Exploring (Alkyl-ω-ol)triphenyltin(IV) Compounds as Renin Inhibitors: Numerical modelling of diffusion process within finite element liver model

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Abstract: Renin is a key regulator in the renin-angiotensin-aldosterone system (RAAS) and an established therapeutic target for hypertension. Although direct renin inhibitors such as Aliskiren are clinically used, new candidates with improved efficacy are still required. This work investigates the transport dynamics of organotin(IV) compounds (Ph_3SnL1–Ph_3SnL5) within a three-dimensional finite element liver model incorporating an embedded vascular network. Diffusion coefficients, estimated via the Stokes–Einstein relation, ranged from 4.31×10^{-4} mm² s⁻¹ (Ph_3SnL_1) to 3.80×10^{-4} mm² s⁻¹ (Ph_3SnL_5), compared to 3.78×10^{-4} mm² s⁻¹ for Aliskiren. Simulations showed rapid compound penetration from capillaries to tissue, with diffusion kinetics strongly dependent on individual coefficients. Among all, Ph_3SnL1 exhibited the fastest and most homogeneous distribution, while Aliskiren displayed slower transport. These findings highlight the capability of advanced computational modeling to evaluate candidate renin inhibitors and suggest organotin(IV) compounds as promising leads for antihypertensive drug development.

Keywords: renin, hypertension, finite element method, organotin(IV) complexes, liver model

1. Introduction

The renin-angiotensin-aldosterone system (RAAS) is a critical regulator of blood volume, electrolyte balance, and systemic vascular resistance, responsible for acute and chronic alterations [1]. Renin, a protease enzyme secreted by the kidneys, plays a crucial and rate-limiting role in this system, catalyzing the hydrolytic cleavage of angiotensinogen, a precursor protein produced by the liver. Renin plays a crucial role in the RAAS, making it an important target for therapeutic interventions aimed at

regulating blood pressure and treating hypertension. The essence is to inhibit the renin to achieve vasodilation which results in decreased blood pressure and less strains in the heart wall. Although there are well known direct renin inhibitors approved for clinical use (i.e. Aliskiren), the pursuit of superior and less risky renin inhibitors persists because of the intricate and multifaceted characteristics of hypertension management. This study investigates the structural parameters and inhibitory activity of specific organotin(IV) compounds against the renin enzyme, focused on the computational modeling of specified compounds transport within the finite element liver model with immersed blood network. The research and proposed computational method for tracking the diffusive transport of these compounds can provide significant insights into their potential as renin inhibitors and their importance in antihypertensive treatment.

2. Methodology

The development of a three-dimensional computational liver model incorporating an embedded vascular network represents a complex and multi-stage modeling task. The initial phase of the process involves the extraction of DICOM image data obtained from high-resolution micro-CT scans of murine liver tissue. Complete procedure, that precedes the micro-computed tomography (micro-CT), as well as the CT scanning and storing the scanned data, is explained in detail in [2]. The DICOM image datasets are subsequently processed using specialized software packages (Mimics Research Medical 20.0 and Geomagic Studio) to generate three-dimensional reconstruction, resulting in an STL file representing the liver tissue and its vascular network.

In the second phase, the reconstructed STL geometry is imported into an in-house computer-aided design (CAD) platform (https://github.com/miljanmilos/CAD-Solid-Field), originally developed at the University of Kragujevac and BioIRC (Bioengineering Research and Development Center, Kragujevac, Serbia). This CAD environment serves as both a pre- and post-processing tool for three-dimensional modeling and visualization. The computational liver model is then developed using the finite element method, employing smeared modeling techniques in conjunction with the Kojic Transport Models to capture the relevant transport phenomena, summarized in [3-5].

The main idea is to consider a continuum as a space divided into two separated yet connected domains – capillary and tissue. The elementary volumes (dV) occupied by those domains within the finite element at considered (integration) points are rVdV for the capillary and (1 - rV)dV for the tissue domain (rV stand for the volumetric fraction of the capillaries) [6]. Four mutually dependent physical fields are incorporated within the finite element: pressure and concentration in capillaries, and pressure and concentration within the tissue.

