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A Theoretical Model for the Fåhræus Effect in Medium-Large Microvessels

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Abstract

This paper presents a mathematical model capable to reproduce a celebrated phenomenon in blood microcirculation known as Fåhræus effect, since its discovery by Robin Fåhræus [1] in 1929. This consists in a decaying of the relative hematocrit in small vessels as the vessel diameter decreases. The key point of the model is a formula, direct consequence of the basic principles of fluid dynamics, that links the relative hematocrit to the reservoir hematocrit and the vessel diameter, which confirms the observed behaviour. To test the model we selected, among the few experiments carried on since then, those performed by Barbee and Cokelet [2]. The agreement is remarkable. An extended comparison is also carried out with a celebrated *empirical* formula proposed by Pries et al. in [3] to describe the same phenomenon.

Keywords: Blood flow in small vessels, Blood viscosity, Hematocrit level, Mathematical modeling, Fåhræus-Lindqvist effect

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1. Introduction

In 1929 Robin Fåhræus [1] published the results of his experiments regarding the hematocrit, i.e. the blood volume fraction occupied by Red Blood Cells (RBCs), when blood flows steadily through glass tubes with decreasing diameters from 1100 μm to 50 μm . The Fåhræus' experimental procedure consisted in driving well-mixed blood with known hematocrit H_F from a reservoir into a single tube. The hematocrit in the tube, denoted as H_T , was determined by stopping the flow, removing the capillary tube and measuring the hematocrit of blood in it by centrifugation.

Table 1: Fåhræus' original data. The hematocrit in the reservoir is $H_F = 40.5\%$. The tube relative hematocrit, i.e. $H_R = H_T/H_F$, results by dividing data in the second column by H_F . The experiments show that H_R is rapidly (non linearly) decreasing by reducing the tube diameter.

Tube diameter (mm)	Tube hematocrit H_T (%)	Plasma ($1 - H_T$)	Rel. hematocrit H_R
1.100	40.5	59.5	1
0.750	40.1	59.9	0.99
0.450	39.8	60.2	0.983
0.250	39.2	60.8	0.968
0.095	33.6	66.4	0.829
0.050	28.0	72.0	0.691

Table 1 reports what Fåhræus obtained, demonstrating the reduction of the hematocrit by reducing the tube diameter. It turns out that, when the diameter of the vessel decreases below 1100 μm , H_T/H_F is no longer equal to one. In particular, H_T decreases more rapidly for tubes with diameter

below 450 μm . We note that the latter effect occurs when the diameter of the capillary falls below a threshold comparable to that characterizing the Fåhræus–Lindqvist effect (about 300-400 μm) which we will discuss later. This leads to reasonably suppose that the two phenomena are somehow related.

Surprisingly, with the exception of a single paper by Thomas [4] in 1961, the entire literature about this phenomenon consisted, up to 1965, just in the six data points reported in the original paper by Fåhræus [1]. We had to wait until 1965 when other sets of data appeared, [5, 6] and 1968 for the paper by Hochmuth and Davis [7]. Barbee and Cokelet [2] were the first to use the term *Fåhræus effect*, (called F effect from now on). In that article, new data were presented together with a complete discussion over all previous data available at that time and over the experimental procedure itself.

Figure 1 (which reproduces Fig. 2 of [2]) shows the *relative hematocrit*, i.e. the ratio H_T/H_F , as a function of both the reservoir hematocrit H_F and the tube diameter. The same figure also suggests that, for a given diameter, the function H_T/H_F is practically linear in H_F and that its derivative increases by decreasing the tube diameter. The latter effect is more pronounced for diameters below 100 μm .

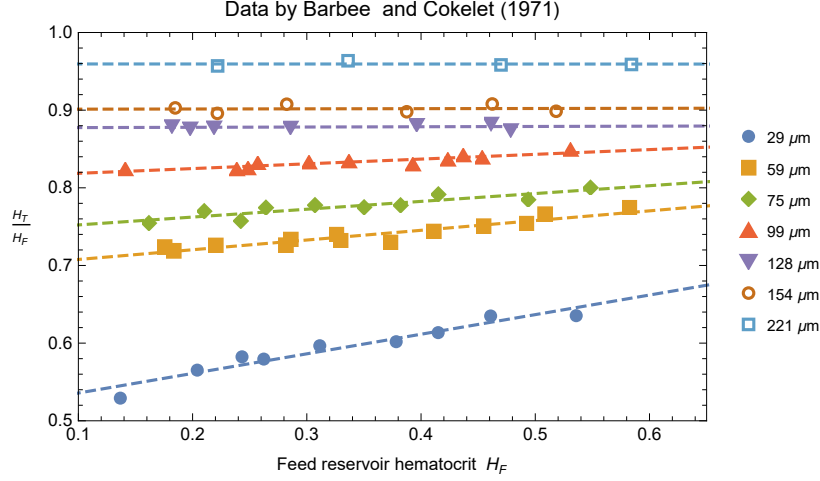


Figure 1: The relative tube hematocrit H_T/H_F as a function of feed hematocrit H_F for various vessel diameters, according to Fig. 2 in Barbee and Cokelet [2]. Dashed lines are linear fits.

Some Authors (see, e.g., [8, 9]), explained the F effect in terms of a difference between the average velocities of plasma and erythrocytes. We refer the readers to Chapter 7 of the book by Cokelet [10] for an in-depth discussion about it.

As far as we know, since the seminal paper by Fåhræus, the F effect has not received a complete theoretical explanation based on the first principles of continuum mechanics. The aim of the present paper is exactly to fill, at least partially, this gap. In particular we present a theoretical model able to reproduce the data in Fig. 1 for diameters not less than 59 μm (thus excluding the case 29 μm considered in [2]). Indeed, this limitation of our model arises from the fact that we treat the blood as a heterogeneous continuum. Clearly this approach does no longer applies when the cell size

66 is comparable with the tube diameter because the RBCs structure and their
67 interactions with the vessel walls start playing a basic role.

68 Many attempts to describe the F effect have been made by using linear as
69 well nonlinear rheological models for the blood flow (see, e.g., [11–20] and the
70 references therein). In most cases, the focussing point was to check the shear
71 stress vs. shear rate relationship to capture the deviation from the linear
72 viscous (Newtonian) model, particularly for diameters below 600 μm . In the
73 present paper we do not follow this line of investigation, since our analysis
74 reveals, a posteriori, that to represent the F effect a linear rheological model
75 is sufficient.

