Recent advances in the mathematical modelling of the Fähræus Linquist effect

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Dedicated to my friend Domingo Tarzia for his 70th birthday

VIII Maci, 3-7 May 2021, Argentina

A celebrated paper

THE VISCOSITY OF THE BLOOD IN NARROW CAPILLARY TUBES

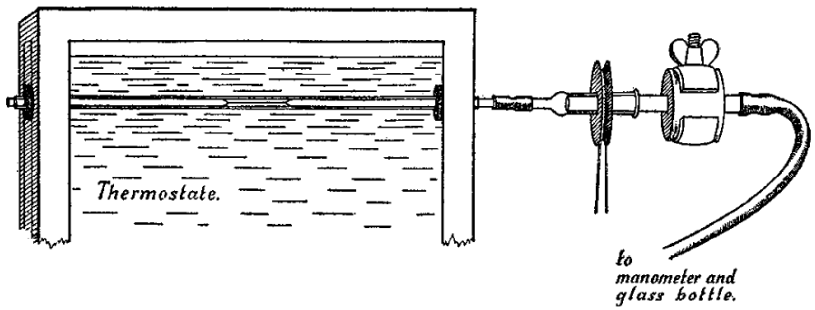
ROBIN FÅHRÆUS AND TORSTEN LINDQVIST

From the Pathological Institute, Uppsala, Sweden

Received for publication December 6, 1930

- The paper appeared on American Journal of Physiology in 1931.
- Since then, many scientists have tried to justify, on the base of the fundamental laws of Fluid Dynamics, the experimental data reported there.
- Our aim today is to tell how this gap has been filled just in these last two years.

The experimental apparatus



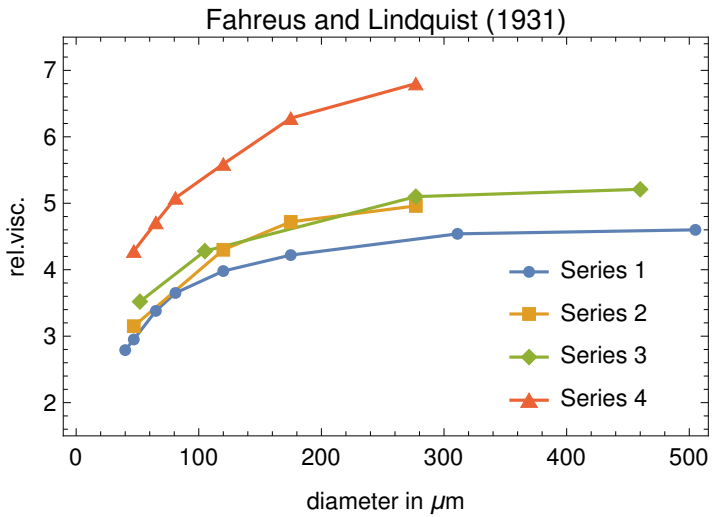
- The liquid is human blood (from the two scientists themselves!)
- The tubes used have very small radius (as those of venules or arterioles) $R \in (25, 150)$ μm
- The measured quantity is the volumetric flow rate Q for given pressure gradient $\dfrac{\Delta P}{L}$ ($L =$ length of the tube).

The experimental data

If water instead of blood *were* used, than the liquid viscosity

$$\eta = \frac{\pi R^4}{8LQ}\Delta P \qquad \text{(Poiseuille's law, 1838)} \tag{1}$$

would be a *constant* (depending only of temperature).
But human blood is not water!

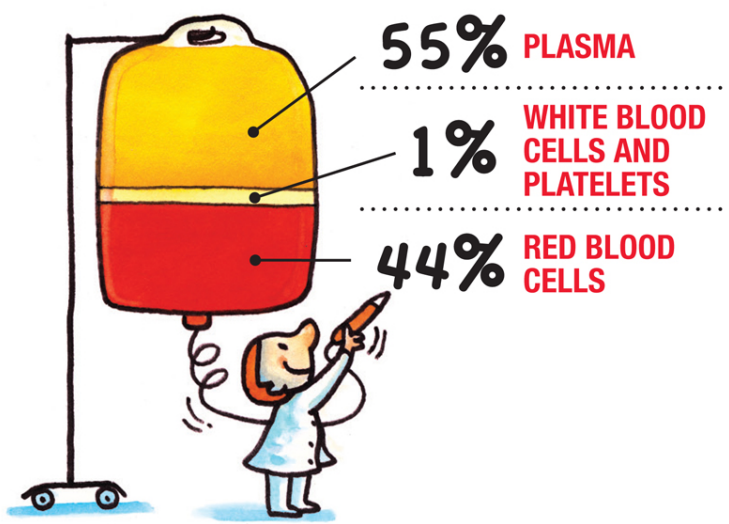


The law of Poiseuille does not apply to the flow of blood in capillary tubes with a diameter below about 0.3 mm.
(from Fähræus and Linquist's paper p.556)

Historical curiosity: the law that carries his name was formulated by Poiseuille just to study the blood flow, and theoretically justified only in 1845 by Stokes.

Why Human blood does not behave like water?

Blood is a *suspension* of various cells in a proteic liquid (plasma). Plasma, as it stands, has rheological properties very close to those of water (almost the same density and viscosity).
However suspended particles make the difference!



RBCs are $\approx 98\%$ of all blood cells. Plasma is water $\approx 92\%$ plus various proteins, electrolytes and organic molecules.

Why Human blood does not behave like water?

In fluid dynamics applications, blood can be considered just plasma plus RBCs.
It is because of RBCs that blood rheology is quite different of that of water!

1. Viscosity is measured at a given shear rate. Thus, in principle, the ratio between the imposed stress and the shear rate, should depend on the latter.
2. For a Newtonian fluid (like water) this ratio is a material constant depending only on temperature.
3. The experiment of FL shows that blood turns from a Newtonian to a non-Newtonian behaviour as soon as the vessel diameter reduces below a threshold value.

In other words, blood rheology (besides the chemistry, dynamics and thermal conditions) depends on the geometry!

The Haynes' conjecture (Amer. J. of Physiology, 1960)

In vessels with diameter smaller than 300 µm, RBCs tend to migrate towards the central part of the vessel, thus leaving close to the wall a layer of plasma, called "marginal zone" free (or almost free) of RBCs. Hayens assumes the layer to be totally free of RBCs (but we are going to weaken this assumption).

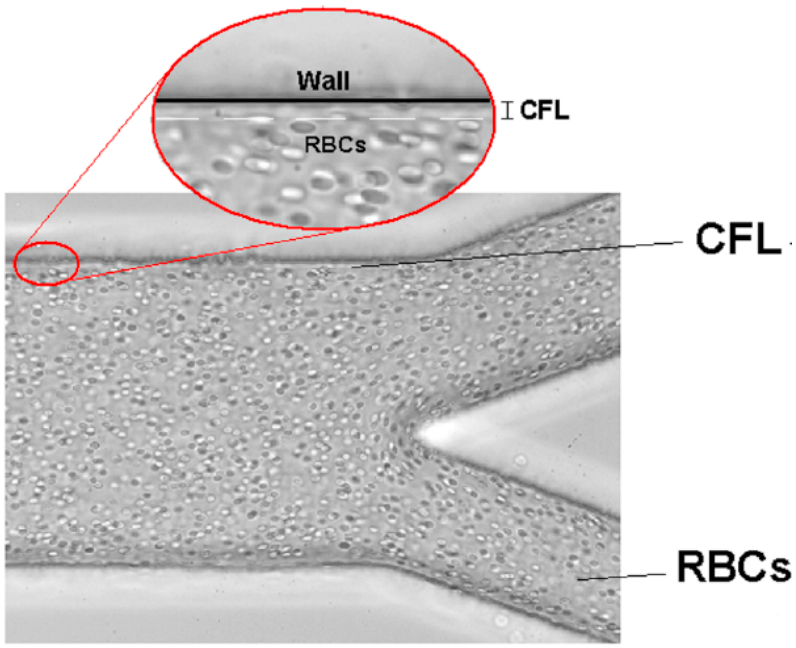
In a suspension flowing in a tube, particles will tend to adopt that motion which, of all possible ones, corresponds to the least dissipation of energy (Jeffery, 1922)

Is a "marginal layer" really observable? YES!

