Recent advances in blood microcirculation

Fabio Rosso

Dipartimento di Matematica e Informatica "Ulisse Dini" Università di Firenze, Italia

IX Maci, 10 May 2023, Argentina

The need of mathematical modeling

Blood is a fluid and it should behave according to the fundamental laws of fluid mechanics. This point has been evident to scientists for almost 200 years.

A pioneer: **Jean-Louis-Marie Poiseuille** (1799-1869) was a physician and physiologist.

Some of his contributions in blood circulation:

- Recherches sur les causes du mouvement du sang dans les vaisseaux capillaires (1839)
- Recherches expérimentales sur le mouvement des liquides de nature différente dans les tubes de très-petits diamétres (1847).

His famous (empirical) law (1836): given the pressure jump Δp, the vessel length L and the volumetric flux Q out of the vessel, then

$$Q \sim R^4 \frac{\Delta p}{L}$$

The need of mathematical modeling

Blood is a fluid and it should behave according to the fundamental laws of fluid mechanics. This point has been evident to scientists for almost 200 years.

A pioneer: **Jean-Louis-Marie Poiseuille** (1799-1869) was a physician and physiologist.

Some of his contributions in blood circulation:

- Recherches sur les causes du mouvement du sang dans les vaisseaux capillaires (1839)
- Recherches expérimentales sur le mouvement des liquides de nature différente dans les tubes de très-petits diamétres (1847).

His famous (empirical) law (1836): given the pressure jump Δp, the vessel length L and the volumetric flux Q out of the vessel, then

$$Q \sim R^4 \frac{\Delta p}{L}$$

The need of mathematical modeling

Blood is a fluid and it should behave according to the fundamental laws of fluid mechanics. This point has been evident to scientists for almost 200 years.

A pioneer: **Jean-Louis-Marie Poiseuille** (1799-1869) was a physician and physiologist.

Some of his contributions in blood circulation:

- Recherches sur les causes du mouvement du sang dans les vaisseaux capillaires (1839)
- Recherches expérimentales sur le mouvement des liquides de nature différente dans les tubes de très-petits diamétres (1847).

His famous (empirical) law (1836): given the pressure jump Δp, the vessel length L and the volumetric flux Q out of the vessel, then

$$Q \sim R^4 \frac{\Delta p}{L}$$

The need of mathematical modeling

Poiseuille law was *mathematically proved* only few years later, via the Navier-Stokes equations (the fundamental laws of fluid dynamics) and the proportionality factor precisely identified:

The need of mathematical modeling

Poiseuille law was *mathematically proved* only few years later, via the Navier-Stokes equations (the fundamental laws of fluid dynamics) and the proportionality factor precisely identified:

$$Q = \frac{\pi}{8\eta} \frac{R^4 \Delta p}{L}$$

where η is the fluid *viscosity*, a material (and measurable) property.

The need of mathematical modeling

Poiseuille law was *mathematically proved* only few years later, via the Navier-Stokes equations (the fundamental laws of fluid dynamics) and the proportionality factor precisely identified:

$$Q = \frac{\pi}{8\eta} \frac{R^4 \Delta p}{L}$$

where η is the fluid *viscosity*, a material (and measurable) property.

However for almost 150-180 years, several experiments in blood circulation have revealed that things are not so simple! The biological nature of blood implies that viscosity has very special characteristics.

Moreover, **a mathematical justification** of several observed phenomena has remained a challenging issue for a long time
(see, e.g., **Hemomath: The Mathematics of Blood** (A. Fasano. and A. Siqueira, 2017) for an extended overview of recent progresses and open problems).

A (partial) list of recent contributions in hemodynamics in Firenze

Most of the following papers are somehow deeply related: the main underlying ideas are sheared among them and my today presentation will devoted to see how and why.

- Modeling peristaltic flow in vessels equipped with valves: Implications for vasomotion in bat wing venules (A. Farina, L. Fusi, A. Fasano, A. Ceretani, F. Rosso, Int. J. of Engineering Sci. 2016)
- The Fåhræus-Lindqvist effect in small blood vessels: how does it help the heart? (M. Ascolese, A. Farina, A. Fasano, J. of Biological Physics 2019)
- Entrance flow of a suspension and particles migration towards the vessel center (S. Guadagni, A. Farina, Int. Journal of Nonlinear Mechanics 2020)
- A continuum mechanics model for the Fåhræus - Lindqvist effect (A. Farina, F. Rosso, A. Fasano, J. of Biological Physics, 2021)
- Mathematical Models for Some Aspects of Blood Microcirculation (A. Farina, A. Fasano, F. Rosso, Symmetry 2021)
- Modeling hemodialysis with albumin retention (A. Farina, A. Fasano, F. Rosso and Y. Shekari, Applicable Analysis 2022)
- **Modeling vasomotion in arterioles (A. Farina, A. Fasano, F. Rosso, J. Theoretical Biology 2022)**
- **A theoretical model for the Fåhræus effect in medium–large microvessels (A. Farina, A. Fasano, F. Rosso, J. Theoretical Biology 2023)**

A (partial) list of recent contributions in hemodynamics in Firenze

Most of the following papers are somehow deeply related: the main underlying ideas are sheared among them and my today presentation will devoted to see how and why.

- Modeling peristaltic flow in vessels equipped with valves: Implications for vasomotion in bat wing venules (A. Farina, L. Fusi, A. Fasano, A. Ceretani, F. Rosso, Int. J. of Engineering Sci. 2016)
- The Fåhræus-Lindqvist effect in small blood vessels: how does it help the heart? (M. Ascolese, A. Farina, A. Fasano, J. of Biological Physics 2019)
- Entrance flow of a suspension and particles migration towards the vessel center (S. Guadagni, A. Farina, Int. Journal of Nonlinear Mechanics 2020)
- A continuum mechanics model for the Fåhræus - Lindqvist effect (A. Farina, F. Rosso, A. Fasano, J. of Biological Physics, 2021)
- Mathematical Models for Some Aspects of Blood Microcirculation (A. Farina, A. Fasano, F. Rosso, Symmetry 2021)
- Modeling hemodialysis with albumin retention (A. Farina, A. Fasano, F. Rosso and Y. Shekari, Applicable Analysis 2022)
- **Modeling vasomotion in arterioles (A. Farina, A. Fasano, F. Rosso, J. Theoretical Biology 2022)**
- **A theoretical model for the Fåhræus effect in medium–large microvessels (A. Farina, A. Fasano, F. Rosso, J. Theoretical Biology 2023)**

A (partial) list of recent contributions in hemodynamics in Firenze

Most of the following papers are somehow deeply related: the main underlying ideas are sheared among them and my today presentation will devoted to see how and why.

- Modeling peristaltic flow in vessels equipped with valves: Implications for vasomotion in bat wing venules (A. Farina, L. Fusi, A. Fasano, A. Ceretani, F. Rosso, Int. J. of Engineering Sci. 2016)
- The Fåhræus-Lindqvist effect in small blood vessels: how does it help the heart? (M. Ascolese, A. Farina, A. Fasano, J. of Biological Physics 2019)
- Entrance flow of a suspension and particles migration towards the vessel center (S. Guadagni, A. Farina, Int. Journal of Nonlinear Mechanics 2020)
- A continuum mechanics model for the Fåhræus - Lindqvist effect (A. Farina, F. Rosso, A. Fasano, J. of Biological Physics, 2021)
- Mathematical Models for Some Aspects of Blood Microcirculation (A. Farina, A. Fasano, F. Rosso, Symmetry 2021)
- Modeling hemodialysis with albumin retention (A. Farina, A. Fasano, F. Rosso and Y. Shekari, Applicable Analysis 2022)
- **Modeling vasomotion in arterioles (A. Farina, A. Fasano, F. Rosso, J. Theoretical Biology 2022)**
- **A theoretical model for the Fåhræus effect in medium–large microvessels (A. Farina, A. Fasano, F. Rosso, J. Theoretical Biology 2023)**

Which kind of liquid is blood?

It is a *suspension* of various living 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.
Hematocrit= % of erythrocytes (red blood cells) in a unit volume of blood

Which kind of liquid is blood?

It is a *suspension* of various living 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.
Hematocrit= % of erythrocytes (red blood cells) in a unit volume of blood

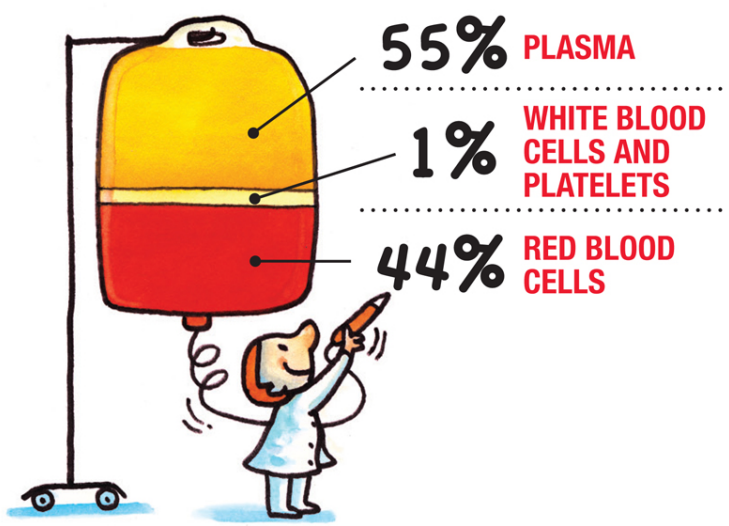
Which kind of liquid is blood?

It is a *suspension* of various living 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.
Hematocrit= % of erythrocytes (red blood cells) in a unit volume of blood

Which kind of liquid is blood?

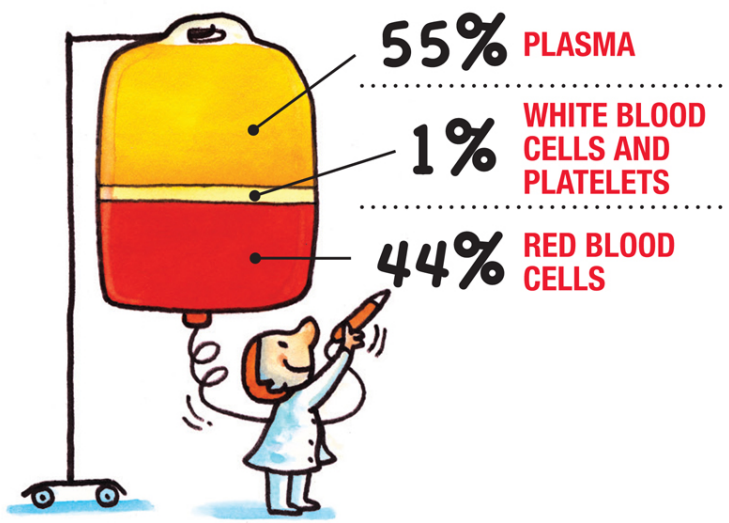
It is a *suspension* of various living cells in a proteic liquid (plasma). Plasma, as it stands, has rheological properties very close to those of water (almost the same density and viscosity).
However suspended particles make the difference!



RBCs are $\approx 98\%$ of all blood cells. Plasma is water $\approx 92\%$ plus various proteins, electrolytes and organic molecules.
Hematocrit= % of erythrocytes (red blood cells) in a unit volume of blood

Which kind of liquid is blood?

It is a *suspension* of various living 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.
Hematocrit= % of erythrocytes (red blood cells) in a unit volume of blood

Non-Newtonian effects in microvessels

Many fluids of everyday life behave *Newtonially*, i. e. the viscous stress and velocity gradient are directly proportional through the fluid *constant* viscosity η (depending, eventually, on temperature).
Blood too behaves Newtonially **but only if the vessel diameter remains above a given threshold**.

A first example of non-newtonian behavior: the Fähræus-Lindqvist effect (1931)

Viscosity (measured through the Poseuille formula) decreases as the vessel diameter decreases below ≈ 300 µm

A very unusual situation in fluid mechanics: viscosity (a material property) depends on the geometry!

Non-Newtonian effects in microvessels

Many fluids of everyday life behave *Newtonially*, i. e. the viscous stress and velocity gradient are directly proportional through the fluid *constant* viscosity η (depending, eventually, on temperature).

Blood too behaves Newtonially **but only if the vessel diameter remains above a given threshold**.

A first example of non-newtonian behavior: the Fähræus-Lindqvist effect (1931)

Viscosity (measured through the Poseuille formula) decreases as the vessel diameter decreases below ≈ 300 µm

A very unusual situation in fluid mechanics: viscosity (a material property) depends on the geometry!

Non-Newtonian effects in microvessels

Many fluids of everyday life behave *Newtonially*, i. e. the viscous stress and velocity gradient are directly proportional through the fluid *constant* viscosity η (depending, eventually, on temperature).
Blood too behaves Newtonially **but only if the vessel diameter remains above a given threshold**.

A first example of non-newtonian behavior: the Fähræus-Lindqvist effect (1931)

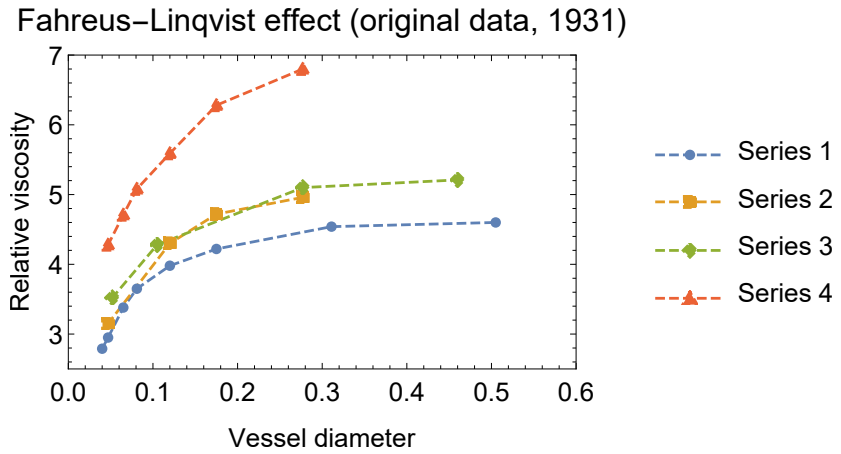
Viscosity (measured through the Poseuille formula) decreases as the vessel diameter decreases below ≈ 300 µm

A very unusual situation in fluid mechanics: viscosity (a material property) depends on the geometry!

Non-Newtonian effects in microvessels

Many fluids of everyday life behave *Newtonially*, i. e. the viscous stress and velocity gradient are directly proportional through the fluid *constant* viscosity η (depending, eventually, on temperature).
Blood too behaves Newtonially **but only if the vessel diameter remains above a given threshold**.

A first example of non-newtonian behavior: the Fähræus-Lindqvist effect (1931)



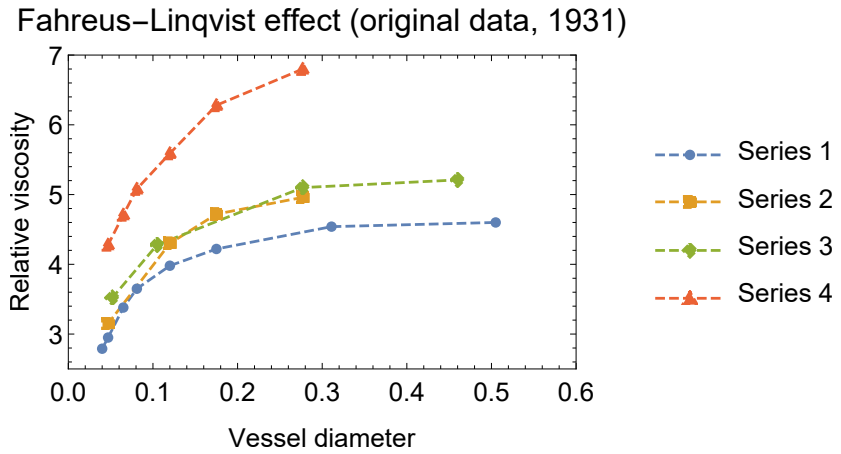
Viscosity (measured through the Poseuille formula) decreases as the vessel diameter decreases below ≈ 300 µm

A very unusual situation in fluid mechanics: viscosity (a material property) depends on the geometry!

Non-Newtonian effects in microvessels

Many fluids of everyday life behave *Newtonially*, i. e. the viscous stress and velocity gradient are directly proportional through the fluid *constant* viscosity η (depending, eventually, on temperature).
Blood too behaves Newtonially **but only if the vessel diameter remains above a given threshold**.

A first example of non-newtonian behavior: the Fähræus-Lindqvist effect (1931)



Viscosity (measured through the Poseuille formula) decreases as the vessel diameter decreases below ≈ 300 µm

A very unusual situation in fluid mechanics: viscosity (a material property) depends on the geometry!

Non-Newtonian effects in microvessels

Another non-newtonian behavior: the Fähræus effect (1929)

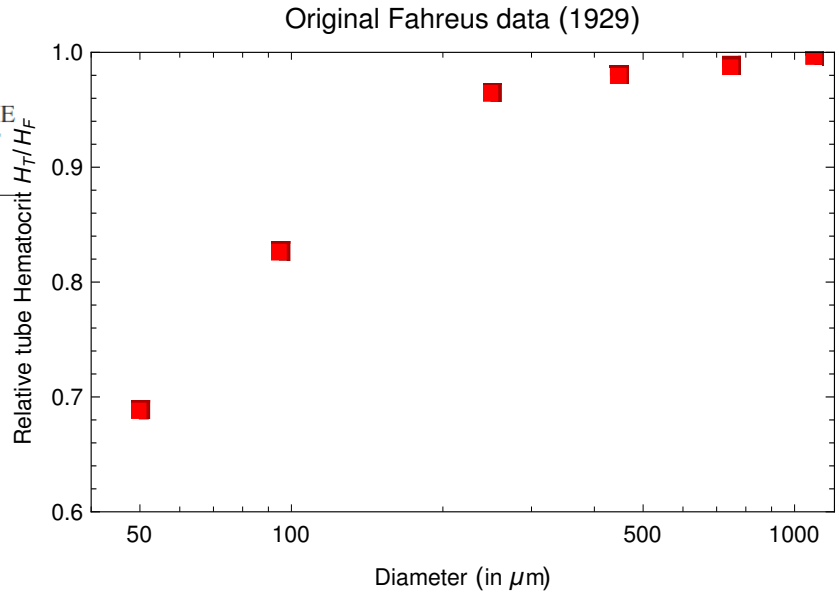
The *relative* hematocrit starts decreasing as the vessel diameter decreases below ≈ 1000 µm. The effect is more pronounced when the vessel diameter is below ≈ 500 µm.

Again a material property influenced by geometry!

Non-Newtonian effects in microvessels

Another non-newtonian behavior: the Fähræus effect (1929)

DIAMETER OF THE TUBES	COMPOSITION OF THE BLOOD		AVERAGE VELOCITY OF THE ERYTHROCYTES, THAT OF THE PLASMA = 100
	Erythrocytes	Plasma	
mm.	*per cent*	*per cent*	
1.100	40.5	59.5	100
0.750	40.1	59.9	101
0.450	39.8	60.2	103
0.250	39.2	60.8	106
0.095	33.6	66.4	135
0.050	28.0	72.0	175



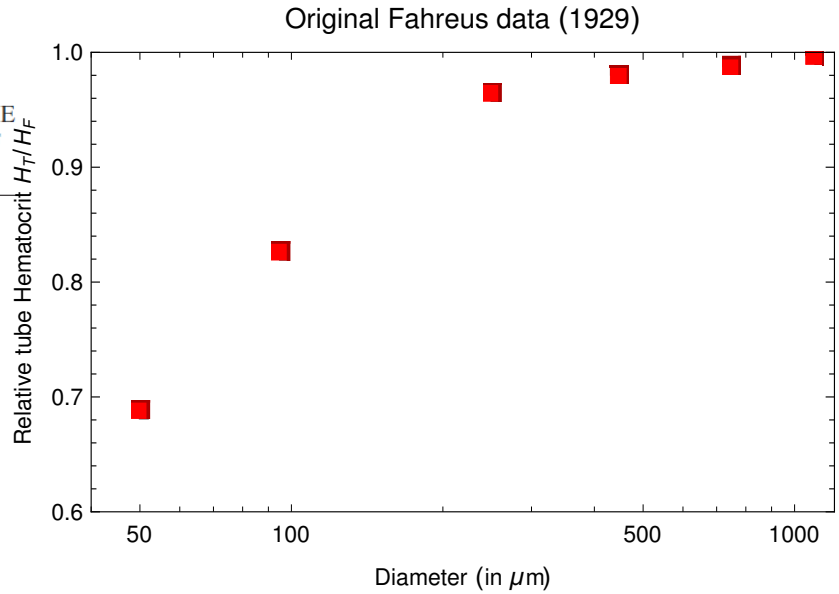
The *relative* hematocrit starts decreasing as the vessel diameter decreases below ≈ 1000 µm. The effect is more pronounced when the vessel diameter is below ≈ 500 µm.

Again a material property influenced by geometry!

