Modeling flow in collecting lymphatic vessels: one-dimensional flow through a series of contractile elements

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The lymphatic system is an important but largely neglected element of the circulatory system. At the level of the microcirculation, plasma filtrate drains into lymphatic capillaries, which converge to form collecting vessels. These possess contractile walls and irregularly spaced one-way valves; spontaneous contraction of the walls acts to pump lymph fluid along the network, and the contractions may be modulated by nerves or by autocrine factors (7, 9, 15). The vessels converge and pump the lymph through lymph nodes to drain into the venous circulation. The importance of the lymphatic system can be seen by the effects of its dysfunction. The accumulation of fluid in the tissue, lymphoedema, caused by the removal of vessels during surgery or occlusion by parasites, results in pain, disfigurement, incapacity, and reduced immunity. There are many unexamined phenomena in lymphatic physiology and little theoretical analysis (22). However, many appropriate modeling techniques have been applied to other components of the cardiovascular system, such as flow in veins and heart valve function (1, 3). This article concentrates on the collecting lymphatics, the larger vessels of the branching system. We follow a path of computational analysis in one dimension supported by experimental measurements. The theoretical model consists of an elastic tube punctuated by valves with a contractile wave passing along it. Experiments were performed on bovine-excised mesenteric lymphangions to determine the elastic properties of the walls for incorporation into the models and to characterize in vitro pumping behavior for comparison with the model predictions.

Previous modeling. The earliest computational model of the lymphatic system was published by Reddy and coworkers (19, 20, 21). Their analysis assumes one-dimensional flow along a succession of lymphangions, each of which is modeled as a single computational node. The fluid mechanics of the laminar flow of lymph fluid are described by the Navier-Stokes equations (NSEs):

\[
\nabla \cdot \vec{u} = 0
\]

\[
\frac{\partial \vec{u}}{\partial t} + \vec{u} \cdot \nabla \vec{u} = -\frac{1}{\rho} \nabla p + \nu \nabla^2 \vec{u}
\]

where \(u\) is the velocity, \(t\) is the time, \(p\) is the density, \(p\) is the pressure, and \(\nu\) is the viscosity. With the assumption that the flow be uniform across the cross section, and with the expression of the NSE in cylindrical coordinates, these equations simplify considerably. Reddy and coworkers (19, 20, 21) chose to use \(Q\), the volumetric flow rate, pressure \(p\), and the radius, \(a\), of the vessel as dependent variables, in which case the NSE can be written as

\[
\frac{\partial Q}{\partial x} = -2\pi a \frac{\partial a}{\partial t}
\]

\[
\frac{\partial Q}{\partial t} = -\frac{\pi a^2}{\rho} \frac{\partial}{\partial x} \left[p - pgz + \frac{2\pi a}{\rho} \tau\right]_{r=a}
\]

where \(\tau = \mu(\partial u/\partial r)\) is the stress term evaluated at the wall, \(x\) is the distance along the tube, and \(pgz\) is the pressure head. Since the flow is laminar, this can be evaluated from Poiseuille’s law. Closure of these equations can be achieved by considering the influence of the elastic wall on the pressure inside, providing a further equation connecting the radius of the vessel, \(a\), and the internal pressure, \(P_i\), Reddy et al. (19) state this in the form:

\[
P_i = p_{ext,i} + \frac{h_i}{a_i} \left[\sigma_{hoop,i} + \sigma_{act,i}\right]
\]

involving the wall thickness at location \(i\), \(h_i\), and the stresses in the wall, \(\sigma_{hoop,i}\) (due to the passive elasticity of the wall) and \(\sigma_{act,i}\) (due to the active contraction of the wall). Each lymphangion in the chain is modeled by a single computational cell, and the valve between neighboring lymphangion is modeled by a fixed resistance to flow (when open) and a constraint on \(Q\) (when closed), with an associated opening resistance. Reddy

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found this relatively simple model exhibited quite complex flow behavior, including the intermittent and random flow and pressure behavior characteristic of pumping in real lymphatics. Later work by the same authors (20) extended this model to investigate branching networks of vessels.

