Mathematical Model

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Friday 7$^{\text{th}}$ September, 2018

The 1D fluid dynamics model presented here predicts time varying blood pressure and flow at any given location in a bifurcating network of blood vessels (see Figure 2). Each vessel within the network is modeled as an axisymmetric surface of revolution with a deformable surface modeled as a linearly elastic material. Vessels have constant length L and variable radius R and dynamics are predicted in cylindrical polar coordinates (r, θ, x). Geometric properties for the network are extracted from micro-CT images and dynamic flow and pressure are measured over one cardiac cycle in the first vessel.

Equations For Single Vessel

Governing equations are based on conservation of fluid volume and balance of axial momentum in the vessel combined with an equation balancing the forces acting on the vessel walls. Fluid equations are derived by averaging the continuity and axial components of the Navier-Stokes equations in cylindrical coordinates over the cross-sectional area. The resulting one-dimensional (1D) system of hyperbolic partial differential equations (Olufsen *et al.*, 2000, Qureshi *et al.*, 2017) is given by

$$\frac{\partial A}{\partial t} + \frac{\partial q}{\partial x} = 0, \qquad \text{(Continuity equation)} \qquad (1)$$

$$\frac{\partial q}{\partial t} + \frac{\partial}{\partial x}\left(\frac{q^2}{A}\right) + \frac{A}{\rho}\frac{\partial p}{\partial x} = -\frac{2\pi\nu r}{\delta}\frac{q}{A}, \qquad \text{(Axial momentum equation)} \qquad (2)$$

$$p - p_0 = \frac{Eh}{r_0}\left(\sqrt{\frac{A}{A_0}} - 1\right), \qquad \text{(Tube law)} \qquad (3)$$

where $0 \leq x \leq L$ and $0 \leq t \leq T$ are the axial and temporal coordinates and T is the length of the cardiac cycle (assumed constant at $T = 0.11$ s). $p(x,t)$ (mmHg) denotes the blood pressure in the vessel, $p_0 = 0$ is the pressure outside the vessel. $q(x,t)$ (ml/s) is the volumetric flow rate, $A(x,t) = \pi R(x,t)^2\,(\text{cm}^2)$ is the cross-sectional area, $0 < r \leq R(x,t)$

(cm) is the vessel radius, and $A_0 = \pi r_0^2$ is the reference cross-sectional area. The blood density $\rho = 1.057\,(\text{g/ml})$, the kinematic viscosity $\nu = 0.0462\,(\text{cm}^2/\text{s})$, and the boundary layer thickness $\delta = 0.03\,(\text{cm})$ are assumed constant and fixed. Each vessel is defined by its reference radius r_0 (cm), length L (cm) (both given in Table (2)), and vessel stiffness Eh/r_0 (cm^2g/s).

The system of equations is solved using the two-step Lax-Wendroff method. The spatial and time steps for the observations are spaced uniformly, where $\Delta x = 2.5 \times 10^{-2}$ cm and $\Delta t = 1.34 \times 10^{-5}$ s, respectively. The number of spatial points varies based on the length of each vessel (see Table (2) for each vessel's measurements). For each vessel, one spatial location is considered and subsequently the code returns pressure and flow across all time points at one spatial point. The spatial location considered for each vessel is the **midpoint** of the discretized values of x (described above). For more details on the mathematical model and numerical methods described here, please refer to Olufsen *et al.* 2000 and Qureshi *et al.* 2017 (equations (1)-(3) correspond to equations (2)-(3) in Qureshi *et al.* 2017).

Network Construction and Boundary Conditions

The network used for the simulations was obtained by segmenting the micro-CT image of a mouse lung (Vanderpool *et al.* 2014). Though the pulmonary tree is expansive, only 21 of the largest arteries were explicitly modeled to form a network of 1D vessels and the remaining vasculature was lumped into circuit type 0D Windkessel models.

Bifurcation conditions: The network is constructed by connecting vessels at bifurcating junctions. At every bifurcation, one parent and two daughter vessels are connected. By ensuring conservation of volumetric flow rate and pressure as

$$\begin{aligned} q_p(L,t) &= q_1(0,t) + q_2(0,t), \\ p_p(L,t) &= p_{d_1}(0,t) = p_{d_2}(0,t), \end{aligned} \quad \begin{aligned} (4) \\ (5) \end{aligned}$$

where the subscripts p and d_i $(i = 1, 2)$ denote the parent and daughter vessels, respectively.

