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Reproducibility study to simulate a chain of collapsible contracting lymphangions with progressive valve closure

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RETROSPECTIVE

Abstract

This paper presents a reproduced computational model of lymphatic collecting vessels. The model was originally introduced by Bertram et al. (2011), and comprises a series of contractile segments, known as lymphangions, interconnected by secondary lymphatic valves. The model focused on elucidating the pumping behavior of contracting lymphangions and deriving pump-characteristic curves, by incorporating pressure-dependent valve resistance, passive elasticity, and active contraction terms in multiple lymphangions. The original model was implemented and solved using MATLAB software. In our work, we reproduce Bertram et al.'s original model within the CellML framework, and present the results.

Keywords: CellML, OpenCOR, computational model, lymphatic vessels, lymphangion, valve

Curated Model Implementation

<http://doi.org/10.36903/physiome.25814500>

Primary Publications

C. D. Bertram, C. Macaskill, and J. E. Moore. Simulation of a chain of collapsible contracting lymphangions with progressive valve closure. *Journal of biomechanical engineering*, 133, 2011.

OPEN ACCESS Reproducible Model

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1 Introduction

The primary paper of Bertram et al. (2011) introduced a model comprising a series of lymphangions connected via inter-lymphangion valves. The objective of their study was to take the first step toward developing a comprehensive model of the lymphatic system. The original contribution of Bertram et al. (2011)'s work lies in incorporating a pressure-dependent valve resistance and the consideration of the constitutive equation of the vessel wall, including passive elasticity and active contraction terms.

The model of Bertram et al. (2011) played a significant role in collecting lymphatic modelling, and subsequent studies (Bertram et al., 2014, 2016, 2017) have improved and validated it by using ex-vivo experimental data published in later years (Davis et al., 2011, 2012). Over the last decade, there has been a surge of interest in lymphatic-related research (Don et al., 2023). Despite this, the lymphatic system remains one of the least explored areas in biomedical research. Freely available and open-source reproducible lymphatic models aim to advance lymphatic research.

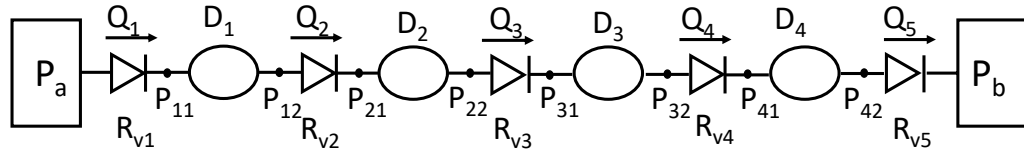


Figure 1. A schematic diagram of the lymphangion-chain model displays the contractile vessel segments, each characterized by its diameter (D). These segments are separated by one-way flow valves, with the flow rate denoted as Q , and the flow resistance as R_v . At each connection point that links these components, effectively covering both the upstream and downstream ends of each segment, the pressure (P) is explicitly defined. P_a and P_b represent constant pressure values at the boundaries.

2 Model description

Figure 1 shows a schematic diagram of a chain of contractile vessel segments linked via secondary valves. Both ends are connected to constant pressure boundary conditions, P_a and P_b . The chain is subjected to uniform external pressure, P_e . The pressure-dependent valve resistance is implemented using a sigmoidal function. Flow inside the vessels is modelled using the Poiseuille flow equation. Additionally, the force balance equation for the vessel walls includes both passive and active contractile components. The resultant ordinary differential equation (ODE) system is non-linear. The parameter values and boundary conditions are listed in Table 1 and Figures 4 and 5 in the captions of the primary paper.

The mathematical model was implemented within the open-source, extensible markup language (XML)-based CellML modeling environment. CellML is widely utilized for representing mathematical models in the field of biology, employing ODE and algebraic equations (Cuellar et al., 2003). All simulations were executed using OpenCOR (Version 0.7) as the simulation platform (Garny and Hunter, 2015). The original CellML file and all the associated code can be accessed by following this link within the PMR: <https://models.physiomeproject.org/workspace/b44>.

3 Computational Simulation

The Bertram2011.cellml file contains the necessary code to execute the simulation. The simulation, conducted over 100 seconds with a time step of 0.0001 seconds, was completed in approximately 4.5 seconds of wall clock time. The CVODE solver was employed, and the simulation was executed on a Windows desktop computer equipped with an Intel Core i7 10th generation CPU. Additionally, the following solver settings were applied: a maximum step of 0.0001 and a total of 5×10^5 steps.

