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Pump efficiency of lymphatic vessels: numeric estimation

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Abstract — A model of lymph flow in the human lymphatic system in the quasi-one-dimensional approach has been created and investigated under different conditions. The model includes an implementation of contractions and valve influence on lymph flow. We consider contractions of lymphatic vessels and their influence on resulting flow in the whole network of lymphatic vessels and lymph nodes. We have investigated flow with zero pressure gradient and have found parameters, which influence the efficiency of contractions most significantly.

Keywords: Lymph flow, quasi-one-dimensional equations, vessel contractions, numerical simulation

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The lymphatic system (LS) is a vessel system in the human body, providing, among others, transport, drainage, and immune functions. LS distributes immune agents through the body, provides drainage of big molecules, cells, and waste products from the interstitial fluid. Modern medicine concerns LS as an important part of the body, but the knowledge about it is still very scarce.

Lymph flows in the vessels under pressure gradient influence and active and passive contractions of the vessel wall. Passive contractions are contractions of the vessel wall as a result of surrounding tissue pressure and massage influence of big blood vessels. Active contractions are contractions because of myocytes in the lymphatic vessel wall [19]. Mechanism of active contractions is still not clear enough and is under investigation. It is believed now [6, 8, 10, 19, 21] that such contractions depend on the current volume of lymphangion (part of the lymphatic vessel between adjacent pairs of valves), time from the previous contraction, and chemistry formulae of lymph.

Lymphatic vessels have valves in their lumen, and these valves restrict flow against the valves. Coupled mechanism of contractions and valves provide lymph propagation through the lymphatic network (which consists of lymphatic vessels and lymph nodes) in the proper direction, and dysfunction of valves or contractions lead to different diseases. For example, in low limb lymphedema, according to [20], more severe stage of the disease is characterized by changing vessel structure, presence of flow in a backward direction, and dysfunctions of contractions.

There are almost no data on contractions of lymphatic vessels *in vivo*, but it is now established [6, 8], that mechanism of active contractions is one of the main forces that provide lymph propagation through the LS. Measurement of parameters

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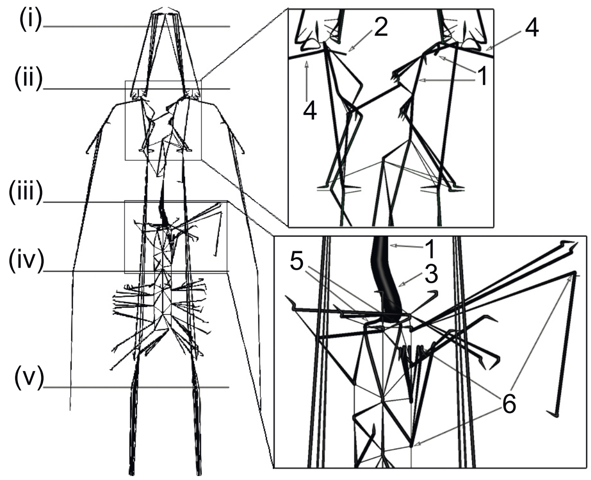

Figure 1. The graph of the LS network: (i) — head, (ii) — neck, (iii) — diaphragm, (iv) — elbows, (v) — groin; 1 — thoracic duct, 2 — right lymphatic duct, 3 — cisterna chyli, 4 — subclavian trunks, 5 — lumbar trunks, 6 — lymph nodes.

of contractions *in vivo* is very hard and complex, and existing methods (for example, measurement via MRI [16]) can't give us satisfactory results.

Groups of physiologists [9, 10, 17, 21] investigate contractions of lymphatic vessels *in vitro*, and so we have some quantity data, characterizing contractions, as well as quality data about patterns of contractions. This data is scanty, but it allows us to create a model of the contractions and investigate this model in a physiologically adequate range of parameters.

