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Mathematical and Computational Modelling of the Lymphatic System: A Review

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Abstract **-** The lymphatic system (LS) is a circulatory system composed of lymph vessels, which are similar to blood vessels. It gets rid of fluid (lymph) that has seeped into the tissues from the blood vessels and sends it back to the circulation through the lymph nodes. The LS's primary purposes are regulating fluid balance of the body and responding to bacteria, cancer cells, and cell products that may otherwise result in illness or diseases. The purpose of this paper is to present a summary of the directions in mathematical and computational modelling of the lymphatic system. A content analysis approach was used to identify relevant journal articles, and the major categories for organising the publications were Theoretical, Mathematical, Computational and Experimental. This paper synthesizes the findings and updates the field with the latest comprehensive reviews, including discussions on recent prototypes not covered in prior reviews. It offers a novel analysis framework that categorizes existing research into more refined sub-topics, facilitating easier navigation and understanding of the field's complexities, and it highlights emerging trends and gaps in the literature, directing future research towards underexplored areas within LS modelling.

Keywords**:** Lymphatic System, Mathematical Modelling, Computational Modelling, and Reduced Order Modelling.

1. Introduction

The LS is essential for immune function and fluid regulation but is not as extensively studied as the circulatory system it supports. It crucially manages fluid overflow and immune surveillance, yet research gaps, particularly in the flow mechanisms and the roles of lymph nodes, hamper effective treatments for related conditions like lymphedema. The LS, lacking a central pump, relies on muscle movements, respiratory changes, and valves to move lymph, which carries proteins, lipids, and immune cells. This movement is vital for draining excess tissue fluid and transporting fats and immune cells, with system efficiency influenced by physical activity and health conditions. Progress in LS modelling is crucial to bridge these knowledge gaps and improve treatments, especially as current models do not fully account for the nuanced functions of lymph nodes. Enhancing these models through advanced mathematical representations and collaborative research could lead to breakthroughs in treating diseases like cancer, where lymphatic function is pivotal.

2. Objectives and Methods

The objectives of this paper are to review literature on the LS as a means of understanding its key components and operational principles and to review the essential features of mathematical and computational models that mimic and analyse the flow patterns in the LS. The studies used in this literature review were published from 1965 to 2024, seen in Fig. 1. Contributions of each article were evaluated from a theoretical, mathematical, computational and experimental perspective as shown in Fig. 2.

Fig. 1: Line Chart showing the number of papers published in 10-year intervals

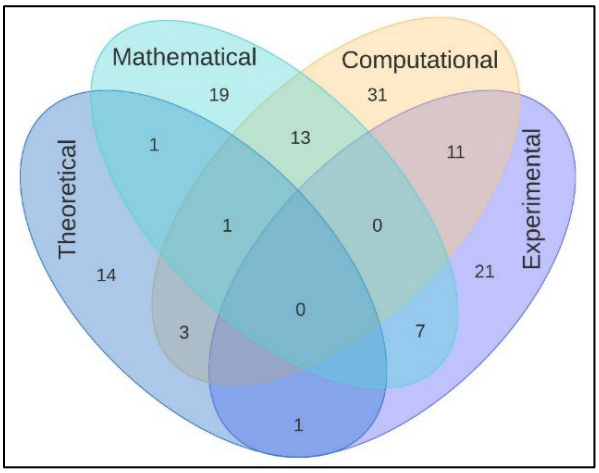

Fig. 2: Venn Diagram showing the types of research used

3. Review of Mathematical Modelling Techniques

3.1. Differential Equations

Differential equations have evolved from foundational tools in early LS models to complex representations capturing the dynamics in both healthy and diseased states. Differential Equation Models can be of two types, lumped parameter and continuum models. Lumped Parameter Models use ODEs to provide discrete, simplified representations of the LS. Despite their simplicity, such models, like those developed by [1,2], offer valuable insights into the general behaviour of the system. They typically assume negligible inertial effects and uniform vessel diameters, simplifying the Navier-Stokes equations into more manageable forms. The use of electrical analogue models [3] represented LV and valves as circuit elements, simplifying complex dynamics into resistance and voltage components to study lymphatic flow. This approach allowed for the integration of multiple vessels into a comprehensive model but often oversimplified the actual non-linear pressure-flow relationships observed in biological systems. In contrast, continuum models use PDEs to account for spatial variations within the LS, offering a more detailed depiction.