OpenCOR offers the capability to export results in CSV format. When exporting the CSV file for a specific set of parameters and boundary conditions, the following data must be selected from the drop-down menu: time, Q1 to Q5 (Valve_1 to Valve_5), D (Vessels_1 to Vessels_4), Mfunc_1 to Mfunc_4, P11, P12, P21, P22, P31, P32, P41, and P42 values. Subsequently, MATLAB scripts (PlotGenerator_figure_4.m and PlotGenerator_figure_5.m), available in the PMR, were utilized to generate plots after reading the CSV result files. Importantly, the column names of the output CSV file must be changed based on the defined variable names in the PlotGenerator .m files.

The column names should be adjusted as follows:

- Rename "environment | time (second)" to "T"

- Rename "Valve_1 | Q1 (ml_per_s)-Valve_5 | Q5 (ml_per_s)" to "Q1-Q5"
- Rename "Vessel_1 | D (cm)-Vessel_4 | D (cm)" to "D1-D4"
- Rename "Vessel_1 | Mfunc_1 (dyn_per_cm2)-Vessel_4 | Mfunc_4 (dyn_per_cm2)" to "M1-M4"
- Remove vessel numbers and units from pressure values (e.g., "Vessel_1 | P11 (dyn_per_cm2)" becomes "P11").

Save the CSV file as "Bertram_2011_Data_figure4/5.csv". Then, running the MATLAB script will produce the correct figures.

4 Model results

The simulated results for a chain of four lymphangions against two sets of prescribed pressures, $P_a=2275 \text{ dyn cm}^{-2}$ $P_b=2875 \text{ dyn cm}^{-2}$ and $P_a=2275 \text{ dyn cm}^{-2}$ $P_b=2375 \text{ dyn cm}^{-2}$, prescribed in the original work are demonstrated here. Figures 2 and 3 show active tension, diameter variation, pressure values at different locations, and flow rates for each lymphangions. Figures 2 and 3 correspond to Figures 4 and 5, respectively, in the primary paper. We employed the exact parameter values as specified in the primary paper. The parameter values used in the CellML model for Figures 2 and 3 are presented in Table 1.

Table 1. Parameter values used in the CellML model.

Parameter values	Figure 4	Figure 5
P_a	2275 dyn cm^{-2}	2275 dyn cm^{-2}
P_b	2875 dyn cm^{-2}	2375 dyn cm^{-2}
t_01_Vessel_1	0.5	0.5
P_d_01_Vessel_1	50 dyn cm^{-2}	50 dyn cm^{-2}
D_d_Vessel_1	0.025 cm	0.025 cm
t_01_Vessel_2	1	1
P_d_01_Vessel_2	75 dyn cm^{-2}	75 dyn cm^{-2}
D_d_Vessel_2	0.022cm	0.022cm
t_01_Vessel_3	1.5	1.5
P_d_01_Vessel_3	100 dyn cm^{-2}	100 dyn cm^{-2}
D_d_Vessel_3	0.019 cm	0.019 cm
t_01_Vessel_4	2	2
P_d_01_Vessel_4	125 dyn cm^{-2}	125 dyn cm^{-2}
D_d_Vessel_4	0.016 cm	0.016 cm

