MODELING AND CHARACTERIZATION OF LYMPHATIC VESSELS USING A LUMPED PARAMETER APPROACH

A Thesis

by

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ABSTRACT

The lymphatic system is responsible for several vital roles in human body, one of which is maintaining fluid and protein balance. There is no central pump in the lymphatic system and the transport of fluid against gravity and adverse pressure gradient is maintained by the extrinsic and intrinsic pumping mechanisms. Any disruption of the lymphatic system due to trauma or injury can lead to edema. There is no cure for lymphedema partly because the knowledge of the function of the lymphatic system is lacking. Thus, a well-developed model of the lymphatic system is crucial to improve our understanding of its function.

Here we used a lumped parameter approach to model a chain of lymphangions in series. Equations of conservation of mass, conservation of momentum, and vessel wall force balance were solved for each lymphangion computationally. Due to the lack of knowledge of the parameters describing the system in the literature, more accurate measurements of these parameters should be pursued to advance the model. Because of the difficulty of the isolated vessel and in-situ experiments, we performed a parameter sensitivity analysis to determine the parameters that affect the system most strongly. Our results showed that more accurate estimations of active contractile force and physiologic features of lymphangions, such as length/diameter ratios, should be pursued in future experiments. Also further experiments are required to refine the valve behavior and valve parameters.

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NOMENCLATURE

P_{fail}	Valve failure pressure
s_{fail}	Valve failure slope
R_{vmin}	Minimum valve resistance
R_{vmax}	Maximum valve resistance
P_{open}	Valve opening pressure
s_{open}	Valve opening slope
μ	Fluid viscosity
L	Lymphangion length
P_{ci}	Pressure constant in vessel wall force balance relation
D_c	Diameter constant in vessel wall force balance relation
M	Active tension
f	Contraction frequency
φ_i	Inter lymphangion phase
P_{ext}	External pressure
P_{in}	Inlet pressure
P_{out}	Outlet pressure
ΔP	Pressure difference at the two ends of the chain
Δp	Pressure difference across valve i

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1. INTRODUCTION

The lymphatic system works in parallel to veins, and is responsible for several important roles (e.g., immune response, lipid absorption, and spread of cancer cells). The lymphatic system collects about 4 liters of fluid every day from the interstitial space and pumps it back to the subclavian vein, to maintain a healthy balance of fluid and proteins. The system is challenged by the need to pump viscous fluid against gravity and pressure. Furthermore, in contrast to the blood circulation system, there is no central pump in the lymphatic network, and the system relies on pumping mechanisms to transport fluid.

Together with valves that prevent backflow, there are two pumping mechanisms in the lymphatic system. Extrinsic pumping is the result of movements outside the lymphatic vessel, such as the arterial pulses or muscle contractions, compressing the vessel and causing the lymph to move, whereas intrinsic pumping is caused by the active contractions of lymphatic muscle cells embedded in the walls of lymphatic vessels. Extrinsic and intrinsic pumping together with the lymphatic valves, help the system overcome the pumping challenges and generate forward flow. The relative contribution of these mechanisms, which varies in different regions of the body, is not completely understood.

Disruption of the lymph due to infection, trauma, or injury results in fluid build up in the tissues, or lymphedema, which affects more than 130 million people worldwide. The lack of an effective cure for this disease can be attributed in part to our insufficient knowledge of the system and its transport mechanisms. Also, despite its

importance, the system has received little attention from bioengineers, and modeling of its pumping mechanisms remains a challenge. As a result, a well-developed mathematical model is necessary to expand our knowledge of the system's performance.

Reddy, conducted the first lymphatic modeling effort in 1977 (Reddy et al., 1977). He developed a 1D model for 7 generations of large lymphatic vessels. The model did not include smaller vessels that are responsible for a considerable load of pumping. Quick et al. developed a lumped model of a single lymphangion, using the same approach that was previously used for ventricular contractions (Quick et al., 2007). Macdonald et al. refined Reddy's model for a chain of lymphangions (Macdonald et al., 2008). Recently Bertram et al. created a lumped parameter model for a chain of lymphangions in series (Bertram et al., 2011). In their model, equations of conservation of mass, conservation of momentum, and vessel wall force balance is solved for each lymphangion. The recent model accounts for both passive behavior of the vessel, and active vessel contractions, also valve resistances are defined as functions of pressure difference across the valve, which is closer to their realistic behavior.