In more recent years, models have included detailed elements such as damping and tension in the transmural pressure equations to simulate the behaviour of lymphatic vessel walls more accurately, despite some physiological inaccuracies like the incorrect assumption of circumferential stress by endothelial cells. Models like those by [4] have innovated by incorporating low permeability porous regions alongside free-flowing fluid channels, using pulsatile pressure gradients and finite element methods to better represent lymph node dynamics and the interaction between porous and non-porous regions. Introduced by [5], these models aim to reduce the computational burden associated with PDEs while still capturing essential dynamic behaviours of the LS, such as the autonomous pulsing of lymphangions.

3.2. Network Analysis Models

Network analysis models have significantly advanced our understanding of the LS's topology and flow dynamics. A pivotal advancement in this domain was introduced by [6], who developed a lumped model using a mixed-mode circuit representation. This model facilitated the construction of complex lymphatic networks capable of simulating both transient and steady-state behaviours. It focuses particularly on the role of lymphangions, the key contractile elements in lymph transport, marking a major step forward in modelling lymphatic flow dynamics. Despite its innovations, this model's scope is limited to a single chain of lymphangions, which constrains its broader applicability to the entire lymphatic network.

3.3. Statistical and Probabilistic Models

Statistical and probabilistic models are employed to address the uncertainties and variability inherent in biological systems. Significant advancements in this area include the development of Statistical Atlas-based models, which have been been particularly influential in studying lymphatic drainage in specific anatomical areas such as the skin and breast. Pioneering studies by [7,8] utilized aggregated lymphoscintigraphy data to create models that offer a statistical framework framework for understanding lymphatic drainage patterns. These models are crucial in clinical contexts, aiding in the planning of surgeries and treatments that could affect the LS by providing insights into the probable pathways and rates of of lymphatic drainage from different body areas. The importance of Statistical Models is threefold. They provide a non-invasive method to study the LS, which is beneficial given the system's complex and variable anatomy that is difficult to visualize and understand through direct methods. By aggregating data from various sources, these models can deliver reliable predictions and identify common patterns in lymphatic flow and drainage, enhancing understanding and treatment approaches. As probabilistic models, they incorporate uncertainty and variability in the system's behaviour, which is essential for making precise predictions applicable across different patient groups.

4. Advances in Computational Modelling

In LS research, computational fluid dynamics (CFD) models are essential for simulating the fluid flow of cells, macromolecules, and interstitial fluid within the lymphatic channels. Recent models have integrated aspects such as tissue mechanics and mechano-sensitive feedback to simulate the self-sustaining cyclical contractions of the LS and the fluid dynamics between valve leaflets. [9] developed a model that highlighted the nonlinear dynamics influenced by fluid pressure and intracellular calcium ions, showing how gravity impacts lymphatic drainage. Models like those by [10] incorporate ex vivo data to validate computer simulations of fluid dynamics in LSs, enhancing the realism and applicability of the models. [11] used a combination of imaging and modelling to demonstrate how non-uniform geometries in primary lymphatics can benefit luminal volume expansion. [12] introduced a computational model using a distributed sink term that uniquely represented lymphatic flow rates as a nonlinear function of interstitial pressure, providing insights into the heterogeneous distribution of these pressures across different states.