The main goal of our work is to create a model of lymph flow in the LS network on the base of the quasi-one-dimensional approach. This model should respect the specific structure of the LS network and functioning of lymphatic vessels. Previous works [12, 13] make us a bit closer to reach this goal: we were able to create a spatial-oriented model of the LS network and perform some numerical simulation with it. Results of simulation [12] show us that contractions must be obligatory implemented in the model to get physiologically reasonable lymph flow. Some results of analytical and numerical analysis of flow in one vessel under contractions are presented in work [13]. We use those results in the current work and investigate flow under contractions in the LS network.

1. Model of lymph flow

Model of lymph flow in the LS network includes a graph of the LS network (Fig. 1) and models of lymph flow in all parts of the network [12].

Arcs of the graph represent lymphatic vessels and lymph nodes, and vertexes represent points of vessel bifurcations and rare valves in the big lymphatic vessels. The graph of LS network is spatially oriented, anatomically adequate and topology consistent with a similar graph of the cardio-vascular system [3].

The graph of the LS network contains 543 arcs, which are divided into groups depending on mechanisms of lymph flow regulation [12]. Each group differs from others by equations used to describe lymph flow.

The first group contains big lymphatic vessels. Lymph flow in such vessels happens under active contractions and is described by the system of quasi-one-dimensional hemodynamic equations:

$$\frac{\partial s}{\partial t}+\frac{\partial us}{\partial x}=0 \tag{1.1}$$

$$\frac{\partial u}{\partial t}+u\frac{\partial u}{\partial x}+\frac{1}{\rho}\frac{\partial p}{\partial x}=-8\pi\nu\frac{u}{s} \tag{1.2}$$

$$s=s(p,x,t)=s_0+\vartheta(p-p_0)+\vartheta A\sin\left(\frac{2\pi}{\lambda}(x-at)\right). \tag{1.3}$$

Here s is the cross-section area of the vessel, u is the lymph velocity, p is the pressure, x is the spatial coordinate, it varies from 0 to length l, and $t>0$ is time, ρ is the lymph density which is proposed to be constant, ν is the viscosity factor, which is also proposed to be constant for vessels of the first group.

The system includes equation of continuity (1.1), equation of momentum conservation (1.2), and so-called ‘state equation’ (1.3). Contractions are taken into account in the state equation (1.3). First two terms describe the change of vessel lumen in response to pressure influence. This response is a linear function of pressure, s_0 is the initial cross-section area, p_0 is the initial pressure (specific average pressure, which is taken to be pressure at $t=0$), term $\vartheta=(s_{\max}-s_{\min})/(p_{\max}-p_{\min})$ characterizes elastic properties of the vessel wall ($s_{\max}$ and $s_{\min}$ are maximum possible and minimum possible cross-section area for the vessel, respectively, $p_{\max}$ and $p_{\min}$ are pressure in which the vessel reaches $s_{\max}$ and $s_{\min}$, respectively). The third term models active contractions of the vessel wall. Contractions in our case are modelled by a sinus function and its amplitude A, wavelength λ, and wave velocity a are parameters of the contractions. Modelling of contractions by a sinus function is a common way to model contractions of lymphatic vessels [11,22].

The second group contains 232 collectors with smaller diameters and frequent valves. Lymph flows in such vessels under contractions and resistance of valves. We use modified system (1.1)–(1.3), where momentum equation (1.2) has following form to describe lymph flow in vessels of this group:

$$\frac{\partial u}{\partial t}+u\frac{\partial u}{\partial x}+\frac{1}{\rho}\frac{\partial p}{\partial x}=-8\pi\nu(u)\frac{u}{s}. \tag{1.4}$$

In equation (1.4) viscosity ν is a function of velocity u. This function gives a normal value of viscosity when lymph flows along with valves and a bigger value in the case of flow against valves. This function allows us to model valve influence on lymph flow as our colleagues have done it to take into account valves in veins [23]. We call this viscosity function ‘anisotropic viscosity’ since viscosity factor depends on fluid flow direction [13]. In following simulations this functions is arctangent of velocity:

$$\nu(u)=\frac{\nu_{\max}-\nu_{\min}}{\pi}\arctan(Cu)+\nu_{\min} \tag{1.5}$$

Table 1. Diameters d (cm) and length l (cm, mean $\pm$ standard deviation) of parts of the LS graph, n is the number of arcs in the group.

