A one-dimensional mathematical model of collecting lymphatics coupled with an electro-fluid-mechanical contraction model and valve dynamics

Christian Contarino1 · Eleuterio F. Toro2

Abstract

We propose a one-dimensional model for collecting lymphatics coupled with a novel Electro-Fluid-Mechanical Contraction (EFMC) model for dynamical contractions, based on a modified FitzHugh–Nagumo model for action potentials. The one-dimensional model for a deformable lymphatic vessel is a nonlinear system of hyperbolic Partial Differential Equations (PDEs). The EFMC model combines the electrical activity of lymphangions (action potentials) with fluid-mechanical feedback (circumferential stretch of the lymphatic wall and wall shear stress) and lymphatic vessel wall contractions. The EFMC model is governed by four Ordinary Differential Equations (ODEs) and phenomenologically relies on: (1) environmental calcium influx, (2) stretch-activated calcium influx, and (3) contraction inhibitions induced by wall shear stresses. We carried out a stability analysis of the stationary state of the EFMC model. Contractions turn out to be triggered by the instability of the stationary state. Overall, the EFMC model allows emulating the influence of pressure and wall shear stress on the frequency of contractions observed experimentally. Lymphatic valves are modelled by extending an existing lumped-parameter model for blood vessels. Modern numerical methods are employed for the one-dimensional model (PDEs), for the EFMC model and valve dynamics (ODEs). Adopting the geometrical structure of collecting lymphatics from rat mesentery, we apply the full mathematical model to a carefully selected suite of test problems inspired by experiments. We analysed several indices of a single lymphangion for a wide range of upstream and downstream pressure combinations which included both favourable and adverse pressure gradients. The most influential model parameters were identified by performing two sensitivity analyses for favourable and adverse pressure gradients.

Keywords One-dimensional model for lymphatics · FitzHugh–Nagumo · Collecting lymphatics · Lymphangions · Lymphatic action potential

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1 Introduction

The lymphatic system is an intricate network of vessels and nodes which connect tissues to the bloodstream. The main functions of the lymphatic system comprise maintenance of tissue fluid balance through drainage of excess interstitial fluid, the transport of proteins and waste products, as well as the transport of immune cells (Swartz 2001). The building block of collecting lymphatic vessels is the lymphangion: a mini-heart like, deformable vessel, which contracts and propels lymph into the next lymphangion and has several mechanobiological auto-regulatory systems to provide optimal flow in various scenarios (Kunert et al. 2015; Munn 2015). The lymphangion is enclosed between valves which promote unidirectional flow. The frequency of lymphatic contractions depends on the circumferential stretch of the vessel wall and on the wall shear stress (Munn 2015; Telinius et al. 2015; Gashev 2002). For complete reviews of the mechanisms of lymphangions and collectors, see Munn (2015), Breslin (2014), Margaris and Black (2012).

There is a substantial gap in the literature between mathematical models for the circulatory (Strocchi et al. 2017; Liang et al. 2009; Müller and Toro 2014; Quarteroni et al. 2016) and lymphatic systems. The first reported attempt to construct a mathematical model for the lymphatic system is attributed to Reddy (1974). In this work, the one-dimensional equations were written but the actual model implemented was zero-dimensional. MacDonald et al. (2008) did further work based on this model. Extensive research has been carried out on the bases of lumped-parameter models (Venugopal et al. 2007; Bertram et al. 2011, 2014a, b; Gajani et al. 2015; Bertram et al. 2016; Jamalian et al. 2016; Caulk et al. 2016). Jamalian et al. (2016) constructed a lumped-parameter model to simulate lymph transport in a network of rat lymphangions. Caulk et al. (2016) combined the lumped-parameter model described by Bertram et al. (2014b) with their four-fibre family constitutive law proposed in Caulk et al. (2015), studied the variation of muscle contractility in response to a sustained elevation in afterload, and included the dependence of contraction frequency from both transmural pressure and wall shear stress (Caulk et al. 2016). A mechanobiological oscillatory model for the lymphatic contraction has been proposed by Kunert et al. (2015). Their contribution included a dynamical model for the contractibility of the vessel wall. The resulting model was able to control lymphatic transport via mechanobiological feedback loops, given by stretch-activated contractions and flow-induced relaxations. Recently, the relevance of this work has been questioned; see Davis (2015). With the aim of constructing a mathematical model of the entire lymphatic system, the previously mentioned mathematical models for lymphangions, except for Kunert et al. (2015), Baish et al. (2016), Caulk et al. (2016), are based on a relatively simple time-dependent contraction dynamics. These models 1) prescribe contraction dynamics by using trigonometric functions and 2) prescribe time delays between adjacent lymphangions. It is no doubt highly desirable to model all mechanisms associated with lymphatic contractions by resorting to basic principles from electro-fluid mechanics. In particular, one would expect that the occurrence of a lymphatic contraction should be dependent on physical quantities, such as transmural pressure and local shear forces.

There is an extensive body of literature on cardiac contractions Quarteroni et al. (2017), Franzone et al. (2014). All these works have been greatly influenced by the pioneering work of Hodgkin and Huxley (1952) on action potentials in neurons. The FitzHugh–Nagumo model (Nagumo et al. 1962) is an example of a simplified, two-parameter formulation of the original Hodgkin–Huxley model, consisting of a system of two ODEs with a fast and a slow variable. The former represents the action potential, while the latter phenomenologically summarizes all the effects of all ionic currents. Many studies have been done to couple modified versions of the FitzHugh–Nagumo model to the heart contractions (Franzone et al. 2014). However, to date no studies have attempted to model contractions of lymphangions with the previously mentioned dynamical and phenomenological set of ODEs for action potentials.

In the present paper, we propose a one-dimensional model for lymph flow in collecting lymphatics coupled with an Electro-Fluid-Mechanical Contraction (EFMC) model for lymphatic vessel wall contractions based on a modified FitzHugh–Nagumo model. The current work presents the first attempt to couple the electrical activity of the lymphatic wall with the dynamics of the lymphatic fluid modelled in a one-dimensional manner. In particular, in this paper we incorporate some of the mechanobiological mechanisms which regulate the lymphatic contractions, such as (1) the positive dependency of frequency on the transmural pressure and (2) the inhibition of lymphatic contraction due to wall shear stresses.

2 Mathematical models

Here, we aim to model the dynamics of flowing lymph inside a collecting lymphatic propelled by lymphatic contractions and pressure gradients, and the dynamics of lymphatic
2.1 A one-dimensional model for lymph flow

Here, we assume the lymph to be an incompressible Newtonian fluid. To derive the one-dimensional flow equations for a deformable lymphatic vessel, one can follow the procedure done for arteries and veins, where Reynolds’ transport theorem is used to obtain the equations for the conservation of mass and momentum in a deformable tube; see Formaggia et al. (2009), Toro (2016). The one-dimensional flow equations for a deformable vessel, and for a lymphatic vessel in particular, are

\[
\begin{aligned}
\frac{\partial A}{\partial t} + \frac{\partial q}{\partial x} &= 0, \\
\frac{\partial q}{\partial t} + \frac{\partial}{\partial x} \left( \frac{q^2}{A} \right) + \frac{A}{\rho} \frac{\partial}{\partial x} p &= -\frac{\mathcal{L}}{\rho},
\end{aligned}
\]

(1)

where \( x \) is the space variable, \( t \) is time, \( A(x, t) \) is cross-sectional luminal area of the vessel, \( q(x, t) = A(x, t)u(x, t) \) is flow, \( u(x, t) \) is velocity, \( p(x, t) \) is pressure, \( \rho \) is lymph density, \( f(x, t) = 2(\gamma + 2)\pi \mu u(x, t) \) is friction force per unit length of the tube, with the parameter \( \gamma \) dependent on the chosen velocity profile (Alastruey 2006), and \( \mu \) is the dynamic viscosity. To close the system of equations, an additional relation between pressure \( p(x, t) \) and cross-sectional area \( A(x, t) \) is required and is called tube law. The lymphatic wall is characterized by an intimal layer of endothelial cells surrounded by a discontinuous basement membrane, a media composed of layers of smooth muscle cells, and an adventitia layer that consists of collagen fibre bundles (Caulk et al. 2015; Rahbar et al. 2012). Elastin fibres give lymphatic vessels a compliant, elastic behaviour, while collagen prevents vessels from stretching beyond their physiological limits. The overall dynamics of elastin and collagen is reflected in highly nonlinear tube laws. Here, we propose the following general tube law:

\[
p(x, t) = K(x, t)\psi(A(x, t); A_0(x)) + p_e(x, t),
\]

(2)

with

\[
\psi(A(x, t); A_0(x)) = \left( \frac{A(x, t)}{A_0(x)} \right)^n - \left( \frac{A(x, t)}{A_0(x)} \right)^m + C \left[ \left( \frac{A(x, t)}{A_0(x)} \right)^z - 1 \right],
\]

(3)

where \( p(x, t) \) is the internal pressure, \( p_e(x, t) \) is the external pressure, \( A_0(x) \) is the vessel cross-sectional area at zero transmural pressure (equilibrium), \( K(x, t) \) is a time-dependent coefficient, \( m \geq 0, n \leq 0, z \geq 0, \) and \( C \geq 0 \) are real numbers to be specified. The transmural pressure is defined as

\[
p_{\text{trans}}(x, t) := p(x, t) - p_e(x, t).
\]

(4)

Inspired by MacDonald et al. (2008), we take the simplified approach to model lymphatic contractions by varying the coefficient \( K(x, t) \) from a minimal value \( K_{\text{min}}(x) \) to a maximum value \( K_{\text{max}}(x) \) as follows:

\[
K(x, t) = K_{\text{min}}(x) + s(x, t)(K_{\text{max}}(x) - K_{\text{min}}(x)),
\]

(5)

where \( s(x, t) \in [0, 1] \) is the state of contraction. The lymphangion is contracted when \( s(x, t) = 1 \) and is relaxed when \( s(x, t) = 0 \).

The tube law can be recast in terms of the active and passive components as follows:

\[
p = f_p \left( \frac{A}{A_0} \right) + f_a \left( \frac{A}{A_0} \right) s + p_e,
\]

(6)
where
\[
f_p \left( \frac{A}{A_0} \right) = K_{\text{min}} \psi (A; A_0) \tag{7}\]
is the passive pressure–area relationship and
\[
f_a \left( \frac{A}{A_0}, s \right) = s (K_{\text{max}} - K_{\text{min}}) \psi (A; A_0) \tag{8}\]
is the active tension contribution. The passive pressure–area relationship mirrors the passive relationship proposed by others (Bertram et al. 2011; Jamalian et al. 2016). The active tension contribution does not rely on a physiologically based model of muscle contractions, but rather emulates the contraction phenomena in terms of pressure–area curves.

Here, we model lymphatic vessels from the mesentery of rats, whose parameters are found in Table 1. The parameters of the tube law and the minimum coefficient \(K_{\text{min}}\) were tuned to fit the experimental measurements shown in Bertram et al. (2014a) and performed by Davis et al. (2011), while the maximum coefficient \(K_{\text{max}}\) was estimated following Caulk et al. (2016) and Scallan et al. (2012). We remark that our diameter at equilibrium was derived from a vessel that was not stress-free due to axial elongation (Davis et al. 2011). As can be seen in Fig. 2, the relationship between pressure and diameter is highly nonlinear.

The Wall Shear Stress (WSS) is fundamental in the auto-regulatory homeostatic mechanisms of lymphatic contractions. Following Alastruey (2006), the WSS in our formulation is
\[
\tau(x, t) = u(x, t) \mu \frac{\gamma + 2}{r(x, t)}, \tag{9}\]
where \(r(x, t)\) is the inner radius of the lymphatic vessel.

### 2.1.1 Conservative formulation of the one-dimensional lymph flow equations

It is possible to write the lymph flow equations in conservative form as follows:
\[
\partial_t Q(x, t) + \partial_x F(Q(x, t), x, t) = S(Q(x, t), x, t), \tag{10}\]
where
\[
Q(x, t) = \begin{bmatrix} A(x, t) \\ A(x, t) u(x, t) \end{bmatrix}, \tag{11}\]
\[
F(Q, x, t) = \begin{bmatrix} Au^2 - \frac{K}{\rho} A_0 \partial A_0 \psi \\ 0 \end{bmatrix}, \tag{12}\]
\[
S(Q, x, t) = \begin{bmatrix} 0 \\ \frac{1}{\rho} \left(f + A_0 p_e + \psi \partial_x K + K \partial_x A_0 \partial A_0 \psi \right) \end{bmatrix}. \tag{13}\]

with
\[
\psi = \int_A \psi(A; A_0) dA = A_0 \left( - \frac{m}{m + 1} \left( \frac{A}{A_0} \right)^{m+1} - \frac{n}{n + 1} \left( \frac{A}{A_0} \right)^{n+1} \right) + C \frac{1}{z + 1} \left( \frac{A}{A_0} \right)^{z+1}, \tag{14}\]
and
\[
\partial A_0 \psi = - \left( \frac{m}{m + 1} \left( \frac{A}{A_0} \right)^{m+1} - \frac{n}{n + 1} \left( \frac{A}{A_0} \right)^{n+1} \right) + C \frac{z}{z + 1} \left( \frac{A}{A_0} \right)^{z+1}. \tag{15}\]

\(Q\) is the vector of the conserved variables, \(F\) is the physical flux, and \(S\) is the source term. The constants arising from the integrals (14) and (15) are set to zero for consistency with (1) and (2); see Toro (2016).