4.1. Computational Techniques and Methodologies

[13] introduced zero-dimensional and one-dimensional modelling techniques that employ a novel numerical formulation to simplify lymph flow calculations within the collecting network. This approach not only facilitated the exploration of basic network units like divergent and convergent bifurcations but also enabled the simulation of sophisticated synchronization behaviours in anatomically realistic networks, thereby enhancing our understanding of the LS's dynamics. Further contributing to this field, [14] utilized image-based modelling techniques to examine how the internal shape of lymph nodes influences fluid flow pathways. Using SPIM imaging to define the structure and geometry of lymph nodes, and integrating COMSOL Multiphysics for simulations, this method enhanced model parameters and provided greater accuracy based on experimental data. In the realm of 2D modelling, [15] employed COMSOL Multiphysics to investigate mass transport from the interstitium to the LS and to simulate the behaviour of lymphatic valves in lymphedema conditions. This model clarified the factors affecting lymphatic transport and confirmed the functionality of unidirectional valves through comprehensive simulations. Additionally, the integration of graph theory into LS research has opened new avenues for detailed system analysis. [16] utilized this technique to convert anatomical data into oriented graphs, thus enabling a nuanced modelling of the lymphatic network. This approach provided a method to assess the steady-state fluid balance of the lymphatic network, offering a fresh perspective on the overall function of this critical system.

4.2. Agent-based and Multi-scale Models

Agent-based models are increasingly used to simulate the detailed interactions and behaviours within the LS, especially at the cellular level. [17,18] developed models to explore immune response dynamics within lymph nodes, focusing on processes such as chemotaxis, trafficking, and T cell population dynamics. These models were further enriched by the integration with microimaging studies by [19,20], which provided detailed 3D visualizations of the lymph nodes' microvascular networks and tracked T cell movements. Such models demonstrate proficiency in capturing the initial stages of lymph production in lymphatic capillaries but are often constrained by the need for extensive microvascular data and

complex boundary conditions. On the other hand, multi-scale models encompass biological processes across various levels—from sub-cellular to tissue scales. The fully coupled multi-scale model developed by [21], examined lymphatic pumping in rat mesenteric lymphatics. This model integrated contractile forces across scales and simulated periodic contractions triggered by spontaneous calcium oscillations, offering insights that aligned closely with experimental observations. These multi-scale approaches represent significant progress in understanding lymphatic pumping and fluid transport, highlighting the system's complex dynamics from larger to smaller scales.

5. Case Studies and Applications

5.1. Disease Modelling

Disease state models play a crucial role in advancing our understanding of various conditions affecting the LS, such as lymphedema, cancer metastasis, and pulmonary edema. These models, although not plentiful, provide essential insights into the pathological changes within the LS and their implications for disease progression and treatment. Models developed by researchers like [22] have specifically focused on lymphedema and lung lymphatics. The development of these models has been prompted by growing understanding of the role of lymphatic physiology in conditions including obesity, multi-organ failure, cancer metastasis, and cardiovascular disease, thereby aiding the development of targeted therapeutic interventions.

Recent advancements include models focusing on primary valves, collecting vessels, and initial lymphatics. For example, [23] introduced a 2D model that explores fluid dynamics within lung air sac walls, providing new insights into the mechanisms of pulmonary edema and the critical role of interstitial pressures in alveolar septa. The integration of these mathematical models with in vitro experimental data has been pivotal. This approach has demonstrated how the LS, particularly through components like lymphangions, functions under various pressure gradients. Lymphangions can act as both active pumps and passive channels, adapting to environmental pressures to regulate lymph flow effectively. This dynamic ability is especially relevant in conditions with high positive pressure gradients, where lymphangion contractions can actively inhibit lymph flow, suggesting potential therapeutic applications for managing edema [24,25].

5.2. Drug Delivery and Therapeutic Strategies

The development of models for drug delivery within the LS focuses on optimizing the delivery mechanisms using lipid-based particles and nanostructured carriers. These delivery methods are advantageous for targeting diseases directly and circumventing first-pass metabolism in the liver. Factors such as particle size, shape, hydrophobicity, and interstitial properties significantly influence lymphatic drug delivery. For instance, [26] introduced models incorporating 3D discrete continuum networks to simulate lymphatic absorption and blood perfusion in human skin, offering a refined view of biotherapeutic absorption. Drug transport efficacy is analysed using models that simulate lymphatic primary valves and incorporate wall permeability and scalar transport equations. These models use 3D geometrical configurations to adjust various parameters like drug bolus shape and fluid dynamics, facilitating precise simulations of drug absorption and transport.

