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A Circuit Based Model of the Lymphatic System

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***Abstract*—The lymphatic system is one of the main, but relatively less understood, systems of the human (and animal) body. As for other systems, having a usable model of the main elements that compose this system can greatly help the process of understanding and modelling normal and pathological conditions. In this paper a simple lumped model of the lymphangion, the basic active building block of the lymphatic system, is presented and is shown to be fully autonomous, describing pulsating behaviour without the use of external periodic sources. The model is based on the circuit analogy and has been implemented both using Matlab and as a standard spice-like netlist including Verilog-A code.**

***Index Terms*—circuit based models, lumped biological models, lymphatic system, simulation**

I. Introduction

Most animals have, among their vital organs, a circulatory system whose role is carrying nutrients and oxygen to all the cells in the body. This is done through the components known as *plasma* and *red blood cells* of the fluid that, in "higher" animals, is commonly called blood (*haemolymph* in simpler animals such as arthropods). This system regulates pH levels in the body and also plays a fundamental role as an aid to the immune system since it also contains white blood cells and platelets; blood also contributes to the elimination of waste byproducts of cells by circulating through filtering organs such as kidneys, liver and lungs. Vertebrates, and, as such, also humans, are characterized by a subsystem complementary to the circulatory system called Lymphatic System (LS). The LS filters excess plasma in the blood through the *lymph nodes* and recirculates lymph to the main circulatory system, this is done to maintain homeostatic equilibrium by regulating the relative volume of interstitial fluid; in humans this is set at about 20% of the body weight, and this set point is held by returning fluid in excess through the thoracic duct to the main circulatory system. The LS has several components: in addition to the lymph nodes with their filtering action, several *lymphoid* organs, such as the thymus, the spleen, the tonsils, etc. are part of the system; these organs do not have an active role in the transport of the lymph but have the important role of generating and distributing *lymphocytes*, major components of the immune system, through the body. This distribution pathway is vital in vertebrates, but, unfortunately, can in some cases also be used by cancer cells [1] [2], and, in case of failure, may determine dangerous health conditions such as *lymphoedema*. While in the main circulatory system there is a centralized pumping organ, the heart, the lymphatic system is characterized by a distributed system of pumping elements, that, connected to each other, are themselves the main constituents of the lymph vessels called *lymphatics*. These distributed pumping organs are called *lymphangions* and are capable, as the heart in the main circulatory system, to pump against a pressure gradient preventing most retrograde flow thanks to mono-directional valves (called secondary valves, in contrast to the primary valves that are present in the *initial lymphatics* and directly collect interstitial fluid).

The pumping function of lymphangions is carried out through active contraction and relaxation of its walls complemented by valves that prevent retrograde flow. While valve operation is essentially passive and determined by the pressure of the fluid inside the lymphangion, the contraction effect is active and is determined by both transmural pressure and dynamic shear stress on the vessel itself; these causes are all local and do not depend on an external action. Most lumped models derived so far rely on an external control mechanism that actually causes contraction. Some more advanced models have some sort of regulation of contraction frequency based on internal fluid parameters, but, also in this case, these simply control an active external periodic source that forces pumping activity. Considering the most recent literature this source is modulated by internal pressure [3] or modeled considering the biochemical interactions that lead to contraction and relaxation [4], where a periodic calcium concentration leads to systolic/diastolic cycles. A similar approach, based on the autonomous oscillations in the membrane voltage and its interaction with calcium concentration, can be found in [5]. For a general introduction to this topic a very nice overview of lymphatic system functions and a review of some of the best known lumped models up to 2018 can be found in [6]. A more recent (2020) and general overview can be found in [7].

In this paper a lumped model that is intrinsically autonomous, i.e. where the only sources present are constant and represent input, output and external pressure values, is presented. It is shown that an appropriate modelling of the lymphangion element yield oscillations that are compatible with contractions observed in real lymphatic systems. The model here presented is an extension of a simpler model

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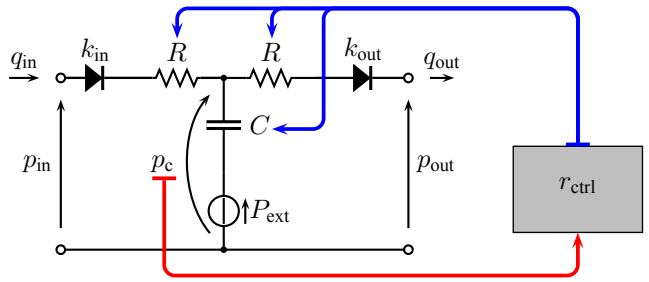