The present formulation allows for a space–time coefficient \(K(x, t)\) in the equations. This enables us to simulate travelling contraction waves through the lymphatic wall by prescribing a space–time-varying contraction state \(s(x, t)\). However, in the present work, we consider the simpler case in which the contraction state is constant throughout the lymphangion, namely \(s = s(t)\), and we also neglect the interaction between adjacent lymphangions. Then, instead of prescribing a trigonometric function for \(s\), here we propose a set of governing ODEs given in Sect. 2.2. We also assume parameters \(K_{\text{min}}(x)\), \(K_{\text{max}}(x)\) and \(p_e(x)\) to be constant. As a result, the source term simplifies in
\[
S(Q, x, t) = S(Q) = \begin{bmatrix} 0 \\ -2 (\gamma + 2) \pi \frac{d}{d} \mu u \end{bmatrix}. \tag{16}\]

The general case of variable material properties poses mathematical Toro and Siviglia (2013) and numerical challenges and requires the use of well-balanced schemes (Müller et al. 2013). The resulting system of PDEs is analysed in Appendix A.

### 2.2 An Electro-Fluid-Mechanical Contraction (EFMC) model

We propose an Electro-Fluid-Mechanical Contraction (EFMC) model for lymphatics, based on the FitzHugh–Nagumo model for action potentials. We assumed that lymphatic
Table 1 Parameters used for the one-dimensional EFMC model for lymph flow.

| Parameter       | Description                              | Value  | Units       | References                      |
|-----------------|------------------------------------------|--------|-------------|---------------------------------|
| **Unknowns**    |                                          |        |             |                                 |
| \( A \)         | Lymphatic cross-sectional luminal (inner) area | \( A(x, t) \) | \( \mu m^2 \) |                                |
| \( q \)         | Lymphatic flow                           | \( q(x, t) \) | \( \mu L \text{ min}^{-1} \) |                                |
| \( v \)         | Excitation variable                      | \( v(t) \) | \( - \)     |                                |
| \( w \)         | Recovery variable                        | \( w(t) \) | \( - \)     |                                |
| \( s \)         | State of contraction (\( 0 \leq s \leq 1 \)) | \( s(t) \) | \( - \)     |                                |
| \( I \)         | Stimulus                                 | \( I(t) \) | \( - \)     |                                |
| \( \xi \)       | State of the lymphatic valve (\( 0 \leq \xi \leq 1 \)) | \( \xi(t) \) | \( - \)     |                                |
| \( q_v \)       | Flow across the lymphatic valve          | \( q_v(t) \) | \( \mu L \text{ min}^{-1} \) |                                |
| **Fluid, material, geometrical, and tube law parameters** | | | | |
| \( \gamma \)    | Parameter for velocity profile           | 2      | \( - \)     | Alastruey (2006)                |
| \( \mu \)       | Lymph dynamic viscosity                  | 1 \( \text{cP} \) | \( - \)     | Bertram et al. (2011)           |
| \( \rho \)      | Lymph density                            | 998 \( \text{kg m}^{-3} \) | \( - \)     | MacDonald et al. (2008)         |
| \( K_{\text{max}} \) | Maximum coefficient                     | 405 \( \text{Pa} \) | \( - \)     | Estimated                       |
| \( K_{\text{min}} \) | Minimum coefficient                     | 105 \( \text{Pa} \) | \( - \)     | Fitted from Bertram et al. (2014a) |
| \( r_0 \)       | Inner radius at zero transmural pressure | 47.7 \( \mu m \) | \( - \)     | Bertram et al. (2014a)          |
| \( A_0 \)       | Cross-sectional area at zero transmural pressure | \( \pi r_0^2 \) | \( \mu m^2 \) |                                |
| \( L \)         | Lymphangion length                       | 3.0 \( \text{mm} \) | \( - \)     | Jamalian et al. (2016)          |
| \( p_e \)       | External pressure                        | 2 \( \text{cmH}_2\text{O} \) | \( - \)     | Jamalian et al. (2016)          |
| \( m \)         | Parameter                                | 0.5 \( - \) | \( - \)     | Fitted from Bertram et al. (2014a) |
| \( n \)         | Parameter                                | −5.0 \( - \) | \( - \)     | Fitted from Bertram et al. (2014a) |
| \( z \)         | Parameter                                | 19.0 \( - \) | \( - \)     | Fitted from Bertram et al. (2014a) |
| \( C \)         | Parameter                                | 1.0e-16 \( - \) | \( - \)     | Fitted from Bertram et al. (2014a) |
| **Electro-Fluid-Mechanical Contraction (EFMC) model** | | | | |
| \( t_{\text{excited}} \) | Required time to perform an action potential | \( \approx 2 \) \( \text{s} \) | \( - \)     | Estimated                       |
| \( t_{\text{activation}} \) | Time required to activate an action potential | \( \text{Eq. (31)} \) \( \text{s} \) | \( - \)     |                                |
| \( f_{\text{min}} \) | Minimum frequency at circumferential stretch \( \hat{\lambda}_a = 1 \) | 3.0 \( \text{min}^{-1} \) | \( - \)     | Gashev et al. (2004)            |
| \( f_{\text{Ca}} \) | Maximum frequency at circumferential stretch \( \hat{\lambda}_a = \lambda_{Ca} \) | 20.0 \( \text{min}^{-1} \) | \( - \)     | Gashev et al. (2004)            |
| \( R_I \)       | Radius of the activation region          | 0.1 \( - \) | \( - \)     | Estimated                       |
| \( n_{Ca} \)    | Stretch-activation parameter             | 20 \( - \) | \( - \)     | Estimated                       |
| \( \lambda_{Ca} \) | Circumferential stretch at which the contraction frequency is \( f_{Ca} \) | 2.784 \( - \) | \( - \)     | Estimated                       |
| \( k_{Ca}^{(1)} \) | Baseline increasing rate of stimulus \( I \) | \( \text{Eq. (34)} \) \( \text{s}^{-1} \) | \( - \)     |                                |
| \( k_{Ca}^{(2)} \) | Stretch-activated increasing rate of stimulus \( I \) | \( \text{Eq. (34)} \) \( \text{s}^{-1} \) | \( - \)     |                                |
| \( k_{rel} \)   | Decreasing rate of the stimulus \( I \)  | 10 \( \text{s}^{-1} \) | \( - \)     | Estimated                       |
| \( a_1 \)       | Parameter                                | 100 \( \text{s}^{-1} \) | \( - \)     | Estimated                       |
| \( a_2 \)       | Parameter                                | 0.5 \( - \) | \( - \)     | Estimated                       |
| \( a_3 \)       | Parameter                                | 25.0 \( - \) | \( - \)     | Estimated                       |
| \( b_1 \)       | Parameter                                | 3.0 \( \text{s}^{-1} \) | \( - \)     | Estimated                       |
| \( b_2 \)       | Parameter                                | 0.0 \( \text{s}^{-1} \) | \( - \)     | Assumed                        |
| \( c_1 \)       | Increasing rate of contraction state \( s \) | 10 \( \text{s}^{-1} \) | \( - \)     | Estimated                       |
| \( c_2 \)       | Decreasing rate of contraction state \( s \) | 3 \( \text{s}^{-1} \) | \( - \)     | Estimated                       |
| \( \tilde{I} \)  | Approximated stimulus required to trigger an action potential | \( \text{Eq. (35)} \) | \( - \)     |                                |
| \( k_{NO} \)    | Contraction inhibition parameter (\( 0 \leq k_{NO} \leq 1 \)) | 0.8 \( - \) | \( - \)     | Estimated                       |
| \( \tau_{NO} \) | Reference wall shear stress              | 6.0 \( \text{dyne cm}^{-2} \) | \( - \)     | Estimated                       |
Table 1 continued

| Parameter | Description | Value | Units | References |
|-----------|-------------|-------|-------|------------|
| \( n_{NO} \) | Wall shear stress inhibition parameter | 1.2 | – | Estimated |

Valve model

| Parameter | Description | Value | Units | References |
|-----------|-------------|-------|-------|------------|
| \( \Delta P_{open} \) | Valve opening threshold pressure difference | 0 | cmH\textsubscript{2}O | Assumed |
| \( \Delta P_{close} \) | Valve closure threshold pressure difference | 0 | cmH\textsubscript{2}O | Assumed |
| \( K_{vo} \) | Rate coefficient valve opening | 1.0 | Pa\textsuperscript{-1} s\textsuperscript{-1} | Estimated |
| \( K_{vc} \) | Rate coefficient valve closure | 1.0 | Pa\textsuperscript{-1} s\textsuperscript{-1} | Estimated |
| \( B \) | Bernoulli resistance | | Eq. (41) | cmH\textsubscript{2}O s\textsuperscript{2} \( \mu \)L\textsuperscript{-2} | – |
| \( L \) | Lymphatic inertia | | Eq. (41) | cmH\textsubscript{2}O s\textsuperscript{2} \( \mu \)L\textsuperscript{-1} | – |
| \( R \) | Viscous resistance to flow | | Eq. (41) | cmH\textsubscript{2}O s \( \mu \)L\textsuperscript{-1} | – |
| \( M_{st} \) | Maximum valve opening (0 \( \leq M_{st} \leq 1 \) ) | 1.0 | – | Mynard et al. (2012) |
| \( M_{rg} \) | Minimum valve closure (0 \( \leq M_{rg} \leq 1 \) ) | 0.0 | – | Mynard et al. (2012) |
| \( L_{eff} \) | Effective length | 0.5 | mm | Estimated |

We adopted the geometrical structure of collecting lymphatics from rat mesentery. Since the parameters of the mathematical model for the electrical activity were not directly available, we fitted the EFMC model parameter to qualitatively reproduce the experimental measurement shown in Telinius et al. (2015).

![Fig. 2](chart.png) Pressure–diameter relation (tube law). Here, we show the tube law used for the lymphatic wall. The parameters were tuned to fit the experimental measurements of Davis et al. (2011) and are found in Table 1. The figure also shows the tube laws at relaxed and contracted states. The external pressure was set to zero here.

Smooth muscle cells act as pacemaker cells (Zawieja 2009) and model the ion dynamics through the FitzHugh–Nagumo model (Nagumo et al. 1962).

The modelling system of ODEs is

\[
\frac{d}{dt} \mathbf{Y} = \mathbf{L} (\mathbf{Y}) ,
\]

where

\[
\mathbf{Y}(t) = \begin{bmatrix} v(t) \\ w(t) \\ I(t) \\ s(t) \end{bmatrix}, \quad \mathbf{L}(\mathbf{Y}) = \begin{bmatrix} a_1 \left[ v(v - a_2) \left( 1 - a_3 v \right) - w + v I \right] \\ b_1 v(1 - v)^2 - b_2 w \\ f_I(\lambda_\theta, \tau, v, w, I) \\ f_s(v, s) \end{bmatrix} ,
\]

and

\[
f_I(\lambda_\theta, \tau, v, w, I) = \begin{cases} \left( \frac{1}{C_a} + k_1^{(1)} \left( \frac{\lambda}{k_C a} \right)^{n_a} \right) f_{NO}(\bar{\tau}) , & \sqrt{v^2 + w^2} \leq R_I , \\ -I_{K_{rel}} , & \sqrt{v^2 + w^2} > R_I , \end{cases}
\]

\[
f_{NO}(\bar{\tau}) = 1 - k_{NO} \left( \frac{2}{1 + \exp \left(-\left| \frac{\bar{\tau}}{k_{NO}} \right| \right)} - 1 \right) ,
\]

and

\[
f_s(v, s) = \begin{cases} +c_1 v (1 - s) , & v > 0 , \\ -c_2 s , & v \leq 0 . \end{cases}
\]

The unknowns of the above system are: the excitation variable \( v(t) \) (membrane potential), the recovery variable \( w(t) \), the stimulus \( I(t) \), and the contraction state \( s(t) \) introduced in Eq. (5). The first two equations in (17) and (18) are based...
on the FitzHugh–Nagumo (FHN) model. In the classical formulation of the FHN model, the stimulus $I$ is constant. In the present work, $I$ varies in time and multiplies the excitation variable $v$. The second equation in (17) has the additional factor $(1 - v)^2$ which increases the rate at which the recovery variable returns to the equilibrium state, reducing the refractory period.