Lambert and Benoit (12) modeled the lymphatic system as a series of contracting pumps separated by valves, with the rate of lymph flow being determined by the Starling relationship. Recent work by Quick et al. (18) has employed a circuit-theory analog of the system, developed from arterial flow models (11). This work has provided important physiological insights but does not involve a detailed analysis of the wall mechanics since it is a lumped parameter model involving only one computational node per lymphangion. This work has been validated against experimental data (18) and extended to investigate the behavior of chains of lymphangions with active walls, showing that the direction of propagation of the contractile wall pulse affects the pumping only minimally (23).

Physics of compliant vessels. Although little modeling work has been done on the lymphatic system, the physics and computation of flow in other types of elastic tube has been the subject of extensive analysis (10). An important development has been the inclusion in the analysis of the longitudinal tension in the wall and viscous damping. In one dimension the NSE, reexpressed in terms of the cross-sectional area, takes the form.

$$\frac{\partial \alpha}{\partial t} + \frac{\partial}{\partial x} (u \alpha) = 0$$

$$\frac{\partial u}{\partial t} + u \frac{\partial u}{\partial x} = -\frac{1}{\rho} \frac{\partial p}{\partial x} - F$$

$$p - p_c = P(\alpha) - T \frac{\partial \alpha}{\partial x} + \gamma \frac{\partial \alpha}{\partial t}$$

Here T is the tube tension, accounting for the effects of the longitudinal bending of the tube, and γ represents a damping term. F represents the viscous effects of the flow, and p − pc is the transmural pressure, i.e. the difference in pressure between the inside and outside of the wall. P(α) is a function describing the elastic behavior of the wall itself. The substitution of \( \alpha = \pi a^2 \) and Q = 2πau, and with the assumption of the convective term to be negligible, gives the equations:

$$\frac{\partial a}{\partial t} = -\frac{1}{\pi a} \frac{\partial Q}{\partial x}$$

$$\frac{\partial Q}{\partial t} = -\frac{\pi a^2}{\rho} \frac{\partial p}{\partial x} + \frac{2\pi a}{\rho} \gamma \frac{\partial a}{\partial t}$$

$$p - p_c = P(a) - 2\pi a T \frac{\partial a}{\partial x} + 2\pi a \gamma \frac{\partial a}{\partial t}$$

The experimental work and implementation of the model are described in Experimental methods and Computation, respectively. Initial validation describes the development of the model. The detailed predictions of the model and comparisons with experiment are presented in Results.

METHODS

Experimental methods. Collecting lymphatics were excised from bovine mesentery at an abattoir (AIBP, Clones, Monaghan, Ireland or Stillmans, Taunton, UK) immediately after death, before the fatty tissue could solidify. The vessels were placed in normal Krebs solution (with 95% O2-5% CO2 gas mix; BOC) and kept at 4°C until warmed for use at 37°C. The vessels were cannulated at both ends and immersed in a purpose-built, Krebs-filled bath at 37°C and connected to pressure reservoirs at both ends. Pressure transducers (radio spoons components) were placed in the inflow and outflow lines. Typically, the vessel segment contained 2–4 lymphangions.

