Comparison of various approaches to calculating the optimal hematocrit in vertebrates

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Stark H, Schuster S. Comparison of various approaches to calculating the optimal hematocrit in vertebrates. J Appl Physiol 113: 355–367, 2012. First published May 17, 2012; doi:10.1152/japplphysiol.00369.2012.—An interesting problem in hemorheology is to calculate the volume fraction of erythrocytes (hematocrit) that is optimal for transporting a maximum amount of oxygen. If the hematocrit is too low, too few erythrocytes are present to transport oxygen. If it is too high, the blood is very viscous and cannot flow quickly, so that oxygen supply to the tissues is again reduced. These considerations are very important, since oxygen transport is an important factor for physical performance. Here, we derive theoretical optimal values of hematocrit in vertebrates and collect, from the literature, experimentally observed values for 57 animal species. It is an interesting question whether optimal hematocrit theory allows one to calculate hematocrit values that are in agreement with the observed values in various vertebrate species. For this, we first briefly review previous approaches in that theory. Then we check which empirical or theoretically derived formulas describing the dependence of viscosity on concentration in a suspension lead to the best agreement between the theoretical and observed values. We consider both spatially homogeneous and heterogeneous distributions of erythrocytes in the blood and also possible extensions, like the influence of defective erythrocytes and cases where some substances are transported in the plasma. By discussing the results, we critically assess the power and limitations of optimal hematocrit theory. One of our goals is to provide a systematic overview of different approaches in optimal hematocrit theory.

The oxygen flow in animals can change by a change in the erythrocyte-to-blood volume ratio. This ratio is called hematocrit (cf. Ref. 26). In healthy humans, it amounts to ~40%. Note that there is a difference in most hematological parameters of men vs. women; for example, the hematocrit amounts to 45.8 ± 2.7 vs. 40.0 ± 2.4% (27). The sex-related variation in parameters of the blood is explained by the difference in age distribution of red blood cells due to menstruation and the subsequent difference in mechanical properties of blood of premenopausal women and men (27). The hematocrit values differ considerably across the animal kingdom (4, 5, 8, 18–23, 29, 32, 45–47, 52, 64, 66, 68, 71, 82–84, 101, 102, 104–106, 110, 111). The values of several species are given in Table 1.

The question arises as to whether the hematocrit values given above are optimal. If the hematocrit is too low, too few erythrocytes are present to transport oxygen. If it is too high, the blood is very viscous and cannot flow quickly, so that oxygen supply to the tissues is again reduced. Within hemorheology (hydrodynamics of the blood), a theoretical framework called “optimal hematocrit theory” has been established (6, 15, 41, 70, 104, 110). That an optimum has been found in evolution is supported by the observation that the hematocrit values are quite robust against temperature changes (1, 44) and are nearly the same in active sportsmen and control persons (88). On the other hand, there is some dependency on water supply and on altitude (see below). A general problem in optimality considerations in biology is that usually several optimality principles are relevant simultaneously, for which a trade-off must be found. Here, we focus on the criterion of maximum oxygen transport velocity, leaving other criteria for future studies.

These considerations are very important, since oxygen transport is an important factor for physical performance. They are especially relevant in medicine (e.g., blood transfusion, dialysis, transplants, stent and shunt implants), sports, and mountaineering. For example, the nonalcoholic fatty liver disease correlates with higher hematocrit levels (58). Regrettably, some sportsmen use blood doping by infusing additional erythrocytes (3, 7, 35, 49, 67, 90).

It is an interesting question whether optimal hematocrit theory allows one to calculate hematocrit values that are in agreement with the observed values in various vertebrate species. In this paper, we first briefly review previous approaches in that theory. Then we check which empirical or theoretically derived formulas describing the dependence of viscosity on concentration in a suspension lead to the best agreement between the theoretical and observed values. We consider both spatially homogeneous and heterogeneous distributions of erythrocytes in the blood. By discussing the results, we critically assess the power and limitations of optimal hematocrit theory.

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Table 1. Literature values of the hematocrit in 57 vertebrate species

