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Computer implementation of myogenic gradient in the retinal network

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Abstract:
Vascular network in the retina is a goog object for in vivo investigation of the blood flow. Different techniques are used for deep study of blood flow and its characteristics , including computional methods. We suggest quantitative mathematical model of retinal vascular network, that represent basic features of the system.

1. Why the retina?

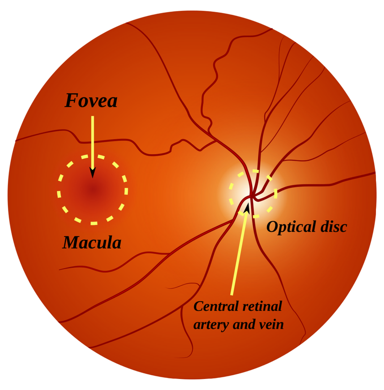


Figure 1: Typical retinal image as seen through the pupil

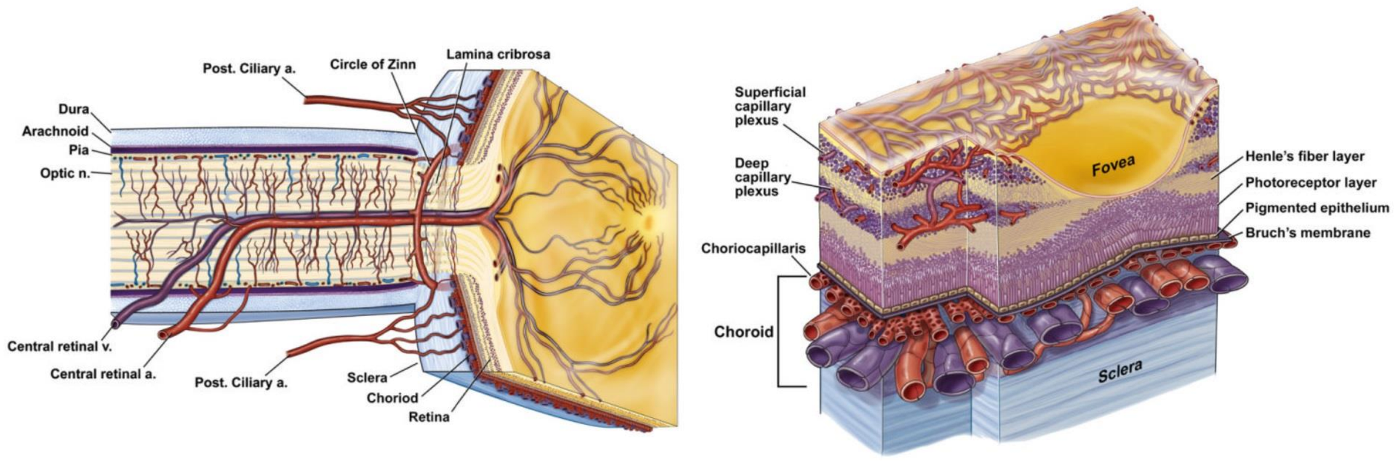
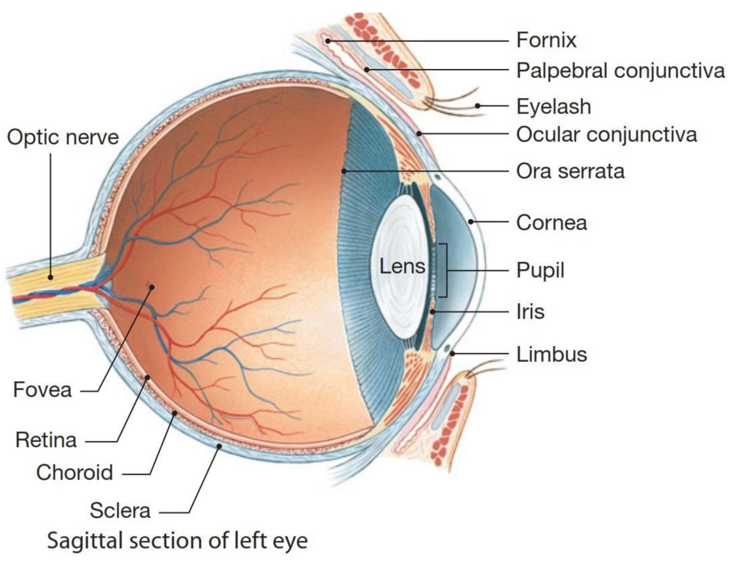


Figure 2: Anatomy of ocular circulation (a-artery, b-vein, n-nerve) a) Cut away drawing along the superior–inferior axis of the human eye through the optic nerve, showing the vascular supply to the retina and choroid. b) Drawing showing vasculature of the retina and choroid. Drawings by Dave Schumick from Anand-Apte and Hollyfield (2009).