The model developed by Bertram et al. offered several improvements to the previous models, specifically in terms of modeling the valve behavior, active contraction, and passive behavior of the vessel. Nonetheless, more accurate estimates of the parameters in the model are crucial for its application to understanding normal and pathologic function. Due to the difficulty of the isolated vessel and in-situ experiments, it is worthwhile to first determine the parameters that have larger effects on system response, and focus the experimental studies on those parameters. Our goal here is to

conduct a parameter sensitivity analysis to determine the parameters with highest effect on the system outcome. Future efforts will focus on refining and designing experiments to measure the parameters determined by the sensitivity analysis study; the measurements from these experiments will then be used to further advance the current model.

2. METHODS

2.1 Modifications of the model

We performed a parameter sensitivity analysis for the lumped parameter model of a chain of lymphangions in series, formerly developed by Bertram et al. (Bertram et al., 2011). The extensive details of the equations used, and method of solution are available in that publication. Our approach differs from the original model in the definition of pressure variables. Initially, pressures were defined only at the two ends of each lymphangion, that is, P_{up} at the upstream and P_{down} at the downstream end. In that case, transmural pressure (P_{tm}) was the average of P_{up} and P_{down} minus the external pressure (P_{ext}). The average of the inlet and outlet flow rates were then calculated from $P_{up} - P_{down}$ using a Poiseuille relation. Here, however, we defined an additional pressure at the center of each lymphangion (P_{mid}) to calculate the transmural pressure (P_{tm}) for the relation of the vessel wall force balance. Addition of this third pressure required two Poiseuille relations to relate $P_{up} - P_{tm}$ and $P_{tm} - P_{down}$ to upstream and downstream flow rates, respectively. The modification in the definition of pressure variables increased the number of equations in the model, but allowed for more realistic simulation of backflow under valve failure at extreme unfavorable pressure differences.

The solution was computed by solving equations of conservation of mass, conservation of momentum, and vessel wall force balance for each lymphangion that resulted in a nonlinear ordinary differential equation for diameter, and two algebraic equations. Bertram et al. previously developed their own computational scheme to solve

these equations; in this study, however, the system of differential-algebraic equations (DAE) was solved with MATLAB (R2010b, MathWorks®). Our new method of solution was capable of replicating the same results in a fast and robust manner. The parameter values and baseline conditions were as used by Bertram et al. (Table 1), and the values assigned to each parameter was the same for all the lymphangions in the chain unless it is stated otherwise (Bertram et al., 2011). The outcome of each simulation was the average flow rate of the last lymphangion. The simulations ran until the outcome was stable and independent of the initial conditions; this was achieved at different simulation times depending on the values of the parameters in the model.

2.2 Parameter sensitivity

The sensitivity analysis study was performed for a chain of four lymphangions in series. Effect of increasing the number of lymphangions in the chain was also investigated. Because the lymphatic network experiences different levels of pressure differences (ΔP), the chain of lymphangions was tested over a range of 2.0-3.6 cmH_2O in outlet pressure (P_{out}), while the inlet pressure remained constant and equal to 2.3 cmH_2O. Then a pump function curve was created to illustrate the capability of the system to generate flow under different pressure differences (figure 1). Based on that curve, we conducted the parameter sensitivity study for pressure differences of 0.1, 0.35, and 0.6 cmH_2O, which corresponded to high, medium, and low or negative flow rates, respectively.

Table 1. Parameters used in the numerical model, including their definition, and baseline value. (i=1:n, where n is the number of lymphangions in the chain)

	Parameter Description	Parameter	Value	Units
Valve Parameters	Valve failure pressure	P_{fail}	-18.4	cmH_2O
	Valve failure slope	s_{fail}	0.049	cm^2/dyn
	Minimum valve resistance	R_{vmin}	600	$g/(cm^5 s)$
	Maximum valve resistance	R_{vmax}	1.2×10^7	$g/(cm^5 s)$
	Valve opening pressure	P_{open}	-0.07	cmH_2O
	Valve opening slope	s_{open}	0.04	cm^2/dyn
Lymphangion parameters	Fluid viscosity	μ	0.01	g/(cm s)
	Lymphangion length	L	0.3	cm
	Pressure constant in vessel wall force balance relation	P_{ci}	50,75,100,125	dyn/cm^2
	Diameter constant in vessel wall force balance relation	D_c	0.025	cm
	Active tension	M	3.6	dyn/cm
	Contraction frequency	f	0.5	Hz
	Inter lymphangion phase	φ_i	$-\frac{\pi}{2}\times(i-1)$	
	External pressure	P_{ext}	2.14	cmH_2O
	Inlet pressure	P_{in}	2.32	cmH_2O
	Outlet pressure	P_{out}	2.42 ($P_{out,1}$) 2.67 ($P_{out,2}$) 2.92 ($P_{out,3}$)	cmH_2O
	Pressure difference at the two ends of the chain	ΔP	P_{out}- P_{in}	
	Pressure difference across valve *i*	Δp	$P_{down(i-1)}$-$P_{up(i)}$	