Lymphangions have the capability to change the contraction frequency depending on local fluid dynamic quantities, such as transmural pressure and wall shear stress (Munn 2015). Such capability is phenomenologically modelled by a time evolution of $I$ which is controlled by the function $f_I$. Three mechanisms are here taken into account: (1) environmental calcium influx, (2) stretch-activated calcium influx, and (3) contraction inhibitions induced by WSS. The environmental baseline influx is regulated by the parameter $k^{(1)}_{Ca}$. The stretch-activated calcium influx is regulated by the parameters $k^{(2)}_{Ca}$, $\lambda_{Ca}$, and $n_{Ca}$. The contraction inhibitions induced by WSS are regulated by the function $f_{NO}$, which depends on parameters $k_{NO}$, $\tau_{NO}$, and $n_{NO}$. The function $f_{NO}$ is bounded by $1 - k_{NO}$ and 1, namely

$$\lim_{|\tau| \to +\infty} f_{NO}(\tau) = 1 - k_{NO} \leq f_{NO} \leq 1 = f_{NO}(0).$$

The contraction state $s$ is controlled by the function $f_s$, which ensures that $s$ lies between 0 and 1. Following Telinius et al. (2015), we assume: (1) that the contraction state $s$ increases to 1 during the depolarization phase and (2) decreases to 0 during the repolarization phase. Maximum tension is then attained at the end of the plateau of the action potential of the FHN model (Nagumo et al. 1962). The rate of change of $s$ is controlled by parameters $c_1$ and $c_2$. Functions $f_I$ and $f_{NO}$ are evaluated at the space-averaged circumferential stretch of the vessel (Caulk et al. 2016) and at the space-averaged WSS, respectively, at the current time

$$\bar{\lambda}_{\theta}(t) = \frac{1}{L} \int_0^L \frac{\tau(x, t)}{r_0} \, dx, \quad \bar{\tau}(t) = \frac{1}{L} \int_0^L \tau(x, t) \, dx,$$  

where $L$ is the length of the lymphangion.

Concerning the choice of parameters for the EFMC model, Table 1 gives values used in the present paper. Most of these parameters could not be obtained by fitting the experiments, and therefore we have estimated such values so as to reproduce the shape of the action potential shown in Telinius et al. (2015).

### 2.2.1 Mathematical analysis of the modified FitzHugh–Nagumo model

Here, we analyse the modified FitzHugh–Nagumo model on which the EFMC model is based. First, we find the stationary state solution, and then we study its nature depending on the stimulus $I$. The stationary points are found by solving the following system

$$F_{FHN}(v, w) = \begin{bmatrix} a_1(v - a_2)(1 - a_3v) - w + vl & b_1v(1 - v)^2 - b_2w \end{bmatrix} = \begin{bmatrix} 0 \\ 0 \end{bmatrix}. \tag{24}$$

Assuming $b_2 = 0$, there are two stationary points: $v = w = 0$ and $v = 1, w = (1 - a_2)(1 - a_3) - I$. In our setting, $v$ and $w$ will always be far from $v = 1, w = (1 - a_2)(1 - a_3) - I$. Therefore, we study the case in which $v = w = 0$. The case in which $b_2 \neq 0$ leads to multiple stationary points and is here neglected. To study the nature of the stationary point, one has to evaluate the Jacobian of $F_{FHN}$ at the stationary state and study the sign of its eigenvalues. The resulting eigenvalues are

$$\lambda_{1,2} = \frac{-a_1(a_2 - I) \pm \sqrt{a_1^2(a_2 - I)^2 - 4a_1b_1}}{2}. \tag{25}$$

One can show that: when $I < a_2$, the stationary solution is stable, and therefore action potentials are not automatically triggered; when $I > a_2$, the stationary solution is unstable, and therefore action potentials can be triggered (see Fig. 3).

For a time-varying stimulus $I$, we assume that the needed stimulus $I$ to trigger an action potential lies between a minimum $I_{\min}$ and a maximum value $I_{\max}$, defined as follows:

$$I_{\min} : = a_2, \quad I_{\max} : = a_2 + 2 \sqrt{\frac{b_1}{a_1}}. \tag{26}$$

These two values will be useful to estimate the frequency of contractions of the EFMC model.

### 2.2.2 Qualitative analysis of the EFMC model

As shown in Fig. 4, when the excitation variable $v$ and the recovery variable $w$ are near the stationary state $(\sqrt{v^2 + w^2} < R_I)$, the stimulus $I$ increases as given by (19). When a certain value $I$ is reached (in this case $I_{\min} < I < I_{\max}$), an action potential is triggered: variables $v$ and $w$ perform a cycle, increase in absolute value, and move far from the stationary state $(\sqrt{v^2 + w^2} > R_I)$, and consequently the stimulus $I$ decreases exponentially to zero. The state of contraction $s$ increases until $v > 0$ and then decreases to zero; see Eq. (21). When the action potential ends, variables $v$ and $w$ return to
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\[ a_2 - 2\sqrt{\frac{b_1}{a_1}} \]

\[ a_2 + 2\sqrt{\frac{b_1}{a_1}} \]

\[ \lambda_1, \lambda_2 < 0 \]

\[ \Re(\lambda_1), \Re(\lambda_2) < 0 \]

\[ \Re(\lambda_1), \Re(\lambda_2) > 0 \]

\[ \lambda_1, \lambda_2 > 0 \]

Fig. 3 Stability analysis of the stationary point \((0, 0)\) of the modified FitzHugh–Nagumo model. The nature of the stationary point depends on the stimulus \(I\). For \(I < a_2 - 2\sqrt{\frac{b_1}{a_1}}\) and \(I > a_2 + 2\sqrt{\frac{b_1}{a_1}}\), the eigenvalues of the modified FHN model are real while for \(a_2 - 2\sqrt{\frac{b_1}{a_1}} < I < a_2 + 2\sqrt{\frac{b_1}{a_1}}\), the eigenvalues are imaginary. Action potentials can be periodically triggered when \(I > a_2\).

Fig. 4 Illustration of the EFMC model in the time domain. Results show the excitation variable, recovery variable, contraction state, and the stimulus for two reference lymphatic cycles. Minimum and maximum triggering values \(\tilde{I}_{\min}\) and \(\tilde{I}_{\max}\) are also shown. The horizontal blue and red shaded areas illustrate the unstable spiral-node and the unstable node regions, respectively. The excited and activation regions can be determined by the different shaded colours (blue and yellow). Here, we solved the system of ODEs (17) with initial condition \(v(0) = 0.001, w(0) = I(0) = s(0) = 0\). The parameters of the EFMC model were taken from Table 1, but here we set \(\tilde{\alpha} = 5\) min\(^{-1}\), and we assumed \(\tilde{\alpha} = 2.8165\) and \(\tilde{\tau} = 0\). The colour gradient of the stimulus \(I\) is the same as in Fig. 5.

As shown in Fig. 5, the circle of radius \(R_I\) centred at \(v = w = 0\) divides the phase space into two regions. The space within the circle of radius \(R_I\) is called activation region, while the one outside is called excited region. In the excited region, the numerical solution quickly performs a cycle and the stimulus \(I\) decreases exponentially to zero. In the activation region, the solution tends to the equilibrium state and the stimulus \(I\) increases. The time required for the solution to perform a cycle within the excited region can be numerically quantified and is denoted by \(t_{\text{excited}}\). The time required to activate an action potential is denoted by \(t_{\text{activation}}\).

2.2.3 Analysis of the EFMC frequency

Lymphangions contract differently according to the location of the vessel, the stretch of the lymphatic wall, and wall shear stress feedback (Gashev et al. 2004). In this section, we aim to analyse the frequency of contraction of the EFMC model and to estimate parameters \(k^{(1)}_{Ca}\) and \(k^{(2)}_{Ca}\) in order to prescribe a baseline frequency \(f_{\min}\) and a frequency \(f_{Ca}\) at circumferential stretch \(\tilde{\lambda}_\theta = \lambda_{Ca}\). The time \(t_{\text{total}}\) between two cycles can be written as follows:

\[ t_{\text{total}} = t_{\text{excited}} + t_{\text{activation}} \]  

(27)

and the corresponding frequency is...
Consequently, under the previous assumption, the activation time $t_{\text{activation}}$ required to attain a triggering value $\bar{I}$ is

$$t_{\text{activation}} = \frac{\bar{I}}{k^{(1)}_{Ca} + k^{(2)}_{Ca} \left( \frac{\bar{\lambda}}{\lambda_{Ca}} \right)^n}.$$

The maximum activation time (when $\left( \frac{\bar{\lambda}}{\lambda_{Ca}} \right)^n \approx 0$) and the activation time at $\bar{\lambda}_0 = \lambda_{Ca}$, both at zero WSS ($\bar{\tau} = 0$), are

$$t_{\text{activation}}^{\text{max}} = \frac{\bar{I}}{k^{(1)}_{Ca}}, \quad t_{\text{Ca}}^{\text{activation}} = \frac{\bar{I}}{k^{(1)}_{Ca} + k^{(2)}_{Ca}}.$$

The maximum activation time, corresponding to the minimum frequency, depends on parameter $k^{(1)}_{Ca}$. In our model, the parameter $k^{(1)}_{Ca}$ phenomenologically represents the environmental calcium influxes. Indeed, in the particular case in which there are no environmental calcium influxes ($k^{(1)}_{Ca} = 0$), the activation time becomes infinite, which means that the lymphangion does not autonomously contract. Parameter $k^{(2)}_{Ca}$, on the other hand, phenomenologically regulates the stretch-induced calcium influxes.

Assuming the frequencies $f_{\text{min}}$ and $f_{Ca}$, corresponding to $t_{\text{activation}}^{\text{max}}$ and $t_{\text{activation}}^{Ca}$, respectively, to be known, we have:

$$\frac{1}{f_{\text{min}}} = t_{\text{excited}} + t_{\text{activation}}^{\text{max}}, \quad \frac{1}{f_{Ca}} = t_{\text{excited}} + t_{\text{activation}}^{Ca}.$$

Using (32) and (33), we can explicitly find parameters $k^{(1)}_{Ca}$ and $k^{(2)}_{Ca}$:

We assume that during the activation time, $\bar{\lambda}_0$ and $\bar{\tau}$ are constant in time because the lymphangion is already at the end of the diastolic phase. Thus, the above initial value problem can be solved exactly as

$$I(t) = t \left( k^{(1)}_{Ca} + k^{(2)}_{Ca} \left( \frac{\bar{\lambda}_0}{\lambda_{Ca}} \right)^n \right) f_{NO} \left( \bar{\tau} \right).$$

Here, we assume the triggering value $\bar{I}$ to be the mean value of $I_{\text{max}}$ and $I_{\text{min}}$ defined in Eq. (26), namely
\( I_{\text{mean}} = \frac{I_{\text{max}} + I_{\text{min}}}{2} = a_2 + \sqrt{\frac{b_1}{a_1}}. \) (35)

Numerical results confirmed that this is a good choice, even though \( I_{\text{min}} \) and \( I_{\text{max}} \) can be used as triggering values too. Substituting \( k_{CA}^{(1)} \) and \( k_{CA}^{(2)} \) and the activation time \( t_{\text{activation}} \) defined in (31) into (28), one obtains a frequency function as
\[
f\left(\tilde{\lambda}_2, \tilde{t}, \tilde{I} \right) = \frac{1}{t_{\text{excited}} + t_{\text{activation}}(\tilde{\lambda}_2, \tilde{t}, \tilde{I})}. \] (36)

Then, one can easily prove the following inequalities:
\[
f\left(\tilde{\lambda}_0, 0, \tilde{I} \right) > f\left(\tilde{\lambda}_0, \tilde{t}_1, \tilde{I} \right) > f\left(\tilde{\lambda}_0, \tilde{t}_2, \tilde{I} \right), \ |\tilde{t}_1| < |\tilde{t}_2|. \] (37)

and
\[
f\left(\tilde{\lambda}_{01}, \tilde{t}, \tilde{I} \right) < f\left(\tilde{\lambda}_{02}, \tilde{t}, \tilde{I} \right), \ \tilde{\lambda}_{01} < \tilde{\lambda}_{02}. \] (38)

The first property (37) says that the frequency decreases as WSS increases, and maximum contraction frequency is attained at zero WSS. The second property (38) says that the frequency increases as the circumferential stretch increases. The influence of the EFMC parameters on frequency–pressure and frequency–WSS relationships is shown in Fig. 6. At the transmural pressure \( p_{CA} \approx 11 \text{ cmH}_2\text{O} \) corresponding to \( \tilde{\lambda}_0 = 2.6458 \), the frequency attains value \( f_{CA} \). From Fig. 6, we see that an increment of \( \lambda_{CA} \) lowers the frequency–pressure curve and shifts rightward the transmural pressure at which \( f_{CA} \) is attained. Parameter \( n_{CA} \) changes the shape of the pressure–frequency curve, while \( n_{NO} \) and \( \tau_{NO} \) affect the WSS–frequency curve. Figure 6 shows that it is possible to emulate pressure–frequency and pressure–WSS curves from experimental measurements of a specific lymphangion by adjusting the EFMC parameters.