Non-Newtonian effects in microvessels

Another non-newtonian behavior: the Fähræus effect (1929)

DIAMETER OF THE TUBES	COMPOSITION OF THE BLOOD		AVERAGE VELOCITY OF THE ERYTHROCYTES, THAT OF THE PLASMA = 100
	Erythrocytes	Plasma	
mm.	*per cent*	*per cent*	
1.100	40.5	59.5	100
0.750	40.1	59.9	101
0.450	39.8	60.2	103
0.250	39.2	60.8	106
0.095	33.6	66.4	135
0.050	28.0	72.0	175

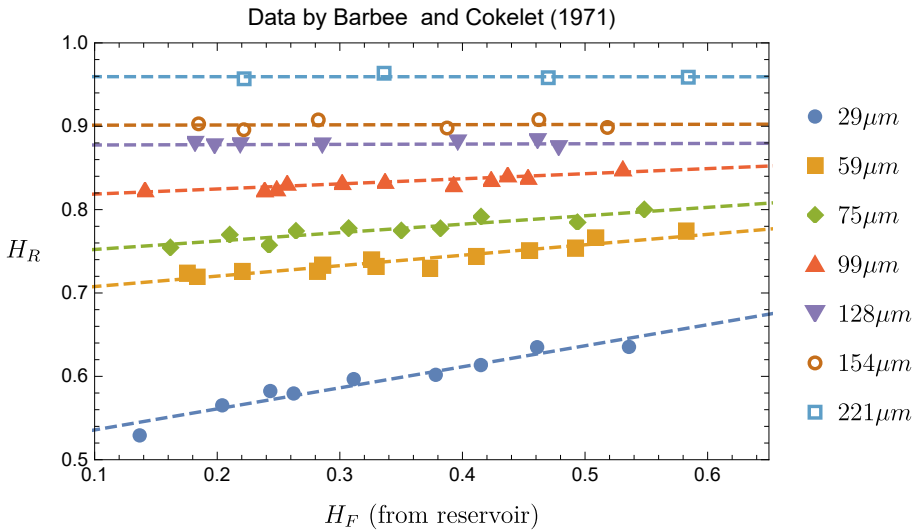


The *relative* hematocrit starts decreasing as the vessel diameter decreases below ≈ 1000 µm. The effect is more pronounced when the vessel diameter is below ≈ 500 µm.

Again a material property influenced by geometry!

Non-Newtonian effects in microvessels

The Fähræus effect according to Barbee and Cokelet (1971)

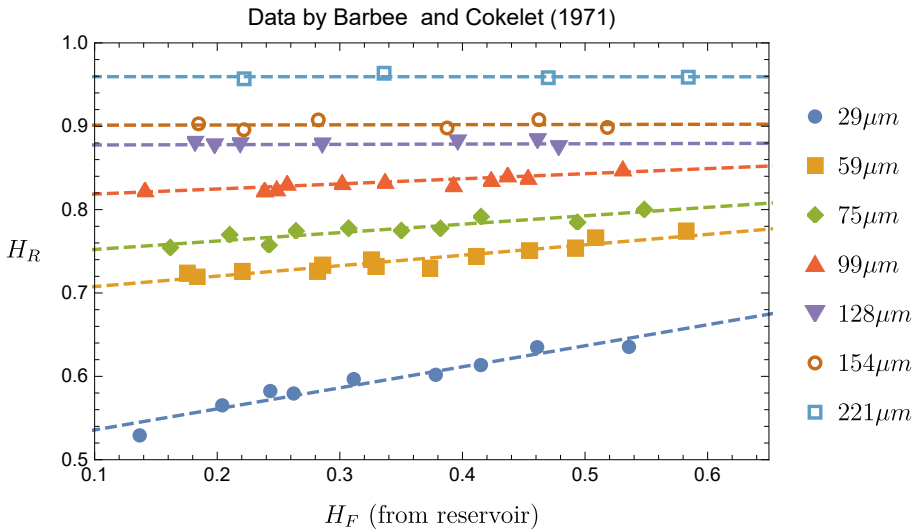


The relative hematocrit $H_R = H_T/H_F$ in human blood decreases as the tube diameter D decreases. A linear trend also appears of H_R as a function of H_F.

At the end of my presentation at MACI VIII I said that a mathematical model for this was missing: form this point of view the today presentation is a continuation of that one!

Non-Newtonian effects in microvessels

The Fähræus effect according to Barbee and Cokelet (1971)

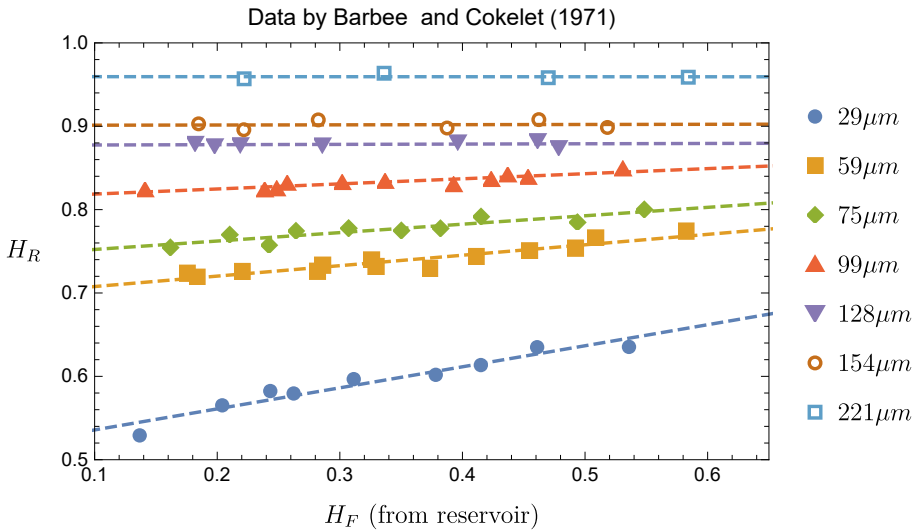


The relative hematocrit $H_R = H_T/H_F$ in human blood decreases as the tube diameter D decreases. A linear trend also appears of H_R as a function of H_F.

At the end of my presentation at MACI VIII I said that a mathematical model for this was missing: form this point of view the today presentation is a continuation of that one!

Non-Newtonian effects in microvessels

The Fähræus effect according to Barbee and Cokelet (1971)



The relative hematocrit $H_R = H_T/H_F$ in human blood decreases as the tube diameter D decreases. A linear trend also appears of H_R as a function of H_F.

At the end of my presentation at MACI VIII I said that a mathematical model for this was missing: form this point of view the today presentation is a continuation of that one!

A mathematical model for the Fähræus effect (and Fähræus-Lindqvist effect too)

Main modeling hypotheses

Blood: a solid-fluid mixture (RBCs and plasma, incompressible in their pure states).

Dynamical state: specified by hematocrit H (volume fraction occupied by RBCs), velocity v and pressure p.

Stationary Navier-Stokes equations:

$$(1) \qquad \begin{cases} v \cdot \nabla H = 0, & \text{(hematocrit conservation law)} \\ \nabla \cdot v = 0, & \text{(volume conservation law)} \\ \rho\,(v \cdot \nabla v) = -\nabla p + \nabla \cdot \mathbb{T}, & \text{(momentum balance)} \end{cases}$$

ρ =blood density (constant and uniform), $\mathbb{T}$ =shear stress tensor

Constitutive equation:

$$(2) \qquad \mathbb{T} = \eta(H)\left(\nabla v + \nabla v^{\,T}\right), \qquad (\eta = \text{viscosity of the mixture})$$

A mathematical model for the Fähræus effect (and Fähræus-Lindqvist effect too)

Main modeling hypotheses

Blood: a solid-fluid mixture (RBCs and plasma, incompressible in their pure states).

Dynamical state: specified by hematocrit H (volume fraction occupied by RBCs), velocity v and pressure p.

Stationary Navier-Stokes equations:

$$(1) \qquad \begin{cases} v \cdot \nabla H = 0, & \text{(hematocrit conservation law)} \\ \nabla \cdot v = 0, & \text{(volume conservation law)} \\ \rho\,(v \cdot \nabla v) = -\nabla p + \nabla \cdot \mathbb{T}, & \text{(momentum balance)} \end{cases}$$

ρ =blood density (constant and uniform), $\mathbb{T}$ =shear stress tensor

Constitutive equation:

$$(2) \qquad \mathbb{T} = \eta(H)\left(\nabla v + \nabla v^{\,T}\right), \qquad (\eta = \text{viscosity of the mixture})$$

A mathematical model for the Fähræus effect (and Fähræus-Lindqvist effect too)

Main modeling hypotheses

Blood: a solid-fluid mixture (RBCs and plasma, incompressible in their pure states).

Dynamical state: specified by hematocrit H (volume fraction occupied by RBCs), velocity $\boldsymbol{v}$ and pressure p.

Stationary Navier-Stokes equations:

$$(1) \qquad \begin{cases} \boldsymbol{v} \cdot \nabla H = 0, & \text{(hematocrit conservation law)} \\ \nabla \cdot \boldsymbol{v} = 0, & \text{(volume conservation law)} \\ \rho\left(\boldsymbol{v} \cdot \nabla \boldsymbol{v}\right) = -\nabla p + \nabla \cdot \mathbb{T}, & \text{(momentum balance)} \end{cases}$$

ρ =blood density (constant and uniform), $\mathbb{T}$ =shear stress tensor

Constitutive equation:

$$(2) \qquad \mathbb{T} = \eta(H)\left(\nabla \boldsymbol{v} + \nabla \boldsymbol{v}^{\,T}\right), \qquad (\eta = \text{viscosity of the mixture})$$

A mathematical model for the Fähræus effect (and Fähræus-Lindqvist effect too)

Main modeling hypotheses

Blood: a solid-fluid mixture (RBCs and plasma, incompressible in their pure states).

Dynamical state: specified by hematocrit H (volume fraction occupied by RBCs), velocity $\boldsymbol{v}$ and pressure p.

Stationary Navier-Stokes equations:

$$(1) \qquad \begin{cases} \boldsymbol{v} \cdot \nabla H = 0, & \text{(hematocrit conservation law)} \\ \nabla \cdot \boldsymbol{v} = 0, & \text{(volume conservation law)} \\ \rho\,(\boldsymbol{v} \cdot \nabla \boldsymbol{v}) = -\nabla p + \nabla \cdot \mathbb{T}, & \text{(momentum balance)} \end{cases}$$

ρ =blood density (constant and uniform), $\mathbb{T}$ =shear stress tensor

Constitutive equation:

$$(2) \qquad \mathbb{T} = \eta(H)\left(\nabla \boldsymbol{v} + \nabla \boldsymbol{v}^{\,T}\right), \qquad (\eta = \text{viscosity of the mixture})$$

A mathematical model for the Fähræus effect (and Fähræus-Lindqvist effect too)

Main modeling hypotheses

Blood: a solid-fluid mixture (RBCs and plasma, incompressible in their pure states).

Dynamical state: specified by hematocrit H (volume fraction occupied by RBCs), velocity $\boldsymbol{v}$ and pressure p.

Stationary Navier-Stokes equations:

$$(1) \qquad \begin{cases} \boldsymbol{v} \cdot \nabla H = 0, & \text{(hematocrit conservation law)} \\ \nabla \cdot \boldsymbol{v} = 0, & \text{(volume conservation law)} \\ \rho\,(\boldsymbol{v} \cdot \nabla \boldsymbol{v}) = -\nabla p + \nabla \cdot \mathbb{T}, & \text{(momentum balance)} \end{cases}$$

ρ =blood density (constant and uniform), $\mathbb{T}$ =shear stress tensor

Constitutive equation:

$$(2) \qquad \mathbb{T} = \eta(H)\left(\nabla \boldsymbol{v} + \nabla \boldsymbol{v}^{\,T}\right), \qquad (\eta = \text{viscosity of the mixture})$$

The Haynes conjecture (Am. J. of Physiology, 1960)

In small vessels the RBCs migrate towards the center of the tube (the CORE), leaving a marginal layer of pure plasma around (the Cell Free Layer).
Since the viscosity of this layer is from 4 to 5 times lower rhan that of the core and the viscous stress takes its maximum at the wall, the whole stress should be drastically reduced.

In simpler words: the marginal layer **fluidizes** the flow!

This idea is not new: according to Jeffery (Proc. Roy. Soc. London, 1922), *particles will tend to adopt that motion which, among all possible ones, corresponds to the least dissipation of energy*

Is this true?

YES: a CFL is really observable (but it is not completely free)! However, it is not true that dissipation is reduced.

Moreover, until 2019, the CFL development had not received a rigorous mathematical justification!
The main problem is to describe how changes the marginal layer as the geometry changes (say, when a given vessel bifurcates into smaller ones)

The Haynes conjecture (Am. J. of Physiology, 1960)

In small vessels the RBCs migrate towards the center of the tube (the CORE), leaving a marginal layer of pure plasma around (the Cell Free Layer).
Since the viscosity of this layer is from 4 to 5 times lower rhan that of the core and the viscous stress takes its maximum at the wall, the whole stress should be drastically reduced.

In simpler words: the marginal layer **fluidizes** the flow!

This idea is not new: according to Jeffery (Proc. Roy. Soc. London, 1922), *particles will tend to adopt that motion which, among all possible ones, corresponds to the least dissipation of energy*

Is this true?

YES: a CFL is really observable (but it is not completely free)! However, it is not true that dissipation is reduced.

Moreover, until 2019, the CFL development had not received a rigorous mathematical justification!
The main problem is to describe how changes the marginal layer as the geometry changes (say, when a given vessel bifurcates into smaller ones)

The Haynes conjecture (Am. J. of Physiology, 1960)

In small vessels the RBCs migrate towards the center of the tube (the CORE), leaving a marginal layer of pure plasma around (the Cell Free Layer).
Since the viscosity of this layer is from 4 to 5 times lower rhan that of the core and the viscous stress takes its maximum at the wall, the whole stress should be drastically reduced.

In simpler words: the marginal layer **fluidizes** the flow!

This idea is not new: according to Jeffery (Proc. Roy. Soc. London, 1922), *particles will tend to adopt that motion which, among all possible ones, corresponds to the least dissipation of energy*

Is this true?

YES: a CFL is really observable (but it is not completely free)! However, it is not true that dissipation is reduced.

Moreover, until 2019, the CFL development had not received a rigorous mathematical justification!
The main problem is to describe how changes the marginal layer as the geometry changes (say, when a given vessel bifurcates into smaller ones)

The Haynes conjecture (Am. J. of Physiology, 1960)

In small vessels the RBCs migrate towards the center of the tube (the CORE), leaving a marginal layer of pure plasma around (the Cell Free Layer).
Since the viscosity of this layer is from 4 to 5 times lower rhan that of the core and the viscous stress takes its maximum at the wall, the whole stress should be drastically reduced.

In simpler words: the marginal layer **fluidizes** the flow!

This idea is not new: according to Jeffery (Proc. Roy. Soc. London, 1922), *particles will tend to adopt that motion which, among all possible ones, corresponds to the least dissipation of energy*

Is this true?

YES: a CFL is really observable (but it is not completely free)! However, it is not true that dissipation is reduced.

Moreover, until 2019, the CFL development had not received a rigorous mathematical justification!
The main problem is to describe how changes the marginal layer as the geometry changes (say, when a given vessel bifurcates into smaller ones)

The Haynes conjecture (Am. J. of Physiology, 1960)

In small vessels the RBCs migrate towards the center of the tube (the CORE), leaving a marginal layer of pure plasma around (the Cell Free Layer).
Since the viscosity of this layer is from 4 to 5 times lower rhan that of the core and the viscous stress takes its maximum at the wall, the whole stress should be drastically reduced.

In simpler words: the marginal layer **fluidizes** the flow!

This idea is not new: according to Jeffery (Proc. Roy. Soc. London, 1922), *particles will tend to adopt that motion which, among all possible ones, corresponds to the least dissipation of energy*

Is this true?

YES: a CFL is really observable (but it is not completely free)! However, it is not true that dissipation is reduced.

Moreover, until 2019, the CFL development had not received a rigorous mathematical justification!
The main problem is to describe how changes the marginal layer as the geometry changes (say, when a given vessel bifurcates into smaller ones)

The Haynes conjecture (Am. J. of Physiology, 1960)

In small vessels the RBCs migrate towards the center of the tube (the CORE), leaving a marginal layer of pure plasma around (the Cell Free Layer).
Since the viscosity of this layer is from 4 to 5 times lower rhan that of the core and the viscous stress takes its maximum at the wall, the whole stress should be drastically reduced.

In simpler words: the marginal layer **fluidizes** the flow!

This idea is not new: according to Jeffery (Proc. Roy. Soc. London, 1922), *particles will tend to adopt that motion which, among all possible ones, corresponds to the least dissipation of energy*

Is this true?

YES: a CFL is really observable (but it is not completely free)! However, it is not true that dissipation is reduced.

Moreover, until 2019, the CFL development had not received a rigorous mathematical justification!
The main problem is to describe how changes the marginal layer as the geometry changes (say, when a given vessel bifurcates into smaller ones)

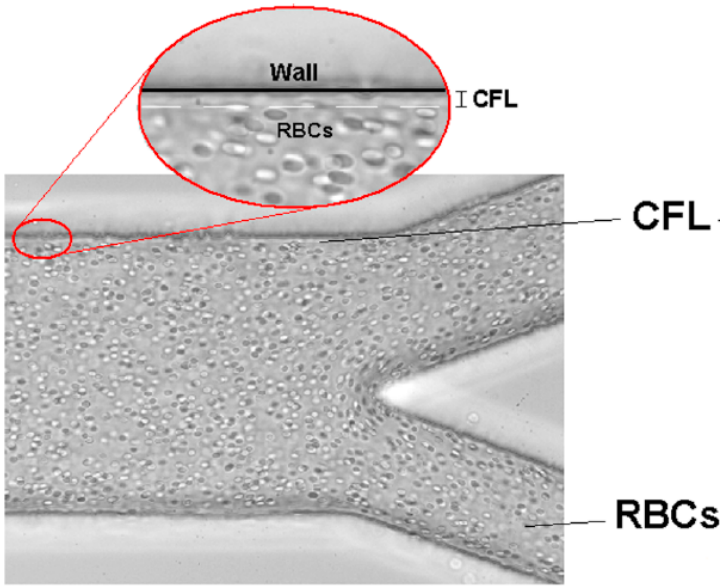
Experimental evidence of the CFL

There are 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), many more "in vitro".

Very sophisticated measurements confirm the hypothesis that the marginalization of RBCs is not complete.

Experimental evidence of the CFL

There are 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), many more "in vitro".



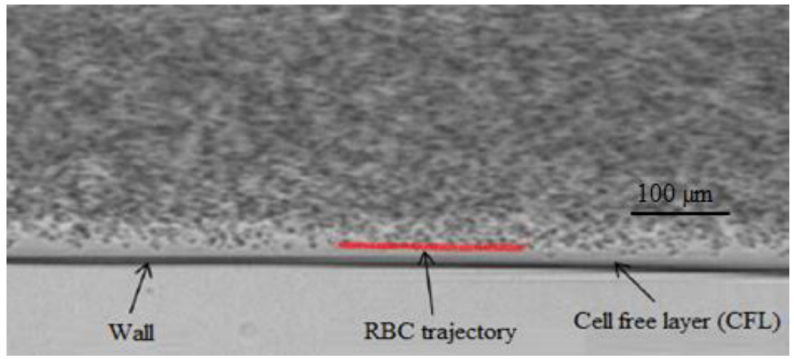
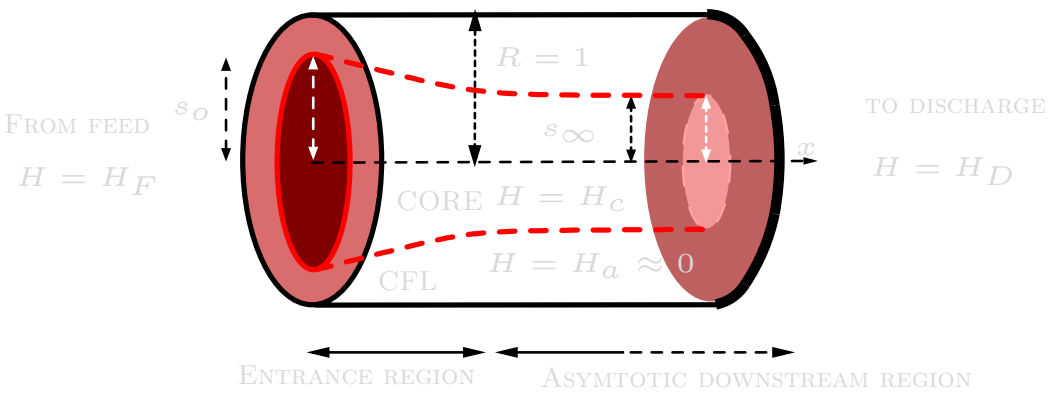


Figure 2.11: A trajectory of RBC flowing around the periphery region of RBC core

Very sophisticated measurements confirm the hypothesis that the marginalization of RBCs is not complete.

