Pump efficacy in a fluid-structure-interaction model of a chain of contracting lymphangions

Hallie Elich 1 · Aaron Barrett 1 · Varun Shankar2 · Aaron L. Fogelson1,3

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Abstract The transport of lymph through the lymphatic vasculature is the mechanism for returning excess interstitial fluid to the circulatory system, and it is essential for fluid homeostasis. Collecting lymphatic vessels comprise a significant portion of the lymphatic vasculature and are divided by valves into contractile segments known as lymphangions. Despite its importance, lymphatic transport in collecting vessels is not well understood.

We present a computational model to study lymph flow through chains of valved, contracting lymphangions. We used the Navier-Stokes equations to model the fluid flow and the immersed boundary method to handle the two-way, fluid-structure interaction. We used our model to evaluate the effects of chain length, contraction style, and adverse axial pressure difference on cycle-mean flow rates (CMFRs).

In the model, longer lymphangion chains generally yield larger CMFRs, and they fail to generate positive CMFRs at higher adverse pressure differences than shorter chains. Simultaneously contracting pumps generate the largest CMFRs at nearly every adverse pressure difference and for every chain length. Due to the contraction timing and valve dynamics, non-simultaneous pumps generate lower CMFRs than the simultaneous pumps; the discrepancy diminishes as the adverse pressure difference increases. Valve dynamics vary with the contraction style and exhibit hysteretic opening and closing behaviors. Interior-valve closure occurs only in the non-simultaneous pumps. In all pumps, the outlet valve remains shut throughout a contraction cycle when the adverse pressure difference is sufficiently large. Our model provides insight into how contraction propagation affects flow rates and transport through a lymphangion chain.

Keywords Computational model · Lymphatic contraction · Lymphatic transport · Lymphatic valves · Pump-function plots

1 Introduction

The lymphatic vasculature is a structural component of the lymphatic system, and its primary function is to return around 4 L/day (Renkin 1986) of interstitial fluid to the venous circulation. Once interstitial fluid enters the blind-ended, initial lymphatic vessels, it is referred to as lymph. Lymphatic transport is crucial for fluid homeostasis, but it is also important more broadly in immunology and cancer biology (Shields et al. 2007; Swartz and Lund 2012; Wiig and Swartz 2012). Impaired lymph transport results in an accumulation of fluid, or lymphedema. Worldwide, secondary lymphedema is often seen in cases of lymphatic filariasis infection or after lymph node removal in cancer-related surgeries (Rockson 2001). However, there are also instances of primary lymphedema stemming from inherent pathologies in the lymphatic vasculature, e.g., related to genetic aberrations (Rockson 2001). Lymphedema can be painful and disfiguring; mainstream treatments are limited to compression garments.

Despite its importance, lymphatic transport is poorly understood. This is somewhat surprising given that lymphatic studies, like those for the cardiovascular system,
date back hundreds of years. However, compared to blood vessels, lymphatic vessels were long-regarded as passive drainage routes, they were difficult to find and dissect, and they lacked specific cell markers until the turn of the 21st century. Given advances in science and technology, lymphatic vascular biology has undergone a resurgence in the past 20-40 years.

Numerous biological experiments have been performed, especially on isolated rat mesenteric collecting lymphatic vessels (Davis et al. 2009a, 2009b, 2011, 2012; Scallan et al. 2012, 2013; Zawieja 2009). Collecting lymphatic vessels are segmented by valves into functional units known as lymphangions. Lymphangions can actively contract in a cyclical manner to propel lymph against an adverse pressure gradient. Considering the fragility and size of most collecting lymphatics, impressively technical biology experiments have been performed to better understand their contractile properties. Complementary to biological studies, computational models have been developed with aims of better understanding lymph flow through these intricate vessels.

Lumped-parameter models of collecting lymphatics first appeared in the literature in the 1970s (Reddy et al. 1975, 1977). Since then, additional quantitative models have been developed though most are also lumped-parameter and generally feature flow through one or more contractile lymphangions with valves modelled as resistors (Bertram et al. 2010; Quick et al. 2007; Venugopal et al. 2007). Lumped-parameter models from the Bertram group comprise most of the recent quantitative lymphatic literature. Various generations of their 2010 model have been developed (Bertram et al. 2014a, 2014b, 2017; Jamalian et al. 2013) and used to simulate pumping in chains of lymphangions (Bertram et al. 2016, 2018; Jamalian et al. 2016, 2017). The model (Jamalian et al. 2013) was also used with an experimentally based constitutive relation for vessel wall mechanics (Caulk et al. 2016; Razavi et al. 2017). Zero-dimensional (lumped) models are tractable and especially useful in simulating flow through vessel networks (Jamalian et al. 2016; Reddy et al. 1977). However, they provide little insight into the fluid-structure interaction (FSI); higher-dimensional models are needed to resolve flow details and elucidate valve behaviors among adjacent, contractile lymphangions. While higher-dimensional models of collecting vessels or their valves have been developed (Ballard et al. 2018; Cooper 2016; Kunert et al. 2015; Li et al. 2019; Macdonald et al. 2008; Rahbar and Moore JE 2011; Watson et al. 2017; Wilson et al. 2013, 2015, 2018), they all make restrictive assumptions on the flow, the FSI, the vessel or valve geometry, or the number of lymphangions.

In the current work, we present a novel, two-way-FSI, computational model that we used to study flow through various-length chains of contracting lymphangions. Simultaneous, forward-travelling (orthograde), and backward-travelling (retrograde) contractions are considered. For all chain lengths and at nearly all adverse axial pressure differences, the simultaneously contracting pumps yield the largest cycle-mean flow rates (CMFRs). Lengthening the chain generally leads to increased CMFRs and higher adverse axial pressure differences at which the pump fails to yield positive CMFR. In addition to performing pump-function studies, we used simulation videos and velocity-field, pressure, diameter, valve-dynamics, flow-rate, and tracer-transport plots to assess pump behaviors. The model provides insight into lymphatic transport and contributes to the quantitative lymphatic biology field.

The paper is organized as follows. In Section 2, we present the model. In Section 3, we provide results from benchmark simulations, pump-function studies, and pump-behavior analyses. In Section 4, we discuss the results and compare them to the literature.

2 Model

We implement the immersed boundary (IB) method to simulate lymph flow through contracting lymphangions. The IB method was developed by Charles Peskin in the 1970s (Peskin 1972, 1977) and numerically implemented to study the fluid dynamics of blood flow around moving valves in a computational model of a contracting heart. Since then, this two-way, fully coupled method has been applied in a wide variety of FSI problems. Some of the biofluid applications involve swimming organisms (Dillon et al. 1995; Fauci and McDonald 1995; Fauci and Peskin 1988; Hamlet et al. 2018; Hoover and Miller 2015; Lim and Peskin 2012), cochlear dynamics (Beyer 1977), biofilm processes (Dillon et al. 1996), insect flight (Miller and Peskin 2004, 2005), esophageal transport (Fogelson 1984; Fogelson and Guy 2008), arteriolar flow (Arthur et al. 1998), heart development (Battista et al. 2017), and bioprosthetic heart valves (Lee et al. 2020).

2.1 Model geometry

We define an in silico model geometry representative of a portion of a collecting lymphatic vessel. The model vessel comprises a chain of one to four contractile lymphangions separated by valves. Define a rectangular region, \( \Omega = [0, aL] \times [0, bL] \) in \( \mathbb{R}^2 \), filled entirely with fluid and define a subset \( \Gamma \subset \Omega \) that is a capsular-shaped, closed curve with semicircular endcaps, arched
protrusions, and interior processes; see Fig. 1 for an illustration of a 4-lymphangion chain. We call $\Gamma$ the immersed boundary (IB). Away from the semicircular endcaps, the IB corresponds to the vessel wall and valves; the arched protrusions correspond to the valve-sinus regions, and the line-segment interior processes represent the valve leaflets.

The semicircular endcaps enclose regions where fluid can enter or leave $\Omega$. The fluid source\(^1\) supports are shown as blue squares in Fig. 1. For each of the two sources inside the vessel, an Ohm’s-law equation governs flow rates based on the difference in pressure between a virtual\(^2\) reservoir (in which pressure is prescribed) and the source support (over which the computational pressure is averaged). Each reservoir and source support are virtually connected with tubing and a cannulation pipette. To allow for volume changes inside the lymphangion chain, a source is placed exterior to the capsule; see Fig. 1. Flow through it is set equal and opposite to the net inflow through the endcap sources. The source setup is similar to that used by Arthurs et al. (1998).

We simulate a vessel filled with lymph and immersed in an interstitial fluid/tissue mix comprising the interstitium. We model the interstitium as a fluid-filled porous medium. The model setup corresponds to those in ex vivo biology experiments on cannulated, isolated vessel segments immersed in physiological solution. However, the porous media in the current work damps the fluid velocity outside the vessel. Additionally, one can readily alter the interpretation of the endcap connections as instead corresponding to virtual upstream and downstream lymphangions. Thus, our model is relevant for simulating flow through lymphangions in either an \textit{ex vivo} or \textit{in vivo} experimental setting. The current work focuses on an \textit{ex vivo} setting.

\(^{1}\) We use the term “source” liberally throughout this work to obviate the need for repeating “source or sink.”

\(^{2}\) By virtual, we describe something that is implicitly rather than explicitly included in the physical model domain.

2.2 Model equations

As in Peskin (1977), we assume $\Omega$ is filled with a viscous, incompressible, Newtonian fluid of constant viscosity and density and that $\Gamma$ is neutrally buoyant. Thus, lymph and interstitial fluid are assumed Newtonian, and the vessel wall and valves are assumed neutrally buoyant in lymph and in the interstitium. The IB formulation of the model consists of the system of equations:

$$
\rho \left( u_t + \nabla \cdot \begin{pmatrix} u \\ u \end{pmatrix} \right) = -\nabla p + \mu \Delta u + f - \kappa \sigma u,
$$  \hspace{1cm} (1)

$$
\nabla \cdot u = \sum_{i=1}^{2} Q_i(t) \psi_i(x),
$$  \hspace{1cm} (2)

$$
Q_i(t) = \frac{1}{R_i} \left\{ p_{i,\text{ext}}^\text{c}(t) - \int_{\Omega_{\text{2D}}} p(x, t) \psi_i(x) \, dx \right\},
$$  \hspace{1cm} (3)

$$
f(x, t) = \int_{\Gamma} F(s, t) \delta(x - X(s, t)) \, ds,
$$  \hspace{1cm} (4)

$$
\frac{\partial X}{\partial t}(s, t) = u(X(s, t), t) = \int_{\Omega_{\text{2D}}} u(x, t) \delta(x - X(s, t)) \, dx,
$$  \hspace{1cm} (5)

$$
u(x, 0) \equiv 0,
$$  \hspace{1cm} (6)

where $u$ is the fluid velocity, $p$ is the pressure, $f$ is the Eulerian force density, and $\sigma$ is an indicator function that is 1 outside the vessel and 0 inside the vessel; each is a function of $x$ and $t$. The functions $Q_i$, $\psi_i$, and $p_{i,\text{ext}}^\text{c}$ are described below. The IB configuration at time $t$ is $X(s, t)$ with $0 \leq s \leq l$, and $F$ is the Lagrangian force density. The Dirac delta distribution appears in Eqs. 4-5. Also, $\rho$ and $\mu$ are the constant fluid density and dynamic viscosity, respectively; $\kappa$ is a Brinkman
damping constant; and \( R_i \) for \( i = 1, 2 \) are resistances associated with cannulation pipettes and tubing.

Because the model geometry lies in a 2D subspace of \( \mathbb{R}^3 \), we assume nothing varies in the z-direction (which is orthogonal to the plane in which \( \Omega \) lies) at least for some distance \( L_z \), and we assume vector z-components are all 0. Define \( I_{2D} := [0, aL] \times [0, bL] \times [0, L_z] \). We use periodic boundary conditions in the x- and y-directions; all dependent variables in Eqs. 1-6 with \( x \)-dependence are periodic functions on \( \Omega \).

Eq. 1 is the Navier-Stokes momentum equation with the advective term written in conservative form, with a body force-density term (the Eulerian force density), and with a Brinkman (porous media) term. The body force-density is present due to the IB forces, and the Brinkman term acts to damp the velocity only outside the vessel due to the interstitium.

The usual incompressibility constraint, \( \nabla \cdot \mathbf{u} = 0 \), is modified in Eq. 2 to account for the fluid sources. The volumetric flow rates at the left and right fluid sources are denoted \( Q_1 \) and \( Q_2 \), respectively. Wherever \( i \) appears and unless specified otherwise, it is for \( i = 1, 2 \). We define \( \psi_i(\mathbf{x}) = \psi_i^f(\mathbf{x}) - \psi_i^c(\mathbf{x}) \), with \( \psi_i^f, \psi_i^c \geq 0 \), and require
\[
\int_{\Omega_{2D}} \psi_i^f(\mathbf{x}) \, d\mathbf{x} = 1 \quad \text{and} \quad \int_{\Omega_{2D}} \psi_i^c(\mathbf{x}) \, d\mathbf{x} = 1. \tag{7}
\]
We also require these functions to not vary in the z-direction. Here, \( \psi_i^f \) corresponds to the (real) source labelled \( i \) inside the vessel segment, and \( \psi_i^c \) corresponds to the (compensatory) source outside the vessel segment. In multiplying \( Q_i \) and \( \psi_i \) in Eq. 2, we distribute the \( \psi_i^c \) and integrate over the support of \( \psi_i^c \) in a weighted manner according to the \( \psi_i^f \) function values. Our treatment of sources and flow rates is similar to that in Arthurs et al. (1998) and in Peskin (1977).

In Eq. 3, we assume \( R_i \) and \( P_i^{ext} \) are given resistances and reservoir pressures, respectively. We set \( P_i^{ext}(t) = P_i^{coeff} \tan(t) \); thus, we ramp up the pressure gradually at the start of each calculation. The computational pressure is averaged over the source support, but in the integral, \( \psi_i = \psi_i^f - \psi_i^c \) appears due to the need for a reference pressure. We average the computational pressure over the compensatory source and use this as the reference pressure. We consider this equal to the pressure with respect to which \( P_i^{ext} \) is measured. We give more details on this in Sect. 1.2 of the Supplementary Information (SI); see Online Resource 0.

In Eqs. 4-5, \( X(s,t) \) appears. In the IB method, a Lagrangian representation of \( \Gamma \) is used. We parameterize each curve comprising \( \Gamma \) with respect to arc length. Namely, there is a closed, capsular curve for the vessel wall and an open-curve line segment for each valve leaflet. We parameterize the capsule using notation \( X_c(s_c,t) \) for \( 0 \leq s_c \leq l_c \) and a valve leaflet using \( X_i(s,v,t) \) for \( 0 \leq s_v \leq l_v \), where \( l_c \) is the arc length of the capsule in its initial configuration, and \( l_v \) is the arc length of the valve leaflet initial configuration. In practice, additional notation is used to distinguish top and bottom leaflets and multiple valves, but for ease of notation and unless stated otherwise, we write \( X(s,t) \) with \( 0 \leq s \leq l \) to indicate the collection of curves comprising \( \Gamma \) (each of whose \( s \)-parameters vary within their individual ranges). The Lagrangian variable \( s \in [0,l] \) labels a material point, namely the point with (Eulerian) coordinates \( X(s,t) \) on \( \Gamma \) at time \( t \). Throughout this work, we generally use capital letters to denote functions of the Lagrangian variable and lowercase letters to denote Eulerian variables and functions thereof.

Eqs. 4-5 are fluid-structure-interaction equations. The kernel is a scaled, 2D Dirac delta distribution, i.e.,
\[ \delta(\mathbf{x}) = \frac{1}{L_z} \delta(x) \delta(y), \]
where \( \delta(x) \) and \( \delta(y) \) are 1D Dirac delta distributions. In Eq. 4, the Lagrangian force density, \( \mathbf{F} \), is recast as an Eulerian force density, \( \mathbf{f} \), which acts on the fluid in Eq. 1. In Eq. 5, the boundary moves with the fluid and satisfies a no-slip condition. The integral part of the equation comes from the defining property of the Dirac delta distribution. In the IB method, the boundary moves at the local fluid velocity, forces are generated in association with the deformed boundary, and these forces are spread to the nearby fluid.