	Effective vessels	Collectors	Lumbar trunks	Other trunks	Ducts	Cisterna chyli	Lymph nodes
d	0.02	0.107	0.15	0.1	0.2	0.4	0.2
l	2.0 ± 5.5	7.8 ± 9.6	1.2 ± 0.1	1 ± 0.5	1.6 ± 1.4	3.1	0.2 ± 0.02
n	111	232	4	18	16	1	161

where $\nu_{\max}$ is viscosity in case of flow against valves (equals 4 cm^2/s), $\nu_{\min}$ is normal viscosity (equals 0.04 cm^2/s), C is a constant (equals 10^{-6} in our case). Contractions in vessels with anisotropic viscosity give us a model of lymph propagation in the quasi-one-dimensional case.

The third group consists of the effective representation of networks of initial lymphatics. There are no contractions and valves in such vessels. Lymph flow in such vessels is described by system (1.1), (1.2) and state equation (1.3) without third term [12].

The fourth group contains 161 lymph nodes. Lymph flow in the lymph nodes is described by system (1.1)–(1.3).

Arcs of the graph connect to each other with conditions of pressure equality and flux conservation in the points of bifurcations:

$$p_i = p_j, \quad i = 1, \ldots, n, \quad j = i+1, \ldots, n, \qquad \sum_{k=1}^{n} u_k S_k = 0$$

where n is a number of vessels in bifurcation point.

Condition of zero backward flux is stated in the case of a valve in graph vertex:

$$Q_2 = \begin{cases} Q_1, & u_1 z > 0 \\ 0, & u_1 z < 0 \end{cases}$$

where $z = \{-1|1\}$ shows in which direction valve allows lymph flow.

The diameters and length of lymphatic vessels and lymph nodes are shown in Table 1 [7, 18, 24].

We take parameters of the contractions from works [9, 10] as a starting point. According to them, the period of contractions is 0.38 s for an afferent vessel (going to a lymph node), 1 s for an efferent vessel (going from a lymph node) and 10 s for a lymph node. Amplitude of contractions (deviation from average value) is about 2.5 mH (0.2 mm Hg). We need one more parameter to fulfill the definition of contractions with equation (1.3), and this parameter is the velocity of contraction wave, which is about 0.4–0.5 cm/s according to [17].

2. Simulation

The graph was created and all calculations were performed in Cardio-Vascular Simulation System (CVSS) software, which has been developed in the Lomonosov Moscow State University, Faculty of Computational Mathematics and Cybernetics, Department of Computational Methods for simulation of blood flow in human cardiovascular system [3]. There are about 15000 computational nodes in the LS network graph. Spatial step is 0.1–0.2 cm, time step is 0.005–0.01 s.

Lymph flow is modelled by finite differences estimation of equations (1.1)–(1.3). The difference scheme is described in detail in works [1, 2, 4, 5, 14], and is modified in order to take into account contractions and valve influence:

$$s_t + (us)^{(\sigma_1)}_{\overset{\circ}{x}} = 0,\; u_t + \left(\frac{u^2}{2}\right)^{(\sigma_2)}_{\overset{\circ}{x}} + \frac{1}{\rho}\,(p)^{(\sigma_3)}_{\overset{\circ}{x}} = -8\pi\left(\nu(u)\frac{u}{s}\right)^{(\sigma_4)}_{\overset{\circ}{x}}, \quad s^n_j = s(p^n_j, x_j, t_n) \tag{2.1}$$

where $y = y(x_j,t_n)$, $\hat{y} = y(x_j,t_{n+1})$, $y^{\sigma_i} = (1-\sigma_i)y + \sigma_i\hat{y}$, $\hat{y}_{\overset{\circ}{x}} = (y(x_{j+1},t_{n+1}) - y(x_{j-1},t_{n+1}))/(2h)$, $\sigma_i \in [0,1]$, $i = 1,2,3,4$, are the coefficients, $x_j = jh$, $t_n = n\tau$, where h and τ are the spatial step and time step, respectively. In following calculations $\sigma_i = 1$, $i = 1,2,3,4$, and scheme (2.1) has the first order approximation on time and the second order on space.