CFL development (Guadagni and Farina, J. Theor. Biology 2019)



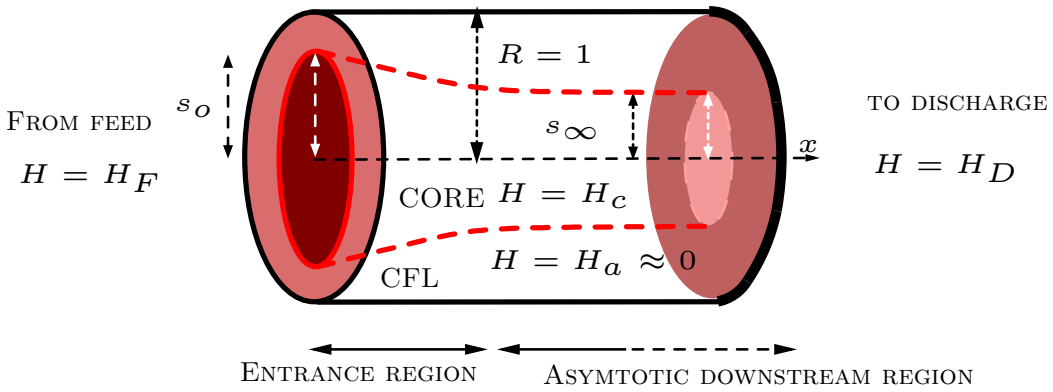
The vessel radius is rescaled to unity. The entrance length is exaggerated for visualization purpose

Through a nice application of boundary layer techniques it is proved that the CORE-CFL separation $s = s(x)$, **a material unknown interface**, quickly stabilizes from $s_o = s(0)$ to s_∞ =constant, since $\vec{v} \cdot \vec{e}_r$ rapidly vanishes and $\vec{v} \to \vec{v}_\infty = v(r)\vec{e}_x$

$$(3)\quad v_\infty(r) = \frac{2}{\frac{s_\infty^4}{\eta_c} + \frac{1}{\eta_a}(1 - s_\infty^4)} \times \begin{cases} \dfrac{s_\infty^2 - r^2}{\eta_c} + \dfrac{1 - s_\infty^2}{\eta_a}, & \text{if } 0 \le r \le s_\infty, \\ \dfrac{1 - r^2}{\eta_a}, & \text{if } s_\infty \le r \le 1. \end{cases}$$

This result is crucial to prove both the FL effect as well the F effect!

CFL development (Guadagni and Farina, J. Theor. Biology 2019)



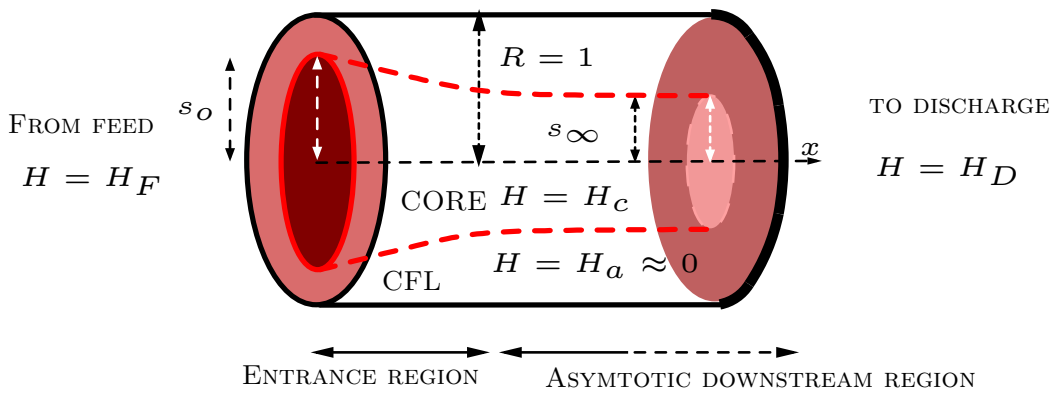
The vessel radius is rescaled to unity.
The entrance length is exaggerated for visualization purpose

Through a nice application of boundary layer techniques it is proved that the CORE-CFL separation $s = s(x)$, **a material unknown interface**, quickly stabilizes from $s_o = s(0)$ to s_∞ =constant, since $\vec{v} \cdot \vec{e}_r$ rapidly vanishes and $\vec{v} \to \vec{v}_\infty = v(r)\vec{e}_x$

$$(3)\quad v_\infty(r) = \frac{2}{\frac{s_\infty^4}{\eta_c} + \frac{1}{\eta_a}(1 - s_\infty^4)} \times \begin{cases} \frac{s_\infty^2 - r^2}{\eta_c} + \frac{1 - s_\infty^2}{\eta_a}, & \text{if } 0 \le r \le s_\infty, \\ \frac{1 - r^2}{\eta_a}, & \text{if } s_\infty \le r \le 1. \end{cases}$$

This result is crucial to prove both the FL effect as well the F effect!

CFL development (Guadagni and Farina, J. Theor. Biology 2019)



The vessel radius is rescaled to unity.
The entrance length is exaggerated for visualization purpose

Through a nice application of boundary layer techniques it is proved that the CORE-CFL separation $s = s(x)$, **a material unknown interface**, quickly stabilizes from $s_o = s(0)$ to s_∞ =constant, since $\vec{v} \cdot \vec{e}_r$ rapidly vanishes and $\vec{v} \to \vec{v}_\infty = v(r)\vec{e}_x$

$$(3)\quad v_\infty(r) = \frac{2}{\frac{s_\infty^4}{\eta_c} + \frac{1}{\eta_a}(1 - s_\infty^4)} \times \begin{cases} \dfrac{s_\infty^2 - r^2}{\eta_c} + \dfrac{1 - s_\infty^2}{\eta_a}, & \text{if } 0 \le r \le s_\infty, \\ \dfrac{1 - r^2}{\eta_a}, & \text{if } s_\infty \le r \le 1. \end{cases}$$

This result is crucial to prove both the FL effect as well the F effect!

Our model for the FL effect (Farina, Rosso, Fasano, J. Theor. Biology, 2022)

- **Hypotheses**

  (a) $s_o(D,a) = 1 - (2a/D)$, (CORE radius at $x = 0$).

  (b) $\eta(r) = \eta_{\rm a}\Theta[r > s_\infty] + \eta_{\rm c}(1 - \Theta[r \geq s_\infty])$, ($\Theta$ = Heaviside function),

  (c) $\eta_{\rm a}(\alpha) = 1 + \alpha(\eta_c - 1)$,

  $\eta_{\rm plasma} = 1$ (because of scaling), η_c =CORE viscosity, η_a = marginal layer viscosity.

- **We prove the "initial–asymptotic state" relation**

(4) $$s_\infty = \frac{s_o(D,a)}{\sqrt{1 + \sqrt{\left(1 - s_o^2\right)\left[1 - s_o^2\left(1 - \eta_a/\eta_c\right)\right]}}},$$

and

(5) $$\eta = \left[s_\infty^4\left(1/\eta_c - 1/\eta_a\right) + 1/\eta_a\right]^{-1}$$

Combining (??) and (??) we get the **the mathematical model for the FL effect**

(6) $$\eta = \mathcal{F}(\eta_c, D; a, \alpha),$$

where $\alpha = O\left(10^{-1}\right)$ and $a = O(1\mu\text{m})$ are two "free" parameters.

Our model for the FL effect (Farina, Rosso, Fasano, J. Theor. Biology, 2022)

- **Hypotheses**

  (a) $s_o(D,a) = 1 - (2a/D)$, (CORE radius at $x = 0$).

  (b) $\eta(r) = \eta_{\rm a}\Theta[r > s_\infty] + \eta_{\rm c}(1 - \Theta[r \geq s_\infty])$, ($\Theta$ = Heaviside function),

  (c) $\eta_{\rm a}(\alpha) = 1 + \alpha(\eta_c - 1)$,

  $\eta_{\rm plasma} = 1$ (because of scaling), η_c =CORE viscosity, η_a = marginal layer viscosity.

- **We prove the "initial–asymptotic state" relation**

(4)
$$s_\infty = \frac{s_o(D,a)}{\sqrt{1 + \sqrt{\left(1 - s_o^2\right)\left[1 - s_o^2\left(1 - \eta_a/\eta_c\right)\right]}}},$$

and

(5)
$$\eta = \left[s_\infty^4\left(1/\eta_c - 1/\eta_a\right) + 1/\eta_a\right]^{-1}$$

Combining (??) and (??) we get the **the mathematical model for the FL effect**

(6)
$$\eta = \mathcal{F}(\eta_c, D; a, \alpha),$$

where $\alpha = O\left(10^{-1}\right)$ and $a = O(1\mu\text{m})$ are two "free" parameters.

Our model for the FL effect (Farina, Rosso, Fasano, J. Theor. Biology, 2022)

- **Hypotheses**

  (a) $s_o(D,a) = 1 - (2a/D)$, (CORE radius at $x = 0$).

  (b) $\eta(r) = \eta_{\rm a}\Theta[r > s_\infty] + \eta_{\rm c}(1 - \Theta[r \geq s_\infty])$, ($\Theta$ = Heaviside function),

  (c) $\eta_{\rm a}(\alpha) = 1 + \alpha(\eta_c - 1)$,

  $\eta_{\rm plasma} = 1$ (because of scaling), η_c =CORE viscosity, η_a = marginal layer viscosity.

- **We prove the "initial–asymptotic state" relation**

(4)
$$s_\infty = \frac{s_o(D,a)}{\sqrt{1 + \sqrt{\left(1 - s_o^2\right)\left[1 - s_o^2\,(1 - \eta_a/\eta_c)\right]}}},$$

and

(5)
$$\eta = \left[s_\infty^4\,(1/\eta_c - 1/\eta_a) + 1/\eta_a\right]^{-1}$$

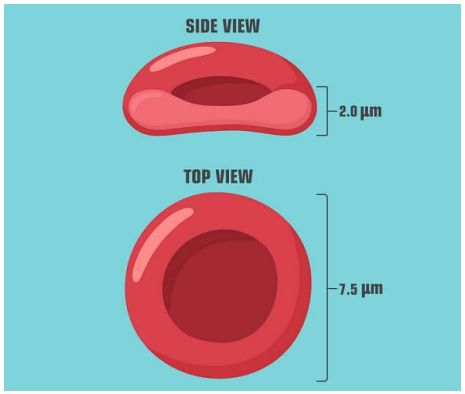
Combining (**??**) and (**??**) we get the **the mathematical model for the FL effect**

(6)
$$\eta = \mathcal{F}(\eta_c, D; a, \alpha),$$

where $\alpha = O\left(10^{-1}\right)$ and $a = O(1\mu\text{m})$ are two "free" parameters.

Why we assume $a = O(1\mu m)$ and $\alpha = O\left(10^{-1}\right)$?

- **"Size Exclusion Effect"** (a Red Blood Cell has a disk-like geometry)



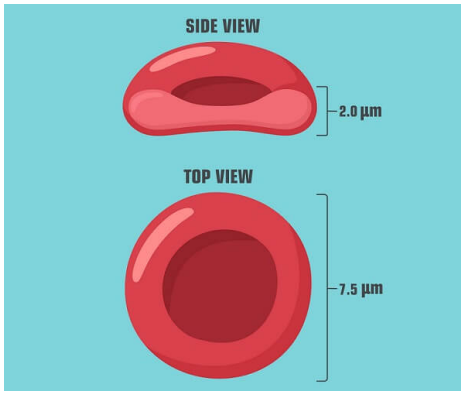
RBCs have a non-negligible physical dimensions (maximum length $7 \sim 8$ µm, minimum thickness $1.8 \sim 2$ µm).
Thus, RBCs cannot approach the vessel wall for less than a half of their minimum dimension. Thus, $s(0) = 1 - 2a/D$ close to 1 but not equal to 1 implies $a = O(1\ \mu m)$

- **Recent observations show that the marginal layer is not pure plasma, which says that a "Cell Depleted (or Poor) Layer" is closer to reality than a "Cell Free Layer"**

Thus, $\eta_a = 1 + \alpha(\eta_c - 1) > 1$ with α in a neighbourhood of 10% (some RBCs in the marginal layer) is more reliable than $\alpha = 0$ (no RBCs in the marginal layer).

Why we assume $a = O(1\mu m)$ and $\alpha = O\left(10^{-1}\right)$?

- **"Size Exclusion Effect"** (a Red Blood Cell has a disk-like geometry)



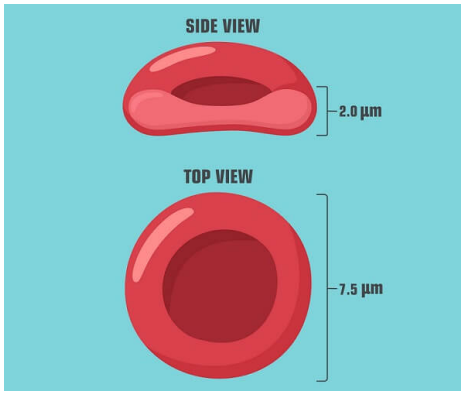
RBCs have a non-negligible physical dimensions (maximum length $7 \sim 8$ µm, minimum thickness $1.8 \sim 2$ µm).
Thus, RBCs cannot approach the vessel wall for less than a half of their minimum dimension. Thus, $s(0) = 1 - 2a/D$ close to 1 but not equal to 1 implies $a = O(1\ \mu m)$

- **Recent observations show that the marginal layer is not pure plasma, which says that a "Cell Depleted (or Poor) Layer" is closer to reality than a "Cell Free Layer"**

Thus, $\eta_a = 1 + \alpha(\eta_c - 1) > 1$ with α in a neighbourhood of 10% (some RBCs in the marginal layer) is more reliable than $\alpha = 0$ (no RBCs in the marginal layer).

Why we assume $a = O(1\mu m)$ and $\alpha = O\left(10^{-1}\right)$?

- **"Size Exclusion Effect"** (a Red Blood Cell has a disk-like geometry)



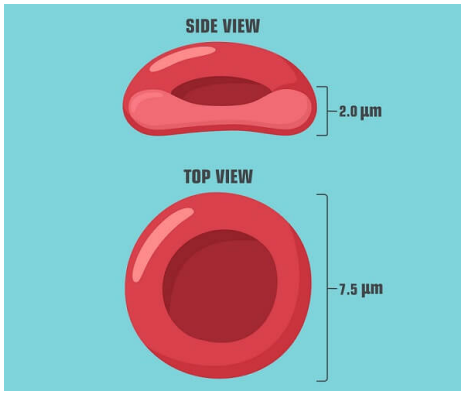
RBCs have a non-negligible physical dimensions (maximum length $7 \sim 8$ µm, minimum thickness $1.8 \sim 2$ µm).
Thus, RBCs cannot approach the vessel wall for less than a half of their minimum dimension. Thus, $s(0) = 1 - 2a/D$ close to 1 but not equal to 1 implies $a = O(1\ \mu m)$

- **Recent observations show that the marginal layer is not pure plasma, which says that a "Cell Depleted (or Poor) Layer" is closer to reality than a "Cell Free Layer"**

  Thus, $\eta_a = 1 + \alpha(\eta_c - 1) > 1$ with α in a neighbourhood of 10% (some RBCs in the marginal layer) is more reliable than $\alpha = 0$ (no RBCs in the marginal layer).

Why we assume $a = O(1\mu m)$ and $\alpha = O\left(10^{-1}\right)$?

- **"Size Exclusion Effect"** (a Red Blood Cell has a disk-like geometry)



RBCs have a non-negligible physical dimensions (maximum length $7 \sim 8$ µm, minimum thickness $1.8 \sim 2$ µm).
Thus, RBCs cannot approach the vessel wall for less than a half of their minimum dimension. Thus, $s(0) = 1 - 2a/D$ close to 1 but not equal to 1 implies $a = O(1\ \mu m)$

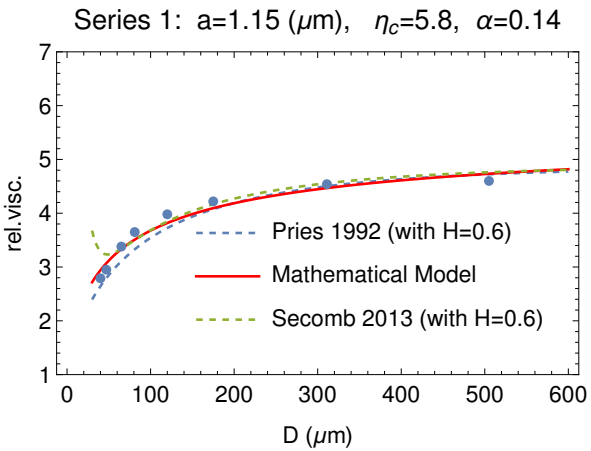
- **Recent observations show that the marginal layer is not pure plasma, which says that a "Cell Depleted (or Poor) Layer" is closer to reality than a "Cell Free Layer"**

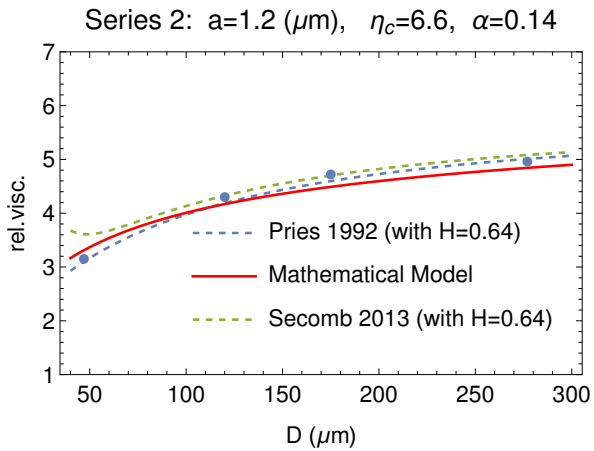
Thus, $\eta_a = 1 + \alpha(\eta_c - 1) > 1$ with α in a neighbourhood of 10% (some RBCs in the marginal layer) is more reliable than $\alpha = 0$ (no RBCs in the marginal layer).

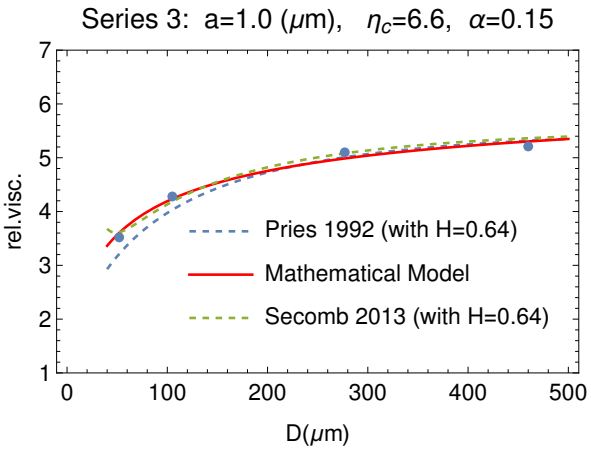
Comparison of the mathematical model with the original experiments of Fähræus and Lindqvist (1931)

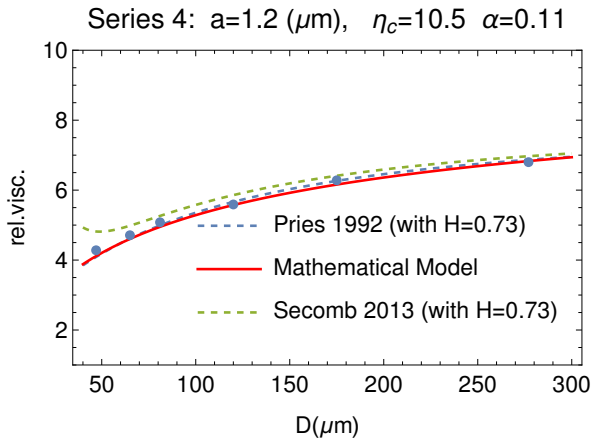
Notice: the fitting values of a and α are in the required range!