The parameters were analyzed into two groups: those related to the valves and those related to the lymphangion segments. One-at-a-time parameter sensitivity analysis (i.e., variation of one parameter while the others remained constant) was performed for valve parameters, minimum and maximum valve resistances (R_{vmin} and R_{vmax}), and lymphangion parameters, external pressure (P_{ext}) and contraction frequency (f). The values of the parameters were varied within what was estimated as their physiologic range. When such information was not available parameters were varied until the system outcome reached a plateau phase. Two-parameter sensitivity study (varying two parameters simultaneously) was conducted for active tension (M) and lymphangion length (L). The number of lymphangions in the chain was also varied and its combined effect with lymphangion length (L), and overall vessel length (L_{vessel}) was studied.

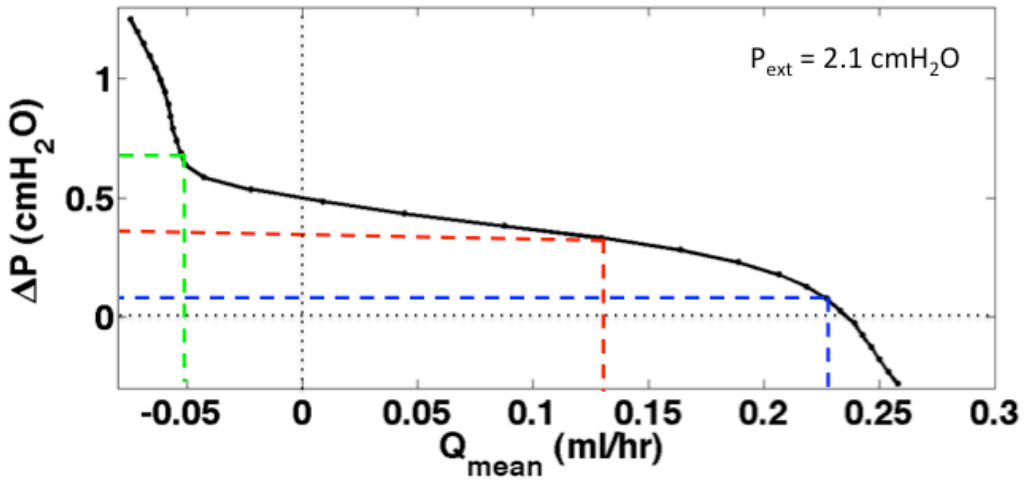

Figure 1. Pump function curve for a chain of four lymphangions in series at P_{ext} = 2.1 cmH_2O, where $P_{ext} = P_{mid} - P_{tm}$. The horizontal axis shows the average flow rate of the last lymphangion in the chain, the vertical axis shows the pressure difference between the two ends of the chain. Three values of pressure difference have been chosen at different regions of the pump function curve, and parameter sensitivity study has been performed for these three pressure differences (ΔP=0.1, 0.35, 0.6 cmH_2O).

3. RESULTS

3.1 Sensitivity to the parameters related to the valves

Sensitivity analysis of a chain of four lymphangions in series showed that the system is most sensitive to minimum valve resistance (R_{vmin}) among the parameters related to the valves (Figure 2). Increasing R_{vmax} increased the average flow rate (Q_{mean}) by less than 0.05 ml/hr for pressure differences (ΔP) of 0.10 and 0.35 cmH_2O. With further increase in ΔP the chain of lymphangions failed to generate forward flow, but backflow decreased as R_{vmax} increased. This behavior can be attributed to higher valve resistance to backflow at higher values of R_{vmax} (Figure 2a). On the other hand, variation of R_{vmin} directly affects forward flow. At ΔP=0.10 and 0.35 cmH_2O, Q_{mean} dropped as much as its maximum value (up to 0.25 ml/hr) and even became negative as R_{vmin} increased. Under the highest ΔP the amount of backflow decreased (maximum reduction was less than 0.03 ml/hr) with increase in R_{vmin} (Figure 2b). Comparison of the results in figures 2a and 2b implies that increasing R_{vmin} in the cases with forward flow, where the valves are open, had higher effect on the system output and reduced the average flow rate even more than its maximum value.

