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LARGE SCALE SIMULATION OF LYMPHATIC MODELS

Giancarlo Storti Gajani[1], Federica Boschetti[1], Andrea Moriondo[2], and Daniela Negrini[2]
[1] Politecnico di Milano, Dipartimento di Elettronica, Informazione e Bioingegneria (DEIB)
[2] University of Insubria, Department of Experimental, Clinical Biomedical Sciences, Italy

SUMMARY

A simple lumped model of the lymphatic system, based on the circuit analogy and implemeted using standard analog netlist languages and Verilog-A, has been presented in [1]. In this paper extention of this model that make it fully aoutonomous and some results concerning the simulation of systems of interconnected lymphangions are presented.

Key words: *lymphatic system modeling, lumped models, large network simulation*

1 INTRODUCTION: BASIC PARAMETERS

The Lymphatic System (LS) has several vital functions; it is a vital part of the circulatory and immune system; among these, one of the most important is, possibly, the regulation of interstitial fluid volume.

One of the main components of the lymphatic system, playing a main role in lymph transport, is the Lymphangion that constitutes a basic element of lymph vessels. Lymphangions actively pump lymph against a pressure gradient and are terminated by secondary valves that prevent reverse flow, even if there is evidence of relevant retrograde flow components in some of the initial lymphatic vessels. To achieve this pumping effects, lymphangions have, in general, an external muscle layer that allows contraction and variation of its internal radius. Most basic lumped models of blood and lymph transport are based on hydraulic resistance, fluid inertia and vessel compliance [2]. Considering a cylindrical vessel of radius r and length l, hydraulic resistance, assuming Reynold number is low, can be modelled using Puisseuille law:

$$R \equiv \frac{p}{q} = \frac{8\mu l}{\pi r^4} \equiv R_0 r^{-4} \tag{1}$$

where p is pressure, q is flux and μ is lymph viscosity, and are summarized in constant R_0 .
Vessel compliance depends on wall stiffness and, in our case, can be defined as the ratio of infinitesimal volume dV (or mass dm) with respect to pressure dp, we have:

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

where s is vessel wall thickness and E its Young's Modulus, summarized in C_0. Fluid inertia has very small values in our case and can be safely neglected.

2 THE MODEL AND ITS IMPLEMENTATION

A natural and effective way to implement any lumped model is based on circuit theory. One of the advantages of this approach is that very fast and efficient simulation programs are readily available. In the circuit analogy, pressure p, flux q and mass m, are, respectively, equivalent to voltage, current and charge; hydraulic resistance and compliance can be modelled using resistors and capacitors (inertia, when needed, is modelled using inductors). Given these analogies a simple equivalent circuit for a lymphangion is shown in Fig. 1. The internal pressure p_c in the lymphangion is represented in this model by the voltage on the capacitor, that represents compliance, the total vessel resistance has been

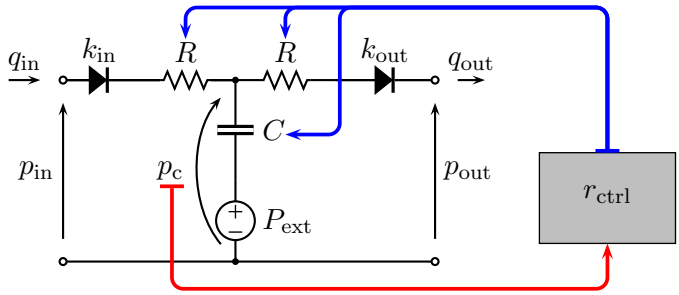

Figure 1: Circuit model of a lymphangion. The r_{ctrl} block controls radius values based on pressure, it is implemented in Verilog-A and described in the text.

then been split in two equal parts R. The secondary valves at each end of the lymphangion are here symbolically represented by two diodes k_{in} and k_{out}, in the simplest implementation ideal diodes can be used, but, if retrograde fluid flow is to be taken into account, more complex non-linear devices with asymmetric hysteresis must be used. Note that the reference pressure for p_{c}, p_{in} and p_{out} is the same; modeling effects due to external pressure P_{ext} phenomena (due to respiration, movement etc.) is modelled by simply adding a pressure (i.e. voltage) generator in series to the capacitor. In nominal conditions this generator is set at zero.

The circuit in Fig. 1 includes a block labeled r_{ctrl} whose input is the internal pressure (and thus stress) and generates systole/diastole events (inhibition effects and shear strain are not yet taken into account). To the authors knowledge, most current lumped models impose radius variations that are "hardwired" and generated by external generators, this can lead to very simple and efficient models, but does not give much insight to the dynamic behaviour of complex networks composed by several lymphangions. The model here presented is fully autonomous.

Consider now the state equations of the circuit in Fig. 1, recalling that the radius is time varying. All elements, except the valves, are linear; this assumption is obviously a simplification (see e.g. [3]). Conservation of mass implies that the capacitor constitutive relation must consider also variations due to compliance value, in other words

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

The behaviour of the "circuit" part of the model is described by a set of ODEs:

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

where k_{in} and k_{out} describe the status function of valves at input and output (in order to allow retrograde flow, an asymmetric tanh() based function has been used). Elements $C = C(r(t)), R = R(r(t))$ are functions of lymphangion radius that changes during contractions and relaxations.