Why we are able to see the retinal vessels network images?

- Cornea is *transparent*
- Pupil is the *opening* of the eye
- Lens *pass* the light

Eye is a unique case when we have ability to investigate vascular system in vivo, both at normal conditions and applying different tests.

Figure 3: Sagittal section of left eye. Drawing from Martini (2011).

2. Modelling of the retinal vessel network

2.1 Network structure

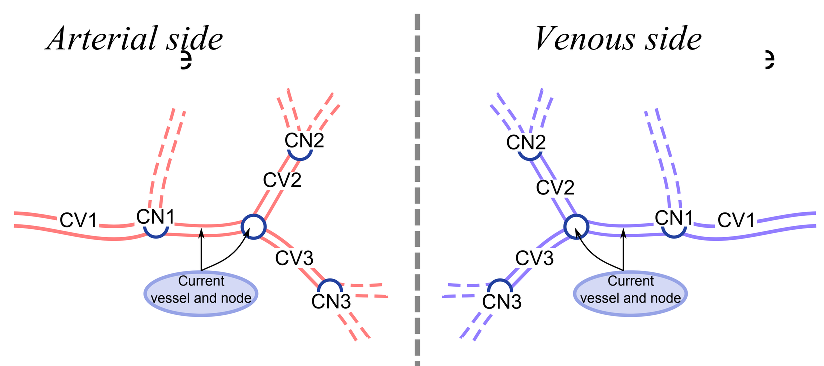
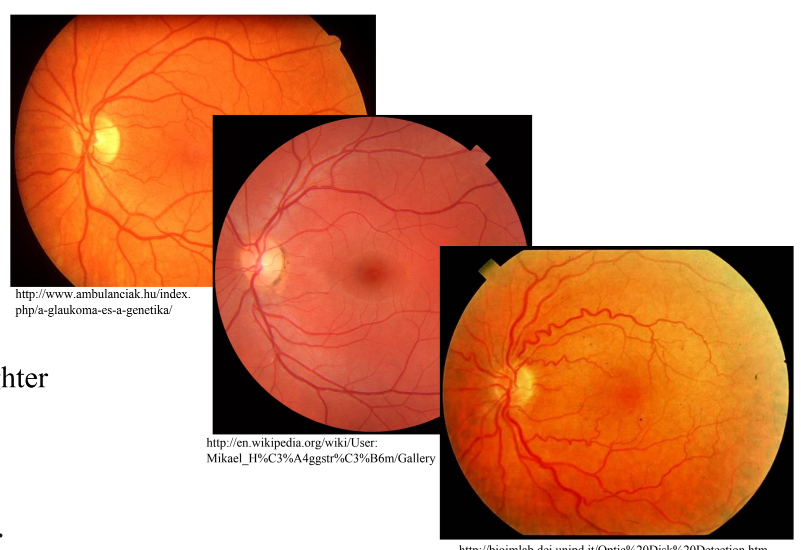


Figure 4: Schematic representation of vessel network. For each vessel on the each side (arterial or venous) we have 1 parent vessel CV1 and 1 parent node CN1 and 2 daughter vessels (CV2 and CV3) and daughter nodes (CV2 and CV3).These denotations are used for making of Vessel Matrix and Node Matrix

After analysing of experimental data (from the internet), we have found that vessel diameter depends from vessel diameter of its parent, besides that, vessel length depends from the number of generation for this vessel. These findings correlate with previously reported data (Kassab,1993; Kassab,1994). These dependencies are observed in both arterial and venous parts of vessel network.



To find vessels lengths and radiuses we used relations:

$r_p^3 = r_{d1}^3 + r_{d2}^3 + r_{d3}^3 + \dots r_{dn}^3$ *Murray's law*, where r_p - radius of parent vessel r_d - radius of daughter vessel

$h = 0.14 r_i + 3.3,$ where h - vessel wall thickness, r_i - vessel inner radius (*Hashimoto, 1986*)

The pressure in each nodes calculates using Kirchhoff's law:

$$\sum_j Q_j^n = \sum_j C_j^n \Delta P_j^n = 0,$$

where is the Q_j^n - inlet/outlet flow, C_j^n - the vascular conductance of the j^{th} vessel and ΔP_j^n - pressure drop in the related vessel.