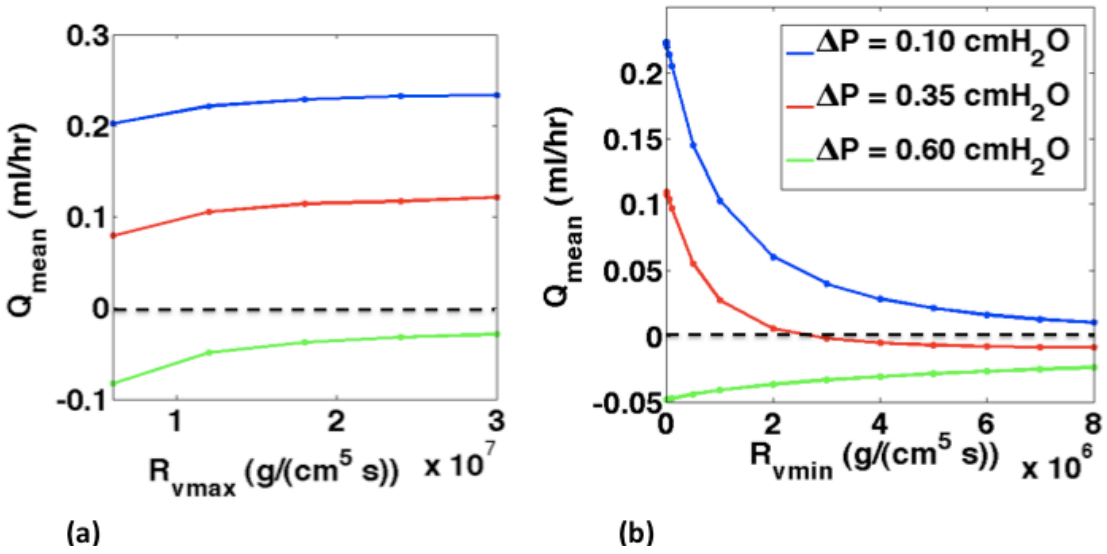

Figure 2. Simulation results with variation of the parameters related to the valves. (a) Plot of Q_{mean} vs. R_{vmax} at ΔP=0.10, 0.35, and 0.60 cmH_2O represented in blue, red, and green, respectively. (b) Plots of Q_{mean} vs. R_{vmin} at ΔP=0.10, 0.35, and 0.60 cmH_2O represented in blue, red, and green, respectively.

3.2 Sensitivity to the parameters related to lymphangions

3.2.1 Sensitivity to contraction frequency

Q_{mean} increased markedly with contraction frequency (f); namely, at ΔP=0.10 cmH_2O, increasing f from 0.2 to 0.4 Hz resulted in 2x increase in Q_{mean} (Figure 3). The effect tapered off at higher (non-physiologic) frequencies. Q_{mean} showed similar increases at ΔP=0.35 cmH_2O, only with lower flow rates. At ΔP=0.6 cmH_2O, the system was not able to generate forward flow even at higher frequencies. This finding, along with the results of the sensitivity to the parameters related to the valves, indicate that variation of R_{vmax}, R_{vmin}, and f is not sufficient to create forward flow at ΔP=0.60 cmH_2O.

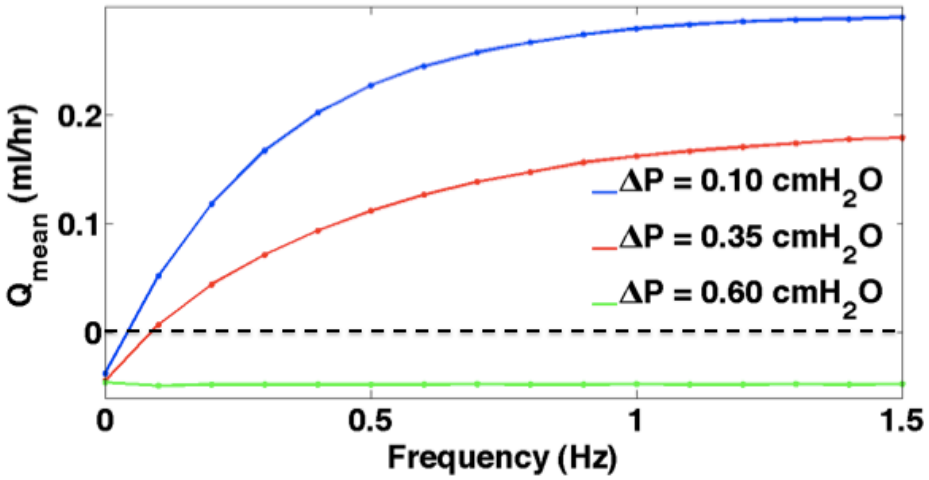

Figure 3. Q_{mean} vs. contraction frequency (f) at different pressure differences. Q_{mean} increased considerably with f, yet system failed to generate forward flow at ΔP=0.6 cmH_2O.