It remains to describe the boundary forces. The Lagrangian force density is often defined as negative the first variational derivative of an energy functional. The energy functional depends on the boundary configuration, \( X(s,t) \). The choice of the energy functional is motivated by the desired material properties of the IB; it is common to use more than one energy functional, each giving rise to a different type of Lagrangian force density. In our model, the vessel wall and valve leaflets resist stretching, compression, and bending. Thus, we consider tension and bending elastic energy functionals (Peskin 2007):
\[
E_T[X(\cdot,t)] = \frac{1}{2} \int_0^l k_t \left( \left\| \frac{\partial X(s,t)}{\partial s} \right\| - l_0(s) \right)^2 \, ds, \tag{8}
\]
and
\[
E_B[X(\cdot,t)] = \frac{1}{2} \int_0^l k_b \left( \frac{\partial^2 X(s,t)}{\partial s^2} - \frac{\partial^2 X^0(s)}{\partial s^2} \right)^2 \, ds, \tag{9}
\]
where \( X^0(s) \) is a reference configuration for the curve \( X(s,t) \) with \( 0 \leq s \leq l \); \( l_0(s) = \left\| \frac{\partial X^0(s)}{\partial s} \right\| \); and \( k_t \) and \( k_b \) are tension and bending constants, respectively.
We use the initial capsule configuration as the reference configuration. The same functionals are used for valve leaflets but with $k_t$ and $k_b$ replaced with $k_t$, and $k_b$, respectively. Each leaflet’s initial configuration is used as its reference configuration. In numerical implementation of the IB method, the energy functionals are discretized, and then finite differences are taken to approximate Lagrangian force densities. The details and equations for the tension and bending Lagrangian force densities are provided in Sect. 2 of the SI.

In addition to tension and bending-resistant forces, we use spring forces to tether portions of the vessel wall or valve leaflets to fixed physical locations. Tether forces act along the semicircular endcaps and aim to keep them relatively fixed in space as if the vessel ends were attached to stationary cannulating pipettes. Additionally, since regions of the vessel wall near the valve-insertion sites are fortified with collagen in vivo in rat mesenteric lymphatics (Rahbar et al. 2012) and in cat mesenteric lymphatics (Vajda and Tomcsik 1971), we tether these “valve-stiffness” regions to their initial locations so they are less mobile; see Fig. 2 which shows regions along the IB where different forces are modelled. We also weakly tether the remaining parts of the vessel wall to their initial locations to represent forces from circumferentially oriented components of the vessel that act to maintain vessel shape.

For strong tether forces used along the semicircular endcaps and valve-stiffness regions, we use a Hookean spring model

$$F_{\text{teth},k} = K_{\text{teth}} \left( X^\text{teth}_k - X_k \right) \quad \text{(10)}$$

for the Lagrangian force density at the IB point $X_k$ arising due to its connection to the tether point $X^\text{teth}_k$. We refer to the collection of points comprising the discretized boundary as IB points. See Sect. 1 of the SI for discretization information and notation. We use a similar equation for capsule IB points weakly tethered to their initial locations but with a smaller spring constant, $K_{\text{teth,weak}}$; see Table 1.

To implicitly model the downstream valve-insertion points that are located outside our 2D model plane, we include conditional tether spring forces (buttress forces) that resist leaflet endpoints from opening too wide or moving upstream of their initial locations. For example, the vertical force at an upper valve leaflet endpoint with $y$-coordinate $Y_k$ is given by

$$G_{bo} = \begin{cases} K_{bo} (Y_{bo} - Y_k) & Y_k > Y_{bo} \\ 0 & Y_k \leq Y_{bo} \end{cases}, \quad \text{(11)}$$

where $Y_{bo}$ is the buttress-opening target point. We set $Y_{bo}$ to be one-half the initial-configuration tube radius above the vessel midline. With slight abuse of notation, we provide the force in Eq. 11 rather than a force density, as it is a force acting only at the leaflet endpoint. A similar conditional force acts at the endpoint of each bottom leaflet. The horizontal force at a valve leaflet endpoint with $x$-coordinate $X_k$ is

$$F_{bu} = \begin{cases} K_{bu} (X_{bu} - X_k) & X_k < X_{bu} \\ 0 & X_k \geq X_{bu} \end{cases}, \quad \text{(12)}$$

where the initial-configuration leaflet endpoint is $X_{bu}$. A similar conditional force acts at the endpoint of each bottom leaflet.

In the model, flow occurs via pressure-driven sources and lymphangion contractions. We drive contraction by prescribing diameter-reducing forces along regions of each lymphangion where the muscle cells are predominantly located and circumferentially oriented (Bridenbaugh et al. 2013). Within a model lymphangion, the contractile region extends along the downstream portion of the sinus region and terminates adjacent to the downstream valve-stiffness region; see Fig. 2. The contraction force pointing downward at each upper contractile-region IB
The peak contraction force occurring approximately 0.89 s after contraction onset is similar to that in Bertram et al. (2016) and to the experimental reports by Zweifach and Prather (1975) on rat mesenteric lymphatics. The steeper descent than ascent of the curve in Fig. 3 yields brisk contractions and slower relaxations which are physiological (Macdonald et al. 2008; Zweifach and Prather 1975).

We use time-delay shifts of $G_c(t)\Delta s$ (on the interval $0 \leq t \leq 2.5$ s) and replicate them periodically in time to construct contraction forces for the non-simultaneous pumps. The time delays vary along the contractile regions. For example, in the orthograde contractions, the leftmost contractile-region IB point in the far-upstream lymphangion has contraction force that is a periodic replication of $G_c(t)\Delta s$. The contraction force at the rightmost contractile-region IB point is given by a periodic replication of $G_c(t-t_{delay})\Delta s$. The delay, $t_{delay}$, is computed by dividing the arc length of the entire portion of the initial-configuration vessel wall between these bounding IB points by the travelling-wave velocity. The intermediate contractile-region IB points have contraction forces with time-delays that are fractional multiples of $t_{delay}$, with the fraction equal to the ratio of the appropriate initial-configuration arc lengths.

We set the travelling-wave velocity to 2 or 4 mm/s. We refer to the former as slow or just orthograde or retrograde, depending on the direction, and the latter as fast-orthograde or fast-retrograde, equivalently orthograde x2 or retrograde x2, and depending on the direction. Contractions in rat mesenteric lymphatics in situ propagate at 4-8 mm/s (Zawieja et al. 1993); in isolated rat mesenteric lymphatics, they propagate at around 6-10 mm/s (Akl et al. 2011; Scallan et al. 2013).

2.3 Parameters, flow meters, and tracers

All parameters are listed in Table 1 or described in the paragraphs that follow and, whenever possible, are based on those in the rat mesenteric lymphatic literature. The radius measured at the valve sinus is 1.5 times the tubular radius; this ratio and the leaflet length are consistent with those reported by Wilson et al. (2015) for rat mesenteric lymphatics, although their vessel diameters were 1/3 as large as those in the present study. The sinus length (measured horizontally) is 0.5 mm which is similar to that reported in Wilson et al. (2015). We estimated and varied other parameters (e.g., $\kappa$ and tension and bending constants) empirically to yield simulations with benchmark output data in the physiological range. The valve-stiffness regions (see Fig. 2) extend a distance of approximately 0.049 mm upstream and 0.041 mm downstream of each valve-insertion point.
(with Euclidean distances reported and measured only in the x-direction). Each contractile region (shown in green in Fig. 2) between two consecutive valves begins 0.1 mm to the left of the sinus-wall junction and ends at the IB point immediately left of the valve-stiffness region. The left-endcap tether region extends from the left up to an x-coordinate of 0.2468 mm; the right-endcap tether region has a farthest-left x-coordinate of 2.753; 3.753; 4.753; or 5.753 mm depending on the number of lymphangions; see red endcaps in Fig. 2.

Flow meters are shown in cyan in Fig. 2 and are vertical line segments where we measure flow rates, velocities, and pressures. One is located 0.048 mm inward from each red-endcap terminus, and there are three flow meters placed around each sinus region: one at the upstream end of the valve-stiffness region, one at the sinus apex, and one at the downstream end of the sinus. The flow meters are numbered from left to right. When we refer to interior flow meters, we mean the set of flow meters excluding the first and last. See Sect. 3 of the SI for details on how flow rates, velocities, and pressures are measured at flow meters.

We seed the flow with tracers (circled red dots in Fig. 2) centered at each valve-insertion x-coordinate. These tracers move at the local fluid velocity but do not affect the flow in any way. They are used to gauge velocities and evaluate transport. In simulation videos (see Online Resources 1-6 and 8-19), ten evenly spaced tracers are shown within each lymphangion and used to visualize passive particle transport through a pumping lymphangion chain.

2.4 Non-dimensionalization, discretization, and numerical implementation

We non-dimensionalize the system by scaling length in the x, y-directions by L, length in the z-direction by Lz, time by L/Uc, velocity by Uc, pressure by µUc/L, the Eulerian force density by µUc/L2, the volumetric flow rate by UcLLz, the resistance by µ/(L2Lz), ψi and δ by 1/(L2Lz), the Lagrangian parameter s by L, the Lagrangian force density by LzµUc/L, and κ by µ/L2. The specific parameter values are displayed in Table 1. We set the characteristic length scale L = 10⁻³ m as the distance between two consecutive valve-insertion points (Zawieja et al. 1993) and set Lz = 3.125 x 10⁻⁴ m as the initial tube diameter which is within physiological range (Dixon et al. 2006). Using the approximate values for density and viscosity of water, we have ρ = 10³ kg/m³ and µ = 10⁻³ kg/(m/s). We take Uc = 10⁻³ m/s based on experimental measurements.

| Table 1 Model parameters with semicolons used to order those that vary with increasing lymphangion-chain length |
|-------------------------------------------------|
| Fluid parameters                                |
| ρ                                               | 10³ kg/m³ |
| µ                                               | 10⁻³ kg/(m/s) |
| κ                                               | 2.0 x 10⁷ kg/sm³ |
| Uc                                              | 10⁻³ m/s |
| Re                                              | 1 |
| Geometry parameters (mm)                         |
| a                                               | 3; 4; 5; 6 |
| b                                               | 1 |
| L                                               | 1 |
| Lz                                              | 0.3125 |
| tube radius, r                                  | 0.15625 |
| tube length                                     | 2.5; 3.5; 4.5; 5.5 |
| sinus radius                                     | 0.2344 |
| sinus length                                     | 0.5 |
| left endcap center                              | (0.25, 0.5) |
| right endcap center                             | (2.75; 3.75; 4.75; 5.75; 0.5) |
| top valve-insertion pts.                        | (0.75; 1.75; 2.75; 3.75; 4.75; 0.6562) |
| bottom valve-insertion pts.                     | (0.75; 1.75; 2.75; 3.75; 4.75; 0.3438) |
| leafllet initial arc length                     | √2r − 2h ≈ 0.1897 |
| leafllet initial angle                          | −π/4 radians |
| Xmn                                            | 0.88; 1.88; 2.88; 3.89; 4.89 |
| Ybm                                            | 0.578125 |
| Misc. parameters                                |
| P₁coeff                                         | 0.076 cmH₂O |
| P₂coeff                                         | 0.076 cmH₂O and higher |
| Rᵢ                                              | 1.6 x 10⁹ kg/sm³ |
| Discretization parameters                       |
| h                                               | 1/64 mm |
| nx                                              | 192; 256; 320; 384 |
| ny                                              | 64 |
| k                                              | 1/32768 s |
| T                                              | 25 s (10 cycles) |
| ∆s ≈ ∆sv                                       | 0.008 mm |
| N                                               | 756; 1012; 1268; 1524 |
| Nₘ                                              | 25 |
| CFL constant C                                  | 0.1 |
| Force parameters                                |
| kₗₗ                                            | 1.5625 x 10⁻⁶ N |
| kₗₘ                                            | 3.125 x 10⁻¹⁷ Nm² |
| kₗₗ                                            | 6.25 x 10⁻₁⁶ Nm² |
| Kₗₗₗₗ                                          | 387 N/m² |
| Kₗₗₗₗ,weak                                     | 77 N/m² |
| Kₗₘ                                            | 3.125 x 10⁻⁴ N/m |
| Kₘₘ                                            | 3.125 x 10⁻⁴ N/m |
| Camp                                           | 39.0625 nN |
| τ                                              | 0.2784 s |
| tdelay (for 2 mm/s)                            | 0.28; 0.80; 1.31; 1.83 s |
| tdelay (for 4 mm/s)                            | 0.14; 0.40; 0.66; 0.91 s |
These parameter values yield a Reynolds number \( Re = \frac{\rho U L}{\mu} = 1 \).

For ease of notation, we omit tildes from the dimensionless system and obtain equations that appear the same as those in the system of Eqs. 1-6 except with the momentum equation replaced with:

\[
\mathbf{Re} (\mathbf{u}_t + \nabla \cdot (\mathbf{u} \mathbf{u}^T)) = -\nabla p + \mathbf{u}_t + f - \kappa \mathbf{u}_t,
\]

\( \Omega_{3D} = [0,a] \times [0,b] \times [0,1], \) and the IB configuration written as \( X(s,t) \) with \( 0 \leq s \leq \frac{L}{2} \). Since we assume all vector third components are identically zero and nothing varies in the \( z \)-direction, we reinterpret these dimensionless equations in 2D. Additionally, because \( p \) and \( \psi_i \) are constant in \( z \), and the \( z \)-integration limits are from 0 to 1, the integral in the dimensionless version of Eq. 4 is equivalent to a 2D integral over \( \Omega \) with the integrand unchanged. Similarly, the integral in the dimensionless version of Eq. 5 is equivalent to a 2D integral over \( \Omega \). In order to simulate the 2D dimensionless system, we discretize the model in space and time.

We discretize \( \Omega \) using a uniform grid of meshwidth \( h \) and let \( n_x = a/h \) and \( n_y = b/h \) denote the number of grid cells in the \( x \)- and \( y \)-directions, respectively. We use a marker-and-cell, or MAC, grid (Harlow and Welch 1965) upon which scalar functions are defined only at cell centers, and vector-valued functions have \( x \)- and \( y \)-components defined only at cell left-edge centers and bottom-edge centers, respectively.

We specify a number of evenly spaced Lagrangian nodes in parameter space so they correspond to IB points on the initial \( \Gamma \) configuration that are evenly spaced and approximately a Euclidean distance of \( h/2 \) apart (as commonly used in the IB method).

A discrete version of the Dirac delta function, \( \delta_h \), is necessary for numerical implementation of the IB method. As in Peskin (1977, 2002), we set \( \delta_h(x) = \delta_h^1(x) \delta_h^2(y) \), where

\[
\delta_h^1(x) = \begin{cases} \frac{1}{4h} & |x| < 2h \\ 0 & |x| \geq 2h. \end{cases}
\]

This function is defined on all of \( \Omega \) (on all of \( \mathbb{R}^2 \) due to periodicity), and its support is an interval of length \( 4h \). We define the dimensionless functions \( \psi_i \) at \( \delta_h \), taking \( \psi_i^r \) equal to a shifted \( \delta_h \) with center at the \( i \)th source center and \( \psi_i^c \) equal to a scaled (multiplied by \( 1/a \)) horizontal tiling of \( \delta_h^1 \) functions, each oriented in the vertical direction with center along \( y = 0 \). Due to the periodic boundary conditions, \( 2h \) of the support lies just above \( y = 0 \) and \( 2h \) of the support lies just below \( y = b \); see Fig. 1.

We use centered differencing and averaging, the latter when quantities are not defined at requisite grid locations, to spatially discretize the 2D dimensionless system and obtain semi-discrete approximations to the system equations. We provide details in the Sect. 1.1 of the SI.

We numerically integrate the semi-discrete system using a second-order-accurate Runge-Kutta method based on the midpoint rule as in Peskin (2002). In both the preliminary and main substeps of the time-stepping scheme, we compute the discrete divergence of the fully discretized momentum equation to obtain a pressure-Poisson problem. Similar to what is done by Arthurs et al. (1998) and Peskin (1977), we decompose the pressure as a linear combination of a source-free pressure and two pressures related to the interior fluid sources. We generate three auxiliary Poisson problems and use MATLAB’s built-in direct solver to solve them. The flow rates appear in the last two terms in the pressure decomposition and are determined by solving a pair of linear equations. Once the pressure is computed, the velocity is then updated by a direct-solve of a Helmholtz equation. Details of the temporal discretization and numerical-implementation scheme are provided in Sects. 1.2-1.3 of the SI.