76 While the choice of the rheological model turns out not to be the real
77 core in the explanation of the F effect, a central role is played by the so-
78 called *marginal layer* assumption, first hypothesized by Haynes [21] in the
79 sixties of the last century. According to Haynes, in small vessels the RBCs
80 migrate towards the center of the tube, leaving a marginal layer of pure
81 plasma around. In two recent papers [22, 23], we have proved that a slight
82 modification of the original idea by Haynes allows to demonstrate, on the
83 basis of fluid dynamics only, another intriguing phenomenon, the Fåhræus–
84 Lindqvist effect (FL effect). The FL effect consists in the decreasing of
85 the blood relative (apparent) viscosity when the vessel diameter falls below
86 600 μm approximately. The generalization of the Haynes’ idea consists in
87 allowing the marginal layer to be not fully depleted of RBCs, a fact actually
88 supported by many observations (see, e.g., [16, 24–26]).

89 In [22], it has been shown that the marginal layer is crucial to explain
90 theoretically the FL effect. Similarly, we are going to prove that the same is

91 true for the F effect. Indeed, we exploit a model, rigorously proved in [27, 28],
 92 which is able to evaluate the marginal layer thickness by describing how the
 93 core flow develops downstream the tube entrance. Indeed the novelty of
 94 the present paper is the application of the explicit formula proved in [28] to
 95 describe theoretically the FL effect. This approach leads to a further formula
 96 relating H_R to H_F , through the thickness of the inlet marginal layer and of
 97 the vessel diameter. The relative hematocrit predicted by the formula is then
 98 tested against the data by Barbee and Cokelet [2]. The agreement is largely
 99 satisfactory and somehow better than the widely used empirical formula by
 100 Pries et al. [3, 29–31], in the range of diameters larger than about 60 μm .

101 The plan of the paper is the following: in Sect. 2 we describe the math-
 102 ematical model. In Sect. 2.2 we discuss the problem of how to express the
 103 blood viscosity as a function of the feeding hematocrit, while in Sect. 2.3
 104 we obtain the main formula for the relative hematocrit as a function of the
 105 feeding hematocrit and vessel diameter. Section 3.2 is devoted to the com-
 106 parison between the model predictions and the data in Fig. 2 of [2]. In
 107 Sect. 3.3 we make a comparison between the mathematical model and the
 108 empirical formula by Pries et al. in [3]. Some final remarks are drawn in the
 109 last section.

110 **2. Model and methods**

111 The model we are going to illustrate stems from a recent paper [22] aimed
 112 to explain, on a purely fluid mechanical base, the well-known FL effect.

113 2.1. Modeling the flow

114 As in [22], we consider a mechanically incompressible stationary laminar
 115 flow in a cylindrical vessel of radius¹ R^* and diameter $D^* = 2R^*$. We de-
 116 note by x^* , r^* the longitudinal and radial coordinate, respectively, and by
 117 $\mathbf{v}^* = v^*\mathbf{e}_x + u^*\mathbf{e}_r$, the velocity field. Following the usual approach of the
 118 boundary layer theory (see, e. g., [32]), we assume $\mathbf{v}^*|_{x^*=0} = V^*\mathbf{e}_x$, with
 119 $V^* = Q^*/\pi R^{*2}$, and Q^* is the inlet discharge.

120 Blood is considered a particle-fluid incompressible mixture of RBCs and
 121 plasma (see [33, 34]). The dynamical state is specified by the independent
 122 variables hematocrit H , velocity $\mathbf{v}^*$ and pressure p^* , which evolve according
 123 to the momentum balance equation, RBCs mass conservation, and incom-
 124 pressibility constraint (see, e.g., [23, 27, 28], for more details).

125 Concerning the non-spherical part of the Cauchy stress tensor, usually
 126 denoted by $\mathbb{T}^*$, we assume

$$\mathbb{T}^* = 2\eta^*(H)\mathbb{D}^*, \quad (1)$$

127 with $\mathbb{D}^* = 1/2(\nabla^*\mathbf{v}^* + \nabla^{*T}\mathbf{v}^*)$ shear rate tensor and η^* viscosity which is
 128 a function of H . Model (1) will be referred to as *linear viscous model*.

129 Concerning the blood viscosity, we write $\eta^* = \eta_p^*\eta(H)$, where η_p^* is the
 130 plasma viscosity and $\eta \geq 1$, dimensionless, is the *relative viscosity*, which
 131 is an increasing monotone function of H , such that $\eta(0) = 1$. The specific
 132 functional form of $\eta(H)$ will be discussed in detail in Section 2.2. For the
 133 moment, we proceed to analyzing those issues that are independent of the

¹Starred quantities are dimensional.

134 choice of $\eta(H)$.

135 Actually, η can be safely approximated as a function depending uniquely
136 on H only at sufficiently large shear rates (i.e. larger than approximately
137 300 s^{-1}). For smaller shear rates, the blood viscosity exhibits some depen-
138 dence on the shear rate too, [35, 36]. However, although the flows we are
139 going to study are characterized by shear rates smaller than 300 s^{-1} (see
140 Secomb [36]), in this paper we simply take $\eta = \eta(H)$. This is the main
141 limitation of the linear viscous model but we will recognize a posteriori that,
142 even ignoring the dependence of η on $|\mathbb{D}^*| = \sqrt{2\text{tr}(\mathbb{D}^*)^2}$, the model succeeds
143 anyway in fully justifying the experimentally observed link of H_T/H_F to the
144 vessel diameter and H_F , i.e. the F effect. Actually, taking $\eta = \eta(H)$ is
145 a considerable advantage because most of the experimental data (see, e.g.,
146 Fig. 4.10 of [37]) do not report any information on the discharge (or on the
147 pressure gradient) which is a fundamental datum when one wishes to make
148 use of a non-Newtonian rheological model. Additionally, neither the empir-
149 ical formulas reported in [3] (and often used to estimate H_T/H_F) take into
150 account the blood discharge nor the pressure gradient.

151 Fåhræus and Lindqvist, [38, p.565], showed that the blood apparent vis-
152 cosity remains practically constant when the vessel diameter is larger than
153 about $400\text{ }\mu\text{m}$, but it keeps decreasing for lower and lower diameters. Such
154 a phenomenon has been discussed ever since, and a qualitative explanation,
155 which received a large consensus, is the one proposed in the sixties by Haynes
156 [21]. In [22, 23, 28], the Authors gave a fully theoretical explanation of the
157 Haynes' conjecture, the so-called marginal layer theory, according to which
158 most of RBCs are confined within a streamtube (central core) whose radius

159 s^* evolves longitudinally, i.e. $s^* = s^*(x^*)$. Indeed, when the vessel radius
 160 suddenly reduces (as, for instance, at the inlet of a bifurcating vessel) the
 161 flow has a radial component (rapidly vanishing downstream) which, by shift-
 162 ing the particles towards the vessel axis, increases the thickness of the outer
 163 layer, [28]. The central core radius s^* quickly decreases from $s_0^* = s^*(x^*)|_{x^*=0}$,
 164 i.e. the radius right at the vessel inlet, to an asymptotic limit, denoted by
 165 s_∞^* . However, the entrance region is rather small compared to the vessel
 166 length L^* , so that the velocity field converges quickly to an axial flow, i.e.
 167 to $\mathbf{v}_\infty^* = v_\infty^* \mathbf{e}_x$ (see again [28]). In particular, since $r^* = s^*(x^*)$ is a material
 168 surface, mass conservation entails

$$Q^* \left(\frac{s_0^*}{R^*} \right)^2 = 2\pi \int_0^{s_\infty^*} v_\infty^*(r^*) r^* dr^*, \quad (2)$$

169 where Q^* is the blood discharge. We remark that in writing (2) we have
 170 implicitly assumed that the flow is uniform at the inlet cross section, namely
 171 $Q^* = \pi R^{*2} V^*$, with V^* uniform inlet velocity.