Experimental evidence (in vitro): in tubes of about 100 µm*, the marginal zone thickness is about 6-8* µm
(Bento et al., Exper. Thermal and Fluid Science,2019)

Experimental evidence "in vivo" of the marginal layer

Very few experiments "in vivo" (real venules/arterioles and human or rat/rabbit blood): Maeda et al. (Amer. J. of Physiology, 1996), Kim et al. (Amer. J. of Physiology, 2007), Ong et al. (Amer. J. of Physiology, 2010), Rajab (PhD thesis, 2018)



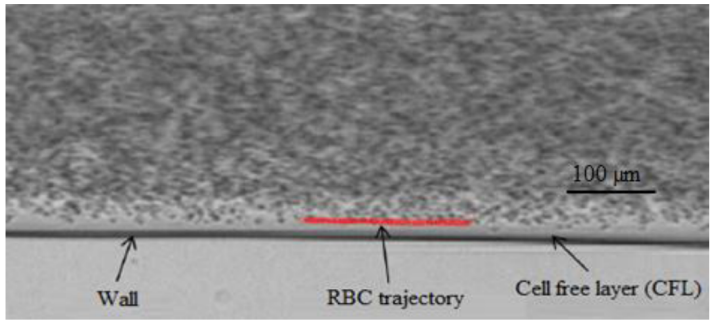


Figure 2.11: A trajectory of RBC flowing around the periphery region of RBC core

Experimental evidence "in vivo" of the marginal layer

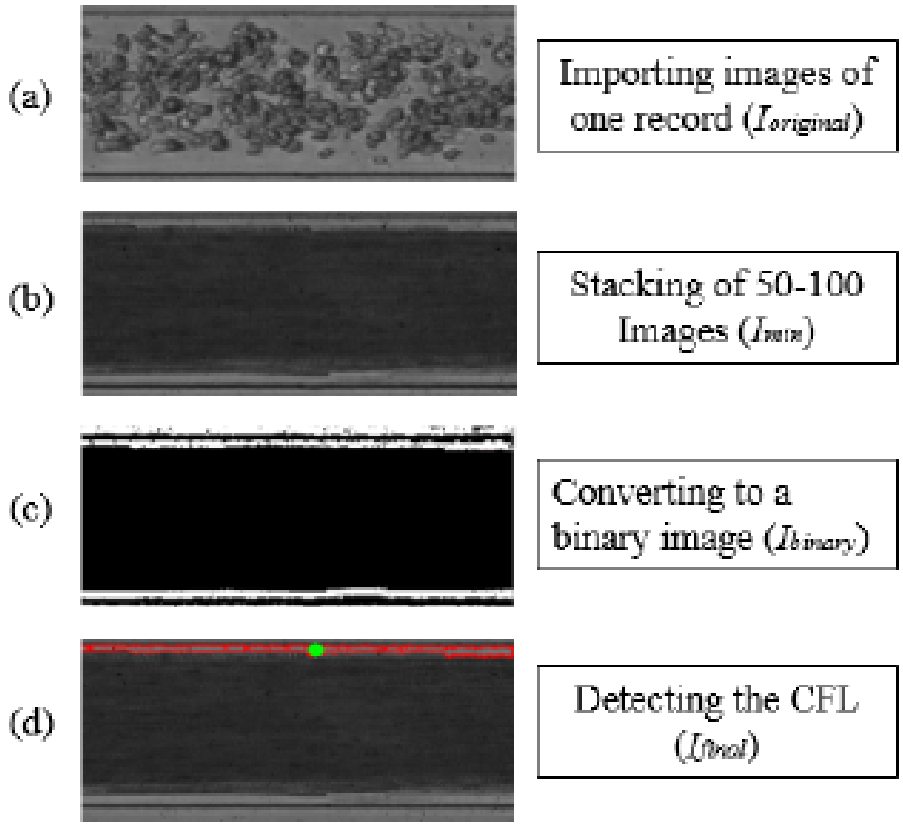


Figure 3.6: Flowchart of the MATLAB image processing code to detect the CFL thickness. (a) The original high-speed camera images, (b) minimum intensity of the stacked images, (c) converted binary image, (d) identified CFL boundary superimposed on the minimum intensity image. The green circle marks the center of mass of the CFL.

Is it true that the marginal layer reduces dissipation?

NO!

Journal of Biological Physics
https://doi.org/10.1007/s10867-019-09534-4

ORIGINAL PAPER

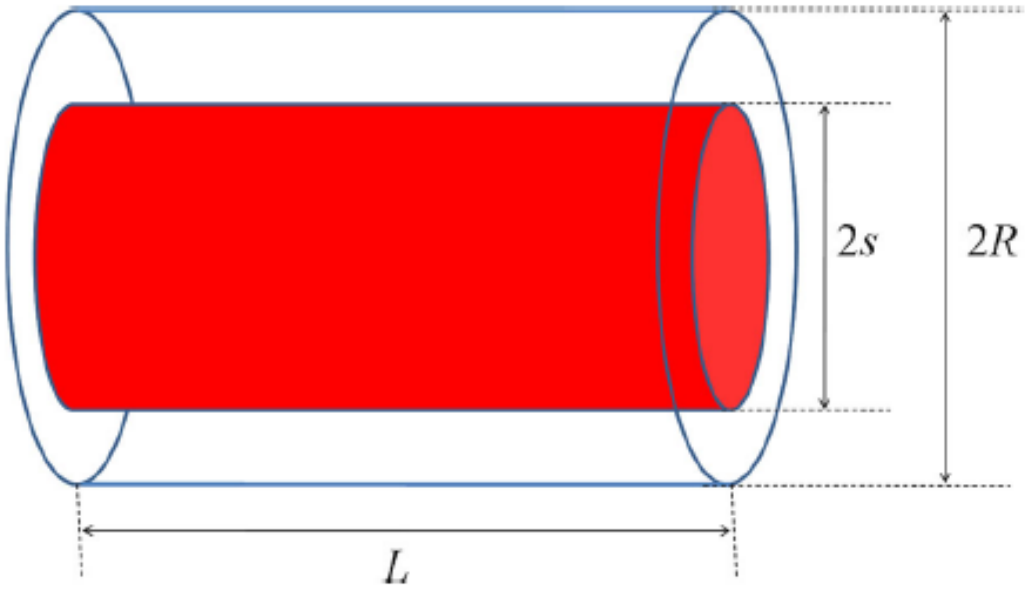
The Fåhræus-Lindqvist effect in small blood vessels: how does it help the heart?

Michela Ascolese[1] · Angiolo Farina[1] · Antonio Fasano[1,2,3]

They prove that the real role of the FL effect in Physiology is to increase the "perfusion effect" towards the peripheral tissues.
Perfusion can be defined as the process in which blood is forced to flow through a network of microscopic vessels within biologic tissue, allowing exchange of oxygen and other molecules across semipermeable microvessels walls. (From: Handbook of Clinical Neurology, 2016)
More technically, blood perfusion, defined as the **blood volume flow rate** through a given volume or mass of living tissue, represents local blood flow through the capillary network and extracellular spaces in the tissue

Geometrical model of a blood vessel in the Haynes' approach

Assume that the vessel is just a tube of radius R, that a core of radius $s < R$ is already formed, and the flow is stationary. Fully developed flow (no transients).



Mathematical model set-up

Blood is treated as an inhomogeneous incompressible Newtonian fluid, whose **viscosity depends on the hematocrit ϕ**, i. e. $\mathbb{T} = -p\mathbb{I} + 2\eta(\phi)\mathbb{D}$, $\mathbb{D} = \frac{1}{2}\left(\nabla \boldsymbol{u} + (\nabla \boldsymbol{u})^T\right)$.