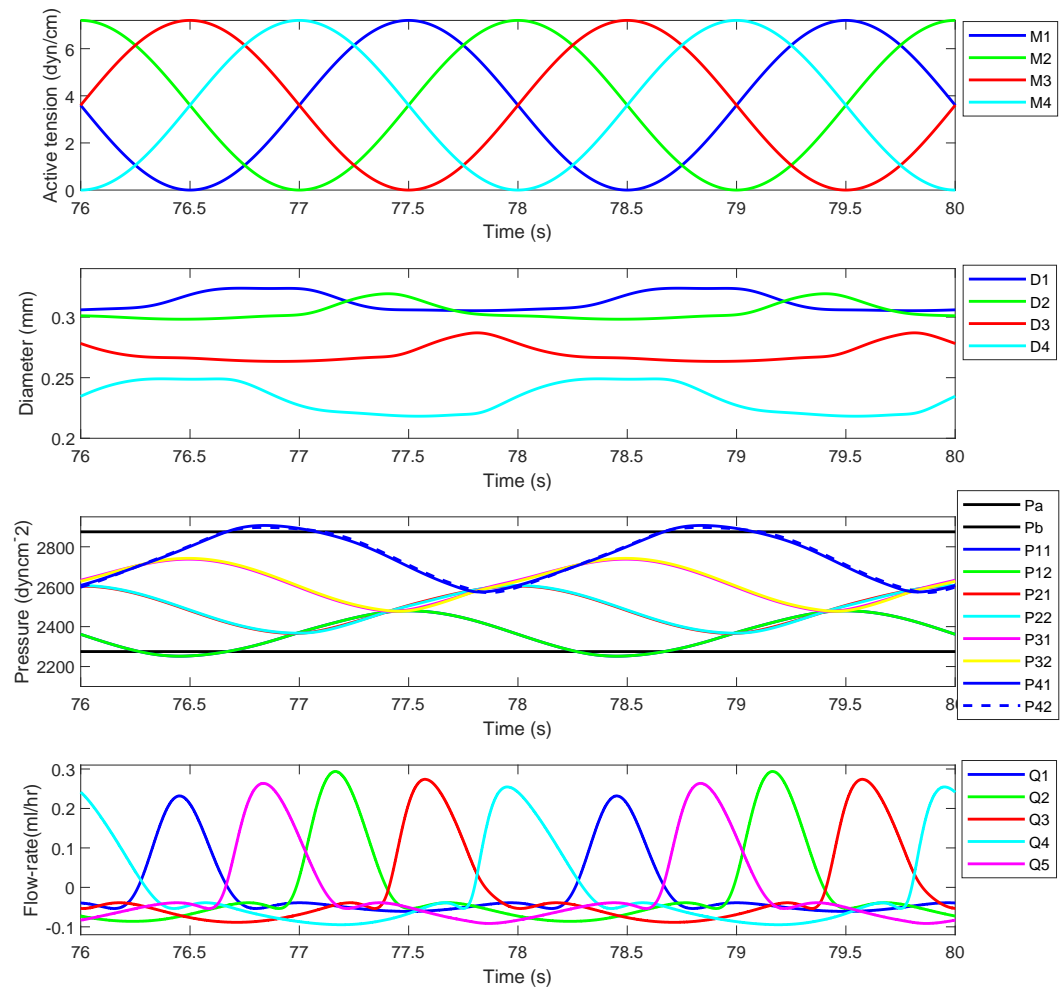


Figure 2. Reproduced results corresponding to Figure 4 in the primary paper, demonstrate the cyclic pumping by a sequence of four lymphangions operating against a pressure differential of 600 dyn cm^{-2} . The top panel illustrates the active tension waveform in each lymphangion. The second panel displays the dynamic variations in the diameters of the four lymphangions. The third panel presents the eight distinct time-varying pressures, with horizontal black lines denoting the inlet and outlet pressures P_a and P_b . The bottom panel illustrates the flow rate through each of the five valves.