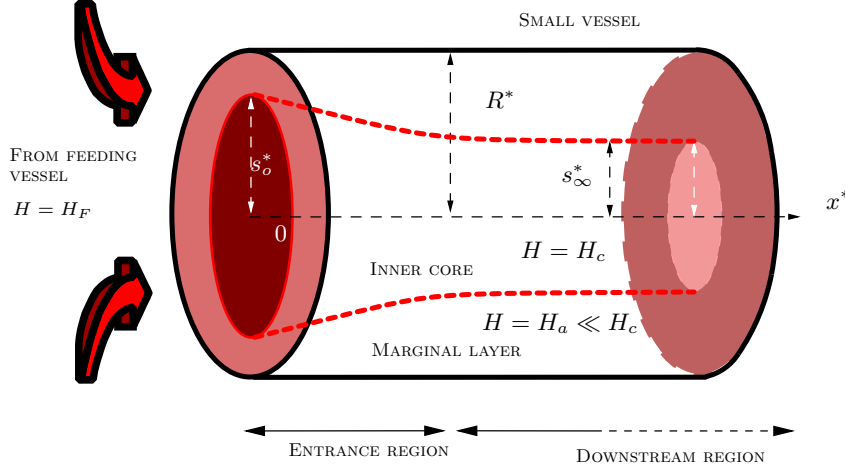


Figure 2: A schematic drawing of the geometrical model (the thickness of the outer layer $R^* - s^*$ is exaggerated for visualization purposes).

Moreover, as in [27], we assume that the hematocrit radial profile is step-wise and define H_c as the hematocrit in the inner core and H_a as the one in the outer layer, namely

$$H = \begin{cases} H_c, & 0 \leq r^* \leq s^*, \\ H_a, & s^* \leq r^* \leq R^*. \end{cases} \quad (3)$$

Unlike Haynes [21], where the marginal layer was assumed to be pure plasma, here H_a can be different from zero although significantly smaller than H_c . Moreover, both H_c , H_a are assumed constant, although this assumption is a simplification of the real biophysical situation, because H_c , H_a may slightly

179 depend on r^* . As a consequence, we set

$$\eta^* = \begin{cases} \eta_p^* \eta_a = \eta_p^* \eta(H_a), & s^* \leq r^* \leq R^*, \\ \eta_p^* \eta_c = \eta_p^* \eta(H_c), & 0 \leq r^* \leq s^*. \end{cases} \quad (4)$$

180 At the vessel entrance, the core radius s_0^* can be estimated in terms of
 181 the RBCs dimension, since, on average, RBCs cannot physically approach
 182 the vessel wall due to their finite size [36, 39–41]. So we estimate

$$s_0^* = R^* - a^* = R^* \left(1 - \frac{2a^*}{D^*} \right), \quad (5)$$

183 with a^* comparable with the average RBCs half-thickness. Concerning hu-
 184 man RBCs, their average thickness in a disk-like configuration is about 2 μm
 185 [42]. We use a^* as a fitting parameter but we limit its values in a physically
 186 acceptable range.

187 The fact that the outer layer is not completely devoid of RBCs has been
 188 suggested by several Authors. Here we just recall Kim et al. [24] who re-
 189 fer to the marginal layer as a *cell-poor layer*. Very appropriately, Ethier
 190 and Simmons ([39], pp. 145–146) suggest that the marginal exclusion effect
 191 should be more understood as a statistical concept. Thus a certain amount
 192 of RBCs may be present in the marginal layer and this value might have
 193 some variability, although we expect H_a to be significantly smaller than H_c .

194 2.2. Models for the blood viscosity as a function of the hematocrit

195 The literature reports numerous empirical formulas expressing the relative
 196 viscosity as a function of hematocrit (see, for example, [37, 43–49]). All these

197 formulas are characterized by the fact that η is an increasing function of H ,
198 and have the general expression

$$\eta(H) = \frac{1}{f(H)}, \quad (6)$$

199 where $f'(H) \leq 0$, and $f(0) = 1$. More specifically, in this paper we shall
200 consider those listed in Table 2.

Table 2: Most used empirical formulas to estimate the blood viscosity.

$f(H)$	Reference
$1 - 0.07H \exp \left[2.49H + \frac{1107}{T} \exp(-1.69H) \right]$ (with T in Kelvin)	Charm and Kurland [44]
$1 - H^{\frac{1}{3}}$	Hatschek [46]
$(1 - H)^{2.5}$	Cokelet [45]
$1 - H$	Bingham and White [50]
$\frac{0.75 - H}{0.75}$	Nubar [48]
$\left(1 - \frac{H}{0.67} \right)^{1.82}$ with $H < 0.67$	Krieger and Dougherty [51]

201 Figure 3 shows $\eta(H)$ according to these classical formulas. Clearly, a precise
202 description of the dependence of the apparent viscosity upon the hematocrit
203 and shear rate, would require to take into account the mechanical properties
204 of individual RBCs and the interactions between the vessel wall and cells
205 as well. An interesting approach in this direction can be found in [52, 53],
206 where by using a coarse-grained molecular dynamics the required dependence
207 is predicted, thus filling the gap between continuum models and cell-level
208 biomechanics. Nevertheless, such an approach does not lead to an explicit
209 expression for $\eta(H)$ in a large range of H .