2.2 Vessel walls' mechanics

Vessel wall stress relations:

$$\sigma = \sigma_p \cdot af_p + \sigma_a \cdot af_a + \sigma_c \cdot af_c$$

$$\sigma_p = C_{p1} \cdot \left(e^{a_{p1} \cdot \varepsilon} - 1\right) + C_{p2} \cdot \left(e^{a_{p2} \cdot \varepsilon} - 1\right)$$

$$\varepsilon = \frac{r_m - r_{slack}}{r_{slack}}$$

$$\dot{\varepsilon} = k_1 \cdot (\bar{\sigma} - \sigma)$$

$$\sigma_{am} = \sigma_{amopt} \cdot e^{-\left(\frac{l - l_{aopt}}{ba}\right)^2}$$

$$\sigma_a = \psi \cdot \sigma_{am}$$

$$\sigma_c = \sigma_{c0} \cdot \frac{e^{bc(l - l_{c0})} - e^{-bc}}{1 - e^{-bc}}$$

$$\bar{\sigma} = P \cdot r_i / h$$

Vessel tone relations:

$$\dot{\psi} = k_2 (\bar{\psi} - \psi)$$

$$\bar{\psi} = \left(\frac{(\sigma + CON)^{hc}}{(\sigma + CON)^{hc} + \sigma_{50}^{hc}}\right)$$

σ - mean wall stress;
σ_p, σ_a, σ_c - stress on element type ***j***, ***j*** = ***p***(assive), ***a***(ctive) or ***c***(ytoskeleton);
af_p, af_a, af_c - fraction of wall area covered by matrix, active/cytoskeletal elements;
C_{p1}, C_{p2} - constants in passive stress-strain curve;
a_{p1}, a_{p2} - constants in passive stress-strain curve;
ε - strain;
r_m - midwall radius; r_{slack} - slack radius (radius at *zero* load);
k_1 - rate constant mechanical radius changes;
σ_{am} - capacity for act. stress generation; σ_{amopt} - max. act. stress at optimal length;
l - SMC length; l_{aopt} - optimal SMC length for active stress;
b_a - width of active length-stress curve;
ψ - vessel tone;
σ_{c0} - cytoskeletal stress at l_{c0}; b_c - steepness cytoskeletal stress curve;
P- midvessel pressure; r_i - inner radius; ***h*** - wall thickness;

CON - constrictor; ***hc*** - Hill coefficient for act. curve;
σ_{50} - stress for half-maximal activation;
k_2 - rate constant tone changes;

Ref.: Integrative Modeling of Small Artery Structure and Function Uncovers Critical Parameters for Diameter Regulation, Ed VanBavel (2014)

