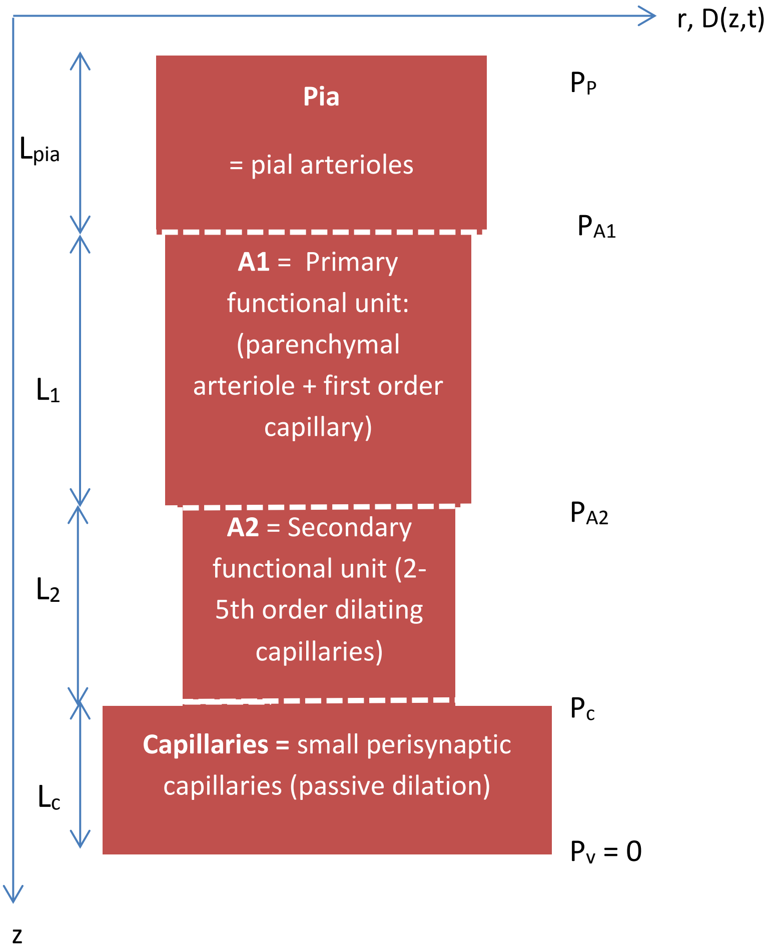
Data File S1. Related to Star Methods.

<u>Modeling RBCs velocity and flow in response to diameter changes due to odor application</u>

We used the following compartmental model :



Order of magnitude of Reynolds Number :

The Reynolds Number is : Re = ρvL / μ

where:

- ρ is the density of the fluid = 1.06 kg/m^3 for blood
- v is the velocity of the fluid with respect to the object ~10^{-3} m/s
- L is a characteristic linear dimension ~10^{-4} m
- μ is the dynamic viscosity of the fluid
  $\mu = \mu_0 \mu_R$
  μ_0 ~ 6 10^{-3} Pa.s
  μ_R depends on vessel diameter. We used the model from in vitro measurements (Pries et al., 1992) (the best in our case as diameter measurements already exclude glycocalyx) :

$$\mu_r(D) = 1 + (\mu_{r0.45}(D) - 1)\frac{(1-Hd)^{C(D)}-1}{(1-0.45)^{C(D)}-1}$$

With : $\mu_{r0.45}(D) = 220e^{-1.3D} + 3.2 - 2.44e^{-0.06D^{0.645}}$

And $C(D) = (0.8 + e^{-0.075D})\left(\frac{1}{1+10^{-11}D^{12}} - 1\right) + \frac{1}{1+10^{-11}D^{12}}$This gives Re ~ 10^{-5}. Therefore the flow is laminar.

Navier stokes Equations:

We assume linear gradient of pressure for each compartment. Calling G the pressure gradient $\frac{\partial P}{\partial z}$.

We use cylindrical coordinates (r, θ, z)

As laminar flow, component of v along r at the end of each segment neglected: $\vec{v} = v_z(r,z,t)\overrightarrow{u_z}$.