There are 113 boundary points in the graph where constant pressure 1 mm Hg is stated. Since there is no pressure gradient in the system, the only forces influencing lymph flow are contractions and anisotropic viscosity. These forces are own and specific for LS, so with such problem formulation, we can investigate and estimate the own propagation ability of LS.

Previous investigations of system (1.1), (1.4) and state equation with simpler form give us results for one vessel that efficiency of such propagation depends on the frequency of contractions [13]. We understand ‘efficiency’ as a difference between fluxes from the right and from the left boundaries of the vessel, which is non-zero. Those results are a starting point for the calculations in current work.

2.1. Different frequency and wavelength of contractions

In [13] we have shown that efficiency of ‘muscle pump’ depends on contraction frequency. Let us check this in the case of contractions of all vessels (except effective ones and lymph nodes) in the LS network.

All calculations are performed under zero pressure gradient: 1 mm Hg in the interstitial space and 1 mm Hg in the upper vena cava. Parameters of contractions, namely wavelength λ and angular frequency $\omega = 2\pi a/\lambda$, are shown in Table 2 with the results of calculations (No. 1–4). Parameters of contractions for all vessels are the same. Contractions are modelled by equation (1.3). The amplitude of contractions is 0.1 mm Hg, and it corresponds to physiologically observed value [9] discussed above.

Pressure gradient up to 1 mm Hg appears in the system as a result of ‘muscle pump’ (contractions in the vessel with valves) influence in the calculations No. 2 and No. 3. The value 0.001 ml/s of output flux (which is time average integral flux from the right lymphatic and from the thoracic ducts) is achieved by increasing frequency of contractions. Increasing frequency leads to increasing of output flux, while de-