Comparison of the mathematical model with the original experiments of Fähræus and Lindqvist (1931)



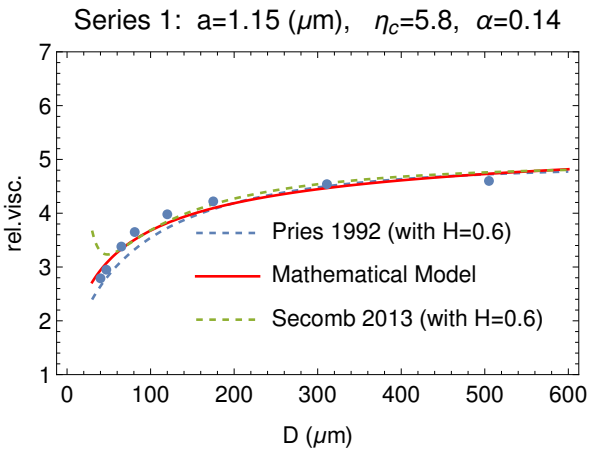


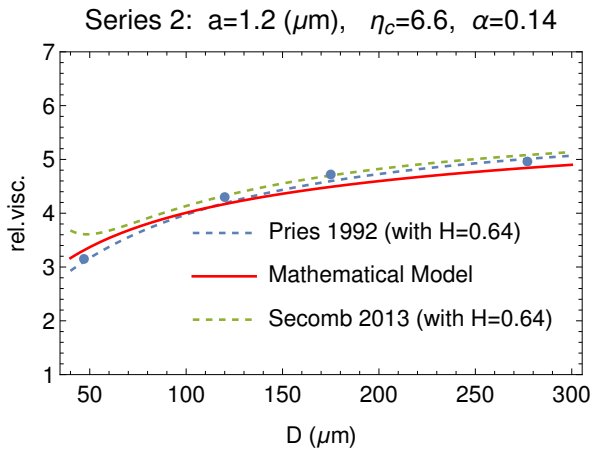


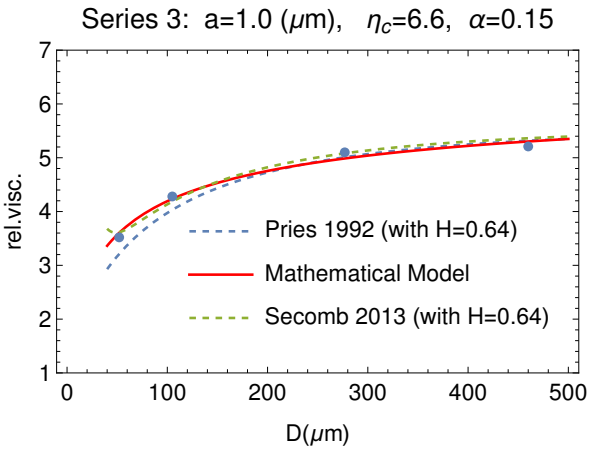


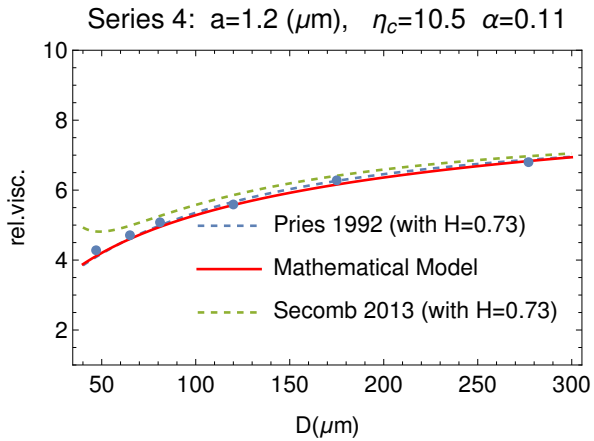
Notice: the fitting values of a and α are in the required range!

Comparison of the mathematical model with the original experiments of Fähræus and Lindqvist (1931)









Notice: the fitting values of a and α are in the required range!

Most famous empirical formulas for $\eta(D)$

Pries et al. 1992

$$\eta^{(P)}(D,\phi) = 1 + \left(\eta^{(P)}_{0.45}(D) - 1\right) \frac{(1-\phi)^{\,c(D)} - 1}{(1-0.45)^{\,c(D)} - 1}, \tag{7}$$

where

$$\eta^{(P)}_{0.45}(D) = 220\exp(-1.3\,D) + 3.2 - 2.44\exp\left(-0.06\,D^{\,0.645}\right),$$

and

$$c(D) = (0.8 + \exp(-0.075\,D))\left(\frac{1}{1+10^{-11}D^{\,12}} - 1\right) + \frac{1}{1+10^{-11}D^{\,12}}.$$

Secomb 2013

$$\eta^{(S)}(D,\phi) = \frac{D^{\,2}\left(\dfrac{D^{\,2}(\eta^{(S)}_{0.45}(D)-1)\left((1-\phi)^{\,c(D)}-1\right)}{(D-1.1)^2\left(0.55^{\,c(D)}-1\right)} + 1\right)}{(D-1.1)^2}, \tag{8}$$

where

$$\eta^{(S)}_{0.45}(D) = 3.2 - 2.44\exp\left(-0.06\,D^{\,0.645}\right) + 6\exp\left(-0.085\,D\right).$$

Formulas (??) and (??) are both based on a "best fitting procedure" using several sets of data collected in the last seventy years, that is they are NOT consequences of a whatsoever mathematical model

Most famous empirical formulas for $\eta(D)$

Pries et al. 1992

$$\eta^{(P)}(D,\phi) = 1 + \left(\eta^{(P)}_{0.45}(D) - 1\right) \frac{(1-\phi)^{\,c(D)} - 1}{(1-0.45)^{\,c(D)} - 1}, \tag{7}$$

where

$$\eta^{(P)}_{0.45}(D) = 220\exp(-1.3\,D) + 3.2 - 2.44\exp\left(-0.06\,D^{\,0.645}\right),$$

and

$$c(D) = (0.8 + \exp(-0.075\,D))\left(\frac{1}{1+10^{-11}D^{\,12}} - 1\right) + \frac{1}{1+10^{-11}D^{\,12}}.$$

Secomb 2013

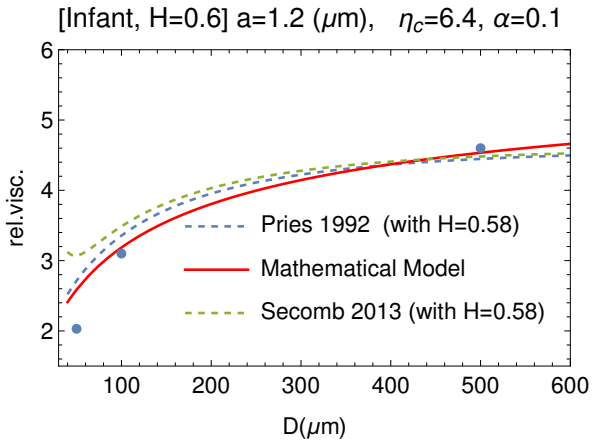
$$\eta^{(S)}(D,\phi) = \frac{D^{\,2}\left(\dfrac{D^{\,2}(\eta^{(S)}_{0.45}(D)-1)\left((1-\phi)^{\,c(D)}-1\right)}{(D-1.1)^2\left(0.55^{\,c(D)}-1\right)} + 1\right)}{(D-1.1)^2}, \tag{8}$$

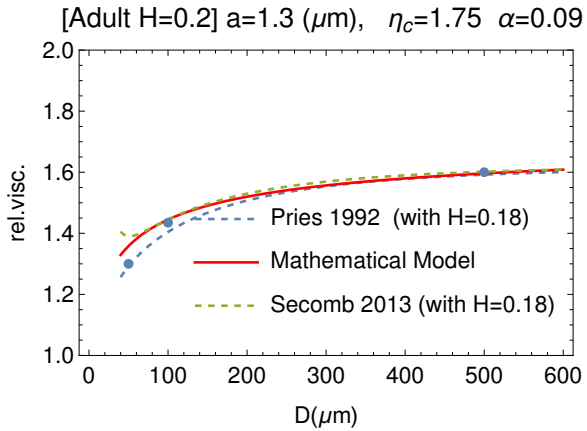
where

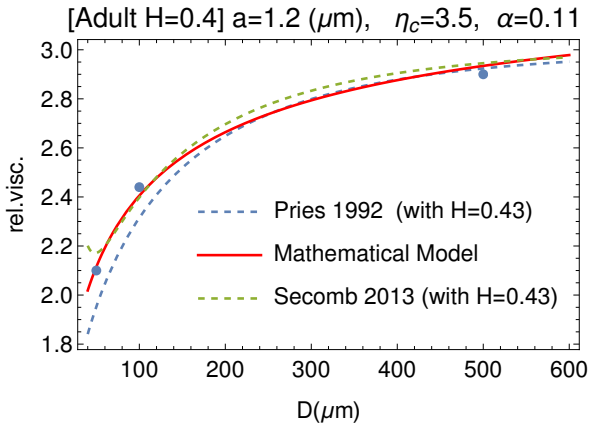
$$\eta^{(S)}_{0.45}(D) = 3.2 - 2.44\exp\left(-0.06\,D^{\,0.645}\right) + 6\exp\left(-0.085\,D\right).$$

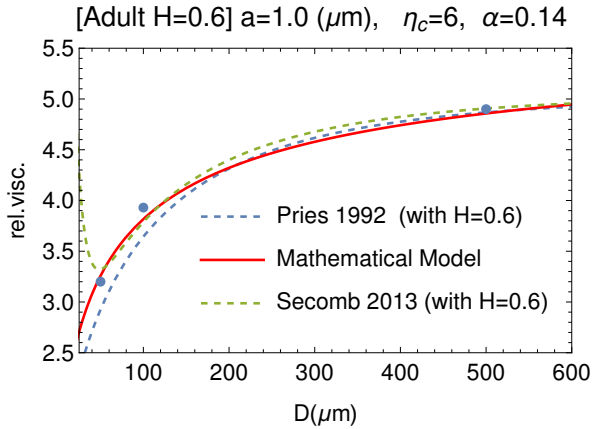
Formulas (??) and (??) are both based on a "best fitting procedure" using several sets of data collected in the last seventy years, that is they are NOT consequences of a whatsoever mathematical model

Comparison of the mathematical model with the experiments of Zilow and Linderkamp (1989)



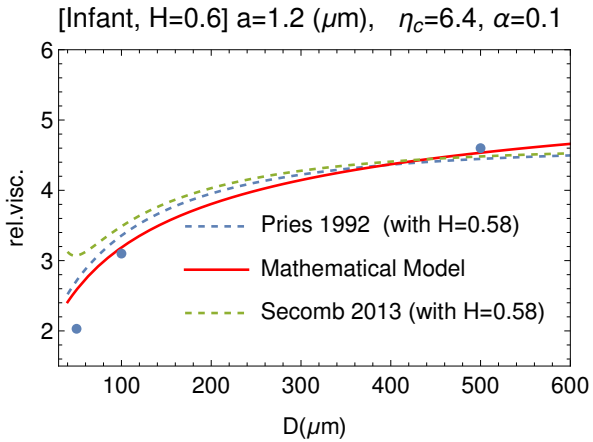


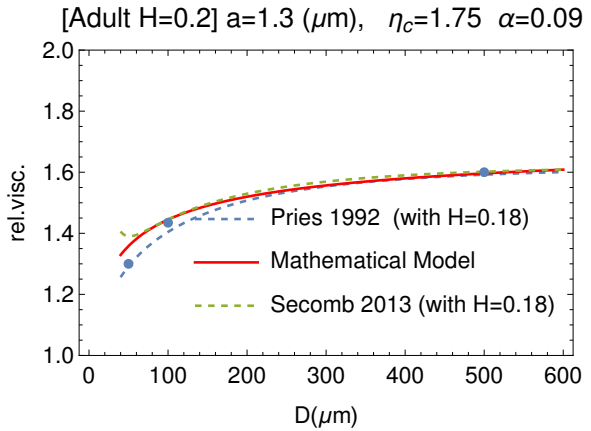


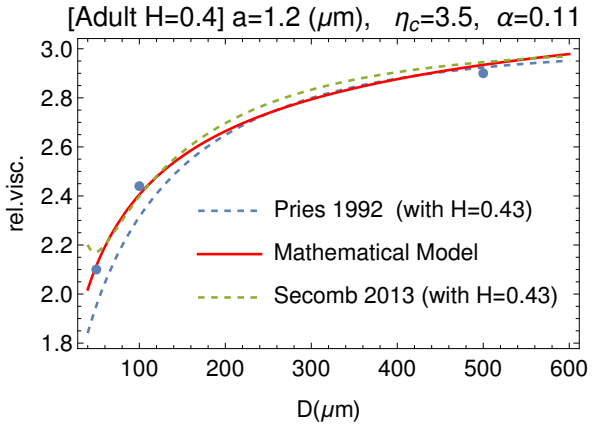


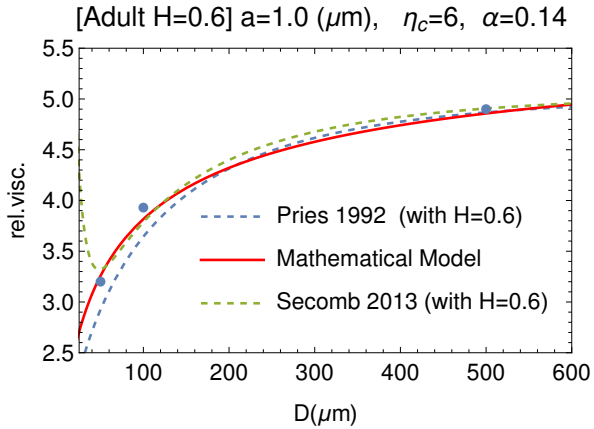
For all experiments we have considered, the mathematical model appears to be more efficient than the empirical formulas

Comparison of the mathematical model with the experiments of Zilow and Linderkamp (1989)









For all experiments we have considered, the mathematical model appears to be more efficient than the empirical formulas

The Fähræus effect experiment (Farina, Fasano, Rosso, J. of Theoretical Biology, 2023)

What are we looking for?

The main feature of $\eta = \mathcal{F}(\eta_c, D; a, \alpha)$ (our model for the FL effect) is that

$$\left.\frac{\partial \mathcal{F}}{\partial D}\right|_{\eta_c=\text{const.}} > 0$$

if $D \geq 60$ µm and $D \leq 500$ µm

A mathematical formula for the Fähræus effect, say $H_R = \mathcal{G}(H_F, D; a, \alpha)$, must have quite analogous characteristics:

$$\left.\frac{\partial \mathcal{G}}{\partial D}\right|_{H_F=\text{const.}} > 0, \qquad \left.\frac{\partial \mathcal{G}}{\partial H_F}\right|_{D=\text{const.}} > 0$$

within a similar range of diameters.

The Fähræus effect experiment (Farina, Fasano, Rosso, J. of Theoretical Biology, 2023)

What are we looking for?

The main feature of $\eta = \mathcal{F}(\eta_c, D; a, \alpha)$ (our model for the FL effect) is that

$$\left.\frac{\partial \mathcal{F}}{\partial D}\right|_{\eta_c = \text{const.}} > 0$$

if $D \geq 60$ µm and $D \leq 500$ µm

A mathematical formula for the Fähræus effect, say $H_R = \mathcal{G}(H_F, D; a, \alpha)$, must have quite analogous characteristics:

$$\left.\frac{\partial \mathcal{G}}{\partial D}\right|_{H_F = \text{const.}} > 0, \qquad \left.\frac{\partial \mathcal{G}}{\partial H_F}\right|_{D = \text{const.}} > 0$$

within a similar range of diameters.

The Fähræus effect experiment (Farina, Fasano, Rosso, J. of Theoretical Biology, 2023)

What are we looking for?

The main feature of $\eta = \mathcal{F}(\eta_c, D; a, \alpha)$ (our model for the FL effect) is that

$$\left.\frac{\partial \mathcal{F}}{\partial D}\right|_{\eta_c = \text{const.}} > 0$$

if $D \geq 60$ µm and $D \leq 500$ µm

A mathematical formula for the Fähræus effect, say $H_R = \mathcal{G}(H_F, D; a, \alpha)$, must have quite analogous characteristics:

$$\left.\frac{\partial \mathcal{G}}{\partial D}\right|_{H_F = \text{const.}} > 0, \qquad \left.\frac{\partial \mathcal{G}}{\partial H_F}\right|_{D = \text{const.}} > 0$$

within a similar range of diameters.

Tube hematocrit

The model in brief Assume the hematocrit to have a radial stepwise profile

$$H_T = \begin{cases} H_c, & 0 \le r \le s(x), \\ H_a, & s(x) \le r \le 1. \end{cases} \tag{9}$$

Same idea as in the FL effect: $H_a \neq 0$, but significantly smaller that H_c. As a consequence

$$\eta = \begin{cases} \eta_a = \eta\left(H_a\right), & s(x) \le r \le 1, \\ \eta_c = \eta\left(H_c\right), & 0 \le r \le s(x). \end{cases} \tag{10}$$

How can we evaluate $\eta(H)$?
In a **real experiment** we need to measure η **before** blood enters the capillary tube **(an easy task)** and then compare it with its value **in the small tube**. To do it, we need to measure the hematocrit **in the tube** (not an easy task!)

Tube hematocrit

The model in brief Assume the hematocrit to have a radial stepwise profile

$$H_T = \begin{cases} H_c, & 0 \le r \le s(x), \\ H_a, & s(x) \le r \le 1. \end{cases} \tag{9}$$

Same idea as in the FL effect: $H_a \neq 0$, but significantly smaller that H_c. As a consequence

$$\eta = \begin{cases} \eta_a = \eta\left(H_a\right), & s(x) \le r \le 1, \\ \eta_c = \eta\left(H_c\right), & 0 \le r \le s(x). \end{cases} \tag{10}$$

How can we evaluate $\eta(H)$?
In a **real experiment** we need to measure η **before** blood enters the capillary tube **(an easy task)** and then compare it with its value **in the small tube**. To do it, we need to measure the hematocrit **in the tube** (not an easy task!)

Tube hematocrit

The model in brief Assume the hematocrit to have a radial stepwise profile

$$H_T = \begin{cases} H_c, & 0 \le r \le s(x), \\ H_a, & s(x) \le r \le 1. \end{cases} \tag{9}$$

Same idea as in the FL effect: $H_a \neq 0$, but significantly smaller that H_c. As a consequence

$$\eta = \begin{cases} \eta_a = \eta\left(H_a\right), & s(x) \le r \le 1, \\ \eta_c = \eta\left(H_c\right), & 0 \le r \le s(x). \end{cases} \tag{10}$$

How can we evaluate $\eta(H)$?
In a **real experiment** we need to measure η **before** blood enters the capillary tube **(an easy task)** and then compare it with its value **in the small tube**. To do it, we need to measure the hematocrit **in the tube** (not an easy task!)

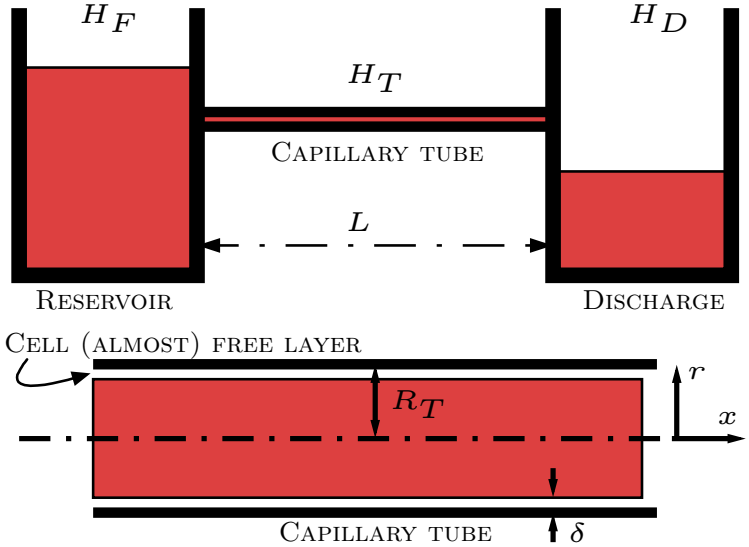
The real experiment

To measure the hematocrit **in the tube** the flow must be stopped and blood sampled from a small portion of the tube. Hematocrit is finally obtained by centrifuging. The delicate steps of this procedure is widely detailed in Barbee's PhD thesis (1970) and measuring errors should not be underestimated.

The Fähræus experimental apparatus: H_F (feed hematocrit) must be equal to H_D (discharge hematocrit) due to mass balance. However, the tube hematocrit H_T decreases in capillaries of smaller and smaller diameter (which makes the relative hematocrit $H_R = H_T/H_F$ to decrease either).

The real experiment

To measure the hematocrit **in the tube** the flow must be stopped and blood sampled from a small portion of the tube. Hematocrit is finally obtained by centrifuging. The delicate steps of this procedure is widely detailed in Barbee's PhD thesis (1970) and measuring errors should not be underestimated.
The Fähræus experimental apparatus: H_F (feed hematocrit) must be equal to H_D (discharge hematocrit) due to mass balance. However, the tube hematocrit H_T decreases in capillaries of smaller and smaller diameter (which makes the relative hematocrit $H_R = H_T/H_F$ to decrease either).