Assume **steady** conditions:

$$\begin{cases} \underbrace{\dfrac{\partial \phi}{\partial t}}_{=\mathbf{0}} + \boldsymbol{u} \cdot \nabla \phi = 0, \\ \nabla \cdot \boldsymbol{u} = 0, \\ \varrho \left(\underbrace{\dfrac{\partial \boldsymbol{u}}{\partial t}}_{=\mathbf{0}} + (\nabla \boldsymbol{u})\boldsymbol{u} \right) = -\nabla p + \nabla \cdot \mathbb{T}, \end{cases} \tag{2}$$

Specializing to the tube geometry and laminar motion

$$\boldsymbol{u} = u(r)\,\boldsymbol{e}_x, \quad \phi = \phi(r), \tag{3}$$

$$0 = -\frac{\partial p}{\partial x} + \frac{1}{r}\frac{\partial}{\partial r}\left(r\eta(\phi)\frac{\partial u}{\partial r}\right). \tag{4}$$

Mathematical model solution

Equation (4) can be solved for $(u(r), \phi(r))$ under standard (no-slip) boundary conditions:

$$u(r) = \frac{\Delta P}{2L} \int_r^R \frac{\xi}{\eta(\phi(\xi))} \, \mathrm{d}\, \xi, \tag{5}$$

and

$$\phi_B \int_0^R \frac{r^3}{\eta(\phi(r))} \, \mathrm{d}\, r = \int_0^R \frac{2r}{\eta(\phi(r))} \left(\int_0^r \phi(\xi) \xi \, \mathrm{d}\, \xi \right) \mathrm{d}\, r, \tag{6}$$

where ϕ_B is the inlet hematocrit (usually between 0.35 and 0.5) and $\Delta P = P(0) - P(L)$ the in-out pressure difference.

Apply the Haynes' conjecture (core-annular structure)

The two regions (core and marginal layer) are separated by an unknown interface s. **Assume $\phi(r)$ to be a uniform stepwise function.** Then

$$\phi(r) = \begin{cases} \phi_c, & 0 \le r \le s, \\ \\ \phi_a, & s < r \le R, \end{cases} \tag{7}$$

where s is a constant. Then, applying the usual continuity interface conditions

$$u(r) = \begin{cases} \dfrac{\Delta P}{4L}\left(\dfrac{s^2 - r^2}{\eta(\phi_c)} + \dfrac{R^2 - s^2}{\eta(\phi_a)}\right), & 0 \le r \le s \\ \\ \dfrac{\Delta P}{4L}\dfrac{R^2 - r^2}{\eta(\phi_a)}, & s \le r \le R, \end{cases} \tag{8}$$

According to Haynes' hypotheses $\phi_a = 0$ (the marginal layer is pure plasma). **More generally, we prefer to assume** $0 < \phi_a \ll \phi_c < 1$.

Tube discharge

$$Q = 2\pi \int_0^R u(r) r \, \mathrm{d}\, r = \frac{\pi \Delta P}{8L} \left(\frac{s^4}{\eta(\phi_c)} + \frac{R^4 - s^4}{\eta(\phi_a)} \right). \tag{9}$$

Recalling the Poiseuille law,

$$\eta_{\mathrm{app}} = \frac{\pi R^4}{8LQ} \Delta P$$

we get a formula for the apparent relative viscosity

$$\eta_{\mathrm{app}} = \frac{\eta(\phi_a)}{1 + \sigma^4 \left(\dfrac{\eta(\phi_a)}{\eta(\phi_c)} - 1 \right)}, \tag{10}$$

where $\sigma = s/R \in (0, 1]$.

Total power dissipation

"Power dissipation" in physiological context: it is the (instantaneous) effort made by heart to pump blood through the circulatory system.

The total power dissipation by the viscous friction along the tube is

$$\mathcal{P} = 2\pi \int_0^L \eta(\phi(r)) \left(\frac{\mathrm{d}}{\mathrm{d}\, r}\ u(r) \right)^2 r \,\mathrm{d}\, r \,\mathrm{d}\, x, \tag{11}$$

while the total flow discharge for a given pressure drop ΔP is

$$\mathcal{Q} = \pi \frac{\Delta P}{L} \int_0^R r \int_r^R \frac{\xi}{\eta(\phi(\xi))} \,\mathrm{d}\, \xi \ \,\mathrm{d}\, r. \tag{12}$$

Discharge and dissipation are proportional!

Thus, by using (8), it follows

$$\mathcal{P} = \Delta P \; \mathcal{Q}. \tag{13}$$

The key point is that $\mathcal{P}$ can be expressed in the form

$$\mathcal{P} = \mathcal{P}_B \Psi(\sigma),$$

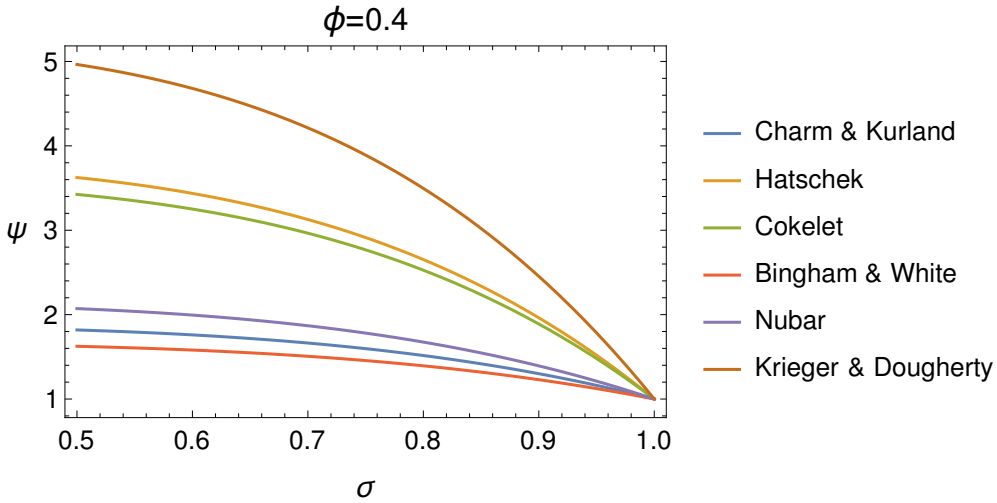
where

$$\mathcal{P}_B = \frac{\pi}{8} \frac{(\Delta P)^2}{L} \frac{R^4}{\eta_B},$$

η_B is the blood viscosity **before** entering the vessel, and $\Psi(\sigma)$ is a dimensionless strictly decreasing function whose explicit form **depends on the way one chooses to evaluate η_B as a function of the hematocrit**. Thus $\mathcal{P}_B$ is the energy dissipation when the RBCs are uniformly distributed over the cross-section (no segregation).

The "true" physiological role of the marginal layer

The bulk viscosity is estimated through *six* different empirical formulas. **Function Ψ changes, but not its global behaviour!**



Thus

- $\mathcal{P}$ (i. e. dissipation) **increases** by decreasing σ (i. e. **by increasing the marginal layer**). Thus the Haynes' conjecture is partially false!
- $\mathcal{Q}$ (i. e. perfusion) **increases** by decreasing σ (i. e. **by increasing the marginal layer**)

Perfusion (not dissipation) is the physiological role of the marginal layer and, probably, the "leitmotiv" of the FL effect itself!

Some questions remain!