Navier Stokes equations become:

- $div(\vec{v}) = \frac{\partial v_z}{\partial z} = 0$
  => $\vec{v} = v_z(r,t)\overrightarrow{u_z}$ for each segment

- by projecting along the z axis, for each segment:

$$\boxed{\rho\frac{\partial v_z}{\partial t} = -G + \frac{\mu}{r}\frac{\partial}{\partial r}\left(r\frac{\partial v_z}{\partial r}\right)} \qquad \text{Eq. 1}$$

The solution of Eq. 1 is given by :

$$\boxed{v_z(r,t) = \frac{G}{4\mu}(R^2 - r^2) - \frac{2GR^2}{\mu}\sum_{n=1}^{\infty}\frac{1}{\lambda_n^3}\frac{J_0(\frac{\lambda_n r}{R})}{J_1(\lambda_n)}e^{\frac{-\lambda_n^2\mu t}{\rho R^2}}} \qquad J_0(\lambda_n) = 0 \qquad \text{Eq. 2}$$

Transient solution:

The transient component $\frac{2GR^2}{\mu}\sum_{n=1}^{\infty}\frac{1}{\lambda_n^3}\frac{J_0(\frac{\lambda_n r}{R})}{J_1(\lambda_n)}e^{\frac{-\lambda_n^2\mu t}{\rho R^2}}$ decreases with the following time constants: $\tau_n = \frac{\rho R^2}{\lambda_n^2\mu}$

λ_n >2 and R < 20 μm. Hence $\tau_n < \frac{\rho R^2}{4\mu} \sim 2\ 10^{-6} s$

Therefore transients are negligible at our time scale.

Steady-state solution:

The steady-state solution is:

$$v_z(r) = \frac{G}{4\mu}\left((\frac{D}{2})^2 - r^2\right)$$ Eq. 3

With D being the diameter of the vessel

We use $\vec{v} = v\,\overrightarrow{u_z}$ average velocity over section.

$v = \frac{4}{\pi D^2}\oiint v_z(s)ds$ with $dS = 2\pi r dr$

$$v = \frac{4}{\pi D^2}\int_0^{D/2} 2\pi r v_z(r)dr$$

$$v = \frac{2G}{\mu D^2}\int_0^{D/2}\left(r(\frac{D}{2})^2 - r^3\right)dr$$

Thus

$$v = \frac{GD^2}{32\pi\mu}$$ Eq. 4

and $v = \frac{v_z(0)}{2}$

As $Q = \frac{\pi D^2}{4}v$:

$$Q = \frac{GD^4}{128\mu}$$ Eq. 5

Furthermore, $G = \frac{\Delta P}{L}$, therefore :

For the pia section:

$$Q_{pia}(t) = \pi\, D_{pia}^4(t)\,\frac{P_{pia} - P_{A1}(t)}{128\mu_{pia}L_{pia}}$$ Eq. 6

$$v_{pia}(t) = D_{pia}^2(t)\,\frac{P_{pia} - P_{A1}(t)}{32\mu_{pia}L_{pia}}$$ Eq. 7

For the A1 section:

$$Q_{A1}(t) = \pi\, D_{A1}^4(t)\,\frac{P_{A1}(t) - P_{A2}(t)}{128\mu_{A1}L_{A1}}$$ Eq. 8

$$v_{A1}(t) = D_{A1}^2(t)\,\frac{P_{A1}(t) - P_{A2}(t)}{32\mu_{A1}L_{A1}}$$ Eq. 9

For the A2 section:

$$Q_{A2}(z,t) = \pi D_{A2}^4(t)\,\frac{P_{A2}(t) - P_c(t)}{128\mu_{A2}L_{A2}}$$ Eq.10

$$\boxed{v_{A2}(z,t) = D_{A2}^2(t)\frac{P_{A2}(t)-P_c(t)}{32\mu_{A2}L_{A2}}}$$ Eq. 11

For the capillary section:

$$\boxed{Q_c(z,t) = \pi D_c^4 \frac{P_c(t)}{128\mu_c L_c}}$$ Eq. 12

$$\boxed{v_c(z,t) = D_c^2 \frac{P_c(t)}{32\mu_c L_c}}$$ Eq. 13

Conservation of flow:

- ***Between pia and A1 :***

$$Q_{pia}(t) = Q_{A1}(t)$$

Thus $D_{pia}^4(t)\frac{P_P - P_{A1}(t)}{\mu_{pia}L_{pia}} = D_{A1}^4(t)\frac{P_{A1}(t)-P_{A2}(t)}{\mu_{A1}L_{A1}}$