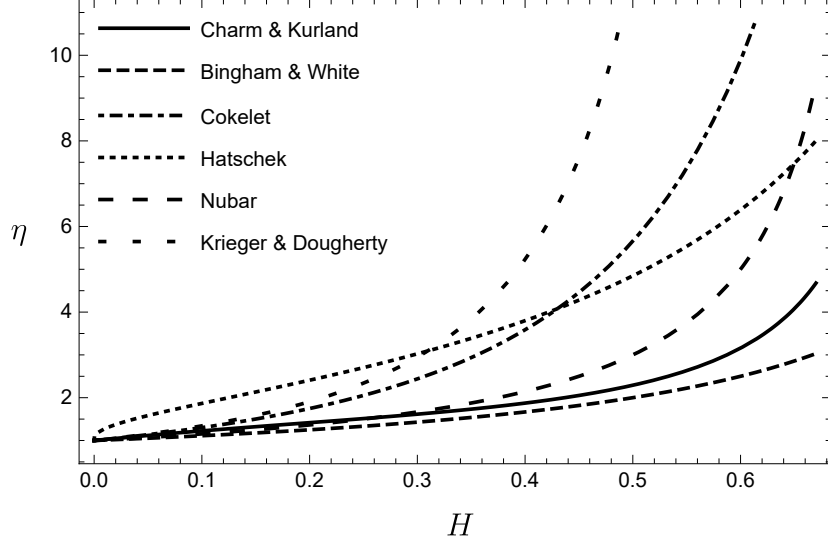


Figure 3: Classical formulas for the relative viscosity of blood as a function of H .

210 Now, by assuming model (1), we can determine the flow far downstream
 211 of entry, i.e. in the region where flow has long since acquired a core-annulus
 212 structure. We introduce the dimensionless variables

$$r = r^*/R^*, \quad s = s^*/R^*, \quad s_\infty = s_\infty^*/R^*, \quad (7)$$

$$s_0 = s_0^*/R^* = 1 - 2a^*/D^*, \quad v_\infty = v_\infty^*/V^*,$$

213 and, following [27, 54], we have

$$v_\infty(r) = \frac{2}{\frac{s_\infty^4}{\eta_c} + \frac{1-s_\infty^4}{\eta_a}} \times \begin{cases} \frac{s_\infty^2 - r^2}{\eta_c} + \frac{1-s_\infty^2}{\eta_a}, & 0 \leq r \leq s_\infty, \\ \frac{1-r^2}{\eta_a}, & s_\infty \leq r \leq 1, \end{cases} \quad (8)$$

214 where η_a and η_c have been defined in (4). Exploiting (8), equation (2) implies

$$s_0^2 = \frac{1}{s_\infty^4 \left(\frac{1}{\eta_c} - \frac{1}{\eta_a} \right) + \frac{1}{\eta_a}} \left[s_\infty^4 \left(\frac{1}{\eta_c} - \frac{2}{\eta_a} \right) + 2 \frac{s_\infty^2}{\eta_a} \right], \quad (9)$$

215 which is a fourth order algebraic equation in s_∞ , having only one physically
216 acceptable solution, i.e. $s_\infty \in (0, 1)$,

$$s_\infty = \frac{s_0}{\sqrt{1 + \sqrt{(1 - s_0^2) \left[1 - s_0^2 \left(1 - \frac{\eta_a}{\eta_c} \right) \right]}}}. \quad (10)$$

217 We notice that the velocity profile (8) implicitly assumes a blunt velocity at
218 the vessel entrance, which occurs only if blood comes from a large reservoir.

219 2.3. The relative hematocrit

220 The relative hematocrit is defined as the ratio between the hematocrit in
221 the tube, H_T , and the one in the feeding reservoir, H_F . The hematocrit of
222 the blood in the capillary tube is determined by stopping the flow and then
223 by pouring the trapped suspension into a specific device for the hematocrit
224 measurement [2]. Hence, H_T is a volume averaged hematocrit (see also [55]
225 at p. 152-153)

$$H_T = \frac{\int_0^{L^*} \int_0^{R^*} \int_0^{2\pi} H \, r^* dr^* d\vartheta dx^*}{\pi R^{*2} L^*}. \quad (11)$$

226 Thus, recalling (3), we have

$$\int_0^{L^*} \int_0^{R^*} \int_0^{2\pi} H \, r^* dr^* d\vartheta dx^* = \pi L^* R^{*2} [H_c s_\infty^2 + H_a (1 - s_\infty^2)], \quad (12)$$

227 and

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

228 Now we have to estimate H_c and H_a in terms of H_F . The complex
 229 interactions between the RBCs and the capillary walls that occur right at
 230 the tube entrance cause, on average, a radial shift of the erythrocytes which
 231 will increase the number of those in the central core, whose radius s_0^* is
 232 estimated by (5). We schematize this phenomenon, whose analysis goes far
 233 beyond the scope of this paper, as a discontinuity across $x = 0$ in the RBCs
 234 radial distribution, which is uniform for $x = 0^-$ (side of the entrance facing
 235 the reservoir) and stepwise for $x = 0^+$ (side of the entrance facing the tube).
 236 Thus imposing the RBCs mass conservation between $x = 0^+$ and $x = 0^-$ we
 237 have

$$\pi R^{*2} V^* H_F = \pi s_0^{*2} V^* H_c + \pi (R^{*2} - s_0^{*2}) V^* H_a, \quad (14)$$

238 where we recall that V^* is the inlet velocity which we assumed to be uniform
 239 over the entire entrance section. We remark that (14) entails the discharge
 240 hematocrit, usually referred to as H_D , to be equal to H_F (see, e. g., [10, 56,
 241 57]).

242 Concerning H_a , we set $H_a = \alpha H_F$, typically $\alpha \lesssim \mathcal{O}(10^{-1})$. Clearly, $\alpha = 0$
 243 corresponds to an outer layer free from RBCs. If we now exploit the fact that
 244 s_0 , given by (7), is significantly smaller than 1 for $D^* \geq 50 \mu\text{m}$, we obtain
 245 the following estimate for H_c

$$H_c = H_F \left[1 + (1 - \alpha) \frac{4a^*}{D^*} \right], \quad (15)$$

246 that entails $H_c \approx H_F$, for “large” diameters (as remarked, for instance, in
 247 [58]). Consequently, (13) rewrites as

$$\frac{H_T}{H_F} = \frac{s_\infty^2}{1 + (1 - \alpha) \frac{4a^*}{D^*}} + \alpha(1 - s_\infty^2), \quad (16)$$

248 which practically reduces to $H_T/H_F = s_\infty^2 + \alpha(1 - s_\infty^2)$, for $D^* \gg a^*$. Fur-
 249 thermore, it can easily be verified that $H_T/H_F \leq 1$ and that it tends to 1 for
 250 “large” values of D^* . Obviously the actual expression of s_∞ strongly depends
 251 on the particular $\eta(H)$ selected.

252 Recalling now (4), we have

$$\eta = \begin{cases} \eta_a = \eta(\alpha H_F), & s \leq r \leq 1, \\ \eta_c = \eta(H_c), & 0 \leq r \leq s, \end{cases} \quad (17)$$

253 and, exploiting (10), we deduce that

$$s_\infty^2 = \frac{s_0^2}{1 + \sqrt{(1 - s_0^2) \left[1 - s_0^2 \left(1 - \frac{\eta(\alpha H_F)}{\eta(H_c)} \right) \right]}}, \quad (18)$$

254 where $\eta(H_c)$ can be evaluated through any of the classical empirical formulas
 255 shown in Fig. 3. Notice that, because of (15) and (17), s_∞ is a function of
 256 H_F , α , and, through s_0 , of both the vessel diameter $D^* = 2R^*$, of the inlet
 257 marginal layer thickness a^* , and, furthermore, on the specific function f in
 258 Tab. 2 used to evaluate $\eta(H)$.