<table>
<thead>
<tr>
<th>Animal</th>
<th>Hematocrit, %</th>
<th>Sample Size, no.</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mammalia (mammals)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weddell seal</td>
<td>63.2</td>
<td>9</td>
<td>Guard and Murray (32)</td>
</tr>
<tr>
<td>Kangaroo</td>
<td>53.0</td>
<td>1</td>
<td>Bartels et al. (5)</td>
</tr>
<tr>
<td>Beluga whale</td>
<td>52.6</td>
<td>2</td>
<td>Shaffer et al. (93)</td>
</tr>
<tr>
<td>Mixed dog breeds</td>
<td>52.1</td>
<td>5</td>
<td>Ohta et al. (68)</td>
</tr>
<tr>
<td>Mongolian gerbil</td>
<td>49.6</td>
<td>5</td>
<td>Ohta et al. (68)</td>
</tr>
<tr>
<td>Leopard seal</td>
<td>49.2</td>
<td>5</td>
<td>Guard and Murray (32)</td>
</tr>
<tr>
<td>Mole</td>
<td>47.2</td>
<td>5</td>
<td>Bartels et al. (5a)</td>
</tr>
<tr>
<td>Hedgehog</td>
<td>47.0</td>
<td>5</td>
<td>Bartels et al. (5a)</td>
</tr>
<tr>
<td>Tasmanian devil</td>
<td>47.0</td>
<td>1</td>
<td>Bartels et al. (5)</td>
</tr>
<tr>
<td>Crab eater seal</td>
<td>46.5</td>
<td>2</td>
<td>Guard and Murray (32)</td>
</tr>
<tr>
<td>Mixed rat breeds</td>
<td>45.5</td>
<td>6</td>
<td>Ohta et al. (68)</td>
</tr>
<tr>
<td>Human</td>
<td>44.4</td>
<td>12</td>
<td>Nemeth et al. (66)</td>
</tr>
<tr>
<td>Women</td>
<td>40.0</td>
<td>40</td>
<td>Kameneva et al. (50)</td>
</tr>
<tr>
<td>Men</td>
<td>45.3</td>
<td>36</td>
<td>Kameneva et al. (50)</td>
</tr>
<tr>
<td>Goat</td>
<td>43.0</td>
<td>3</td>
<td>Yamaguchi et al. (111)</td>
</tr>
<tr>
<td>Mixed rabbit breeds</td>
<td>42.9</td>
<td>5</td>
<td>Ohta et al. (68)</td>
</tr>
<tr>
<td>Lemur</td>
<td>42.8</td>
<td>16</td>
<td>Dhindasa et al. (21)</td>
</tr>
<tr>
<td>Pong horn antelope</td>
<td>42.7</td>
<td>4</td>
<td>Dhindasa et al. (21)</td>
</tr>
<tr>
<td>Lion</td>
<td>42.5</td>
<td>2</td>
<td>Parer et al. (71)</td>
</tr>
<tr>
<td>Elephant</td>
<td>42.1</td>
<td>7</td>
<td>Dhindasa et al. (21)</td>
</tr>
<tr>
<td>Mixed rat breeds</td>
<td>38.7</td>
<td>5</td>
<td>Riegela et al. (82)</td>
</tr>
<tr>
<td>Sheep</td>
<td>35.9</td>
<td>15</td>
<td>Usami et al. (102)</td>
</tr>
<tr>
<td>Cat</td>
<td>42.0</td>
<td>15</td>
<td>Ohta et al. (68)</td>
</tr>
<tr>
<td>Gorilla</td>
<td>42.0</td>
<td>2</td>
<td>Riegela et al. (83)</td>
</tr>
<tr>
<td>Pig</td>
<td>41.0</td>
<td>22</td>
<td>Weng et al. (106)</td>
</tr>
<tr>
<td>Orangutan</td>
<td>40.9</td>
<td>1</td>
<td>Riegela et al. (83)</td>
</tr>
<tr>
<td>Killer whale</td>
<td>40.1</td>
<td>3</td>
<td>Dhindasa et al. (20)</td>
</tr>
<tr>
<td>Chimpanzee</td>
<td>39.8</td>
<td>1</td>
<td>Riegela et al. (83)</td>
</tr>
<tr>
<td>Galago</td>
<td>39.4</td>
<td>8</td>
<td>Dhindasa et al. (19)</td>
</tr>
<tr>
<td>Sheep</td>
<td>37.0</td>
<td>9</td>
<td>Usami et al. (102)</td>
</tr>
<tr>
<td>Alpaca</td>
<td>37.0</td>
<td>10</td>
<td>Weng et al. (106)</td>
</tr>
<tr>
<td>Shrew</td>
<td>35.5</td>
<td>11</td>
<td>Bartels et al. (5a)</td>
</tr>
<tr>
<td>Horse</td>
<td>35.0</td>
<td>12</td>
<td>Weng et al. (106)</td>
</tr>
<tr>
<td>Cow</td>
<td>34.0</td>
<td>10</td>
<td>Weng et al. (106)</td>
</tr>
<tr>
<td>Vicuna</td>
<td>34.0</td>
<td>1</td>
<td>Yamaguchi et al. (111)</td>
</tr>
<tr>
<td>Camel</td>
<td>34.0</td>
<td>2</td>
<td>Yamaguchi et al. (111)</td>
</tr>
<tr>
<td>Llama</td>
<td>30.9</td>
<td>3</td>
<td>Yamaguchi et al. (111)</td>
</tr>
<tr>
<td>Tiger</td>
<td>29.8</td>
<td>2</td>
<td>Parer et al. (71)</td>
</tr>
<tr>
<td>Armadillo</td>
<td>29</td>
<td>4</td>
<td>Dhindasa et al. (18)</td>
</tr>
</tbody>
</table>

| Aves (birds)            |               |                  |               |
| Blue-eyed shag          | 55.9          | 8                | Guard and Murray (32) |
| Gentoo penguin          | 52.6          | 13               | Guard and Murray (32) |
| Pigeon                  | 52.5          | 8                | Munday and Blane (64) |
| Adelie penguin          | 47.8          | 11               | Guard and Murray (32) |
| Turkey                  | 47.0          | not given        | Isaacks et al. (46) |
| Chinstrap penguin       | 47.0          | 2                | Guard and Murray (32) |
| South polar skua        | 45.5          | 11               | Guard and Murray (32) |
| Giant petrel            | 44.9          | 12               | Guard and Murray (32) |
| Ostrich                 | 42.6          | not given        | Isaacks and Harkness (47) |

Table 1. Literature values of the hematocrit in 57 vertebrate species—Continued

<table>
<thead>
<tr>
<th>Animal</th>
<th>Hematocrit, %</th>
<th>Sample Size, no.</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mixed chicken breeds</td>
<td>40.5</td>
<td>not given</td>
<td>Isaacks et al. (46)</td>
</tr>
<tr>
<td>Mallard duck</td>
<td>38.4</td>
<td>31</td>
<td>Guard and Murray (32)</td>
</tr>
<tr>
<td>Guinea fowl</td>
<td>33.7</td>
<td>4</td>
<td>Isaacks et al. (46)</td>
</tr>
<tr>
<td>Quail</td>
<td>33.5</td>
<td>not given</td>
<td>Isaacks and Harkness (47)</td>
</tr>
<tr>
<td>Pea fowl</td>
<td>29.0</td>
<td>not given</td>
<td>Isaacks and Harkness (47)</td>
</tr>
<tr>
<td>Pheasant</td>
<td>24.0</td>
<td>not given</td>
<td>Isaacks and Harkness (47)</td>
</tr>
</tbody>
</table>

**Crocodilia (crocodylidae)**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Hematocrit, %</th>
<th>Sample Size, no.</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estuarine crocodile</td>
<td>19.2</td>
<td>11</td>
<td>Wells et al. (105)</td>
</tr>
</tbody>
</table>

**Testudina (turtles) and Serpentes (snakes)**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Hematocrit, %</th>
<th>Sample Size, no.</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>American bullfrog</td>
<td>27.2</td>
<td>6</td>
<td>Withers et al. (110)</td>
</tr>
<tr>
<td>Grass snake</td>
<td>37.0</td>
<td>17</td>
<td>Weathers (104)</td>
</tr>
<tr>
<td>Loggerhead sea turtle</td>
<td>27.2</td>
<td>2</td>
<td>Isacks and Harkness (47)</td>
</tr>
</tbody>
</table>

**Osteichthyes (bony fishes)**

<table>
<thead>
<tr>
<th>Animal</th>
<th>Hematocrit, %</th>
<th>Sample Size, no.</th>
<th>Reference No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yellowfin tuna</td>
<td>35.0</td>
<td>24</td>
<td>Gingerich et al. (29)</td>
</tr>
<tr>
<td>Rainbow trout</td>
<td>23.0</td>
<td>7</td>
<td>Tetens and Christensen (101)</td>
</tr>
</tbody>
</table>

