). By demonstrating the measured device power consumption fluctuations throughout the cardiac and respiratory cycles (Fig 6C), the PSCOPE also reveals in detail how the physical operation of the Jarvik 2000 is impacted by physiologic rhythms. The solution of the PSCOPE in this case converged to a residual of 1.9% within 17 iterations, requiring a total run time of 1.8 hours. In general, each PSCOPE iteration requires 5~10 minutes of run time; of this, the computation time is negligible and most of the run time is spent on data acquisition and the fine-tuning of actuation control in the physical experiment.

DISCUSSION

Significant advances in biomedical science often leverage powerful computational and experimental modeling platforms. The PSCOPE integrates the two in a unified hybrid framework that can flexibly draw on the strengths of each for constructing a compact and realistic model. The main strength of PSCOPE is that it can experimentally model a scenario that is challenging for numerical simulations (i.e. fluid-structure interactions), and fully couple

the experimental results with a physiology simulation (which is challenging to produce experimentally). The design of the PSCOPE framework features a modular perspective towards the physical experiment, where it is treated as a black box with inputs and outputs. Therefore, the framework is valid for any physical experiment exhibiting a consistent behavior (i.e. a specific combination of inputs produces a specific combination of outputs). The PSCOPE's modular nature also makes it immediately compatible with a range of physiology models such as those incorporating autoregulation[35] or patient-specific tuning[7]. Furthermore, the absence of the real-time operation requirement of this framework means that the hardware bandwidth limitation has minimal restraint on the type of dynamic system that can be modeled and that compatibility with sophisticated numerical methods (those that cannot be performed in real-time, such as 3D simulations) is possible.

The PSCOPE is distinctly different from fixed-input in-vitro models in that the flow condition in the hydraulic experiment dynamically responds to the physiology simulation through closed-loop coupling. This is advantageous in scenarios where it may be difficult to accurately characterize device operating behavior when it interacts with physiology. For example, a blood pump driven in pulsatile mode or implemented in locations where blood flow is highly pulsatile may possess hysteresis in its pump speed and pressure-flow characteristics. In such scenarios closed-loop coupling between the experiment and physiology simulation is necessary to obtain the correct flow condition for the device under test.

Our approach to coupling the experimental and numerical domains contains an iterative design that inherently enables the direct evaluation of the solution quality and the iterative improvement of the solution to satisfy a desired residual. This addresses the technical limitations of previous hybrid model implementations and successfully achieves a high-fidelity hybrid model. The iterative method allows the processing of sensor measurements to remove any interfering signals and averaging to increase the signal-to-noise ratio. The effects of delays due to the signal chain, physical wave propagation, or actuator bandwidth limitation as well as errors due to actuator non-linearity can be removed (as illustrated by the data processing described in the supplemental materials). Through verification against established multi-scale modeling results we confirm that the coupling method we propose for the PSCOPE indeed produces a closed-loop integration of the experimental and computational domains. The verification setup is specifically designed to pose a challenging scenario: the physical experiment represents a part of the venous circulation where the hydraulic signals are small and must be highly precise, and the physiology model contains a sophisticated lumped-parameter network with closed-loop cardiac dynamics. The verification result demonstrates that the practical implementation of PSCOPE can achieve high accuracy in these challenging and physiologically realistic scenarios.

The main limitation of the PSCOPE framework is that its iterative nature results in potentially significant time needed for model execution. In the current study, the PSCOPE runtime for the verification cases were less than the corresponding numerical simulations executed on high-performance computing clusters by one order of magnitude. However, for a PSCOPE model with an experimental section containing multiple outlets, the higher number of flow waveforms to be identified would expand the solution space and can increase the number of iterations and model execution time. The factors affecting model runtime include the input

(actuator response) and output (sensor measurement) signal qualities of the *in-vitro* experiment which affect the number of cyclic repetitions needed in each iteration, the initial solution estimation, the nature of the *in-vitro* experiment, and the desired residual which affect the number of iterations needed to solve each particular model.