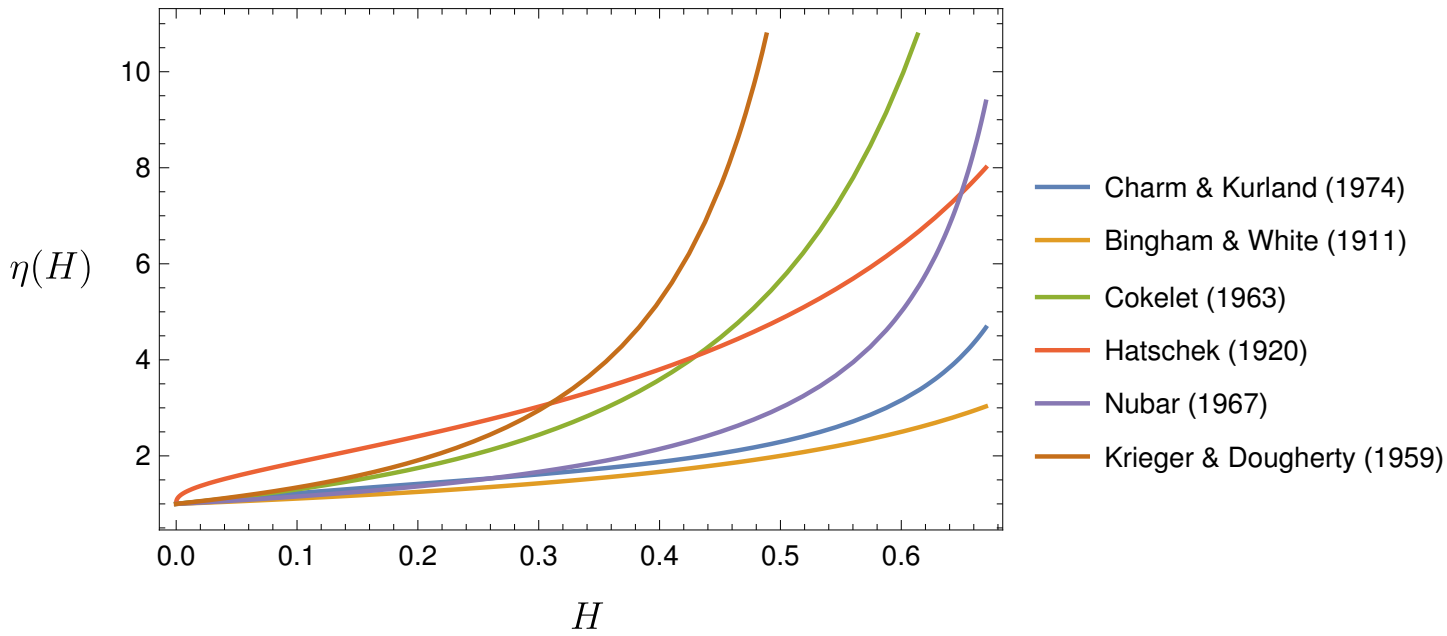
Measuring $\eta(H)$ in the reservoir

Bio-physiology literature provides several empirical formulas. **These are more or less equivalent from the model viewpoint, which make irrelevant which one we choose.** However, one may fit data better than another, which has to be considered in model validation.

All these formulas are characterized by the fact that η is an increasing function of H

$$\eta(H) = \frac{1}{f(H)}, \tag{11}$$

where $f'(H) \leq 0$, and $f(0) = 1$.



The relative hematocrit from the model viewpoint

By definition $H_R = H_T/H_F$ and

$$H_T = \int_{\text{Tube volume}} H(\mathbf{x})\, \mathbf{dx}. \tag{12}$$

As a consequence (far from the entrance)

$$H_R = \frac{H_c}{H_F} s_\infty^2 + \frac{H_a}{H_F}(1 - s_\infty^2). \tag{13}$$

Then, we estimate H_c and H_a in terms of H_F.

Mass conservation through the entrance at $x = 0$ implies

$$H_F = s_o^2 H_c + (1 - s_o^2) H_a$$

The relative hematocrit from the model viewpoint

By definition $H_R = H_T/H_F$ and

$$H_T = \int_{\text{Tube volume}} H(\mathbf{x})\, \mathbf{dx}. \tag{12}$$

As a consequence (far from the entrance)

$$H_R = \frac{H_c}{H_F} s_\infty^2 + \frac{H_a}{H_F}(1 - s_\infty^2). \tag{13}$$

Then, we estimate H_c and H_a in terms of H_F.

Mass conservation through the entrance at $x = 0$ implies

$$H_F = s_o^2 H_c + (1 - s_o^2) H_a$$

The relative hematocrit from the model viewpoint

By definition $H_R = H_T/H_F$ and

$$H_T = \int_{\text{Tube volume}} H(\mathbf{x})\ \mathbf{dx}. \tag{12}$$

As a consequence (far from the entrance)

$$H_R = \frac{H_c}{H_F} s_\infty^2 + \frac{H_a}{H_F}(1 - s_\infty^2). \tag{13}$$

Then, we estimate H_c and H_a in terms of H_F.

Mass conservation through the entrance at $x = 0$ implies

$$H_F = s_o^2 H_c + (1 - s_o^2) H_a$$

The relative hematocrit from the model viewpoint

Finally, we set $H_a = \alpha H_F$, typically $\alpha \lesssim \mathcal{O}\left(10^{-1}\right)$, and recall that

$$s_o(a, D) = 1 - \frac{2a}{D}, \tag{14}$$

with a comparable with the average RBCs half-thickness.

Recall also that $a = O(1\ \mu\text{m})$ and $D \geq 50\ \mu\text{m}$, so that $s_o = s_o(\varepsilon) = 1 - \varepsilon$ with $2a/D = \varepsilon \ll 1$. This yields

$$H_F(\varepsilon, \alpha) = (1-\varepsilon)^2 H_c + [1 - (1-\varepsilon)^2]\alpha H_c$$

Solving for H_c, we find, at the first order in ε,

$$H_c(\varepsilon, \alpha) \approx H_F\left[1 + 2\left(1 - \alpha\right)\varepsilon\right], \tag{15}$$

that entails $H_c \approx H_F$, for "large" diameters.

The relative hematocrit from the model viewpoint

Finally, we set $H_a = \alpha H_F$, typically $\alpha \lesssim \mathcal{O}\left(10^{-1}\right)$, and recall that

$$s_o(a, D) = 1 - \frac{2a}{D}, \tag{14}$$

with a comparable with the average RBCs half-thickness.

Recall also that $a = O(1\ \mu\text{m})$ and $D \geq 50\ \mu\text{m}$, so that $s_o = s_o(\varepsilon) = 1 - \varepsilon$ with $2a/D = \varepsilon \ll 1$. This yields

$$H_F(\varepsilon, \alpha) = (1-\varepsilon)^2 H_c + [1 - (1-\varepsilon)^2]\alpha H_c$$

Solving for H_c, we find, at the first order in ε,

$$H_c(\varepsilon, \alpha) \approx H_F\left[1 + 2\left(1 - \alpha\right)\varepsilon\right], \tag{15}$$

that entails $H_c \approx H_F$, for "large" diameters.

The relative hematocrit from the model viewpoint

Finally, we set $H_a = \alpha H_F$, typically $\alpha \lesssim \mathcal{O}\left(10^{-1}\right)$, and recall that

$$s_o(a, D) = 1 - \frac{2a}{D}, \tag{14}$$

with a comparable with the average RBCs half-thickness.

Recall also that $a = O(1\ \mu\text{m})$ and $D \geq 50\ \mu\text{m}$, so that $s_o = s_o(\varepsilon) = 1 - \varepsilon$ with $2a/D = \varepsilon \ll 1$. This yields

$$H_F(\varepsilon, \alpha) = (1-\varepsilon)^2 H_c + [1 - (1-\varepsilon)^2]\alpha H_c$$

Solving for H_c, we find, at the first order in ε,

$$H_c(\varepsilon, \alpha) \approx H_F\left[1 + 2\left(1 - \alpha\right)\varepsilon\right], \tag{15}$$

that entails $H_c \approx H_F$, for "large" diameters.

The relative hematocrit from the model viewpoint

Thus (**??**) becomes

$$H_R = [1 + 2\,(1-\alpha)\,\varepsilon]\, s_\infty^2 + \alpha(1 - s_\infty^2)$$

Finally, recalling

$$s_\infty = \frac{s_o(D,a)}{\sqrt{1 + \sqrt{(1-s_o^2)\left[1 - s_o^2\left(1 - \dfrac{\eta_a}{\eta_c}\right)\right]}}}. \tag{16}$$

and

$$\begin{cases} \eta_a = \eta\,(H_a)\,, & s_\infty \le r \le 1, \\ \eta_c = \eta\,(H_c)\,, & 0 \le r \le s_\infty. \end{cases} \tag{17}$$

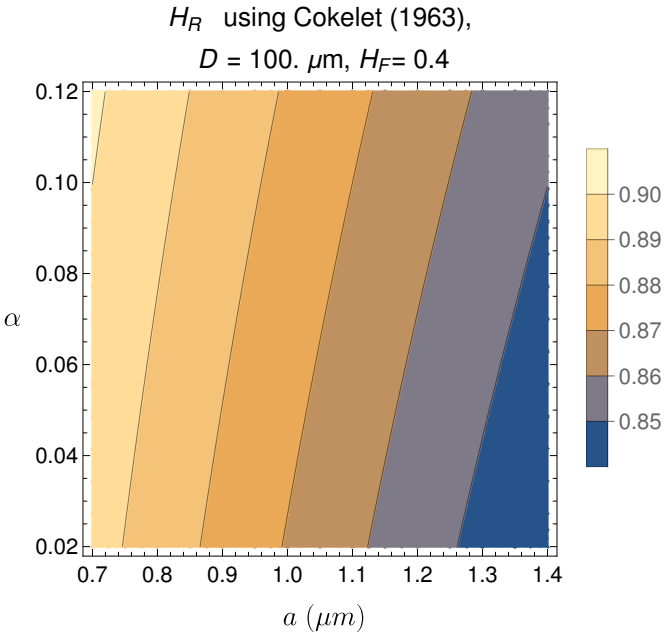
we get our final formula

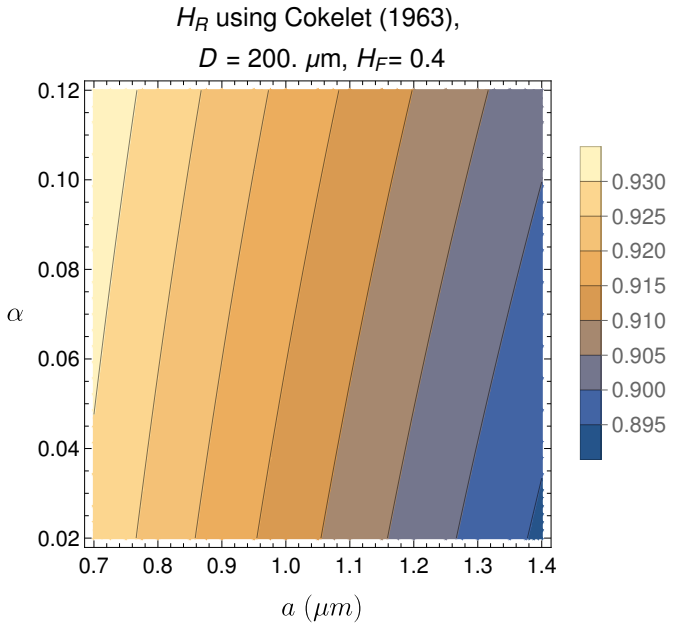
$$H_R = \mathcal{G}_f\,(H_F, D; a, \alpha)\,. \tag{18}$$

the dependency on f being related to the empirical formula used to evaluate $\eta(H_F)$.

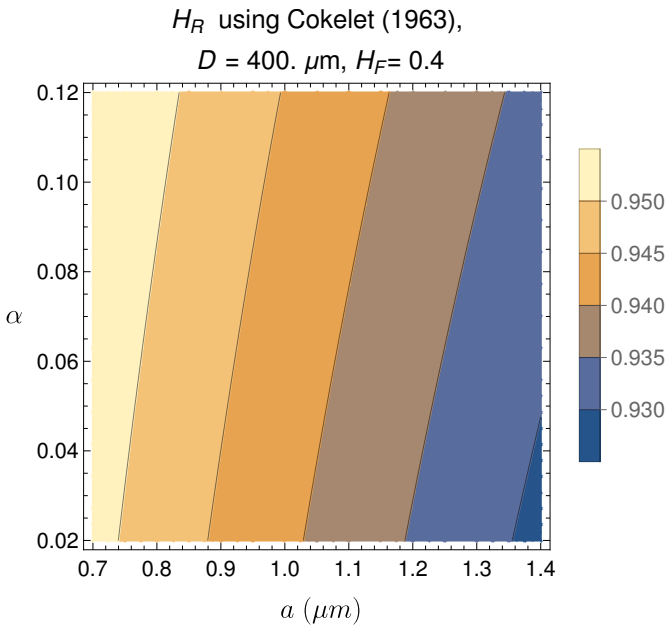
The relative influence of a and α on the level set of H_R by changing D

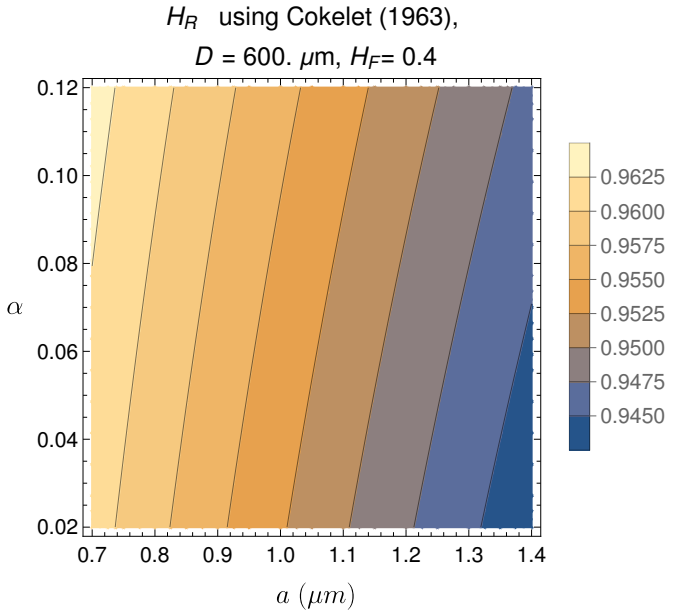
Variability of the relative hematocrit with α and a for $D = 100, 200, 400, 600$





The relative influence of a and α on the level set of H_R by changing D

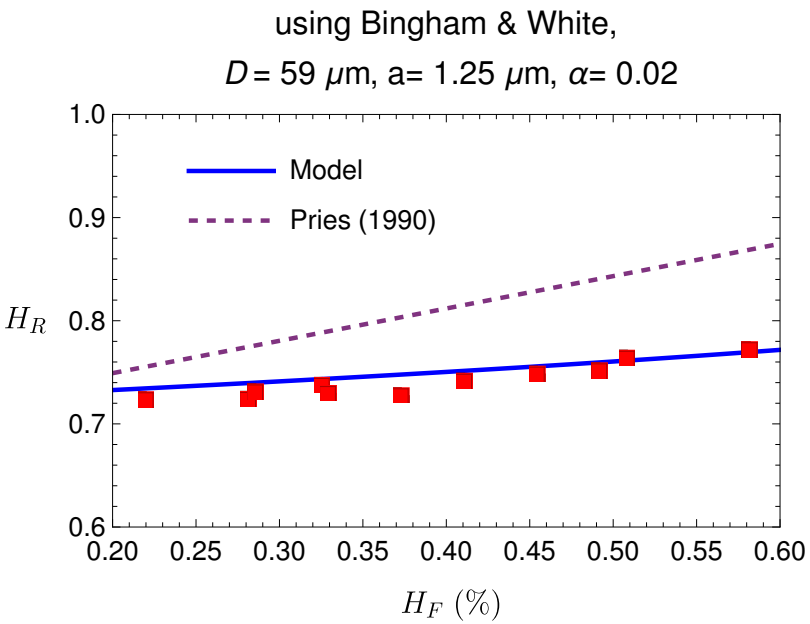


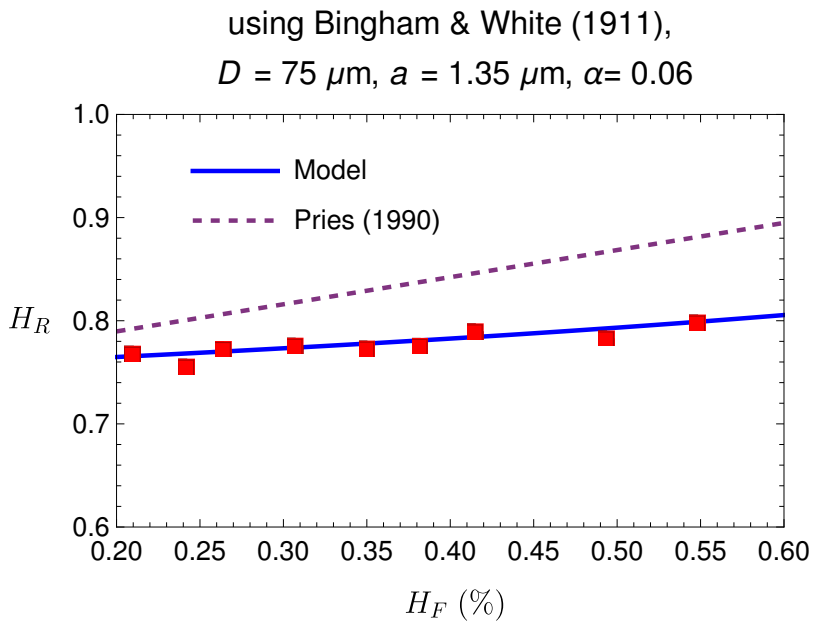


The effect of varying α is very limited compared with that of a.
It is not difficult to verify that (as expected)

$$\left.\frac{\partial \mathcal{G}_f}{\partial D}\right|_{H_F=\text{const.}} > 0, \qquad \left.\frac{\partial \mathcal{G}_f}{\partial H_F}\right|_{D=\text{const.}} > 0, \qquad \text{for all } f$$

Comparing the mathematical model for the Fahræus effect with Barbee and Cokelet data





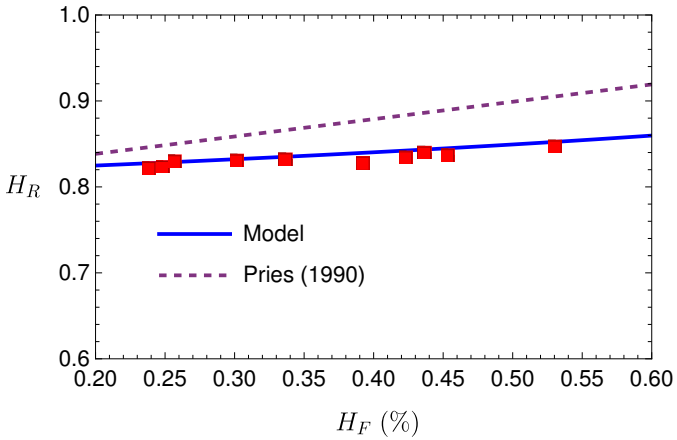
Pries et al. empirical formula (Circulation Research, 1990 and The American Journal of Physiology, 1992):

$$H_R = H_F + (1 - H_F)\left[1 + 1.7\,e^{-0.35D} - 0.6\,e^{-0.011D}\right],$$

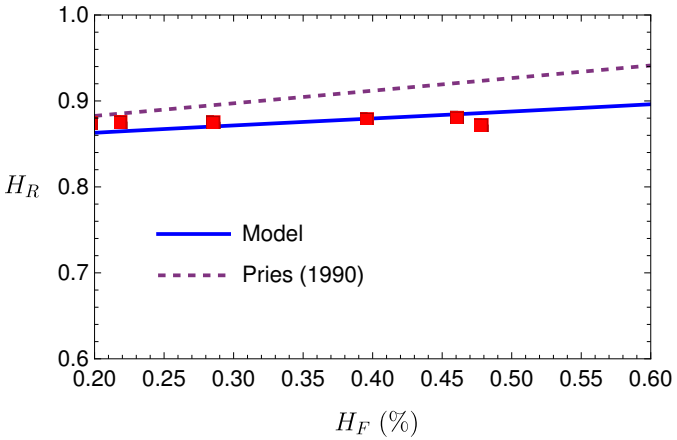
with D given in (units of) μm

Comparing the model with Barbee and Cokelet data

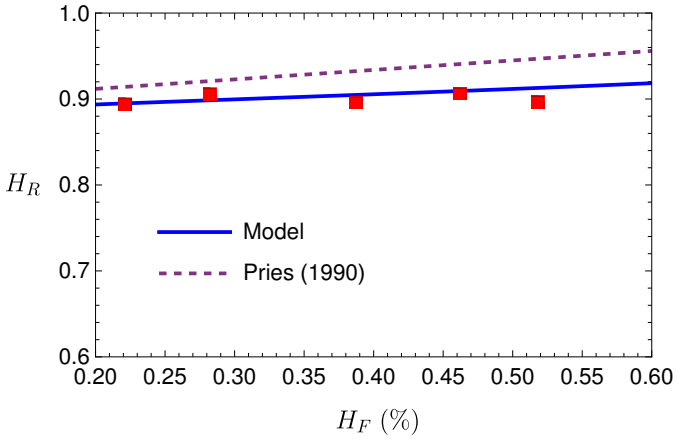
using Bingham & White (1911),
D = 99 μm, a = 0.98 μm, α= 0.05