**Glossary**

- $a$: Proportionality factor for substances transported in the plasma
- $b$: Proportionality factor for substances transported in erythrocytes
- $D$: Tube diameter
- $\eta$: Viscosity of fluid (viscosity of suspension)
- $\eta_0$: Viscosity of fluid solvent (so-called embedding fluid)
- $\eta_{rel}(D, \varphi)$: Viscosity relationship between $D$ and $\varphi$
- $J$: Total flow across the blood vessel (Hagen-Poiseuille law)
- $J_{oxygen}$: Total oxygen flow across the blood vessel
- $l$: Tube length
- $\Delta P$: Pressure difference
- $\varphi$: Volume fraction of particles in the suspension
- $\varphi_m$: Maximum volume fraction (maximal packing density)
- $\varphi_{opt}$: Optimal volume fraction of particles in the suspension
- $\varphi_{int}$: Volume fraction of intact particles in the suspension
- $\varphi_{def}$: Volume fraction of defective particles in the suspension
- $\nu$: Fluid velocity

**MATERIALS AND METHODS**

First, we briefly review some fundamentals from rheology needed for the subsequent calculations.
The Hagen-Poiseuille Law

A central parameter characterizing the flow behavior of a liquid is its viscosity, \( \eta \). Consider a blood vessel (e.g., an artery) with circular cross section. Let \( R \) and \( l \) denote the radius and length of the tubular vessel, respectively. The blood flow is driven by a pressure difference, \( \Delta P \). A basic assumption in hydrodynamics, which is well justified by experiment, is that the velocity of the liquid very near to a rigid surface is zero (or is the same as that of the surface if that is moving). This is because a thin layer of molecules of the fluid are attached to the surface. Moreover, for symmetry reasons, we can assume that the velocity of a liquid being in a stationary flow in a circular tube forms a profile with rotational symmetry. Thus it depends only on the radial coordinate \( r \) (with \( 0 < r < R \)). This is justified as long as the flow is nonturbulent, i.e., for low velocities. To calculate this velocity profile, we can use the equilibrium of forces between driving pressure and resistance due to the viscous properties of the liquid. It is a well-known result from fluid mechanics that the velocity obeys Eq. 1 (33, 75–77, 98).

\[
v = \frac{R^2 - r^2}{4\eta l} \Delta P
\]

(1)

This is a parabolic velocity profile, in which the highest velocity is reached in the middle of the blood vessel (Fig. 1, left). It is of interest to know the total flow across the blood vessel. To calculate this, we need to integrate over the cross-section, \( A \), of the tube:

\[
J = \int_0^R \frac{R^2 - r^2}{4\eta l} \Delta P dA = \Delta P \int_0^R \frac{R^2 - r^2}{4\eta l} 2\pi r dr \text{ with } J = \frac{V}{t}
\]

(2)

\[
J = \frac{\pi \Delta P}{2\eta l} \left( \frac{R^4 - 4r^2}{2} - \frac{r^4}{4} \right) = \frac{\pi \Delta P R^4}{8\eta l}
\]

(3)

Equation 4 is called the Hagen-Poiseuille law (cf. Ref. 26). In a stationary, nonturbulent flow across a cylindrical tube, the total flux of liquid is proportional to the fourth power of the tube radius.

Dependence of Viscosity on Hematocrit

Dilute suspensions. The question is now how the viscosity depends on the hematocrit, \( \varphi \). Blood can be considered as a suspension (rather than a solution) because erythrocytes are much larger than molecules. The solid phase (erythrocytes) is dispersed throughout the fluid phase (plasma) through mechanical agitation. Note that other blood cells, such as leucocytes and thrombocytes, contribute a negligible volume (<1%) compared with erythrocytes (27). For suspensions of spherical particles with low concentration (but not considering blood at that time), Albert Einstein (24, 25) derived the formula:

\[
\eta = \eta_0(1 + 2.5\varphi)
\]

(5)

(Fig. 2A) with \( \eta = \) viscosity of suspension, \( \eta_0 = \) viscosity of fluid solvent (so-called embedding fluid, e.g., water), and \( \varphi = \) volume fraction of particles in the suspension (i.e., hematocrit in the case of blood).

Suspensions with higher concentrations. Einstein’s formula has been extended in various ways to cope with higher concentrations. For example, the formula of Saitô (86) reads

\[
\eta = \eta_0\left[1 + \frac{2.5\varphi}{(1 - \varphi)}\right]
\]

(6)

while the formula of Gillespie (28) reads

\[
\eta = \eta_0\left[1 + \frac{\varphi}{2(1 - \varphi)}\right]^2
\]

(7)

and the formulas of Quemada (80) and Krieger and Dougherty (55) read

\[
\eta = \eta_0\left[1 - \frac{\varphi}{\varphi_m}\right]^{2.5}\eta_m
\]

(8)

\[
\eta = \eta_0\left[1 - \frac{\varphi}{\varphi_m}\right]^{2.5}\eta_m
\]

(9)

respectively, where \( \varphi_m \) is the maximum volume fraction possible (Fig. 2A). For example, spheres can be packed with a maximum volume fraction of \( \pi/18 = 74\% \) (43). Formulas 6, 7, and 9 and, with some restriction, formula 8, have the properties that they converge to Einstein’s formula in the case of low \( \varphi \) (as shown below) and obviously diverge in the limit \( \varphi \to 1 \) and \( \varphi \to \varphi_m \), respectively. In this limit, the suspension becomes practically solid and cannot flow any longer, so that the viscosity becomes infinite. A maximum volume fraction <1 can easily be included in Saitô’s and Gillespie’s formulas, as well by replacing \( \varphi \) by \( \varphi/\varphi_m \).

The case of low \( \varphi \) can be treated by a Taylor expansion up to the linear term. In the case of the Saitô equation, this reads:

\[
\eta(\varphi) = \eta_0 + \frac{\partial \eta}{\partial \varphi}_{\varphi=0} \varphi = \eta_0 \left[1 + \frac{2.5}{(1 - 0)^2}\varphi\right] = \eta_0 (1 + 2.5\varphi)
\]

(10)

This shows that the formula is consistent with Einstein’s equation for low \( \varphi \).

The proof for the case of the Gillespie equation is as follows:

\[
\eta(\varphi) = \eta_0 + \frac{\partial \eta}{\partial \varphi}_{\varphi=0} \varphi = \eta_0 \left[1 + \frac{-(5 + 0)}{2(1 - 0)^2}\varphi\right] = \eta_0 (1 + 2.5\varphi)
\]

(11)

For the case of Quemada’s formula, we can write a Taylor series, as \( \varphi/\varphi_m \) is then a small parameter,

\[
\eta(\varphi) = \eta_0 + \frac{\partial \eta}{\partial \varphi}_{\varphi=0} \varphi = \eta_0 \left[1 + \frac{2}{(1 - 0)}\varphi\right] = \eta_0 (1 + 2.5\varphi)
\]

(12)

Thus Quemada’s formula is consistent with Einstein’s formula only for a maximum volume fraction of 80%.