Reformulating : $\mu_{A1}L_{A1}D_{pia}^4(t)(P_{pia} - P_{A1}(t)) = \mu_{pia}L_{pia}D_{A1}^4(t)(P_{A1}(t) - P_{A2}(t))$

Reformulating :

$$\boxed{\mu_{A1}L_{A1}D_{pia}^4(t)P_{pia} - (\mu_{A1}L_{A1}D_{pia}^4(t) + \mu_{pia}L_{pia}D_{A1}^4(t))P_{A1}(t) + \mu_{pia}L_{pia}D_{A1}^4(t)P_{A2}(t) = 0}$$ Eq. 14

- ***Between A1 and A2 :***

$$Q_{A1}(t) = Q_{A2}(t)$$

Thus $D_{A1}^4(t)\frac{P_{A1}(t)-P_{A2}(t)}{\mu_{A1}L_{A1}} = D_{A2}^4(t)\frac{P_{A2}(t)-P_c(t)}{\mu_{A2}L_{A2}}$

Reformulating : $\mu_{A2}L_{A2}D_{A1}^4(t)\big(P_{A1}(t) - P_{A2}(t)\big) = \mu_{A1}L_{A1}D_{A2}^4(t)(P_{A2}(t) - P_c(t))$

Reformulating :

$$\boxed{\mu_{A2}L_{A2}D_{A1}^4(t)P_{A1}(t) - (\ \mu_{A2}L_{A2}D_{A1}^4(t) + \mu_{A1}L_{A1}D_{A2}^4(t)P_{A2}(t) + \mu_{A1}L_{A1}D_{A2}^4(t)P_c(t) = 0}$$ Eq. 15

- ***Between A2 and C :***

$$Q_{A2}(t) = Q_c(t)$$

Thus $D_{A2}^4(t)\frac{P_{A2}(t)-P_c(t)}{\mu_{A2}L_{A2}} = D_c^4\frac{P_c(t)}{\mu_c L_c}$

Reformulating : $\mu_c L_c D_{A2}^4\big(P_{A2}(t) - P_c(t)\big) = \mu_{A2}L_{A2}D_c^4 P_c(t)$

Reformulating :

$$\boxed{\mu_c L_c D_{A2}^4(t) P_{A2}(t) - (\mu_c L_c D_{A2}^4(t) + \mu_{A2} L_{A2} D_c^4) P_c(t) = 0}$$ Eq. 16

Expression of $P_1(t)$, $P_2(t)$ and $P_c(t)$ from Eq.14, Eq.15 and Eq.16 :

$\mu_{A2} L_{A2} D_{A1}^4(t)$ Eq. 14 + $(\mu_{A1} L_{A1} D_{pia}^4 + \mu_{pia} L_{pia} D_{A1}^4(t))$ Eq. 15 gives

$$(\mu_{A1} L_{A1} D_{pia}^4(t) \mu_{A2} L_{A2} D_{A1}^4(t)\ P_{pia} + (\mu_{pia} L_{pia} \mu_{A2} L_{A2} D_{A1}^8(t) - (\mu_{A1} L_{A1} D_{pia}^4(t) + \mu_{pia} L_{pia} D_{A1}^4(t))\ (\mu_{A2} L_{A2} D_{A1}^4(t) + \mu_{A1} L_{A1} D_{A2}^4(t))) P_{A2}(t) + (\mu_{A1} L_{A1} D_{pia}^4(t) + \mu_{pia} L_{pia} D_{A1}^4(t))\ \mu_{A1} L_{A1} D_{A2}^4(t) P_c(t) = 0$$

Reformulating :

$$\boxed{\mu_{A1} L_{A1} D_{pia}^4(t) \mu_{A2} L_{A2} D_{A1}^4(t)\ P_0 - (\mu_{A1}^2 L_{A1}^2 D_{A2}^4(t) D_{pia}^4(t) + (\mu_{A1} L_{A1} D_{pia}^4(t) \mu_{A2} L_{A2} + \mu_{A1} L_{A1} D_{A2}^4(t) \mu_{pia} L_{pia}) D_{A1}^4(t)) P_{A2}(t) + (\mu_{A1} L_{A1} D_{pia}^4(t) + \mu_{pia} L_{pia} D_{A1}^4(t)) \mu_{A1}\ L_{A1} D_{A2}^4(t) P_c(t) = 0}$$