While this study demonstrates the application of PSCOPE on modeling a periodic system, the framework is applicable to modeling transient responses. This would require repeating the same physical experiment with the same initial conditions multiple times to reduce signal noise, then using the iterative method we presented to couple the conditioned experimental data with the numerical simulation. In such a case, the solution waveform to be identified is likely to be lengthy and thus the model execution time can be significant.

Current *in-vitro* methods are capable of investigating a variety of medical devices including pulsatile blood pumps, valves, stents, balloons, and occlusion devices, all of which can be physically implemented as part of a PSCOPE model; albeit physical experiments containing deformable sections or multiple outlets will require the development of a more capable waveform identification algorithm. As physiology simulations continue to advance, the PSCOPE can enable cardiovascular devices to be physically tested in-vitro with physiologic feedback as if implanted in a living patient. Since the bench top physical experiment is coupled directly in-the-loop with a computational physiology simulation, it operates in a dynamically changing feedback environment with the physiology simulation. This allows one to obtain the same relevant information such as device operation and physiologic impacts as if performing an in-vivo human experiment. Potential applications of the PSCOPE in interventional planning and clinical decision support may also help advance a variety of cardiovascular procedures. For example, in addition to further investigations of blood pumps for Fontan cavopulmonary support, we plan to extend the application of PSCOPE to study the efficacy and outcomes of transcatheter pulmonary valve replacement procedures. Continued advancements and validation of the available physiology models as well as clinical validation of the predictions made by the PSCOPE are critical issues that need to be addressed before clinical translation of this tool.

ACKNOWLEDGMENTS:

We are grateful to the reviewers for their constructive feedback; J. Teal and J. Triolo at Jarvik Heart Inc. for the equipment loan; B. Ramirez for manuscript editing assistance; T. Crain and C. Mahaffey for assistance with figure preparation and photography; G. Fadel for providing 3D printing; A. Updegrove and A. Verma for their assistance in meshing and CFD methods; and Clemson University for generous allotment of compute time on the Palmetto cluster.

FUNDING

This work was supported by Clemson University, an award from the American Heart Association and The Children's Heart Foundation (16SDG29850012), and an award from the National Science Foundation (CAREER1749017). The funding sponsors of this work have no

involvement in the study design, the collection, analysis and interpretation of data, in the writing of the manuscript, and in the decision to submit the manuscript for publication.

NOMENCLATURE

CFD = computational fluid dynamics
HIL = hardware-in-the-loop
IVC = inferior vena cava
LPN = lumped parameter network
MET = metabolic equivalent
NRMSE = normalized root-mean-square error
PSCOPE = Physiology Simulation COuPled Experiment

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Figures and Figure Legends

Fig. 1 Overall structure of a (A) Numerical multiscale simulation and (B) Hardware-in-the-loop hybrid model. The PSCOPE framework is a high-fidelity implementation of the hardware-in-the-loop hybrid modeling approach.

Fig. 2 (A) Schematic of an example PSCOPE model. $R_{subscript}$ and $C_{subscript}$ are resistance and capacitance values, respectively. $P_{subscript}$ represent pressures at the corresponding locations; Q is the volumetric flow rate through the physical experiment. (B) Overall structure of the protocol for identifying the solution Q waveform coupling the experimental and numerical domains. (C to E) Convergence of the PSCOPE model solution in a scenario containing a realistic numerical physiology model and a physical Jarvik 2000 blood pump operating at 5000 RPM. (C) The Q waveform initial estimate is updated and improved across iterations. (D) The difference between the ΔP_{num} and ΔP_{exp} waveforms decreases with iterations. (E) The decreasing residual errors between ΔP_{num} and ΔP_{exp} show the convergence of the PSCOPE model over iterations.

Fig. 3 PSCOPE verification and example application setup.

Hour-glass symbol denotes the insertion location where either a physical experiment (A, C) or a computational fluid dynamic (CFD) simulation (B) is coupled to the lumped-parameter circuit physiology model of the single-ventricle circulation. (A and B) Verification of the PSCOPE against multiscale CFD simulations. Flow through a stenosis geometry is replicated in a hydraulic experiment (A) and simulated by CFD (B), resulting in a PSCOPE model and a multiscale simulation, respectively. (C) An application of the PSCOPE modeling a scenario where a Jarvik 2000 blood pump device is implemented for cavopulmonary support.