For the Krieger-Dougherty formula, we obtain the more general result:

\[
\eta(\varphi) = \eta_0 + \frac{\partial \eta}{\partial \varphi}_{\varphi=0} \varphi = \eta_0 \left[1 + \frac{2.5\varphi_m}{(1 - 0)}\varphi\right] = \eta_0 (1 + 2.5\varphi)
\]

(13)

Fig. 1. Left: parabolic velocity profile in the case of homogeneous concentration. Middle: oblate velocity profile in the case where particles are concentrated in the middle (Fähraeus-Lindqvist effect). Right: extreme situation with a blood thread moving in the middle of the vessel.
(Fig. 2B) as has first been proposed by Arrhenius (2). However, they have the disadvantage not to diverge in the limit \( \varphi \to \varphi_m \). To be consistent with Einstein’s formula in the case of low \( \varphi \), the parameters must be chosen as follows: \( p = 2.5, q = 0 \), as can again be shown by a Taylor series.

\[
\eta(\varphi) = \eta_0 + \frac{\partial \eta}{\partial \varphi} \bigg|_{\varphi=0} \varphi = \eta_0 (1 + e^{0.25+0.6} \varphi) = \eta_0 (1 + 2.5 \varphi)
\]

Nearby exponential curves with \( p \) values of \( \sim 2.5 \) have indeed been measured in experiments (15, 110).

The question arises what the theoretical basis for the exponential function is. One possible explanation is that it is a simple function showing the appropriate monotonicity properties. Another explanation would be that it is the solution of a differential equation \( \partial \eta / \partial \varphi = \text{const.} \varphi \), which means that the increase in viscosity upon an increase in the volume fraction is proportional to the volume fraction.

To comply with a divergence at high volume fractions, Mooney (62) proposed the following formula:

\[
\eta = \eta_0 e^{2.5 \varphi / (1-\varphi \varphi_m)}
\]

(Fig. 2B). At low \( \varphi \), we can write:

\[
\eta(\varphi) = \eta_0 + \frac{\partial \eta}{\partial \varphi} \bigg|_{\varphi=0} \varphi = \eta_0 \left[ 1 + \frac{2.5}{1-0/\varphi_m} \varphi + \frac{2.5+0}{(1-0/\varphi_m) \varphi_m} \varphi \right] = \eta_0 (1 + 2.5 \varphi)
\]

Formula based on experimental data. Pries et al. (79) have compiled their own and literature data to a description of relative apparent blood viscosity as a function of tube diameter and hematocrit. The combined data base comprises measurements at high shear rates in tubes with diameters ranging from 3.3 to 1.978 \( \mu \)m at hematocrit values of up to 90%. It includes also the Fåhraeus-Lindqvist effect (see below), which implies a significant decrease of apparent blood viscosity in tubes with diameters ranging between \( \sim 500 \) and 50 \( \mu \)m. This is important because human blood vessels exhibit diameter variations over four orders of magnitude, ranging from \( \sim 3 \) cm in the large systemic vessels down to 3 \( \mu \)m in skeletal muscle capillaries (27). The hematocrit-viscosity relationship (\( \varphi \) and \( \eta_{\text{rel}} \)) is described by the steepness \( B(D) \) and curvature \( C(D) \) in relation to the tube diameter \( D \):

\[
\eta_{\text{rel}} = 1 + B(D) \cdot \left[ (1 - \varphi)^{C(D)} - 1 \right]
\]

(Fig. 2C). The parameter \( C \) describes the curvature of the relationship between relative apparent blood viscosity and hematocrit. Its dependence on \( D \) had been fitted by the empirical equation:

\[
C(D) = \frac{1}{1 + \frac{D^{12}}{10^{14}}} \left[ -1 + \frac{1}{1 + \frac{D^{12}}{10^{14}}} \right] (0.8 + e^{-0.075 \cdot D})
\]

After solving the relative viscosity (Eq. 18) (with a measured hematocrit value of 45%) for \( B(D) \)

\[
\eta_{\text{rel}0.45}(D) = 1 + B(D) \cdot \left[ (1 - 0.45)^{C(D)} - 1 \right]
\]

one obtains:

\[
B(D) = \frac{\eta_{\text{rel}0.45}(D) - 1}{(1 - 0.45)^{C(D)} - 1}
\]

With substitution of \( \eta_{\text{rel}0.45}(D) \) (from a fit of experimental data with a hematocrit of 45%)

\[
\eta_{\text{rel}0.45}(D) = 3.2 - 2.44e^{-0.06D^{0.645}} + 220e^{-1.3D}
\]

into Eq. 21 results in:

\[
B(D) = \frac{2.2 - 2.44e^{-0.06D^{0.645}} + 220e^{-1.3D}}{1 + 0.55W(e^{-0.8e^{-0.075D}})} \quad \text{with} \quad W = \frac{1}{1 + \frac{D^{12}}{10^{14}}}
\]

Substitution of Eqs. 19 and 23 into Eq. 18 results in:
The Case of Inhomogeneous Concentration

Above, we have assumed that the concentration of particles is the same everywhere in one given artery. However, when a suspension is flowing, the concentration is becoming inhomogeneous. The mechanical explanation is that the velocity of the fluid is different at different distances from the artery wall, so that each particle is influenced by different velocities. Different velocities cause different pressures (Bernoulli effect), so that a force acting on the particles in the direction perpendicular to the artery axis results. This force is directed such that the particles are driven toward the center of the artery, because the pressure is lower the higher the velocity is.

An explanation arising from irreversible thermodynamics is the principle of minimum entropy production (30). It says that nonequilibrium systems that are not too far from thermodynamic equilibrium tend, at constant boundary conditions, to a state at which entropy production is minimal. The flow of a liquid is an irreversible process, because mechanical energy is permanently converted into heat due to the inner friction of the liquid. In other words, the flow is producing entropy. If the particles are enriched in the center, the regions where the velocity gradient is high (low) show a low (high) viscosity (Fig. 1, center). Thus the total entropy production due to inner friction is lower than if the viscosity were the same everywhere. For the case of inhomogeneous concentration, this phenomenon is called Fährnpr-Lindqvist effect (cf. Ref. 25).

The Optimality Principle

To phrase the optimality principle in a general way, we take into account that the substance of interest, for example, purine nucleotides, may not only be transported by erythrocytes, but also in the plasma. This case is also relevant for insects feeding on blood proteins, which occur both in erythrocytes and in the plasma (16) and for oxygen transport in organisms without red blood cells, for example, arthropods.