Formula

$$\eta_{\text{app}} = \frac{\eta(\phi_a)}{1 + \sigma^4 \left(\dfrac{\eta(\phi_a)}{\eta(\phi_c)} - 1 \right)}$$

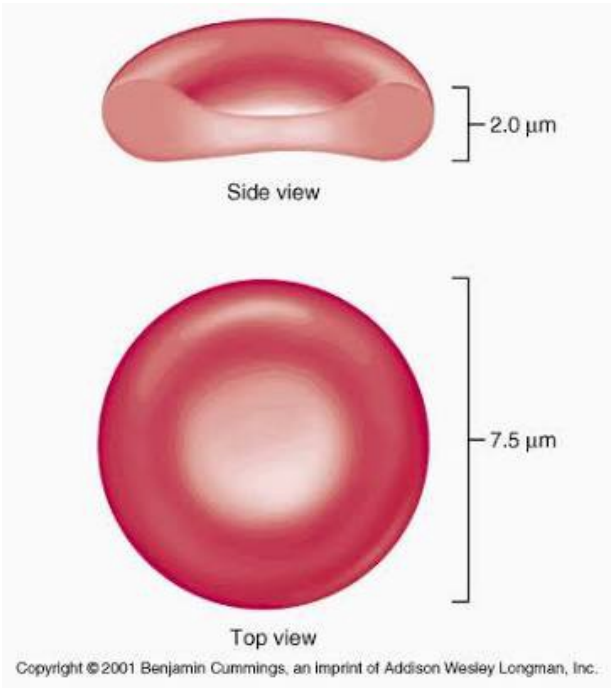
is a direct consequence of Haynes' conjecture and the calculus of the total discharge. It allows to obtain the interface $\sigma = s/R$ from measurable data, once a reliable law for $\eta(\phi)$ is given.

Still waiting for an answer:

- *is a marginal layer already present* **also** *in "large" vessels?*
- *In the affirmative case,* **how can we justify on the bases of the principles of mechanics** *that the layer thickness increases when blood flows from a given vessel to a smaller one (FL effect)?* Why does this effect occur exactly below $\approx 300\mu$m and not, say below 200 or below 400?
- *Are we sure that a marginal layer* **fully depleted** *of RBCs is the correct way to apply Haynes' hypothesis?*

Answer to the first question: the "size exclusion effect"

Red cells cannot pass through the vessel wall. Assume that the *location* of the cell is defined by the location of its center. Thus the *center* of the red cell must lie at least half-thickness away from the wall (which means 1-1.2 μm). Therefore a "minimum" marginal layer should exist **also** in large vessels.



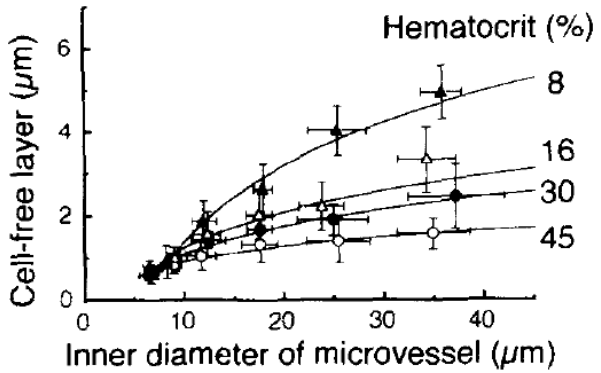
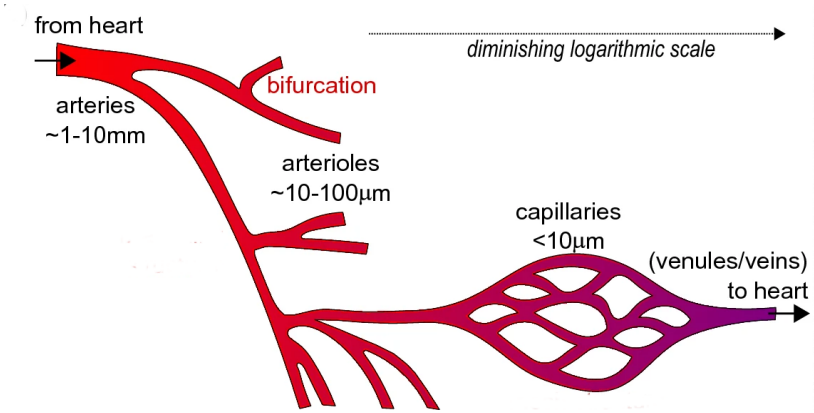


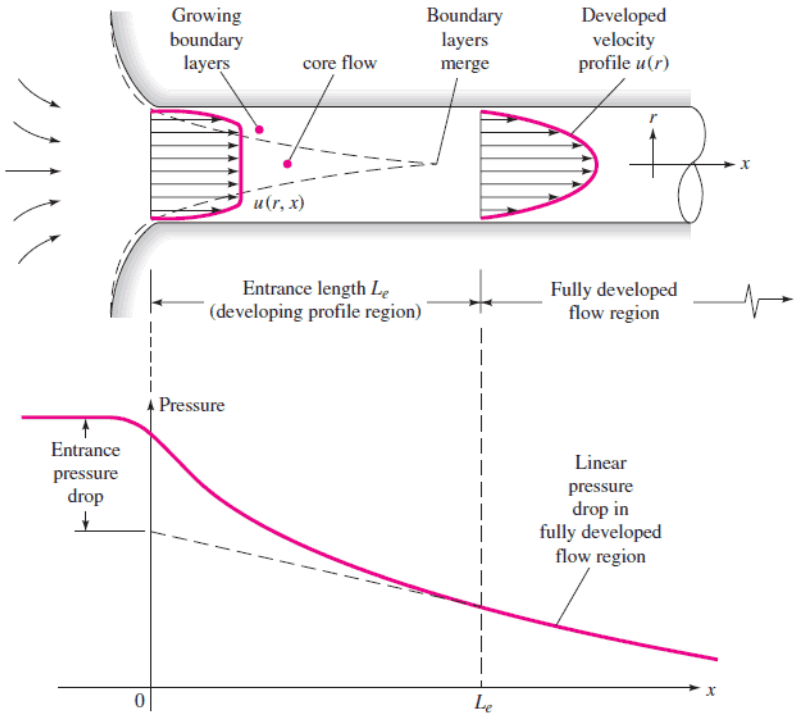
Fig. 5. Effect of hematocrit on the thickness of the cell-free layer measured in microvessels of various inner diameters.

Maeda measurements (1996) have uncertainty of 30% and more.

Answer to the second question.

A possible explanation: the increase of the marginal layer when the vessel radius decreases is nothing but an "entrance effect", i. e. RBCs close to the wall migrate toward the center reaching, quite rapidly, a stationary "core annular" configuration.





Answer to the second question.

From a given vessel to a smaller one: evolution of the marginal layer.

Guadagni, Farina (Int. Journal of Nonlinear Mechanics, 2020) use Prandtl boundary layer theory in plane geometry.

Farina, Rosso, Fasano (Symmetry, 2021 to appear): extension to tube geometry

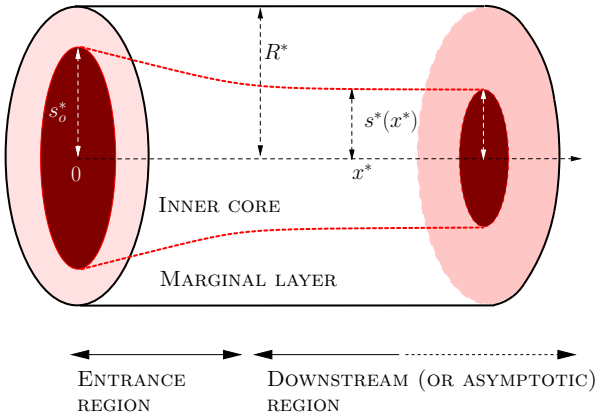
Inner layer (dimensionless)

$$
\begin{cases}
\dfrac{\partial (ru)}{\partial x} + \dfrac{\partial (rv)}{\partial r} = 0, & x \geq 0, \quad 0 \leq r < \sigma(x), \\
u \dfrac{\partial u}{\partial x} + v \dfrac{\partial u}{\partial r} = -\dfrac{\partial p}{\partial x} + \dfrac{\varepsilon\, \eta_c}{r} \dfrac{\partial}{\partial r} \left(r \dfrac{\partial u}{\partial r} \right), & x \geq 0, \quad 0 \leq r < \sigma(x), \\
p = p(x), & x \geq 0, \\
\dfrac{\partial u}{\partial r} = 0, \quad v = 0, & x \geq 0, \quad r = 0, \\
u = 1, \quad v = 0, & x = 0, \quad 0 \leq r \leq 1 - \delta,
\end{cases}
\tag{14}
$$