Fig. 1. A lymphangion model based on the circuit analogy. Radius values are controlled by pressure by the r_{ctrl} block. Pressures (p_{in} and p_{out}) are modelled by voltages and fluid flux (q_{in} and q_{out}) by currents. Fluid inertia effects, equivalent to an inductance, will be omitted.

previously described in [8] and [9], these previous models did not consider maximum and minimum radius dependence on internal pressure and did not provide modulate refractory time modulation as a function of pressure and flow. In section II the basic model is presented in all its parts; in Section III results of optimization of the model parameters with respect to real data is shown, along with model behaviour.

II. The Lymphangion Model

The starting point to build any lumped model of fluid transport rely on the characterization of vessel compliance, fluid inertia and hydraulic resistance [10]. In our model effects of fluid inertia can be shown to be negligible and, as such, can be safely omitted.

If a cylindrical duct of length l and radius r is considered and assuming a low Reynolds number, Puisseuille law can be used to approximate its hydraulic resistance:

$$R \equiv \frac{\text{pressure}}{\text{flux}} = \frac{8\mu l}{\pi r^4} \equiv R_0 r^{-4} \tag{1}$$

where μ is fluid, in our case lymph, viscosity; all these parameters can be summarized by constant R_0 .

If the duct being considered has, as in our case, some degree of elasticity, it is possible to define its compliance as the ratio of a volume differential dV (or mass dm) with respect to a pressure differential dp; wall stiffness is modeled by Young's Modulus E and wall thickness s so that we have:

$$C \equiv \frac{dV}{dp} = \frac{2\pi r^3 l}{sE} \equiv C_0 r^3 \tag{2}$$

the constant and geometry dependent parameters are summarized by constant C_0.

Lumped models of physical phenomena can be conveniently represented using the "circuit analogy". Using this analogy for hydraulic systems it is common to represent mass m, flux q and pressure p as, respectively, charge, current and voltage. As a consequence compliance, hydraulic resistance and inertia are modeled using equivalent circuit models, capacitors, resistors and inductors, respectively.

The lymphangion equivalent circuit based on the electric circuit analogy is shown in Fig. 1. The value of p_c. i.e. the voltage in the capacitor plus the pressure source P_{ext} in this model represents the internal pressure in the lymphangion. The purpose of the source P_{ext} is to model the external pressure and, eventually, its variations that may be due to movement, respiration etc. it is considered constant and in nominal conditions it is simply set to zero, nonetheless this source allows to introduce exogenous time varying pressure variations if desired. The total vessel hydraulic resistance is split in two parts, here represented by the two resistors R. The unidirectional valves in the lymphangion are here modelled by the two diodes k_{in} and k_{out}. In the most simple model these can be ideal diode, in this case no retrograde flux is allowed. If a more realistic model allowing some retrograde flux is required, more complex nonlinear devices can be used.

In Fig. 1 there is also a box labelled r_{ctrl} that receives as input the internal pressure p_c, and thus transmural stress, and controls the radius of the vessel, generating systole and diastole events. To the author's knowledge, most lumped models available in literature force the onset and period of systole/diastole cycles by means of an external generator. This undoubtedly leads to much simpler models and more efficient simulation times, on the other hand, if the dynamic behaviour of networks of interacting lymphangions is considered a fully autonomous system is needed, otherwise the network behaviour would be forced by the time base in each one of its elements.

The circuit in Fig. 1 can be described by a set of state equations, note that all elements are linear except for the valves, represented by diodes, this simplifies the problem but an even more realistic model would require the introduction of some nonlinearity in the resistors and capacitor (see e.g. [11]). From Eq. (2) one can see that compliance depends on radius, and, for this reason, the capacitor in our model is time varying an this must be taken into account when writing its constitutive relation:

$$m = Cp \quad \rightarrow \frac{d}{dt} \rightarrow \quad q = C\dot{p} + \dot{C}p \tag{3}$$

Note that this effect is justified by conservation of mass. Given Eq. (3) it is possible to write a first ODE describing the behaviour of the equivalent circuit of Fig. 1:

$$C\dot{p} + \dot{C}p = k_{in}\left[\frac{p_{in} - p}{R}\right] - k_{out}\left[\frac{p - p_{out}}{R}\right] \tag{4}$$

where the behaviour of the valves k_{in} and k_{out} will be discussed later.