For static compliance measurements, the vessels were imaged with a long focal-length microscope (adapted Wild 10) with a Nikon Coolpix 4500 camera attached. The external diameter was measured as luminal pressure was varied between 0 and 1,500 Pa (0–15 cmH2O), with particular attention to the 0-500 Pa range where few previous data are available (4, 17). The preparation was stabilized before measurement by performing a number of cycles over the full pressure range, and images were acquired immediately after each pressure step. The images were analyzed in ImageJ (National Institutes of Health) to derive the diameter at several locations along the vessel. The resolution was 7.5 μm/pixel. The Young’s modulus was calculated using the thick wall model (Eq. 6). The largest uncertainty in the calculation arose from the difficulty in measuring wall thickness. Our vessels were too thick walled to employ the microscopic computational methods developed by previous authors (5). Several methods of obtaining the wall thickness were investigated (including density measurements, histological sectioning, and traveling microscopy), and the most consistent method proved to be to add Evan’s blue to the lumen after the pressure-radius measurements to render the inner wall clearly visible and allow measurements from the digital images.

Pumping vessels were observed using a video camera (Canon XL2 Mini DV) in the same experimental apparatus. Stills were taken from the output video to determine radius-time relationships. Pressure-diameter measurements were taken in the states of maximum and minimum contraction.

The damping coefficient, γ, in Eq. 4 was obtained by the use of a purpose-made mechanical testing rig. Loops of the vessel ~1.5 mm long were placed over two steel rods (0.8 mm diameter), one fixed and attached to a force transducer (World Precision Instruments) and the other fixed and attached to a computer-controlled stepper motor. The vessels were stretched and relaxed six times at 0.09 mm/s before force-extension data were taken at extension rates between 0.09 and 0.50 mm/s. γ was calculated as the gradient of force against the strain rate (at constant strain) curve. The area of the sample was defined as the width of the loop × the thickness; the latter parameter was determined from photographs being clearly visible around the support wire. The extension was taken within the toe region of the force-extension curve, which covers the physiologically relevant range.

Computation. Our computational model was based on Eq. 5, A–C, including the bending and damping terms, together with an appropriate wall model. The model was implemented for a vessel 2 cm length with an unstretched radius of 1.25 mm with valves at each end (see Table 1 for all input parameters). Eq. 5, A–C, was discretized using a finite difference approach to create an explicit time-marching algorithm, which was coded in MatLab and run on a Linux workstation. Some degree of smoothing was included using a value of \( \gamma = 7 \times 10^7 \) Ns/m4 (the value determined experimentally as described in Experi-
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Table 1. Reference values of computational input parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Reference Value</th>
<th>Range</th>
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</thead>
<tbody>
<tr>
<td>Length of lymphangion, mm</td>
<td>20</td>
<td>—</td>
</tr>
<tr>
<td>Time step, ms</td>
<td>0.002</td>
<td>5 × 10⁻⁵–2</td>
</tr>
<tr>
<td>Unstretched radius, mm</td>
<td>1.25</td>
<td>0.75–1.8</td>
</tr>
<tr>
<td>Young’s modulus, N/m²</td>
<td>5,000</td>
<td>1,250–7,500</td>
</tr>
<tr>
<td>Tensile stress, N/m²</td>
<td>0.2 P</td>
<td>0.01P–5P</td>
</tr>
<tr>
<td>Damping coefficient, Nsm⁻¹</td>
<td>7 × 10⁷</td>
<td>7 × 10⁵–2–10⁸</td>
</tr>
<tr>
<td>Inlet pressure, Pa</td>
<td>500</td>
<td>—</td>
</tr>
<tr>
<td>Outlet pressure, Pa</td>
<td>800</td>
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<td>Valve opening/closing time, ms</td>
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<td>0–20</td>
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<tr>
<td>Period, s</td>
<td>40</td>
<td>5–40</td>
</tr>
<tr>
<td>Contraction time, s</td>
<td>0.5 T_p</td>
<td>0.25 T_p–T_p</td>
</tr>
<tr>
<td>Phase, radians</td>
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<td>π–π</td>
</tr>
<tr>
<td>Density, kg/m³</td>
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<td>—</td>
</tr>
<tr>
<td>Poisson’s ratio</td>
<td>0.5</td>
<td>—</td>
</tr>
<tr>
<td>Valve–triggering pressure, Pa</td>
<td>10</td>
<td>0–10</td>
</tr>
<tr>
<td>Wall thickness, mm</td>
<td>0.7a</td>
<td>0.036a–0.1a</td>
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<tr>
<td>Viscosity, kg·m⁻¹·s⁻¹</td>
<td>0.0008904</td>
<td>—</td>
</tr>
</tbody>
</table>