The model was coded in MATLAB and run on clusters at the Center for High-Performance Computing (CHPC) at the University of Utah. Spatial and temporal refinement studies were performed to assess convergence. Results (not shown) indicate approximate second-order convergence for velocity and the IB structure in space and approximate first-order convergence for both in time (in the 2-norm for grid functions (LeVeque 2007)).

3 Results

We investigated lymphangion chains of various lengths with different contraction styles that pumped against a range of adverse axial pressure differences. Our aims were to assess and compare the pumps’ abilities to generate positive CMFR and transport lymph (pump efficacy). We used velocity plots, pressure plots, and simulation videos (see Online Resources 1-6 and 8-19) to glean insight into pump behaviors. We analyzed diameter, valve-state, and pressure data in timecourse plots similar to those appearing in the literature. Additionally, we examined trans-valve pressure differences and flow-rate timecourse data. Pump-function plots were also constructed and analyzed. In what follows, we refer to a pump operating at an adverse pressure, we mean an adverse axial pressure difference (arising from connections with the virtual reservoirs in which
3.1 Velocity and pressure in different valve states

As representative model output, we provide velocity and pressure plots for a 4-lymphangion chain with fast-orthograde contractions operating at a moderate adverse axial pressure of 0.051 cmH$_2$O. All valves in this pump opened and closed during each 2.5-s contraction cycle. The pump was simulated for 25 s or equivalently, 10 contraction cycles. The difference in CMFR averaged among interior flow meters from cycle 9 to cycle 10 was less than 1%; thus, cycle-10 ($T = 22.5-25$ s) results were considered to be quasi-steady state.

Velocity and pressure plots at times exhibiting valve-state changes are shown in Figs. 4-5. At 22.9 s, valves 1-4 are open with positive, horizontal fluid velocity between the leaflets. Valve 5 is shut and has a negative trans-valve pressure (see panels (a) of both figures). At 23.6 s, the first two lymphangions are contracting. Valves 2-5 are open with large flow velocities through valves 3 and 4; valve 1 is shut and bears a negative trans-valve pressure (see panels (b)). At 24.4 s, valve 1 is opening, valve 2 is shut, valve 3 is closing, and valves 4-5 are open (see panels (c)). At this time, contraction is prominent among lymphangions 3 and 4, though there is backflow through valve 4. After an additional 0.2 s, valve 3 is shut and all other valves are open with prominent positive velocity through valve 1 and backflow through valves 4 and 5 (see panels (d)). Lastly at 24.8 s, valve 4 is closed, valve 3 is opening, and valves 1, 2, and 5 are open (see panels (e)).

3.2 Vortices in the valve-sinus region

Flow patterns around valve 3 of the same 4-lymphangion, fast-orthograde pump are provided in Fig. 6. The plots display a portion of the overall domain and velocity field, although the entire model geometry and fluid region were simulated. The central valve is bounded on both sides by contractile lymphangions, so its motion and flow patterns are considered most native to the model. Notably, the sinus region features counter-rotating vortices at nearly all time snapshots which include periods of forward flow and valve closure.

3.3 Wall, valve, and pressure dynamics

We provide diameter, valve gap-distance, pressure, and flow-rate timecourse plots for a 4-lymphangion, simultaneously contracting chain at an adverse axial pressure of 0.051 cmH$_2$O during cycles 9 and 10 in Fig. 7. Also, the timecourse of the vertical component of the contractile
Fig. 6 Velocity field surrounding the central valve (valve 3) at select times during cycle 10 in a 4-lymphangion, fast-orthograde pump with an adverse axial pressure difference of 0.051 cmH$_2$O. Every other velocity vector is included in the plot, and the vectors are scaled by a factor of 0.125.

3.3.1 Diameter changes and physiological ejection fraction

The diameter was measured at an axial location approximately 0.25 mm to the left of the downstream valve in each lymphangion. The diameter tracings for all four lymphangions are shown in panel (b) of Fig. 7. They exhibit shapes similar to those in the literature (e.g., Fig. 1 in Davis et al. (2011)) with brisk contractions and slower relaxations. In cycle 10, e.g., the lymphangion 1 maximal diameter (end-diastolic diameter, EDD) was 0.372 mm, and its minimal diameter (end-systolic diameter, ESD) was 0.180 mm. The minimal diameter occurred 0.988 s after the maximal diameter; the velocity of shortening is estimated as 0.194 mm/s. The ESD was 48.3% of EDD; this is a physiological contraction amplitude (Davis et al. 2012; Zawieja 2009). Assuming no backflow and a cylindrical geometry, these ESD and EDD values yield an ejection fraction (EF) of 76.6% (EF = ((EDD$^2$ − ESD$^2$)/EDD$^2$) × 100%) which agrees with the literature (Scallan et al. 2012).

3.3.2 Valve gap-distance dynamics

For each valve, the distance between the top and bottom leaflet endpoints was measured throughout a simulation and is referred to as the gap distance. Gap-distance plots for all five valves are shown in panel (c) of Fig. 7. Notably, only valves 1 and 5 close. The three interior valves remain open throughout a contraction cycle with only small gap-distance fluctuations when valves 1 and 5 change state. Moreover, the gap-distance plots for valves 1 and 5 are out of phase; when one is closed, the other is open. Valve 5 is closed longer and opens more abruptly than valve 1. Starting at 22.5 s around end-diastole, valve 5 is closed, and valve 1 is open. As contraction commences, the valve-1 gap distance decreases as it begins to close. Around 23 s, valve 1 closes, and valve 5 abruptly opens. Valve 5 remains open until about 0.25 s after end-systole, and then its gap distance decreases. As the lymphangions are relaxing and the diameters are increasing, valve 5 closes around 24 s, and valve 1 opens. These valves remain in these states for the remainder of the cycle through 25 s. The simultaneous-pump interior valve behaviors differ from those in the fast-orthograde pump. Because only the first and last valves open and close each cycle in the simultaneous pump, the 4-lymphangion chain is essentially functioning as a single, long lymphangion. This behavior was also reported by Bertram et al. (2016).

3.3.3 Cyclical intraluminal pressure variation and periods of forward flow

The pressure at the vessel midline was measured at each flow meter and plotted over time in panel (d) of Fig. 7. Starting at 22.5 s and as contraction commences, pressures measured at flow meters just upstream of valves 2-5 gradually rise above the (nearly constant) pressure just upstream of valve 1. They then rise in tandem
Fig. 7 Timecourse plots for a 4-lymphangion, simultaneous pump with adverse axial pressure difference of 0.051 cmH$_2$O. Panel (a) is the inward contraction force acting simultaneously along all lymphangion upper contractile regions; the negative of this force acts along the lower contractile regions. Green and red dashed line segments have the same meaning as in Fig. 3. Panel (b) is the lymphangion diameter measured at axial locations approximately 0.25 mm to the left of each downstream valve of lymphangions 1-4 (L1-L4). Panel (c) is the distance between valve leaflet endpoints for each of the five valves. Panel (d) is the pressure measured at flow-meter centers (vessel midline) just upstream of each valve (v$_{1u}$-v$_{5u}$) and downstream of valve 5 (v$_{5d}$). Panel (e) displays the trans-valve pressure for each valve; it is the pressure measured at the flow-meter center just upstream of each valve minus the pressure at the center of the flow meter located at the sinus-wall junction. Panel (f) shows the flow rate measured at flow meters just upstream of each valve.

briskly and surpass the pressure downstream of valve 5 around 23 s. During the time between 22.5 s and 23 s, valve 1 is closing and valve 5 is opening. The rising pressures measured upstream of valves 2-5 peak around the time valve 5 is fully open and prior to end-systole. During the time period between 23 s and just before 24 s, pressures decrease moving down the chain at flow meters just upstream of valves 2-5. During this time period, valve 1 is shut and valve 5 is open; there is a period of forward flow through the tube. As relaxation ensues, pressures drop sharply and in tandem, first with valve 5 closing just before 24 s and then with valve 1 opening just after 24 s. During the time period just after 24 s and until 25 s, pressures moving down the chain just upstream of valves 2-5 again decrease; there is a period of forward flow through the tube. Thus, significant forward flow occurs twice per cycle in the simultaneous pump: once during systole and again during diastole.

3.3.4 Trans-valve pressure differences

Next, trans-valve pressures were computed as the difference in midline pressures measured at flow meters upstream and downstream of each valve near sinus-wall junctions and plotted over time in panel (e) of Fig. 7. Consistent with their lack of closure, trans-valve pressures for the three interior valves are nearly 0 and exhibit little fluctuation. The shapes of the gap-distance
plots in panel (c) and the trans-valve pressure plots in panel (e) are similar in spirit; we relate time periods of valve openness or closure to time periods during which the trans-valve pressure difference is positive or negative, respectively. Notice that the trans-valve pressure for valve 5 features a positive spike, but the same is not true for valve 1. Also, the trans-valve pressure for valve 1 is more negative than that for valve 5; thus, valve 1 bears a larger adverse trans-valve pressure.

### 3.3.5 Strong forward flow during both systole and diastole

Flow rates measured at the flow meters just upstream of each valve are plotted in panel (f) of Fig. 7. During each cycle, there are two pronounced periods of forward flow and two periods of backflow. The forward flow rates are much larger than the backward flow rates, and forward flow occurs over a longer time period than the backflow. Recall the pressure drops that occur moving down the chain in panel (d) between approximately 23-24 s with valve 1 shut and valve 5 open and again between approximately 24-25 s with valve 1 open and valve 5 shut. These pressure-drop periods correspond to periods of forward flow during both systole and diastole. The backflow occurs when valves 1 and 5 are closing.

### 3.3.6 Valve hysteresis

Next, the gap-distance vs. trans-valve pressure is plotted for valves 1 and 5 in Fig. 8; both variables are plotted at the same times from 20-25 s (cycles 9 and 10). Plots for valves 2 through 4 are omitted because they remained open each cycle and exhibited little gap-distance variation. As time advances, these plots are traced out in the counter-clockwise direction. Animations of dual curve-traversal over cycle 10 are provided (Online Resource 7). These plots are multivalued; for each valve, a given trans-valve pressure is associated with two gap-distances whose values depend on whether the valve is opening or closing. Viewed another way, specifying a threshold gap distance beyond which a valve is considered open, a given valve opens and closes at different trans-valve pressures. This phenomenon is oft-cited in the literature as valve hysteresis (Ballard et al. 2018; Bertram et al. 2014b; Davis et al. 2011; Wilson et al. 2018).

Also, experiments by Davis et al. (2011) indicate the pressures at which valves open and close depend not only on valve state but also on pressure and vessel distension.

In Fig. 8, starting from the state of a tightly closed valve (minimal gap distance), as time advances, the trans-valve pressure increases, but the gap distance initially does not change much. As the trans-valve pressure increases further, the gap distance increases, and the valve opens. For an open valve, as the trans-valve pressure begins to decrease, the gap distance initially does not change much. This is likely related to fluid inertia; flow-reversal is not instantaneous. Further decreases in trans-valve pressure are associated with decreases in gap distance and valve closure.

When closed, valve 1 bears a larger trans-valve pressure than valve 5; also, its gap distance is more responsive to initial increases in trans-valve pressure. In contrast, valve 5 is harder to open; it experiences a large, positive trans-valve pressure prior to opening. This is likely related to the fact that valve 1 opens while the vessel is relaxing and valve 5 is shut. Compared to valve 5, valve 1 is less exposed to the downstream reservoir pressure; its opening does not require overcoming as large a pressure as valve 5 (in fact, it opens when the trans-valve pressure is adverse). In order for valve 5 to open, the pressure raised during systole must overcome the high downstream pressure. Also, valve 1 is easier to close than valve 5; to achieve the same gap distance in valve 5, it generally takes a larger trans-valve adverse pressure. Similar to experiments by Davis et al. (2011) indicating transmural-pressure-dependent hysteresis (though in non-contractile, single-valved lymphangion segments), the variation in trans-valve pressures for opening and closing valves 1 and 5 indicate that hysteretic properties may vary along a lymphangion chain (in valves of uniform construction) due to variations in pressure and flow.
Pump efficacy in a fluid-structure-interaction model of a chain of contracting lymphangions

![Fig. 9](image)

**Fig. 9** Tracer displacement for tracers seeded at valve-insertion centers at the start of cycle 7 ($T = 15$ s) in a 4-lymphangion, simultaneous pump with an adverse axial pressure difference of 0.051 cmH$_2$O. Tracers are numbered from left to right according to valve number. Red and green dashed lines as in Fig. 3

### 3.3.7 Assessing transport with tracers

We seeded the flow in the 4-lymphangion, simultaneous pump with passive tracers initially centered at each valve; see Fig. 2. Figure 9 illustrates the tracer displacement timecourse for five tracers seeded at the start of cycle 7 ($T = 15$ s) and numbered according to the valve at which they are originally centered. By the end of the simulation ($T = 25$ s), each tracer was located at the downstream source. It took tracer 1 just under 3.5 contraction cycles to traverse the tube and reach the downstream source where it stagnated. Non-stagnant tracer cycle-mean velocities of up to 0.59 mm/s were observed; maximum instantaneous velocities of 9.48, 9.69, 7.71, 6.47, and 7.62 (all in mm/s) were observed for tracers 1-5, respectively during contraction cycles 10, 9, 8, 7, and 7, respectively. Tracers generally moved the fastest just prior to end-systole (near red dashed vertical lines in Fig. 9). Our model enables the study of tracer movement in the flow, much like microparticle velocimetry experiments but without confounding factors that arise from particle-insertion.

### 3.3.8 Open-valve resistance

By virtue of the interior valves remaining open throughout each contraction cycle in the simultaneous, 4-lymphangion pump, we estimated the open-valve resistance. This resistance estimate is for the tube and valve in a contractile setting. We assumed an Ohm’s-law relation-ship and divided the trans-valve pressure drop by the flow rate to estimate the resistance. Based on cycle-mean pressures measured at the centers of flow meters bounding each valve-sinus region and cycle-mean flow rates, we obtained an open-valve resistance of approximately $4.02 \times 10^4$ dyn·s/cm$^5$ (averaged among the three interior valves).

### 3.4 Pump-function behavior

Pump-function plots are useful in assessing pump performance. Chains of one to four lymphangions operating at various axial pressures were simulated for 25 s, or 10 contraction cycles. The adverse pressure differences among the left and right virtual reservoirs had approximate values of 0, 0.010, 0.020, 0.031, 0.041, 0.051, 0.061, 0.071, 0.082, 0.092, 0.102, and 0.112 cmH$_2$O for all chain lengths; adverse differences of 0.122, 0.133, 0.143, 0.153, and 0.163 cmH$_2$O were also simulated for chains with more than one lymphangion; and adverse differences of 0.173 and 0.184 cmH$_2$O were also simulated for 3- and 4-lymphangion chains. Moreover, each chain was simulated with simultaneous, orthograde, retrograde, fast-orthograde, or fast-retrograde contractions. Thus, 20 types of pumps operating at various adverse pressures were considered. The CMFR data averaged over the interior flow meters from cycle 10 was considered quasi-steady state (QSS) and plotted as the CMFR if the percent change among the average cycle-10 CMFR and average cycle-9 CMFR differed by no more than 1%. If QSS was not attained by cycle 10, additional cycles were run. The CMFR data from the first cycle after the 10th featuring $\leq 1\%$ change from the previous cycle was considered QSS.

| Table 2 Pump-function linear regression slope, intercept, and $R^2$ data. | simult ortho retro ortho x2 retro x2 |
|---|---|---|---|---|---|
| 1 LA | | | | | |
| slope | -0.002312 | -0.002323 | -0.002312 | -0.002319 | -0.002312 |
| int. | 0.096951 | 0.097003 | 0.096951 | 0.096998 | 0.096951 |
| $R^2$ | 0.985473 | 0.985475 | 0.985473 | 0.985426 | 0.985473 |
| 2 LA | | | | | |
| slope | -0.001277 | -0.001270 | -0.001516 | -0.001273 | -0.001301 |
| int. | 0.119847 | 0.099403 | 0.118162 | 0.113602 | 0.118482 |
| $R^2$ | 0.997029 | 0.989047 | 0.990261 | 0.987739 | 0.997734 |
| 3 LA | | | | | |
| slope | -0.000892 | -0.001227 | -0.002034 | -0.000864 | -0.001065 |
| int. | 0.126676 | 0.111377 | 0.136890 | 0.112472 | 0.125534 |
| $R^2$ | 0.998350 | 0.948896 | 0.979237 | 0.998102 | 0.994456 |
| 4 LA | | | | | |
| slope | -0.000711 | -0.001716 | -0.002573 | -0.000775 | -0.001057 |
| int. | 0.129907 | 0.134558 | 0.162173 | 0.117511 | 0.129696 |
| $R^2$ | 0.995006 | 0.972854 | 0.987260 | 0.978714 | 0.978466 |
3.4.1 Effect of chain length

For each type of pump (specified chain length and contraction style), the QSS data points were plotted and exhibited a negatively sloped, linear trend among low and moderate adverse pressures and a vertical trend in the high adverse-pressure regime; see Fig. 10. Linear regression was performed for the non-vertical data points for which CMFRs were positive (asterisk data points), and lines of best fit are displayed. The circled data points were not included in the regression due to vertical orientation or negative CMFRs. The legend applies to panels (a)-(d).