Eq. 17

Eq. 17 + $(\mu_{A1} L_{A1} D_{pia}^4(t) + \mu_{pia} L_{pia} D_{A1}^4(t))\ \mu_{A1} L_{A1} D_{A2}^4$ Eq. 16 gives

$$(\mu_C L_c D_{A2}^4(t) + \mu_{A2} L_{A2} D_c^4) \mu_{A1} L_{A1} D_{pia}^4(t) \mu_{A2} L_{A2} D_{A1}^4(t)\ P_0 + ((\mu_{A1} L_{A1} D_{pia}^4(t) + \mu_{pia} L_{pia} D_{A1}^4(t)) \mu_{A1} L_{A1} \mu_C L_c D_{A2}^8(t) - (\mu_C L_c D_{A2}^4(t) + \mu_{A2} L_{A2} D_c^4)\ (\mu_{A1}^2 L_{A1}^2 D_{A2}^4(t) D_{pia}^4(t) + (\mu_{A1} L_{A1} D_{pia}^4(t) \mu_{A2} L_{A2} + \mu_{A1} L_{A1} D_{A2}^4(t) \mu_{pia} L_{pia}) D_{A1}^4(t)) P_{A2}(t) = 0$$

Reformulating :

$$(\mu_C L_c D_{A2}^4(t) + \mu_{A2} L_{A2} D_c^4) \mu_{A1} L_{A1} D_{pia}^4(t) \mu_{A2} L_{A2} D_{A1}^4(t)\ P_0 - (\mu_{A2} L_{A2} D_c^4 \mu_{A1}^2\ L_{A1}^2 D_{A2}^4(t) D_{pia}^4(t) + (\mu_C L_c D_{A2}^4(t) \mu_{A1} L_{A1} D_{pia}^4(t) \mu_{A2} L_{A2} + \mu_{A2} L_{A2} D_c^4 (\mu_{A1} L_{A1} D_{pia}^4(t) \mu_{A2} L_{A2} + \mu_{A1} L_{A1} D_{A2}^4(t) \mu_{pia} L_{pia}) D_{A1}^4(t)) P_{A2}(t) = 0$$

Reformulating :

$$D_{pia}^4 (\mu_C L_c D_{A2}^4(t) + \mu_{A2} L_{A2} D_c^4) D_{A1}^4(t)\ P_0 - (\mu_{A1} L_{A1} D_{A2}^4(t) D_{pia}^4 D_c^4\ + (\mu_C L_c D_{A2}^4 D_{pia}^4(t) + D_c^4 (D_{pia}^4(t) \mu_{A2} L_{A2} + D_{A2}^4(t) \mu_{pia} L_{pia}) D_{A1}^4(t)) P_{A2}(t) = 0$$

setting

$$\beta(t) = D_{pia}^4(t)(\mu_C L_c D_{A2}^4(t) + \mu_{A2} L_{A2} D_c^4)$$

$$\gamma(t) = \mu_C L_c D_{A2}^4(t) D_{pia}^4(t) + D_c^4(\mu_{A2} L_{A2} D_{pia}^4(t) + \mu_{pia} L_{pia} D_{A2}^4(t))$$

$$\delta(t) = \mu_{A1} L_{A1} D_c^4\ D_{A2}^4(t) D_{pia}^4(t)$$

Then $\beta D_{A1}^4(t)\ P_{pia} - (\delta + \gamma D_{A1}^4(t)) P_{A2}(t) = 0$

Thus

$$\boxed{P_{A2}(t) = \frac{\beta(t) D_{A1}^4(t)\, P_{pia}}{\delta(t) + \gamma(t) D_{A1}^4(t)}} \quad \text{Eq. 18}$$

From Eq. 16 : $P_c(t) = \frac{\mu_C L_c D_{A2}^4(t) P_{A2}(t)}{(\mu_C L_c D_{A2}^4 + \mu_{A2} L_{A2} D_C^4)}$

Setting $\varepsilon(t) = \frac{\mu_C L_c D_{A2}^4(t)}{(\mu_C L_c D_{A2}^4(t) + \mu_{A2} L_{A2} D_C^4)}$