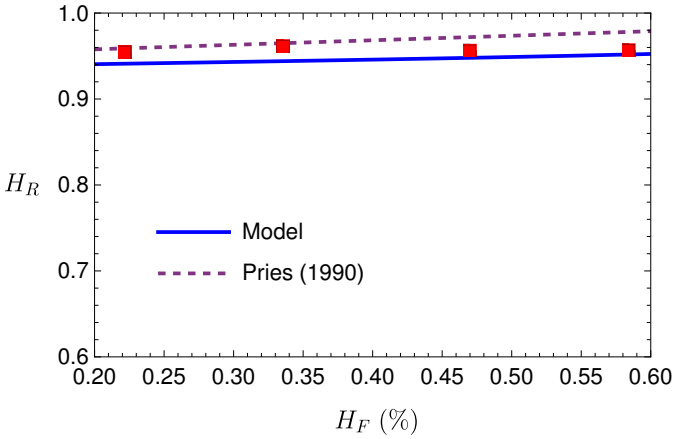
using Hatschek (1920),
D = 128 μm, a = 1.02 μm, α= 0.03



using Hatschek (1920),
D = 154 μm, a = 0.877 μm, α= 0.15

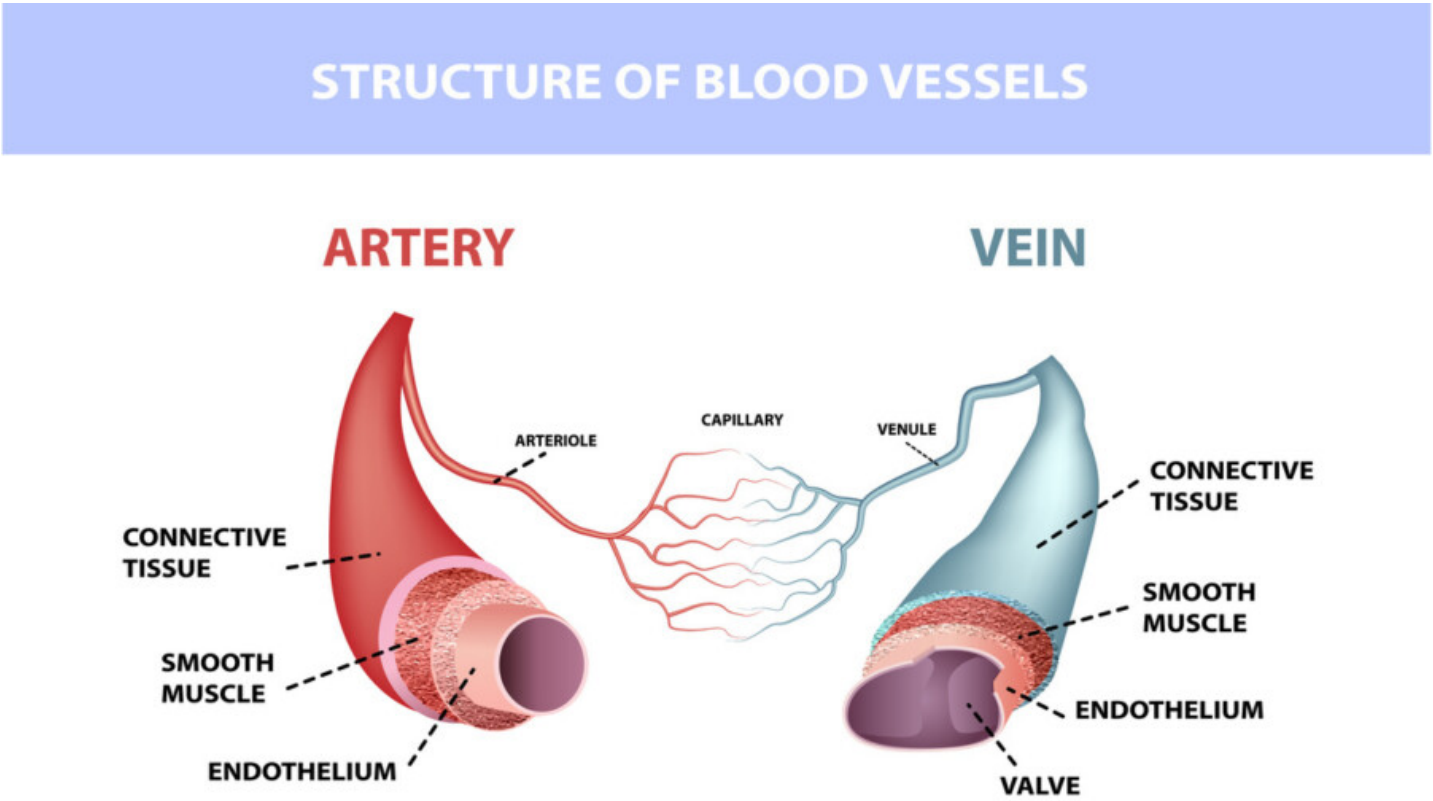


using Hatschek (1920),
D= 221 μm, a= 0.7 μm, α= 0.4



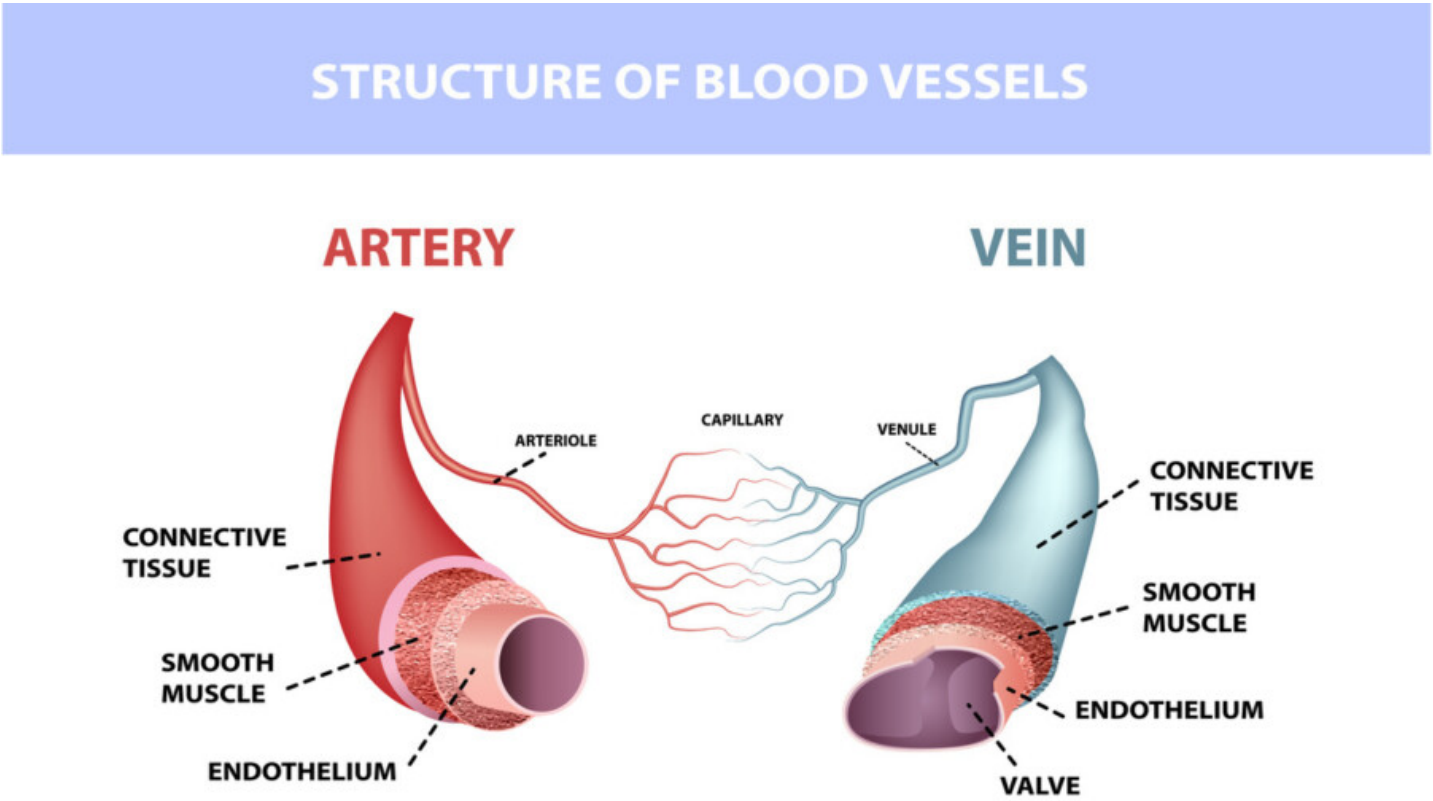
Vasomotion

"Vasomotion "means" motion generated by the vessel wall contraction". It is a phenomenon which has been observed since 1852 in bat wings (T. W. Jones, Trans. Philos. Trans. of the Royal Soc. of London, vol 142). However, veins/arterioles and arteries/arterioles have quite different characteristics and behavoir.



Vasomotion

"Vasomotion "means" motion generated by the vessel wall contraction". It is a phenomenon which has been observed since 1852 in bat wings (T. W. Jones, Trans. Philos. Trans. of the Royal Soc. of London, vol 142). However, veins/arterioles and arteries/arterioles have quite different characteristics and behavoir.



Vasomotion

Main differences/characteristics (for our purposes)

- In venules, pressure (and therefore blood motion) is provided by wall contractions. In arterioles, pressure is provided by the heart pumping action (so pressure values are very different, much higher in arterioles than in venules)
- In venules the presence of unidirectional valves prevents backflow. In arterioles there are no valves.
- Ordinary values of frequency and oscillation amplitude vary significantly with the vessel type and diameter.
- Abundant literature for vein/venules, very scarce for arterias/arterioles
- The benefit of vasomotion to microcirculation (that is venules and arterioles where the vessel resistance becomes large) is still a matter of debate among physiologists.

A mathematical model in venules:
Modeling peristaltic flow in vessels equipped with valves: implications for vasomotion in bat wing venules, A. Farina, L. Fusi, A. Fasano, A. Ceretani, F. Rosso, Int. J. Engineering Sci. 2016

Vasomotion

Main differences/characteristics (for our purposes)

- In venules, pressure (and therefore blood motion) is provided by wall contractions. In arterioles, pressure is provided by the heart pumping action (so pressure values are very different, much higher in arterioles than in venules)
- In venules the presence of unidirectional valves prevents backflow. In arterioles there are no valves.
- Ordinary values of frequency and oscillation amplitude vary significantly with the vessel type and diameter.
- Abundant literature for vein/venules, very scarce for arterias/arterioles
- The benefit of vasomotion to microcirculation (that is venules and arterioles where the vessel resistance becomes large) is still a matter of debate among physiologists.

A mathematical model in venules:
Modeling peristaltic flow in vessels equipped with valves: implications for vasomotion in bat wing venules, A. Farina, L. Fusi, A. Fasano, A. Ceretani, F. Rosso, Int. J. Engineering Sci. 2016

Vasomotion

Main differences/characteristics (for our purposes)

- In venules, pressure (and therefore blood motion) is provided by wall contractions. In arterioles, pressure is provided by the heart pumping action (so pressure values are very different, much higher in arterioles than in venules)
- In venules the presence of unidirectional valves prevents backflow. In arterioles there are no valves.
- Ordinary values of frequency and oscillation amplitude vary significantly with the vessel type and diameter.
- Abundant literature for vein/venules, very scarce for arterias/arterioles
- The benefit of vasomotion to microcirculation (that is venules and arterioles where the vessel resistance becomes large) is still a matter of debate among physiologists.

A mathematical model in venules:
Modeling peristaltic flow in vessels equipped with valves: implications for vasomotion in bat wing venules, A. Farina, L. Fusi, A. Fasano, A. Ceretani, F. Rosso, Int. J. Engineering Sci. 2016

Vasomotion

Main differences/characteristics (for our purposes)

- In venules, pressure (and therefore blood motion) is provided by wall contractions. In arterioles, pressure is provided by the heart pumping action (so pressure values are very different, much higher in arterioles than in venules)
- In venules the presence of unidirectional valves prevents backflow. In arterioles there are no valves.
- Ordinary values of frequency and oscillation amplitude vary significantly with the vessel type and diameter.
- Abundant literature for vein/venules, very scarce for arterias/arterioles
- The benefit of vasomotion to microcirculation (that is venules and arterioles where the vessel resistance becomes large) is still a matter of debate among physiologists.

A mathematical model in venules:
Modeling peristaltic flow in vessels equipped with valves: implications for vasomotion in bat wing venules, A. Farina, L. Fusi, A. Fasano, A. Ceretani, F. Rosso, Int. J. Engineering Sci. 2016

Vasomotion

Main differences/characteristics (for our purposes)

- In venules, pressure (and therefore blood motion) is provided by wall contractions. In arterioles, pressure is provided by the heart pumping action (so pressure values are very different, much higher in arterioles than in venules)
- In venules the presence of unidirectional valves prevents backflow. In arterioles there are no valves.
- Ordinary values of frequency and oscillation amplitude vary significantly with the vessel type and diameter.
- Abundant literature for vein/venules, very scarce for arterias/arterioles
- The benefit of vasomotion to microcirculation (that is venules and arterioles where the vessel resistance becomes large) is still a matter of debate among physiologists.

A mathematical model in venules:
Modeling peristaltic flow in vessels equipped with valves: implications for vasomotion in bat wing venules, A. Farina, L. Fusi, A. Fasano, A. Ceretani, F. Rosso, Int. J. Engineering Sci. 2016

Vasomotion

Main differences/characteristics (for our purposes)

- In venules, pressure (and therefore blood motion) is provided by wall contractions. In arterioles, pressure is provided by the heart pumping action (so pressure values are very different, much higher in arterioles than in venules)
- In venules the presence of unidirectional valves prevents backflow. In arterioles there are no valves.
- Ordinary values of frequency and oscillation amplitude vary significantly with the vessel type and diameter.
- Abundant literature for vein/venules, very scarce for arterias/arterioles
- The benefit of vasomotion to microcirculation (that is venules and arterioles where the vessel resistance becomes large) is still a matter of debate among physiologists.

A mathematical model in venules:
Modeling peristaltic flow in vessels equipped with valves: implications for vasomotion in bat wing venules, A. Farina, L. Fusi, A. Fasano, A. Ceretani, F. Rosso, Int. J. Engineering Sci. 2016

Vasomotion

Modeling vasomotion in arterioles (A. Farina, A. Fasano, F. Rosso, J. Theoretical Biology 2022): the main points.

- **A mechanical fact:** because of contractions, the vessel lumen reduces which implies that the hydraulic resistance increases!
- **Question:** which role has the FL effect in vasomotion?
- **What we already knew:** (M. Ascolese, A. Farina, A. Fasano, J. of Biological Physics 2019)
  1. (unlike the Haynes' idea) the FL effect **increases** the mechanical dissipation **but it favours the volumetric flux** and, consequently, it **increases the tissue perfusion** (probably the true physiological role of the FL effect)
- **What we proved:**
  2. In arterioles, the FL effect mitigates the increment of hydraulic resistance
  3. Though vasomotion appears not to be beneficial for the blood flow in a single arteriole, it becomes an efficient mechanism for the spatial regulation in a network of vessels (confirming what recently hypothesized by Lapi et al., Frontiers in Physiology 2019)

Vasomotion

Modeling vasomotion in arterioles (A. Farina, A. Fasano, F. Rosso, J. Theoretical Biology 2022): the main points.

- **A mechanical fact:** because of contractions, the vessel lumen reduces which implies that the hydraulic resistance increases!
- **Question:** which role has the FL effect in vasomotion?
- **What we already knew:** (M. Ascolese, A. Farina, A. Fasano, J. of Biological Physics 2019)
  1. (unlike the Haynes' idea) the FL effect **increases** the mechanical dissipation **but it favours the volumetric flux** and, consequently, it **increases the tissue perfusion** (probably the true physiological role of the FL effect)
- **What we proved:**
  2. In arterioles, the FL effect mitigates the increment of hydraulic resistance
  3. Though vasomotion appears not to be beneficial for the blood flow in a single arteriole, it becomes an efficient mechanism for the spatial regulation in a network of vessels (confirming what recently hypothesized by Lapi et al., Frontiers in Physiology 2019)

Vasomotion

Modeling vasomotion in arterioles (A. Farina, A. Fasano, F. Rosso, J. Theoretical Biology 2022): the main points.

- **A mechanical fact:** because of contractions, the vessel lumen reduces which implies that the hydraulic resistance increases!
- **Question:** which role has the FL effect in vasomotion?
- **What we already knew:** (M. Ascolese, A. Farina, A. Fasano, J. of Biological Physics 2019)
  1. (unlike the Haynes' idea) the FL effect **increases** the mechanical dissipation **but it favours the volumetric flux** and, consequently, it **increases the tissue perfusion** (probably the true physiological role of the FL effect)
- **What we proved:**
  2. In arterioles, the FL effect mitigates the increment of hydraulic resistance
  3. Though vasomotion appears not to be beneficial for the blood flow in a single arteriole, it becomes an efficient mechanism for the spatial regulation in a network of vessels (confirming what recently hypothesized by Lapi et al., Frontiers in Physiology 2019)

Vasomotion

Modeling vasomotion in arterioles (A. Farina, A. Fasano, F. Rosso, J. Theoretical Biology 2022): the main points.

- **A mechanical fact:** because of contractions, the vessel lumen reduces which implies that the hydraulic resistance increases!
- **Question:** which role has the FL effect in vasomotion?
- **What we already knew:** (M. Ascolese, A. Farina, A. Fasano, J. of Biological Physics 2019)
  1. (unlike the Haynes' idea) the FL effect **increases** the mechanical dissipation **but it favours the volumetric flux** and, consequently, it **increases the tissue perfusion** (probably the true physiological role of the FL effect)
- **What we proved:**
  2. In arterioles, the FL effect mitigates the increment of hydraulic resistance
  3. Though vasomotion appears not to be beneficial for the blood flow in a single arteriole, it becomes an efficient mechanism for the spatial regulation in a network of vessels (confirming what recently hypothesized by Lapi et al., Frontiers in Physiology 2019)

Vasomotion

Modeling vasomotion in arterioles (A. Farina, A. Fasano, F. Rosso, J. Theoretical Biology 2022): the main points.

- **A mechanical fact:** because of contractions, the vessel lumen reduces which implies that the hydraulic resistance increases!
- **Question:** which role has the FL effect in vasomotion?
- **What we already knew:** (M. Ascolese, A. Farina, A. Fasano, J. of Biological Physics 2019)
  1. (unlike the Haynes' idea) the FL effect **increases** the mechanical dissipation **but it favours the volumetric flux** and, consequently, it **increases the tissue perfusion** (probably the true physiological role of the FL effect)
- **What we proved:**
  2. In arterioles, the FL effect mitigates the increment of hydraulic resistance
  3. Though vasomotion appears not to be beneficial for the blood flow in a single arteriole, it becomes an efficient mechanism for the spatial regulation in a network of vessels (confirming what recently hypothesized by Lapi et al., Frontiers in Physiology 2019)

Vasomotion

Modeling vasomotion in arterioles (A. Farina, A. Fasano, F. Rosso, J. Theoretical Biology 2022): the main points.

- **A mechanical fact:** because of contractions, the vessel lumen reduces which implies that the hydraulic resistance increases!
- **Question:** which role has the FL effect in vasomotion?
- **What we already knew:** (M. Ascolese, A. Farina, A. Fasano, J. of Biological Physics 2019)
  1. (unlike the Haynes' idea) the FL effect **increases** the mechanical dissipation **but it favours the volumetric flux** and, consequently, it **increases the tissue perfusion** (probably the true physiological role of the FL effect)
- **What we proved:**
  2. In arterioles, the FL effect mitigates the increment of hydraulic resistance
  3. Though vasomotion appears not to be beneficial for the blood flow in a single arteriole, it becomes an efficient mechanism for the spatial regulation in a network of vessels (confirming what recently hypothesized by Lapi et al., Frontiers in Physiology 2019)

The FL effect mitigates the increment of hydraulic resistance

We used, basically, the same mathematical apparatus as for the FL and F effect and the lubrication approximation (the aspect ratio *vessel mean radius/vessel length* $\leq O(10^{-2})$) in the Navier-Stokes model with viscosity dependent of the hematocrit.

The dimensionless average (over a period) vessel resistance provided by our model is

$$\overline{\mathcal{R}} = \frac{1}{\int_0^1 \left[s_o^4(1-\eta)\left(1+\sqrt{\left(1-\frac{s_o^2}{R^2(t)}\right)\left[1-\frac{s_o^2}{R^2(t)}\left(1-\frac{1}{\eta}\right)\right]}\right)^2 + \eta R(t)^4 \right] dt}$$

where

$$R(t) = (1-\delta(1-\cos(\omega t))), \quad s_o(a, D, R(t)) = R(t) - 2a/D, \quad \eta = \eta_c/\eta_a$$

and ω is the oscillation frequency (in Lapi et al., δ from 0.3 to 0.6 and frequency of order 0.1 Hertz)

The FL effect mitigates the increment of hydraulic resistance

We used, basically, the same mathematical apparatus as for the FL and F effect and the lubrication approximation (the aspect ratio *vessel mean radius/vessel length* $\leq O(10^{-2})$) in the Navier-Stokes model with viscosity dependent of the hematocrit.