Among the 335 pumps that were simulated, 12 pumps featured CMFRs that alternated each cycle or every four cycles and attained QSS among the alternating cycles. Each of these pumps was operating in the high adverse-pressure regime; their data points are included in the pump-function plots as circles, but they were not included in any regression. This behavior is under current investigation.

As seen in panel (a) of Fig. 10, all five 1-lymphangion pumps yielded nearly identical QSS data sets and thus pump-function curves. One-lymphangion pumps have a single contractile region bounded by two valves that border fluid sources. There are no interior valves whose behaviors would be modulated by the contraction style and affect CMFRs.

Panel (b) shows pump-function curves and data for 2-lymphangion chains. These curves are extremely similar for the simultaneous and fast, non-simultaneous pumps. At a given pressure difference, the largest CMFRs were generated by the simultaneous pump and
then by the fast, non-simultaneous pumps. Also, the disparity among the trio of the simultaneous and fast, non-simultaneous pumps vs. the retrograde pump shrinks with rising adverse pressure. As seen in Table 2, slopes are quite similar for all 2-lymphangion pumps except the retrograde pump. Its larger-magnitude slope indicates that a one-unit increase in CMFR requires a larger pressure drop. The 2-lymphangion intercepts are similar and largest for the simultaneous and both retrograde pumps and lowest for both orthograde pumps. Thus, the orthograde pumps are expected to fail (i.e., produce CMFR ≤ 0) at lower adverse pressures than the other pumps.

Panels (c) and (d) of Fig. 10 show pump-function curves and data for the 3- and 4-lymphangion chains, respectively. In both panels, the simultaneous pumps yielded the largest CMFRs except at the highest pressures. Also, in the low and moderate adverse-pressure regimes, the fast-orthograde and fast-retrograde pumps yielded larger CMFRs than the orthograde and retrograde pumps. For both chain lengths, the fast-orthograde and fast-retrograde pump-function curves intersect; the same is true for the orthograde and retrograde curves. Also, as reflected in the differences in the slopes, the advantage of the simultaneous pumps in producing the largest CMFRs diminishes as the adverse pressure increases.

As seen from the 3- and 4-lymphangion slope information in Table 2, compared to the orthograde and retrograde pumps, the simultaneous and fast, non-simultaneous pumps have CMFRs that are more responsive to pressure changes. Based on the intercept information, the retrograde pumps are expected to fail at higher adverse pressures than the other pumps; the orthograde and fast-orthograde pumps are expected to fail at lower adverse pressures than the other 3- and 4-lymphangions pumps, respectively.

The 3- and 4-lymphangion pump-function data are more spread out among the different contraction styles at low and moderate adverse pressure differences than are those for the 1- and 2-lymphangion pumps. We expect this is related to the greater number of interior valves in longer chains whose dynamics are influenced by the contraction style.

3.4.2 Effect of contraction style

Lengthening the chain by adding a lymphangion generally yielded larger CMFRs, smaller pump-function slopes, and larger intercepts—though there were a few exceptions; see Fig. 11. For the retrograde pump, there was a reduction in CMFR when lengthening the chain from two to three lymphangions at low adverse pressures; there was an increase in CMFR when lengthening the chain at moderate and high adverse pressures. For orthograde and retrograde pumps, there was a slight reduction in CMFR when lengthening the chain from three to four lymphangions at low adverse pressures; there was a slight increase in CMFR when lengthening the chain from three to four lymphangions at moderate and high adverse pressures. We expect the reduction in CMFR in lengthening these chains is related to greater flow resistance stemming from the additional valves (which open and close each cycle). Also, the orthograde and retrograde pump-function curves steepened as the chain lengthened from three to four lymphangions; the retrograde pump-function curves also steepened as the chain lengthened from two to three lymphangions. Lastly, the intercept for the fast-orthograde pump decreased in going from a 2- to a 3-lymphangion chain.

3.5 Valve dynamics in pump failure

Various valve dynamics were observed in the pump-function simulations. Only the first and last valves in simultaneous pumps opened and closed during contraction cycles. All interior valves remained open. Valve opening and closing in orthograde and retrograde pumps generally occurred in forward and backward sequences,
respectively. This is consistent with the contractile travelling-wave direction. In general, valves closed more tightly in simulations with higher downstream pressures. At the highest downstream pressures, the last valve remained closed throughout a contraction cycle with the other valves generally opening and closing each cycle. Also, there was a tendency for the first valve to exhibit hindered opening as the downstream pressure rose. Generally, other valves also opened less wide as the downstream pressure increased, but the hindrance to the first-valve occurred at lower downstream pressures than for the other valves. It often was observed that at sufficiently high downstream pressures, the first valve remained closed while the other valves generally exhibited some degree of opening and closing throughout each contraction cycle. At even higher downstream pressures, there was recovery of the first-valve opening with further increases in downstream pressure associated with the last valve remaining closed and all other valves generally opening and closing each cycle.

3.6 Comparison of 4-lymphangion chains with different contraction styles

The pump-function plots show that simultaneous pumps yield the largest CMFRs at all pressures below pump failure. The simultaneous advantage is particularly pronounced for the 4-lymphangion chain at low and moderate pressures. However, the advantage diminishes as the downstream pressure increases. To better understand these pump characteristics, we compared the 4-lymphangion chains with different contraction modes at select adverse pressure differences of 0, 0.051 (moderate), and 0.092 (high) cmH$_2$O.
3.6.1 Video comparison

Videos showing the last 5 cycles from $T = 12.5-25$ s are provided for the simultaneous, orthograde, and retrograde pump trio at adverse axial pressures differences of 0, 0.051, and 0.092 cm H$_2$O (Online Resources 1, 3, 5, respectively). Similar videos are provided for simultaneous, fast-orthograde, and fast-retrograde pumps at the same adverse axial pressure differences (Online Resources 2, 4, 6). These videos show passive tracer transport with tracers color-coded according to which lymphangion they originate in and are particularly helpful in visualizing the flow’s progression through the lymphangions.

At 0 axial pressure difference, we observe swift tracer propulsion by the simultaneous pump during both systolic and diastolic periods with essentially no backflow. Due to the slowly propagating contractile travelling wave and the associated interior-valve closure, the orthograde and retrograde pumps feature slower and less coordinated valve movement with periods of flow stagnation and backflow. The tracers get shuttled down the lymphangion chain in a back-and-forth motion. On the other hand, the fast-orthograde and fast-retrograde travelling waves are sufficiently fast that they yield more coordinated valve movement with significant forward flow and less backflow than the orthograde and retrograde pumps. In the simultaneous pump, only valves 1 and 5 open and close each cycle. In the orthograde and retrograde pumps, all valves open and close each cycle. In the fast-orthograde pump, valve 2 remains open, and all other valves open and close each cycle. In the fast-retrograde pump, valves 3 and 4 remain open, and all other valves open and close each cycle.

At an adverse axial pressure difference of 0.051 cm H$_2$O, the simultaneous pump still exhibits two significant periods of forward flow, though peak flow rates are smaller than they are at 0 axial pressure difference, and there is slight backflow. Again, only valves 1 and 5 open and close each cycle; all interior valves remain open. The orthograde and retrograde pumps again exhibit uncoordinated transport with periods of forward flow, backward flow, and stagnation. All valves open and close, and valves 1 and 5 generally operate in phase; they both open and close during the same time periods. The fast-orthograde and fast-retrograde pumps exhibit more rapid tracer transport than the orthograde and retrograde pumps but slower tracer transport than the simultaneous pump. All valves open and close in the fast, non-simultaneous pumps. Also, in the fast-orthograde pump, pressures in the four lymphangions rise in tandem during the systolic period and drop in sequence (from left to right) during the diastolic period (Online Resource 14). In the fast-retrograde pump, pressures in the four lymphangions rise in sequence (from right to left) during the systolic period and drop in tandem during the diastolic period (Online Resource 15).

At an adverse axial pressure difference of 0.092 cm H$_2$O, tracer transport in all pumps occurs more slowly than at lower downstream pressures, but the same general trends observed at a pressure of 0.051 cm H$_2$O persist in terms of tracer transport and valve behaviors. Also, the systolic diameters are larger than at lower pressures but feature marked constriction just downstream of the sinus for all pump types. The pressure rise/fall trends in the fast-orthograde and fast-retrograde pumps also persist (Online Resources 18-19).

3.6.2 Flow-rate and pressure comparison

Flow-rate and pressure plots corroborate the video observations. As shown in Fig. 12 panel (a) (reproduction of panel (a) in Fig. 7), the simultaneous pump at a moderate pressure difference of 0.051 cm H$_2$O generates two significant periods of concerted forward flow each cycle with minimal back flow (associated with the closure of valves 1 and 5). One period of forward flow corresponds to downstream ejection and one to refilling from upstream. The largest flow rate occurs just upstream of valve 5 during systole; the second-largest flow rate occurs just upstream of valve 1 during diastole.

As seen in panels (b)-(c), the flow rates generated by the orthograde and retrograde pumps are smaller than those in the simultaneous pump. They are also unorganized with significant periods of forward and backward flow, consistent with the back-and-forth tracer movement. On the other hand, the fast, non-simultaneous-pump flow rates (panels (d)-(e)) exhibit features similar to those from the simultaneous pump, though they are lagged in time. Namely, the fast-orthograde pump has two organized periods of forward flow with the largest flow-rates measured just upstream of valve 5 during the systolic period (e.g., $T = 23.25-24.25$ s) and the second-largest collection of flow rates measured just upstream of valve 1 during diastole. The fast-retrograde pump similarly exhibits two organized periods of forward flow but with the largest flow rates measured just upstream of valve 1 during the diastolic period ($T = 21.75-23.25$ s). The fast-retrograde pump similarly exhibits two organized periods of forward flow but with the largest flow rates measured just upstream of valve 1 during the diastolic period ($T = 22-23$ s) and the second-largest flow rates occurring just upstream of valve 5 during the systolic period ($T = 20.5-22$ s). In the fast, non-simultaneous pumps, two periods of backflow also occur each cycle prior to valve closure and are more pronounced than for the simultaneous pump. Thus the simultaneous and fast, non-simultaneous pumps exhibit...
Fig. 12 Flow rates in 4-lymphangion chains with different contraction styles pumping at an adverse axial pressure difference of 0.051 cmH$_2$O. Flow rates were measured at flow meters just upstream of each valve and are displayed over cycles 9-10 ($T = 20-25$ s). The legend applies to panels (a)-(e), e.g., v1u indicates flow rates measured upstream of valve 1.

two prominent periods of forward flow each cycle with comparatively little back flow; their CMFRs are larger than those for the orthograde and retrograde pumps.

We next examine pressure plots in Fig. 13. As seen in panel (a) (same as panel (d) in Fig. 7), the simultaneous-pump pressures measured just upstream of each valve rise and fall in tandem. The fast-orthograde pressures similarly rise in tandem, but they fall in sequence moving down the chain from left to right; see panel (d). The fast-retrograde pressures rise in sequence from right to left and fall in tandem; see panel (e). Thus, the fast-orthograde pump resembles the simultaneous pump during the systolic period with its coordinated pressure rise, whereas the fast-retrograde pump resembles the simultaneous pump during the diastolic period with its coordinated pressure drop.

Taken together, the flow-rate and pressure information reveal that the fast-orthograde pump quickly ejects fluid and has sustained, slower fluid intake, and the fast-retrograde pump quickly pulls fluid in and has sustained, slower ejection. The simultaneous pump has coordinated systolic and diastolic periods with prominent peak flow rates during both these times. Like the fast-orthograde pump, it also exhibits larger peak ejection flow rates than peak entry flow rates. The orthograde pump pressures also rise in tandem and fall in sequence, but the sequential pressure drops occur while other pressures are still rising; see panel (b) of Fig. 13. Similarly the retrograde pump pressures rise in sequence and fall in tandem, though the partially coordinated pressure drops occur while other pressures are rising; see panel (c). Attributable to the contraction travelling-wave velocity, periods of rising and falling pressures overlap in a more pronounced way than they do for the fast, non-simultaneous pumps.

Flow-rate plots at axial pressure differences of 0 cmH$_2$O and 0.092 cmH$_2$O are similar in spirit to those at 0.051 cmH$_2$O with the exception that the simultaneous pump at 0.092 cmH$_2$O has larger peak flow rates upstream of valve 1 rather than valve 5 (data not shown).
Fig. 13 Pressures in 4-lymphangion chains with different contraction styles pumping at an adverse axial pressure difference of 0.051 cmH\textsubscript{2}O. Pressures were measured at the vessel midline at flow meters just upstream of each valve and also downstream of valve 5; pressure timecourse plots are displayed over cycles 9-10 (T = 20-25 s). Due to the fluid-source proximity, pressures just upstream of valve 1 (black, v1u) and just downstream of valve 5 (green, v5d) are nearly constant and equal for all subplots. The legend applies to panels (a)-(e)

Pressure plots at 0 cmH\textsubscript{2}O and 0.092 cmH\textsubscript{2}O exhibit different shapes than at 0.051 cmH\textsubscript{2}O, but the sequential and synchronized temporal patterns of the non-simultaneous pump pressures persist (data not shown). Interestingly, peak pressures increase with the downstream pressure for all pump types, though this is perhaps unsurprising since at 0.092 cmH\textsubscript{2}O, all five pumps still yield positive CMFRs.

3.6.3 Tracer-transport comparison

Tracer-transport plots showing displacement for tracer 1 (originating at the vessel midline near valve 1) for simultaneous, orthograde, and retrograde pumps operating at adverse axial pressures of 0, 0.051, and 0.092 cmH\textsubscript{2}O are provided in Fig. 14. We only show results for these three types of pumps because they exhibit the greatest differences in tracer transport. As the downstream pressure increased, tracers took longer to reach the downstream source in all three pumps. The simultaneous pump transported tracer 1 to the downstream source most rapidly at all three adverse axial pressures. Counter-intuitively, the time between the tracer 1 arrival at the downstream source in the simultaneous vs. orthograde or retrograde pumps was longer at a pressure of 0.051 cmH\textsubscript{2}O than at 0 despite CMFRs being more similar at 0.051 cmH\textsubscript{2}O. At 0.092 cmH\textsubscript{2}O, only the simultaneous pump transported tracer 1 to the downstream source by the end of the simulation. The largest cycle-mean velocities and the largest instantaneous velocities for tracer 1 attained in any cycle for the three pump types at the three axial pressure differences are displayed in Table 3.
Fig. 14 Tracer 1 displacement in simultaneous, orthograde, and retrograde 4-lymphangion chains pumping at low, moderate, and high adverse axial pressure differences. Displacement timecourse plots are shown over cycles 2-10 (T = 2.5-25 s). The displacement is the distance from the initial position of tracer 1 (see left-most target symbol in Fig. 2); tracers remain along the vessel midline throughout each simulation.