The optimality principle can be written as a maximization of the flow of the substance of interest:

\[
\text{maximize } J_{\text{substance}} = \left[ a(1 - \varphi) + b\varphi \right] / \left[ \eta(\varphi) \right]
\]

subject to the side constraint

\[
0 \leq \varphi \leq 1
\]

(25)

(26)

\( J \) is the blood flow as calculated by the Hagen-Poiseuille law (Eq. 4). This depends on the viscosity, which, in turn, depends on hematocrit. Constraint (26) is of importance because otherwise unrealistic values of \( \varphi > 1 \) could be obtained.

Substitution of the Hagen-Poiseuille law (Eq. 4) into Eq. 25 results in:

\[
J_{\text{substance}} = \left[ a(1 - \varphi) + b\varphi \right] \left[ \frac{\pi \Delta P R^4}{8 \eta(\varphi) l} \right]
\]

(27)

It can be seen that \( \varphi \) enters the equation at least twice: once in the numerator and once in the denominator. This can lead to the occurrence of an optimum.

RESULTS

In RESULTS, we focus on the case of oxygen transport. Since the transport of oxygen in the blood plasma can be neglected in mammals, we can put the parameter \( a \) in Eq. 27 equal to zero. Interestingly, the remaining parameter \( b \) then does not affect the optimum, because it is a proportionality factor. In the general case, the ratio between the substance concentrations in the erythrocytes and plasma needs to be known.

Einstein’s Formula

We now try to substitute formula 5 into the Eq. 27 for the oxygen flow:

\[
J_{\text{oxygen}} = \frac{\pi \Delta P R^4 b \varphi}{8 \eta_0 (1 + 2.5\varphi) l}
\]

(28)

We now look for a maximum of \( J_{\text{oxygen}} \) with respect to varying \( \varphi \). It becomes clear that all the factors such as \( \Delta P \), \( R^4 \), etc., do not play any role. In the Hagen-Poiseuille law, it is only important for our purpose here that the flow is proportional to \( 1/\eta \). The function

\[
\frac{\varphi}{1 + 2.5\varphi}
\]

(29)

is monotonic increasing in the form of a saturation function (Fig. 3A). So it would lead to the erroneous result that \( \varphi \) should have its maximum value, 100%. Then, however, the blood flow of the substance of interest:
would consist of erythrocytes only. The reason for this failure of the calculation is that Einstein’s equation cannot be applied to our case because blood is not a dilute suspension; that is, the concentration of erythrocytes is not low enough to allow usage of this equation.

**Saitô’s Formula**

Now we substitute Saitô’s formula in the equation for the oxygen flow:

\[
J_{oxygen} = \frac{\text{const} \cdot \varphi}{\eta_0 \left[ 1 + 2.5 \frac{\varphi}{1 - \varphi} \right]}
\]

(30)

As the function is continuous and differentiable (Fig. 3A), we can find the maximum by differentiation.

\[
\frac{\partial J_{oxygen}}{\partial \varphi} = \text{const.} \frac{\left[ -\varphi \left( 1 + 2.5 \frac{\varphi}{1 - \varphi} \right) \right]}{\eta_0} + \frac{1}{\left( 1 + 2.5 \frac{\varphi}{1 - \varphi} \right)^2} = 0
\]

(31)

\[
1 - 2\varphi - 1.5\varphi^2 = 0
\]

(32)

Equating the numerator with zero leads to a quadratic equation, which has two zeros:

\[
\varphi_{1,2} = \frac{1}{3} \left( -2 \pm \sqrt{10} \right)
\]

(33)

Only the positive solution is relevant. We obtain

\[
\varphi_{opt} = \frac{-2 + \sqrt{10}}{3} \approx 0.387
\]

(34)

Thus an optimal hematocrit of \(~39\%\) is obtained. This is already quite near to the experimentally determined values.

**Gillespie’s Formula**

Now we substitute Gillespie’s formula:

\[
J_{oxygen} = \frac{\text{const} \cdot \varphi (1 - \varphi)^2}{\eta_0 (1 + \varphi/2)}
\]

(35)

It can be seen that this formula has a maximum because it is zero for \(\varphi = 0\) and \(\varphi = 1\) and positive in between (Fig. 3A). As the function is continuous and differentiable, we can find the maximum by differentiation.

\[
\frac{\partial J_{oxygen}}{\partial \varphi} = \text{const.} \frac{\left[ (1 - \varphi)^2 - 2\varphi(1 - \varphi)(1 - \varphi/2) - \varphi(1 - \varphi)^2 \right]}{(1 + \varphi/2)^2}
\]

(36)

The numerator involves the factor \((1 - \varphi)\). Therefore, \(\varphi = 1\) is a solution, but certainly not a maximum. The remainder of the numerator gives

\[
(1 - \varphi - 2\varphi)(1 + \varphi/2) - \varphi(1 - \varphi)/2 = 0
\]

(37)

\[
1 + \varphi/2 - 3\varphi - 3\varphi^2/2 - \varphi/2 + \varphi^2/2 = 0
\]

(38)

\[
1 - 3\varphi - \varphi^2 = 0
\]

(39)

This quadratic equation has two zeros:

\[
\varphi_{1,2} = \frac{3 \pm \sqrt{13}}{2}
\]

(40)

Only the positive solution is relevant. We obtain

\[
\varphi_{opt} = \frac{-3 + \sqrt{13}}{2} = 0.303
\]

(41)

This is fairly close to the experimentally observed values of about \(40\%\), but less close than the result from Saitô’s formula.

**Krieger-Dougherty Formula**

Now we try the Krieger-Dougherty formula:

\[
J_{oxygen} = \frac{\text{const} \cdot \varphi (1 - \varphi/\varphi_m)^{2.5\varphi_m}}{\eta_0}
\]

(42)

This has a maximum as well, because it is zero for \(\varphi = 0\) and \(\varphi = \varphi_m\) (Fig. 3A). Differentiation gives

\[
\frac{\partial J_{oxygen}}{\partial \varphi} = \text{const.} \frac{\left[ (1 - \varphi/\varphi_m)^{2.5\varphi_m} - 2.5\varphi_m\varphi(1 - \varphi/\varphi_m)^{2.5\varphi_m - 1}/\varphi_m \right]}{\eta_0}
\]

(43)

We can divide by the term in parentheses to the power of \(2.5\varphi_m - 1\) and obtain:

\[
\left( 1 - \frac{\varphi}{\varphi_m} \right)^{2.5\varphi_m - 1} \left( 1 - \frac{\varphi}{\varphi_m} \right) = 2.5\varphi
\]

(44)

\[
1 = \varphi \left( \frac{2.5\varphi_m + 1}{\varphi_m} \right)
\]

(45)

\[
\varphi = \left( \frac{\varphi_m}{1 + 2.5\varphi_m} \right)
\]

(46)

The solution strongly depends on the packing density of blood. It can be assumed that this is the range from the packing density of spheres, \(\pi/18\), and the maximum value of \(100\%\). The latter can, as an extreme case, nearly be reached when blood is centrifuged.