Inflow condition: The flow $q_{\text{in}}(t)$ over one cardiac cycle, extracted from hemodynamic data, is imposed at the inlet of the first vessel. We assume that predictions are periodic and that the flow is repeated at the onset of each cardiac cycle.

Outflow conditions: At each of the terminal vessels, a Windkessel model (represented by an RCR-circuit) relating pressure and flow is applied at each terminal vessel (see Figures 1 and 2). The Windkessel model can be formulated as a first order ordinary differential equation relating pressure and flow as

$$(p(L,t) - p_c) + R_2 C_p \frac{dp(L,t)}{dt} = (R_1 + R_2) q(L,t) + R_1 R_2 C_p \frac{dq(L,t)}{dt}, \quad (6)$$

where R_1, R_2 (mmHg s/ml) denote resistance and C_p (ml/mmHg) the capacitance. The term p_c denotes the pressure in the capillary beds. We assume that the maximum pressure drop occurs across the Windkessels, implying that $p_c = 0$. Physiologically, R_1 and R_2 represent the resistance due to the proximal and distal vasculature. The sum $R_1 + R_2$ gives the total peripheral resistance R_T and C_p denote the total peripheral compliance of the vascular region beyond each terminal vessel. The right hand side of equation (6) is calculated for each vessel by distributing the $q_{in}(t)$ based on the geometric structure of the network.

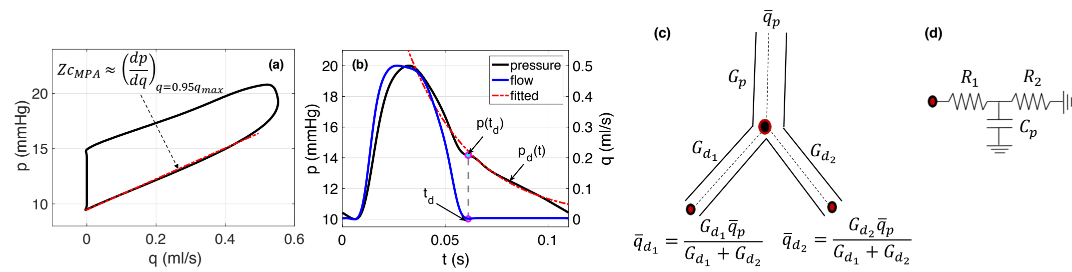

Figure 1: Nominal parameter values are predicted from pressure and flow values data by (a) approximating total compliance Z_c from the slope of the pressure-flow loop during early ejection, (b) estimating the time constant $\tau = C_p R_T$ by fitting a exponential curve through the diastolic part of the pressure curve, (c) predicting the flow distribution across a bifurcation as a function of the vessel radius of the daughter vessels. These quantities are used to predict resistance and compliance for the Windkessel model applied at each terminal vessel (d).

Nominal (*a priori*) parameter values

Parameter values for this model include internal parameters needed to specify the fluid (density ρ, viscosity μ, and boundary layer thickness δ), the elastic membrane of each vessel in the network (Eh/r_0), and the specific terminal vessel boundary conditions. At the inlet we impose measured flow whereas a Windkessel model with three parameters (R_1, R_2, C_p) is prescribed at the outlet of each terminal vessel. A network with N generations have $2^N - 1$ vessels and $2^{(N-1)}$ outlets. If all parameters were assumed independent the model would have $2^N - 1 + 3 \cdot 2^{N-1} + 3$ parameters. The network studied here (see Figure 2) has 7generations, giving between 322 parameters. To make this problem tractable we assume that:

- Vessel stiffness is constant throughout the network.
- Boundary conditions for each vessel can be calculated from total network resistance and compliance.
- Fluid properties ρ, μ, and δ are known and constant.

Imposing these conditions allows us to reduce the number of parameters to be inferred to vessel stiffnesses Eh/r_0 for each terminal vessel and parameters R_1, R_2, and C_p for each vessel. In our previous studies (e.g. Olufsen *et al.* 2000), the vessel stiffness was modeled as

$$\frac{Eh}{r_0} = k_1 e^{k_2 r_0} + k_3. \tag{7}$$

However, k_1, k_2 and k_3 are unidentifiable in this setting. Instead, we fix $k_1 = 0$ and only infer the parameter k_3, making the stiffness constant throughout the network. To reduce the parameter space further, we impose global scaling factors $0 < r_1, r_2, c_1$ to adjust the nominal parameters (R_{1j}, R_{2j}, and C_{pj}) as

$$\widehat{R}_{1j} = r_1 R_{1j}, \quad \widehat{R}_{2j} = r_2 R_{2j}, \quad \widehat{C}_{pj} = c_1 C_{pj}, \tag{8}$$

for all terminal vessels j in the network.