3.6.4 Summary

The videos, flow-rate plots, pressure plots, and tracer-transport plots elucidate differences in pump characteristics that affect CMFRs. Due to the synchronous contraction, the simultaneous, 4-lymphangion chain essentially functioned as a single, long, pumping lymphangion with only its bounding valves opening and closing each cycle. At all but the highest adverse pressures, this yielded organized, concerted periods of forward flow with little backflow; the interior valves conferred low flow resistance due to their persistent openness. Different behaviors were observed in the non-simultaneous pumps and were associated with reductions in their CMFRs. As the adverse axial pressure increased from 0, the CMFRs decreased linearly for all pumps though with different slopes. The simultaneous pump CMFR was most responsive to changes in axial pressure (smallest-magnitude slope); thus its marked advantage in generating large CMFRs at low adverse axial pressures diminished as the downstream pressure rose. When the adverse pressure was sufficiently large, all pumps failed to yield positive CMFR. Also, at the three adverse axial pressures 0, 0.051, and 0.092 cmH$_2$O, valves 1 and 5 in the simultaneous pumps experienced the largest adverse, cycle-mean trans-valve pressures among all the pump types (results not shown). In the high adverse-pressure regime, large trans-valve pressures are exceedingly difficult to overcome. Unlike the simultaneous pump, the interior-valve closure in the non-simultaneous pumps shields valves 1 and 5 from prolonged exposure to high pressures.
Table 3 Tracer 1 velocities in simultaneous, orthograde, and retrograde 4-lymphangion pumps. The largest cycle-mean velocities (avg. vel.) and the largest instantaneous velocities (inst. vel.) over all cycles are displayed for tracer 1 for each contraction style and each adverse axial pressure difference (press.)

| style | press. (cmH₂O) | avg. vel. (mm/s) | inst. vel. (mm/s) |
|-------|----------------|-----------------|------------------|
| simult | 0 | 0.79 | 7.91 |
| | 0.051 | 0.57 | 6.69 |
| | 0.09 | 0.33 | 6.50 |
| ortho | 0 | 0.74 | 3.94 |
| | 0.051 | 0.42 | 2.99 |
| | 0.092 | 0.25 | 2.55 |
| retro | 0 | 0.56 | 3.99 |
| | 0.051 | 0.37 | 2.39 |
| | 0.092 | 0.22 | 1.67 |

4 Discussion

Lymphatic transport is critically important for maintaining fluid balance. However, it is challenging to study and modulate in vivo. Understanding properties of lymph flow and valve behaviors in the contractile, collecting lymphatic vessels can aid the development of much-needed lymphedema therapeutics. To this end, ex vivo experiments have been performed, but they remain technically challenging in terms of vessel dissection and the assessment of flow rates, pressures, and valve behaviors—especially in more than a couple lymphangions in series. Thus, there is an important role for computational modelling of lymph flow through adjacent, contractile lymphangions to probe questions that may be challenging or impossible to study in direct, bio-experimental settings.

Lymphangions can be highly contractile with 10-20 contractions per minute (Zawieja 2009) and undergo contractions with amplitudes around 40-50% of their diastolic diameter (Davis et al. 2012; Zawieja 2009). Moreover, the presence of valves additionally complicates Poiseuille-flow assumptions which are often made in computational models. Reynolds numbers of 16-160 have been estimated (Moore JE and Bertram 2018) for flow through lymphangions and vary depending on the species, anatomical location, and lymph velocities. The existing computational models in the literature are mostly lumped parameter, and the few higher-dimensional models make limiting assumptions on the flow, geometry, valves, fluid-structure interaction (FSI), or number of lymphangions.

We have developed a computational model of flow through a chain of contracting lymphangions using the immersed boundary method. We simulated pumps of one to four lymphangions with different-style contractions at various adverse axial pressure differences. To our knowledge, our work is the first fully coupled, two-way, FSI model of a chain of contracting lymphangions with physically modelled valves to appear in the literature. Our velocity and pressure plots, simulation videos, tracer-transport plots, and pump-function and pump-behavior analyses provide new insight into lymphatic transport through a chain of valved, contracting lymphangions. We compare our results from Sect. 3 to those in the literature.

4.1 Wall, valve, and pressure dynamics

The timecourse data in Fig. 7 are similar to the type of plots reported in the experimental literature. The concurrent diameter, valve-state, and pressure plots are similar to those generated from isolated lymphatic vessel experiments (Bertram et al. 2018; Davis et al. 2011; Scallan et al. 2012, 2013). Our model exhibits physiological behavior in terms of diameter changes, contraction cycles, and naturally opening and closing valves. Also, for a 4-lymphangion, simultaneous pump operating at a moderate adverse axial pressure difference of 0.051 cmH₂O, we obtained a largest cycle-mean tracer velocity of 0.57 mm/s and a largest instantaneous tracer velocity of 9.69 mm/s (see Table 3). These values are close to those reported by Dixon et al. (2006) for in situ rat mesenteric prenodal lymphatics (average lymph velocity of 0.87 mm/s with peaks from 2.2-9.0 mm/s). Dixon et al. (2006) also reported an average volumetric flow rate of 13.95 µL/hr for individual mesenteric collecting lymphatics. It is unclear how many lymphangions were involved. Our 1-lymphangion pumps at 0.051 cmH₂O yielded CMFRs around 19 µL/hr, and the CMFRs increased with the chain length. It is unclear if the Dixon et al. (2006) flow rate is a cycle-mean flow rate like ours or a different type of average. Also, pressures in the in situ setting were not reported, so the comparable axial pressure difference is unclear.

Timecourse plots (for tension, diameter, pressure, and flow rates) were reported by Bertram et al. (2010) for lumped-parameter simulations of 4-lymphangion chains whose adjacent lymphangions contracted periodically at 0.5-s orthograde lags. They reported a staircase progression in pressures inside the lymphangion chain that overcame the outlet pressure each cycle. We observe similar pressure patterns for the 4-lymphangion, orthograde pump in Fig. 13.

4.2 Valve hysteresis

The gap-distance vs. trans-valve pressure plots in Fig. 8 exhibit similar shapes to hysteresis plots generated from 3D computational models (Ballard et al. 2018; Wilson et al.
Both of these models assume a rigid vessel wall and feature a single valve with a contraction cycle simulated via pressure waveforms. The Ballard et al. (2018) model does not incorporate the valve-sinus geometry, and snapshots and videos of the valve at different times in an opening-closing cycle do not exhibit much leaflet motion or characteristic bulge-back (Zawieja 2009) in the vicinity of the upstream valve-insertion locations. Based on expected symmetry, only 1/4 the full vessel geometry was simulated in Wilson et al. (2018), and simulations were stopped to avoid leaflet contact and numerical issues. Despite the model and geometry differences, the leaflet gap-distance vs. trans-valve pressure plots in these references exhibit similar shapes to ours.

4.3 Tracer transport and vortices

We are unaware of any results in the literature comparable to our tracer-transport plots. Particles are used to assess flow properties in microparticle image velocimetry experiments (Margaris et al. 2016). However, particle-insertion can confound properties of the flow. Margaris et al. (2016) reported eddies in valve-sinus regions (with ±0.5 cmH2O axial gradients in rat mesenteric lymphatics). Our Fig. 6 shows vortices in this region at several times in a contraction cycle including when the valve is opening or closing. Wilson et al. (2018) also reported persistent eddies in the valve-sinus region that were most prominent during peak forward flow.

4.4 Open-valve resistance

The flow resistance associated with an open-valve is an important parameter when valves are modelled as resistors in lumped-parameter models. We estimated the open-valve resistance for a valve that remained open throughout a contraction cycle in a simultaneous pump operating at a moderate adverse pressure as approximately 4.02 \times 10^{4} \text{dyn} \cdot \text{s/cm}^{5}. Open-valve resistance parameters in the literature vary: 0.25 \text{dyn} \cdot \text{s/cm}^{5} was used by Venugopal et al. (2007); 0.6 \times 10^{6} \text{dyn} \cdot \text{s/cm}^{5} was estimated by Bertram et al. (2014a), though in earlier work they used a value of 600 \text{dyn} \cdot \text{s/cm}^{5} (Bertram et al. 2010); and 2.68 \times 10^{6} \text{dyn} \cdot \text{s/cm}^{5} was estimated by Wilson et al. (2018). Hence, our open-valve resistance estimate is one to two orders of magnitude smaller than the largest ones in the literature. This may be attributable to differences in the models, experimental setups, and definitions of open-valve resistance. The 2D nature of our model might also reduce the open-valve resistance. In our model, the valve opening is effectively a channel in the z-direction, and there is no resistance offered by the walls of the lymphangion in this direction.

For the sake of comparison, pipette resistances in our model are set to 1.6 \times 10^{9} \text{kg/s/m}^{4} = 1.6 \times 10^{4} \text{dyn} \cdot \text{s/cm}^{5} and are about 2.5 times smaller than our open-valve resistance estimate. In Bertram et al. (2016), pipette resistances were approximately four times larger than the open-valve resistance. Pipette resistances in Venugopal et al. (2007) were nearly three orders of magnitude larger than the open-valve resistance. If cannulated vessel experiments are designed to emulate what occurs in vivo and for inlet and outlet pressures to be meaningful, it seems desirable for pipette resistances to be the same order of magnitude as the open-valve resistance.

4.5 Pump-function behavior: comparison with lumped-parameter models with different chain lengths

Pump-function plots appear in the lumped-parameter literature (Bertram et al. 2010, 2016; Razavi et al. 2017). We are unaware of any pump-function plots from higher-dimensional models. Bertram et al. (2010) reported pump-function plots for chains of three to five lymphangions whose lymphangions contracted at 0.5-s orthograde lags. Their pump-function curves (see their Fig. 8(b)) were concave-down with a pronounced bend in the moderate adverse-pressure regime. At low adverse pressures, all three pumps yielded similar cycle-mean flow rates (CMFRs) around 0.18 ml/hr. At larger adverse pressures, the pumps exhibited variation with longer chains yielding a given CMFR at larger adverse pressures than shorter chains.

Pump-function plots for chains of 8, 12, 24, and 36 lymphangions (presumably contracting in 0.5-s orthograde lags) reported by Razavi et al. (2017) from a modified lumped-parameter model (Bertram et al. 2010; Jamalian et al. 2013) also exhibit little variation in CMFR when there is 0 axial pressure difference but pronounced variation in CMFR when the pumps are operating at moderate and high adverse axial pressures. The plots exhibit a slight concave-down shape (when the axes are interchanged in their Fig. 5A) though less so than those in Bertram et al. (2010).

The contractions in our orthograde and fast-orthograde pumps propagated with velocities of 2 and 4 mm/s, respectively and correspond to approximate contraction lag times of 0.5 s and 0.25 s between successive lymphangions. However, we compare both orthograde and fast-orthograde pumps to the 0.5-s, orthograde-lag, lumped-parameter pumps. Our pump-function data are linear and negatively sloped for positive CMFRs and nearly vertical in the high-pressure/low-CMFR regime.
This is in direct contrast to the concave-down, non-linear pump-function curves in Bertram et al. (2010) but is similar to their 1-lymphangion pump-function plot which becomes vertical at sufficiently high downstream pressures. Also, our orthograde pump-function data are quite similar for chains of two to four lymphangions; see Fig. 11. However, our fast-orthograde data exhibit greater variability in the low and moderate adverse-pressure regimes than in the high adverse-pressure regime, and this differs from the other results (Bertram et al. 2010; Razavi et al. 2017). The observation that longer chains yielded 0 CMFR at higher adverse axial pressures than shorter chains (Bertram et al. 2010; Razavi et al. 2017) is consistent with our findings.

4.6 Pump-function behavior: comparison with lumped-parameter models with different contraction styles

Pump-function plots were also provided by Bertram et al. (2010) for a 4-lymphangion chain whose lymphangions contracted at various lags (simultaneous; 0.25-s retrograde; or 0.25, 0.5, 0.75, or 1-s orthograde); see their Fig. 13. At all adverse pressures, the largest CMFRs were generally attained in pumps with longer lags, and the lowest CMFRs were produced by the simultaneous pump. This suggests larger CMFRs occur in pumps with slowly propagating contractile waves than faster ones. Additionally, compared to the lagged pumps, the simultaneous pump failed to yield positive CMFR at the lowest adverse pressure. These are opposite our results. The Bertram et al. (2010) results indicate an advantage for 0.25-s orthograde pumps over 0.25-s retrograde pumps in terms of large CMFRs, and the advantage diminished as the downstream pressure increased; this is consistent with our findings. Similar to our data, their pump-function curve appears nearly linear for the simultaneous pump, but in contrast, their other pump-function curves are concave-down with a bend that sharpens with lag length.

With further developments to the 2010 model, in particular with regards to hysteretic and transmural-pressure-dependent valve opening and closing, Bertram et al. (2016) simulated a 5-lymphangion pump at various adverse axial pressure differences with different refractory periods (delayed successive contractions) and different orthograde and retrograde lags. In direct contrast to their 2010-model results, they found the highest CMFRs occurred at each adverse pressure difference with simultaneous pumping and a positive refractory period. In each case, only the first and sixth valves were operational, and all interior valves remained open each cycle. These results are fully consistent with our observations.

4.7 Valve dynamics in pump failure

In later work, Bertram’s group investigated pump-failure modes in one lymphangion featuring a valve that remained closed throughout a contraction cycle (Bertram et al. 2017). We observed two of their eight-listed failure modes in our 1-lymphangion simulations (results not shown). At an adverse pressure of 0.112 cmH$_2$O, we observed the inlet valve to remain closed each cycle and the outlet valve to open and close each cycle. In the other case, at an adverse pressure of 0.122 cmH$_2$O, the outlet valve remained closed, while the inlet valve opened and closed each cycle. Interestingly, at 0.133 cmH$_2$O both valves closed and opened slightly each cycle. Valve behaviors at higher adverse pressures are under current investigation. Also, unlike the Bertram et al. (2017) results, neither the inlet nor outlet valve remained open each cycle at any pressure in any of our 1-lymphangion pumps. Due to the complex valve treatment in Bertram et al. (2017), it is unclear if the failure modes are physical, though some were also observed experimentally.

4.8 Contraction delays and flow rates

Additional investigations of the effects of contraction delays on CMFRs appear in other low-dimensional models (Macdonald et al. 2008; Venugopal et al. 2007). Venugopal et al. (2007) created a lumped-parameter model corresponding to bovine mesenteric lymphatics and reported little variation in CMFR when contractions among adjacent lymphangions in a 3-lymphangion chain occurred in an orthograde or retrograde lags with delays ranging from 0 up to 1 s. The authors indicate the CMFR was slightly greater for orthograde than retrograde delays. They state that the vessel behavior (presumably CMFR trends) did not change as they increased the number of lymphangions to four or more, but results were not shown. They generated pump-function data for a 2-lymphangion chain, although contraction delays, if any, among the lymphangions were unclear. The model flow-rate data were linear. Linear regression of corresponding experimental data had a reciprocal slope magni-
tude of 0.0005665 cmH$_2$O/(µL/hr) which is an order of magnitude smaller than any of our 2-lymphangion pump-function slope magnitudes. Their adverse pressures were larger than ours by an order of magnitude. Although the linearity of their pump-function data and larger CMFRs in orthograde vs. retrograde pumps are qualitatively similar to our results, at low pressures we observed marked differences in CMFRs as contraction styles and chain lengths varied.

Macdonald et al. (2008) modified a version of the Reddy et al. (1975) model to develop a 1D-flow model inside a bovine, contractile lymphangion with valves modelled as resistors. They examined contractile wave-propagation along a single lymphangion and reported little difference in flow whether the 1 cm/s travelling wave propagated forward or backward. The best pumping occurred when all sections of the lymphangion wall contracted in a quickly propagating wave; large phase differences among neighboring computational cells within the lymphangion reportedly shuttled fluid back and forth. This is generally consistent with our results and the only other work we are aware of where contractile travelling waves were explicitly modelled.

4.9 Conclusions

The model and results presented herein provide new insight into lymphatic transport in chains of variously contracting lymphangions. We simulated the full Navier-Stokes fluid equations with no restrictive assumptions on the flow and utilized the immersed boundary method for the two-way FSI. To our knowledge, no reports of fully coupled, two-way, FSI models of contracting lymphangion chains with physical valves exist. While the model is limited in its 2D nature, it is computationally tractable for simulatingvalved chains of lymphangions. We acknowledge that valves have complicated geometries in 3D. Also, the adverse axial pressures in our study were on the low end of those that are used in biology experiments. We ignored gravitational effects which may become significant in longer chains (Bertram et al. 2010). Also, contractions were prescribed, but in reality, contractile behavior exhibits adaptation to pressure and shear. In future work, we plan to investigate pumping in longer chains, further examine valve dynamics and mechanical properties, and modulate contractions based on pressure conditions.