Customized graph-based models of the LS are being developed to tailor treatments to individual human models, potentially revolutionizing immune responses, especially in HIV. The creation of individualized LS graphs could improve the precision and effectiveness of drug delivery, especially where lymphatic flow is crucial. Studies that explore how lymph flow through lymph nodes impacts immune responses, critical for diseases like HIV. By simulating the intricate cellular interactions and substance transfers within lymph nodes, researchers aim to gain a deeper understanding of the immune mechanisms in HIV-positive patients.

5.3. Surgical Planning and Prosthetics Design

Mathematical and computational models are increasingly utilized in oncology and reconstructive surgery to enhance the design of lymphatic prostheses and refine surgical techniques. These models, particularly through the use of lymphoscintigraphy imaging, have significantly improved surgical planning for cancers such as melanoma and breast cancer. The identification of sentinel lymph nodes (SLNs), which directly drain from primary tumour sites, is critical for effective cancer treatment. Imaging techniques like CT, MRI, SPECT/CT, and PET/CT, integrated into

computational models, have been pivotal in this process. [7] has advanced this area by challenging old assumptions and creating modern atlases for superficial lymphatic drainage, enhancing the precision of SLN mapping and thereby optimizing optimizing surgical intervention strategies.

As knowledge expands, the potential for developing novel lymphatic prosthetics that mimic or support lymphatic functions grows, particularly benefiting individuals with lymphatic damage or dysfunction such as those suffering from lymphedema or post-lymph node dissection. Computational tools like COMSOL Multiphysics facilitate the modelling of lymph propulsion by analysing flow dynamics within the LS's surrounding structures. Computational models are essential for conducting parametric analyses to explore how various factors influence lymph propulsion in healthy and pathological conditions. For instance, the creation of a 2D model for lymph uptake in a single terminal lymphatic vessel has provided insights into the primary lymphatics' operation, informing better management strategies for lymph-related conditions.

6. Methodological Considerations

6.1. Data Sources and Acquisition

In CFD modelling of LS, accurately acquiring anatomical and physiological data is a significant hurdle. Most models rely on simpler lumped parameter models due to these data acquisition challenges, as these models require less detailed information and are easier to develop. However, they may not capture all physiological conditions accurately, such as those influenced by skeletal muscle contractions. Technological advances in imaging, such as μ-CT, have improved the collection of morphological data at the microscale, enhancing lymph propulsion and absorption models. Despite these advancements, developing models that authentically represent the human LS continues to be challenging. Both Lymphangion-Based Models and Whole-Organ Lymphatic Flow Models have limitations; the former may oversimplify the broader LS and face scalability issues, while the latter might not capture detailed microscale dynamics and require extensive data for accuracy. The use of ex vivo and animal study data further limits model applicability to human conditions. Integrating computational models with experimental data from imaging studies like lymphoscintigraphy has been invaluable in optimizing drug delivery systems but highlights the need for more sophisticated models that balance simplicity with the complexity needed to accurately reflect LS behaviour. Addressing these challenges will require the development of advanced models that can integrate data across various biological scales and adapt to physiological variability.

6.2. Model Calibration and Validation Techniques

Calibration and validation are essential processes for ensuring the accuracy and reliability of lymphatic system (LS) models. These steps involve adjusting model parameters to align with empirical data and validating model predictions against real-world or experimental observations. For example, [27] specifically calibrated a model of cyclically contracting lymphangions using data from isolated rat lymphatics. Meanwhile, [28] employed in vivo imaging and ex vivo studies to validate how changes in the length of lymphangion chains affect pressure dynamics within the system. Such studies are vital for correlating model simulations with actual biological behaviours. Advanced modelling techniques like fluid-structure interaction (FSI) models have been developed to closely replicate experimental flow characteristics observed in microfluidic environments. These models, which utilize the immersed boundary approach combined with the Navier-Stokes equations, assess various impacts such as valve compliance on lymphatic flow, both under normal and pathological conditions. This approach not only enhances understanding of lymphatic dynamics but also integrates biomechanical functions into the models. For instance, innovations in mechanobiological valve modelling have provided new insights into the biomechanics of lymphatic flow, including factors like nitric oxide production influenced by wall shear stress.