All equations necessary to model diffusion transport are incorporated in our computational tools for executing simulations are PAK [7] (Serbian abbreviation - Program za Analizu Konstrukcija; Program for Structural Analysis), high-performance finite element analysis (FEA) software, developed and implemented at the University of Kragujevac, designed for solving complex coupled multi-physics/multi-scale problems.

3. Results

The geometry of the model is shown in Figure 1a. The finite element model consists of 1D pipe FEs for larger vessels (7742 elements), 3D composite smeared elements (38994 elements), and connectivity elements (732 elements) for connecting large vessels with continuum nodes of smeared FEs. The total number of FE nodes is 55110.

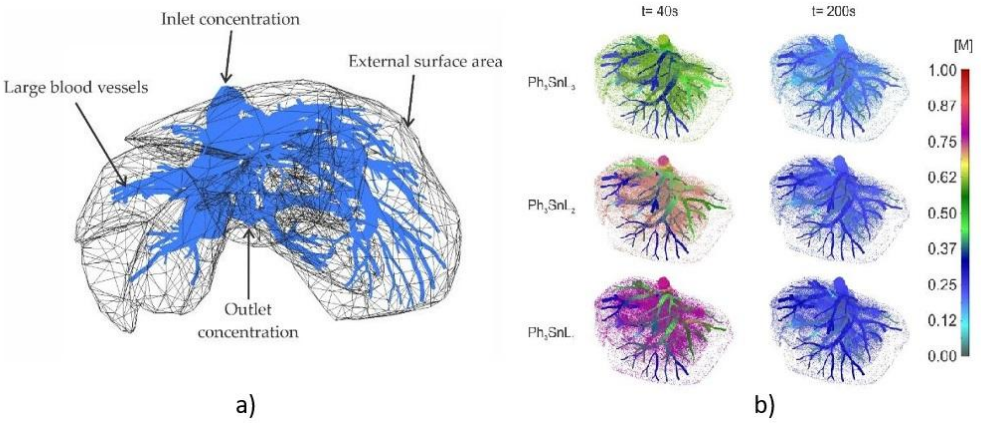

Figure 1. a) The finite element model of the liver represents large blood vessels and the surrounding tissue surface with denoted prescribed inlet and outlet concentrations. b) Mean concentration evolution inside the capillary domain within the liver, represented for three different compounds Ph_3SnL_3, Ph_3SnL_2, and Ph_3SnL_1, respectively, for t = 40 and 200s

The material data applied in this computational model are used as in [8] with the addition of different diffusion coefficients for six different compounds, Ph_3SnL_1–Ph_3SnL_5, and ALI – all used to represent the concentration field within the computational liver model. The diffusion coefficients of all the compounds, estimated using the Stokes-Einstein equation, are as follows: Ph_3SnL_1 (4.31×10^{-4} mm^2 s–1), Ph_3SnL_2 (4.24×10^{-4} mm^2 s–1), Ph_3SnL_3 (3.96×10^{-4} mm^2 s–1), Ph_3SnL_4 (3.87×10^{-4} mm^2 s–1), Ph_3SnL_5 (3.80×10^{-4} mm^2 s–1), and ALI (3.78×10^{-4} mm^2 s–1). The simulation lasts for 1000 s and is divided into 50 time steps. The concentration field for two different time steps, in the vertical plane, within the capillary domain for all the compounds is shown in Figures 1b. At the beginning of the diffusion process compounds steer to diffuse from the capillary to the tissue domain (notable delay in the tissue domain is obvious) while after the 40s (Figure 1b; t = 40s) concentration reaches maxima for all the compounds concerning the differences in concentration values due to the diffusion coefficient values. The end of the diffusion process is shown in (Figure 1b; t = 200s), where the concentration of compounds drops to zero, due to the inlet concentration character.

4. Conclusions

The results yield that the selected organotin(IV) complexes, especially Ph_3SnL_4 and Ph_3SnL_5, possess a very good affinity for renin, positioning them as potential drug candidates for the development of new antihypertensive drugs. The modelling of the vascular network of the liver made possible the simulation of these complexes flowing

through the liver tissues and resulted in the organotin(IV) complexes being homogenously distributed inside the liver vascular system.

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