Reference values of parameters used in the modeling together with the respective ranges applied during parameter testing. The reference value was deemed close to the likely physiological mean and was used while other parameters were varied.

mental results); however, the stability restrictions mentioned earlier still dictated quite a small time step (5 × 10⁻⁵ of the period).

Initial validation. As an initial validation test of the numerical methods, we set out to replicate Reddy et al.’s results (19). For this case, a single computational cell was used to represent the lymphangion, with valves at each end, but we changed the wall model to a thick-walled tube:

\[ \Delta P = E \Delta a_{\text{rel}} \frac{(a_{\text{out}}^2 - a_{\text{in}}^2)}{(1 - \sigma) \Delta a_{\text{mol}} a_{\text{out}}} \]  

(6)

where \( a_{\text{out}} \) and \( a_{\text{in}} \) are the external and internal radii of the tube, respectively, \( \Delta a_{\text{rel}} \) is the change in radius caused by a difference in pressure, \( \Delta P \), between the inside of the vessel and the outside, and \( \sigma \) is the Poisson ratio. The pressure change was driven by an imposed contraction, causing a difference in the unstretched radius of the vessel, \( \gamma \) and \( T \) were set to zero, and this initial model used a pure sine wave to drive the contraction.

By varying the parameters, we could recreate the flow characteristics described by Reddy, including the fluctuating behavior during the open-valve flow phase. However, the results were strongly dependent on the time step chosen, and too large a time step resulted in instability and a nonphysical solution. Since we, like Reddy, employed an explicit algorithm, it is probable that there is an associated stability requirement on the time step relating to the propagation of dilatation waves along the walls. To stabilize this, the damping term \( \gamma \) was included, which resulted in stable, nontime step-dependent behavior (although time steps of 5 × 10⁻⁵ of the period were required), which exhibited much less of the high-frequency oscillation observed by Reddy. It seems likely, therefore, that much of the behavior observed by Reddy (21) is numerical rather than physical, but the inclusion of the \( \gamma \) and \( T \) terms in the wall equation to stabilize the behavior may well better represent the physiological situation.

Model refinement. The main aim of this research was to investigate in more detail the interaction between the contractility of the wall and flow generation. To accomplish this, we modified Reddy’s model in a number of important ways. First, we increased the spatial resolution of the system; instead of treating each individual lymphangion as a separate computational cell, with a valve model at each end, we used six computational cells to resolve the behavior spatially along the length of the lymphangion, the first and last containing the model valves. Given the length of the lymphangion (2 cm) and its diameter (1 to 2 mm), this gave the individual computational cells an aspect ratio of around 3:1 (length:diameter). Some computations were repeated for an eight-cell model without significant differences. Because the approach is based on the concept of the lymphangion as a series of compliant circular pipes, with radial variation in each element being unimportant (or more precisely, governed by Poiseuille’s law), significantly higher resolution in the flow direction would have been inconsistent with this model.

The second refinement was to investigate the behavior of the lymphangion wall in more detail, and we implemented more complex wall models to reflect this behavior. The wall behavior has two components. First is its passive behavior, in which it responds as an elastic (but not necessarily linear elastic, as found experimentally; Fig. 1) membrane to the pressures in the fluid. Second is its active behavior due to muscular activity. Stimulating or relaxing the wall muscle will change some mechanical properties of the system, although not necessarily the vessel diameter. Furthermore, neighboring elements of the wall may vary their state of relaxation either randomly (indicating that the vessel is undergoing spasm) or coherently, with some phase shift relative to each other. In this case, the effect is one of a contraction wave propagating along the length of the lymphangion.