3.2.2 Sensitivity to external pressure

Figure 4a shows that there exists an optimum value of external pressure (P_{ext}) which results in peak flow rate. The optimum value of P_{ext} depended on ΔP, and ranged from 2.08 cmH_2O at ΔP=0.10 cmH_2O to 2.19 cmH_2O at ΔP=0.6 cmH_2O. The peak flow rate was 2.8 ml/hr higher at ΔP=0.10 cmH_2O than ΔP=0.6 cmH_2O. The system was capable of generating forward flow at ΔP=0.60 cmH_2O at the corresponding optimum P_{ext}.

To better understand this behavior, we chose four points on the Q_{mean}-P_{ext} curve at ΔP=0.10 cmH_2O, and superimposed the pumping loops (similar to cardiac pressure-volume loops) on the transmural pressure versus diameter (P_{tm}-D) curve. These points were chosen in the ascending, maximum, descending, and far right-end regions of the curve, corresponding to P_{ext}=1.8, 2.0, 2.3, and 2.9 cmH_2O, respectively. Recall that the slope of the P_{tm}-D curve is representative of the rigidity of the tube (Figures 4b and 4c).

A comparison between plots of Q_{mean}-P_{ext} and P_{tm}-D shows that the peak flow rate is generated when the vessel is least rigid (most compliant), that is, the flattest region of the P_{tm}-D curve. As we move away from that region in either direction, the vessel becomes more rigid and flow rate decreases. The considerable decrease in flow rate at the far right end of the Q_{mean}-P_{ext} curve is due to the collapsed tube behavior, which makes contraction more difficult and increases impedance to upstream pumping. These are the results for the fourth lymphangion in the chain, however, in other lymphangions the peak flow rate occurred near the most compliant state of the vessel as well; it only shifted slightly in the P_{tm}-D curve depending on the upstream and downstream impedances.

3.2.3 Sensitivity to lymphangion length and active tension

Pumping ability showed a mixed sensitivity to variations in both lymphangion length (L) and active tension (M). At ΔP=0.10 cmH_2O peak flow rate happened when L was around 0.3 cm. Initially, increasing M caused stronger contractions, which resulted in higher values of Q_{mean} up to 0.25 ml/hr, but as M continued to increase beyond 5 dyn/cm, Q_{mean} dropped (peak Q_{mean} as low as 0.2 ml/hr) because the vessel remained in the constricted state for a longer time, increasing impedance to upstream pumping (Figure 5). The chain of lymphangions exhibited similar behavior with lower flow rates under higher values of ΔP. Under those pressures the peak flow rate still occurred at L=0.3 cm, but the highest Q_{mean} of 0.24 and 0.22 ml/hr were achieved at M=6 and 8 dyn/cm for ΔP=0.35 and 0.60 cmH_2O, respectively.