In addition to reporting pressure and velocity plots, we generated pump-function data for many types of pumps. No such data from higher-dimensional models appear in the literature. The simultaneous pumps generally yielded the largest CMFRs, and these pumps were the most responsive to pressure changes. Moreover, the first and last valves in the simultaneous pumps bore the largest trans-valve pressures. The interior valves in non-simultaneous pumps generally opened and closed each cycle thus breaking up the pressure column and reducing the trans-valve pressure burden. In light of this, there may be an important role for non-simultaneous contractions in the high adverse-pressure regime. Also, in long chains of lymphangions, simultaneous contraction is not expected to occur along the entire length of the chain (Bertram et al. 2016). Perhaps there are functional subgroups of lymphangions in series whose contractile behaviors are closely related (due to variable gap-junctions, muscle-cell coverage, or pacemaker sites), and these groups would be interesting to simulate. Nonetheless, if therapeutics could be designed to selectively target and reduce contraction propagation, to resemble the slow orthograde or retrograde pumps in the current investigation, it may be advantageous to regulate the CMFR and limit the trans-valve pressures when a chain of lymphangions is facing a large adverse pressure difference.

Novel tracer-transport plots were also reported in the present work, and simulation videos with tracers are helpful for visualizing transport. Importantly, non-simultaneous contractions propagated along the lymphangion chains in travelling waves (rather than crude lags), and various valve behaviors were observed and undoubtedly affected by the contraction style. Reports from other higher-dimensional models have been restricted to the case of a rigid vessel wall in a non-contractile setting, or they feature only a single, contracting lymphangion. Thus, the simulations with different travelling-wave contractions in the valved, lymphangion chains in the present work are a novel contribution to the quantitative lymphatic biology field.

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Conflict of interest

The authors declare that they have no conflict of interest.

References

Akl TJ, Coté GL, Nepiyuschikh ZV, Gashev AA, Zawieja DC (2011) Measuring contraction propa-
Pump efficacy in a fluid-structure-interaction model of a chain of contracting lymphangions 25

Arthurs KM, Moore LC, Peskin CS, Pitman E, Layton HE (1998) Modeling Arteriolar Flow and Mass Transport Using the Immersed Boundary Method. J Comput Phys 147(2):402–440. https://doi.org/10.1006/jcph.1998.6097

Ballard M, Wolf KT, Nepiyushchikh Z, Dixon JB, Alexeev A (2018) Probing the effect of morphology on lymphatic valve dynamic function. Biomech Model Mechanobiol 17(5):1343–1356. https://doi.org/10.1007/s10237-018-1030-y

Battista NA, Lane AN, Liu J, Miller LA (2017) Fluid dynamics in heart development: effects of hematocrit and trabeculation. Math Med Biol A J IMA 35(4):493–516. https://doi.org/10.1093/imammb/dqx018

Bertram CD, Macaskill C, Moore JE Jr (2010) Simulation of a Chain of Collapsible Contracting Lymphangions With Progressive Valve Closure. J Biomech Eng 133(1). https://doi.org/10.1115/1.4002799

Bertram CD, Macaskill C, Davis MJ, Moore JE Jr (2014a) Ascending aorta: development of a model of a multi-lymphangion lymphatic vessel incorporating realistic and measured parameter values. Biomech Model Mechanobiol 13(2):401–416. https://doi.org/10.1007/s10237-013-0505-0

Bertram CD, Macaskill C, Moore JE Jr (2014b) Incorporating measured valve properties into a numerical model of a lymphatic vessel. Comput Methods Biomech Biomed Engin 17(14):1519–1534. https://doi.org/10.1080/10255842.2012.753066

Bertram CD, Macaskill C, Davis MJ, Moore JE Jr (2016) Consequences of intravascular lymphatic valve properties: a study of contraction timing in a multi-lymphangion model. Am J Physiol Circ Physiol 310(7):H847–H860. https://doi.org/10.1152/ajpheart.00669.2015

Bertram CD, Macaskill C, Davis MJ, Moore JE Jr (2017) Valve-related modes of pump failure in collecting lymphatics: numerical and experimental investigation. Biomech Model Mechanobiol 16(6):1987–2003. https://doi.org/10.1007/s10237-017-0933-3

Bertram CD, Macaskill C, Davis MJ, Moore JE Jr (2018) Contraction of collecting lymphatics: organization of pressure-dependent rate for multiple lymphangions. Biomech Model Mechanobiol 17(5):1513–1532. https://doi.org/10.1007/s10237-018-1042-7

Cooper L (2016) Investigations of lymphatic fluid flow. PhD thesis. University of Southampton

Davis MJ, Davis AM, Ku CW, Gashev AA (2009a) Myogenic constriction and dilation of isolated lymphatic vessels. Am J Physiol Circ Physiol 296(2):H293–H302. https://doi.org/10.1152/ajpheart.01040.2008

Davis MJ, Davis AM, Lane MM, Ku CW, Gashev AA (2009b) Rate-sensitive contractile responses of lymphatic vessels to circumferential stretch. J Physiol 587(1):165–182. https://doi.org/10.1113/jphysiol.2008.162438

Dillon R, Fauci L, Gaver D III (1995) A Microscale Model of Bacterial Swimming, Chemotaxis and Substrate Transport. J Theor Biol 177(4):325–340. https://doi.org/10.1006/jtbi.1995.0251

Dillon R, Fauci L, Mogensen A, Gaver D III (1996) Modeling Biofilm Processes Using the Immersed Boundary Method. J Comput Phys 129(1):57–73. https://doi.org/10.1006/jcph.1996.0233

Fauci LJ, McDonald A (1995) Sperm motility in the presence of boundaries. Bull Math Biol 57(5):679–699. https://doi.org/10.1006/bulm.1995.0010
Fauci LJ, Peskin CS (1988) A computational model of aquatic animal locomotion. J Comput Phys 77(1):85–108. https://doi.org/10.1016/0021-9991(88)90158-1

Fogelson AL (1984) A mathematical model and numerical method for studying platelet adhesion and aggregation during blood clotting. J Comput Phys 56(1):111–134. https://doi.org/10.1016/0021-9991(84)90086-X

Fogelson AL, Guy RD (2008) Immersed-boundary-type models of intravascular platelet aggregation. Comput Methods Appl Mech Eng 197(25):2087–2104. https://doi.org/10.1016/j.cma.2007.06.030

Hamlet CL, Hoffman KA, Tytell ED, Fauci LJ (2018) The role of curvature feedback in the energetics and dynamics of lamprey swimming: A closed-loop model. PLOS Comput Biol 14(8):1–29. https://doi.org/10.1101/1.1.766178

Harlow FH, Welch JE (1965) Numerical Calculation of Time-Dependent Viscous Incompressible Flow of Fluid with Free Surface. Phys Fluids 8(12):2182–2189. https://doi.org/10.1063/1.1761178

Hope A, Miller L (2015) A numerical study of the benefits of driving jellyfish bells at their natural frequency. J Theor Biol 374:13–25. https://doi.org/10.1016/j.jtbi.2015.03.016

Jamalian S, Bertram CD, Richardson WJ, Moore JE Jr (2013) Parameter sensitivity analysis of a lumped-parameter model of a chain of lymphangions in series. Am J Physiol Circ Physiol 305(12):H1709–H1717. https://doi.org/10.1152/ajpheart.00403.2013

Jamalian S, Davis MJ, Zawieja DC, Moore JE Jr (2016) Network Scale Modeling of Lymph Transport and Its Effective Pumping Parameters. PLOS One 11(2):1–18. https://doi.org/10.1371/journal.pone.0148384

Jamalian S, Jafarnejad M, Zawieja SD, Bertram CD, Gashev AA, Zawieja DC, Davis MJ, Moore JE Jr (2017) Demonstration and Analysis of the Suction Effect for Pumping Lymph from Tissue Beds at Subatmospheric Pressure. Sci Rep 7(1):12080. https://doi.org/10.1038/s41598-017-11599-x

Kou W, Griffith BE, Pandolfini JE, Kahri-las PJ, Patankar NA (2017) A continuum mechanics-based musculo-mechanical model for esophageal transport. J Comput Phys 348:433–459. https://doi.org/10.1016/j.jcp.2017.07.025

Kunert C, Baish JW, Liao S, Padera TP, Munn LL (2015) Mechanobiological oscillators control lymph flow. Proc Natl Acad Sci 112(35):10938 – 10943. https://doi.org/10.1073/pnas.1508330112

Lee JH, Rygg AD, Kolahdouz EM, Rossi S, Retta SM, Duraiswamy N, Scotten LN, Craven BA, Griffith BE (2020) Fluid–Structure Interaction Models of Bioprosthetic Heart Valve Dynamics in an Experimental Pulse Duplicator. Ann Biomed Eng 48(5):1475–1490. https://doi.org/10.1007/s10439-020-02466-4

LeVeque RJ (2007) Finite Difference Methods for Ordinary and Partial Differential Equations: Steady-State and Time-Dependent Problems. Other Titles in Applied Mathematics. Society for Industrial and Applied Mathematics

Li H, Mei Y, Maimon N, Padera TP, Baish JW, Munn LL (2019) The effects of valve leaflet mechanics on lymphatic pumping assessed using numerical simulations. Sci Rep 9(1):10649. https://doi.org/10.1038/s41598-019-46669-9

Lim S, Peskin CS (2012) Fluid-mechanical interaction of flexible bacterial flagella by the immersed boundary method. Phys Rev E 85(3):36307. https://doi.org/10.1103/PhysRevE.85.036307

Macconald AJ, Arkill KP, Tabor GR, McHale NG, Winlove CP (2008) Modeling flow in collecting lymphatic vessels: one-dimensional flow through a series of contractile elements. Am J Physiol Circ Physiol 295(1):H305–H313. https://doi.org/10.1152/ajpheart.00004.2008

Margaris K, Nepiyushchikh Z, Zawieja D, Moore J Jr, A Black R (2016) Microparticle image velocimetry approach to flow measurements in isolated contracting lymphatic vessels. J Biomed Opt 21:25002. https://doi.org/10.1117/1.JBO.21.2.025002

Miller LA, Peskin CS (2004) When vortices stick: an aerodynamic transition in tiny insect flight. J Exp Biol 207(17):3073–3088. https://doi.org/10.1242/jeb.01138

Miller LA, Peskin CS (2005) A computational fluid dynamics of ‘clap and fling’ in the smallest insects. J Exp Biol 208(2):195–212. https://jeb.biologists.org/content/208/2/195

Moore JE Jr, Bertram CD (2018) Lymphatic System Flows. Annu Rev Fluid Mech 50(1):459–482. https://doi.org/10.1146/annurev-fluid-122316-045259

Peskin CS (1972) Flow patterns around heart valves: A numerical method. J Comput Phys 10(2):252–271. https://doi.org/10.1016/0021-9991(72)90065-4

Peskin CS (1977) Numerical analysis of blood flow in the heart. J Comput Phys 25(3):220–252. https://doi.org/10.1016/0021-9991(77)90100-0

Peskin CS (2002) The immersed boundary method. Acta Numer 11:479–517. https://doi.org/10.1017/S0962492902000077

Peskin CS (2007) Energy functions for the representation of immersed elastic boundaries. https://www.math.nyu.edu/faculty/peskin/ib_lecture_notes/lecture3.pdf. accessed 13 November 2020
Quick CM, Venugopal AM, Gashev AA, Zawieja DC, Stewart RH (2007) Intrinsic pump-conduit behavior of lymphangions. Am J Physiol Integr Comp Physiol 292(4):R1510–R1518. https://doi.org/10.1152/ajpregu.00258.2006

Rahbar E, Moore JE Jr (2011) A model of a radially expanding and contracting lymphangion. J Biomech 44(6):1001–1007. https://doi.org/10.1016/j.jbiomech.2011.02.018

Rahbar E, Weimer J, Gibbs H, Yeh A, D Bertram C, J Davis M, Hill M, Zawieja D, Moore JE Jr (2012) Passive Pressure–Diameter Relationship and Structural Composition of Rat Mesenteric Lymphangions. Lymphat Res Biol 10. https://doi.org/10.1089/lrb.2011.0015

Razavi MS, Nelson TS, Nepiyushchikh Z, Gleason RL, Dixon JB (2017) The relationship between lymphangion chain length and maximum pressure generation established through in vivo imaging and computational modeling. Am J Physiol Circ Physiol 313(6):H1249–H1260. https://doi.org/10.1152/ajpheart.00003.2017

Reddy NP, Krouskop TA, Newell PH Jr (1975) Biomechanics of a lymphatic vessel. Blood Vessels 12(5):261–278. https://doi.org/10.1016/0007-1612(75)90041-2

Reddy NP, Krouskop TA, Newell PH Jr (1977) A computer model of the lymphatic system. Comput Biol Med 7(3):181–197. https://doi.org/10.1016/0010-4825(77)90023-3

Renkin EM (1986) Some consequences of capillary permeability to macromolecules: Starling’s hypothesis reconsidered. Am J Physiol Circ Physiol 250(5):H706–H710. https://doi.org/10.1152/ajpheart.1986.100.5.H706

Rockson SG (2001) Lymphedema. Am J Med 110(4):288–295. https://doi.org/10.1016/S0022-9349(00)00727-0

Scallan JP, Wolpers JH, Muthuchamy M, Zawieja DC, Gashev AA, Davis MJ (2012) Independent and interactive effects of preload and afterload on the pump function of the isolated lymphangion. Am J Physiol Circ Physiol 303(7):H809–H824. https://doi.org/10.1152/ajpheart.01098.2011

Scallan JP, Wolpers JH, Davis MJ (2013) Constriction of isolated collecting lymphatic vessels in response to acute increases in downstream pressure. J Physiol 591(2):443-459. https://doi.org/10.1113/jphysiol.2012.237909

Shields JD, Fleury ME, Yong C, Tomei AA, Randolph GJ, Swartz MA (2007) Autologous Chemotaxis as a Mechanism of Tumor Cell Homing to Lymphatics via Interstitial Flow and Autocrine CCR7 Signaling. Cancer Cell 11(6):526–538. https://doi.org/10.1016/j.ccr.2007.04.020

Swartz MA, Lund AW (2012) Lymphatic and interstitial flow in the tumour microenvironment: linking mechanobiology with immunity. Nat Rev Cancer 12(3):210–219. https://doi.org/10.1038/nrc3186

Vajda J, Tormos M (1971) The structure of the valves of the lymphatic vessels. Cells Tissues Organs 78(4):521–531. https://doi.org/10.1015/00014361

Venugopal AM, Stewart RH, Laine GA, Dongaonkar RM, Quick CM (2007) Lymphangion coordination minimally affects mean flow in lymphatic vessels. Am J Physiol Circ Physiol 293(2):H1183–H1189. https://doi.org/10.1152/ajpheart.01340.2006

Watson DJ, Sazonov I, Zawieja DC, Moore JE Jr, van Loon R (2017) Integrated geometric and mechanical analysis of an image-based lymphatic valve. J Biomech 64:172–179. https://doi.org/10.1016/j.jbiomech.2017.09.040

Wiig H, Swartz MA (2012) Interstitial Fluid and Lymph Formation and Transport: Physiological Regulation and Roles in Inflammation and Cancer. Physiol Rev 92(3):1005–1060. https://doi.org/10.1152/physrev.00037.2011

Wilson JT, Wang W, Hellerstedt AH, Zawieja DC, Moore JE Jr (2013) Confocal Image-Based Computational Modeling of Nitric Oxide Transport in a Rat Mesenteric Lymphatic Vessel. J Biomech Eng 135(5). https://doi.org/10.1115/1.4023986

Wilson JT, van Loon R, Wang W, Zawieja DC, Moore JE Jr (2015) Determining the combined effect of the lymphatic valve leaflets and sinus on resistance to forward flow. J Biomech 48(13):3584–3590. https://doi.org/10.1016/j.jbiomech.2015.07.045

Wilson JT, Edgar LT, Prabhakar S, Horner M, van Loon R, Moore JE Jr (2018) A fully coupled fluid-structure interaction model of the secondary lymphatic valve. Comput Methods Biomech Biomed Engin 21(16):813–823. https://doi.org/10.1080/10255842.2018.1521964

Zawieja DC (2009) Contractile Physiology of Lymphatics. Lymphat Res Biol 7(2):87–96. https://doi.org/10.1089/lrb.2009.0007

Zawieja DC, Davis KL, Schuster R, Hinds WM, Granger HJ (1993) Distribution, propagation, and coordination of contractile activity in lymphatics. Am J Physiol Circ Physiol 264(4):H1283–H1291. https://doi.org/10.1152/ajpheart.1993.264.4.H1283

Zweifach BW, Prather JW (1975) Micromanipulation of pressure in terminal lymphatics in the mesentery. Am J Physiol Content 228(5):1326–1335. https://doi.org/10.1152/ajplegacy.1975.228.5.1326
Supplementary Information

Pump efficacy in a fluid-structure-interaction model of a chain of contracting lymphangions

Hallie Elich, Aaron Barrett, Varun Shankar, Aaron L. Fogelson

Biomechanics and Modeling in Mechanobiology

Corresponding author: Hallie Elich, Department of Mathematics, University of Utah (elich@math.utah.edu)

1 Discretization

We provide additional details for the spatial discretizations of $\Omega$ and $\Gamma$, the finite difference discretization of spatial differential operators in our model equations, the temporal discretization, and the numerical-implementation scheme.