In the extreme case where \(\varphi_m = 1\), the optimal value would be

\[
\varphi_{opt} = \frac{2}{7} \approx 0.286
\]

(47)

and for the sphere packing, where \(\varphi_m = \pi/18\), we obtain

\[
\varphi_{opt} = \frac{2\pi}{6\sqrt{2 + 5\pi}} \approx 0.260
\]

(48)

The other solution is a minimum.
Generally, when \( \phi_m < 1 \), then \( \phi_{opt} \) would be smaller than the value given in Eq. 47. In any case, it is smaller than the result based on Gillespie’s formula.

A Surprisingly Simple Solution

A solution that is very near to the experimental value can be derived as follows. The factor 2.5 in Einstein’s formula would give the desired result of 40% just by dividing 1 by 2.5. This results indeed from the formula proposed by Arrhenius (2):

\[
\eta = \eta_0 e^{-2.5\phi}
\]

Substituting this formula into the equation for the oxygen flow gives

\[
J_{\text{oxygen}} \propto \phi e^{-2.5\phi}
\]

This formula has a maximum, since it is zero for \( \phi = 0 \), tends to zero for \( \phi \to \infty \), and is positive in between (Fig. 3B). The question is whether the maximum lies at a value smaller than 1. Differentiation gives

\[
\frac{\partial J_{\text{oxygen}}}{\partial \phi} = e^{2.5\phi} - 2.5\phi e^{-2.5\phi} = 0
\]

\[
1 - 2.5\phi = 0
\]

\[
\phi_{opt} = 0.4
\]

This is a surprisingly simple and excellent solution. The derivation does not take into account the criterion that \( \eta \) should diverge for \( \phi \to 1 \) (or even earlier, when the maximal packing density \( \phi_m \) of cells is reached).

The more complex formula 16 of Mooney leads to results less consistent with reality (see Fig. 3B and Table 2).

Table 2. Optimal hematocrit values calculated by different formulas

<table>
<thead>
<tr>
<th>Reference No.</th>
<th>Viscosity Formula</th>
<th>Optimal Hematocrit, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Einstein (24, 25)</td>
<td>( \eta = \eta_0 (1 + 2.5\phi) )</td>
<td>38.7</td>
</tr>
<tr>
<td>Saijö (86)</td>
<td>( \eta = \eta_0 + (1 - \phi)e^{2.5\phi} )</td>
<td>30.3</td>
</tr>
<tr>
<td>Gillespie (28)</td>
<td>( \eta = \eta_0 (1 - \phi)^{2.5} )</td>
<td>24.7 (( \phi_m = \pi/18 ))</td>
</tr>
<tr>
<td>Quemada (80)</td>
<td>( \eta = \eta_0 (1 - \phi)^{2.5} )</td>
<td>33.3 (( \phi_m = 1 ))</td>
</tr>
<tr>
<td>Krieger and Dougherty (55)</td>
<td>( \eta = \eta_0 (1 - \phi)^{2.5} )</td>
<td>26.0 (( \phi_m = \pi/18 ))</td>
</tr>
<tr>
<td>Arhenius (2)</td>
<td>( \eta = \eta_0 e^{2.5\phi} )</td>
<td>28.6 (( \phi_m = 1 ))</td>
</tr>
<tr>
<td>Mooney (62)</td>
<td>( \eta = \eta_0 e^{-2.5\phi} )</td>
<td>20.7 (( \phi_m = \pi/18 ))</td>
</tr>
<tr>
<td>Pries et al. (79)</td>
<td>See Eq. 24</td>
<td>23.4 (( \phi_m = 1 ))</td>
</tr>
</tbody>
</table>

Note that the Pries formula has an asymptotic behavior such that the viscosity does not practically depend on \( D \) anymore for \( D \) values \( >1,000 \) \( \mu \)m.

The good agreement of the calculated optimal value with the real hematocrit is not surprising, since the Pries formula is based on experimental data. Interesting is the region \( <1,000 \) \( \mu \)m, where we obtain optimal values from 0.392 up to 1 (see Fig. 4). The Fähraeus-Lindqvist effect, which occurs mainly at tube diameters of \( <300 \) \( \mu \)m, leads to an increase in the optimal hematocrit (see Discussion for further explanation).

Possible Extensions of the Theory

An approximative solution in the spatially inhomogeneous case. Now we include the Fähraeus-Lindqvist effect. The extreme situation is reached when all particles are shifted to the middle axis and compressed there, so that a quasi-solid cylinder occurs (Figs. 1, right, and 5). This has indeed been discussed for the case of blood for sufficiently wide vessels (26, 37, 38, 78). The cylinder (with radius \( R_0 \)) can have a certain packing density, \( \phi^* \), e.g., the maximal packing density, \( \phi_m \). This cylinder then moves as a whole without velocity gradients in its interior. Outside of it, the pure liquid (water, or blood serum in our case) is flowing.

The value \( \phi \) is now an averaged, effective quantity. It is related to the packing density \( \phi^* \) in the moving cylinder by the following formula, which corresponds to the cross-sectional area of the blood vessel (Fig. 5):

\[
\pi R_0^2 \phi^* = \pi R^2 \phi
\]

This allows us to calculate the radius of the cylinder:
in the centrifuge), assumed that the erythrocytes are compressed completely (like which is very near to the experimental value of 40%. If it were assumed that the erythrocytes are deformed approximately into spheres, so that the maximal packing density is \( \pi/18 \). This yields \( \varphi_{\text{opt}} = 37\% \) which is very near to the experimental value of 40%. If it were assumed that the erythrocytes are compressed completely (like in the centrifuge), \( \varphi^{*} \) would be 100%, so that \( \varphi_{\text{opt}} = 50\% \) would be obtained.

Influence of defective erythrocytes. As mentioned above, the observed hematocrit in humans differs between women and men. Typical values are 40.0 ± 2.4% and 45.8 ± 2.7%, respectively (27, 50, 51). A straightforward explanation is menstruation. This causes a periodic outflow of erythrocytes, including defective ones in women. Since they are replaced by new erythrocytes, the percentage of defective erythrocytes is lower in women than in men. This explanation is supported by the observation that the hematocrit in women increases after menopause (11).