Fig. 4 Multiscale simulation results at peak flow

Vorticity results at the peak flow time point from multiscale CFD simulation modeling the 85% IVC stenosis at 5 MET physiology. The maximum normalized vorticity is the maximum vorticity at the slice location normalized to that at the inlet.

Fig. 5 (A) 60% stenosis cases. (B) 85% stenosis cases. Blue and red lines represent physiologies of 1 and 5 MET. Solid and dashed lines represent PSCOPE and multi-scale simulation results. Q_{ivc}, P_{pul}, and ΔP represent the IVC flow, pulmonary artery pressure, and pressure drop across the stenotic 3D geometry, respectively. The normalized root-mean-square error (NRMSE) of important parameters demonstrates the accuracy of the PSCOPE. Data from one respiratory cycle (four cardiac cycles) is shown.

Fig. 6 An example application of the PSCOPE for modeling a scenario beyond the current capabilities of numerical simulations; the PSCOPE captures the closed-loop interactions between the physical experiment involving the Jarvik 2000 and the simulated physiology. (A) Mean values of important physiologic parameters corresponding to different pump rotor speed settings show favorable physiology at approximately 5,000 RPM, below the normal operating range of the commercial device. (B and C) Detailed results at pump speed setting of 5,000 RPM; data from one respiratory cycle (four cardiac cycles) is shown. (B) Ventricular pressure-volume loops show increased preload, stroke volume, and aortic pressure with cavopulmonary support compared to the reference case without pump support. (C) The physical operation of the Jarvik 2000 is impacted by physiologic rhythms as the device power consumption fluctuates with the changing IVC flow throughout the cardiac and respiratory cycles.

FIGURES:

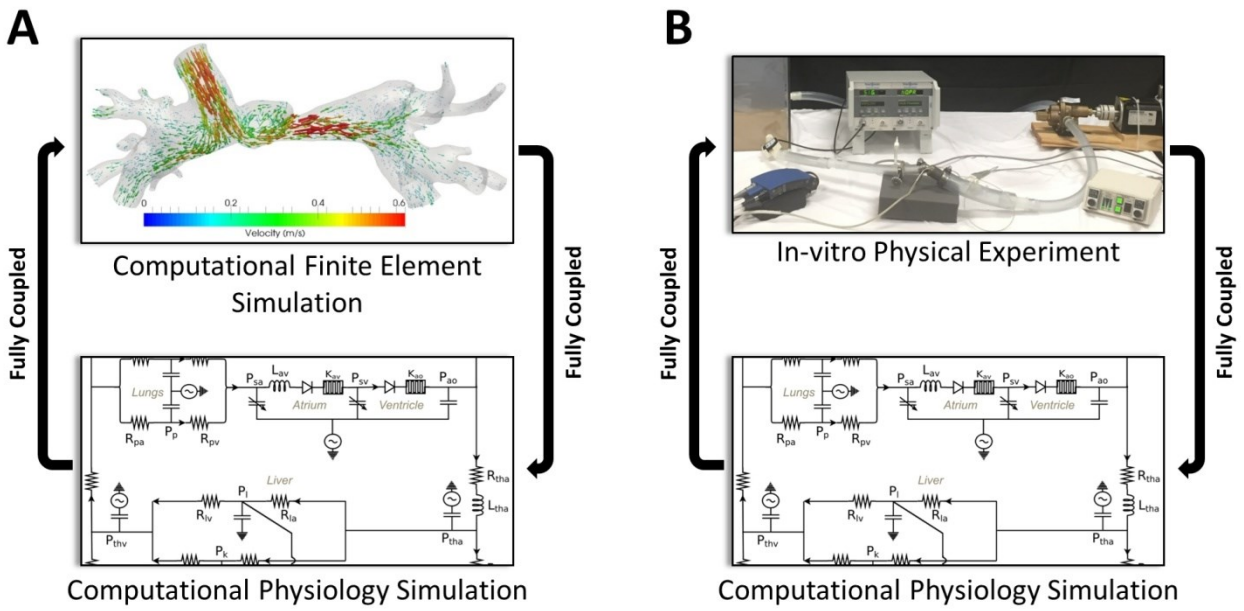

Fig 1.