Nominal (*a priori*) values for these quantities are computed from data as discussed below.

Vessel stiffness As illustrated in Figure 1a, Eh/r_0 is approximated using the "upslope method" (see Qureshi *et. al.* 2017) using dynamic pressure and flow data. The interval for physiologically valid stiffness values is approximated to be $[10^4, 10^5]$.

Outflow boundary parameters By definition, the total vascular resistance, $R_T = \overline{p}/\overline{q}$, where $\overline{p}$ and $\overline{q}$ denote the time averaged pressure and flow in the first vessel. The total resistance is distributed to each of the terminal values from approximations of flow ratios to each terminal branch j, giving $R_{Tj} = \overline{p}/\overline{q}_j$, where $\overline{p}$ is the time averaged pressure (obtained from data) and $\overline{q}_j$ is the averaged flow to that vessel predicted by recursively applying Poiseuille's law relating flow to the vessel radius. Denoting daughter vessels d_1 and d_2 connected to a parent vessel p at any bifurcation, we get

$$\overline{q}_{d_1} = \frac{G_{d_1}}{G_{d_1} + G_{d_2}} \overline{q}_p \qquad \text{and} \qquad \overline{q}_{d_2} = \frac{G_{d_2}}{G_{d_1} + G_{d_2}} \overline{q}_p, \tag{9}$$

where G is the vessel conductance, defined by

$$G = \frac{\pi r_0^4}{8\mu L} \tag{10}$$

for any vessel in the network.

For each terminal branch, the total resistance to the specific branch R_{Tj} is distributed between the proximal R_{1j} and distal R_{2j} resistances using a constant factor $a = 0.2$, so that

$$R_{1j} = (0.2)R_{Tj} \qquad \text{and} \qquad R_{2j} = (0.8)R_{Tj}. \tag{11}$$

The compliance C_{pj} associated with the Windkessel models attached to the terminal vessels j is defined by

$$C_{pj} = \frac{\tau}{R_{Tj}}, \tag{12}$$

where τ is the time constant, approximated from the available pressure data fitting a decaying exponential function to the diastolic part of the pressure curve as illustrated on Figure 1b.

Nominal Windkessel Parameters Nominal parameter estimates using equations (9) - (12) are provided in Table 1. **These values are hardcoded in `sor06.c` for the given pulmonary geometry and should not be changed.** The Windkessel adjustment parameters have been set to $r_1 = 2.0193 \times 10^{-1}$, $r_2 = 8.8890 \times 10^{-1}$, and $c_1 = 1.4665 \times 10^0$ in the MATLAB file `main.m`.

Table 1: Nominal Windkessel Estimates

terminal vessel index	R_{1j} (mmHg s / ml)	R_{2j} (mmHg s / ml)	C_{pj} (ml / mmHg)
5	5.1041×10^2	2.0416×10^3	5.2546×10^{-3}
7	3.8800×10^2	1.5520×10^3	6.9124×10^{-3}
9	5.3883×10^2	2.1553×10^3	4.9775×10^{-3}
11	4.6696×10^2	1.8679×10^3	5.7435×10^{-3}
12	1.8078×10^3	7.2310×10^3	1.4836×10^{-3}
13	1.1737×10^4	4.6947×10^3	2.3900×10^{-3}
15	2.6608×10^3	1.0643×10^3	1.0542×10^{-2}
17	1.0412×10^4	4.1649×10^3	2.6940×10^{-3}
19	1.0711×10^3	4.2845×10^2	2.6188×10^{-2}
20	1.1697×10^3	4.6790×10^2	2.3980×10^{-2}
21	8.3431×10^2	3.3372×10^2	2.3362×10^{-2}