The passive component was modeled using Eq. 6, characterizing the vessel in terms of its inside diameter \( a = a_{\text{in}} \) and wall thickness \( h \) (assumed constant), so \( a_{\text{out}} = a_{\text{in}} + h \). The results presented below were obtained using a value of \( E = 2,500 \) N/m², being midway between the pumping and nonpumping values we measured experimentally (see Experimental results). Because of the range of the experimental data, discussed in Experimental results, we also undertook a parametric study to investigate the effect of varying this and other parameters of the model. The effect of stimulating or relaxing the wall muscle can be represented as a change in the fundamental properties of the wall. Thus in Eq. 6, either \( E \) (the elastic modulus) or \( a_{\text{in}} \) (the unpressurized radius) can be modified; a stimulated vessel will have a higher \( E \) or a smaller \( a_{\text{in}} \). These are probably equivalent ways of modeling the same situation, and it is unclear which more closely approximates the physiological condition; for our models, we have changed the value of \( E \).

Developing an active wall model is more complex. We parameterize the state of relaxation of the muscle in terms of a variable \( \chi \in [0, 1] \), so that the Young’s modulus varies as

\[ E = E_{\text{related}} + (E_{\text{contracted}} - E_{\text{related}})\chi(t) \]  

(7)

(or a similar relationship for the zero-pressure radius \( a_{\text{in}} \)). Use of \( \chi \) enables us to discuss the contraction function independent of the specific wall model. For this work, we used two different contraction functions with the overall period, \( T_p \): a pure sine wave and a sine wave

Fig. 1. Compliance measurement for a typical nonpumping vessel at 2 positions along the vessel. The measurement locations are remote from a valve.
with a pause at relaxation; the ratio of contraction time, $T_c$, to the overall period, $T_p$, could also be varied.

These functions are plotted in Fig. 2. Introducing a time lag, $t_0$ (equivalent to a phase difference), in the contraction function $\chi(t + t_0)$ between adjacent computational cells is equivalent to the propagation of a contractile wave along the lymphangion. Depending on the sign of $t_0$, we get waves propagating in the prograde or retrograde sense, i.e., in the direction of the flow or against it. The magnitude of $t_0$ relates to the speed of propagation of the wave, with smaller $t_0$, indicating faster wave speeds.

Figure 3 shows the functional relationship between $P$ and $a$ for the wall model, together with representative experimental data for a dynamic vessel (also shown in Fig. 4), on which the wall model is based. The shape of the experimental data depends on the state of relaxation of the muscle in the wall. Hence the $p(a)$ relationship used in the computational model must vary; the extremes of this relationship for the fully relaxed and fully contracted are shown, and the response for any state between these extremes can be developed by interpolation using $\chi$. Shown in this figure are also experimental data for relaxed (lower) and stimulated (higher) vessels. It can be seen that the region covered by our wall model spans the physiological range exhibited by the experimental lymphangion.

**RESULTS**

**Experimental results.** Static compliance measurements all showed the same characteristic shape, illustrated in Fig. 1. Initially, there is a linear slope followed by a sharp transition to a region where the vessel no longer expands with increased pressure. The calculated Young’s modulus in the former domain is $(1,200 \pm 700) \text{ N/m}^2$ ($n = 10$ samples measured), which agrees with the value obtained by Deng et al. (4), who had limited data at these pressures, although it is lower than other reports (17) based on data at higher pressures. The variance in the measurements was largely due to uncertainties in the wall thickness and the initial diameter measurements. The marked increase in Young’s modulus occurred at a strain of $1.1 \pm 0.4$. Although some positional differences were observed, no consistent pattern of variation in elastic properties...
The effects of mean luminal pressure (with no net pressure gradient along the vessel) on contractility are shown in Fig. 4. The data agree with previous work (8, 16). In relaxed vessels, there is an initial linear relationship followed by a pressure-independent region of less compliance, similar in shape to the static compliance curve. In the contracted vessel, an almost converse pattern is observed with an initial pressure-independent region giving way to a linear portion. The slopes of the two linear regions are almost identical. The largest contractile radius change occurs at approximately the radius and pressure at which the change in Young’s modulus occurs.