259 Finally, substituting (15) into (18) we obtain a functional relation of the

260 form

$$\frac{H_T}{H_F} = \mathfrak{F}(H_F, D^*, a^*, \alpha). \quad (19)$$

261 **3. Results**

262 Here we first present a graphical analysis of relation (19). Then, we
263 compare our results with the experimental data by Barbee and Cokelet in
264 [2]. Finally, a similar comparison is made with the well known empirical
265 formula proposed by Pries et al. in [3].

266 *3.1. Analysis of relation (19)*

267 In Fig. 4 we present the contours plots of $\mathfrak{F}(H_F, D^*, a^*, \alpha)$ as a function
268 of α and a^* for $H_F = 0.4$ and four choices of D^* . In this case we used only
269 the Cokelet formula. The use of any of the other empirical formulas does not
270 modify significantly these plots.

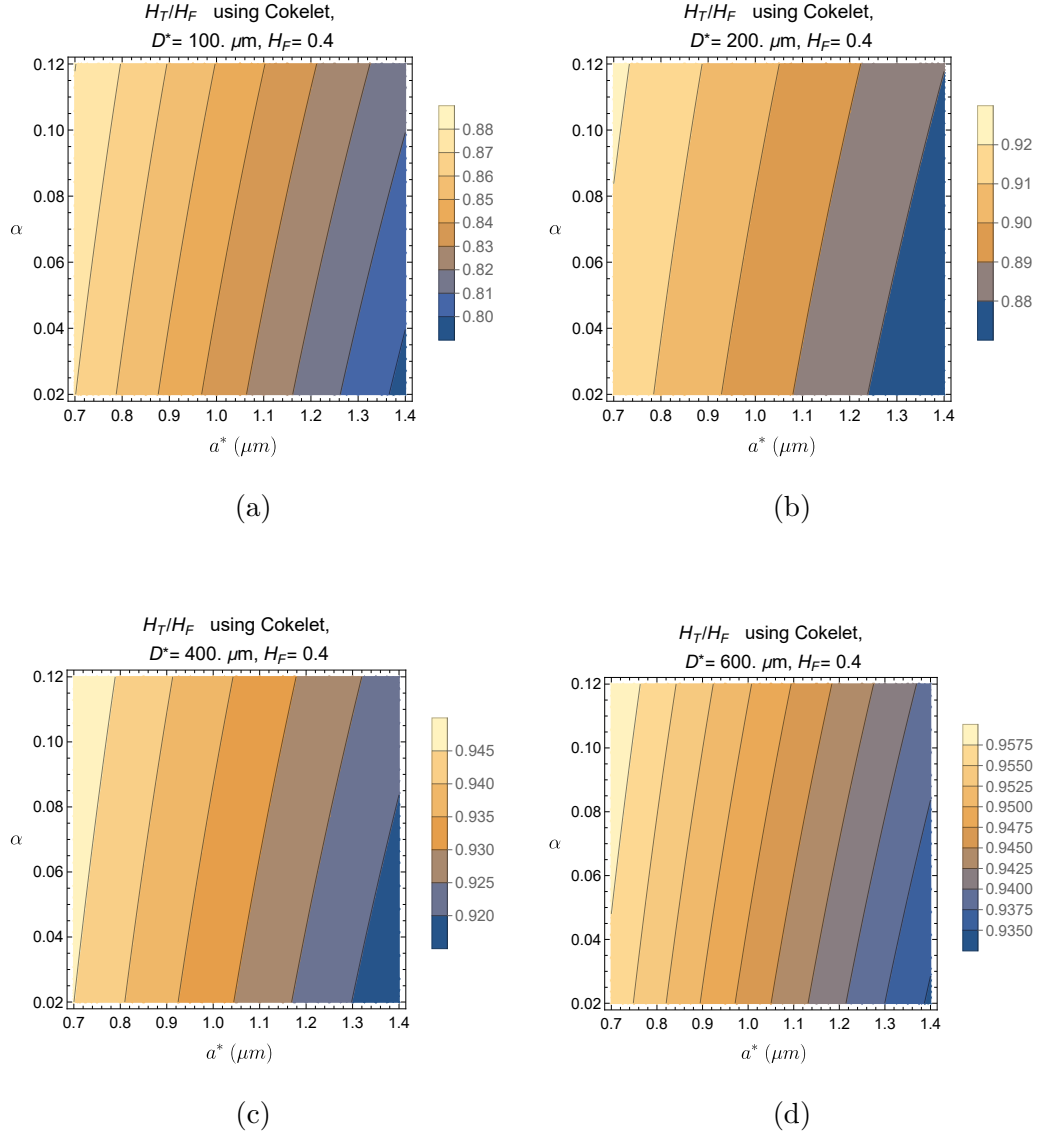


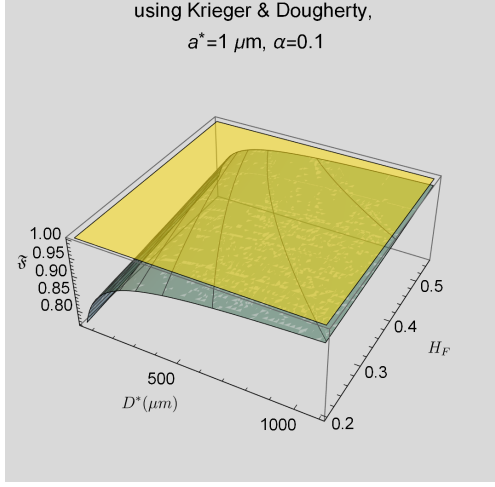
Figure 4: Variability of the relative hematocrit with α and a^* for four values of D^* .

271 All graphs in Fig. 4 indicate that α has a very modest effect on the value
 272 of H_T/H_F , while a change of $0.1 \mu\text{m}$ in a^* determines a change of 1 to 2 %

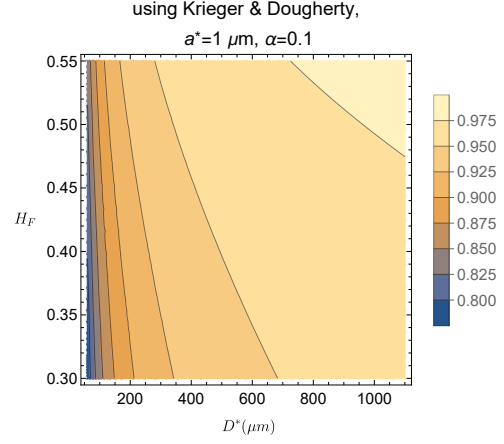
273 in the relative hematocrit. In particular panel 4d shows that $H_T/H_F \approx 0.96$
 274 for $a^* = 1 \mu\text{m}$ and $\alpha \approx 0.1$. This suggests that for $D^* \gtrsim 600 \mu\text{m}$ the F effect
 275 has become negligible.