Outer layer (dimensionless)

$$\begin{cases} \dfrac{\partial(ru)}{\partial x} + \dfrac{\partial(rv)}{\partial r} = 0, & x \geq 0, \quad \sigma(x) < r \leq 1, \\ u\dfrac{\partial u}{\partial x} + v\dfrac{\partial u}{\partial r} = -\dfrac{\partial p}{\partial x} + \dfrac{\varepsilon\,\eta_a}{r}\dfrac{\partial}{\partial r}\left(r\dfrac{\partial u}{\partial r}\right), & x \geq 0, \quad \sigma(x) < r \leq 1, \\ p = p(x), & x \geq 0, \\ u = 0, \quad v = 0, & x \geq 0, \quad r = 1 \\ u = 1, \quad v = 0, & x = 0, \quad 1 - \delta < r \leq 1, \end{cases} \tag{15}$$

From a given vessel to a smaller one: evolution of the marginal layer



Free boundary conditions (dimensionless)

$$\begin{cases} -u(x,\sigma(x))\sigma'(x) + v(x,\sigma(x)) = 0, \quad \text{(kinematic condition)} \\ [\![u]\!] = [\![v]\!] = [\![p]\!] = 0, \quad \eta_c \left.\dfrac{\partial u}{\partial r}\right|_{r=\sigma^-} = \eta_a \left.\dfrac{\partial u}{\partial r}\right|_{r=\sigma^+}, \end{cases} \tag{16}$$

Applying the Langhaar's method (linearization of the inertia terms) it is possible transform the problem into an (extremely complex but numerically solvable) system of coupled ODEs, one of which gives the evolution of the free boundary $\sigma(x)$.

Evolution of the free boundary

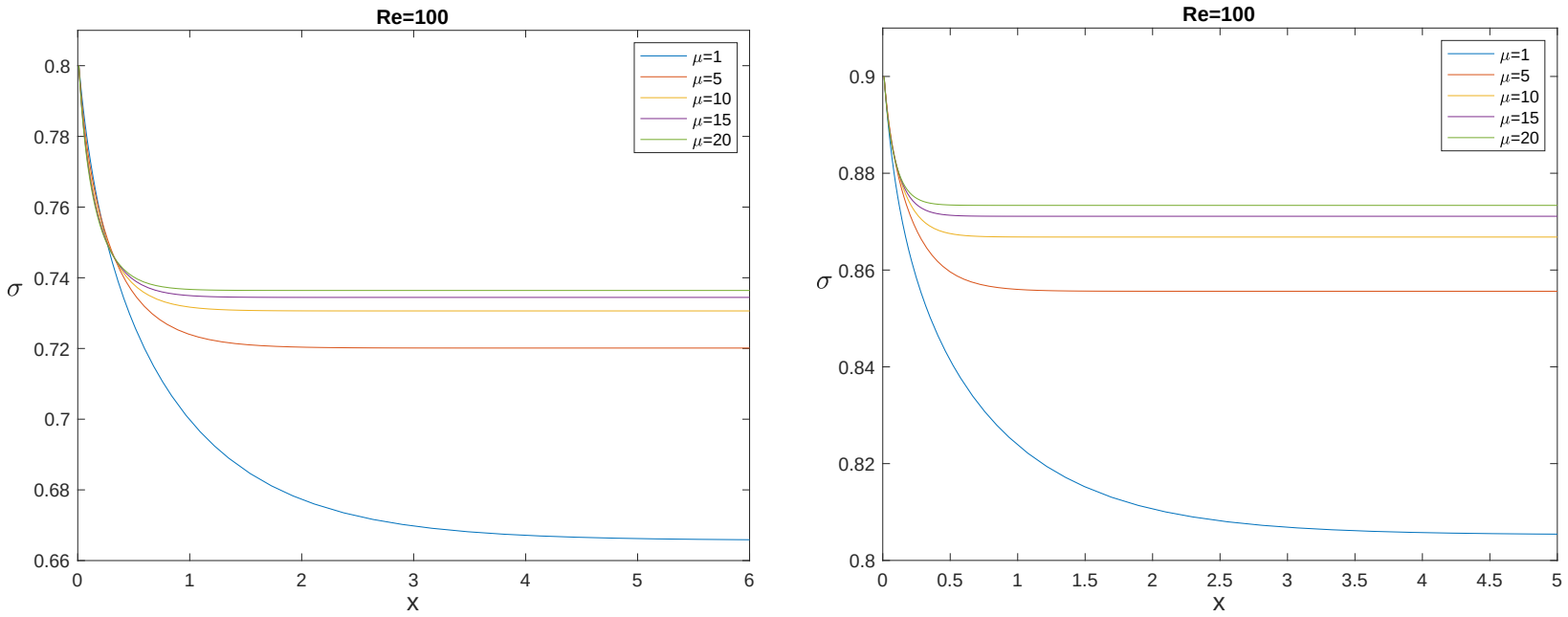


Figure: *The evolution of* $\sigma(x)$ *for* $\mathrm{Re} = 100$, $\sigma(0) = 0.8, 0.9$ *and for five values of the ratio* $\mu = \eta_c/\eta_a$.

The dimensionless "entrance length" and the asymptotic behaviour are clearly identified.

Evolution of the free boundary

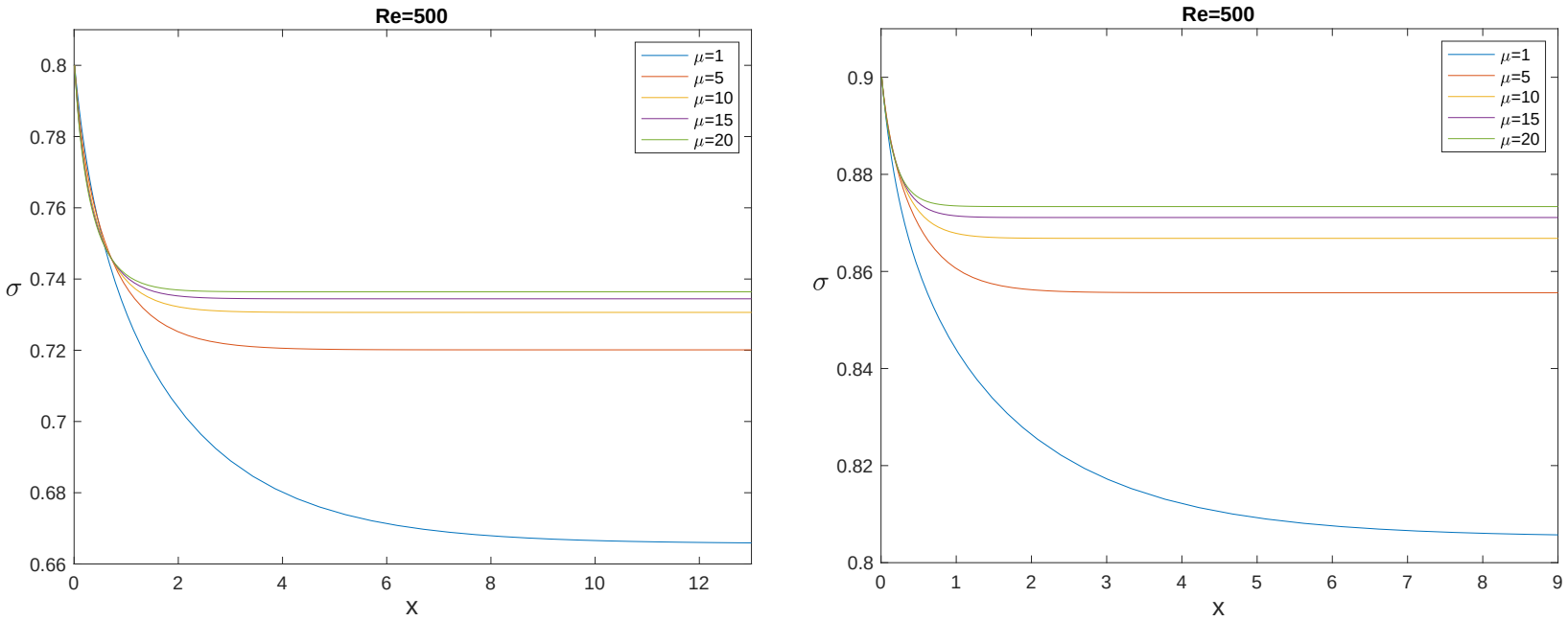


Figure: *The evolution of* $\sigma(x)$ *for* $\mathrm{Re} = 500$, $\sigma(0) = 0.8, 0.9$ *and for five values of the ratio* $\mu = \eta_c/\eta_a$.