To compute the optimal value in the presence of defective erythrocytes, Eq. 27 (with \( a = 0 \)) needs to be modified. Let \( \varphi_{\text{int}} \) and \( \varphi_{\text{def}} \) denote the hematocrit values corresponding to intact and defective erythrocytes, respectively. Then the numerator in Eq. 27, which describes oxygen transport, should involve \( \varphi_{\text{int}} \) only. In contrast, the denominator, which corresponds to the viscous flow, should involve the sum \( \varphi_{\text{int}} + \varphi_{\text{def}} \), so that Eq. 27 should be extended as:

\[
J_{\text{oxygen}} = \left[ a(1 - \varphi_{\text{int}}) + b\varphi_{\text{int}} \right] \frac{\pi \Delta P R^4}{8\eta(\varphi_{\text{int}} + \varphi_{\text{def}})l} \tag{64}
\]

This equation can now be used to compute the optimal values based on the different formulas given in Table 2. However, this is beyond the scope of this paper. Here, we show, by way of example, the calculation for the Arrhenius equation. \( \varphi_{\text{def}} \) is assumed to be a given parameter determined by physiological properties.

\[
J_{\text{oxygen}} \propto \varphi_{\text{int}} e^{-2.5(\varphi_{\text{int}} + \varphi_{\text{def}})} \tag{65}
\]

The optimum is computed to be

\[
\frac{\partial J_{\text{oxygen}}}{\partial \varphi_{\text{int}}} = e^{-2.5(\varphi_{\text{int}} + \varphi_{\text{def}})} - 2.5\varphi_{\text{int}} e^{-2.5(\varphi_{\text{int}} + \varphi_{\text{def}})} = 0
\]

So that \( \varphi_{\text{int,opt}} = 0.4 + \varphi_{\text{def}} \tag{69} \)

Case where some substance is transported in the plasma. As mentioned in MATERIALS AND METHODS, the substance of interest may be transported not only by erythrocytes, but also in the plasma. To analyze this case, nonzero values of the parameter \( a \) should be used. Again, the different formulas given in Table 2 can be used. Here, we only use, by way of example, the Arrhenius equation. We have

\[
J_{\text{substance}} \propto \left[ a(1 - \varphi) + b\varphi \right] e^{-2.5\varphi} \tag{70}
\]

The optimum is computed to be

\[
\frac{\partial J_{\text{substance}}}{\partial \varphi} = (-a + b) e^{-2.5\varphi}
\]

\[
-2.5[a(1 - \varphi) + b\varphi] e^{-2.5\varphi} = 0
\]

So that \( \varphi_{\text{opt}} = \frac{7a - 2b}{5a - 5b} \tag{73} \)

In the special case \( a = 0 \), this leads again to Eq. 53.

DISCUSSION

Here, we have derived theoretical optimal values of hematocrit in vertebrates and collected, from the literature, experimentally observed values for 57 animal species. The theoretical values are based on different formulas for the dependence of viscosity on the volume fraction of suspended particles taken from the literature. We have shown that relatively simple approaches based on Newtonian fluid dynamics provide results
that are consistent with experimentally observed values. Although blood is, of course, a non-Newtonian fluid, the simplification to Newtonian properties appears to be justified here.

Similar considerations are certainly of interest also in the suction of nectar by insects (cf. Refs. 15, 39, 51, 52, 71, 72) and in technological applications with respect to suspensions other than blood. This concerns, for example, the question which concentration a cement-water suspension should have to enable a maximum pumping flow of cement along tubes (65, 85).

We started with trying Einstein’s formula for dilute suspensions. Although this has not led to realistic results, we included it into the paper to show the step-wise way of finding good descriptions in science.

The observed values differ considerably among species, ranging from 19% (estuarine crocodile) to 63% (Weddell seal). Also, the theoretical values differ in about that range. The deviations between theoretical and observed values may provide an indication of the extent to which other optimality criteria are relevant as well, so that a trade-off must have been found in evolution, as discussed earlier in the case of optimal stoichiometries of metabolic pathways (107). As for the Weddell seal and beluga (white) whale, the rather large hematocrit value may be due to an additional criterion relevant for diving animals. Since they have to store as much oxygen as possible before diving, the storage capacity of the blood for oxygen needs to be particularly high. However, this does not appear to be a consistent feature for all diving animals, since the killer whale and crabeater seal show hematocrit values <50% (Table 1). Also for birds, the values differ considerably. This might be due to a different activity, although optimal hematocrit theory would not predict any dependency on activity. It may be assumed that, again, additional criteria are relevant.

The exponential function (Arrhenius’ formula) and Saitô’s formula lead to the surprisingly simple solutions of 40% and 39%, respectively, which excellently match the observed values in humans, chimpanzee, gorilla, rabbit, cat, pig, and several other species. Mooney’s equation leads to a value of 23% (assuming a maximal packing density of one), which is in perfect agreement with the observed value in the rainbow trout. The Krieger-Dougherty and Gillespie formulas yield ~30%, matching with llama, tiger, armadillo, pea fowl, and quail.

The question arises why more complex formulas, such as the Gillespie and Krieger-Dougherty equations, do not give such good results for the species with high hematocrit as the simple exponential function, while they may be relevant for species with lower hematocrit.

A possible answer is that blood is a very complicated fluid involving a lot of effects, while most of the formulas used here for the dependence of viscosity on volume fraction had been derived for other types of suspensions, such as plastic globules or cement (60, 61, 63, 69, 81, 85). Erythrocytes are not usually spheres. In humans and many animals, they are biconcave disks, while in camels and llamas, they are elliptical (97). They aggregate to each other, orient, and are deformed in flowing blood. Brinkman et al. (10) found that erythrocyte aggregation could be divided into four types: no rouleaux formation type (ox, sheep, and goat), slight rouleaux formation type (rabbit), moderate type (human, pig, dog, cat, and rat), and excessive type (horse) (cf. Ref. 66). Due to all of these effects, blood is a non-Newtonian fluid. That means that viscosity depends on the velocity gradient.

Interestingly, for complex situations or processes, simple formulas sometimes lead to better results than complicated ones, even if the simple ones do not have a firm theoretical basis. This is, in fact, the essence of modeling, since a model is a simplified representation of some aspect of reality. Different models can be built for the same process, and it is decided by the practical application which one works best. As mentioned above, in hemorheology, many effects play a role, such the dependence on flow velocity, diameter, etc. Here, we have simplified things considerably to concentrate on the essential properties. Despite these simplifications, realistic results can be derived in optimal hematocrit theory.