Since 2011, the development of lumped parameter computational models has increasingly incorporated ex vivo data from collecting LVs to refine and enhance the models. These models have demonstrated strong correlations with experimental data, particularly in analysing the effects of different contraction styles and axial pressure variations on flow rates. Additionally, finite element modelling (FEM) has been used to study mechanical aspects such as the expansion of primary lymphatic vessel gaps under tension. This method aligns well with experimental data illustrating how lymph production rates vary with the frequency of massage applied to tissues, highlighting the dynamic interaction between mechanical forces and lymphatic function.

7. Future Directions

The future of LS modelling is promising, fuelled by advances in computational power and imaging technologies. developments will enable handling larger datasets and more intricate simulations, while improved imaging will yield anatomical and functional data, essential for refining LS models. Multiscale modelling approaches that combine data molecular to organ levels are expected to become more prevalent. These models will improve understanding of how processes at the microscopic level influence the LS on a macroscopic scale, providing a comprehensive view of lymphatic functions and pathologies. Artificial Intelligence (AI) and machine learning will also play a significant role, helping to optimize model parameters, identify patterns in complex datasets, and automate aspects of the modelling process. This will enhance the efficiency and accuracy of models, making them more representative of the actual LS. Innovative research efforts are also contributing to more detailed and biologically accurate models. Studies such as those by [29] are integrating advanced modelling techniques with empirical observations to propose new hypotheses about lymphatic mechanics, such as the 'sliding door' hypothesis for fluid uptake. Lastly, interdisciplinary collaboration will be vital for advancing LS modelling. Integrating knowledge from biology, medicine, physics, and engineering will help create holistic models that more effectively simulate lymphatic functions in health and disease, facilitating the development of targeted therapeutic strategies.

7.1. Prototypes

The development of organ-on-a-chip (OOC) and human-on-a-chip (HOC) systems marks a significant milestone in lymphatic research. These systems utilize microfluidics and tissue bioengineering to simulate human pathophysiology in vitro, offering a more accurate replication of biological processes. OOC systems, for example, use perfusable microfluidic platforms that mimic the vascular compartments of living organisms, enhancing disease modelling, personalized therapy, and drug testing efficacy. Innovations such as the artificial LS (ALS) used in canine osteosarcoma treatment show how mechanical devices can impact clinical outcomes. [30] demonstrated that ALS could enhance blood flow and drug uptake in tumours, although it did not improve median survival. Such findings are vital for understanding the therapeutic potential and limitations of new devices. The lymph node-on-a-chip, proposed by [31], simulates the lymph node microenvironment, providing a dynamic platform for studying immune cell interactions and lymphatic fluid flow in a controlled setting. This innovation is particularly useful for examining immune responses and testing immunotherapeutic strategies. The development of neural network models by [32] for predicting lymph node drainage illustrates another cutting-edge approach in lymphatic modelling. These models can replace traditional physical models with computational ones that require significantly less processing time, facilitating faster and potentially more accurate predictions.

8. Conclusion

This paper has critically reviewed mathematical and computational models that have significantly advanced our understanding of lymphatic functions in health and disease. Techniques like fluid dynamics, network analysis, and probabilistic modelling have offered deep insights into lymphatic flow, tissue interactions, and valve dynamics. The use of multiscale modelling, machine learning, and advanced imaging has enhanced our understanding of disease mechanisms, aiding the development of new therapies and drug delivery systems. The future of LS research hinges on refining these models and overcoming challenges like data scarcity and model complexity. Furthermore, from Fig. 2, the intersections involving multiple research approaches are less populated. To further our understanding of the lymphatic system, future research could benefit from a more interdisciplinary approach that integrates theoretical and mathematical insights with computational and experimental findings.

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