C++ and MATLAB files

The code (provided in the "Model" folder) includes the C++ files for the model and the numerical solver, as well as a MATLAB wrapper (`main.m`) that passes parameters to the model. The model outputs pressure ($p(x,t)$), flow ($q(x,t)$), area ($A(x,t)$), and the pulse wave speed ($c(x,t)$) in each of the vessels, and prints the outputs to the files `pu1_id.2d`, `pu2_id.2d`, and `pu3_id.2d`, which corresponds to vessels 1, 2 and 3 shown in Figure 2. The term `id` corresponds to the argument *id* that is passed to the model, which can be used to label model outputs for different parameter combinations. For the model to run appropriately, there are 7 arguments that need to be passed to the function `sor06.C`:

- k_3: Corresponds to Eh/r_0 in the model equations.
- r_1, r_2, c_1: Corresponds to the scaling parameters defined in equation (8).
- HB: The number of heartbeats for the model to run in order to reach a steady state solution.
- *cycles*: The number of cycles that need to be printed to the output files (i.e. the number of heartbeats you wish to see in your model output plots).
- *id*: The identifier (an integer) to be attached to the output file `puX_id.2d` in order to track model outputs with different parameter estimates.

Additional information about the C++ files used can be found in the `README.txt` file.

Table 2: Dimensions of vessels in the 21-vessel network.

		Control	
vessel index	connectivity (daughters)	$r_0 \times 10^{-1}$ (cm)	$L \times 10^{-1}$ (cm)
1*	(2,3)	0.47	4.10
2	(4,5)	0.26	4.45
3	(6,7)	0.37	3.72
4	(8,9)	0.24	2.41
5	–	0.13	0.52
6	(14,15)	0.32	2.02
7	–	0.17	2.12
8	(10,11)	0.23	3.11
9	–	0.17	1.77
10	(12,13)	0.20	2.62
11	–	0.16	0.69
12	–	0.15	1.40
13	–	0.14	0.62
14	(16,17)	0.26	0.81
15	–	0.19	1.84
16	(18,19)	0.25	0.83
17	–	0.15	3.02
18	(20,21)	0.24	4.69
19	–	0.15	1.77
20	–	0.22	1.78
21	–	0.18	0.55

* first vessel. Connectivity (i, j), i denotes the left daughter and j the right daughter. Vessels indicated by – are terminal.

Acknowledgments

This work is supported by the National Science Foundation, NSF-DMS 1615820 and NSF-DMS 1246691.

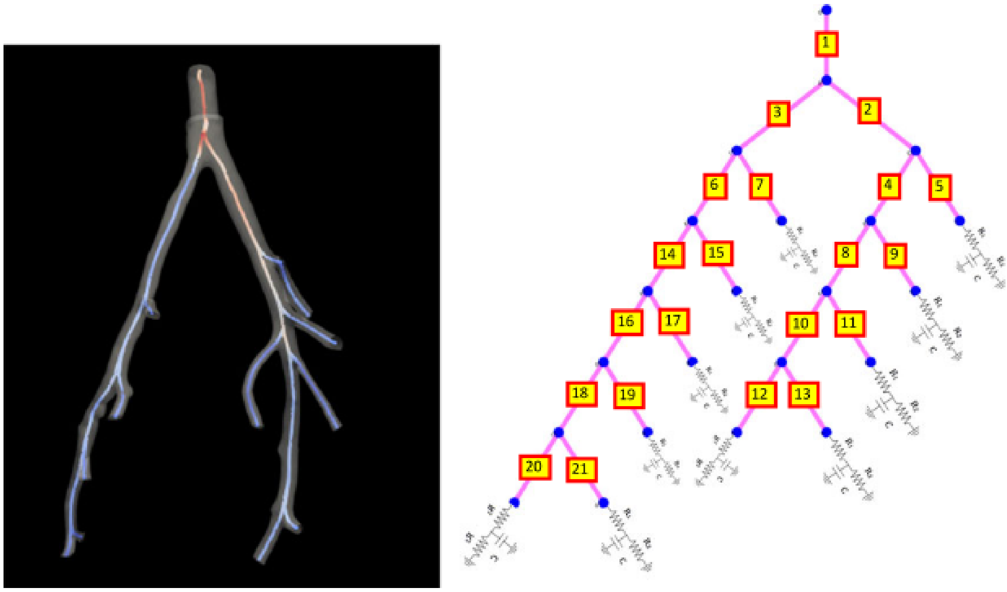

Figure 2: 21 Vessel network with 3-Element Windkessel attached at each boundary (from Paun et. al. 2018).

1 References

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