### 2.3 A lumped-parameter model for lymphatic valves

To model valves in lymphatic vessels, we adopt the work of Mynard et al. (2012), an improvement of Sun et al. (1995). Such model has already been applied to the venous system (Toro et al. 2015). The time variation of the flow across the valve \( q_v (t) \) is modelled as
\[
\frac{d}{dt} q_v = \frac{1}{L(\xi)} \left( \Delta p (t) - R(\xi) q_v - B(\xi) q_v |q_v| \right), \] (39)
where
\[ \Delta p (t) = p_u (t) - p_d (t). \] (40)

Here, \( p_u \) and \( p_d \) are the upstream and downstream pressures, respectively. The above formula can be regarded as the lumped version of a lymphatic vessel of a given length. Coefficients \( B, L, \) and \( R \) are the Bernoulli resistance, the lymphatic inertia, and the viscous resistance to flow, given, respectively, as
\[
B(\xi) = \frac{\rho}{2A_{\text{eff}}^2(\xi)}, \quad L(\xi) = \rho \frac{\ell_{\text{eff}}}{A_{\text{eff}}(\xi)}, \quad R(\xi) = \frac{2 (\gamma + 2) \pi \mu}{A_{\text{eff}}^2(\xi)} L_{\text{eff}}, \] (41)

where \( L_{\text{eff}} \) is the effective length and \( A_{\text{eff}} \) is the effective area, which varies from a minimum value to a maximum value as
\[
A_{\text{eff}}(\xi) = A_{\text{eff, min}} + \xi(t) (A_{\text{eff, max}} - A_{\text{eff, min}}), \] (42)

with \( \xi \in [0, 1] \). Compared to the work of Mynard et al. (2012), we have added the Poiseuille-type viscous losses insofar as the Reynolds number for lymphatics is low (Rahbar and Moore 2011), and therefore this term plays a dominant role. Although the Bernoulli resistance might not contribute significantly to lymphatic flow, in the current work we chose to keep it to maintain a general framework of both high and low Reynolds numbers. The minimum and the maximum effective areas are evaluated as follows:
\[
A_{\text{eff, min}} = M_{rg} A_0, \quad A_{\text{eff, max}} = M_{sl} A_0, \] (43)

where \( M_{rg} \) is a parameter that controls the minimum closure, while \( M_{sl} \) controls the maximum opening. \( A_0 \) is taken as the mean value between the cross-sectional areas at equilibrium of the adjacent lymphangions. The valve state \( \xi (t) \) is governed by the following ODE:
\[
\frac{d}{dt} \xi = f_i (\xi, t)
\]
\[
= \begin{cases} 
K_{vo} (1 - \xi) (\Delta p (t) - \Delta p_{\text{open}}), & \Delta p (t) > \Delta p_{\text{open}}, \\
K_{vc} \xi (\Delta p (t) - \Delta p_{\text{close}}), & \Delta p (t) < \Delta p_{\text{close}}, 
\end{cases} \] (44)

where \( K_{vo} \) and \( K_{vc} \) are the valve opening/closure rates, and \( \Delta p_{\text{open}} \) and \( \Delta p_{\text{close}} \) are the opening/closure threshold pressures. For further details, see also Mynard et al. (2012).

We simplify the valve dynamics by assuming both the opening and closure thresholds to be zero, although it is widely accepted that lymphatic valves are biased to stay open (Davis et al. 2011). The resulting system of ODEs is
\[
\frac{d}{dt} Y = L (Y, t), \] (45)
A one-dimensional mathematical model of collecting lymphatics coupled with an electro-fluid...

Fig. 6 Effects of EFMC model parameters on the pressure–frequency and WSS–frequency relationships. In the top row, we show theoretical results for transmural pressure against frequency varying $f_{Ca}$, $f_{\text{min}}$, $\lambda_{Ca}$, and $n_{Ca}$. In the bottom row, we show theoretical results for WSS against the frequency varying $n_{NO}$, $\tau_{NO}$, and $k_{NO}$. Results are based on expression (36) and assuming a baseline value of $\bar{\lambda} = 2.6458$. The parameters were taken from Table 1.

where

\[
Y(t) = \begin{bmatrix} q_v(t) \\ \xi(t) \end{bmatrix},
\]

\[
L(Y, t) = \begin{bmatrix} \frac{1}{L(\xi)} (\Delta p(t) - R(\xi) q_v - B(\xi) q_v|q_v|) \\ f(\xi, t) \end{bmatrix}.
\]

(46)

3 Results

In this section, we assemble all components of the model and show three selected test problems. Table 1 gives parameters used in the numerical simulations. The numerical methods to solve the coupled system of PDEs and ODEs are described in Appendix B.

3.1 Three representative test problems for lymphatic vessels

In the first test, we show a numerical example of a lymphatic cycle. The second test highlights the frequency–transmural pressure relationship. The third test shows the negative chronotropic effect given by the WSS.

3.1.1 Test 1: representative case of a single lymphangion

Here, we show a representative test of a single lymphangion; see top of Fig. 7, where the EFMC model, the valve model, and the one-dimensional model for lymph flow are coupled. As shown in Fig. 7, as soon as the stimulus $I$ goes beyond the unstable spiral-node region and falls into the unstable node region, an action potential occurs. The fast depolarization at 0.5 s is followed by a plateau period of $\approx 1.2$ s, during which the following phenomena occur in sequence: 1) stimulus $I$ exponentially decreases to zero; 2) the contraction state $s$ increases and reaches its maximum value at the end of the plateau; 3) the internal pressure increases and induces 4) the closure of the upstream valve with a short transient period of backflow caused by the valve closure; 5) the downstream valve opens; 6) the downstream transvalve flow rate increases; and 7) the diameter of the lymphangion decreases. After the hyperpolarization at $\approx 1.6$ s and during the repolarization phase of $\approx 1.4$ s, the contraction state exponentially decreases to zero. This causes the following chain of events: 1) the internal pressure decreases below the downstream pressure $P_{\text{out}}$; 2) the downstream valve closes; 3) there is a short period of reflux from the downstream valve determined by the valve closure which causes 4) the diameter to increase somewhat at $\approx 1.5$ s; 5) the internal pressure
Fig. 7 Test 1: representative case of a single lymphangion. From the top to the bottom frames, we show the following: illustration of the lymphangion, time-varying valve states (open $\xi = 1$ and closed $\xi = 0$), flow rates across the valves, internal pressure, diameter, contraction state, excitation variable, and stimulus. Pressure and diameter were calculated at the centre of the lymphangion. The colours shown from the second to the last panels refer the colour configuration shown in the top panel. In the bottom panel, blue and red shaded areas illustrate the unstable spiral-node and the unstable node regions, respectively. In this test, we used $M = 100$ computational cells to discretize the lymphangion. Boundary pressures: $P_{\text{in}} = 5$ cmH$_2$O and $P_{\text{out}} = 7$ cmH$_2$O. Results are shown over a representative lymphatic cycle.

decreases below the upstream pressure $P_{\text{in}}$; 6) the upstream valve opens; 7) the transvalve flow from the upstream valve increases; and 8) the diameter of the lymphangion increases. From here on, the stimulus starts to increase until the next action potential is triggered.

Diameter decreases almost uniformly throughout the lymphangion, as shown in the space–time representation in Fig. 8. During the systolic phase, flow rate reaches its maxi-

Fig. 8 Test 1: representative case of a single lymphangion (space-time). Here, we show numerical results in space and time for diameter, flow, and pressure. We applied the boundary conditions explained in B.2. Blue and red lines represent the numerical solutions close to the upstream and downstream valves, respectively. The green line depicts the numerical solution at the centre of the lymphangion. In this test, we used $M = 501$ computational cells to discretize the lymphangion. Boundary pressures: $P_{\text{in}} = 5$ cmH$_2$O and $P_{\text{out}} = 7$ cmH$_2$O. Results are shown over a representative lymphatic cycle.
...mum at the downstream side, while it reaches its minimum at the upstream side. The red and blue lines in the flow rate are similar to the valve flow rates shown in Fig. 7. The diameter is practically independent of the space variable. This is due to the approximation $K = K(t)$ throughout the domain. The result shown in Fig. 8 highlights that the mathematical model gives quantitative information throughout the domain of the lymphangion.

### 3.1.2 Test 2: contraction frequency increases as the intraluminal pressure increases

The test shown here was inspired by the experiments performed in several works (Davis et al. 2011, 2012; Scallan et al. 2012) where time-varying pressures were imposed at the boundaries of the collector. More specifically, this test emulates the ramp-wise $P_{out}$ elevation shown in Davis et al. (2012). We simulated a collector composed of one complete lymphangion and two part-lymphangions with an overall number of two valves, and we imposed the following time-varying pressures

$$P_{out}(t) = \begin{cases} \frac{p_1 - p_1}{t_1} (t - t_1) + p_2, & t < t_1, \\ p_2, & t_1 < t < t_{output}. \end{cases}$$

(47)

$$P_{in}(t) = p_{in}.$$  

(48)

where $p_1 = 7\text{ cmH}_2\text{O}$, $p_2 = 15\text{ cmH}_2\text{O}$, $p_{in} = 5\text{ cmH}_2\text{O}$, $t_1 = 60\text{ s}$, $t_{output} = t_1 + 10\text{ s}$. Applying the boundary conditions explained in B.3, the inlet pressure $P_{in}$ was imposed at the leftmost interface of the upstream part-lymphangion, while the output pressure was imposed at the rightmost interface of the downstream part-lymphangion. Only an adverse transaxial pressure difference is taken into account.

Even though the upstream and downstream part-lymphangions contract, their pressures are controlled, as shown in Fig. 9. The downstream pressure (red line) follows the behaviour of the imposed output pressure $P_{out}$, while the upstream pressure (blue line) is almost constantly $P_{in}$. The complete lymphangion responds to these changes in boundary pressures (green line). Initially, both valves closed and open, but when the downstream pressure $P_{out}$ reaches a certain value ($\approx 14\text{ cmH}_2\text{O}$), the lymphangion cannot open the downstream valve anymore. In the space–time representation, our model predicts periods of discontinuous diameters across valves (result not shown), which is consistent with our simplified model for valve dynamics, which admits discontinuities of the diameters.

Since the pressure of the downstream part-lymphangion increases during the numerical simulation, its frequency of contraction rises as well. The contraction frequency of the complete lymphangion is not affected by the increase in the frequency of the downstream part-lymphangion. This comes from having neglected the interaction between adjacent lymphatic vessels in the EFMC model. In reality, the electrical signal in the lymphatic wall would travel through gap junctional communications. The only interaction which would alter the frequency of contractions in the current mathematical model comes from changes in the intraluminal pressure and WSS. Therefore, this computational result highlights that the current EFMC model can only model cases in which lymphangions are electrically decoupled.

In our computational model, lymphatic valves prevent retrograde flow at any transvalve pressure difference, apart from a short transient period determined by the valve closure. This is particularly evident at $\approx 50\text{ s}$, where the lymphangion cannot entirely eject the lymphatic fluid into the downstream part-lymphangion and the diameter increases as the upstream part-lymphangion contracts. These coupled events induce the frequency of contraction of the lymphangion to increase somewhat, shortening the preceding diastole of the very last contraction.

This computational result illustrates the transmural pressure dependence of the frequency of contractions, as incorporated in our mathematical model. Also, the result shows that the lymphangion tries to overcome the downstream time-varying pressure by increasing the end-systolic pressure.