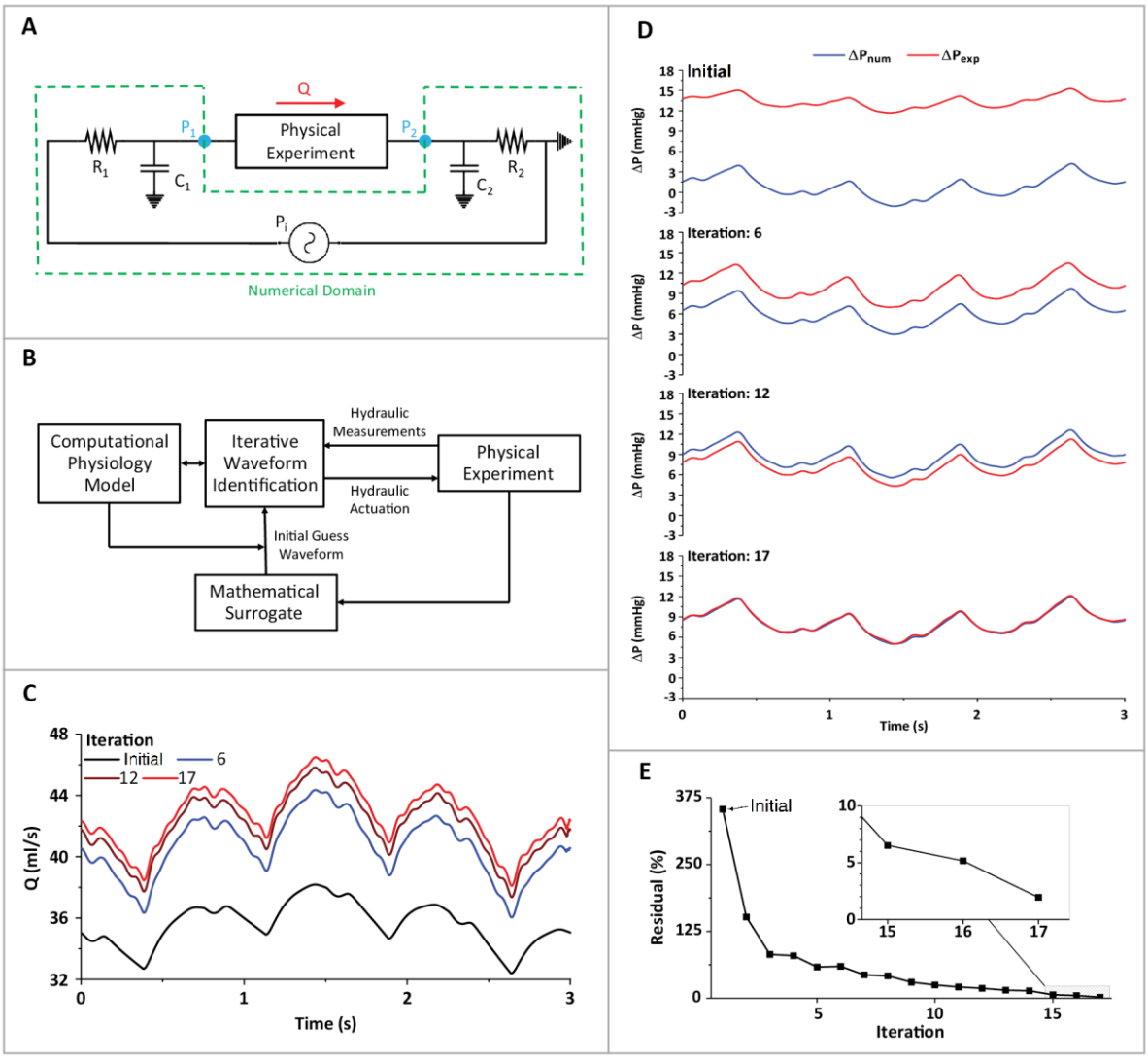
A
Q
P1
P2
Physical Experiment
R1
C1
C2
R2
Pi
Numerical Domain
B
Computational Physiology Model
Iterative Waveform Identification
Hydraulic Measurements
Hydraulic Actuation
Physical Experiment
Initial Guess Waveform
Mathematical Surrogate
C
Iteration
Initial
6
12
17
Q (ml/s)
Time (s)
D
ΔPnum
ΔPexp
Initial
Iteration: 6
Iteration: 12
Iteration: 17
ΔP (mmHg)
Time (s)
E
Initial
Residual (%)
Iteration