Then $P_c(t) = \varepsilon(t) P_{A2}(t)$

Thus

$$\boxed{P_c(t) = \frac{\beta(t)\varepsilon(t) D_{A1}^4(t) P_{pia}}{\delta(t) + \gamma(t) D_{A1}^4(t)}} \quad \text{Eq. 19}$$

$$\mu_{A2} L_{A2} D_{A1}^4(t) P_{A1}(t) - (\ \mu_{A2} L_{A2} D_{A1}^4(t) + \mu_{A1} L_{A1} D_{A2}^4(t) P_{A2}(t) + \mu_{A1} L_{A1} D_{A2}^4(t) P_c(t) = 0$$

From Eq. 15 : $P_1(t) = \frac{(\mu_{A2} L_{A2} D_{A1}^4(t) + \mu_{A1} L_{A1} D_{A2}^4(t)) P_{A2}(t) - \mu_{A1} L_{A1} D_{A2}^4(t) P_C(t)}{\mu_{A2} L_{A2} D_{A1}^4(t)}$

Reformulating :

$$P_{A1}(t) = (\ 1 + \frac{\mu_{A1} L_{A1} D_{A2}^4(t)}{\mu_{A2} L_{A2} D_{A1}^4(t)} (1 - \varepsilon(t))) P_{A2}(t)$$

Setting

$$\theta(t) = \frac{\mu_{A1} L_{A1} D_{A2}^4(t)}{\mu_{A2} L_{A2} D_{A1}^4(t)}$$

Then $P_{A1}(t) = (\ 1 + \theta(t)(1 - \varepsilon(t))) P_{A2}(t)$

Thus

$$\boxed{P_{A1}(t) = \frac{\beta(t) D_{A1}^4(t)(1 + \theta(t)(1 - \varepsilon(t)))\, P_0}{\delta(t) + \gamma(t) D_{A1}^4(t)}} \quad \text{Eq. 20}$$

Equivalent cylinders for each compartment:

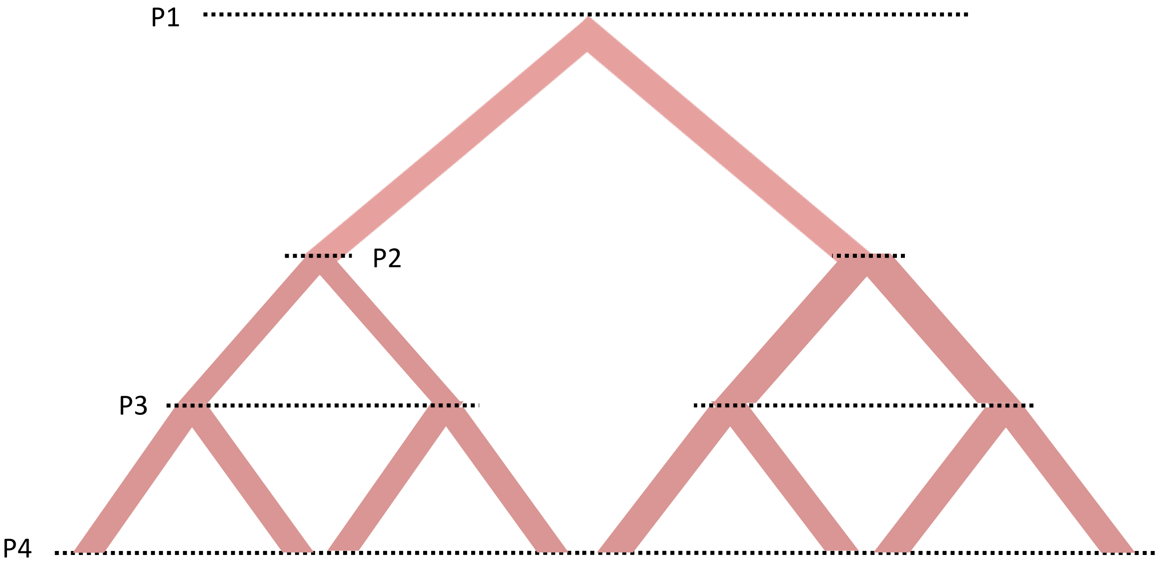
To model a vascular network as a single cylinder we need to estimate its parameters:

Let's assume :

- N primary branches at entrance of the same length L:
  $Q = N\, Q_i$
  where Q_i is the flow through a individual primary branch. Hence

$$\boxed{Q(t) = \pi\, N\, D_i^4(t)\frac{P_{entrance}(t) - P_{exit}(t)}{128\mu L}} \qquad \text{Eq. 21}$$