Red blood cells of camels and llamas are elliptical, as contrasted to the disk-shaped biconcave red cells of other mammals (97). The resistance to flow, which is offered by a suspension of asymmetric particles, such as blood cells, must depend on their orientation with respect to the direction of flow. It is possible that elliptical cells might orient in the direction of flow more easily than discoidal cells, but, with the methods used in this study, we did not find differences in viscosity that could be attributed to the difference in shape. The rationale behind the study was that the elliptical cells of camel and llama might be of advantage in their respective environments: desert and high altitude (97). The camel is confronted with intense heat and potential dehydration with hemococoncentration, and the llama encounters low oxygen pressures where a high red cell concentration is an advantage.

It is interesting to discuss the physiological advantages of the emergence of erythrocytes during evolution. One advantage over oxygen-transporting molecules dissolved in the plasma is the Fåhraeus-Lindqvist effect, which allows the blood cells to concentrate in the center of the vessels and thus to decrease effective viscosity. Moreover, the kidneys can filter blood cells much more easily than heme molecules (12). A further advantage is that the interaction of heme with other molecules is avoided.

A phenomenon worth being discussed here is blood doping (7, 49, 88, 90). First of all, we stress that we are against such a practice for legal and medical reasons. Nevertheless, it is of academic interest to discuss whether this doping is efficient (within certain limits), despite the assumed optimality property of hematocrit in the physiological standard situation. This assumption is supported by the observation that the hematocrit is nearly the same in active sportsmen and control persons (88). Böning et al. (7) called the effect of blood doping the hematocrit paradox.

Blood doping (induced erythrocythemia) is the intravenous infusion of more concentrated blood to produce an increase in the blood’s oxygen-carrying capacity. This can increase the hemoglobin level and hematocrit by up to 20%. Does this falsify our above calculations? There are at least four factors to be considered.

1) The addition of erythrocytes increases blood volume. As the blood vessels are rather elastic, they can be dilated, so as to take up the increased volume. This, however, increases the parameter $R$ (artery radius) in our calculations.

2) We assumed the pressure difference, $AP$, to be constant. However, the heart does not produce the same pressure under all conditions. If blood viscosity and thus the resistance against heart contraction increase, the heart tries to pump harder, to reach the same blood flow velocity. However, this is possible
only over a small range of viscosity above the optimal one. Above that range, the increased viscosity indeed reduces oxygen transport. And even in the range where increasing the hematocrit seems to be beneficial, the heart is more stressed. There is a hyperviscosity syndrome, which can lead to heart failure in the long term.

3) We cannot be completely sure that the hematocrit found in humans or other animals is really optimal. One has to be careful that no circular reasoning is used. Such a reasoning would be to ask whether the hematocrit is optimal, then try various calculations until one of them gives the experimental value and then say the answer is positive: the hematocrit is optimal. It might be that the hematocrit is slightly below the optimum to give the organism the chance to realize a better oxygen flow under special circumstances. For example, at high altitudes, where oxygen pressure is lower, the hematocrit indeed increases. The hematocrit also changes in camels during longer dry seasons and after drinking much water (95).

4) Böning et al. (7) mention the following additional potential factors: augmented diffusion capacity for oxygen in lungs and tissues because of the enlarged red cell surface area, increased buffer capacity, vasoconstriction, reduced damage by radicals, and even perhaps placebo effects. They suggested that blood doping has multifactorial effects not restricted to the increase in blood oxygen content.

In summary, blood doping is dangerous (and anyway illegal). One of the risks in the hyperviscosity syndrome is blood clotting inside of the blood vessels due to higher density of erythrocytes.

It is an empirical fact that hematocrit increases at higher altitudes. In the case of humans, this can be easily observed in mountaineering (39, 89, 100); for the llama, see Table 1. At the first sight, this is intuitively understandable because the lower oxygen pressure should be compensated. One of the most surprising results in mountaineering (39, 89, 100); for the llama, see Table 1. At the end of the RESULTS section, we have outlined several interesting extensions of the theory. One extension concerns the consideration of spatially heterogeneous distributions of erythrocytes. Here, we have modeled the Fåhraeus-Lindqvist effect by considering the extreme case in which all particles move in the middle of the blood vessel as a quasi-solid cylinder. This leads to higher optimal hematocrit values than in spatially homogeneous suspensions. This can be explained as follows: the cylinder moves as a whole without velocity gradients in its interior. Thus a high erythrocyte concentration can be reached without inner friction. At the boundary of the cylinder, a steep velocity gradient occurs because, there, viscosity is lower. A similar reasoning can be applied to spatially heterogeneous suspensions in general.

To simulate continuous spatial concentration gradients, variational calculus (34, 48, 59, 80, 94) can be used (not done here). Both the velocity and the concentration would then be written as functions of the radial coordinate $r$. From the principle of minimum entropy production (30), a minimization principle can be written, from which the optimal velocity and concentration profiles can be computed by variational calculus. Averaging the concentration over the cross section leads to the optimal hematocrit.

The second potential extension concerns the difference in the observed hematocrit values of men vs. women. A straightforward explanation is the different percentage of defective erythrocytes in the two sexes due to menstruation. A similar effect has been discussed for the case of blood doping by erythropoietin: the percentage of young red blood cells with good functional properties increases. This sex difference can be included in the equations relatively easily.

The third generalization concerns the case in which the substance of interest is transported not only by erythrocytes, but also in the plasma. We have considered this in the equations from the outset, but focused for most calculations on the case in which the substance (e.g., oxygen) is only transported by erythrocytes. The general case requires an additional parameter: the ratio between the substance concentrations in the erythrocytes and plasma.

A promising calculation is the following. Based on the theory presented here, the additional pumping power of the heart necessary to achieve the same oxygen transport in the case of high hematocrit values (larger than 40%) can be calculated. Optimal hematocrit theory can be extended also in other ways. For example, non-Newtonian fluid mechanics can be used (16), although Newtonian approaches lead to very good results, as shown here. Moreover, in very small capillaries, such as sinusoids in the liver, the theory based on viscous flow is not valid, because just one erythrocyte can pass at a time. Then the discrete, corpuscular nature of cells needs to be considered.

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H.S. and S.S. conception and design of research; H.S. and S.S. performed experiments; H.S. and S.S. analyzed data; H.S. and S.S. interpreted results of experiments; H.S. and S.S. prepared figures; H.S. and S.S. drafted manuscript; H.S. and S.S. edited and revised manuscript; H.S. and S.S. approved final version of manuscript.

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