Fig 2.

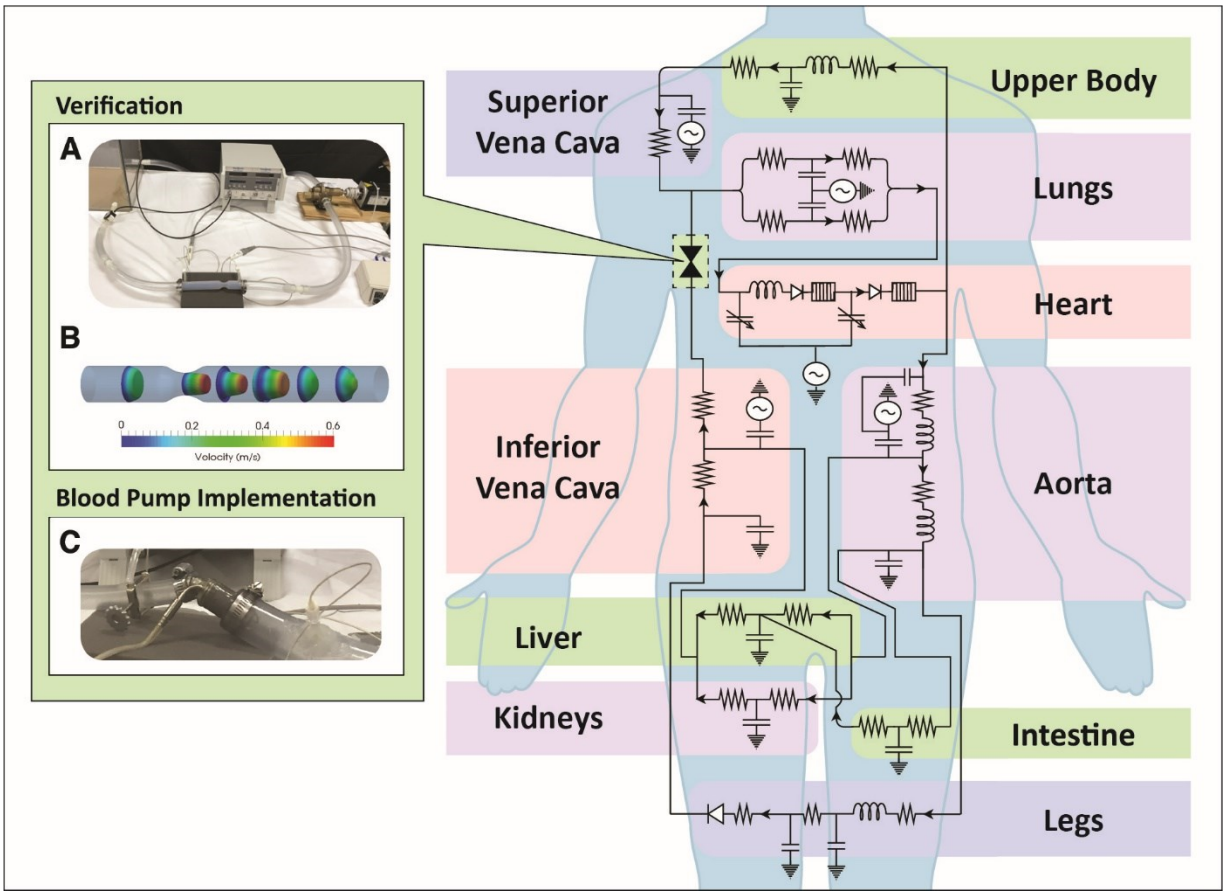
Verification
A
B
0
0.2
0.4
0.6
Velocity (m/s)
Blood Pump Implementation
C
Superior Vena Cava
Upper Body
Lungs
Heart
Inferior Vena Cava
Aorta
Liver
Kidneys
Intestine
Legs