276 We can also visualize graphically the mutual influence of H_F and D^* on
 277 $\mathfrak{F}$ keeping fixed $a^* = 1 \mu\text{m}$ and $\alpha = 0.1$. Though the actual values of $\mathfrak{F}$
 278 depend upon the choice of the empirical f , $\mathfrak{F}(H_F, D^*)$ invariably shows two
 279 peculiarities (which are the distinctive features of the F effect). First, for
 280 $D^* \gtrsim 600 \mu\text{m}$, $\mathfrak{F}$ approaches asymptotically 1. Second, $\mathfrak{F}$ shows a significant
 281 dependence on H_F when D^* is less than about $200 \mu\text{m}$. These characteris-
 282 tics are highlighted in Figs 5 and 6 where for $\eta(H)$ we have selected² the
 283 empirical formula by Krieger and Dougherty [51]. Figure 5 shows a 3D view
 284 of $\mathfrak{F}$ and its level lines, for $D^* \geq 100 \mu\text{m}$ and in the whole significant range
 285 of H_F . Figure 6 focuses on the interval $D^* \in (100, 200) \mu\text{m}$, with the aim of
 286 emphasizing the stronger dependence of $\mathfrak{F}$ on H_F for smaller diameters.

²For the sake of shortness, since the other formulas show quite similar behaviours.



(a)



(b)

Figure 5: Panel 5a provides a 3D representation of $\mathfrak{F}$ as a function of H_F and D^* solely, for $a^* = 1 \mu\text{m}$ and $\alpha = 0.1$, when $\eta(H)$ is given by the Krieger and Dougherty empirical formula. Panel 5b shows the corresponding level lines. Both panels emphasize clearly the asymptotic tendency to unity for the larger diameters.

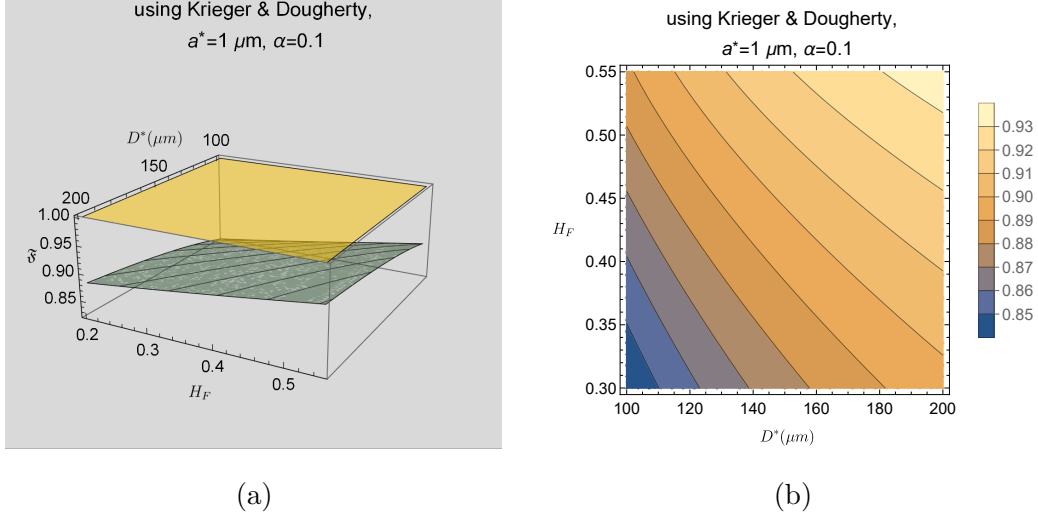


Figure 6: This figure is quite similar to Fig. 5. The sole difference consists in a closer view to the interval $D^* \in (100, 200) \mu\text{m}$. It can be noticed that in this interval a change in H_F produces a more significant change in $\mathfrak{F}$ than the corresponding change for larger diameters.

287 3.2. Comparison with Barbee and Cokelet's data in[2]

288 In the sequel we compare our model (18),(19) and the data from Barbee
 289 and Cokelet [2]. We also compare our model with the empirical formula
 290 proposed by Pries et al. in [3] to match all the available data (at that time)
 291 for the relative hematocrit versus the vessel diameter, namely

$$\frac{H_T}{H_F} = H_F + (1 - H_F) [1 + 1.7 e^{-0.35D} - 0.6 e^{-0.011D}] , \quad (20)$$

292 with D given in μm^3 .

³Formula (20) appears formally wrong since the exponent of an exponential must be dimensionless. Of course, this means only that the reference length is exactly $1 \mu\text{m}$.

293 Concerning the uncertainty of the experimental data, we remark that
 294 most of the literature data do not report explicitly any detail regarding the
 295 errors. A possible benchmark is provided by Goldsmith (see Fig 1A in [9])
 296 who claims that all data available at that moment (1989) are contained in
 297 a region between two curves. In the present context, these curves are sig-
 298 nificant only for diameters above $\approx 60 \mu\text{m}$. In this connection, it is worth
 299 noticing that the difference between the curves proposed by Goldsmith gives
 300 an estimate of the variability of the measures available in the literature,
 301 which ranges from almost 20% for diameters of $50 \mu\text{m}$ decreasing to 5% for
 302 diameters of $400 \mu\text{m}$. Therefore the data from [2] are likely to be affected
 303 by a significant error, particularly large for very small diameters.

304 To evaluate the relative viscosity as a function of H_F , required by formula
 305 (18), we used the empirical formulas shown in Fig. 3. Figure 7 shows that the
 306 mathematical model (18), (19) is able to describe the F effect for all diameters
 307 considered by Barbee in [2]. We disregarded the case $D^* = 29 \mu\text{m}$, this value
 308 being beyond the limit of applicability of the continuum hypothesis. The
 309 fitting parameters a^* , α and the formula among those listed in Table 2, are
 310 selected by using the NonlinearModelFit package in Mathematica[®], which is
 311 based on the optimization of the standard error, P-value, and t-Student test.
 312 In all cases the obtained values for a^* and α are largely reasonable because
 313 $2a^*$ is close to $2 \mu\text{m}$ and $\alpha \leq 0.2$, as expected. The only exception seems to be
 314 the largest diameter considered by Barbee, namely $D^* = 221 \mu\text{m}$, where a^*
 315 is a little too small and α a little too high. It must be pointed out, however,
 316 that if we assume a reasonable error (2 or 3 % is sufficient) in the Barbee's
 317 data, both a^* and α update to more satisfying values. In drawing Fig. 7,

318 we confined ourselves, for the sake of shortness, to the empirical formulas by
319 Hatsheck [46] and by Bingham and White [50]. The other formulas listed in
320 Sect. 2.2 would have provided very similar matching with comparable values
321 of a^* and α .