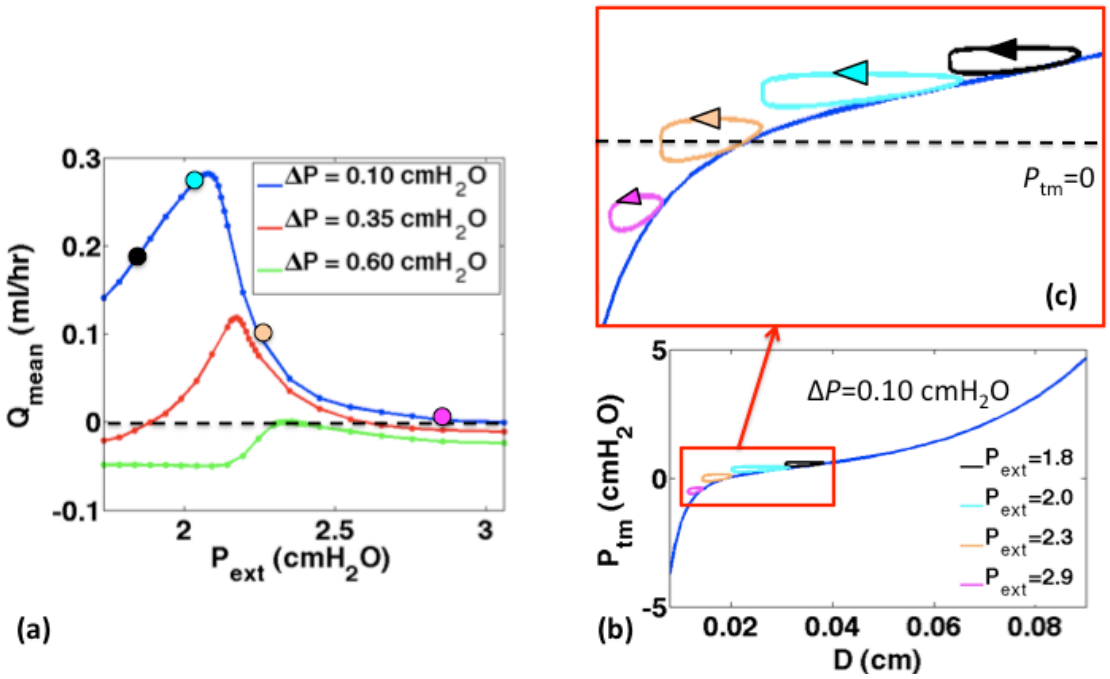

Figure 4. Sensitivity to external pressure. (a) Q_{mean} vs. P_{ext} at different pressure differences, where $P_{ext} = P_{mid} - P_{tm}$. Peak Q_{mean} occurred at an optimum value of P_{ext}. Transmural pressures versus diameter (P_{tm}-D) curves were evaluated for the four locations indicated on the graph. (b) Pressure diameter curves for the four points chosen in (a), peak flow rate occurred when the vessel was most compliant. (c) Shows a zoomed view of the four pressure diameter curves.

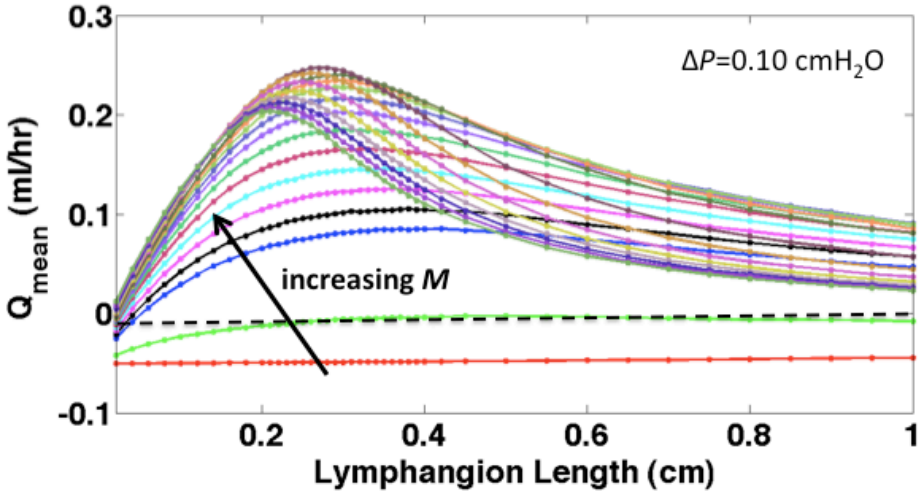

Figure 5. Q_{mean} vs. lymphangion length (L) at different values of active tension (M) under ΔP=0.10 cmH_2O. M was varied from 0 to 12 dyn/cm, and highest Q_{mean} occurred at M=5 dyn/cm. Peak flow rate was achieved at L=0.3 cm.

3.3 Effect of increasing the number of lymphangions in the chain

The outcome of simulations with variation in the number of lymphangions in the chain (n) showed that increasing n does not necessarily increase the flow rate. To study this effect we considered two scenarios; first, number of lymphangions and lymphangion length varied simultaneously, this determined the optimal number of lymphangions in the chain required to generate the highest Q_{mean} at each lymphangion length, whereas in the second case the results of variation of n and overall chain length (L_{vessel}) were used to find the optimum number of lymphangions for a specific L_{vessel}.

For the first case, we observed that at ΔP=0.10 cmH_2O system reached the highest Q_{mean} of 0.22 ml/hr with four lymphangions when L<0.5 cm. For L>0.5, however, having more lymphangions in the chain increased the flow rate up to 0.18 ml/hr. This result indicates that adding lymphangions to the chain does not necessarily increase the pumping because it imposes additional impedance to upstream pumping (Figure 6). Furthermore, similar to the results of sensitivity to active tension and lymphangion length, peak Q_{mean} of 0.22 ml/hr was observed when L was around 0.3 cm. At ΔP=0.35 and 0.60 cmH_2O, the results followed the same pattern as observed for L>0.5 cm in figure 6 and the system reached highest Q_{mean} of 0.28 and 0.19 ml/hr, with more and longer lymphangions.