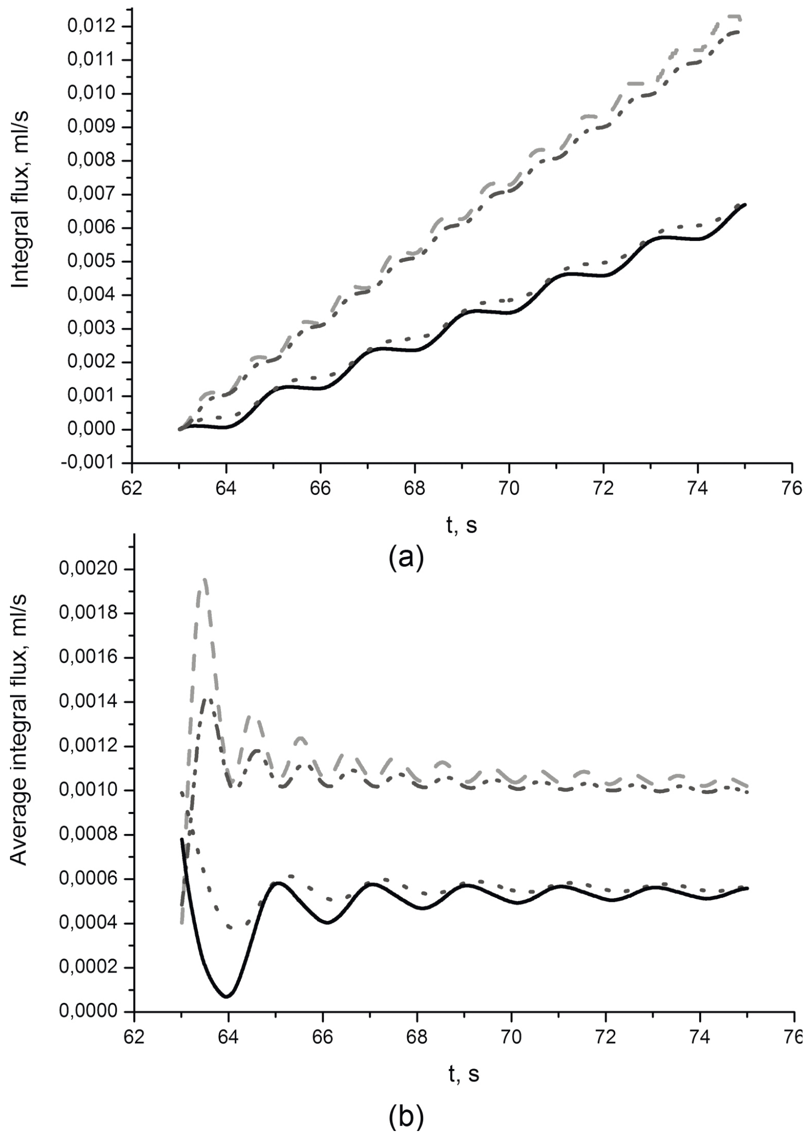

Figure 2. Integral flux (a) and average integral flux (b) for calculations with different frequencies ω and wavelength λ of contractions. Solid line is $\lambda = 1$ cm, $\omega = \pi$ s^{-1} (Table 2, No. 1), dashed line is $\lambda = 1$ cm, $\omega = 2\pi$ s^{-1} (Table 2, No. 2), dotted line is $\lambda = 0.4$ cm, $\omega = \pi$ s^{-1} (Table 2, No. 3), dash-dot-dotted line is $\lambda = 0.4$ cm, $\omega = 2\pi$ s^{-1} (Table 2, No. 4).

creasing wavelength has almost no effect on resulting flow, and therefore does not improve the efficiency of the muscle pump. Integral fluxes and their averages upon time for these calculations are shown in Fig. 2.

Table 2. Parameters of contractions, used in numerical simulation, and output data. 'No.' is number of calculation. Parameters of calculations: λ (cm) — wavelength, ω (s^{-1}) — angular frequency of contractions: (vessels) — for lymphatic vessels, (nodes) — for lymph nodes. s_{max} (cm^2) — maximum cross-section area of lymph nodes, ν_{max} (cm^2/s) — viscosity coefficient when lymph flows against valves. Output results: P_{min} (mm Hg) — minimum pressure, P_{max} (mm Hg) — maximum pressure, dP (mm Hg) — pressure gradient, which appears in the system as a result of calculation ($dP = P_{max} - P_{min}$), Y (ml/s) — time average integral flux from the right lymphatic and the thoracic ducts.

No.	λ	ω (vessels)	s_{max}	ω (nodes)	ν_{max}	P_{min}	P_{max}	dP	Y
1	1	π	0.0314	0	4	0.41	1.03	0.62	0.00054
2	1	2π	0.0314	0	4	0.05	1.05	1.0	0.001
3	0.4	π	0.0314	0	4	0.41	1.03	0.62	0.00056
4	0.4	2π	0.0314	0	4	0.03	1.04	1.01	0.001
5	1	2π	1.0	0	4	0.44	1.07	0.63	0.0016
6	1	2π	1	0.2π	4	0.13	1.11	0.98	0.0026
7	1	2π	0.0314	0	0.04	0.96	1.0	0.04	0.00014

2.2. Lymph nodes influence on lymph transport

2.2.1. Results in Section 2.1 were obtained without taking into account possible reflections and interference of contraction waves.

There are two types of vertexes representing vessel bifurcations in the LS network graph. The first one is vertexes, which connect vessels to vessels. Reflections and interference of waves in the LS network correspond to physiology in this case. The second type is vertexes, connecting vessels to lymph nodes. In this case, the wave from one afferent vessel (vessel, which goes to the lymph node) potentially can go to others afferent vessels, while such situations impossible in real LS (let us thank Yu. V. Vassilevski for pointing out this narrow space in the model). Possible reflections and interference in the model do not correspond with physiology for such vertexes, so we increase the possible maximum cross-section area of lymph nodes. It leads to decreasing of reflection coefficients [15], and thus we have less or no reflections and interference in points, where there are no reflections and interference according to physiology.