### 3.1.3 Test 3: contraction frequency decreases with increasing WSS

The test proposed here simulates the same lymphatic vessel described in Sec. 3.1.2. We model a collector composed of one complete lymphangion and two part-lymphangions. This test problem highlights the effect of the WSS on the frequency of contractions. As done for test 2, we imposed the following time-varying pressures at the terminal interfaces of the collector

$$P_{out}(t) = \begin{cases} p_1, & t < t_1, \\ \frac{p_{out} - p_1}{t_2 - t_1} (t - t_2) + p_{out}^2, & t_1 < t < t_2, \\ p_{out}^2, & t_2 < t < t_{output}. \end{cases}$$

(49)

$$P_{in}(t) = \begin{cases} p_1, & t < t_1, \\ \frac{p_{in} - p_1}{t_2 - t_1} (t - t_2) + p_{in}^2, & t_1 < t < t_2, \\ p_{in}^2, & t_2 < t < t_{output}. \end{cases}$$

(50)

where $p_1 = 10\text{ cmH}_2\text{O}$, $p_{out}^2 = 5\text{ cmH}_2\text{O}$, $p_{in}^2 = 15\text{ cmH}_2\text{O}$, $t_1 = 10\text{ s}$, $t_2 = t_1 + 40\text{ s}$, and $t_{output} = t_2 + 20\text{ s}$. This test emulates the experimental set-up of Gashev (2002): we imposed a range of transaxial pressure differences maintaining an almost constant average transmural pressure of the lymphangion.
Fig. 9 Test 2: the contraction frequency increases as the intraluminal pressure increases. Time-varying boundary pressures can be found in Eq. (47). See caption of Fig. 7 for explanation of traces. The lymphangion (green lines) tries to overcome the time-varying downstream pressure. The frequency of contraction of the downstream part-lymphangion (red lines) increases with the increase of the imposed boundary pressure. At a certain output pressure (≈ 14 cmH$_2$O), the lymphangion cannot open the downstream valve, forcing the flow through the valves to become zero.

Initially, all lymphatic vessels contract at the same frequency and share the same internal pressure ≈ 10 cmH$_2$O (see Fig. 10). When the upstream pressure $P_{in}$ rises and the downstream pressure $P_{out}$ decreases, the lymphatic valves open, the transvalve flows increase while the transmural pressure of the lymphangion does not change greatly. The increment on the WSS gives a negative chronotropic effect on all lymphatic vessels, decreasing the frequencies of contractions. The complete lymphangion contracts at slower rates as lymph flow increases. Since the upstream part-lymphangion has a greater internal pressure (≈ 15 cmH$_2$O at the centre), its rate of contraction is greater than the remaining vessels. The
Fig. 10 Test 3: contraction frequency decreases with increasing WSS. Time-varying boundary pressures can be found in Eq. (49). See caption of Fig. 7 for explanation of traces. When a favourable pressure gradient occurs, flow increases for all lymphatic vessels, reducing the rate at which the stimulus I increases and decreasing the frequency of contractions even in the upstream part-lymphangion where the transmural pressure increases. For this test, we set $\tau_{NO} = 3 \text{ dyne cm}^{-2}$ and $k_{NO} = 0.9$. downstream part-lymphangion has a lower contraction frequency since its internal pressure is lower. These variations come from changes in the rate of increase in time of stimulus I within the activation region. For instance, the downstream part-lymphangion (red lines) has substantial changes on the dynamics of stimulus I after 27 and 41 s, leading the contraction frequency to decrease to almost $\approx 2 \text{ min}^{-1}$. This result confirms that the mathematical model emulates the experimentally observed effect of the WSS on the frequency of contraction (Gashev 2002).
ESP End-systolic pressure – Pressure at the end of lymphatic contraction cmH 2O

SW Stroke work

CPF Calculated pump flow SV × EF

ESD End-systolic diameter – Diameter at the end of lymphatic contraction µm

ESD End-systolic diameter – Diameter at the beginning of filling µm

ESD End-systolic diameter – Diameter at the end of lymphatic contraction µm

ESD End-systolic pressure – Pressure at the end of lymphatic contraction cmH 2O

EDP End-diastolic pressure – Pressure at the beginning of filling cmH 2O

ESV End-systolic volume \( \frac{L^2}{\pi} ESD^2 \) Volume at the end of lymphatic contraction nL

EDV End-diastolic volume \( \frac{L^2}{\pi} EDD^2 \) Volume at the beginning of filling nL

FREQ Frequency – Frequency of lymphatic contractions min⁻¹

EF Ejection fraction \( 1 - \frac{EDV}{ESV} \) Fractional amount of ejected lymph –

SV Stroke volume EDV - ESV Ejected volume amount nL

FPF Fractional pump flow \( \frac{EF \times FREQ}{ESV} \) Fractional change in lymphatic volume per minute min⁻¹

CPF Calculated pump flow \( SV \times FREQ \) Flow produced by lymphatic contraction µL h⁻¹

PD Pulse diameter EDD - ESD Difference between end-diastolic and end-systolic diameter µm

SW Stroke work \( \int PdV \) Area inside the pressure–volume loop nL cmH 2O

PP Pulse pressure ESP - EDP Pressure amplitude generated by a lymphatic contraction cmH 2O

WSS Time-averaged wall shear stress \( \frac{1}{t_2 - t_1} \int_{t_1}^{t_2} \tau \left( \frac{L}{2}, t \right) dt \) Averaged WSS during a lymphatic cycle dyne cm⁻²

qmean Time-averaged Flow \( \frac{1}{t_2 - t_1} \int_{t_1}^{t_2} q \left( \frac{L}{2}, t \right) dt \) Averaged flow during a lymphatic cycle µL h⁻¹

Table 2 Lymphatic indices

| Index   | Formula                     | Description                                                      | Units |
|---------|-----------------------------|------------------------------------------------------------------|-------|
| ESD     | End-systolic diameter       | Diameter at the end of lymphatic contraction µm                   |       |
| EDD     | End-diastolic diameter      | Diameter at the beginning of filling µm                          |       |
| ESP     | End-systolic pressure       | Pressure at the end of lymphatic contraction cmH 2O               |       |
| EDP     | End-diastolic pressure      | Pressure at the beginning of filling cmH 2O                      |       |
| ESV     | End-systolic volume         | \( \frac{L^2}{\pi} ESD^2 \) Volume at the end of lymphatic contraction nL |       |
| EDV     | End-diastolic volume        | \( \frac{L^2}{\pi} EDD^2 \) Volume at the beginning of filling nL |       |
| FREQ    | Frequency                   | Frequency of lymphatic contractions min⁻¹                        |       |
| EF      | Ejection fraction           | \( 1 - \frac{EDV}{ESV} \) Fractional amount of ejected lymph –   |       |
| SV      | Stroke volume               | EDV - ESV Ejected volume amount nL                               |       |
| FPF     | Fractional pump flow        | \( \frac{EF \times FREQ}{ESV} \) Fractional change in lymphatic volume per minute min⁻¹ |       |
| CPF     | Calculated pump flow        | \( SV \times FREQ \) Flow produced by lymphatic contraction µL h⁻¹ |       |
| PD      | Pulse diameter              | EDD - ESD Difference between end-diastolic and end-systolic diameter µm |       |
| SW      | Stroke work                 | \( \int PdV \) Area inside the pressure–volume loop nL cmH 2O     |       |
| PP      | Pulse pressure              | ESP - EDP Pressure amplitude generated by a lymphatic contraction cmH 2O |       |
| WSS     | Time-averaged wall shear stress | \( \frac{1}{t_2 - t_1} \int_{t_1}^{t_2} \tau \left( \frac{L}{2}, t \right) dt \) Averaged WSS during a lymphatic cycle dyne cm⁻² |       |
| qmean   | Time-averaged Flow          | \( \frac{1}{t_2 - t_1} \int_{t_1}^{t_2} q \left( \frac{L}{2}, t \right) dt \) Averaged flow during a lymphatic cycle µL h⁻¹ |       |

\( t_1 \) and \( t_2 \) correspond to the initial and ending time of the lymphatic cycle, and \( L \) is the lymphangion length. Diameter, pressure, and flow were calculated at the centre of the lymphangion.
Fig. 12 Counterplots of lymphatic indices in the $P_{\text{in}} - P_{\text{out}}$ plane. The indices shown are: frequency of contraction, FPF, CPF, WSS, EF, SV, mean flow, PD, ESD, SW, PP, and EDD. See Table 2 for the definition of the indices. We constructed a grid of points ($P_{\text{out}}, P_{\text{in}}$) with all possible combinations of $P_{\text{in}} = (1, 1.1, \ldots, 13.9, 14)$ and $P_{\text{out}} = (1, 1.1, \ldots, 13.9, 14)$. For each combination of $P_{\text{in}}$ and $P_{\text{out}}$, we simulated a single lymphangion with two terminal valves, $t_{\text{output}} = 160$ s and $M = 20$ computational cells to discretize the lymphangion. The indices were calculated based on last cycle or the last two cycles, as appropriate, and using the values at the centre of the lymphangion. The total number of simulations was $131 \times 131 = 17161$. We applied the boundary conditions as explained in B.2.
surprising because it is well known that contraction waves propagate between lymphangions through gap junctional communications (Zawieja et al. 1993). Moreover, for the sake of simplicity, the gap junctional communications between lymphangions have not been modelled in this paper. EF tends to decrease as $P_{\text{out}}$ increases, while increases when $P_{\text{in}}$ increases. FPF combines both frequency and EF: it increases when $P_{\text{in}}$ rises, and it decreases when $P_{\text{out}}$ increases. The maximum of FPF is when $P_{\text{in}} \approx P_{\text{out}} \approx 8 \text{ cmH}_2\text{O}$. For larger pressures, FPF decreases. The results for FPF are not comparable with those shown by Davis et al. (2012), as in our results the frequency remains constant when $P_{\text{out}}$ rises. The SV and PD follow the same behaviour of EF. ESD increases only when $P_{\text{out}}$ rises, and it remains constant when $P_{\text{in}}$ increases. On the contrary, EDD remains constant when $P_{\text{out}}$ increases, and this is in agreement with Davis et al. (2012). SW is maximum for $P_{\text{out}} \approx 8.5 \text{ cmH}_2\text{O}$ and $P_{\text{in}} \approx 5 \text{ cmH}_2\text{O}$, and it tends to decrease elsewhere. Mean flow and CPF are comparable almost everywhere.

Favourable pressure difference $\Delta P = P_{\text{in}} - P_{\text{out}} > 0$. Here, the upstream and downstream valves remain open for most of the time during the lymphatic cycle (results not shown). Averaged flow exhibits a highly nonlinear behaviour when $\Delta P$ changes sign. Lymph flow is generated only by muscle contractions when $\Delta P$ is negative, with values $< 1 \mu L \text{ min}^{-1}$. However, for positive sign of $\Delta P$, lymph flow is dominated by pressure forces with permanently opened valves, with values over hundreds of $\mu L \text{ min}^{-1}$. Mean flow increases as $P_{\text{in}}$ rises, and it decreases as $P_{\text{out}}$ increases. Subsequently, the WSS rises when $P_{\text{in}}$ increases, and this gives a negative chronotrophic effect on the frequency; this comes from the function $f_{\text{NO}}$ in (19). CPF differs from the mean flow insofar as the CPF only takes into account the flow given by contractions. ESD and EDD increase when $P_{\text{in}}$ and $P_{\text{out}}$ rise. EF, SV, and PD share a similar behaviour and reach their maximum values at $P_{\text{in}} = P_{\text{out}} \approx 6 \text{ cmH}_2\text{O}$.

### 3.4 Sensitivity analyses of the mathematical model

The mathematical model for lymphatic collectors proposed here depends on several parameters which strongly influence the indices shown in Section 3.3. To investigate the influence of each parameter on the indices, we performed two sensitivity analyses based on van Griensven et al. (2006). The methodology is described in Appendix C. Based on the results shown in Sect. 3.3, we performed two sensitivity analyses: one for an adverse pressure difference $\Delta P = P_{\text{in}} - P_{\text{out}} < 0$ (Table 3) and one for a favourable pressure difference $\Delta P = P_{\text{in}} - P_{\text{out}} > 0$ (Table 4).

