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What can we learn from Einstein and Arrhenius about the optimal flow of our blood?

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ABSTRACT

Background: The oxygen flow in humans and other higher animals depends on the erythrocyte-to-blood volume ratio, the hematocrit. Since it is physiologically favourable when the flow of oxygen transport is maximum it can be assumed that this situation has been achieved during evolution. If the hematocrit was too low, too few erythrocytes could transport oxygen. If it was too high, the blood would be very viscous, so that oxygen supply would again be reduced.
Methods: The theoretical optimal hematocrit can be calculated by considering the dependence of blood viscosity on the hematocrit. Different approaches to expressing this dependence have been proposed in the literature. Here, we discuss early approaches in hydrodynamics proposed by Einstein and Arrhenius and show that especially the Arrhenius equation is very appropriate for this purpose.
Results & conclusions: We show that despite considerable simplifications such as neglecting the deformation, orientation and aggregation of erythrocytes, realistic hematocrit values of about 40% can be derived based on optimality considerations. Also the prediction that the ratio between the viscosities of the blood and blood plasma at high shear rates nearly equals Euler's constant (2.718) is in good agreement with observed values. Finally, we discuss possible extensions of the theory. For example, we derive the theoretical optimal hematocrit for persevering divers among marine mammals to be 65%, in excellent agreement with the values observed in several species.
General significance: These considerations are very important for human and animal physiology since oxygen transport is an important factor for medicine and physical performance.
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"Blood is thicker than water."(German and English proverb)

1. Introduction

In higher animals, oxygen is transported in the blood by red blood cells (erythrocytes). Obviously, it is physiologically favourable when the flow of oxygen transport is at the maximum. This can be phrased as an optimality principle. Such principles are often used in biology, based on Darwinian evolutionary theory.

The oxygen flow in animals depends on the erythrocyte-to-blood volume ratio, the hematocrit (HCT). Within hemorheology (hydrodynamics of the blood), a theoretical framework called 'optimal hematocrit theory' has been established [1–6]. It is an interesting question whether that theory allows one to calculate HCT values that are in agreement with the observed values in healthy humans. Various approaches have been put forward to calculate this [2,4,5,7,8]. If the HCT was very low, too few erythrocytes would be present to transport oxygen. If it was too high, the blood would be very viscous and could not flow quickly, so that oxygen supply to the tissues would again be reduced (Fig. 1).

In healthy humans, the HCT amounts to about 40%. There is a difference in HCT between men and women: 45.8 ± 2.7% vs. 40.0 ± 2.4%, respectively [9]. A scatter plot of numerous experimental data depending on age [10–13] is shown in Fig. 2. In contrast, the mean plasma viscosity values are not significantly different between men and women [14]. Altered HCT values occur in numerous diseases such as in fatty liver disease [15] and heart failure [16]. Changes in HCT and viscosity are also investigated in ageing research [17,18].

Many other higher animals show nearly the same HCT values as humans, while several others show different values. For example, many deep-diving marine mammals have a higher HCT. We will investigate this special case below.

Blood is a very complicated fluid involving a lot of effects. Erythrocytes are not usually spheres. In humans, they are biconcave discs. They show phenomena such as aggregation, orientation, and deformation. Interestingly, for complex situations or processes, simple formulas sometimes lead to surprisingly good results and enable better understanding, even if they do not have a sound theoretical basis. This is, in fact, the essence of mathematical modelling, since a model is a simplified

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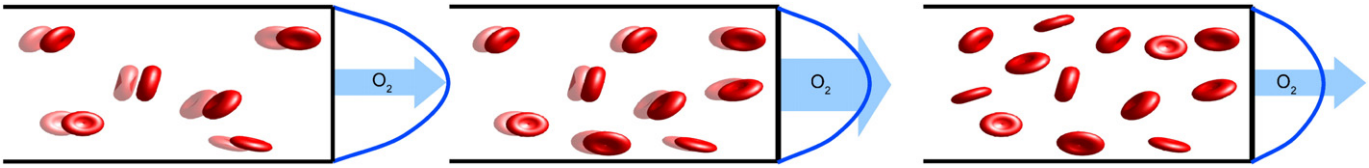

Fig. 1. Parabolic velocity profile (blue) and oxygen transport (arrow) in the case of homogeneous concentration. While the hematocrit increases from left to right, the velocity of flow decreases due to the increasing viscosity. Thus, the oxygen transport flow reaches a maximum in the middle panel.

representation of some aspect of reality. Different models can be built for the same process, and it is decided by practical application which one works best.