The dimensionless average (over a period) vessel resistance provided by our model is

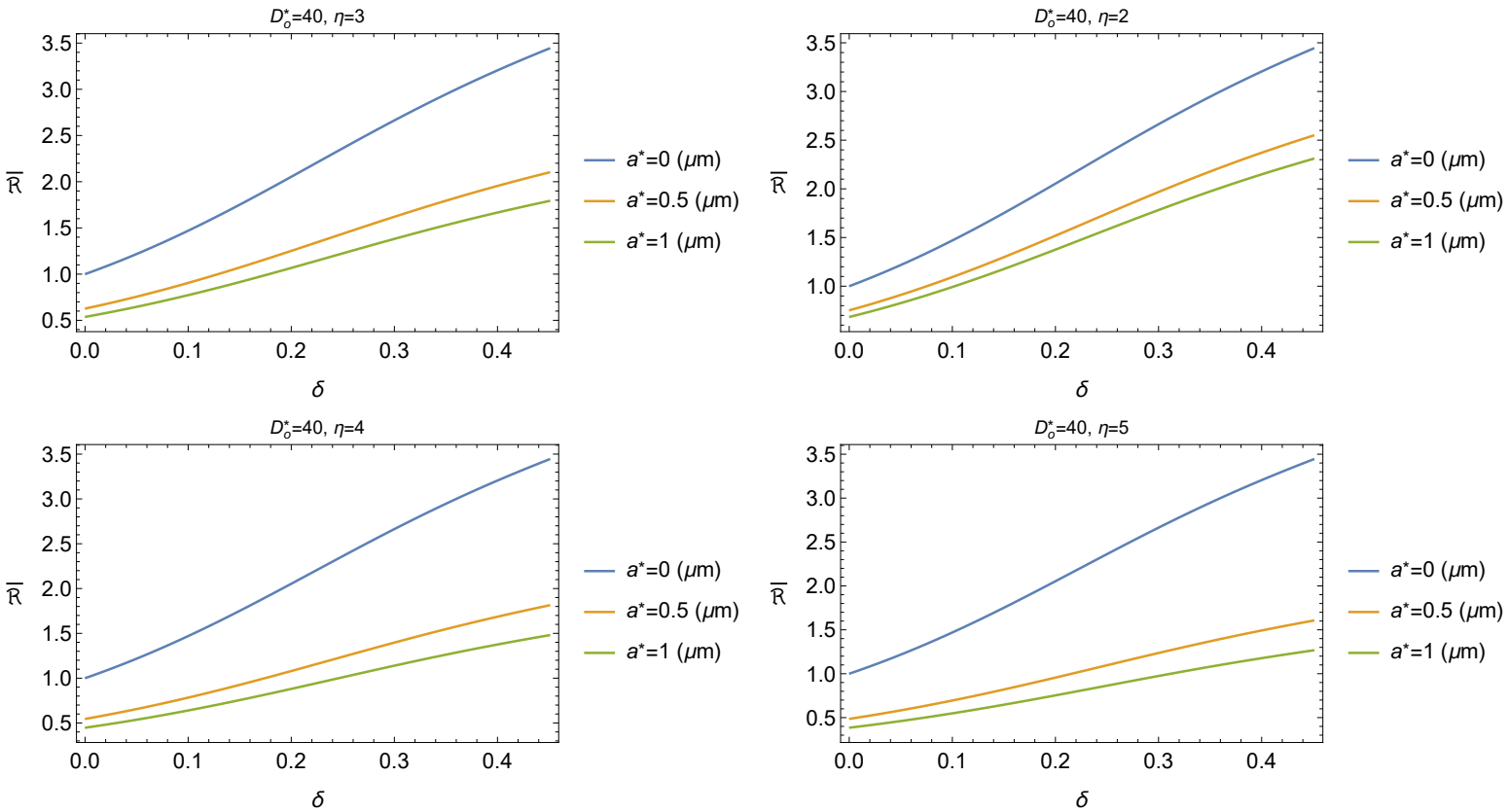
$$\overline{\mathcal{R}} = \frac{1}{\int_0^1 \left[s_o^4(1-\eta)\left(1+\sqrt{\left(1-\frac{s_o^2}{R^2(t)}\right)\left[1-\frac{s_o^2}{R^2(t)}\left(1-\frac{1}{\eta}\right)\right]}\right)^2 + \eta R(t)^4 \right] dt}$$

where

$$R(t) = (1-\delta(1-\cos(\omega t))), \quad s_o(a, D, R(t)) = R(t) - 2a/D, \quad \eta = \eta_c/\eta_a$$

and ω is the oscillation frequency (in Lapi et al., δ from 0.3 to 0.6 and frequency of order 0.1 Hertz)

The FL effect mitigates the increment of hydraulic resistance



Average hydraulic resistance as a function of δ (recall that $1-\delta$ is the minimum lumen) with the FL effect ($a > 0$) or without ($a = 0$) for $D = 40$µm.

Measurements by Gratton et al. 1998

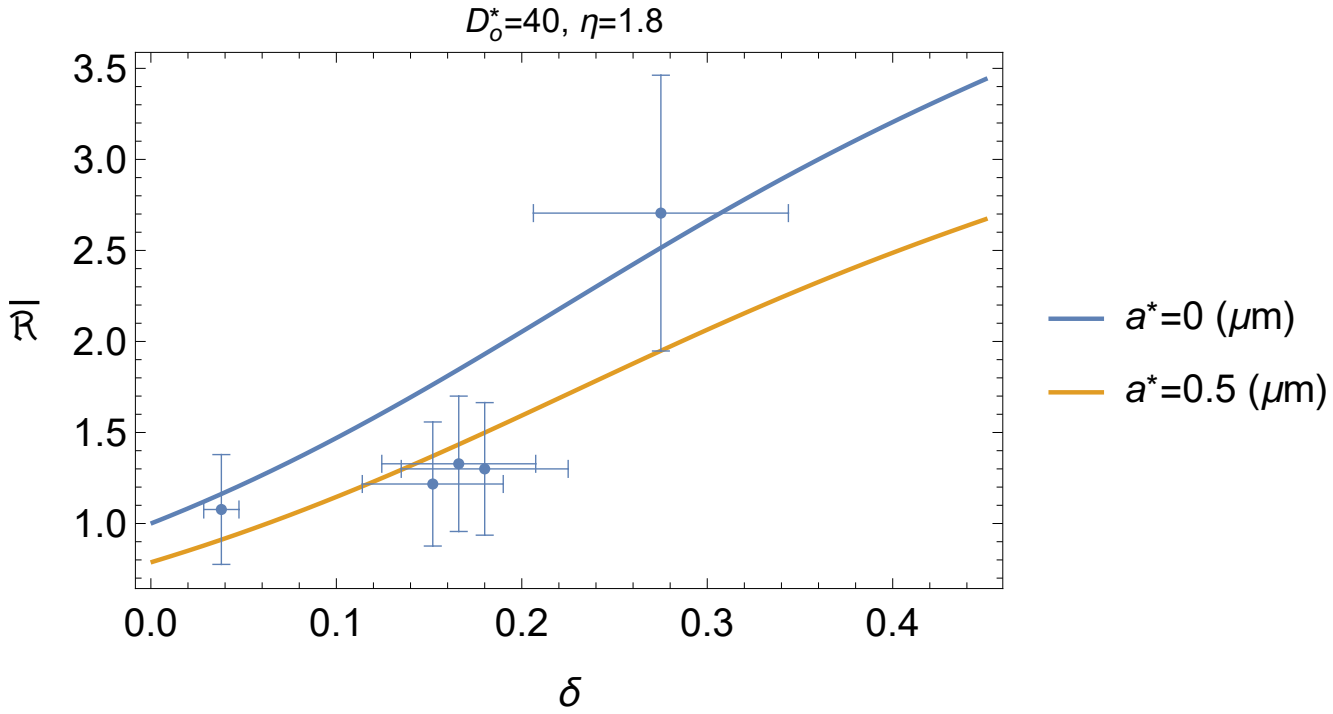
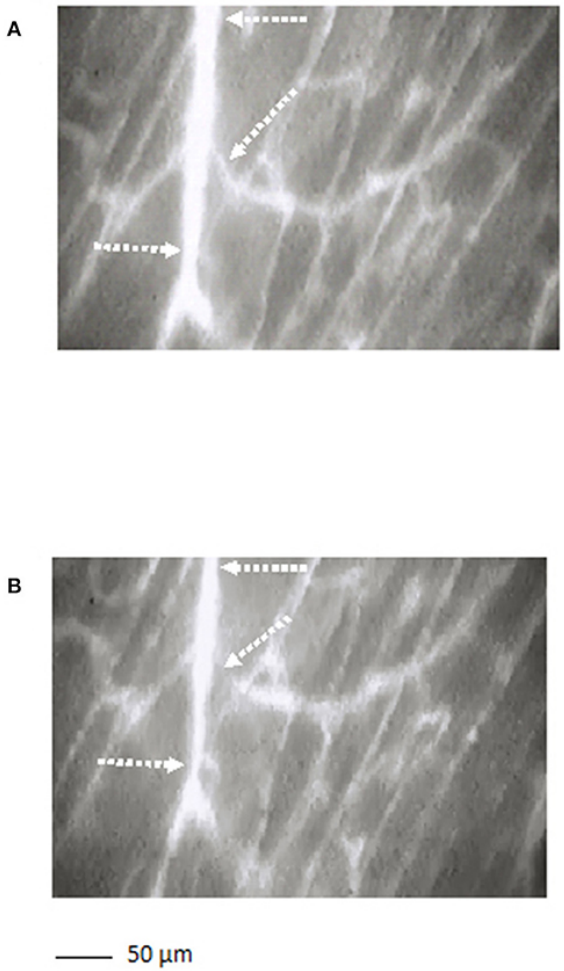


Figure: The relative average hydraulic resistance $\overline{\mathcal{R}}$ according to the mathematical model, either considering the FL effect ($a^* = 0.5\,\mu\text{m}$) or not ($a^* = 0\,\mu\text{m}$), when $D_o^* = 40\,\mu\text{m}$ and $\eta = 1.8$. The data points are taken from Gratton et al. (J. Appl. Physiol. 1998). Even considering an uncertainty of 25% of the measured values, the correction induced by the FL effect appears to fit the available data better than in the opposite case.

Vasomotion: a regulatory mechanism in capillary perfusion

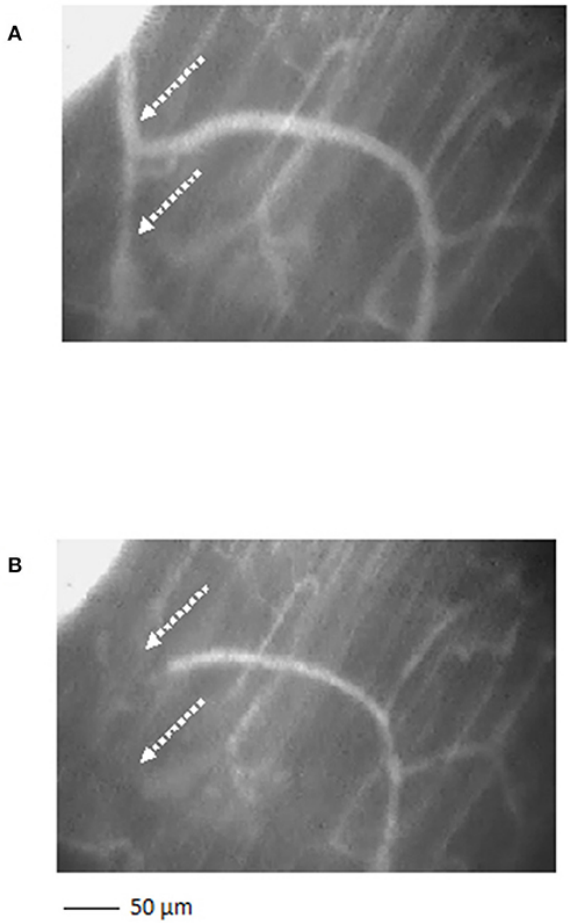
Lapi et al. experiments, Frontiers in Physiology (2019)
Capillary blood flow is modulated by changes in diameter of terminal arterioles facilitating redistribution of blood flow according to the metabolic demands of tissues.



A terminal arteriolar tree spreading from arcadic parent vessel undegoing vasomotion:

(A) dilation indicated by the dotted arrows,
(B) constriction indicated by the dotted arrows

Vasomotion: a regulatory mechanism in capillary perfusion

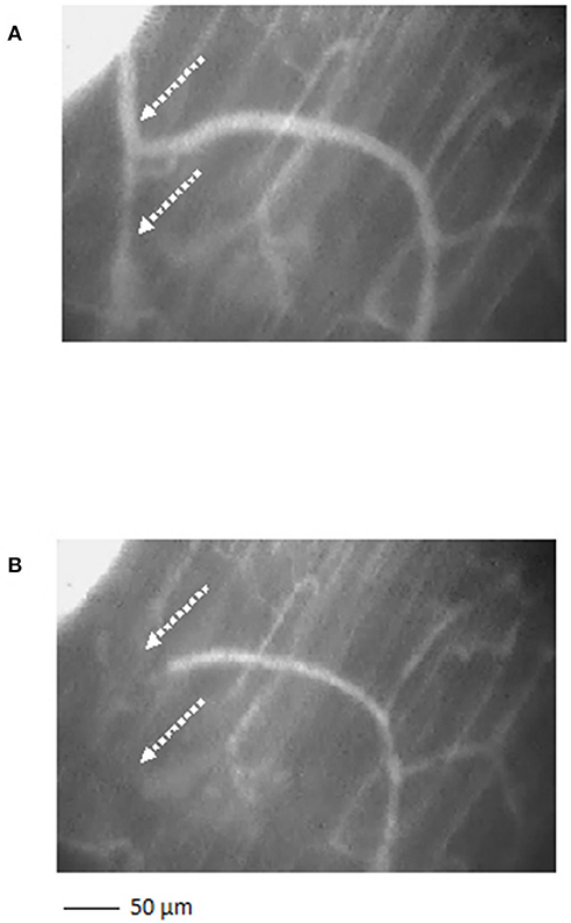


A terminal arteriolar tree spreading from arcadic parent vessel undegoing vasomotion:

(A) dilation indicated by the dotted arrows,
(B) constriction indicated by the dotted arrows

These images are taken from a movie (courtesy by D. Lapi)

Vasomotion: a regulatory mechanism in capillary perfusion



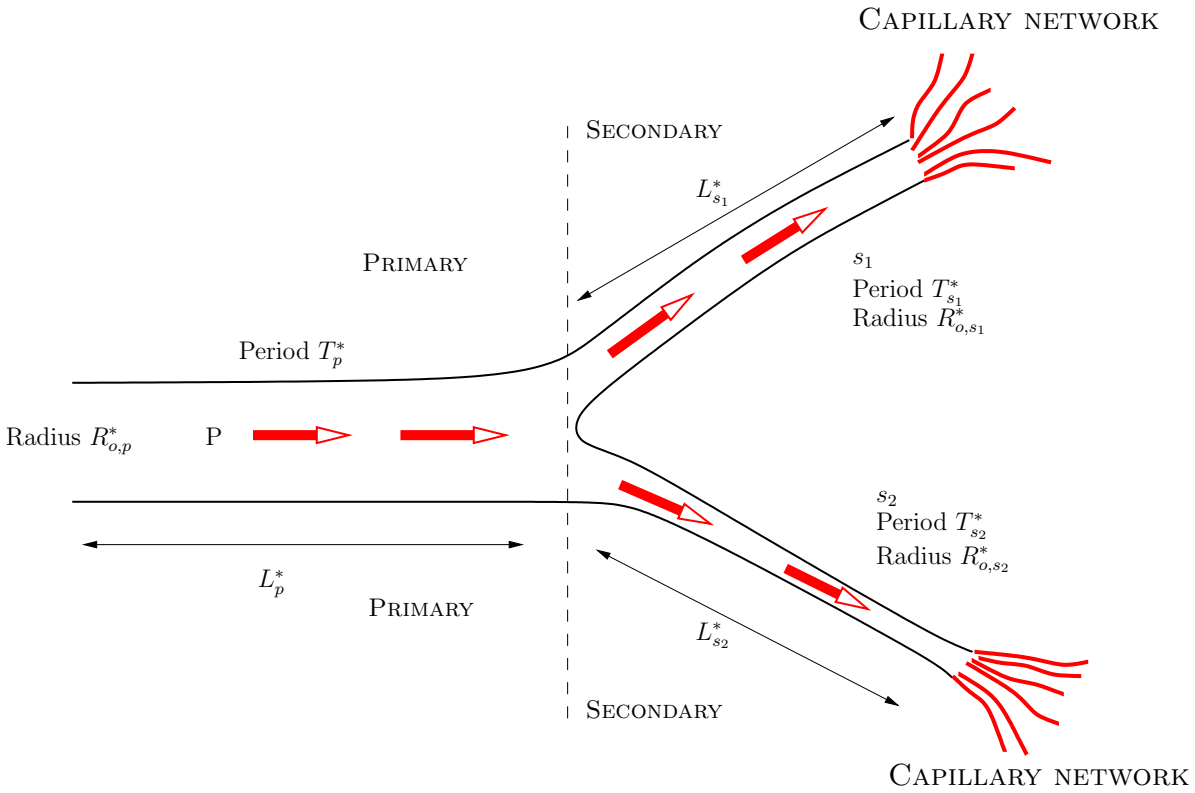
A terminal arteriolar tree spreading from arcadic parent vessel undegoing vasomotion:

(A) dilation indicated by the dotted arrows,
(B) constriction indicated by the dotted arrows

These images are taken from a movie (courtesy by D. Lapi)

Mathematical model in a network of arterioles

Here we extend our modelling approach from a single vessel to a network of arterioles. For simplicity, we consider a simple **pitchfork bifurcating vessel**. Our aim is to model the resistance in the whole vessels tree which undergoes vasomotion with different frequencies and phases.



Mathematical model in a network of arterioles

In dimensionless variables

$$R_\alpha(t) = 1 - \delta_\alpha(1 - \cos(2\pi f_\alpha t + \phi_\alpha)), \qquad \alpha = p, s_1, s_2$$

ϕ_α is the phase shift (in general the oscillations of the arteriolar branches are not in phase). In particular, we take $\phi_p = 0$, and $\phi_{s_1} \neq \phi_{s_2}$.
The dimensionless volumetric flux in the α^{th} branch is

$$\mathfrak{D}_\alpha = s_{\infty,\alpha}^4 + \eta\left(R_\alpha^4(t) - s_{\infty,\alpha}^4\right)$$

where (recall our "magic" formula)

$$s_{\infty,\alpha} = \frac{R_\alpha - a_\alpha}{\sqrt{1 + \sqrt{\left[1 - \left(1 - \frac{a_\alpha}{R_\alpha}\right)^2\right]\left[1 - \left(1 - \frac{a_\alpha}{R_\alpha}\right)^2\left(1 - \frac{1}{\eta}\right)\right]}}}, \tag{19}$$

and a_α has the usual meaning related to the size exclusion effect with the same order of magnitude.

Mathematical model in a network of arterioles

- **Aim of the model**: to evaluate the flux through each secondary vessel.
- **Geometry:** a parent vessel followed by two branches with a capillary network at their end, each characterized by their own effective hydraulic (dimensional) resistances $H^*_{c_1}$ and $H^*_{c_2}$, respectively.
- **The leading idea:** the whole network is modeled as a simple electric circuit with resistors whose ends have the same voltage (i. e. the pressure at the end of the capillary network 1 is equal to that at the end of the capillary network 2). Then the total hydraulic resistance turns out to be

$$H^*_{\text{tot}} = H^*_p + \left(\frac{1}{H^*_{s_1} + H^*_{c_1}} + \frac{1}{H^*_{s_2} + H^*_{c_2}} \right)^{-1}.$$

Main question: is the model able to determine flow rates in the secondary vessels during the period of oscillation of the mother vessel p?

Additional question: can we show that, through an appropriate phase shift between the oscillations of the vessels s_1 and s_2, the blood flow can be periodically and unequally distributed in the two branches?

Mathematical model in a network of arterioles

- **Aim of the model**: to evaluate the flux through each secondary vessel.
- **Geometry:** a parent vessel followed by two branches with a capillary network at their end, each characterized by their own effective hydraulic (dimensional) resistances $H^*_{c_1}$ and $H^*_{c_2}$, respectively.
- **The leading idea:** the whole network is modeled as a simple electric circuit with resistors whose ends have the same voltage (i. e. the pressure at the end of the capillary network 1 is equal to that at the end of the capillary network 2). Then the total hydraulic resistance turns out to be

$$H^*_{\text{tot}} = H^*_p + \left(\frac{1}{H^*_{s_1} + H^*_{c_1}} + \frac{1}{H^*_{s_2} + H^*_{c_2}} \right)^{-1}.$$

Main question: is the model able to determine flow rates in the secondary vessels during the period of oscillation of the mother vessel p?

Additional question: can we show that, through an appropriate phase shift between the oscillations of the vessels s_1 and s_2, the blood flow can be periodically and unequally distributed in the two branches?

Mathematical model in a network of arterioles

- **Aim of the model**: to evaluate the flux through each secondary vessel.
- **Geometry:** a parent vessel followed by two branches with a capillary network at their end, each characterized by their own effective hydraulic (dimensional) resistances $H^*_{c_1}$ and $H^*_{c_2}$, respectively.
- **The leading idea:** the whole network is modeled as a simple electric circuit with resistors whose ends have the same voltage (i. e. the pressure at the end of the capillary network 1 is equal to that at the end of the capillary network 2). Then the total hydraulic resistance turns out to be

$$H^*_{\text{tot}} = H^*_p + \left(\frac{1}{H^*_{s_1} + H^*_{c_1}} + \frac{1}{H^*_{s_2} + H^*_{c_2}} \right)^{-1}.$$

Main question: is the model able to determine flow rates in the secondary vessels during the period of oscillation of the mother vessel p?