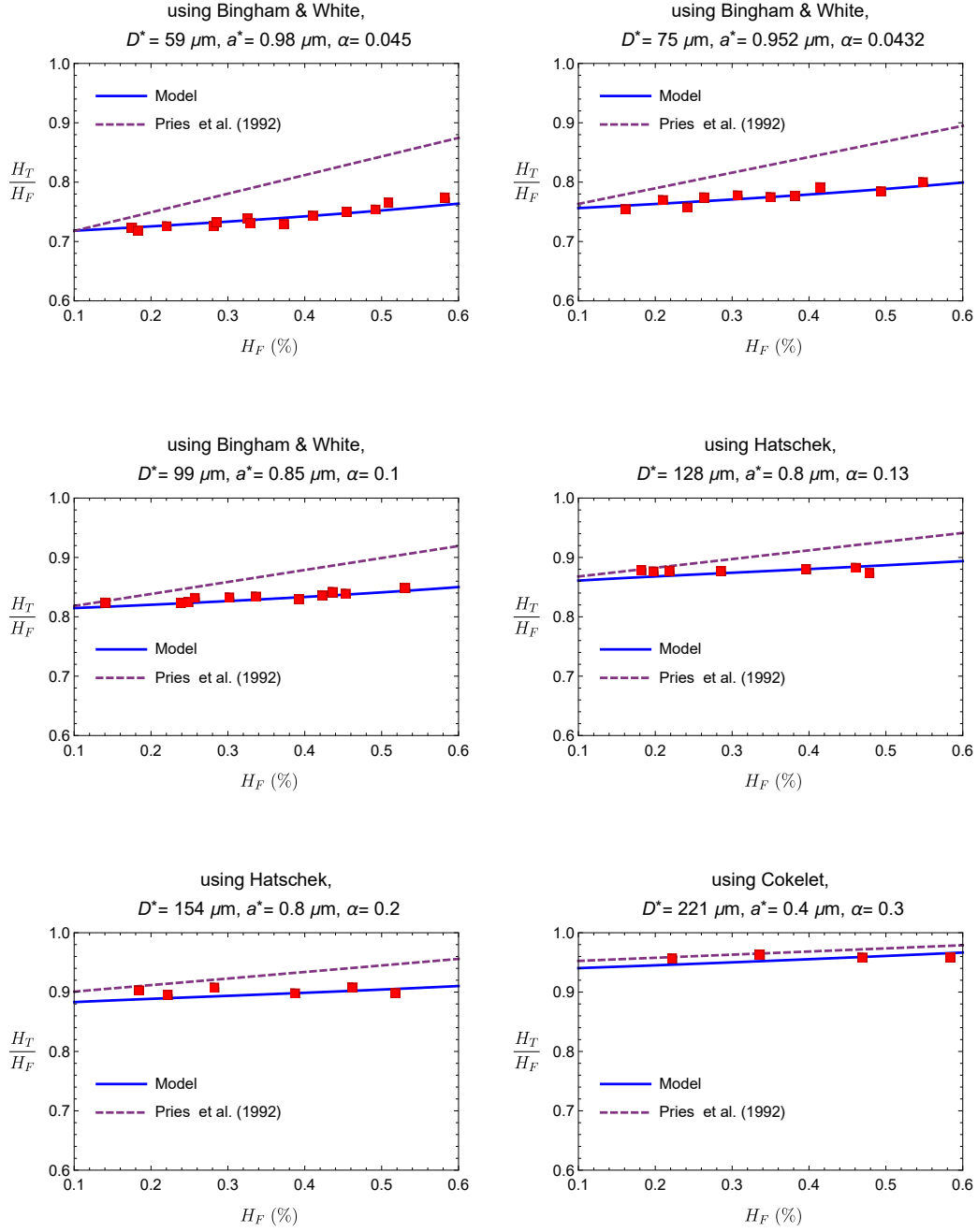


Figure 7: Comparison of the mathematical model (18), (19) with data extracted from Fig. 2 in [2]. The graph provided by the formula (20) proposed by Pries et al. is also shown.

322 *3.3. Comparison between the model and formula proposed by Pries et al. in*
323 *[3]*

324 It is interesting to compare the relative hematocrit as predicted by the
325 model versus that predicted by formula (20). Thus, we define

$$\mathcal{C} = \left| \left(\frac{H_T}{H_F} \right)_{\text{Model}} - \left(\frac{H_T}{H_F} \right)_{\text{Pries}} \right|. \quad (21)$$

326 Clearly, there are several options to present this comparison, since $\mathcal{C}$ depends,
327 besides on D^* , H_F , a^* and α also on the empirical $f(H)$. For simplicity, we
328 fixed $a^* = 1 \mu\text{m}$ and $\alpha = 0.1$. Figure 8 shows the results, by plotting $\mathcal{C}$ versus
329 H_F . It is interesting to notice that both in panel 8a and in panel 8b, the
330 Krieger and Dougherty formula gives the smallest values of $\mathcal{C}$ vs. H_F (about
331 0.03 for $D^* = 170 \mu\text{m}$, and between 0.04 and 0.05 for $D^* = 400 \mu\text{m}$). For
332 some of the other empirical formulas these values can even double (e.g., the
333 Charm and Kurland one).

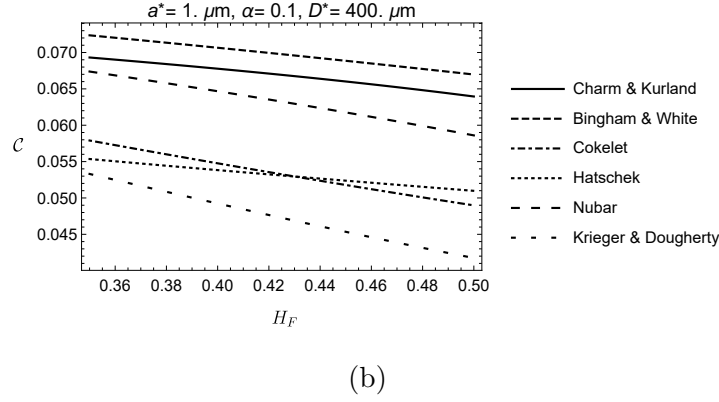
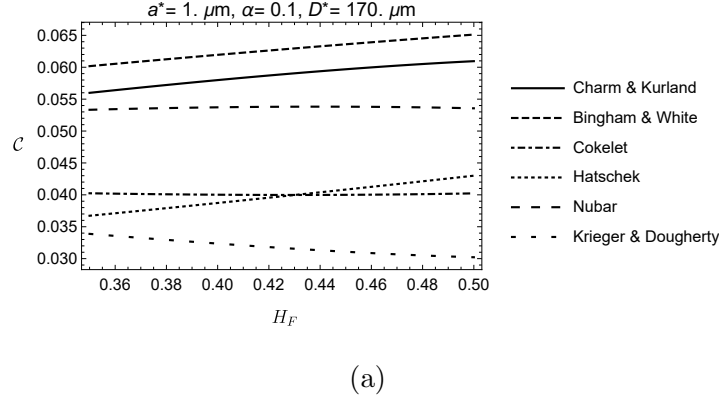


Figure 8: All graphs represent $\mathcal{C}$ given by (21) versus H_F . Panel 8a refers to $D^* = 170 \mu\text{m}$ while panel 8b refers to $D^* = 400 \mu\text{m}$. In both cases the Krieger and Dougherty formula provides the minimum difference in the range considered for H_F .