The radius-time measurements during pumping (Fig. 5) showed a distinctive shark fin shape over the cycle with a short contractile phase and a longer relaxation phase. The variation is slightly greater in amplitude at the midpoint of the lym-
phangion than at the valve. There is also a sharp increase in diameter immediately before the onset of the contractile phase in the vicinity of the valve, which is not evident elsewhere. In the trace shown, the contractile wave is in the opposite direction to the flow direction. The pressure, therefore, peaks at the valve as the fluid is trapped between the contractile wave and the closed valve.

The damping coefficient, $\gamma$, has a value of $(7.0 \pm 3.0) \times 10^{7}$ Ns/m$^4$ (10 measurements from 5 different vessels).

**Computational results.** Figure 6, ii–iv, shows the output of our model with parameters chosen to reproduce the experimental observations presented in Fig. 5. A value of $E_{\text{relaxed}} = 2,750$ N/m$^2$ ($E_{\text{contracted}} = 4,000$ N/m$^2$) was used with a sine-relax contraction function $\chi$ with a period of 40 s and a forward-wave propagation with $t_0 = \frac{1}{2}$ s. This gives a wave propagation speed of $c = 1$ cm/s, comparable with the speed estimated from the videos. The primary experimental comparison is with

![Fig. 6. Numerical simulation of a pumping lymphatic: i: sine-pause wave form of elastic modulus used to simulate contraction (Eq. 7). ii–iv: predicted changes in vessel radius, luminal pressure, and volumetric flow. v and vi: phases of opening and closing of the upstream (1) and downstream (2) valves. The parameters employed are listed in Table 1. vii–xii: predictions for the same parameters but with the contraction wave propagating in the reverse direction.]
the radius strain in the vessel (Fig. 6, ii). In both the experimental and computational results, we observe a shark fin shape to the time course of this parameter, with a slow buildup to the maximum state of contraction, followed by a swift decrease in the strain rate as the valve opens.

The flow rate $Q$ (Fig. 6, iv) increases in successive computational cells downstream of the valve. This arises because as the first segment in the vessel contracts earlier than the others, it forces fluid into the next segment; when this segment, in turn, begins to contract, it must transfer this additional fluid load into the third segment, and so on. This behavior also accounts for the slight spike in the radius curves for the later segments just before the valve opens, which was also evident in the experimental data. When the valve opens, the flow is greatly increased throughout all the segments as the lymphangion pumps. The direction of propagation of the wave seems to make very little overall difference, as can be seen from Fig. 6, vii–xii; the only significant difference is the negative peak at the start of every contraction, before the downstream valve opens in the case of retrograde propagation due to propulsion by the wave against the direction of flow. In the case of forward propagation, there is a similar, but positive, peak.

Increasing the speed of propagation of the contraction wave (increasing $t_0$) has little effect for small values of $t_0$, representing the propagation of relatively slow contraction pulses along the lymphangion. Very large values of $t_0$ were found, however, to significantly inhibit the pumping action. Very large values of $t_0$ correspond to large phase differences between successive computational cells, to the point at which neighboring cells are essentially operating in antiphase; the resulting squeezing and relaxing of alternate cells merely shuttles fluid back and forth between neighboring cells without ever building up the pressure upstream of the valve necessary to open it.