Adverse pressure difference $\Delta P = P_{\text{in}} - P_{\text{out}} < 0$. As expected, radius at equilibrium $r_0$ positively influences indices SV, CPF, ESD, EDD, WSS, and mean flow. This is not surprising as $r_0$ defines the geometry of the studied collecting lymphatic. Among the parameters of the EFMC model, $a_2$ is the most influential one, followed by $a_3$ and $b_1$. Indeed, $a_2$ is the threshold to change the nature of the stationary point described in Sect. 2.2.1 from stable to unstable. $a_3$ modifies the local maximum peak value of the nullcline represented in Fig. 5 and modifies the maximum value of the recovery variable attained during the action potential. Increments on $b_1$ cause the recovery variable to increase faster during the plateau period, resulting in shorter duration of action potentials. Parameters $K_l$ and $k_{\text{rel}}$ do not significantly influence the studied output parameters. As shown in Figs. 6c and 6d, respectively, of Fig. 6, parameters $\lambda_{\text{CA}}$ and $n_{\text{CA}}$ determine the frequency–pressure relationship, and therefore changes on these parameters significantly affect frequency of contractions, and thus FPF and CPF. Parameters $k_{\text{NO}}, \tau_{\text{NO}}, \gamma_{\text{NO}}$, which are related to WSS and flows, do not affect the lymphatic indices since $\Delta P < 0$. The parameters of the valve model $K_{\text{val}}, K_{\text{vC}},$ and $L_{\text{eff}}$ do not affect the indices. $\mu$ and $\gamma$ only affect the WSS, while the density $\rho$ does not affect the indices. The maximum and minimum coefficients $K_{\text{max}}$ and $K_{\text{min}}$ are related to the slope of the pressure–area relationships (contracted and relaxed) of the collecting lymphatic, consequently affecting the ESD and EDD, respectively, the frequency of contractions, EF, SV, FPF, CPF, and mean flow.

Favourable pressure difference $\Delta P = P_{\text{in}} - P_{\text{out}} > 0$. Compared to the adverse pressure difference case, there are significant changes. The most influential parameters are: $r_0, a_2, b_1,$ and $K_{\text{min}}$. The effects of parameters $k_{\text{NO}}, \tau_{\text{NO}},$ and $n_{\text{NO}}$ are more evident than in the case of an adverse pressure difference. An increase of parameter $k_{\text{NO}}$ decreases the contraction frequency; the greater this parameter, the greater the influence of the contraction inhibition given by the WSS. On the contrary, an increment of parameter $\tau_{\text{NO}}$ increases the frequency. Results for $k_{\text{NO}}$ and $\tau_{\text{NO}}$ are in agreement with Frames 6g and 6f, respectively, of Fig. 6. An increase of parameters $L_{\text{eff}},$ density $\rho,$ dynamic viscosity $\mu,$ and $\gamma$ causes the mean flow to decrease. Between the $K_{\text{min}}$ and $K_{\text{max}},$ the most influential one is $K_{\text{min}},$ as it affects the frequency, SV, FPF, and CPF.

### 4 Discussion

The main contribution of this paper is the construction of a one-dimensional model for lymph flow in deformable lymphatic vessels coupled to a model for muscle contraction with fluid-mechanically dependent frequency, and the numerical implementation of the full model involving the deployment of modern numerical methods for solving the coupled systems of equations.

Most of the computational results shown here are qualitatively comparable to those from zero-dimensional models for lymph flow. For instance, the simulation of a lymphatic
Table 3  Sensitivity analysis of the one-dimensional lymph flow equations coupled to the EFMC model and valve dynamics. Adverse pressure difference case

| Parameter X | Output parameter P(X) | Frequency | EF | SV | FFF | CPF | WSS | ESD | EDD | ESP | EDP | Mean Pressure | Mean Flow |
|-------------|------------------------|-----------|----|----|-----|-----|-----|-----|-----|-----|-----|----------------|-----------|
|             |                        | 50.14 ± 8.29 | 0.75 ± 0.04 | 92.79 ± 27.75 | 7.26 ± 5.96 | 50.46 ± 4.08 | -0.36 ± 0.19 | 115.93 ± 16.28 | 220.69 ± 42.52 | 7.38 ± 0.36 | 5.04 ± 0.10 | 5.18 ± 0.15 | 41.55 ± 31.23 |

The first column from the left shows parameters X of the model while the second column shows their means ± SDs. The first row from the top shows the studied indices P with two terminal valves, \( I_{\text{ave}} = 60 \text{ s} \) and \( M = 20 \) computational cells to discretize the lymphangion. Here, we used \( P_{\text{in}} = 5 \text{ cmH}_2\text{O} \) and \( P_{\text{out}} = 6 \text{ cmH}_2\text{O} \). The indices were calculated based on last cycle or the last two cycles, as appropriate, and using the values at the centre of the lymphangion. Definitions and technical details can be found in Appendix C.
Table 4  Sensitivity analysis of the one-dimensional lymph flow equations coupled to the EFMC model and valve dynamics. Favourable pressure difference case

| $P_{in} - 4$ | $P_{out} = 2$ | Output parameter P(X) | Frequency | EF | SV | FPF | CPF | WSS | ESD | EDD | ESP | EDP | Mean Pressure | Mean Flow |
|-------------|-------------|-----------------------|-----------|---|----|-----|-----|-----|-----|-----|-----|-----|-----------|-------|
| $X$         | $\bar{s}$   |                      | $8.25 \pm 12.10$ | $0.29 \pm 0.10$ | $9.86 \pm 5.33$ | $2.16 \pm 3.30$ | $3.92 \pm 5.63$ | $-10.85 \pm 1.48$ | $97.34 \pm 12.55$ | $16.99 \pm 16.64$ | $3.48 \pm 0.36$ | $3.15 \pm 0.05$ | $3.16 \pm 0.03$ | $61.40 \pm 314.22$ |
| $a$         | $17.31 \pm 7.83$ (μm) | $-3.16 \pm 1.5$ | $-5.86 \pm 19.12$ | $-7.46 \pm 17.17$ | $-8.4 \pm 6.68$ | $-12 \pm 10$ | $-3.16 \pm 1.5$ | $-5.86 \pm 19.12$ | $-7.46 \pm 17.17$ | $-8.4 \pm 6.68$ | $-12 \pm 10$ | $-0.5 \pm 0.2$ | $45.9 \pm 251.2$ |
| $b$         | $0.83 \pm 17.06$ (s⁻¹) | $1.6 \pm 0.1$ | $6.7 \pm 7.7$ | $17 \pm 21$ | $24.1 \pm 16.5$ | $28.4 \pm 25.3$ | $-0.5 \pm 0.2$ | $45.9 \pm 251.2$ |
| $c$         | $24.84 \pm 14.41$ (s⁻¹) | $-7.1 \pm 3.6$ | $15 \pm 17$ | $-8.4 \pm 6.68$ | $-9.7 \pm 9.1$ | $-1.1 \pm 1.3$ | $-0.5 \pm 0.2$ | $45.9 \pm 251.2$ |
| $e$         | $3.6 \pm 0.51$ (s⁻¹) | $-8.6 \pm 13.0$ | $-11.4 \pm 17.1$ | $-12.9 \pm 19.7$ | $-1.1 \pm 0.9$ | $-0.5 \pm 0.2$ | $45.9 \pm 251.2$ |
| $f$         | $0.1 \pm 0.02$ (s⁻¹) | $1.5 \pm 2.3$ | $2.1 \pm 3.0$ | $2.4 \pm 3.7$ | $-0.5 \pm 0.2$ | $45.9 \pm 251.2$ |
| $g$         | $9.5 \pm 17.2$ (s⁻¹) | $-8.6 \pm 13.0$ | $-11.4 \pm 17.1$ | $-12.9 \pm 19.7$ | $-1.1 \pm 0.9$ | $-0.5 \pm 0.2$ | $45.9 \pm 251.2$ |
| $h$         | $10.0 \pm 1.16$ (s⁻¹) | $-8.6 \pm 13.0$ | $-11.4 \pm 17.1$ | $-12.9 \pm 19.7$ | $-1.1 \pm 0.9$ | $-0.5 \pm 0.2$ | $45.9 \pm 251.2$ |
| $k$         | $2.7 \pm 0.48$ (s⁻¹) | $-8.6 \pm 13.0$ | $-11.4 \pm 17.1$ | $-12.9 \pm 19.7$ | $-1.1 \pm 0.9$ | $-0.5 \pm 0.2$ | $45.9 \pm 251.2$ |
| $L_{NO}$    | $0.49 \pm 0.09$ (s⁻¹) | $-8.6 \pm 13.0$ | $-11.4 \pm 17.1$ | $-12.9 \pm 19.7$ | $-1.1 \pm 0.9$ | $-0.5 \pm 0.2$ | $45.9 \pm 251.2$ |
| $t_{NO}$    | $5.97 \pm 105$ (s⁻¹) | $29.4 \pm 7.9$ | $43.1 \pm 17.4$ | $51.0 \pm 30.6$ | $-0.7 \pm 0.5$ | $-0.5 \pm 0.2$ | $45.9 \pm 251.2$ |
| $v_{NO}$    | $1.20 \pm 0.20$ (s⁻¹) | $36.2 \pm 5.3$ | $-23.3 \pm 9.8$ | $-28.1 \pm 17.4$ | $-0.5 \pm 0.2$ | $45.9 \pm 251.2$ |
| $K_{a}$     | $1.0 \pm 0.18$ (s⁻¹) | $-36.2 \pm 5.3$ | $-23.3 \pm 9.8$ | $-28.1 \pm 17.4$ | $-0.5 \pm 0.2$ | $45.9 \pm 251.2$ |
| $K_{b}$     | $1.0 \pm 0.18$ (s⁻¹) | $-36.2 \pm 5.3$ | $-23.3 \pm 9.8$ | $-28.1 \pm 17.4$ | $-0.5 \pm 0.2$ | $45.9 \pm 251.2$ |
| $K_{c}$     | $1.0 \pm 0.18$ (s⁻¹) | $-36.2 \pm 5.3$ | $-23.3 \pm 9.8$ | $-28.1 \pm 17.4$ | $-0.5 \pm 0.2$ | $45.9 \pm 251.2$ |
| $L_{HF}$    | $49.5 \pm 83.98$ (μm) | $11.8 \pm 4.5$ | $-68.1 \pm 15.7$ | $-12.9 \pm 9.0$ | $-39.0 \pm 28.9$ | $27.7 \pm 4.4$ | $-6.7 \pm 3.8$ | $-4.2 \pm 0.4$ | $-0.7 \pm 0.2$ | $-4.4 \pm 0.4$ | $-0.9 \pm 0.3$ | $45.9 \pm 251.2$ |
| $P$         | $99.9 \pm 175.32$ (s⁻¹) | $0.7 \pm 2.5$ | $0.5 \pm 1.5$ | $1.4 \pm 4.5$ | $14 \pm 0.3$ | $-0.7 \pm 0.2$ | $-4.4 \pm 0.4$ | $-0.9 \pm 0.3$ | $45.9 \pm 251.2$ |
| $\gamma$    | $2.0 \pm 0.34$ (s⁻¹) | $-1.1 \pm 2.4$ | $-0.8 \pm 2.0$ | $-3.3 \pm 4.3$ | $-2.7 \pm 0.5$ | $-0.7 \pm 0.2$ | $-4.4 \pm 0.4$ | $-0.9 \pm 0.3$ | $45.9 \pm 251.2$ |
| $K_{out}$   | $100.55 \pm 68.66$ (Pa) | $30 \pm 4.5$ | $22.3 \pm 7.1$ | $43 \pm 16.5$ | $20.8 \pm 9.1$ | $-0.7 \pm 0.2$ | $-12 \pm 0.3$ | $-0.9 \pm 0.3$ | $45.9 \pm 251.2$ |
| $K_{max}$   | $105.9 \pm 18.61$ (Pa) | $30 \pm 4.5$ | $22.3 \pm 7.1$ | $43 \pm 16.5$ | $20.8 \pm 9.1$ | $-0.7 \pm 0.2$ | $-12 \pm 0.3$ | $-0.9 \pm 0.3$ | $45.9 \pm 251.2$ |

See caption of Table 3 for explanations. Here, we used $P_{in} = 4$ cmH$_2$O and $P_{out} = 2$ cmH$_2$O
cycle shown in Fig. 7 resembles the results shown in Fig. 10 of Bertram et al. (2014a). This is indeed not surprising as zero-dimensional models are special cases of one-dimensional models; the latter, however, exhibit the additional ability of accurately capturing wave propagation and transport features, which are badly smeared by zero-dimensional models, as demonstrated in Borsche and Kall (2016). Under resting conditions and average values, zero-dimensional models are an optimal choice in terms of resolution, simplicity, and computational times. However, such models would be of limited accuracy for spatial resolution of flow quantities and especially under postural changes as the nonlinear terms could play a significant role. In this regard, pathological cases and abnormal pressure wave propagation can be studied through the one-dimensional approach at a higher but still acceptable computational cost.