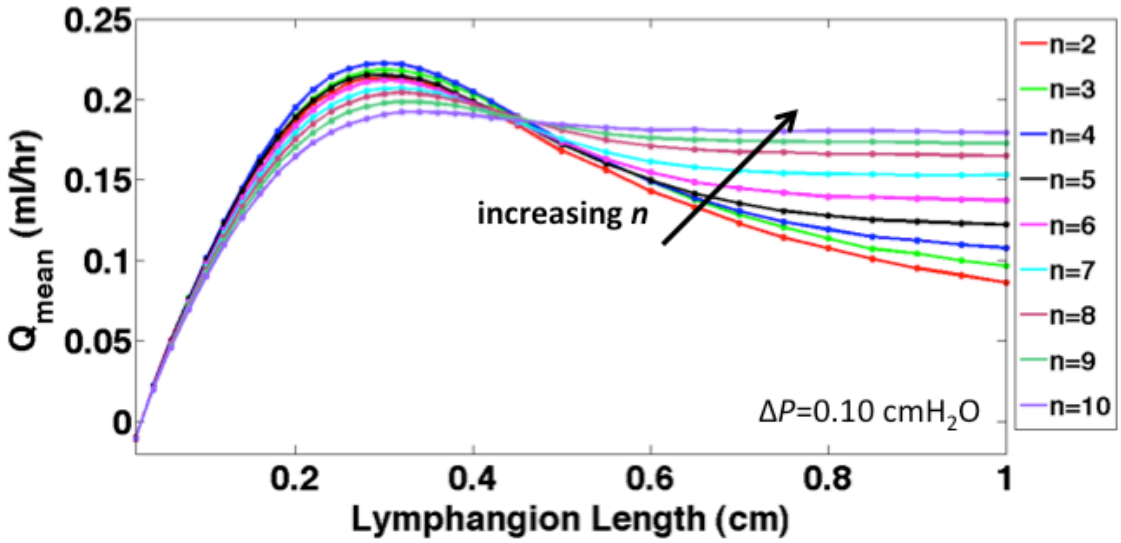

Figure 6. Q_{mean} vs. lymphangion length (L) with different number of lymphangions in the chain (n) at ΔP=0.10 cmH_2O. For L<0.5 cm, peak flow rate occurred at L=0.3 cm, highest flow rate were achieved with n=4. For L>0.5 cm, Q_{mean} increased with n.

Figure 7 shows the results of variation of n and L_{vessel} at ΔP=0.1 cmH_2O. An optimum number of lymphangions was found for each L_{vessel} (e.g., n=6 at L_{vessel} = 2cm). The ratio of the overall chain length to the optimum number of lymphangions was the same as the optimum lymphangion length found in the first study.

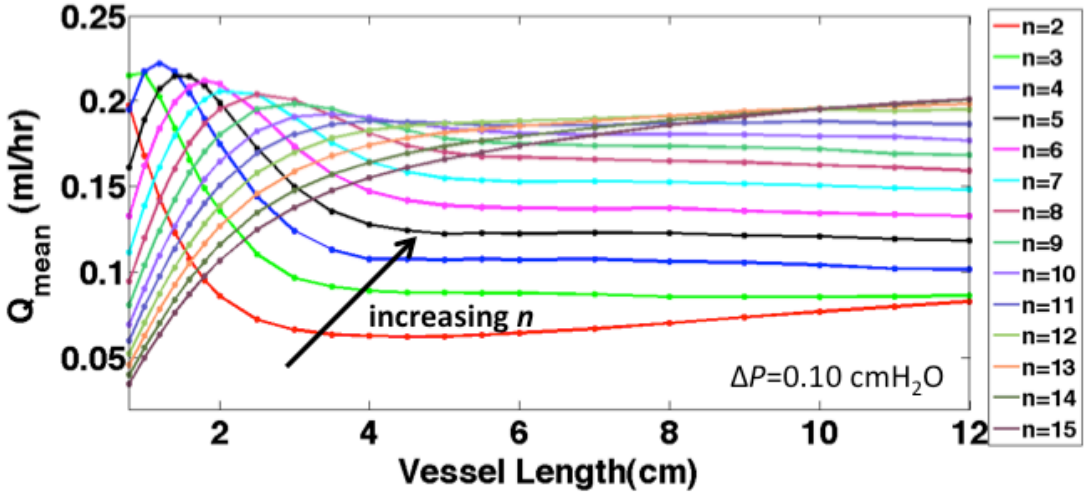

Figure 7. Q_{mean} vs. overall chain length (L_{vessel}) with different number of lymphangions in the chain (n) at ΔP=0.10 cmH_2O.

4. DISCUSSION

We performed the parameter sensitivity analysis for the model developed by Bertram et al. for a chain of lymphangions in series (Bertram et al., 2011). This model was different from the previous modeling efforts (Reddy et al. 1974, Quick et al. 2007, Macdonald et al. 2008) specifically in terms of considering the pressure dependent behavior of the valves, and also passive and active behavior of the vessel. Due to the lack of information on the large number of parameters required for such a model, more accurate measurements of these parameters are required to improve the model. Parameter sensitivity analysis can help prioritize the difficult experiments involved in estimating these parameters.