2.3. Modelling of myogenic gradient

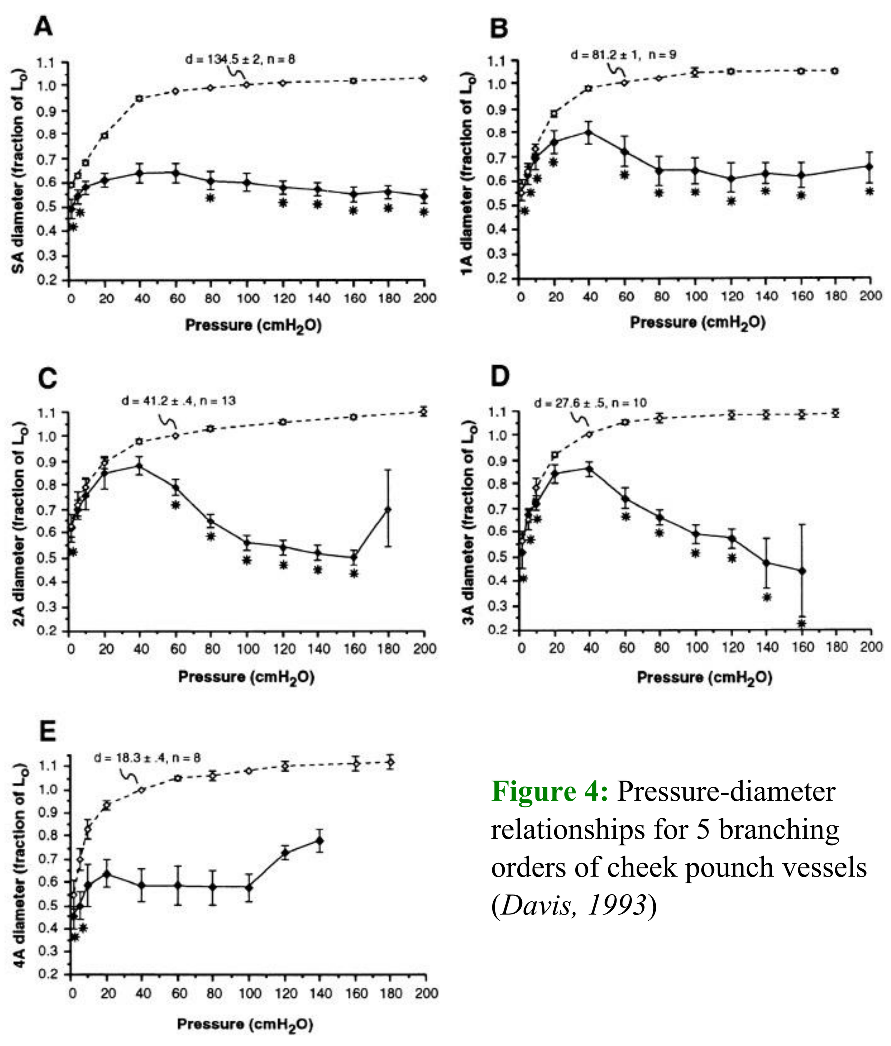
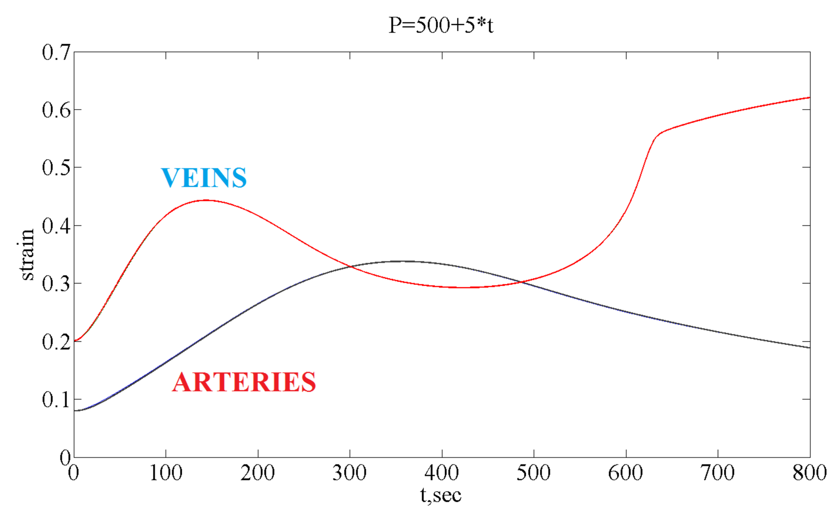


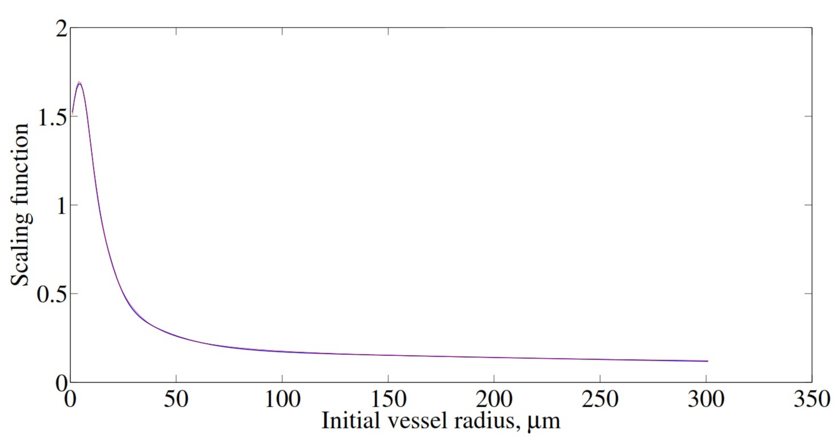
Figure 4: Pressure-diameter relationships for 5 branching orders of cheek pounch vessels (*Davis, 1993*)

- *Myogenic response* is reaction of smooth muscle in the vessel wall on the external stimulas, that contacts in response to increasing intraluminal pressure and relax in response to decresing pressure, in order to balances optimal vessel diameter.
- Myogenic response observed in different vascular beds *in both small and large vessels.*
- It was shown that, intensity of myogenic response of hamsters' isolated arterioles depends from vessel radius and most intensive for the terminal vessels (Davis, 1993).
- Also, it was found, that myogenic response gradient are also exist in human retinal arterioles (Jeppesen et al., 2007).
- Longevity of myogenic response depends from vessel radius, too. Vessels with smaller diameter, and, hence, thicker vessel wall are able to maintain smaller vessel radius during increasing inlet pressure less than larger vessels.