Additional question: can we show that, through an appropriate phase shift between the oscillations of the vessels s_1 and s_2, the blood flow can be periodically and unequally distributed in the two branches?

Mathematical model in a network of arterioles

- **Aim of the model**: to evaluate the flux through each secondary vessel.
- **Geometry:** a parent vessel followed by two branches with a capillary network at their end, each characterized by their own effective hydraulic (dimensional) resistances $H^*_{c_1}$ and $H^*_{c_2}$, respectively.
- **The leading idea:** the whole network is modeled as a simple electric circuit with resistors whose ends have the same voltage (i. e. the pressure at the end of the capillary network 1 is equal to that at the end of the capillary network 2). Then the total hydraulic resistance turns out to be

$$H^*_{\text{tot}} = H^*_p + \left(\frac{1}{H^*_{s_1} + H^*_{c_1}} + \frac{1}{H^*_{s_2} + H^*_{c_2}} \right)^{-1}.$$

Main question: is the model able to determine flow rates in the secondary vessels during the period of oscillation of the mother vessel p?

Additional question: can we show that, through an appropriate phase shift between the oscillations of the vessels s_1 and s_2, the blood flow can be periodically and unequally distributed in the two branches?

Mathematical model in a network of arterioles

- **Aim of the model**: to evaluate the flux through each secondary vessel.
- **Geometry:** a parent vessel followed by two branches with a capillary network at their end, each characterized by their own effective hydraulic (dimensional) resistances $H^*_{c_1}$ and $H^*_{c_2}$, respectively.
- **The leading idea:** the whole network is modeled as a simple electric circuit with resistors whose ends have the same voltage (i. e. the pressure at the end of the capillary network 1 is equal to that at the end of the capillary network 2). Then the total hydraulic resistance turns out to be

$$H^*_{\text{tot}} = H^*_p + \left(\frac{1}{H^*_{s_1} + H^*_{c_1}} + \frac{1}{H^*_{s_2} + H^*_{c_2}} \right)^{-1}.$$

Main question: is the model able to determine flow rates in the secondary vessels during the period of oscillation of the mother vessel p?

Additional question: can we show that, through an appropriate phase shift between the oscillations of the vessels s_1 and s_2, the blood flow can be periodically and unequally distributed in the two branches?

Mathematical model in a network of arterioles

- **Aim of the model**: to evaluate the flux through each secondary vessel.
- **Geometry:** a parent vessel followed by two branches with a capillary network at their end, each characterized by their own effective hydraulic (dimensional) resistances $H^*_{c_1}$ and $H^*_{c_2}$, respectively.
- **The leading idea:** the whole network is modeled as a simple electric circuit with resistors whose ends have the same voltage (i. e. the pressure at the end of the capillary network 1 is equal to that at the end of the capillary network 2). Then the total hydraulic resistance turns out to be

$$H^*_{\text{tot}} = H^*_p + \left(\frac{1}{H^*_{s_1} + H^*_{c_1}} + \frac{1}{H^*_{s_2} + H^*_{c_2}} \right)^{-1}.$$

Main question: is the model able to determine flow rates in the secondary vessels during the period of oscillation of the mother vessel p?

Additional question: can we show that, through an appropriate phase shift between the oscillations of the vessels s_1 and s_2, the blood flow can be periodically and unequally distributed in the two branches?

Mathematical model in a network of arterioles

Branch volumetric flux:

$$Q_{s_1}(t) = \mathcal{F}(t)\left(1 + H_{c_2}\mathfrak{D}_{s_2}(t)\right)\mathfrak{D}_{s_1}(t), \quad Q_{s_2}(t) = \mathcal{F}(t)\left(1 + H_{c_1}\mathfrak{D}_{s_1}(t)\right)\mathfrak{D}_{s_2}(t),$$

where

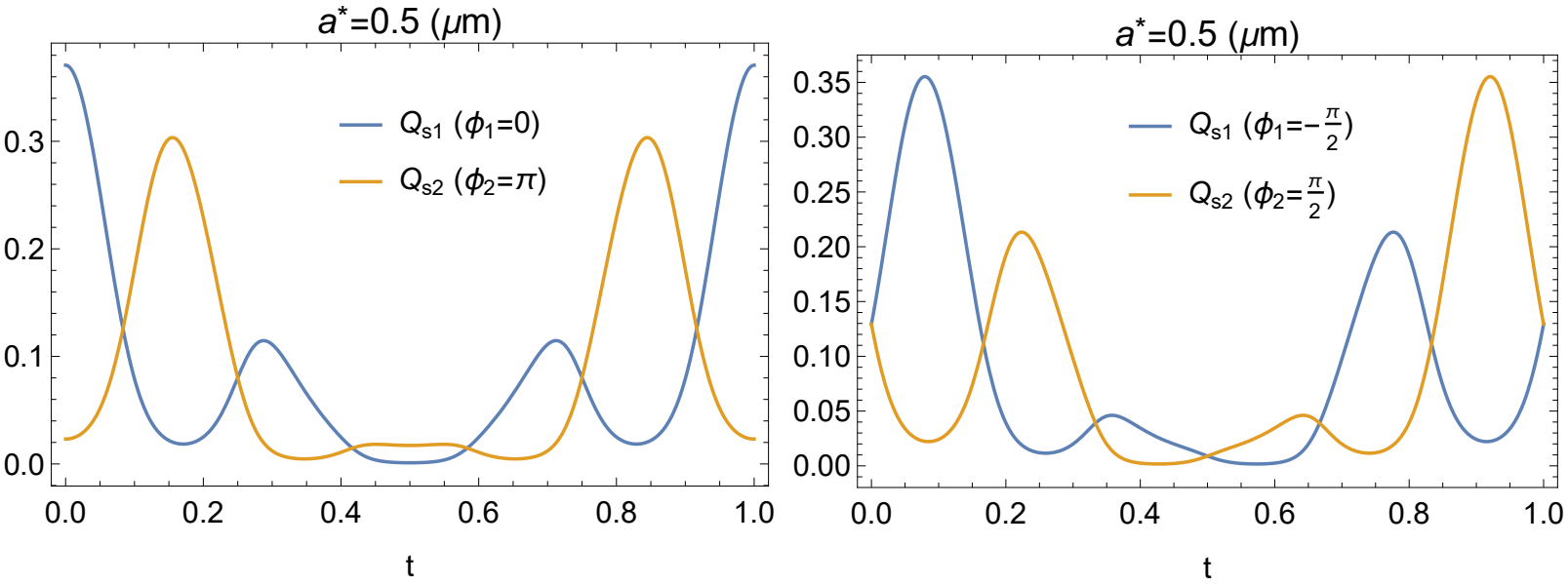
$$\mathcal{F}(t) = \frac{\mathfrak{D}_p}{\gamma_{ps}\mathfrak{D}_p\left(1 + H_{c_2}\mathfrak{D}_{s_2}\right)\left(1 + H_{c_1}\mathfrak{D}_{s_1}\right) + \mathfrak{D}_{s_1} + \mathfrak{D}_{s_2} + \mathfrak{D}_{s_1}\mathfrak{D}_{s_2}\left(H_{c_2} + H_{c_1}\right)},$$

$$\gamma_{ps} = \frac{C_p^*}{C_s^*} = \left(\frac{R_{o,p}^*}{R_{o,s}^*}\right)^4 \frac{L_s^*}{L_p^*}, \quad H_{c_1} = \frac{H_{c_1}^*}{C_s^*}, \quad H_{c_2} = \frac{H_{c_2}^*}{C_s^*},$$

$$H_\alpha^*(t) = \frac{1}{C_\alpha^*\mathfrak{D}_\alpha(t)}, \qquad \text{with} \quad C_\alpha^* = \frac{\pi R_{o,\alpha}^{*\,4}}{8\eta_c^* L_\alpha^*}, \quad \alpha = p, s_1, s_2.$$

(starred quantities are dimensional)

Mathematical model in a network of arterioles



Q_{s_1} and Q_{s_2} in the two bifurcating branches for $\phi_1 = 0$, $\phi_2 = \pi$ (left panel) and for $\phi_1 = -\pi/2$, $\phi_2 = \pi/2$ (right panel). In both cases $H_{c_1} = H_{c_2} = 0$. The parameter γ_{sp} has been computed using experimental data

What this model network suggests. I

The previous figure clearly highlights that it is possible, with suitable phase shifts, to periodically direct most of the flow towards the branch s_1 and then towards s_2.

In particular, the flows in branches s_1 and s_2 depend both on the phase shift between branches themselves but also on the phase shift with respect to the parent vessel p (which, however, oscillates at a lower frequency).

In fact, the right panel shows a different pattern from the left one, even if the relative phase shift between the two branches is still π. Figure seems also to indicate that the FL effect plays a marginal role at this diameter size. Indeed setting $a_\alpha = 0$, $\alpha = s_1, s_2$, does not change significantly Q_{s_1} and Q_{s_2}

What this model network suggests. I

The previous figure clearly highlights that it is possible, with suitable phase shifts, to periodically direct most of the flow towards the branch s_1 and then towards s_2.

In particular, the flows in branches s_1 and s_2 depend both on the phase shift between branches themselves but also on the phase shift with respect to the parent vessel p (which, however, oscillates at a lower frequency).

In fact, the right panel shows a different pattern from the left one, even if the relative phase shift between the two branches is still π. Figure seems also to indicate that the FL effect plays a marginal role at this diameter size. Indeed setting $a_\alpha = 0$, $\alpha = s_1, s_2$, does not change significantly Q_{s_1} and Q_{s_2}

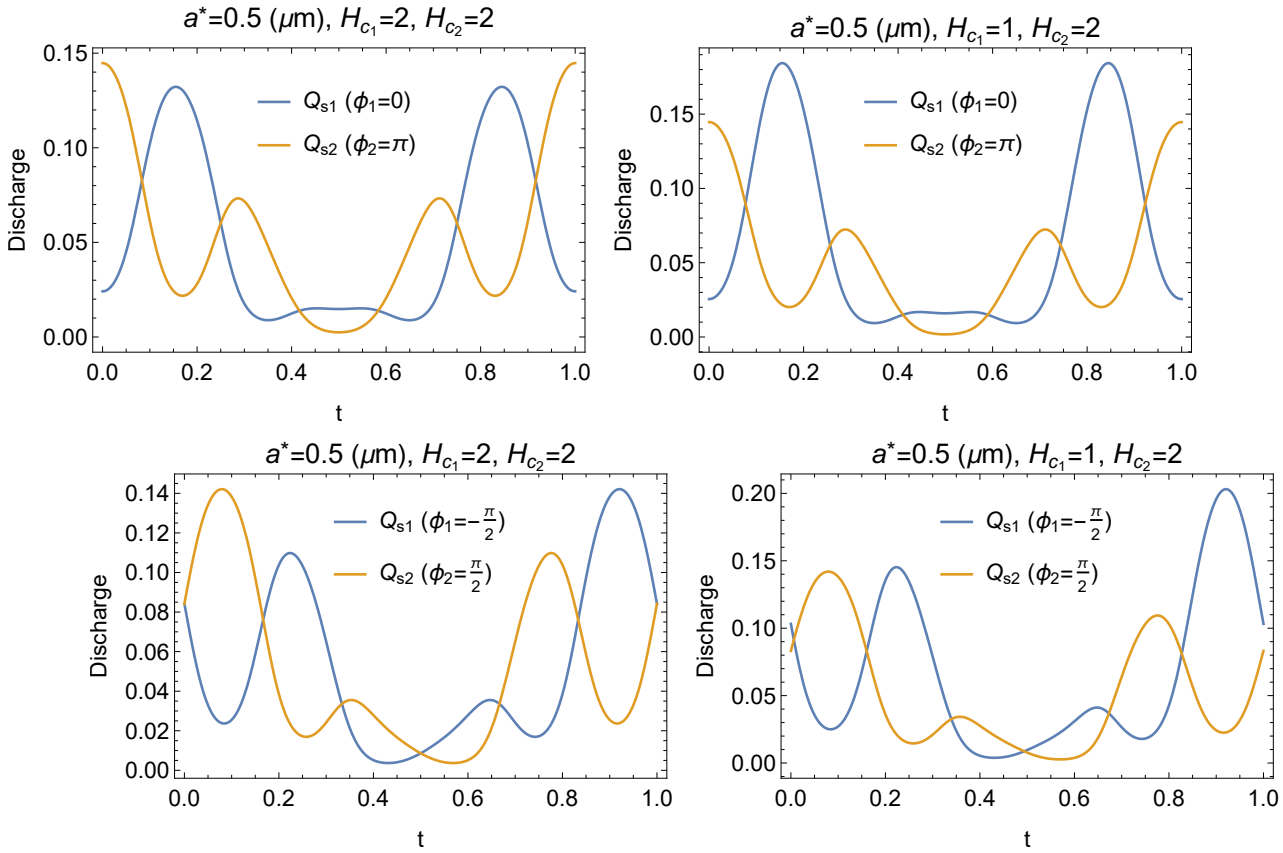
What this model network suggests. I

The previous figure clearly highlights that it is possible, with suitable phase shifts, to periodically direct most of the flow towards the branch s_1 and then towards s_2.

In particular, the flows in branches s_1 and s_2 depend both on the phase shift between branches themselves but also on the phase shift with respect to the parent vessel p (which, however, oscillates at a lower frequency).

In fact, the right panel shows a different pattern from the left one, even if the relative phase shift between the two branches is still π. Figure seems also to indicate that the FL effect plays a marginal role at this diameter size. Indeed setting $a_\alpha = 0$, $\alpha = s_1, s_2$, does not change significantly Q_{s_1} and Q_{s_2}

Mathematical model in a network of arterioles



Q_{s_1} and Q_{s_2} in the two bifurcating branches for $\phi_1 = 0$, $\phi_2 = \pi$ (left panel) and for $\phi_1 = -\pi/2$, $\phi_2 = \pi/2$ (right panel). The presence of a terminal capillary network is taken into account: we considered the case of equal capillary resistance ($H_{c_1}/H_{c_2} = 1$) and a different one $H_{c_1}/H_{c_2} = 1/2$.

What this model suggests. II

The previous figure shows the effect of including a capillary network at the very end of the two branches. Since we are not able to estimate neither H_{c_1} nor H_{c_2} we assume that the hydraulic resistances of the capillary networks are in any case comparable with each other and with those of the branches s_1 and s_2.

In the four panels we plot Q_{s_1} and Q_{s_2} for two phase difference and two different capillary resistance. It is evident that as the value of H_c of one branch increases with respect to the other, the flow in that branch is disadvantaged.

We note that the presence of the capillary network downstream of the secondary vessels s_1 and s_2, does not cancel the effect of periodically redirecting the flow in the two branches caused by the relative phase shift.

What this model suggests. II

The previous figure shows the effect of including a capillary network at the very end of the two branches. Since we are not able to estimate neither H_{c_1} nor H_{c_2} we assume that the hydraulic resistances of the capillary networks are in any case comparable with each other and with those of the branches s_1 and s_2.

In the four panels we plot Q_{s_1} and Q_{s_2} for two phase difference and two different capillary resistance. It is evident that as the value of H_c of one branch increases with respect to the other, the flow in that branch is disadvantaged.

We note that the presence of the capillary network downstream of the secondary vessels s_1 and s_2, does not cancel the effect of periodically redirecting the flow in the two branches caused by the relative phase shift.

What this model suggests. II

The previous figure shows the effect of including a capillary network at the very end of the two branches. Since we are not able to estimate neither H_{c_1} nor H_{c_2} we assume that the hydraulic resistances of the capillary networks are in any case comparable with each other and with those of the branches s_1 and s_2.

In the four panels we plot Q_{s_1} and Q_{s_2} for two phase difference and two different capillary resistance. It is evident that as the value of H_c of one branch increases with respect to the other, the flow in that branch is disadvantaged.

We note that the presence of the capillary network downstream of the secondary vessels s_1 and s_2, does not cancel the effect of periodically redirecting the flow in the two branches caused by the relative phase shift.

Mathematical model in a network of arterioles

Model implications:

1. The mathematical model is able to reproduce the experimental data documented in Gratton et al. (1998).
2. The model emphasizes the mitigating role of the FL effect: the hydraulic resistance increases significantly with the wall oscillation, although the FL effect limits this increment. This confirms what emphasized by Ascolese et al. (2019)
3. Though vasomotion appears not to be beneficial for the blood flow in a single valveless vessel (like an arteriole), it becomes an efficient mechanism for the spatial regulation of the flow when considering a network of vessels.
4. Even considering a simple tree structure with three classes of vessels, the last of which representing the capillaries, the mathematical model justifies and explains what has recently been hypothesized by Lapi et al. (2019). The parent arteriole (vessel p in our model) acts as a blood reservoirs, the blood redistribution through the secondary branches (vessel s_α, $\alpha = 1, 2$ in our model) and the subsequent capillary networks occurs through an alternation (i.e. a phase shift) in the oscillations of the vessel walls.

Mathematical model in a network of arterioles

Model implications:

1. The mathematical model is able to reproduce the experimental data documented in Gratton et al. (1998).
2. The model emphasizes the mitigating role of the FL effect: the hydraulic resistance increases significantly with the wall oscillation, although the FL effect limits this increment. This confirms what emphasized by Ascolese et al. (2019)
3. Though vasomotion appears not to be beneficial for the blood flow in a single valveless vessel (like an arteriole), it becomes an efficient mechanism for the spatial regulation of the flow when considering a network of vessels.
4. Even considering a simple tree structure with three classes of vessels, the last of which representing the capillaries, the mathematical model justifies and explains what has recently been hypothesized by Lapi et al. (2019). The parent arteriole (vessel p in our model) acts as a blood reservoirs, the blood redistribution through the secondary branches (vessel s_α, $\alpha = 1, 2$ in our model) and the subsequent capillary networks occurs through an alternation (i.e. a phase shift) in the oscillations of the vessel walls.

Mathematical model in a network of arterioles

Model implications:

1. The mathematical model is able to reproduce the experimental data documented in Gratton et al. (1998).
2. The model emphasizes the mitigating role of the FL effect: the hydraulic resistance increases significantly with the wall oscillation, although the FL effect limits this increment. This confirms what emphasized by Ascolese et al. (2019)
3. Though vasomotion appears not to be beneficial for the blood flow in a single valveless vessel (like an arteriole), it becomes an efficient mechanism for the spatial regulation of the flow when considering a network of vessels.
4. Even considering a simple tree structure with three classes of vessels, the last of which representing the capillaries, the mathematical model justifies and explains what has recently been hypothesized by Lapi et al. (2019). The parent arteriole (vessel p in our model) acts as a blood reservoirs, the blood redistribution through the secondary branches (vessel s_α, $\alpha = 1, 2$ in our model) and the subsequent capillary networks occurs through an alternation (i.e. a phase shift) in the oscillations of the vessel walls.

Mathematical model in a network of arterioles

Model implications:

1. The mathematical model is able to reproduce the experimental data documented in Gratton et al. (1998).
2. The model emphasizes the mitigating role of the FL effect: the hydraulic resistance increases significantly with the wall oscillation, although the FL effect limits this increment. This confirms what emphasized by Ascolese et al. (2019)
3. Though vasomotion appears not to be beneficial for the blood flow in a single valveless vessel (like an arteriole), it becomes an efficient mechanism for the spatial regulation of the flow when considering a network of vessels.
4. Even considering a simple tree structure with three classes of vessels, the last of which representing the capillaries, the mathematical model justifies and explains what has recently been hypothesized by Lapi et al. (2019). The parent arteriole (vessel p in our model) acts as a blood reservoirs, the blood redistribution through the secondary branches (vessel s_α, $\alpha = 1, 2$ in our model) and the subsequent capillary networks occurs through an alternation (i.e. a phase shift) in the oscillations of the vessel walls.

General conclusions

Objective limitations in model validation (independent of us)

- Most experiments are performed *in vitro* and very few *in vivo* (for obvious reasons). However, the major interest is in the latter case.
- Most available data in the literature do not report an estimate of the experimental errors. This fact should always be taken into account in our modeling work.

Modeling advantages

- We proved that mathematical modeling based on the fundamental laws of fluid dynamics is the starting point to justify numerous behaviors observed in blood microcirculation.
- Although we neglected the complexity of cell interactions and diffusion effects, the model maintains a reasonable simplicity and provides relatively simple theoretical laws.
- Despite the above limitations, our models for some observable phenomena in microcirculation seem to provide a reasonable fitting of the **available** data.

General conclusions

Objective limitations in model validation (independent of us)

- Most experiments are performed *in vitro* and very few *in vivo* (for obvious reasons). However, the major interest is in the latter case.
- Most available data in the literature do not report an estimate of the experimental errors. This fact should always be taken into account in our modeling work.

Modeling advantages

- We proved that mathematical modeling based on the fundamental laws of fluid dynamics is the starting point to justify numerous behaviors observed in blood microcirculation.
- Although we neglected the complexity of cell interactions and diffusion effects, the model maintains a reasonable simplicity and provides relatively simple theoretical laws.
- Despite the above limitations, our models for some observable phenomena in microcirculation seem to provide a reasonable fitting of the **available** data.

Hasta la próxima ves

Thanks for your kind attention

Muchas gracias por su fina atención