Here, our aim is to simplify the description of blood flow to concentrate on the essential properties, even more than in earlier approaches in optimal hematocrit theory [7,19]. It turns out that equations proposed in hydrodynamics very early by Einstein and Arrhenius are highly appropriate for this purpose. We show that despite the simplifications, realistic HCT values can be derived based on optimality considerations.

2. Calculating the theoretical optimal hematocrit

In rheology, a distinction is made between Newtonian and non-Newtonian fluids. Newtonian fluids represent the simpler case. In these liquids, viscosity depends neither on the velocity distribution nor on shear stress. Since blood is a complex mixture, it is a non-Newtonian fluid. Phenomena such as aggregation, orientation and deformation of red blood cells cause its viscosity not to be constant [7,9]. Nevertheless, several basic properties of the blood can be explained even for the idealized case where we consider it to be a (quasi-)Newtonian fluid. The Hagen–Poiseuille law is a good approximation for blood flow provided the appropriate value for the apparent viscosity is used [20]. Higher shear stresses lead to decreasing viscosity.

When a Newtonian fluid flows along a cylindrical tube, its velocity distribution (profile) is a quadratic function of the radial coordinate, that is, of the distance from the tube axis. The total flow J, that is, the volume flowing per time unit, can be described by the Hagen–Poiseuille law [20–24]:

$$J = \frac{\pi \Delta p R^4}{8\eta l} \tag{1}$$

with the following significance of symbols: Δp: pressure difference; R, tube radius, η, viscosity, l, tube length.

For the following calculations, the exact expression of the function (Eq. (1)) is irrelevant, as long as J is inversely proportional to η:

$$J = \frac{K}{\eta}. \tag{2}$$

As shown by Mortensen et al. [25], this form applies to flows of Newtonian fluids along tubes with cross-sections other than circular, for example, elliptical. Moreover, flows through porous media can be described by Darcy's law [26,27]. This equation fits into the general form (Eq. (2)) as well. Thus, we may assume that the calculations are valid for a wide range of geometries of blood vessels (e.g. liver sinusoids), even if the Hagen–Poiseuille law does not apply strictly.

To compute the optimal HCT, it is important to know the dependence of viscosity on HCT. To what extent the flow gets slower (due to an increase in viscosity) if the HCT is increased? It is non-trivial to derive this dependence because the suspended particles perturb the flow of the pure liquid. No less a scientist than Albert Einstein dealt with this question. In [28,29], he derived the function:

$$\eta = \eta_0(1 + 2.5\varphi). \tag{3}$$

This is a linear dependence. As mentioned by Einstein himself [28,29], it only holds true for dilute suspensions, that is, for low φ. For example, Eirich found Eq. (3) to be applicable for suspensions of fungal spores up to $\varphi = 2\%$ [30,31]. In the case where φ tends to 100%, that is, where there is almost no liquid anymore, Einstein's equation would predict a viscosity of 3.5 η_0. The real viscosity, however, is much higher in that case of an almost solid, granular medium. Therefore, several authors have suggested nonlinear equations, which describe a steep increase of viscosity at large φ.

The Swedish physicochemist Svante Arrhenius, who is well-known for his equation describing the dependence of activation energy on temperature, proposed an exponential function:

$$\eta = \eta_0 e^{\alpha\varphi}. \tag{4}$$

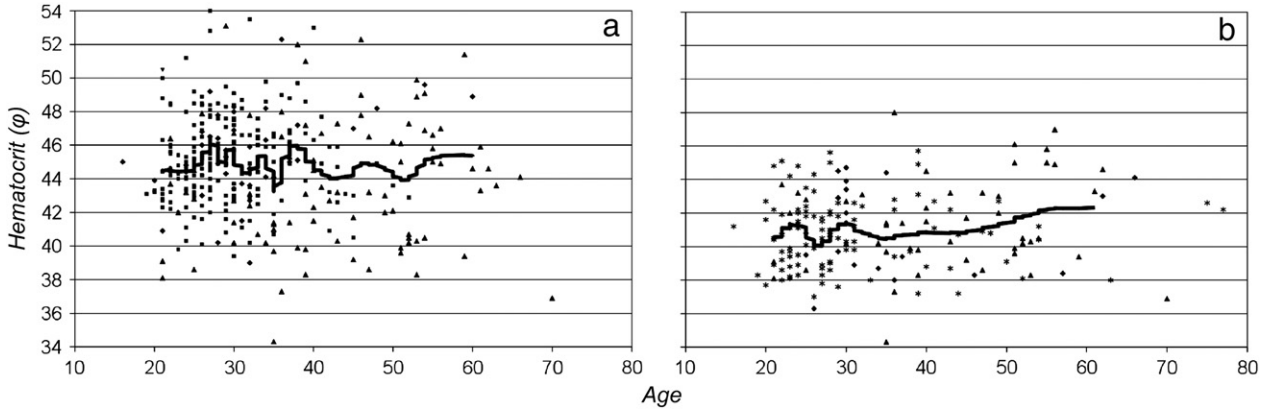

Fig. 2. Plot of the hematocrit vs. age in a) men (n = 333) and b) women (n = 171), based on data from [11] (squares), [13] (stars), [12] (diamonds) and [10] (triangles). In b), the increase in the hematocrit after menopause can clearly be seen. Solid line, sweeping average.