The dimensionless "entrance length" and the asymptotic behaviour are clearly identified.

Evolution of the free boundary

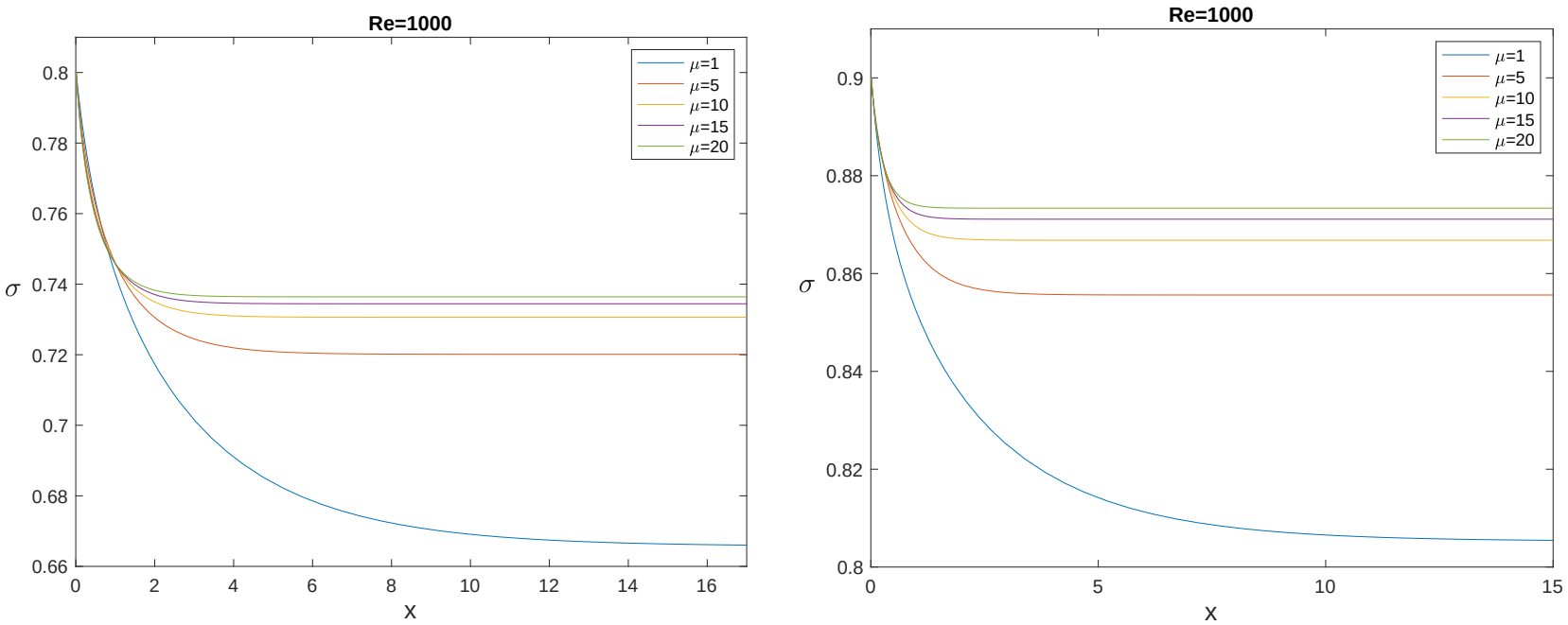


Figure: *The evolution of* $\sigma(x)$ *for* $\mathrm{Re} = 1000$, $\sigma(0) = 0.8, 0.9$ *and some values of the ratio* $\mu = \eta_c/\eta_a$.

The dimensionless "entrance length" and the asymptotic behaviour are clearly identified.

Asymptotic solution

The most evident effect outlined by previous Figs. is that, for fixed μ, the entrance length increases by increasing Re, while for any given Re, it decreases significantly by increasing μ. Moreover, simulations confirm that the σ_∞ depends only on μ and $\sigma(0)$, not on Re (as it must be, see next formula (19))

System (14), (15), (16) allows, in particular, an asymptotic solution of Poiseuille type for $x \to \infty$, namely $v_\infty(r) = 0$ and

$$u_\infty(r) = \frac{2}{(1-\sigma_\infty^4)\,\dfrac{1}{\eta_a} + \dfrac{\sigma_\infty^4}{\eta_c}} \times \begin{cases} \dfrac{\sigma_\infty^2 - r^2}{\eta_c} + \dfrac{1-\sigma_\infty^2}{\eta_a}, & 0 \le r \le \sigma_\infty \\ \dfrac{1-r^2}{\eta_a}, & \sigma_\infty \le r \le 1, \end{cases} \tag{17}$$

where $\sigma_\infty = \lim_{x\to\infty} \sigma(x)$.

A fundamental formula

The interface $\sigma(x)$ is a material curve: apply mass conservation

$$\int_0^{\sigma_o} u(0,r)\, r \,\mathrm{d}\, r = \int_0^{\sigma_\infty} u_\infty(r)\, r \,\mathrm{d}\, r.$$

Solving, the initial core radius and its asymptotic value are related through

$$\sigma_o^2 = \frac{1}{\sigma_\infty^4 \left(\frac{1}{\eta_c} - \frac{1}{\eta_a}\right) + \frac{1}{\eta_a}} \left[\sigma_\infty^4 \left(\frac{1}{\eta_c} - \frac{2}{\eta_a}\right) + \frac{2\sigma_\infty^2}{\eta_a}\right]. \tag{18}$$

A key step: (18) is a fourth order algebraic equation in the unknown σ_∞, with only one physically significant solution i. e. $\sigma_\infty \in (0,1)$,

$$\sigma_\infty = \frac{\sigma_o}{\sqrt{1 + \sqrt{(1-\sigma_o^2)\left[1 - \sigma_o^2\left(1 - \frac{\eta_a}{\eta_c}\right)\right]}}}. \tag{19}$$

Proving the Fähræus Linquist effect

Farina, Rosso, Fasano (J. Biological Physics, 2021)

Use formula (19) with

$$\eta_a = 1 + \alpha(\eta_c - 1), \tag{20}$$

$\alpha = O(10^{-1})$ being a fitting parameter.

Meaning: we consider the marginal layer *not completely free* of RBCs.

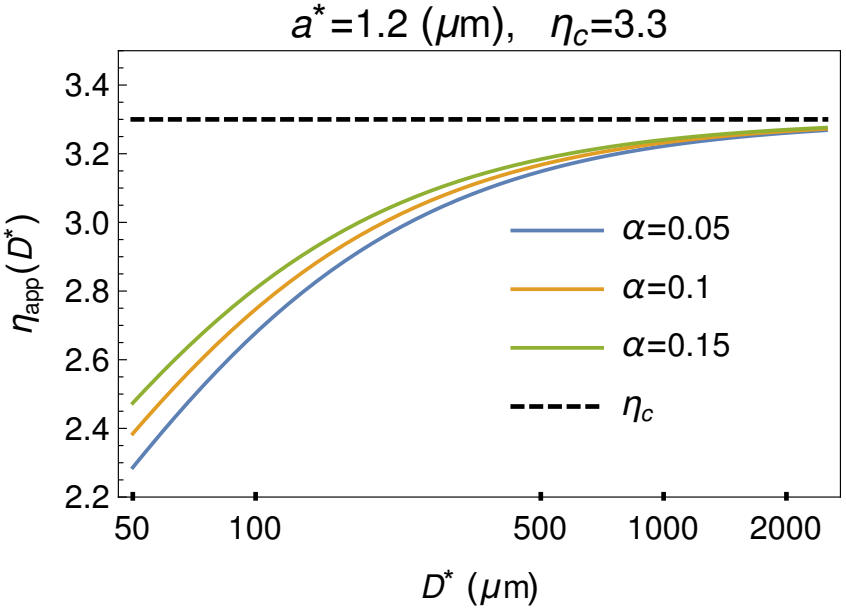
Physical justification: the "marginal exclusion effect" cannot be precisely stated (as it would be if the RBCs were rigid spheres) and it should be more understood as a statistical concept (Ethier and Simmons, Introductory Biomechanics, 2007).