Fig 3.

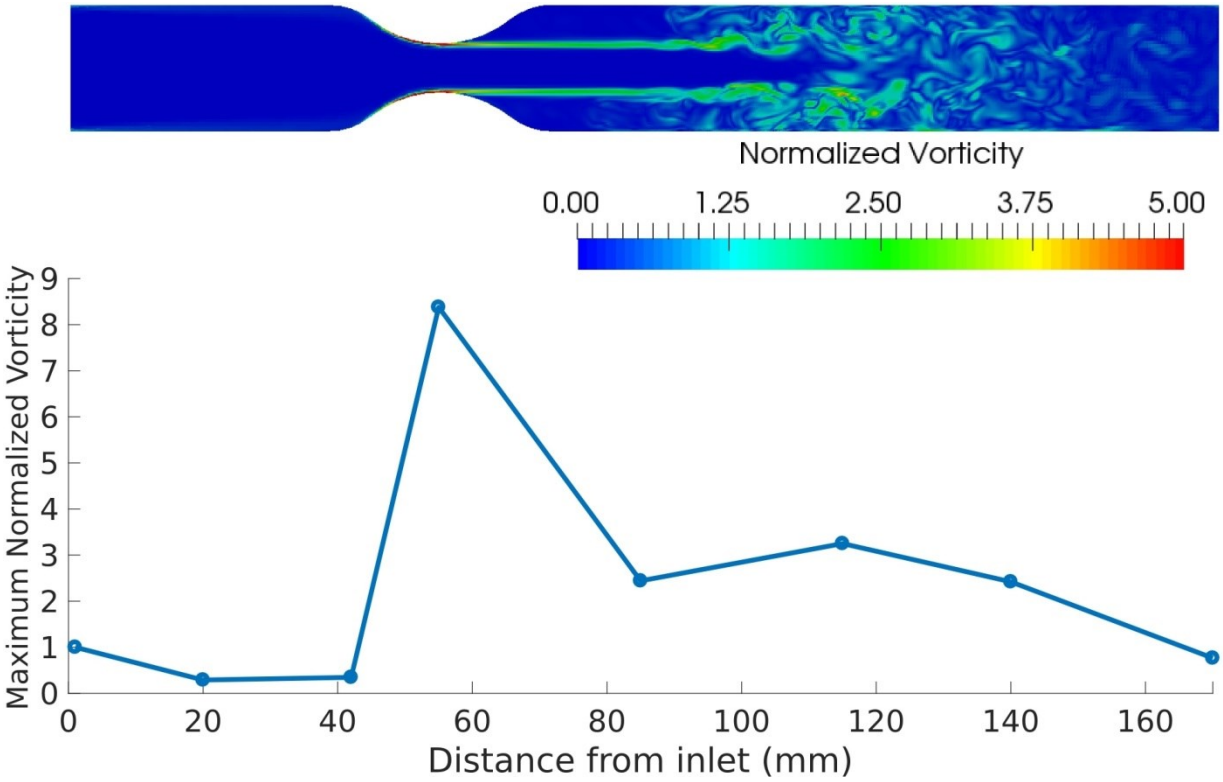
Normalized Vorticity
0.00
1.25
2.50
3.75
5.00
Maximum Normalized Vorticity
0
1
2
3
4
5
6
7
8
9
0
20
40
60
80
100
120
140
160
Distance from inlet (mm)