There are so far just a few works on computational modelling of the lymphatic electrical activity (Baish et al. 2016; Kunert et al. 2015) in the open literature. Here, building upon existing works, we propose a model for the electrical activity of the lymphatic wall, based on the FitzHugh–Nagumo model, coupled to the vessel wall mechanics. As shown in Fig. 6, the action potential of the EFMC model is divided into four phases: (1) fast depolarization, (2) plateau period, (3) hyperpolarization, and (4) repolarization. The profile of the action potential, for the rat in the present case, resembles well that described by Telinius et al. (2015) for human mesenteric vessels. There are, however, some differences, namely: (1) the plateau duration here is 1.2 s compared to 1.7 ± 0.2 s and (2) there are no spikes preceding and following the plateau phase. The overall agreement is encouraging even though the works are for different species. The shape of the pressure variation during a lymphatic contraction mimics the pressure measurements by Davis et al. (2012), where a fast increase of the internal pressure is followed by an exponential-like pressure decay. Compare the internal pressure of the lymphangion of Fig. 9 at t ≈ 60 s with Fig. 6 of Davis et al. (2012).

Lymphatic constrictions are a complex phenomenon. The activation of an action potential and the subsequent lymphatic constriction depend on local fluid dynamic quantities, such as transmural pressure and wall shear stress (Munn 2015). The dynamics of frequencies in bovine mesenteric vessels were described by McHale and Roddie (1976) by varying the intraluminal pressure. The authors showed that the frequency of contractions increases as the circumferential stretch increases. Gasheev (2002) studied mesenteric lymphatics in response to imposed flow and showed that the frequency dropped from 9.0 ± 1.6 to 3.1 ± 1.4 min⁻¹ when flow changed from zero to a positive value given by a transaxial pressure difference of 7 cmH₂O. Both features are incorporated by our computational model. The frequency of constriction in the EFMC model strongly depends on both circumferential stress and wall shear stress, as illustrated in Figs. 9, 10, and 11, and the frequency–pressure and frequency–WSS curves can be modified so as to fit experimental measurements and regional variability, as demonstrated in Fig. 6.

The occurrence of lymphatic constrictions in a network of lymphangions is challenging to model. Jamalian et al. (2016) studied the effect on the time-averaged flow of the temporal coordination of constrictions in different vessels in a branched network. Bertram et al. (2017) proposed a formula of the transmural pressure–frequency dependence through experimental measurements, for a single lymphangion. Caulk et al. (2016) proposed a frequency–pressure relationship based on the experiments performed by Davis et al. (2012) and a frequency–WSS relationship which aims to maintain an averaged homeostatic WSS value. However, for a network of lymphangions, the following problem arises: how can we prescribe refractory periods and time delays, including both transmural pressure and wall-shear-stress regulatory mechanisms? The EFMC model of this paper represents an attempt to solve this problem. The governing laws of the EFMC model naturally trigger action potentials by local fluid dynamic quantities and provide the contraction state s. This gives each lymphangion the autonomous capability to trigger a lymphatic contraction, which is desirable for a network of lymphangions.

Lymphatic valves perform an important function for lymphatic homeostasis, as their primary role is to prevent backflow. The forward flow resistance associated with an open valve state has been the subject of studies, as it is extremely complicated to acquire measurements on these microvessels at low pressure differences Bertram et al. (2014a). The computational model proposed here builds on the previous work of Mynard et al. (2012), is based on a lumped-parameter model of a deformable vessel, and provides the resistance value for flow dynamics. Our valve model depends on the geometrical parameters of the vessel and on the fluid dynamic properties, including the dynamic viscosity, the length of the lymphatic valve, and the cross-sectional area of the lymphangion and has the ability to model flow at both high and low Reynolds numbers. The flow resistance predicted by our mathematical model agrees with reported literature values. At maximal valve opening (ξ = 1), the flow resistance is $R = 2.4594 \times 10^6 \text{ g cm}^{-4} \text{s}^{-1}$, which is comparable with $2 \times 10^6 \text{ g cm}^{-4} \text{s}^{-1}$ used in run 2 of Bertram et al. (2014a) and is fourfold greater than $0.6 \times 10^6 \text{ g cm}^{-4} \text{s}^{-1}$, estimated through experimental measurements by Bertram et al. (2014a). Using the geometrical parameters of Wilson et al. (2015) (valve length to $L_{\text{eff}} = 240 \mu m$ and radius at equilibrium to $r_0 = 50 \mu m$), the resistance value is $R = 0.98 \times 10^6 \text{ g cm}^{-4} \text{s}^{-1}$, which closely agrees with $0.95 \times 10^6 \text{ g cm}^{-4} \text{s}^{-1}$ predicted by Wilson et al. (2015). This agreement gives
us a degree of confidence on the results obtained through the valve model and suggests that valves in larger vessels, such as in human lymphatic vessels, can be modelled by our modelling framework.

Regarding limitations of the present model, there are several issues that need to be addressed. Lymphatic contraction modelling poses several challenges. The tensile forces generated by muscle cells result in increased load bearing by muscle cells, decreased load bearing by extracellular matrix and depend on calcium dynamics as well as the length–tension relationship. Previous contraction models (Caulk et al. 2016; Bertram et al. 2016) could not be used in our one-dimensional setting because the resulting systems of equations turned out to be mixed elliptic–hyperbolic and thus ill-posed. Our current model is based on the previous work of MacDonald et al. (2014), is hyperbolic, and mimics the contraction phenomena in terms of pressure–diameter curves. Although the computational results shown in the current work are encouraging, they need to be considered with caution. The model has several drawbacks, as seen from the active component in Eq. (8): 1) it neglects the length–tension relationship; 2) the tensile active stress increases as the circumferential stress increases; and 3) the estimation of the range of variation of coefficients \( K_{\text{min}} \) and \( K_{\text{max}} \) comes only through the external manifestation of the pressure–diameter relationship. Our work could be improved by implementing the contraction model based on the work of others but in a hyperbolic setting (Caulk et al. 2016; Bertram et al. 2016).

The mathematical model for the excitability of the lymphatic wall is based on the FitzHugh–Nagumo model, which might not adequately represent the lymphatic electrical dynamics. We assumed that the lymphatic wall exhibits an electrical behaviour similar to that of cardiac cells. In addition, we assumed lymphatic contractions to be homogeneous throughout the lymphangion. Experimental observations have shown that contractions propagate at a certain speed \( (4 \sim 8 \text{ mm s}^{-1}) \) (Ohhashi et al. 1980), and there can be dephasing between parts of the same lymphangion. Therefore, we might not have taken full advantage of the one-dimensional model to describe lymphatic contractions; the spatial variation contained in the PDEs is not operational. Moreover, adjacent lymphangions do not communicate through a lymphatic valve, in our model. This caused unrealistic behaviours in the computational results, where adjacent lymphangions are regarded as electrically decoupled; see Fig. 9. There are approaches to overcome this problem, used in other contexts, for example adding an ad hoc diffusion term in the FitzHugh–Nagumo (Franzone et al. 2014).

Another important characteristic of lymphatic valves is that they display hysteresis and are biased to stay open even when facing small negative pressure drop. The opening and closure thresholds are assumed to be zero for lymphatic valves in the current work, but experimental measurements have shown that the thresholds depend on transmural pressure. Our assumption might affect the computational results. For instance, the indices shown in Sect. 3.3 might display a higher nonlinear behaviour for different combinations of upstream and downstream pressures. Also, the behaviour of the pressure ramp test shown in Fig. 9 might not be comprised in the behaviours described by Bertram et al. (2017). However, one of our primary goals of this work was to propose in the lymphatic framework a preliminary extension of the valve model (Mynard et al. 2012), leaving room for possible future improvements, such as the incorporation of the formula for the valve threshold proposed by Bertram et al. (2014b).

## 5 Conclusion

In this paper, we have proposed a one-dimensional model for collecting lymphatics coupled to a novel Electro-Fluid-Mechanical Contraction (EFMC) model for dynamical contractions based on a modified FitzHugh–Nagumo model for action potentials and to a lumped-parameter model for valve dynamics. The full model has been implemented in a practical computational set-up. By using the computational model, we quantified several lymphatic indices for a wide range of upstream and downstream pressure combinations. Our theoretical analysis, together with numerical experiments, showed that the contraction frequency strongly depends on both circumferential stretch and wall shear stress. Inspired by reported experiments on cannulated collectors, we carried out numerical computations, the results of which showed good agreement with the observed experimental trend.

The modelling framework proposed here has some distinctive advantages, such as the ability to model flow in deformable vessels at both high and low Reynolds numbers, and in the longer term, could provide the basis for more general models that include networks of arteries, veins, lymphatics, lymph nodes, and other relevant fluid districts. Furthermore, the current mathematical model of collecting lymphatics can be coupled to multi-scale, closed-loop mathematical model of the cardiovascular system and can give quantitative information in healthy and pathological cases. The success of the proposed research directions is strongly limited by the existence of many parameters in models which are difficult to measure or estimate.

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Compliance with ethical standards

Conflict of Interest The authors declare that they have no conflict of interests.

Appendices

A Mathematical analysis of the one-dimensional lymph flow equations

Here, we study the mathematical properties of (10) assuming constant parameters along the lymphatic vessel. The equations in (10) are a generalization of the one-dimensional blood flow equations (Toro 2016). As a matter of fact, the main difference is an additional term in the tube law (3). For this reason, here we summarize the main mathematical structure of the lymph flow equations without proofs. System (10) can be written in quasi-linear form as

$$\partial_t Q + A(Q, t)\partial_x Q = S(Q),$$  \hspace{1cm} (51)

where

$$A(Q, t) = \left[\frac{A}{\rho} K \partial_A \psi - u^2 \left(\frac{1}{2}\right)\right], \quad S(Q) = \left[\frac{0}{-\frac{c}{\rho}}\right].$$  \hspace{1cm} (52)

The eigenvalues of matrix $A$ are

$$\lambda_1 = u - c, \quad \lambda_2 = u + c,$$  \hspace{1cm} (53)

where $c$ is the wave speed

$$c = \sqrt{\frac{A}{\rho} K \partial_A \psi} = \sqrt{\frac{K}{\rho} \left[m \left(\frac{A}{A_0}\right)^m - n \left(\frac{A}{A_0}\right)^n + Cz \left(\frac{A}{A_0}\right)^z\right]}.$$  \hspace{1cm} (54)

We assume parameters $m \geq 0$, $n \leq 0$, $z \geq 0$, and $C \geq 0$ for the tube law. Thus, the wave speed $c$ is always real. The wave speed increases during contraction as it depends on the coefficient $K$. This means that during lymphatic contraction, the lymphatic wall becomes stiffer and waves propagate at a faster rate. The eigenvectors of $A$ are

$$R_1 = \gamma_1 \left[\frac{1}{u - c}\right], \quad R_2 = \gamma_2 \left[\frac{1}{u + c}\right],$$  \hspace{1cm} (55)

where $\gamma_1$ and $\gamma_2$ are arbitrary scaling factors. It can be shown that system (10) is hyperbolic, as the eigenvalues are real and distinct and the eigenvectors $R_1$ and $R_2$ are linearly independent. Following proofs in Toro (2016) and references therein, the $\lambda_1$ and $\lambda_2$ characteristic fields are genuinely nonlinear outside the locus of the following function

$$G \left(\frac{A}{A_0}\right) = m (m + 2) \left(\frac{A}{A_0}\right)^m - n (n + 2) \left(\frac{A}{A_0}\right)^n + Cz (z + 2) \left(\frac{A}{A_0}\right)^z.$$  \hspace{1cm} (56)

With the choice of parameters $m$, $n$, $z$, and $C$ in Table 1, there exists at least one solution of $G \left(\frac{A}{A_0}\right) = 0$. This means that the two characteristic fields are neither genuinely nonlinear nor linearly degenerate. The consequences of this are unclear to the authors and might require further investigations. See LeFloch (2002) for details. The Generalized Riemann Invariants (GRIs) for $\lambda_1$ and $\lambda_2$ characteristic fields are, respectively,

$$\lambda_1 - \text{GRI}: \quad u + \int c \frac{(A)}{A} dA = \text{constant},$$
$$\lambda_2 - \text{GRI}: \quad u - \int c \frac{(A)}{A} dA = \text{constant}.$$  \hspace{1cm} (57)

In the present work, the generalized Riemann invariants will be used to couple valves with lymphangions and to impose the pressure at the terminal interfaces of the collector.

B Numerical methods

Here, we briefly describe the finite volume schemes used for the one-dimensional lymph flow equations, explain how lymphatic valves and lymphangions are coupled, and illustrate the treatment of the boundary conditions at the terminal interfaces of the lymphangion. Then, we summarize the numerical methods used for the valves and the EFMC models.