(20) generalizes Haynes' hypothesis: a small percentage of hematocrit is present in the marginal layer and this value may have some variability. Thus it is more appropriate to speak of a "cell–poor" rather than of a "cell-free" layer (Kim et al.,2007)

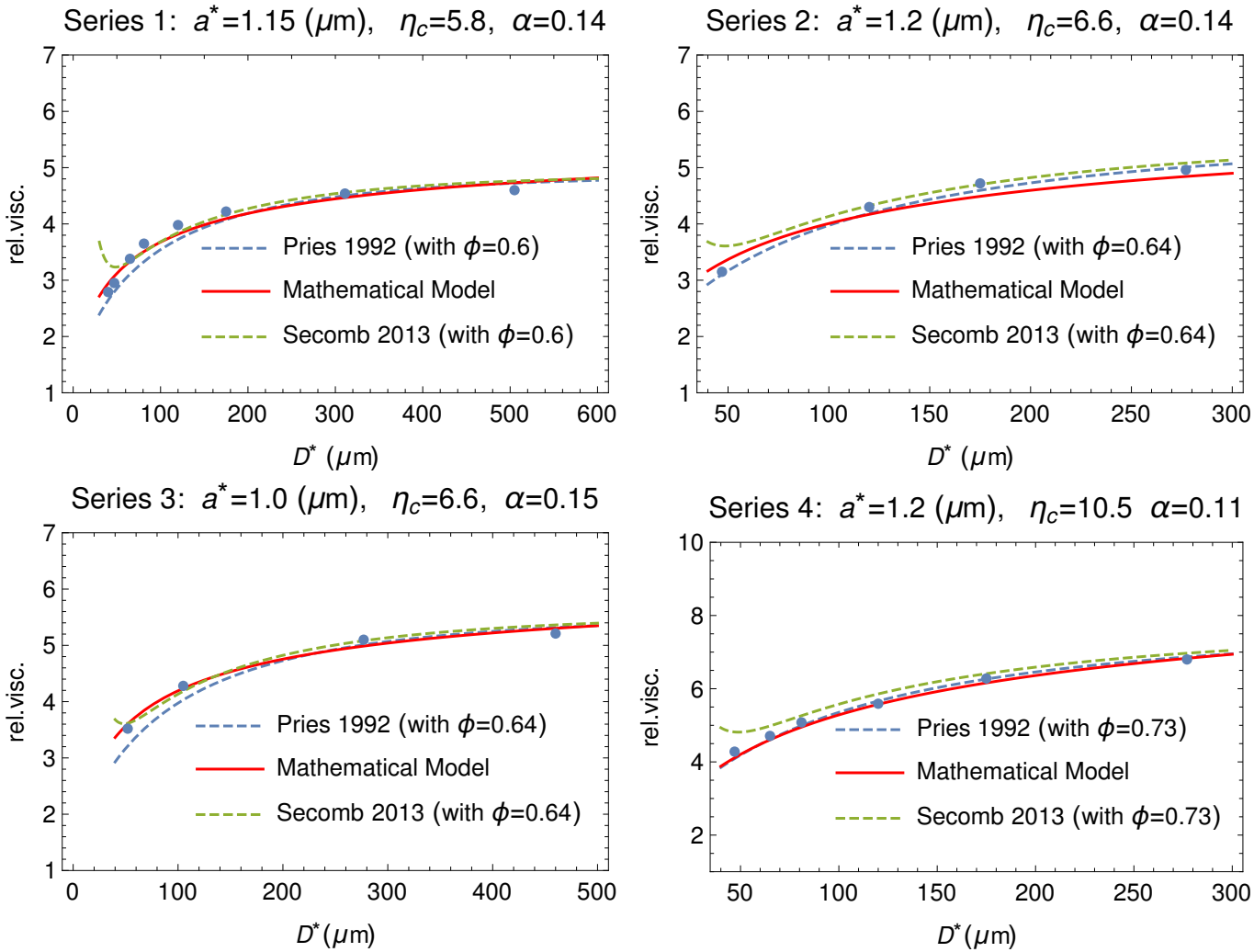
Basic model parameters

- α (range 5-15%) which quantifies the (small) RBCs volume fraction in the "poor-cell" layer
- η_c, the viscosity of the core (range 3-10).
- a^* initial marginal layer thickness (range 1-1.5 μm)

The latter has a precise physical meaning: η_c identifies with the asymptotic limit of $\eta_{\rm app}$ for D^* sufficiently large, i. e. the "bulk" viscosity (viscosity of blood in large vessels).

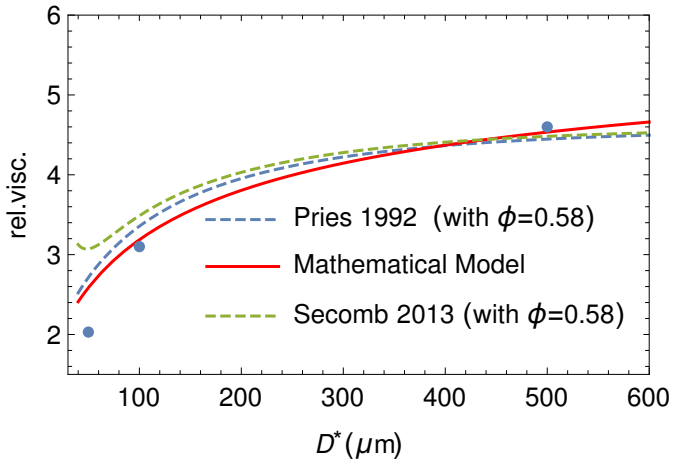


The model vs. the experiments of Fähræus and Linquist

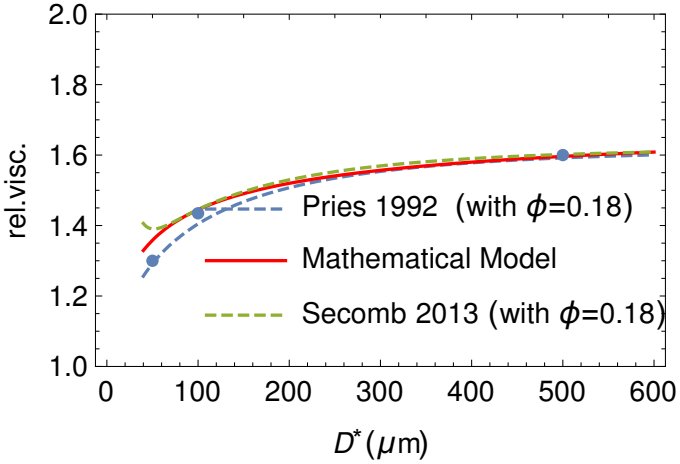


The model vs. the experiments of Zilow and Linderkamp (1989)

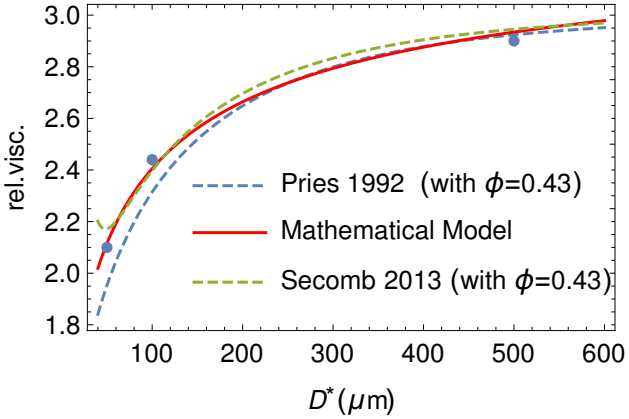
[Infant, ϕ=0.6] a^*=1.2 (μm), η_c=6.4, α=0.1