Fig 4

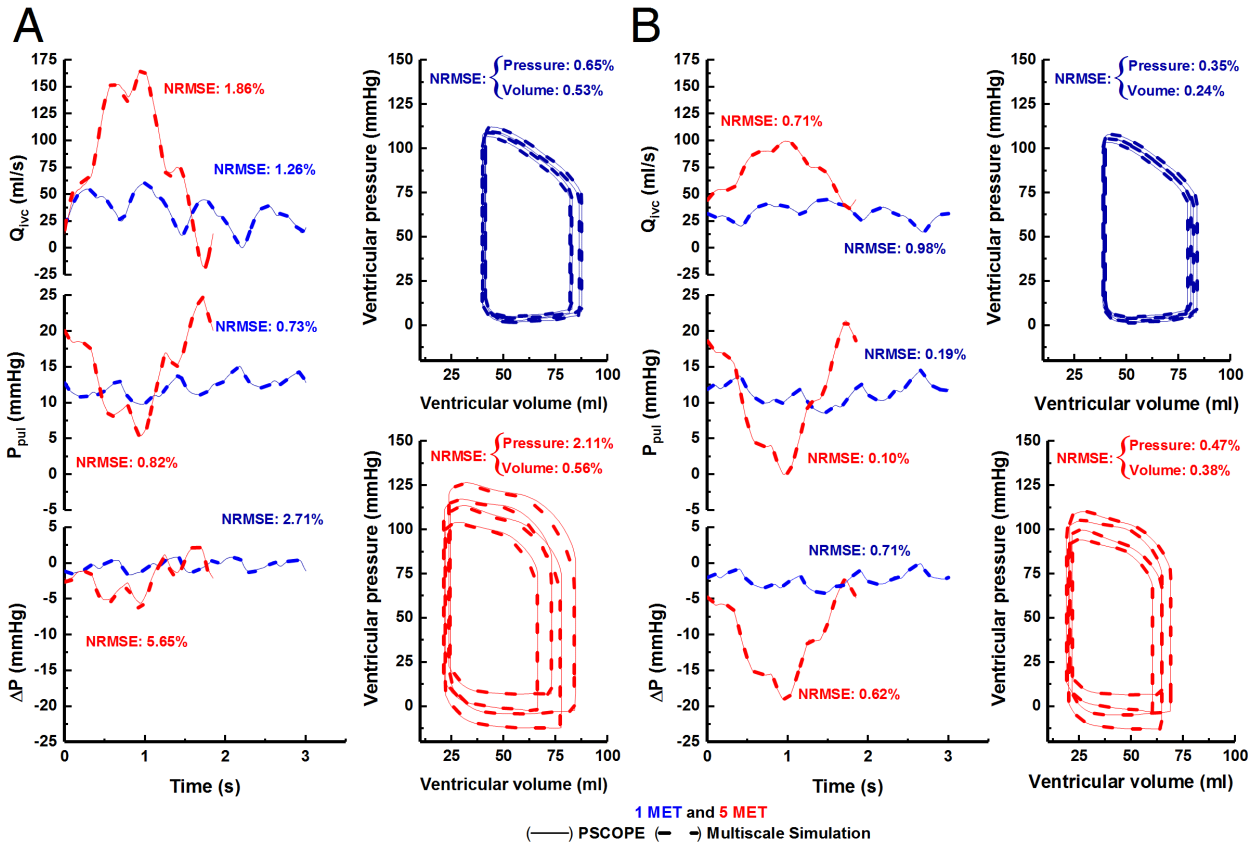
A
B
NRMSE: 1.86%
NRMSE: 1.26%
NRMSE: 0.73%
NRMSE: 0.82%
NRMSE: 2.71%
NRMSE: 5.65%
NRMSE: 0.71%
NRMSE: 0.98%
NRMSE: 0.19%
NRMSE: 0.10%
NRMSE: 0.71%
NRMSE: 0.62%
NRMSE: Pressure: 0.65% Volume: 0.53%
NRMSE: Pressure: 2.11% Volume: 0.56%
NRMSE: Pressure: 0.35% Voume: 0.24%
NRMSE: Pressure: 0.47% Volume: 0.38%
Q_ivc (ml/s)
P_pul (mmHg)
ΔP (mmHg)
Time (s)
Ventricular pressure (mmHg)
Ventricular volume (ml)
1 MET and 5 MET
(——) PSCOPE (- - -) Multiscale Simulation

Fig 5.