Our results demonstrated that the system was most sensitive to R_{vmin} among the parameters related to the valves. Increasing R_{vmin} relates directly to an increase in the impedance to forward flow, whereas R_{vmax} is only related to pumping efficiency through backflow prevention. Higher sensitivity to R_{vmin} implies that, although preventing backflow is crucial for overall function of the lymphatic system, the system is more sensitive to impedance to forward flow. Despite the importance of R_{vmin}, measurement of this parameter remains a challenge. Davis et al. characterized valve gating and behavior in collecting lymphatic vessels from rat mesentery (Davis et al., 2011). Their results showed that valves are slightly biased in the open position, with the axial pressure gradients necessary to open and close the valves strongly dependent on transmural pressure (behaviors not represented in this model). However, specific measurements of

R_{vmin} requires simultaneous measurement of flow rate, which is currently not possible in the isolated vessel preparation.

Among the lymphangion parameters, pumping output was most sensitive to f, P_{ext}, active tension (M), and L. Flow rate increased with f, with sensitivity to f being highest at the relatively low frequencies typical of in vivo performance. Experiments by Gashev et al. showed that lymphatic vessels utilize variations in contraction frequency as an adaptation mechanism to different levels of adverse pressure difference (increasing f as adverse pressure difference increases) (Gashev et al., 2002). This behavior is similar to that observed in the cardiovascular system (e.g., heart rate increases with exercise).

The identification of an optimal value of P_{ext} was unexpected. Superposition of flow loops on the pressure-diameter curves suggested that peak flow rate occurs when the vessel is in its most compliant state, with a slight shift depending on the upstream and downstream impedances. This result can be related to the usage of external compression methods to treat lymphedema. The existence of an optimum value of external pressure may explain why this method works for a small percentage of patients. Recent experiments by Rahbar et al. 2012 (under publication) showed that the vessel remains in its most compliant state over a wider range of diameters compared to pressure diameter relationship used in this study. Consequently, the sensitivity to external pressure in vivo might be lower than what is evaluated herein. Thus, more accurate modeling of the passive behavior of the vessel is required to further advance the model.

Increasing active tension initially increased the pumping, but further increases caused the vessel to stay longer in the constricted state, thus increasing the impedance to forward flow. Experiments by Davis et al. also showed augmented pumping activity with increasing active contraction (Davis et al., 2012). In our study, the optimum value of M increased as the pressure difference across the chain increased. This result implies that for a given lymphangion, M only needs to be high enough to overcome the impedances. Additional increases in M cannot necessarily further improve pumping. Note that there was no similar point of diminishing returns for contraction frequency, at least over the range of frequencies tested here (which exceeded the physiologic range).

Under the three tested pressure differences (Δp = 0.10, 0.35, 0.60 cmH_2O) peak flow rate for $L \approx 0.3$ cm, regardless of the value of M. This length corresponds closely to the physiologic range for the lymphatic vessels on which our baseline models were based. These results however were for a chain of four lymphangions in a certain diameter ranges. It is expected that the optimum length would change for different diameter changes and variations of other parameters.

We also investigated chains with different numbers of lymphangions. The physiological question to address was that for a given length, how many lymphangions should fill out that space to generate the optimum flow rate. As a fluid mechanics problem we first looked at the effect of simply adding/removing lymphangions to/from the chain of four lymphangions. This approach, of course, resulted in different overall chain lengths for each case. The outcome of the simulations showed that at higher pressure differences utilizing more lymphangions improved the pumping, and longer

lymphangions helped the pumping when n was large. Then we considered the more physiologic case in which the overall chain length remained constant and the number of lymphangions varied, this scenario resulted in different lymphangion lengths for each case. The output of these simulations, however, was similar to what was observed in the first case. Increasing the number of lymphangions can improve the pumping if the pumping/contractile power added to the system by that lymphangion overcomes the additional impedance. In studying the effect of number of lymphangions, we ignored the effect of gravity because the chains were long enough to develop significant hydrostatic pressures. This will be included in later models encompassing more extensive series and parallel vessel networks.

It should be noted that the current model has limitations in addition to those mentioned above. The equations used in the model, although more realistic than the previous models, are still very simplified. The model does not take into account some of the physiological behaviors of the system observed experimentally. Namely, irregular contractions (Zawieja et al., 1993), pressure difference and shear stress dependent active tension (Davis et al., 2009; Gashev et al., 2002). We have also assumed that the fluid is homogeneous, with no cellular content.

5. CONCLUSIONS

In summary, our results suggest that further experimental measurements are required to refine the description of the valve behavior and valve parameters. Future experiments should focus on more accurate estimations of active contractile force and geometric features of lymphangions, specifically length/diameter ratios.

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