B.1 A finite volume method for the one-dimensional model

Consider the system of $m$ hyperbolic balance laws

$$\partial_t Q + \partial_x F(Q) = S(Q).$$  \hspace{1cm} (58)

By integrating (58) over the control volume $V = [x_{i-\frac{1}{2}}, x_{i+\frac{1}{2}}] \times [t^n, t^{n+1}]$, we obtain the exact formula

$$Q_i^{n+1} = Q_i^n - \frac{\Delta t}{\Delta x} (F_{i+\frac{1}{2}} - F_{i-\frac{1}{2}}) + \Delta t S_i,$$  \hspace{1cm} (59)

with definitions

$$Q_i^n = \frac{1}{\Delta x} \int_{x_{i-\frac{1}{2}}}^{x_{i+\frac{1}{2}}} Q(x, t^n) dx.$$  \hspace{1cm} (60)
Fig. 13 Framework for a finite volume scheme. Top: illustration of a computational volume for a lymphangion. Bottom: illustration of the space–time control volume.

The numerical source and integral average at interface \( x \) and then formula (59) becomes a finite volume method. To compute the time step \( \Delta t \) of the conserved variable \( Q \) while Eqs. (59) depart from (59) to (60), where integrals are approximated, and then formula (59) becomes a finite volume method, where the approximated integrals in (60) are called numerical flux and numerical source, respectively. Here, index \( i \) runs from 1 to \( M \), where the cell \( i = 1 \) is the leftmost cell with \( x_{1\frac{1}{2}} \) being the first interface, and the cell \( i = M \) is the rightmost cell with \( x_{M\frac{1}{2}} \) being the last interface. See Fig. 13 for an illustration of the finite volume framework. To compute the time step \( \Delta t \), the Courant–Friedrichs–Lewy condition is applied for each \( i \) of the finite volume framework. To compute the time step \( \Delta t \), namely \( \Delta t = \min (\Delta t^j) \), we used a first-order Godunov-type method based on the solution of a classical Riemann problem at the interface.

### B.2 Coupling between valves and lymphangions

Here, we aim to couple valves and lymphangions. For each lymphangion, we need to calculate the numerical flux at the interface in which the valve is located, which can be either \( F_{1\frac{1}{2}} \) or \( F_{M\frac{1}{2}} \) according to Fig. 13. There are three possible modelling configurations for a lymphatic valve. It can be the leftmost or rightmost valve of a collector, or it can be interposed between two lymphangions. In every case, the flow across the lymphatic valve is calculated from (45), where the pressure difference \( \Delta p \) in (39) is evaluated at the current time \( t^n \) using either of the two lymphangions, or one of the lymphangions and a prescribed time-varying pressure. Specifically, at \( t = t^n \) the pressure difference \( \Delta p(t^n) \) is

\[
\Delta p(t^n) = p_u(t^n) - p_d(t^n),
\]

where values \( p_u(t^n) \) and \( p_d(t^n) \) are

\[
p_u(t^n) := \begin{cases} 
  p^u_M, & \text{lymphatic pressure at } i = M, t = t^n, \\
  P_{\text{in}}(t^n), & \text{prescribed upstream pressure at } t = t^n,
\end{cases}
\]

and

\[
p_d(t^n) := \begin{cases} 
  p^d_1, & \text{lymphatic pressure at } i = 1, t = t^n, \\
  P_{\text{out}}(t^n), & \text{prescribed downstream pressure at } t = t^n,
\end{cases}
\]

where pressures \( p^u_M \) and \( p^d_1 \) refer to the upstream and downstream lymphangions, respectively, and \( P_{\text{in}} \) and \( P_{\text{out}} \) are...
prescribed functions of time. The three possible configurations are summarized here

\[
\Delta p(t^n) :=
\begin{cases}
  p_{\text{in}}(t^n) - p^n_1, & \text{leftmost valve}, \\
  p^n_M - p^n_1, & \text{valve between two lymphangions}, \\
  p^n_M - P_{\text{out}}(t^n), & \text{rightmost valve}.
\end{cases}
\]

Once we numerically solve system (45), the flow across the valve at the future time \( t^n + 1 \) is determined.

In the present paper, to find \( A^* \) and calculate the numerical flux at the boundary, we follow the numerical methodology proposed by Alastruey et al. (2008). This method has already been used in Müller and Toro (2014), Contarino et al. (2016). To find \( A^* \), we solve the following nonlinear algebraic equation based on the Riemann invariant

\[
\mathcal{F}(A^*) := \dot{q}^{n+1}_v + A^* \left( -u^* + \beta \int_{A^n}^A \frac{c(\tau)}{\tau} \, d\tau \right) = 0,
\]

using the Newton-Raphson iterative method. \( A^* \) and \( u^* \) are the cross-sectional area and the velocity at the cell adjacent to the boundary at current time \( t = t^n \), \( q^{n+1}_v \) is the known flow rate across the valve, and

\[
\beta = \begin{cases} -1 & \text{downstream lymphangion}, \\ 1 & \text{upstream lymphangion}. \end{cases}
\]

Then, the numerical flux at the boundary is

\[
\mathbf{F}_{1/2} = \mathbf{F}(\mathbf{Q}^*),
\]

where

\[
\mathbf{Q}^* = \begin{bmatrix} A^* \\ q^{n+1}_v \end{bmatrix}.
\]

As shown in Fig. 14, when a valve is interposed between two lymphangions, then the nonlinear problem (67) has to be solved twice: one for the upstream lymphangion (\( \beta = 1 \)) and one for the downstream lymphangion (\( \beta = -1 \)).

**B.3 Imposed pressure at boundaries**

The numerical procedure to impose a pressure in one of the extremities of a lymphatic vessel is similar to the coupling method for valves and lymphangions. Consider a time-varying pressure \( p_I(t) \) at a terminal interface. From pressure \( p_I(t) \), cross-sectional area \( A_I(t) \) can be calculated by using the inverse of the tube law (2). The flow rate \( q^* \) can be found by applying the Riemann invariants as described in B.2, and in this case it can be explicitly calculated as

\[
q^* + \dot{A}_I^* \left( -u + \int_{A_I^n}^A \frac{c(\tau)}{\tau} \, d\tau \right) = 0.
\]

\[
\dot{q}^* = A_I(t^n) \left( u^n - \beta \int_{A^n}^A \frac{c(\tau)}{\tau} \, d\tau \right),
\]

where \( A^n, u^n, \) and \( \beta \) are the cross-sectional area and the velocity at the cell adjacent to the boundary at current time \( t = t^n \) and \( \beta \) is given by Eq. (68). As before, the numerical flux at the boundary is given by (69) with

\[
\mathbf{Q}^* = \begin{bmatrix} A_I(t^n) \\ q^* \end{bmatrix}.
\]

**B.4 Numerical method for the systems of ODEs**

The systems of ODEs (45) and (17) were numerically solved with a second-order implicit Runge–Kutta method using the Lobatto IIIC method. The Butcher tableau is

\[
\begin{array}{c|ccc}
0 & 1/2 & -1/2 & 1/2 \\
1 & 1/2 & 1/2 & 1/2 \\
\hline
1/2 & 1/2 \\
\end{array}
\]

In the next section, we present the coupling of the systems of PDEs and ODEs, through an algorithm description.

**B.5 Complete algorithm**

Here, we provide the complete algorithm to update the solution from time \( t^n \) to time \( t^{n+1} = t^n + \Delta t \). When not specified, the initial conditions are: \( p(x, 0) = P_{\text{in}}(0), u(x, 0) = 0, v(0) = 0.1, w(0) = s(0) = I(0) = 0, \) and \( q_v(0) = \xi(0) = 0 \).

1. Assume data for all variables at \( t = t^n \).
2. Calculate the time step \( \Delta t \) as explained in Section B.1.
3. Evolve the valve flow \( q^* \) and valve state \( \xi \) of each lymphatic valve from time \( t^n \) to \( t^{n+1} \) by applying a
second-order implicit Runge–Kutta method to the system of ODEs (45) and assuming the pressure difference \( \Delta p \) at time \( t^n \).

4. Calculate the numerical fluxes at the boundaries \( \mathbf{F}_{1/2} \) and \( \mathbf{F}_{M+1/2} \) of each lymphangion, as described in Sections B.2 and B.3, using the lymphatic valve flow rates at time \( t^{n+1} \).

5. Using the contraction state \( s \) at the current time \( t^n \), calculate the numerical fluxes \( \mathbf{F}_{i+1/2} \) within each domain of the lymphangions using the SLIC method (Section 14.5.3 of Toro (2009)).

6. Using the contraction state \( s \) at the current time \( t^n \), calculate the numerical sources \( \mathbf{S} \) within each domain of the lymphangions using a second-order method in space and time (Chapter 19 of Toro (2009)).

7. Update the conserved variables \( \mathbf{Q} \) of the PDEs of each lymphangion from time \( t^n \) to \( t^{n+1} \) according to finite volume formula (59).

8. Evolve the variables of the EFMC model of each lymphangion from time \( t^n \) to \( t^{n+1} \) by applying a second-order implicit Runge–Kutta method to the system of ODEs (17) and using the space–time-averaged cross-sectional area and WSS at time \( t^{n+1} \).

The EFMC model and the system of PDEs are coupled through the contraction state \( s \). The variable \( s \) gives the actual value of the coefficient \( K (t) \) in Eq. (5) to be used to calculate the physical flux in Eq. (12). Observe that even though we use second-order methods for every model, the accuracy of the global algorithm is formally of order one. This is caused by the coupling methods. As a matter of fact, we couple the set of ODEs and PDEs using only a first-order method. There are more sophisticated high-order coupling methods in the literature; see, for instance, Borsche and Kall (2016).

### C Sensitivity Analysis

The method is divided into a local and global analysis. In the local analysis, we calculated \( N \) local sensitivity matrices \( S^k_{i,j} \), for \( k = 1, \ldots, N \), as follows: starting from the reference value in Table 1, we randomly varied each parameter from 70% to 130% and obtained a new set of parameters. Here, the baseline value for \( k_{NO} \) was set to 0.5. With this varied set of parameters, we calculated the local sensitivity matrix as follows:

\[
S^k_{i,j} = \left. \frac{\partial P_j (\mathbf{X})}{\partial x_i} \right|_{\mathbf{X}} \times 100, \tag{73}
\]

where \( \mathbf{X} = (x_1, x_2, \ldots, x_m) \) is the vector of the varied model parameters, \( \mathbf{P} = (P_1, P_2, \ldots, P_n) \) is the vector of the lymphatic indices, and \( S^k = \left( S^k_{i,j} \right)_{i,j} \) is local sensitivity matrix. The value \( S^k_{i,j} \) represents the non-dimensional relative change in \( P_j \) to the relative change in parameter \( x_i \), expressed as a percentage. If the model parameter \( x_i \) does not influence index \( P_j \), then \( S^k_{i,j} \) will be zero. Vice versa, if there is a significant influence of \( x_i \) on \( P_j \), then the absolute value of \( S^k_{i,j} \) will be greater than zero. For instance, if 1% change in \( x_i \) leads to 1% change in \( P_j \), then \( S^k_{i,j} \) is 100%. A positive sign of \( S^k_{i,j} \) indicates that an increase of parameter \( x_i \) induces an increase of index \( P_j \). Vice versa, a negative sign of \( S^k_{i,j} \) indicates that an increase of parameter \( x_i \) induces a decrease of index \( P_j \).

Subsequently, in the global analysis, we performed a statistical analysis of \( S^k_{i,j} \) by calculating its mean \( \bar{S}_{i,j} \) and its standard deviation \( \sigma_{i,j} \). A large standard deviation \( \sigma_{i,j} \) indicates a strong correlation of the studied parameter with the remaining parameters in determining the sensitivity index. To calculate \( \bar{S}_{i,j} \) and \( \sigma_{i,j} \), we removed possible outliers by discarding the data below the third percentile and above the 97th percentile.

The partial derivative in Eq. (73) was approximated using a second-order finite difference method based on a percentage change of the parameter as follows:

\[
S^k_{i,j} \approx \frac{\text{sgn}(\epsilon) \ P_j (\mathbf{X}^i, \epsilon) - P_j (\mathbf{X}^i, -\epsilon)}{2\epsilon} \times 100, \tag{74}
\]

where \( \mathbf{X}^{i,\pm\epsilon} = (x_1, x_2, \ldots, x_i (1 \pm \epsilon), \ldots, x_m) \). The parameter \( \epsilon \) was chosen as \( \epsilon = 0.05 \). Compared to van Griensven et al. (2006), we did not construct a stratified sampling space, but rather a simple random variation in the considered range.

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