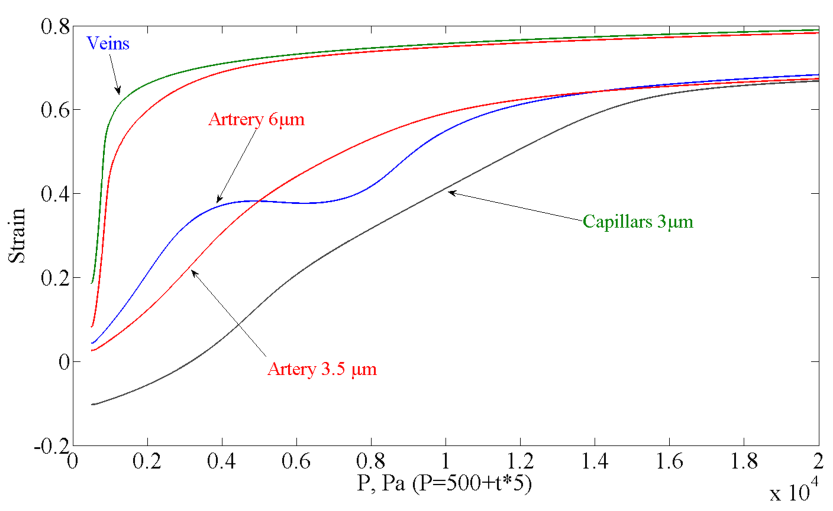
Myogenic response in the retinal network without dependence from initial vessel radius



To take into accound these features of myogenic response we introduces function of scaled mean stress



Myogenic response in the retinal network with dependence from initial vessel radius



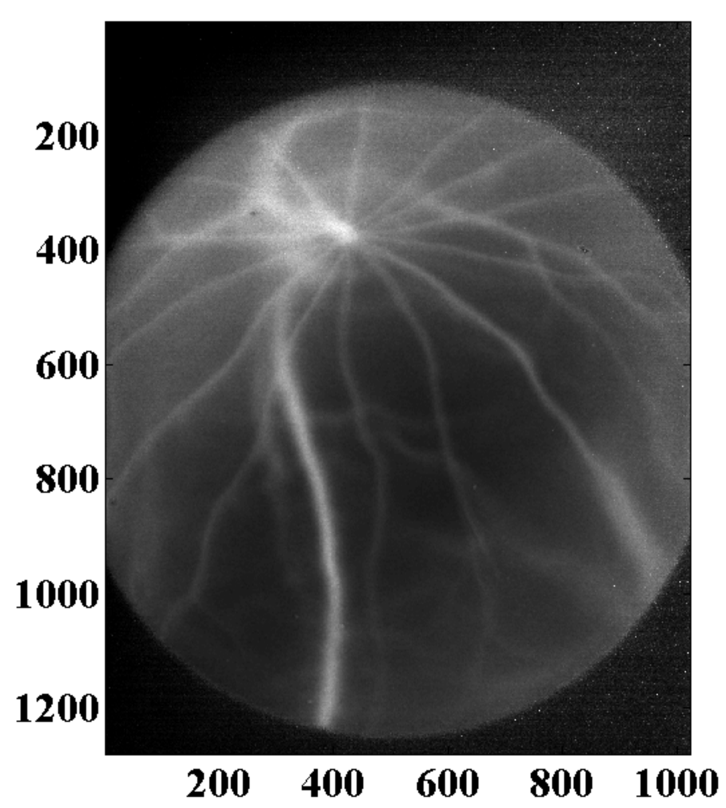
We introduced new variable - scaled mean stress σ_{sc} which reflects dependence of mean stress (where h - wall thickness) from initial vessel radius:

$$\sigma = P \cdot r_i / h$$
$$\sigma_{sc} = \sigma \cdot Scale_{func}$$

$$Scale_{func} = a_1 e^{-((radius - b_1)/c_1)^2} + a_2 e^{-((radius - b_2)/c_2)^2} + a_3 e^{-((radius - b_3)/c_3)^2} + a_4 e^{-((radius - b_4)/c_4)^2},$$

where:
$a_1 = 0.6357$, $b_1 = 4.336$, $c_1 = 6.62$
$a_2 = 0.4003$, $b_2 = 8.791$, $c_2 = 12.59$
$a_3 = 4.785$, $b_3 = -128.9$, $c_3 = 88.75$
$a_4 = 1.975e+04$, $b_4 = -1.402e+04$, $c_4 = 4130$