334 Figure 9 shows the results, by plotting $\mathcal{C}$ versus D^* . Also in this case
335 we notice that both in panel 9a and in panel 9b, the Krieger and Dougherty
336 formula gives the smallest values of $\mathcal{C}$ vs. H_F (between 0.025 and 0.052 for
337 $H_F = 0.35$, and between 0.025 and 0.041 for $H_F = 0.5$). Again, for some of

the other empirical formulas these values can even double (e.g., the Bingham
and White one).

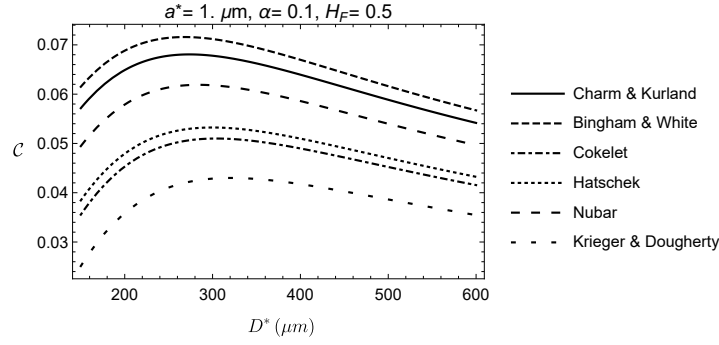
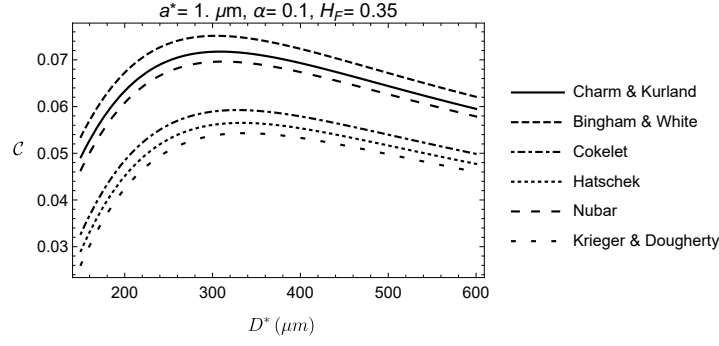


Figure 9: All graphs represent $\mathcal{C}$ given by (21) versus D^* . Panel 9a refers to $H_F = 0.35$ while panel 9b refers to $H_F = 0.5$. In both cases the Krieger and Dougherty formula provides the minimum difference in the range considered for D^* .

340 4. Conclusions

341 The mathematical model presented in this study allows for predictions
 342 of the relative hematocrit in tubes whose diameter is larger than about
 343 60 μm . In particular, we have obtained a system i.e. formulas (15), (18),
 344 (19), which gives the relative hematocrit in terms of H_F as well as of the
 345 capillary diameter D^* . The model, being based on the laws of fluid dynamics,
 346 provides a rigorous theoretical explanation of the F effect, at least in “large”
 347 capillaries. The only “empirical” aspect of the theory is the formula that gives
 348 the relative viscosity in terms of H , i.e. $\eta(H)$. In particular, since the current
 349 literature reports numerous empirical formulas for $\eta(H)$, we have considered
 350 six of them in order to keep our approach as general as possible. However,
 351 though the model depends significantly on the specific $\eta(H)$ selected (and it
 352 could not be otherwise), in all cases it is able to replicate both qualitatively
 353 and quantitatively the two fundamental characteristics of the F effect. First,
 354 H_T/H_F approaches 1 for D^* larger than about 600 μm . Second, the model
 355 reproduces quite well the dependence of the relative hematocrit on H_F for
 356 diameters less than about 200 μm , while it is not very sensitive to the feeding
 357 reservoir hematocrit H_F , when $D^* > 200 \mu\text{m}$.

358 The model predictions have been validated against the classical experi-
 359 mental data by Barbee and Cokelet [2], obtaining, in general, a satisfactory
 360 agreement.

361 We also compared the model with the benchmark given by the empirical
 362 law (20). The results, though depending on the specific $\eta(H)$ selected, are
 363 however comforting. For instance, if we take the Krieger and Dougherty
 364 formula for $\eta(H)$, the model does not deviate from formula (20) for more

365 than 0.05.

366 We must point out that our model does not provide a definitive explana-
367 tion of the F effect, essentially for two reasons. First the model contains two
368 parameters that need to be estimated by fitting procedures, while in a com-
369 plete theory they should be determined through blood physical properties
370 only (say, shear rate, RBCs interactions and so on). Secondly, our model,
371 being based on the continuum hypothesis, can be acceptable only for suffi-
372 ciently large microvessels, while the empirical formula by Pries et al. covers
373 a larger interval of capillary diameters, starting from 5 μm . Therefore, al-
374 though its accuracy for larger vessels might be less than that of the present
375 model, its range of validity is a strength for modeling studies of networks
376 containing a large range of vessel sizes.

377 As a final remark, we share the general opinion that, although many
378 steps forward have been made in the past one hundred years, other questions
379 concerning microcirculation effects still need further clarifying efforts. The
380 major difficulty to face to get significant advances has always been the very
381 limited possibility to perform experiments *in vivo*, so that the great majority
382 of available data are obtained by operating *in vitro*. As many researchers
383 have pointed out (see, e.g., [9, 10, 59], data coming out from *in vitro* tests
384 cannot be extrapolated so easily to the *in vivo* situation. Reasons are several
385 and complex, and regard not only the geometry (a single capillary glass tube
386 is very far from a real microvascular network) but also the blood behavior
387 at the capillary wall (the resistance at the glass surface is lower than the
388 endothelium resistance).

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392 **Conflict of interest**

393 The Authors declare that they have no known competing financial in-
394 terests nor personal relationships that could have appeared to influence the
395 work reported in this paper.

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