The calculations were performed under zero pressure gradient: 1 mm Hg in the interstitial space, and 1 mm Hg in the upper vena cava. Maximum cross-section area s_{max} of lymph nodes is 1 cm^2 now (maximum diameter equals 1.1 cm). Increasing of s_{max} increases vessel elasticity, so lymph nodes now are more elastic than in the previous case. The calculations were performed under contractions of lymphatic vessels with $\omega = 2\pi$, $\lambda = 1$ cm (No. 5 in Table 2).

The results of calculations are shown in Table 2, No. 5. Pressure gradient, appearing in the system, less than in the case for a lesser diameter of lymph nodes (No. 2) while resulting flux increases by 60%. The calculation shows that there were not-physiological reflections and interference of waves strongly influencing lymph flow. These waves have been reduced by correcting model according to physiology (increasing depositing abilities of lymph nodes in our case).

Integral fluxes and average integral fluxes are shown in Fig. 3 (dashed line) compared to results of calculation No. 2 (solid line) with the same parameters for

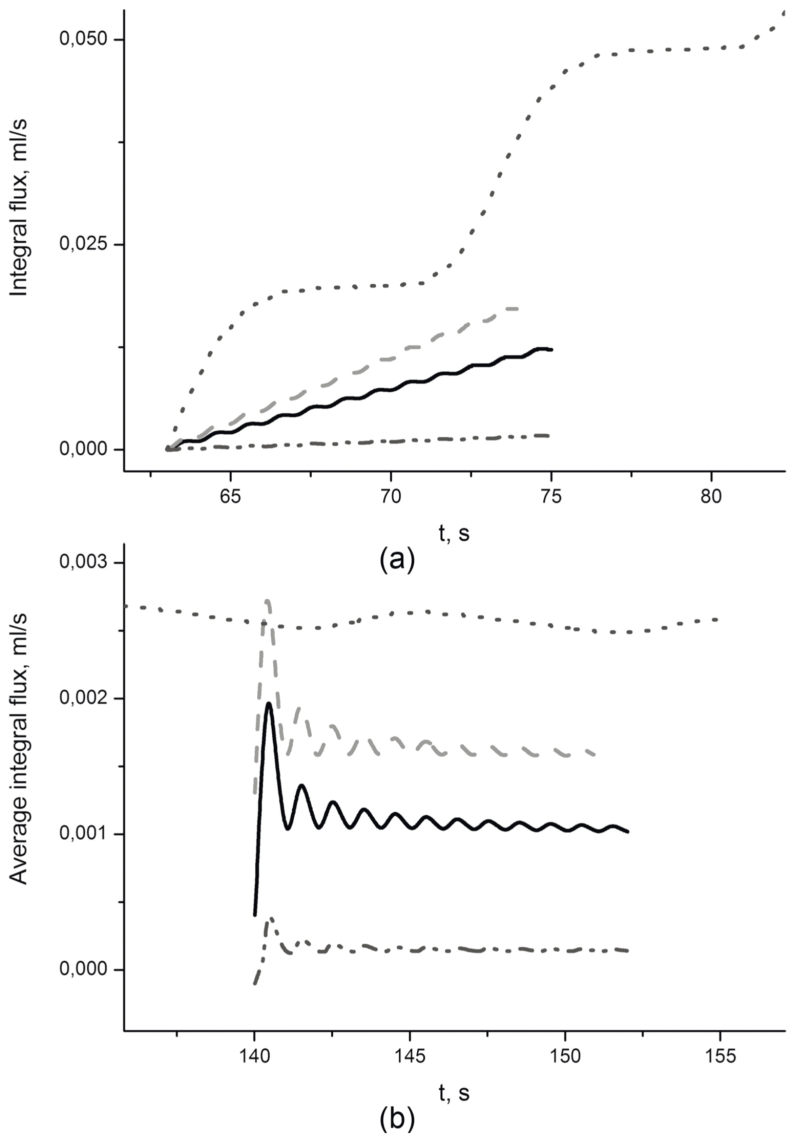

Figure 3. Integral flux (a) and average integral flux (b) for calculations with different parameters of lymph nodes: solid line is $s_{\max} = 0.0314$ cm^2 for lymph nodes (Table 2, No. 2), dashed line is $s_{\max} = 1$ cm^2 for lymph nodes (Table 2, No. 5), dotted line is $s_{\max} = 1$ cm^2 for lymph nodes and there are contractions of lymph nodes with $\omega = 0.2\pi$ s^{-1} (Table 2, No. 6), dash-dot-dotted line is $\nu \equiv$ const (equation (1.2)) — no anisotropic viscosity (Table 2, No. 7).

contractions and less lymph node depositing ability (less maximum cross-section area $s_{\max}$ of lymph nodes).

2.2.2. According to [9], lymph nodes produce low-frequency contractions, which help to squeeze out lymph through the lymph node's complicated structure. The next calculation has been performed to study if there is any influence from contractions of lymph nodes on the flow in the model.

The calculations are still performed under zero pressure gradient: 1 mm Hg in the interstitial space, and 1 mm Hg in the upper vena cava. Lymph flows under contractions of lymphatic vessels with the same parameters $\omega = 2\pi$, $\lambda = 1$ cm. Contractions of lymph nodes are modelled by equation (1.3) with $\omega = 0.2\pi$, $\lambda =$ 1 cm. Amplitude for all contractions (lymphatic vessels and lymph nodes) is still 0.1 mm Hg.