Note that elements $C \equiv C(r(t))$ and $R \equiv R(r(t))$, i.e. they are both dependent on r, i..e. the radius of the vessel, whose value depends on lymphangion contraction and relaxation states.

The proposed lumped lymphangion model can be described by two distinct states:

- **passive**: the element does not cause radius variations and will change radius in a passive way as a function of p_c, the internal pressure; this happens, for instance, during diastole, when the lymphangion expands and relaxes while recovering after a systolic contraction.

- **active**: a systolic (contraction) event has been triggered by conditions on pressure and/or flow. The radius of the vessel reduces according to a relatively fast time constant reaching its minimum possible radius. Whatever model has been chosen for the valves, the one at the input will close while that at the output will open allowing lymph flow. This is due to the fact that, by reducing the radius the internal pressure will rise and eventually become larger than both input and output pressures.

One of the fundamental aspects of any lumped model of a lymphangion is describing the conditions that lead to a systolic contraction event. For this reason we will initially consider radius dynamic behaviour as an unknown non-linear function of pressure and radius. One way to do this is to consider the radius of the element as the solution of a nonlinear ODE. In order to do this we need an equation that can be written in the form $\dot{r} = f(r, p)$, i.e. where radius variation depends on pressure and the radius itself.

Using the initial equations Eqs. (1) and (2) that describe the basic model parameters and substituting them in (4) we have, using the chain rule for derivatives:

$$\begin{aligned} 3C_0 r^2 \dot{r} p + C_0 r^3 \dot{p} &= \frac{r^4}{R_0} \left[k_{\text{in}}(p_{\text{in}} - p) - k_{\text{out}}(p - p_{\text{out}})\right] \\ \dot{r} &= f(p, r) \end{aligned} \tag{5}$$

that, solving for $\dot{p}$ and $\dot{r}$ yields:

$$\begin{aligned} \dot{p} &= \frac{r}{C_0 R_0} \left[k_{\text{in}}(p_{\text{in}} - p) - k_{\text{out}}(p - p_{\text{out}})\right] - \frac{3p}{r} f(p, r) \\ \dot{r} &= f(p, r) \end{aligned} \tag{6}$$

A. Radius Behaviour Function

In passive conditions, internal pressure determines the radius value, this relation holds up to a limit point. If pressure is constant so is the radius and, if the pressure changes in a non dramatic way, the radius will evolve towards the new value in a smooth way.

Contraction events, i.e. systole, occur when the lymphangion is in active mode. Time constants are, in this case, faster then in passive mode and are a function of the pressure and flow in the element. Considering first passive mode, one may expect that pressure will cause the radius to expand or contract up to some limit value. Pressure is given by the state equations in Eq. (6), but, to make notation simpler, we may disregard this for the time being and describe this expected behaviour through equation:

$$\dot{r} = \alpha(r_t(p) - r) \tag{7}$$

with $r_t(p)$ the "correct" radius when pressure is p. It is expected that $r_t(p)$ is a nonlinear function that has a minimum value r_0 when there is no pressure difference between inside and outside the lymphangion [12], i.e. when the intramural pressure P_{ext}, is in equilibrium with the internal pressure p; furthermore, it is assumed that only very large pressure values can cause the radius to reach its maximum possible value. Note that, given state equations Eq. (6) the model will prevent divergent values for pressure. A simple function that satisfies the conditions just stated is:

$$r_t(p) = (r_0 - r_{\max})\mathrm{e}^{\beta(P_{\text{ext}} - p)} + r_{\max} \tag{8}$$

where the constant value β is a parameter related to the "elasticity" of the lymphatic vessel. By using equation (8) and substituting in (7) we finally have:

$$\dot{r} = \alpha(r_{\max} + (r_0 - r_{\max})\mathrm{e}^{\beta(P_{\text{ext}} - p)} - r) \tag{9}$$

in this equation the parameter α is constant and defines, for the passive mode of the lymphangion element, its natural frequency

Nominal pressure P_{ext} is the equilibrium pressure that corresponds to the nominal radius value. Obviously changes in radius affect resistance and compliance values of the vessel, and, specifically for what concerns compliance, different dynamic behaviours of the radius have different effects on compliance.