Average blood flow image



Experimental setup includes:
- Endoscope
- Laser
- Camera
- PC software

Future plans:

- LSI experiment, tests with chemicals which induce constriction/relaxation retinal vessel
- Rewriting mathematical model on CUDA C language
- Test simulations on realistic network with thousands vessels, find the circumstances under which network could show vasomotion

Rat retina Laser Speckle Imaging (Blood flow visualization)

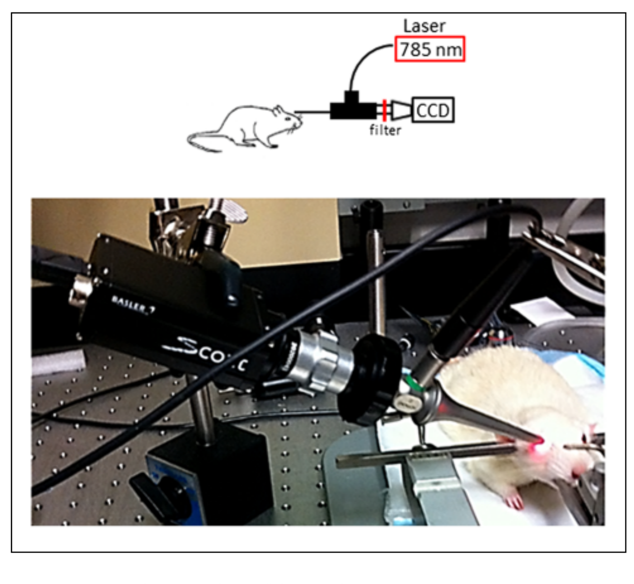
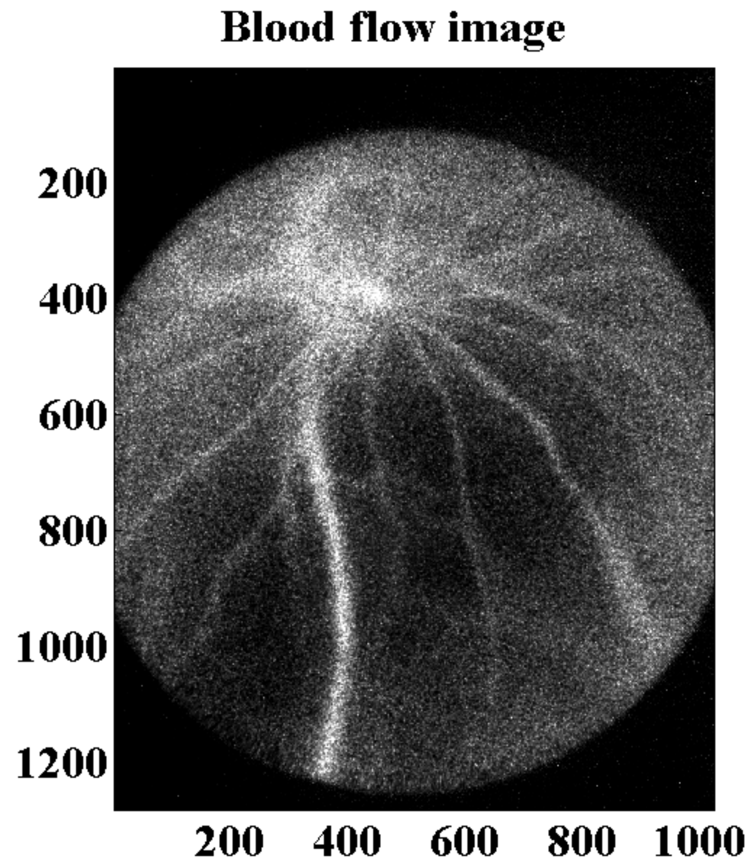


Figure 5: Schematic of imaging setup. A photograph of the imaging system is also shown (*Drawing from Ponticorvo, 2013*)

Blood flow image



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