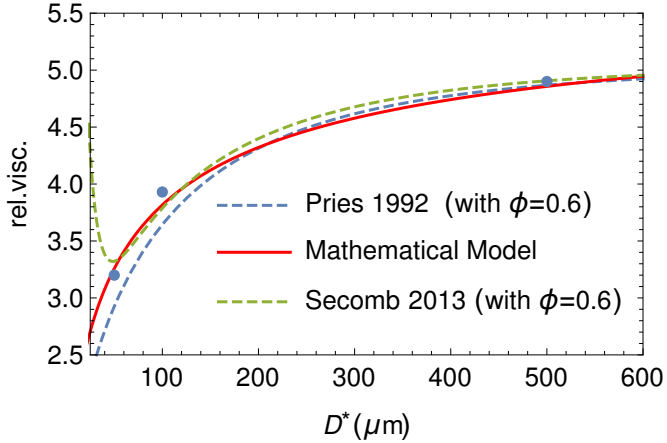
[Adult ϕ=0.2] a^*=1.3 (μm), η_c=1.75 α=0.09



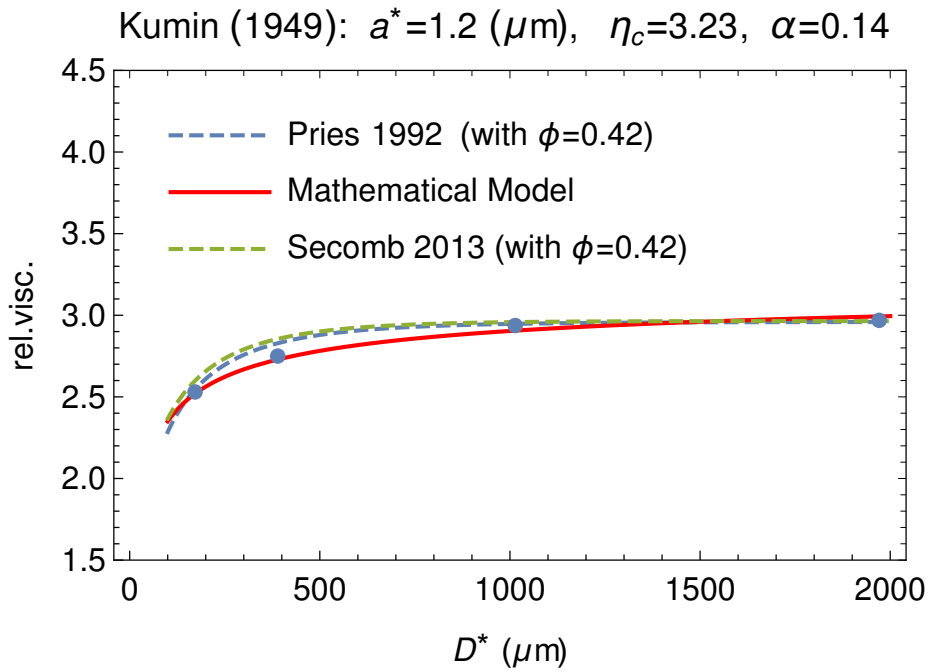
[Adult ϕ=0.4] a^*=1.2 (μm), η_c=3.5, α=0.11



[Adult ϕ=0.6] a^*=1.0 (μm), η_c=6, α=0.14



The model vs. the experiments of Kümin (1949)



Thickness of the marginal layer: the model vs. the experiments of Maeda et al. (1994)

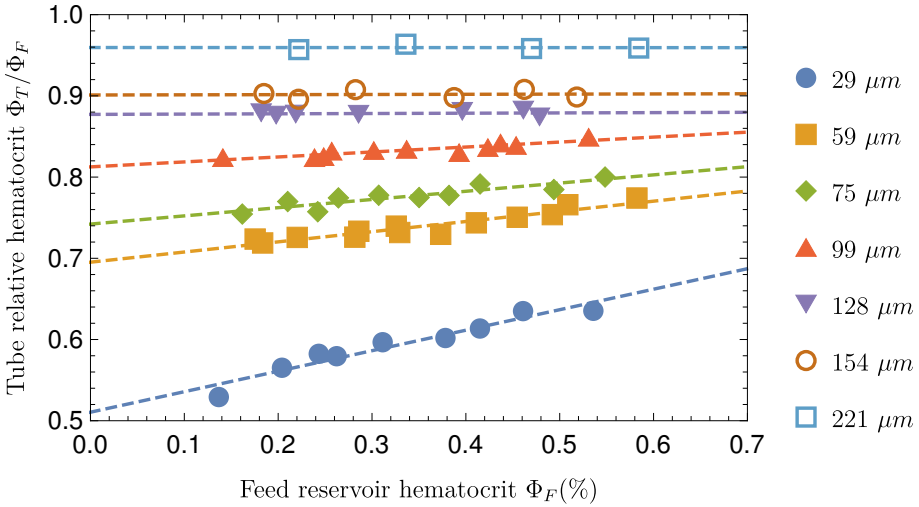
ϕ	η_{CK} $[-]$	$(R^* - s^*_\infty)$ (meas.)	$(R^* - s^*_\infty)$ (theor.)
0.08	1.18	3.9 ± 1.0 µm	2.7 µm
0.16	1.34	3.1 ± 0.5 µm	2.7 µm
0.30	1.61	2.3 ± 0.8 µm	2.6 µm
0.45	2.05	1.6 ± 0.5 µm	2.6 µm

Thickness of the marginal layer: the model vs. the experiments of Kim et al. (2008)

	D^*	$(R^* - s^*_\infty)$ (meas.)	$(R^* - s^*_\infty)$ (theor.)
$\phi = 0.42$, $\eta_{\mathrm{CK}} = 1.94$	72.3 µm	2.7±0.5 µm	3.4 µm
	49.2 µm	3.1±0.6 µm	2.9 µm
	45.3 µm	2.3±0.4 µm	2.8 µm
	30.8 µm	2.1±0.4 µm	2.4 µm
$\phi = 0.41$, $\eta_{\mathrm{CK}} = 1.90$	71.1 µm	3.2±0.7 µm	3.2 µm
	60.2 µm	2.2±0.4 µm	3.0 µm
	54.2 µm	2.9±0.6 µm	2.9 µm
	51.7 µm	2.3±0.4 µm	2.8 µm

Before concluding...

Another enigmatic phenomenon: the "Fähræus" effect



It consists in a decrease of the average concentration Φ (hematocrit) of red blood cells (RBCs) in human blood as the diameter of the tube in which it is flowing decreases
Fähræus, Physiol. Rev. (1929)

The "F" effect is, someway, related to the "FL" effect, but **exactly as for the FL effect, also the F effect is lacking a complete mathematical justification from basic principles of fluid mechanics.**
Future challenge: to justify mathematically the F effect too!

Conclusions

In 2016, Tim Secomb (a famous physiologist) referring to his own empirical formula for the blood apparent viscosity, wrote:

> *During the past 20 years, the above equations*[1] *for the apparent viscosity of blood in vitro and in vivo have been used extensively in theoretical analyses of blood flow in networks of microvessels. However, these equations are empirical and not derived from analyses of the fluid mechanical phenomena involved. The development, from first principles based on knowledge of the mechanical properties of RBCs and other components of the system, of theories capable of predicting the behaviors described by these equations has proved to be a formidable challenge.*

Our model is not a conclusive step to win this challenge, since other questions (as the "Fähræus effect") claim for an answer. However, we believe now that the night is not so dark as before.

[1] Here Secomb refers to his own equation and that by Pries

Hasta la próxima ves

Thanks for your kind attention

Muchas gracias por su fina atención