The model described by the first equation in Eq. (6) complemented by (9) represents the model behaviour only when in passive mode. From observations it is possible to consider, as a first approximation, the time width of a systolic event as fixed. This is what we are assuming for this model, adding pressure and/or flux dependence is anyway quite simple. The condition that triggers a contraction event is:

$$p_c > p_{\text{th}}, \quad \text{with} \quad p_{\text{th}} < p_{\text{in}} < p_{\text{out}} \tag{10}$$

where p_{th} a pressure threshold value for the internal pressure. Above this value an impulse of fixed time length is generated directly controlling the radius value.

It is possible to obtain this effect by adding a linear term to (9):

$$r_{\text{active}} = \gamma(r_{\min} - r) \tag{11}$$

with $\gamma >> \alpha$. This term is added only during the systolic phase of the contraction/relaxation cycle, and it presence is controlled by a "digital" state equation. The value of $r_{\min}$ is a function of the output pressure in relation to the input pressure, as shown in experimental work in [13]. The duration of the systolic pulse is assumed constant, while the duration of the following diastolic (relaxation) phase depends on transmural pressure and on the pressure gradient between output and input.

In order to achieve and verify active pumping, corresponding to lymph being carried upstream against a pressure gradient, it has been assumed, in (10), that $p_{\text{in}} < p_{\text{out}}$. In the opposite condition, with $p_{\text{in}} > p_{\text{out}}$ all valves will be open and the element will allow simple fluid flow from input to output.

Note that pulse generation seems to depend, according to literature, on two different effects: one due to pressure strain, and the other due to strain caused by flow (shear strain). The latter tends to inhibit pulse generation, the former causes pulse generation. This means that the simple model used in this paper should be complemented with shear strain effects.

The overall behaviour of several lymphangions connected to one another in order to form a vessel can be easily inferred by considering that each upstream element, if forced to contract due to increased input pressure, will cause a pressure spike at the input of the following element; in this ways it is expected to observe a propagation of contraction events along the vessel as observed in nature. Once a lymphangion has contracted and transmitted the pressure spike to the following one, it will relax an be ready for a new cycle after refractory period that also depends on pressure and flow.

B. Valve behaviour

In the model of Fig. 1 the valves are drawn as simple diodes. Real valve behaviour is actually more complex than that modeled by a diode (see e.g. [14] for some recent reference). Nevertheless in our model the valves have been described with different detail; in the simplest case they may be simply be assumed to be ideal and described by equation:

$$k_{in} = \begin{cases} 0 & p > p_{in} \\ 1 & p \leq p_{in} \end{cases} \qquad k_{out} = \begin{cases} 1 & p \geq p_{out} \\ 0 & p < p_{out} \end{cases} \tag{12}$$

equivalent to an ideal diode. In a more complex situation a "softer" function, such as $\tanh(\cdot)$ may be used, allowing also some retrograde flux;

$$\begin{aligned} k_{in} &= \frac{1 + \tanh\left(p_{\text{in}} - p\right)}{2} \\ k_{out} &= \frac{1 + \tanh\left(p - p_{\text{out}}\right)}{2} \end{aligned} \tag{13}$$

The observed behaviour of the secondary valves of lymphangions seems to display some hysteresis effects, and a non symmetric behaviour while opening and closing. This type of valve has been implemented as a Matlab class and used for all simulations and results shown in the next section.

III. Results

The model described in section II has been implemented both in Matlab and using Verilog-A along with a standard spice-like simulator netlist language. In both cases some adjustment due to the nature of the numerical methods employed has been necessary. Numerical methods may have serious convergence problems if large scale differences are present among the values of parameters and variables, and this is our case, in fact, if expressed using standard SI units, all parameter values in Eq. (1) and Eq. (2) have numerical values ranging through several orders of magnitude. For this reason all values have been re-scaled avoiding floating point representation problems.

In order to have some baseline data for comparison, model behaviour has been compared with radius data obtained from micro-photographic videos of lymphatic vessels*. A sample frame of one of the videos used is shown in Fig. 2. All data has been collected using the free ImageJ software [15] that allows, among other things, the automatic collection of geometric properties in a single picture or in a set of consecutive frames. The radius data obtained from the video

*see Acknowledgment for credits.