The results of calculations are shown in Table 2, No. 6. Pressure gradient, appearing in the system, is more than in the previous case, and output flux again increases by 60% in comparison to previous calculation No. 5. So contractions of lymph nodes have a sensible influence on the efficiency of the pumping ability of the LS network in the model, and this result corresponds to physiological observations. Integral flux and average integral flux are shown in Fig. 3 by a dotted line.

2.3. Anisotropic viscosity

It is necessary to make some notes about the influence of anisotropic viscosity on the resulting flow in the LS network graph.

Equations (1.1), (1.4), and (1.3) describe muscle pump in presence of both contractions ($A \neq 0$) and anisotropic viscosity ($\nu(u) \not\equiv$ const). In the case of constant viscosity factor ν in (1.2), no unidirectional flux is obtained in one vessel, nor in the vessel nets. The importance of anisotropic viscosity for the model of lymph flow in the LS is well illustrated by following simulation.

The calculations were performed in the graph of LS network with 25 valves in vertexes, with no anisotropic viscosity and with contractions of all vessels. Parameters of contractions are listed in Table 2, No. 7 (the same as for calculation No. 2). The pressure gradient is still 0 mm Hg: 1 mm Hg in the interstitial space, and 1 mm Hg in the upper vena cava. As a result, we get output flux (average integral) $1.4 \cdot 10^{-4}$ ml/s. This flux is five times less than flux for the case No. 2 with anisotropic viscosity, so the presence of anisotropic viscosity influences the efficiency of muscle pump of LS network the most. Non-zero value of flux is obtained because of the presence of 25 valves in vertexes, which represent valves in lymphatic trunks and ducts. Integral flux and average integral flux are also shown in Fig. 3 by dash-dot-dotted line.

3. Conclusion

Efficiency of quasi-one-dimensional muscle pump, describing by equations (1.1), (1.4), and (1.3) in the LS network graph was investigated in the work. The results show that growth of frequency value leads to the growth of efficiency of the muscle pump. It corresponds to results for one vessel [13]. However, the value of the wavelength itself has no effect on muscle pump efficiency in the frame of the considered model. Parameters of lymph nodes also influence the efficiency of transport function in the model of LS: increasing of the maximum diameter of nodes increases output flux. This factor is specific to the LS network. Including contractions of nodes in the model according to physiological data also has a great influence on resulting flow: output flow increases with the presence of lymph contractions.

Contractions are reported as an extremely important mechanism of lymph flow regulation in the physiology literature, and the results of simulation show that it is also true in our model.

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