The factor a in the exponential can be determined from the condition that this equation must be consistent with Einstein's equation in the case of low φ. Expanding Arrhenius' equation into a Taylor series gives:

$$\eta = \eta_0\left(1 + a\varphi + \frac{a^2\varphi^2}{2} + \ldots\right). \tag{5}$$

Neglecting the nonlinear terms, we obtain $a = 2.5$. An exponential dependence with factors near 2.5 is indeed often found in hemorheology, notably 3.62–2.88 in the bullfrog in the temperature range 0°–30° [2], 3.27 in the same species at 22° [4] and 3.35 in marine mammal species [32]. Arrhenius [33] determined the value empirically to be 2.56 for gamboge suspensions.

Like Einstein's equation, also Arrhenius' equation gives a finite viscosity when φ tends to 100%, notably $e^{2.5}\eta_0 \simeq 12.18\eta_0$. Since red blood cells are no rigid particles, but contain a colloid cytoplasm, a finite viscosity in that case is quite realistic. Note that the Arrhenius function is convex, that is, it increases more than linearly. This is physically meaningful because at higher and higher HCT values, less and less blood plasma remains to enable a rapid flow. For suspensions consisting of rigid particles like cement or latex, an even steeper increase in viscosity upon increasing φ is relevant, leading to infinite viscosity in the case $\varphi = 100\%$. This can be interpreted in that the suspension is completely dried out and adopts the properties of a solid.

A relatively simple approach to describe such a very steep dependence of viscosity on φ with a singularity at $\varphi = 100\%$ is to divide the term 2.5 φ in Einstein's equation by $(1 - \varphi)$. This formula was proposed by Saitô [34]:

$$\eta = \eta_0\left(1 + \frac{2.5\varphi}{1-\varphi}\right). \tag{6}$$

For low φ, the factor $(1 - \varphi)$ is nearly unity, while it implies a divergence in the above-mentioned extreme case.

An even steeper increase is implied by the formula proposed by Gillespie [35]:

$$\eta = \eta_0\frac{1 + \varphi/2}{(1-\varphi)^2}. \tag{7}$$

By a Taylor series, it can again be shown that both Eqs. (6) and (7) are consistent with Einstein's equation in the case of low φ.

Besides the formulas proposed by Einstein, Arrhenius, Saitô and Gillespie, there are several other formulas describing the dependence of viscosity on the volume fraction of suspended particles (for review, see [36], further equations were proposed by Hughes [30] and Batchelor and Green [37]).

The principle of maximum oxygen flow can be written as follows:

$$\text{maximize } J_{\text{oxygen}} = a\varphi J(\eta(\varphi)) \tag{8}$$

subject to the side constraint

$$0 \le \varphi \le 1. \tag{9}$$

J is the blood flow as calculated by the Hagen–Poiseuille law (Eq. (1)) and a is a proportionality constant. This depends on viscosity, which in turn depends on HCT. The constraint (Eq. (9)) is of importance because otherwise unrealistic values of $\varphi > 1$ could be obtained.

The factor φ in front of J (Eq. (8)) has been written because the amount of transported substance is proportional to the number of erythrocytes. Substitution of the Hagen–Poiseuille law (Eq. (1)) into Eq. (8) results in:

$$J_{\text{oxygen}} = a\varphi\left(\frac{\pi\Delta p R^4}{8\eta(\varphi)l}\right). \tag{10}$$

We now consecutively substitute the different formulas for the dependence of η on φ (Eqs. (3), (4), (6) and (7)) into Eq. (10) for the oxygen flow. Using Einstein's Eq. (3), we obtain

$$J_{\text{oxygen}} = \frac{\text{const.}\ \varphi}{\eta_0(1 + 2.5\varphi)}. \tag{11}$$

We now look for a maximum of J_{oxygen} with respect to varying φ. All the factors such as Δp, R^4, l etc. do not play any role for the optimum because they drop out when equating the first derivative with respect to φ with zero. Moreover, it can be seen that in the Hagen–Poiseuille law, it is only important for our purpose here that the flow is proportional to $1/\eta$.