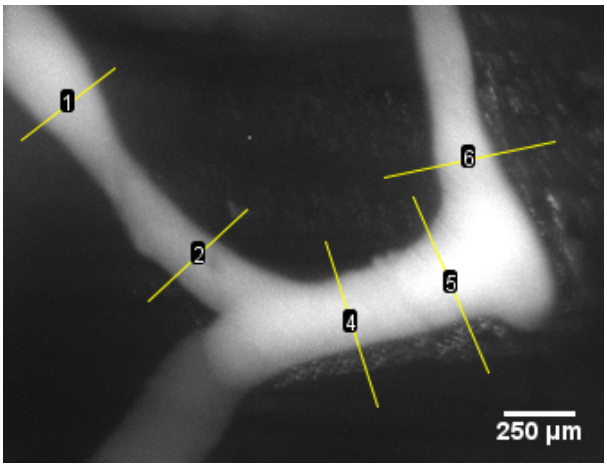

Fig. 2. One sample frame of one of the video used to analyse real Lymphangion radius behaviour

allowed optimization of the less obvious model parameters, such as α, β, γ and the base value for the relaxation refractory period using a standard least square non linear method. Results of optimization are shown in Fig. 3. This optimization phase

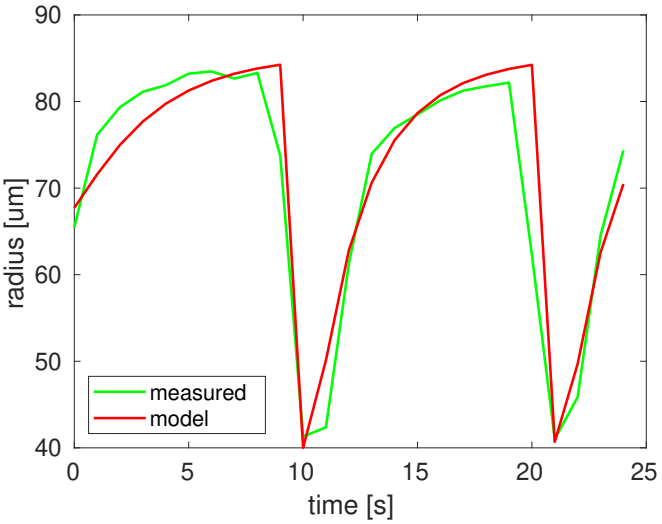

Fig. 3. Parameter optimization over two periods of *in vivo* measured data.

has been performed with standard input, output and transmural pressure as expected in the specific situation of the micro-photografic video.

After parameter optimization the model was tested by comparing its behaviour with that available in recent literature such as [16] [13]. To this end a pressure ramp is applied at the output of the lymphangion model, while keeping the input pressure fixed, the output pressure, in this case, is larger than the input one, so that autonomous systolic/diastolic behaviour can be observed. The values of input, output and internal pressure expressed in mmHg units as a function of time is shown in Fig. 4. The corresponding radius as a function of time is shown in Fig. 5. As expected, and in accordance

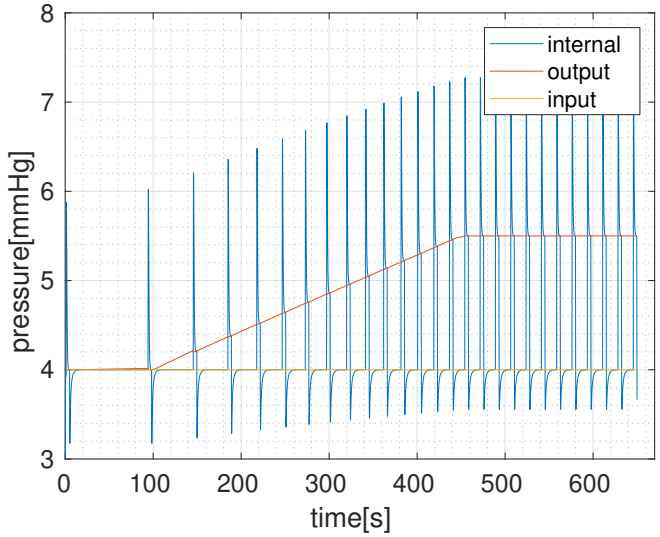

Fig. 4. Internal, input and output pressure in the lymphangion model. Input pressure is kept constant, while a ramp of output pressure is applied.