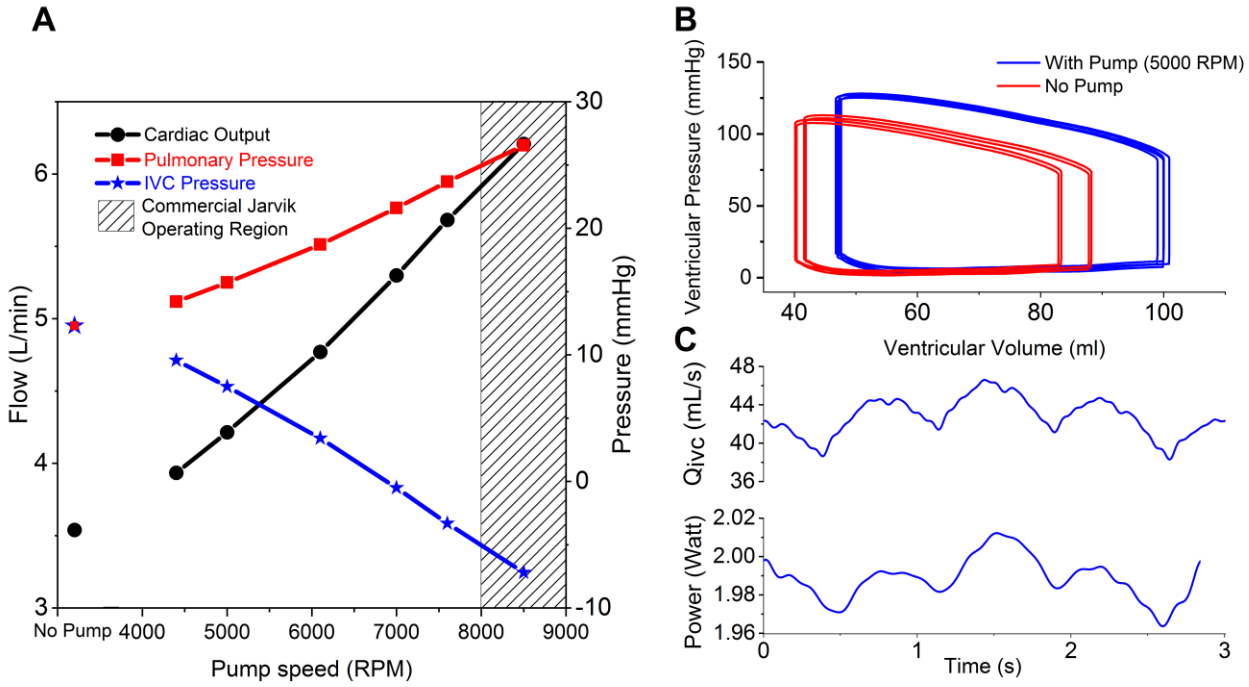
A
Cardiac Output
Pulmonary Pressure
IVC Pressure
Commercial Jarvik
Operating Region
Flow (L/min)
Pressure (mmHg)
No Pump
Pump speed (RPM)
B
With Pump (5000 RPM)
No Pump
Ventricular Pressure (mmHg)
Ventricular Volume (ml)
C
Qivc (mL/s)
Power (Watt)
Time (s)

Fig 6.

Table Caption List

Table 1 Final residual and number of iterations of the PSCOPE execution for the verification test cases.

TABLES:

MET		60% stenosis case	85% stenosis case
1	Final Residual	6.12%	2.04%
	Number of iterations	7	9
5	Final Residual	2.71%	1.19%
	Number of iterations	10	5

Table 1.