The shape of the input wall function, $\chi$, also affects the output, although it is not the sole determinant. We have investigated adjusting the ratio $t_c:t_p$. As $t_c$ becomes shorter, i.e., the input becomes more spiky, the response becomes more strongly influenced by the wall properties. The most important factor is the rate of relaxation of the wall when the forcing function is removed, which is determined by the elastic and inertial properties of the tissue. We have investigated this sensitivity in the model by determining the effects of changes in input parameters on the time required for the wall to return to 99% of its equilibrium position. Results are shown in Fig. 7. Increasing the Young’s modulus results in a quicker return to the equilibrium while increasing the initial radius and the parameter $\gamma$ (related to the inertia of the wall) both result in slower relaxation. The effects of changes in these parameters on the overall flow rate can be seen in Fig. 8. In particular, increased Young’s modulus and a decreased radius both result in a reduced volume of fluid being pumped through the system, whereas changing the parameters $\gamma$ and $T$ results in little change in the behavior of the pumping.

The pressure gradient along a lymphatic vessel can change, or even reverse, under different physiological conditions. We therefore investigated these effects in our model. Under normal conditions, the system is pumping against a negative pressure gradient, and we find that flow rate is lower when the gradient is reversed. If the pressure gradient is sufficiently large and positive, the flow rate can actually be increased by stopping contraction entirely.

![Graph A](http://example.com/graphA.png)

**Graph A:** Variation with vessel radius.

**Graph B:** Variation with Young’s modulus $E$ (N/m$^2$).

**Graph C:** Variation with $\gamma$ (N s$^{-1}$).

**Fig. 7.** The relaxation time of the vessel. A: variation with vessel radius. B: variation with Young’s modulus $E$. C: variation with $\gamma$.

**DISCUSSION**

In this work we have developed and validated a fine-scale computational model of the behavior of a single lymphangion, including upstream and downstream valves. The model is based on detailed experimental observations, including some parameters not measured previously, and has been validated in particular against radius/time measurements (Fig. 5). For a
realistic choice of parameters, the model faithfully reproduced the behavior of a real vessel, including small features such as the sudden sharp increase in diameter before the valve could open. Furthermore, when the input parameters were changed over the physiological range, the changes in pumping characteristics were acceptable and stable.

The physiological measurements showed considerable variations between vessels. We measured the Young’s modulus, $E$, for a static (nonpumping) lymphangion and also for individual lymphangions during pumping. The average value of $E$ from the static lymphangions agrees with published values; however, the values covered a large range. Much of this variation is likely to be due to factors such as vessel size, and the position within the lymphatic system and animal age, which have not been controlled (age was partially controlled since all samples here were taken from bovines aged 18–36 mo). In individual vessels, $E$ measured for the pumping lymphangions was significantly larger. Perhaps coincidentally, the lymphangions that we successfully set to pump tended to be larger in size than average. Further work to quantify this variability would be valuable, but our immediate concern was the difficulties it created in the choice of parameters for modeling, necessitating an investigation of parameter sensitivity. For our modeling, we adopted the value of $E_{\text{relaxed}} = 2,500$ N/m², being in the middle of the range of our measurements. Since our model used variations in $E$ to generate the contraction, the actual value of $E$ varied; Fig. 3 shows that these variations compared well with the elastic properties of the pumping vessel. Varying $E_{\text{relaxed}}$ around the chosen value, we were still able to generate qualitatively similar pumping behavior.

We employed a preparation containing 3 to 4 lymphangions, whereas other recent work (18) has employed a single lymphangion. We chose this to avoid influencing wall dynamics, in particular the propagation of the contractile wave, through the attachment to rigid cannulae. The vessels often tapered along their length and during contraction were observed to change length and rotate and did not always maintain a rigid cross section. Another consideration was that the vessel was freed from the surrounding tissue and, therefore, free of potential constraints on its mechanical behavior and muscular activity of the tissue. However, the latter has been shown to have little effect on lymph flow under normal physiological conditions (13).