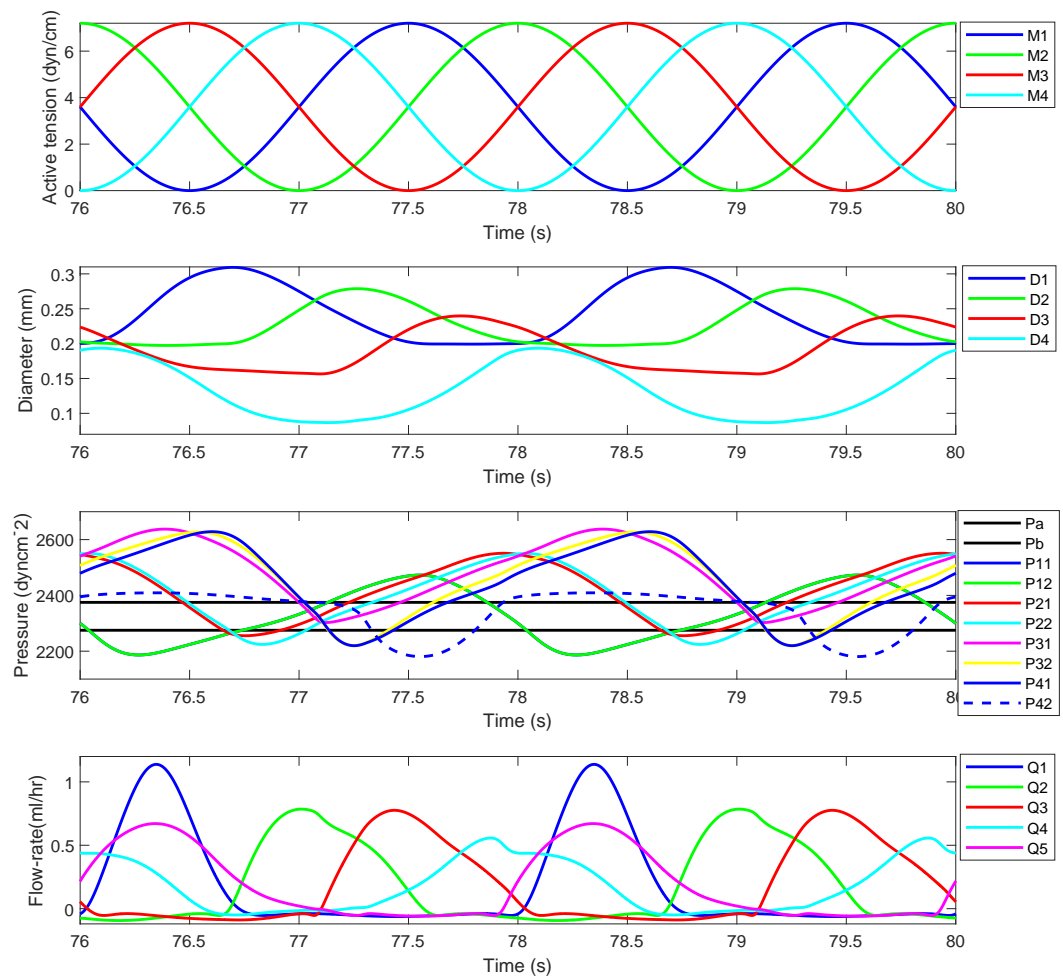


Figure 3. Reproduced results corresponding to Figure 5 in the primary paper, demonstrate the cyclic pumping by a sequence of four lymphangions operating against a pressure differential of 100 dyn cm^{-2} . The top panel illustrates the active tension waveform in each lymphangion. The second panel displays the dynamic variations in the diameters of the four lymphangions. The third panel presents the eight distinct time-varying pressures, with horizontal black lines denoting the pressures at points P_a and P_b . The bottom panel illustrates the flow rate through each of the five valves.

5 Discussion

This lymphangion chain model is an efficient computational framework for comprehending the pumping performance and nonlinear dynamics of lymphatic vessel diameter fluctuations. There is no overlap between the authors of the primary paper and our Physiome paper. Our goal was to test the reproducibility of the model originally published by Bertram et al. (2011), independent of the original authors' involvement. Utilizing the reported parameter values, we have effectively replicated and validated the results presented in Figures 4 and 5 of the primary paper. As previously mentioned, subsequent studies have enhanced the intricacy of this model. Consequently, we will be able to curate additional lymphatic models within the PMR, building upon this reproduced model of Bertram et al. (2011).

6 Acknowledgement

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Reproducibility report for: Reproducibility study to simulate a chain of collapsible contracting lymphangions with progressive valve closure.

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Curation outcome summary: We successfully reproduced Figure 2 and Figure 3 as presented in the manuscript.

Box 1: Criteria for repeatability and reproducibility

■ **Model source code provided:**

- Source code: a standard procedural language is used (e.g. MATLAB, Python, C)
 - There are details/documentation on how the source code was compiled
 - There are details on how to run the code in the provided documentation
 - The initial conditions are provided for each of the simulations
 - Details for creating reported graphical results from the simulation results

■ Source code: a declarative language is used (e.g. SBML, CellML, NeuroML)

- The algorithms used are defined or cited in previous articles
- The algorithm parameters are defined
- Post-processing of the results are described in sufficient detail

Executable model provided:

- The model is executable without source (e.g. desktop application, compiled code, online service)
 - There are sufficient details to repeat the required simulation experiments

■ **The model is described mathematically in the article(s):**

- Equations representing the biological system
- There are tables or lists of parameter values
- There are tables or lists of initial conditions
- Machine-readable tables of parameter values
- Machine-readable tables of initial conditions

■ **The simulation experiments using the model are described mathematically in the article:**

- Integration algorithms used are defined
- Stochastic algorithms used are defined
- Random number generator algorithms used are defined
- Parameter fitting algorithms are defined
- The paper indicates how the algorithms yield the desired output



Box 2: Criteria for accessibility

- Model/source code is available at a public repository or researcher's web site
 - Prohibitive license provided
 - Permissive license provided
 - Open-source license provided
- All initial conditions and parameters are provided
- All simulation experiments are fully defined (events listed, collection times and measurements specified, algorithms provided, simulator specified, etc.)

Box 3: Rules for Credible practice of Modeling and Simulation^a

^aModel credibility is assessed using the Interagency Modeling and Analysis Group conformance rubric:
<https://www.imagwiki.nibib.nih.gov/content/10-simple-rules-conformance-rubric>

- Define context clearly: Extensive
- Use appropriate data: Extensive
- Evaluate within context: Extensive
- List limitations explicitly: Insufficient
- Use version control: Adequate
- Document adequately: Adequate
- Conform to standards: Adequate

Box 4: Evaluation

- Model and its simulations could be repeated using provided declarative or procedural code
- Model and its simulations could be reproduced

Summary comments: Model and source code are available in the associated OMEX archive. This was used in our attempt to reproduce the results presented in the paper. We successfully ran the CellML models with the parameter settings as stated in the manuscript, and ran the associated Matlab script to reproduce the figures as presented.



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