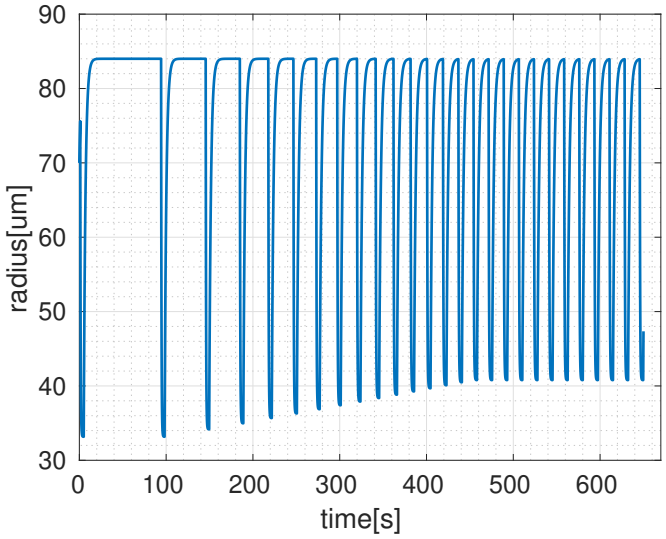

Fig. 5. Radius of the lymphangion model as autonomous systolic events are generated.

with data in literature, the maximum and minimum values of internal pressure become larger as the output pressure increases; moreover, the frequency of the systolic and diastolic events also increases as a function of output pressure.

A zoomed in image of the relationship between radius and internal pressure is shown in Fig. 6, note that internal pressure sharply rises as the systolic event takes place causing the input valve to close and the output one to open. Lymph can then overcome the output pressure and flow, lowering internal pressure at the same time. As the diastolic phase starts internal pressure is at a minimum value, but soon rises to a value just slightly higher than the input pressure, preparing the lymphangion for another systolic event as soon as the refractory period ends.

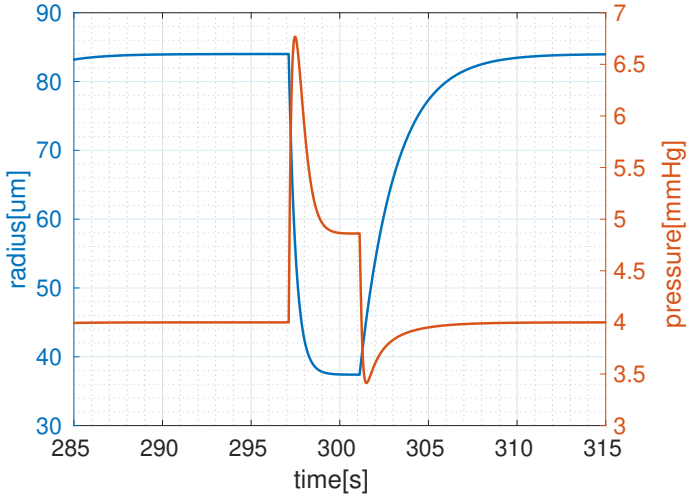

Fig. 6. Radius and internal pressure in proximity of a systolic event.

IV. Conclusions

The main contribution of this work is the definition of a circuit based model of one of the main components of the lymphatic system. Unlike most lumped models available in literature, the model here presented is a fully autonomous dynamic system capable of generating spontaneous systole and diastole events without the need of any external time base and with a frequency that depends on pressure. The reaction to exogenous inputs, such as pressure variation, are coherent with the experimental data available. Due to its implementation it is possible to use the model to build more complex networks of lymphangions and use these to study the behaviour of the lymphatic system in normal or pathological conditions.

While the model has the advantage of being fully autonomous and, thanks to its simplicity, is well suited for the simulation of complex networks of lymphangion elements, its main drawback is that, if compared with models such as those in [3] or [4], it does not directly model biochemical interactions that are present in the real physical lymphatic systems. As such this model can be considered as a *black box* model, displaying correct input vs. output behaviour and capturing the dynamic behaviour of real lymphatic vessels, but not giving more insight on the biological processes. In the present version of the model shear effects have not yet been included, these effects will be included in future versions.

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