We now assume that the lymphangion can be in two different states:

- **active**: conditions on pressure and or flow have triggered a contraction (systolic) event. Radius reduces with a relatively fast time constant and reaches a minimum radius. Internal pressure will also quickly become quite large so that, eventually, the input valve will close and the output one will open so that lymph will flow.
- **passive**: the lymphangion passively expands or contracts depending on internal pressure, this also corresponds to diastolic behaviour, when the lymphangion will recover after a systolic contraction

Modelling the onset of a systolic event and its end is one of the critical aspects of all lymphatic models. Let's now assume that we have a nonlinear ODE that describes radius behaviour in time as a

function of radius and pressure, i.e. $\dot{r} = f(r, p)$. Substituting Eqs. (1) and (2) in (4) and using chain rule for derivatives we have:

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

$$\dot{r} = f(p, r) \tag{6}$$

simplifying and solving for $\dot{p}$ and $\dot{r}$ we finally have:

$$\dot{p} = \frac{r}{C_0 R_0} \left[k_{\text{in}}(p_{\text{in}} - p) - k_{\text{out}}(p - p_{\text{out}})\right] - \frac{3}{r} f(p, r) \tag{7}$$

$$\dot{r} = f(r, p) \tag{8}$$

radius behaviour must be modeled so that, when in passive conditions, it is stable at a given value that depends, up to a limit value, on pressure. When in active mode, contraction occurs; speed and extents of the contractions depend on pressure and flow in the lymphangion. Time constants of active mode are faster than those of passive mode.

2.1 Pulse triggering mechanism and radius dynamics

When in passive mode the radius will tend to expand as a function of pressure up to a limit value. Assuming pressure is in this case equivalent to an external input, a simple ODE implementing this behaviour is

$$\dot{r} = \alpha(r_t(p) - r) \tag{9}$$

with $r_t(p)$ the "target" radius defined as a function of p and limited by an inferior "nominal" radius r_0, when internal pressure p is in equilibrium with intramural pressure P_{ext}, that, disregarding external effects due to movement, respiration etc. is assumed to be 0, and a maximum radius that is reached only for arbitrarily large pressure values (of course maximum possible pressures will be limited by the model). A simple function implementing this behaviour is:

$$r_t(p) = (r_0 - r_{\max})\mathrm{e}^{\beta(P_{\text{ext}} - p)} + r_{\max} \tag{10}$$

substitution of (10) in (9) finally yields

$$\dot{r} = \alpha(r_{\max} + (r_0 - r_{\max})\mathrm{e}^{\beta(P_{\text{ext}} - p)} - r) \tag{11}$$

Where constant α represents the natural frequency of the passive part of radius behaviour, and constant β is proportional to the "elasticity" of the lymphatic vessel.

The model described by (7) and (11) represents only the passive part of the model behaviour. In this model we assume that the contraction impulse has a fixed time width, so that, when triggered by condition

$$p_c > p_{\text{th}}, \quad \text{with} \quad p_{\text{th}} < p_{\text{in}} < p_{\text{out}} \tag{12}$$

i.e. when internal pressure rises above a pressure threshold value p_{th}, a fixed width impulse is generated and used to control vessel radius. This is modelled by adding to (11) a linear term

$$r_{\text{active}} = \gamma(r_{\min} - r) \tag{13}$$

with $\gamma >> \alpha$, i.e. with a much larger time constant, only for the duration of the systolic phase of the pulse, that is controlled by a "digital" state equation. In (12) we have assumed that $p_{\text{in}} < p_{\text{out}}$, this corresponds to lymph flow against a pressure gradient, i.e. active pumping. In case $p_{\text{in}} > p_{\text{out}}$ the model, as expected, behaves as a simple conduit, with all valves open.

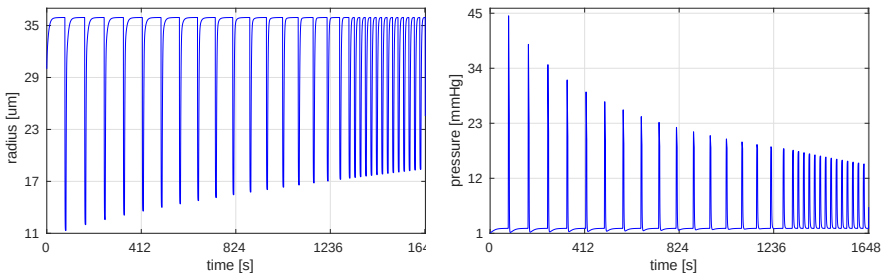

Figure 2: Autonomous radius and pressure response of a single lymphangion to a pressure ramp. As input pressure increases minimum radius decreases and contraction frequency increases.

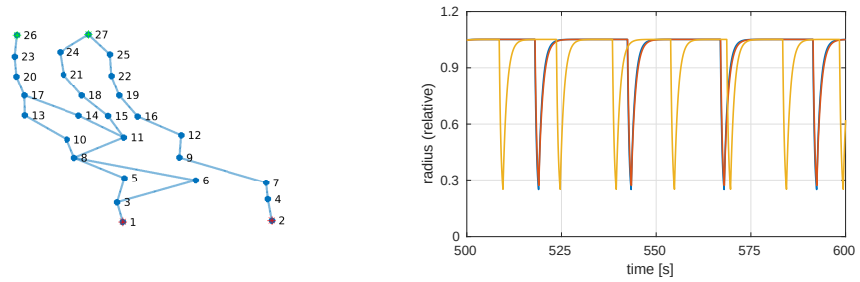

Figure 3: A relatively complex lymphangion network and the radius response along the network. Contraction frequency is not the same in different parts of the network.

3 RESULTS

The model has been implemented in the PAN circuit simulator [4] using its native netlist language and Verilog-A for the behavioural code. A matlab version has also been implemented essentially to fit model parameters validate the code. Basic testing of the model was essentially finalized to check coherence with some basic behaviour patterns found in literature. A first test was made to check results and behaviour with respect to data available in recent litterature such as [5].

Systolic period acceleration and radius modulation as response to a pressure ramp has been observed in the model and is shown in Fig. 2. A complex network of lymphangions has then been generated and simulated using the full model. Results are shown in Fig. 3.

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