- Each of the primary branches divides M-1 times and each sub-branch of the same length Li and diameter Di



$Lj = L/M$
At order j between 1 and M : $Q_{j+1}(t) = Q_j(t) / 2$
where Q_j is the flow through an individual arteria at order j

Hence $Q_j(t) = Q_1(t) / 2^{j-1}$

$$Q_j(t) = \pi\, D_i^4(t)\frac{P_j(t) - P_{j+1}(t)}{128\mu L_j}$$

⇨ $Q_j(t) = \pi\, M D_i^4(t)\frac{P_j(t) - P_{j+1}(t)}{128\mu L}$

⇨ $\frac{128\mu L Q_1(t)}{\pi M\, D_i^4(t)} = 2^{j-1}(P_j(t) - P_{j+1}(t))$

⇨ $P_{j+1}(t) = P_j(t) - \frac{128\mu L Q_1(t)}{2^{j-1}\,\pi M D_i^4(t)}$

⇨ $P_{j+1}(t) = P_1(t) - \frac{128\mu L Q_1(t)}{\pi M D_i^4(t)}\sum_{k=1}^{j}\frac{1}{2^{k-1}}$

$$\boxed{P_{j+1}(t) = P_1(t) - \frac{256\mu L Q_1(t)}{\pi M D_i^4(t)}(1 - \left(\frac{1}{2}\right)^j)}$$ Eq. 22

The flow through the vascular network i is : $Q(t) = Q_1(t)$

From Eq.22 : $P_M(t) = P_1(t) - \frac{256\mu L Q_1(t)}{\pi M D_i^4(t)}\left(1 - \left(\frac{1}{2}\right)^{M-1}\right)$

Therefore

$$\boxed{Q(t) = \frac{\pi M\, 2^{M-2} D_i^4(t)}{128\mu L(2^{M-1}-1)}(P_1(t) - P_M(t))}$$ Eq. 23

Combination of both levels give:

$$\boxed{Q(t) = \frac{\pi N M\, 2^{M-2} D_i^4(t)}{128\mu L(2^{M-1}-1)}(P_1(t) - P_M(t))}$$ Eq. 24

To simplify we define: $D_{NM}(t) = \left(\frac{NM2^{M-2}}{2^{M-1}-1}\right)^{1/4} D_i(t)$

Then

$$\boxed{Q(t) = \frac{\pi D_{NM}^4(t)}{128\mu L}(P_1(t) - P_M(t))}$$ Eq. 25

At order j between 1 and M :

$$v_j(t) = D_i^2(t)\frac{P_j(t) - P_{j+1}(t)}{32\mu L_j} = MD_i^2(t)\frac{P_j(t) - P_{j+1}(t)}{32\mu L}$$

But $P_j(t) - P_{j+1}(t) = \frac{128\mu L Q_1(t)}{2^{j-1}\pi M\, D_i^4(t)} = \frac{128\mu L Q(t)}{2^{j-1}\pi M\, D_i^4(t)} = \frac{N2^{M-2}}{2^{j-1}(2^{M-1}-1)}(P_1(t) - P_M(t))$

Therefore

$$\boxed{v_j(t) = \frac{NM2^{M-2}D_i^2(t)}{2^{j-1}(2^{M-1}-1)}\frac{P_1(t)-P_M(t)}{32\mu L}}$$ Eq.26

The average speed is then:

$$v(t) = \frac{\sum_{j=1}^{M} 2^{j-1} v_j(t)}{\sum_{j=1}^{M} 2^{j-1}} = \frac{\sum_{j=1}^{M} \frac{NM2^{M-2}D_i^2(t)}{(2^{M-1}-1)}\frac{P_1(t)-P_M(t)}{32\mu L}}{2^M - 1}$$

Thus

$$\boxed{v(t) = \frac{2^{M-2}M^2 N D_i^2(t)(P_1(t)-P_M(t))}{(2^M-1)(2^{M-1}-1)32\mu L}}$$ Eq.27

Model input parameters: estimates of compartment length and branching

	pia	*A1*	*A2*	*Capillaries*
L	*300*	*100*	*100*	*300*
N	*1*	*1*	*4*	*3*
M	*2*	*2*	*4*	*2*