1.1 Spatial discretization

Recall the 2D dimensionless system, i.e., dimensionless 2D versions of Eqs. 1-6 from the main text and with Eq. 1 replaced with Eq. 14. For convenience, that system is reproduced here (tildes are omitted):

\[
\text{Re} \left( \vec{u}_t + \nabla \cdot \left( \vec{u} \vec{u}^T \right) \right) = -\nabla \mathbf{p} + \Delta \vec{u} + f - \kappa \sigma \vec{u}, \tag{1}
\]

\[
\nabla \cdot \vec{u} = \sum_{i=1}^{2} Q_i(t) \psi_i(\vec{x}), \tag{2}
\]

\[
Q_i(t) = \frac{1}{R_i} \left\{ P_{\text{ext}}^i(t) - \int_{\Omega} p(\vec{x}, t) \psi_i(\vec{x}) \, d\vec{x} \right\}, \tag{3}
\]

\[
f(\vec{x}, t) = \int_{\Gamma} F(s, t) \delta(\vec{x} - X(s, t)) \, ds, \tag{4}
\]

\[
\frac{\partial X}{\partial t}(s, t) = \vec{u}(X(s, t), t) = \int_{\Omega} \vec{u}(\vec{x}, t) \delta(\vec{x} - X(s, t)) \, d\vec{x}, \tag{5}
\]

\[
\vec{u}(\vec{x}, 0) = \vec{0}. \tag{6}
\]

where $\Omega = [0, a] \times [0, b]$, and the IB configuration is $X(s, t)$ with $0 \leq s \leq \frac{l}{L}$. Let $\vec{u}(\vec{x}, t) = (u(x, t), v(x, t))^T$, $f(x, t) = (f(x, t), g(x, t))^T$, $F(s, t) = (F(s, t), G(s, t))^T$, and $x = (x, y)^T$. In the main text, $\Omega$ is discretized into a uniform MAC grid of meshwidth $h$. The $(j, l)$-th MAC grid cell has center $\vec{x}_{j,l} = (x_j, y_l) = \left( \left(j - \frac{1}{2}\right) h, \left(l - \frac{1}{2}\right) h \right)$, left-edge center $\vec{x}_{j-1/2,l} = (x_{j-1/2}, y_l) = \left( \left(j - \frac{1}{2}\right) h, \left(l - \frac{1}{2}\right) h \right)$, and bottom-edge center $\vec{x}_{j,l-1/2} = (x_j, y_{l-1/2}) = \left( \left(j - \frac{1}{2}\right) h, \left(l - \frac{1}{2}\right) h \right)$, for $j = 1, \ldots, n_x$ and $l = 1, \ldots, n_y$; see Fig. 1.


We denote by $\Delta s$ the uniform increment in parameter space and index Lagrangian nodes with a subscript, $k$, i.e., $s_k$ for $k = 1, \ldots, N$. The valve IB points have $\Delta s_v \approx \Delta s$; each leaflet IB point is indexed $k = 1, \ldots, N_v$.

With $\Omega$ and $\Gamma$ spatially discretized, we introduce notation for the solution to the discrete approximation of the 2D dimensionless system Eqs. 1-6. Let

$$U_{j-1/2,l}(t) \approx u(x_{j-1/2,l}, t),$$
$$V_{j-l}(t) \approx v(x_{j-l}, t),$$
$$U_j = (U_{j-1/2,l}, V_{j-l/2})^T,$$
$$P_{j,l}(t) \approx p(x_{j,l}, t),$$
$$f_{j-l/2}(t) \approx f(x_{j-l/2}, t),$$
$$g_{j-l/2}(t) \approx g(x_{j-l/2}, t),$$
$$F_k(t) \approx F(s_k, t),$$
$$G_k(t) \approx G(s_k, t),$$
$$F_k(t) = (F_k(t), G_k(t))^T,$$ and
$$X_k(t) = X(s_k, t).$$

Thus other than for $f$, $F$, and their components, we use capital letters to denote quantities corresponding to the discrete-approximation solution. Whenever $f$, $F$, or their component functions appear with a subscript, usage of the corresponding discrete function is implied. Since the components of $U_{j,l}$ are defined at grid left-edge centers and bottom-edge centers, we define a separate Brinkman indicator for each component. The first component indicator is 1 at left-edge centers outside the structure and 0 at all other left-edge centers and similarly for the second component indicator at bottom-edge centers. Let $\sigma_{j,l} = (\sigma_{L_{j-l/2}}, \sigma_{B_{j-l/2}})^T$, with $\sigma_{L_{j-l/2}}(t) = \sigma(x_{j-l/2}, t)$, and $\sigma_{B_{j-l/2}}(t) = \sigma(x_{j-l/2}, t)$. Define $\Psi_{j,l}^r = \psi_l(x_{j,l}), \Psi_{j,l}^c = \psi_c(x_{j,l}),$ and $\Psi_{j,l} = \Psi_{j,l}^r - \Psi_{j,l}^c$. These functions satisfy

$$\sum_{j,l} \Psi_{j,l}^r h^2 = \sum_{j,l} \Psi_{j,l}^c h^2 = 1.$$ (7)
which are discretized 2D integrals and analogues of the integrals in Eq. 7 of the main text (each dimensionless 3D integral features an integrand that is constant in z and with z-integration limits from 0 to 1).

We write the momentum (Eq. 1) and continuity (Eq. 2) equations in component/expanded form:

\[
\begin{align*}
\text{Re} \left( \frac{\partial u}{\partial t} + \frac{\partial}{\partial x} (u^2) + \frac{\partial}{\partial y} (uv) \right) &= - \frac{\partial p}{\partial x} + \frac{\partial^2 u}{\partial x^2} + \frac{\partial^2 u}{\partial y^2} + f - \kappa \sigma u, \\
\text{Re} \left( \frac{\partial v}{\partial t} + \frac{\partial}{\partial x} (uv) + \frac{\partial}{\partial y} (v^2) \right) &= - \frac{\partial p}{\partial y} + \frac{\partial^2 v}{\partial x^2} + \frac{\partial^2 v}{\partial y^2} + g - \kappa \sigma v,
\end{align*}
\]

(8) (9)

We use centered differencing and averaging, when quantities do not live at required locations, to spatially discretize Eqs. 8-10. We focus on the \((j, l)\)-th grid cell and use Fig. 1 to aid our work. We use the following approximations for terms in Eq. 8, each of which must live at the left-edge center, \(x_{j-1/2, l}\):

| \[ \frac{\partial}{\partial x} (u^2) \]_{x_{j-1/2, l}} & \approx \frac{U_{j+1/2, l}^2 - U_{j-3/2, l}^2}{2h}, \\
| \[ \frac{\partial}{\partial y} (uv) \]_{x_{j-1/2, l}} & \approx \frac{(U_{j-1/2, l+1} + U_{j-1/2, l-1} + V_{j-1, l+1/2} + V_{j-1, l-1/2})}{2h} - \frac{(U_{j-1/2, l} + U_{j-1/2, l-1})}{2h} \frac{(V_{j, l+1/2} + V_{j, l-1/2})}{2h}, \\
| \frac{\partial p}{\partial x} \bigg|_{x_{j-1/2, l}} & \approx \frac{P_{j+1/2} - P_{j-1/2}}{h} =: (D_h^p)_j, \\
| \frac{\partial^2 u}{\partial x^2} \bigg|_{x_{j-1/2, l}} & \approx \frac{U_{j+1/2, l} - 2U_{j-1/2, l} + U_{j-3/2, l}}{h^2}, \\
| \frac{\partial^2 u}{\partial y^2} \bigg|_{x_{j-1/2, l}} & \approx \frac{U_{j-1/2, l+1} - 2U_{j-1/2, l} + U_{j-1/2, l-1}}{h^2}.
\]

(11) (12) (13) (14) (15)

Similarly, we use the following approximations for terms in Eq. 9, each of which must live at the bottom-edge center, \(x_{j, l-1/2}\):

| \[ \frac{\partial}{\partial x} (uv) \]_{x_{j, l-1/2}} & \approx \frac{(U_{j+1/2, l} + U_{j+1/2, l-1} + V_{j+1, l+1/2} + V_{j+1, l-1/2})}{2h} - \frac{(U_{j-1/2, l} + U_{j-1/2, l-1})}{2h} \frac{(V_{j, l+1/2} + V_{j, l-1/2})}{2h}, \\
| \frac{\partial p}{\partial x} \bigg|_{x_{j, l-1/2}} & \approx \frac{P_{j+1/2} - P_{j-1/2}}{h} =: (D_h^p)_j, \\
| \frac{\partial^2 u}{\partial x^2} \bigg|_{x_{j, l-1/2}} & \approx \frac{U_{j+1/2, l} - 2U_{j-1/2, l} + U_{j-1/2, l-1}}{h^2}, \\
| \frac{\partial^2 u}{\partial y^2} \bigg|_{x_{j, l-1/2}} & \approx \frac{U_{j-1/2, l} - 2U_{j-1/2, l} + U_{j-1/2, l-1}}{h^2}.
\]

(16)
\[
\frac{\partial}{\partial y} (v^2) \bigg|_{x_{j-\frac{1}{2}}} \approx \frac{V_{j+1,\frac{1}{2}}^2 - V_{j-\frac{1}{2}}^2}{2h}, \quad (17)
\]
\[
\frac{\partial p}{\partial y} \bigg|_{x_{j-\frac{1}{2}}} \approx \frac{P_{j+1}-P_{j-1}}{h} =: (D_{h_y}^c P)_{j-\frac{1}{2}}, \quad (18)
\]
\[
\frac{\partial^2 y}{\partial x^2} \bigg|_{x_{j-\frac{1}{2}}} \approx \frac{V_{j+1,\frac{1}{2}} - 2V_{j,\frac{1}{2}} + V_{j-1,\frac{1}{2}}}{h^2}, \quad (19)
\]
\[
\frac{\partial^2 y}{\partial x^2} \bigg|_{x_{j+\frac{1}{2}}} \approx \frac{V_{j+1,\frac{1}{2}} - 2V_{j,\frac{1}{2}} + V_{j-1,\frac{1}{2}}}{h^2}, \quad (20)
\]
Lastly, for Eq. 10 we have at the cell center \(x_{j,\frac{1}{2}}\):
\[
\frac{\partial u}{\partial x} \bigg|_{x_{j,\frac{1}{2}}} \approx \frac{U_{j+\frac{1}{2}} - U_{j-\frac{1}{2}}}{h} =: (D_{h_x}^L U)_{j,\frac{1}{2}} \quad (21)
\]
and
\[
\frac{\partial u}{\partial y} \bigg|_{x_{j,\frac{1}{2}}} \approx \frac{V_{j+\frac{1}{2}} - V_{j-\frac{1}{2}}}{h} =: (D_{h_y}^R V)_{j,\frac{1}{2}}. \quad (22)
\]
Note that Eqs. 12 and 16 involve approximations to the product \(UV\) located at the vertical and horizontal pairs, respectively, of \(x\)'s in Fig. 1. Also note the discrete spatial difference operators \(D_{h_x}^e\), \(D_{h_y}^e\), \(D_{h_x}^c\), and \(D_{h_y}^c\) defined in Eqs. 13, 18, 21, and 22, respectively.

We introduce additional spatial difference operators \(\Delta_{h_x}^L\), \(\Delta_{h_y}^L\), and \(C_h(U)\), where \((\Delta_{h_x}^L U)_{j-\frac{1}{2}}\) is given by the sum of the right-hand sides of Eqs. 14-15, \((\Delta_{h_y}^L V)_{j-\frac{1}{2}}\) is given by the sum of the right-hand sides of Eqs. 19-20, \((C_h^{(1)}(U))_{j-\frac{1}{2}}\) is given by the sum of the right-hand sides of Eqs. 11-12, and \((C_h^{(2)}(U))_{j-\frac{1}{2}}\) is given by the sum of the right-hand sides of Eqs. 16-17.

Putting this all together, we define the discrete gradient operator \(D_h^e := (D_{h_x}^e, D_{h_y}^e)^T\), where \(D_{h_x}^c P = (D_{h_x}^c P, D_{h_y}^c P)^T\); we define the discrete divergence operator \(D_h^{\cdot B} := (D_{h_x}^{\cdot B}, D_{h_y}^{\cdot B})^T\), where \(D_{h_x}^{\cdot B} \cdot U = D_{h_x}^c U + D_{h_y}^c V\); we define the discrete vector Laplacian \(\Delta_h^{LB} = (\Delta_{h_x}^L, \Delta_{h_y}^L)^T\), where \(\Delta_h^{LB} U = (\Delta_{h_x}^L U, \Delta_{h_y}^L V)^T\); and we define the discrete conservative-form, advective-term operator \(C_h(\cdot) = (C_h^{(1)}(\cdot), C_h^{(2)}(\cdot))^T\), where \(C_h(U) = (C_h^{(1)}(U), C_h^{(2)}(V))^T\). We also define \(\Delta_h^c = D_h^{\cdot B} \cdot D_h^e\) which yields the 5-point Laplacian operator which maps discrete scalar functions (i.e., cell-centered quantities) to discrete scalar functions. For example, \((\Delta_h^c P)_{j,\frac{1}{2}} = \frac{p_{j+1,\frac{1}{2}} - 2p_{j,\frac{1}{2}} + p_{j-1,\frac{1}{2}}}{h^2} + p_{j,\frac{1}{2}} - 2p_{j,\frac{1}{2}} + p_{j+1,\frac{1}{2}}\).

We have defined operators \(D_h^e, D_h^{\cdot B}, \Delta_h^{LB}, C_h, \) and \(\Delta_h^c\). We streamline notation and use \(D_h, \Delta_h, C_h, \) and \(\Delta_h\), thus omitting the \(c\) and \(L, B\) superscripts. It will be clear from context precisely which operator is being used.
Spatial discretization yields these semi-discrete approximations to Eqs. 1-6:

\[ \text{Re} \left( U'_{j,l}(t) + C_h(U_{j,l}(t)) \right) = -D_h P_{j,l}(t) + \Delta_h U_{j,l}(t) + f_{j,l}(t) - \kappa \sigma_{j,l}(t) U_{j,l}(t), \]

\[ D_h \cdot U_{j,l}(t) = \sum_{i=1}^{2} Q_i(t) \psi_{j,l}, \]

\[ Q_i(t) = \frac{1}{R_i} \left\{ F_i^{\text{ext}}(t) - \sum_{j,l} P_{j,l}(t) \psi_{j,l} h^2 \right\}, \]

\[ f_{j-1/2,l}(t) = \sum_k F_k(t) \delta_h(x_{j-1/2,l} - X_k(t)) \Delta s, \]

\[ g_{j,l-1/2}(t) = \sum_k G_k(t) \delta_h(x_{j,l-1/2} - X_k(t)) \Delta s, \]

\[ X'_k(t) = \sum_{j,l} U_{j-1/2,l}(t) \delta_h(x_{j-1/2,l} - X_k(t)) h^2, \]

\[ Y'_k(t) = \sum_{j,l} V_{j-1/l}(t) \delta_h(x_{j,l-1/2} - X_k(t)) h^2, \]

\[ U_{j,l}(0) = 0. \]

These equations hold for all \( j = 1, \ldots, n_x; \quad l = 1, \ldots, n_y; \quad i = 1, 2; \) and the boundary conditions are periodic. The prime superscript indicates a derivative with respect to time. The semi-discrete versions of Eqs. 4 and 5 have been written in component form. In Eqs. 26 and 28, each \( \delta_h \) is centered at an IB point and is evaluated at cell left-edge centers; in Eqs. 27 and 29, \( \delta_h \) is evaluated at cell bottom edge-centers. In Eq. 23, the corresponding components of \( \sigma_{j,l} \) and \( U_{j,l} \) are multiplied.