For reasons of computational cost only, a single lymphangion was modeled numerically. We believe that the wall dynamics would not be affected by the length of segment being modeled. We recognize, however, that an isolated lymphangion will have different boundary conditions than a unit in a chain where upstream and downstream boundary conditions will be varying due to the pumping of the other elements. We aim to investigate this in subsequent work, along with the three-dimensional geometric effects such as twisting noted above. The change in the length of the vessel during pumping and the associated change in tension have also not been included. The change in tension is probably within the range already covered within the
modeling, but the associated volume changes might be significant, particularly for a whole network, and may need to be included in future models.

A mechanical parameter that has not previously been considered is the damping term, $\gamma$. The experimentally determined value showed a large variation probably arising from the difficulty in determining the point of zero extension as well as the error in wall thickness. This variation did not significantly alter the outcome of the modeling, and the inclusion of a realistic $\gamma$ was sufficient to stabilize the computation. We suggest that there maybe a physical basis for including this term in the numerical system and further suggest that some of the behavior observed by Reddy et al. (19, 20, 21), who used a similar computational scheme to ours with no damping, may well be numerical rather than physical in origin.

The present study explored the relationships between the contraction pattern of the wall and flow generation. In the computational model, the lymphangions pump best if all sections of the wall contract simultaneously, irrespective of the direction of propagation of the contraction wave. Simultaneous contraction of all sections increases the pressure throughout the lymphangion until the pressure difference is sufficient to open the valve and drain the segment. If the wave propagates more slowly, i.e., the contractions are nonsimultaneous, the effect is merely to pump the lymph fluid from one part of the vessel to another, without ever building enough pressure difference to open the valve. Differences between the forward and reverse propagating contractile wave are minimal; for the reverse wave, the maximum flow is slightly increased, which is probably due to the later opening of the valve, but the average flow is slightly reduced for the same reason. Similar behavior has been reported in detail by Venugopal et al. (23), who also note that in conditions such as oedema where the pressure gradient is reversed pumping may actually reduce flow. Our model displayed this behavior at sufficiently large pressure gradients, due to the added resistance from the vessel walls as the radius decreases rather than from the behavior of the valves.

Retrograde pumping has been observed by our laboratory (15) and others (2), and we suggest that this condition might be preferable in a branching network. A reverse wave would be able to propagate up both branches at a bifurcation, whereas a forward propagating wave arriving at a bifurcation would need to coordinate with any wave propagating down the other branch, otherwise lack of coherence between the waves would likely lead to reduced efficiency.

We find that the pumping of the lymphangion depends on both the passive and active behavior of the wall. Experimentally, we found two distinct elastic states for the relaxed lymphangion and a third for the contracted vessel. It seems likely that these states are determined by the differing mechanical properties of the muscle and the collagen and elastin of the extracellular matrix. It is probable that the biphasic behavior of the relaxed tissue reflects the properties of the extracellular matrix, with small strains being carried by the more elastic elements and loads transferring to stiffer collagen-based structures at larger strains (probably exceeding the physiological range), as occurs in blood vessels (6). It appears that when the muscle is activated, it contributes to the behavior at small strains leading to a higher initial elastic modulus. Beyond a critical strain, however, the muscle appears to enter a plastic rather than elastic region (in other words, the force exerted by the muscle is independent of the strain imposed), and the elastic behavior of the wall is governed again by the extracellular matrix, with an initial fall in elastic modulus, followed by an increase as load is transferred to the collagen network. Stronger contraction of the muscle seems not to increase the modulus of elasticity for the muscle contribution but rather to increase the critical strain that the muscle can react to. It therefore appears that a contractile pulse of very simple form generates complex time series behavior in the fluid mechanics.

**Conclusions**

We have developed a detailed computational model of the behavior of a single lymphangion, based on and validated against experimental measurements of the elastic properties of lymph vessels measured in the laboratory. The computational model is able to reproduce the pumping behavior of the real vessel using a simple contraction function, which suggests that lymphatic pumping is governed by simple, fast contraction pulses traveling in the retrograde direction to the flow.

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