1.2 Temporal discretization

We numerically integrate Eqs. 23-24 using a second-order-accurate Runge-Kutta method based on the midpoint rule as in ?. For current purposes, we assume body forces are known. In time-stepping from level \( n \) to level \( n + 1 \), there is first a preliminary substep from time-level \( n \) to time-level \( n + 1/2 \) followed by a main step, which utilizes results of the preliminary substep, from time-level \( n \) to time-level \( n + 1 \).

The preliminary substep involves the fully discretized system (omitting \( j, l \) subscripts):

\[ \text{Re} \left( \frac{U^{n+1/2} - U^n}{\Delta t/2} + C_h(U^n) \right) = -D_h \tilde{P}^{n+1/2} + \Delta_h U^{n+1/2} + f^{n+1/2} - \kappa \sigma^n U^n, \]

\[ D_h \cdot U^{n+1/2} = \sum_{i=1}^{2} Q_i^{n+1/2} \psi_i, \]
and
\[
Q_i^{n+1/2} = \frac{1}{R_i} \left\{ \rho_{\text{ext},i}^{n+1/2} - \sum \tilde{p}_i^{n+1/2} \psi_i h^2 \right\},
\]  \hspace{1cm} (33)

where \(\tilde{p}_i^{n+1/2}\) is an approximation to the pressure at the half-time level. We rewrite Eq. 31 with only unknowns on the left-hand side and condense the known quantities on the right-hand side with new notation:
\[
\left( \text{Re} - \frac{\Delta t}{2} \Delta h \right) U_i^{n+1/2} + \frac{2}{\Delta t} D_h \tilde{p}_i^{n+1/2} = \text{Re} U_i^n - \frac{\Delta t}{2} \text{Re} C_h U_i^n + \frac{\Delta t}{2} f_i^{n+1/2} - \frac{\Delta t}{2} \kappa \sigma_i^n U_i^n =: \mathbf{R}_{pc,n+1/2}.
\]  \hspace{1cm} (34)

We next take the discrete divergence\(^1\) of Eq. 34 to obtain the following pressure-Poisson equation:
\[
\frac{\Delta t}{2} \Delta h \tilde{p}_i^{n+1/2} = D_h \cdot \mathbf{R}_{pc,n+1/2} - \sum_{i=1}^2 Q_i^{n+1/2} \left( \text{Re} - \frac{\Delta t}{2} \Delta h \right) \psi_i.
\]  \hspace{1cm} (35)

Similar to what is done in \(?\) and \(?\), we consider three auxiliary problems:
\[
\frac{\Delta t}{2} \Delta h \phi_i = \left( \text{Re} - \frac{\Delta t}{2} \Delta h \right) \psi_i \quad i = 1, 2, \hspace{1cm} (36)
\]
\[
\frac{\Delta t}{2} \Delta h \phi_i^{n+1/2} = D_h \cdot \mathbf{R}_{pc,n+1/2}.
\]  \hspace{1cm} (37)

Since the \(\psi_i\)'s do not change with time, the \(\phi_i\)'s bear no time indices. We use MATLAB's built-in, direct solver on Eqs. 36-37. The problems are singular due to the periodic boundary conditions. The discrete compatibility condition is that the right-hand sides of Eqs. 36-37 sum to 0 on the grid; this is satisfied due to the definition of \(\psi_i\) and since we have taken the discrete divergence of a periodic vector field. Equipped with solutions to Eqs. 36-37, we define (with \(Q_i^{n+1/2}\) to-be-determined):
\[
\tilde{p}_0^{n+1/2} = \phi_0^{n+1/2} - \sum_{i=1}^2 Q_i^{n+1/2} \phi_i.
\]  \hspace{1cm} (38)

This \(\tilde{p}_0^{n+1/2}\) satisfies Eq. 35 for any pair \(Q_i^{n+1/2}\). Moreover, it is only defined up to an additive constant. We define
\[
\tilde{p}_i^{n+1/2} = \tilde{p}_0^{n+1/2} - (\psi_i, \tilde{p}_0^{n+1/2})_h,
\]  \hspace{1cm} (39)
where
\[
(\alpha, \beta)_h = \sum_{j,l} \alpha(x_j,l) \beta(x_j,l) h^2
\]
denotes the discrete inner product. Now, \(\tilde{p}_i^{n+1/2}\) has average value 0 over the compensatory source, and we consider this 0 to be equal to the experimental

\(^1\) The discrete spatial difference operators commute due to the periodic boundary conditions, i.e., \(D_h \cdot \Delta h = \Delta h D_h\) and \(D_h \cdot \Delta h = \Delta h\).
reference pressure with respect to which \( P_{\text{ext}} \) is measured (gauge pressure 0). Substituting Eq. 39 into Eq. 33 yields the matrix equation:

\[
\begin{pmatrix}
    R_1 - (\phi_1, \Psi_1)_h & - (\phi_2, \Psi_1)_h \\
    - (\phi_1, \Psi_2)_h & R_2 - (\phi_2, \Psi_2)_h
\end{pmatrix}
\begin{pmatrix}
    Q_{1}^{n+1/2} \\
    Q_{2}^{n+1/2}
\end{pmatrix}
= \begin{pmatrix}
    (P_{\text{ext}}, P_{\text{ext}}^{n+1/2} - (\phi_0^{n+1/2}, \Psi_1)_h) \\
    (P_{\text{ext}}, P_{\text{ext}}^{n+1/2} - (\phi_0^{n+1/2}, \Psi_2)_h)
\end{pmatrix},
\]

(40)

Solving this system yields \( Q_{i}^{n+1/2} \) for \( i = 1, 2 \). Now \( \tilde{P}_{\text{ext}}^{n+1/2} \) is fully determined in Eq. 39. We then return to Eq. 34 and obtain the Helmholtz problem:

\[
\left( \text{Re} I - \frac{\Delta t}{2} \Delta h \right) U_{n+1/2} = R_{p_{\text{bc}}}^{n+1/2} - \frac{\Delta t}{2} D_{h} \tilde{P}_{\text{ext}}^{n+1/2}.
\]

(41)

This problem is nonsingular, solved directly in MATLAB, and decouples for the \( U \) and \( V \) components. The main step involves the fully discretized system \(^2\):

\[
\text{Re} \left( \frac{U_{n+1} - U_{n}}{\Delta t} + C_{h}(U_{n+1/2}) \right) = -D_{h} P_{\text{bc}}^{n+1/2} + \Delta h \left( \frac{U_{n} + U_{n+1}}{2} \right) + f_{n+1/2} - \kappa \left( \frac{3\sigma_{n} - \sigma_{n-1}}{2} \right) U_{n+1/2},
\]

(42)

\[
D_{h} \cdot U_{n+1} = \sum_{i=1}^{2} Q_{i}^{n+1/2} \Psi_{i},
\]

(43)

and

\[
Q_{i}^{n+1} = \frac{1}{R_{i}} \left\{ P_{i}^{\text{ext}, n+1} - \sum P_{n+1/2} \Psi_{i} h \right\},
\]

(44)

where \( P_{n+1/2} \) is another approximation to the pressure at the half-time level. This system is solved in the same way as that in the preliminary substep.

1.3 Numerical-implementation scheme

We describe how to proceed from time-level \( n \) to time-level \( n + 1 \). At time-level \( n \), we know \( U^{n} \) and \( X^{n} \).

1. Move the IB points to the half-time level via:

\[
\frac{X_{k}^{n+1/2} - X_{k}^{n}}{\frac{\Delta t}{2}} = \sum_{j,l} U_{j-1/2,l}^{n} \delta h_{j} (x_{j-1/2,l} - X_{k}^{n}) h^{2},
\]

(45)

\[
\frac{Y_{k}^{n+1/2} - Y_{k}^{n}}{\frac{\Delta t}{2}} = \sum_{j,l} V_{j,l-1/2}^{n} \delta h_{j} (x_{j,l-1/2} - X_{k}^{n}) h^{2}.
\]

(46)

2. Use the new boundary configuration \( X^{n+1/2} \) to compute the Lagrangian force density \( F_{n+1/2} \).

\(^2\) We acknowledge the difference in time-level for the pressure and flow-rate in Eq. 44 but postpone consideration for future work. We have linearly extrapolated \( \sigma_{n-1} \) and \( \sigma_{n} \) to approximate \( \sigma_{n+1/2} \).
3. Spread the Lagrangian forces to the Eulerian grid using the half time-level $\delta_h$ values

\[
\begin{align*}
  f_{j,-1/2,l}^{n+1/2} &= \sum_k F_k^{n+1/2} \delta_h(x_{j-1/2,l} - X_k^{n+1/2}) \Delta s, \\
g_{j,l-1/2}^{n+1/2} &= \sum_k G_k^{n+1/2} \delta_h(x_{j,l-1/2} - X_k^{n+1/2}) \Delta s. 
\end{align*}
\]

(47)

(48)

4. Use $f_{n+1/2} = (f_{n+1/2}, g_{n+1/2}^T)^T$ and the numerical integration described in Sect. 1.2 to obtain $U^{n+1/2}$ and $U^{n+1}$.

5. Find the IB-point locations at the full-time level using the preliminary substep velocity and IB positions at the $n$ and $n+1/2$ time-levels:

\[
\begin{align*}
  \frac{X_{k}^{n+1} - X_{k}^{n}}{\Delta t} &= \sum_{j,l} U_{j-1/2,l}^{n+1/2} \delta_h(x_{j-1/2,l} - X_k^{n+1/2}) h^2. \\
  \frac{Y_{k}^{n+1} - Y_{k}^{n}}{\Delta t} &= \sum_{j,l} V_{j,l-1/2}^{n+1/2} \delta_h(x_{j,l-1/2} - X_k^{n+1/2}) h^2. 
\end{align*}
\]

(49)

(50)

Thus, we obtain $U^{n+1}$ and $X^{n+1}$.

We used an advective CFL condition $\frac{Ch}{\Delta t} \geq \max_j ||U_{j,l}^{n}||_2$, to guide the size of the initial time step based on velocity estimates. We used the Euclidean 2-norm for the velocity at each grid cell and a CFL constant, $C = 0.1$. The inequality was enforced at every time step. To reduce machine error that otherwise contributed to a loss of horizontal (vessel-midline) symmetry (also observed in ?), we symmetrized the vessel-wall and valve IB points at half- and full-time levels about the midline by averaging corresponding diametrically opposed IB-point $x$-locations and reassigning the average as the new $x$-locations for the corresponding top and bottom points. Similarly, we averaged corresponding $y$-coordinate distances to the midline and reset top and bottom $y$-coordinates so each their distance to the midline was equal to the average.

2 Tension and bending Lagrangian force densities

We provide equations for the tension and bending Lagrangian force densities. We present these equations in a dimensional setting, though they are non-dimension-alized with scalings described in Sect. 2.4 of the main text for use in Eqs. 47-48 of this supplement.

Each valve leaflet originates at a vessel wall IB point and comprises an open curve. We discretize the tension and bending elastic energy functionals in Eqs. 8-9 of the main text first for the valve leaflets (thus with $k_t$ and $k_b$ replaced with $k_{tv}$ and $k_{vb}$, respectively). As in ?, we discretize $E_T$ as

\[
E_{T,D}(X_1 \cdots X_{N_v}) := \frac{k_{tv}}{2} \sum_{k=1}^{N_v-1} \left( \frac{\|X_{k+1} - X_k\|}{\Delta s_v} - \frac{\|X_{k+1}^0 - X_k^0\|}{\Delta s_v} \right)^2 \Delta s_v. 
\]

(51)
This discretized energy functional is differentiated with respect to each of the two components of $X_k$ to yield Lagrangian forces at $X_k$. The force at the $l$-th point is given by

$$F_l \Delta s_v = - \frac{\partial E_{B,D}}{\partial X_l} = \left[ (l \neq N_v) T_{l+1/2} \tau_{l+1/2} - (l \neq 1) T_{l-1/2} \tau_{l-1/2} \right],$$

for $l = 1, \ldots, N_v$,

where $T_{l+1/2} = k_t \left( \frac{\|X_{l+1} - X_{l}\|}{\Delta s_v} - \frac{\|X_{l+1}^0 - X_{l}^0\|}{\Delta s_v} \right)$, and $\tau_{l+1/2} = \frac{\|X_{l+1} - X_{l}\|}{\Delta s_v}$,

$(l \neq N_v) = 1$ if $l \neq N_v$ and 0 if $l = N_v$, and $(l \neq 1) = 1$ if $l \neq 1$ and 0 if $l = 1$. The Lagrangian force density at the $l$-th point is $F_l$.

For an open curve, we discretize $E_B$ as in

$$E_{B,D}(X_1 \cdots X_{N_v}) := \frac{k_b}{2} \sum_{k=2}^{N_v-1} |C_k - C_0|^2 \Delta s_v,$$

with

$$C_k = \frac{X_{k+1} - 2X_k + X_{k-1}}{(\Delta s_v)^2},$$

and

$$C_0 = \frac{X_{k+1}^0 - 2X_k^0 + X_{k-1}^0}{(\Delta s_v)^2},$$

for $k = 2, \ldots, N_v - 1$. This discretized energy functional is differentiated with respect to each of the two components of $X_k$ to yield Lagrangian forces. The force at the $l$-th point is given by

$$F_l \Delta s_v = - \frac{\partial E_{B,D}}{\partial X_l} =$$

$$= -k_b \left\{ \left( \frac{(l \geq 3) C_{l-1} + (2 \leq l \leq N_v - 1) 2 C_l + (l \leq N_v - 2) C_{l+1}}{(\Delta s_v)^2} \right) \Delta s_v, \right.$$

using similar parenthetical logical expressions as in Eq. (52) and with $F_l$ the Lagrangian force density at the $l$-th valve point.

For capsule IB points, the Lagrangian tension force density is the same as for leaflet points but without the parenthetical logical expressions $(l \neq N_v)$ and $(l \neq 1)$, it has $\Delta s_v$ replaced with $\Delta s$, and it has tension constant $k_t$. The bending force density at capsule IB points is the same as for leaflet points but without the parenthetical logical expressions, with bending coefficient $k_b$, and with $\Delta s_v$ replaced with $\Delta s$.

In numerical implementation, all capsular and leaflet Lagrangian force densities are accumulated at each IB point and spread to the fluid via Eqs. 47-48. In the case where a Lagrangian force (rather than force density is specified), it is interpreted as the product of a Lagrangian force density and the nodal increment, and it is spread to the fluid via the same equations.
3 Measuring flow rates, velocities, and pressures at flow meters

Flow meters are shown in cyan in Fig. 2 of the main text and are vertical line segments where we measure flow rates, velocities, and pressures. In numerical implementation, at each full-time level, a set of flow meter points is evenly distributed between the diametrically opposed IB points at each end of each flow meter with spacing approximately $h/2$. At these “auxiliary IB points,” which do not affect the flow in any way, we interpolate velocity and pressure. We can measure velocity or pressure at just the vessel midline or along all flow-meter points, using measurements at the latter to estimate flow rates.

We obtain the horizontal velocity component at each flow meter point at time level $n + 1$ by using the right-hand side of Eq. 49 but with $n + 1/2$ replaced with $n + 1$ and $X_k$ replaced with the flow-meter point. If $X_{FM_k}$ denotes a flow-meter point, then the interpolated horizontal velocity component at that point at time level $n + 1$, $U_{n+1}^{FM_k}$, is approximated

$$U_{n+1}^{FM_k} \approx \sum_{j,l} U_{n+1}^{\pm1/2,l} \delta_h (x_{j,l} - X_{FM_k}^{n+1}) h^2. \quad (55)$$

We approximate the flow rate using the midpoint rule to approximate the $y$-integral of the horizontal velocity component along the flow meter and obtain

$$\int_{y_l}^{y_u} u(x_0, y, (n + 1) \Delta t) dy \approx \sum_k U_{FM_k}^{n+1} \Delta y_k, \quad (56)$$

where $\Delta y_k \approx h/2$ is the uniform spacing of the flow-meter points, $y_l$ and $y_u$ are lower and upper bounding $y$-values corresponding to the bottom and top flow-meter points, and $x_0$ is the $x$-coordinate of the flow-meter location.

We similarly interpolate pressures at flow-meter points via

$$P_{n+1/2}^{FM_k} \approx \left( \sum_{j,l} P_{n+1/2,l} \delta_h (x_{j,l} - X_{FM_k}^{n+1}) h^2 \right) - (P_{n+1/2}^{n+1}, \Psi_c) h. \quad (57)$$

evaluating the discrete Delta function at cell centers and having subtracted the computational reference pressure.