The function

$$\frac{\varphi}{1 + 2.5\varphi} \tag{12}$$

entering Eq. (11) is monotonic increasing in the form of a saturation function (Fig. 3). So, it would lead to the erroneous result that φ should have its maximum value, 100%. Then, however, the blood 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.

Now we try the Arrhenius equation (Eq. (4)). Substituting this formula into the equation for the oxygen flow (Eq. (10)) gives

$$J_{\text{oxygen}} \propto \varphi e^{-2.5\varphi} \tag{13}$$

(see Fig. 3). Differentiation gives

$$\frac{\partial J_{\text{oxygen}}}{\partial \varphi} = e^{-2.5\varphi} - 2.5\varphi e^{-2.5\varphi} = 0 \tag{14}$$

$$1 - 2.5\varphi = 0 \tag{15}$$

$$\varphi_{\text{opt}} = 0.4. \tag{16}$$

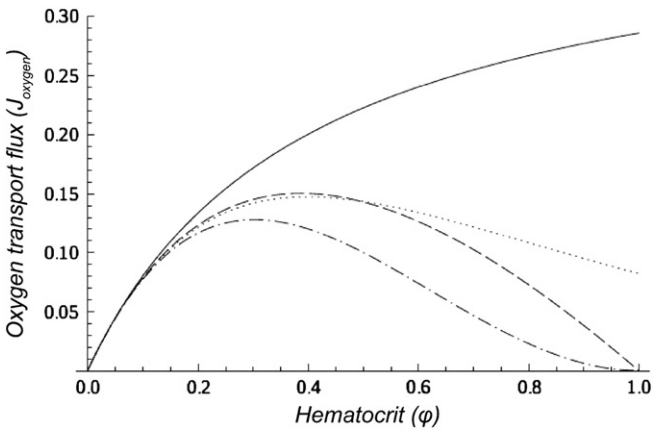

Fig. 3. Plot of the oxygen transport flux vs. hematocrit based on different equations. Einstein (–), Arrhenius (· · ·), Saitô (– –) and Gillespie (· –). In traffic research, such a plot is called fundamental diagram [65].

The second derivative of Eq. (13) reads

$$\frac{\partial^2 J_{\text{oxygen}}}{\partial \varphi^2} = -5e^{-2.5\varphi} + 6.25\varphi e^{-2.5\varphi}. \quad (17)$$

At the value $\varphi_{\text{opt}} = 0.4$, this gives $\simeq -0.92$, which is negative. Thus, we indeed found a maximum. This is a surprisingly simple and elegant solution because we only used the Arrhenius equation (having a simple structure) and the indirect proportionality between flow and viscosity. The calculated value of 0.4 is near the observed values for men and, even more so, for women.

This solution can be validated by substituting it into Arrhenius' equation (Eq. (4)). This gives the following relation between the viscosities of the blood and blood plasma: $\eta = e^{2.5 * 0.4}\eta_0 = e\eta_0 \simeq 2.718\eta_0$. Experimental values for whole blood viscosity (WBV) vary considerably with shear rate. At high shear rates, notably above 100 to 200 s^{-1}, the normal blood viscosity is about 4.5 mPa·s and is relatively insensitive to further increase in shear rate [38]. As shear rates decrease, blood viscosity increases. However, low shear WBV is difficult to measure and, thus, the results differ between labs depending on the method used. For example, Rosenson et al. reported WBV values of 3.26, 4.37 and 5.46 mPa·s for shear rates of 100, 50 and 1 s^{-1}, respectively [14], while Baskurt et al. [38] gave typical values of 5, 10 and 20 mPa·s for shear rates of 100, 10 and 1 s^{-1}, respectively (similar values were given in [18,39]). At even lower shear rates, WBV can increase even more. Based on an experimentally measured range from 1.1 to 2.46 mPa·s for plasma viscosity [14,18,38,39], Arrhenius' equation leads, in the optimal case, to $\eta =$ 3.0–6.7 mPa·s. With the average value of 1.7 mPa·s for plasma viscosity given by Ziegler et al. [39], $\eta = 4.6$ mPa·s is obtained. These values are in good agreement with the range of measured values in the range of high shear rates [14,18,38]. For lower shear rates, which are relevant in capillaries, venules and arterioles, the theory should be refined. Then, the non-Newtonian properties of the blood should be considered.

Similar calculations as in Eq. (14) on the basis of Saitô's and Gillespie's equations lead to values of $\varphi_{\text{opt}} = 38.7\%$ and $\varphi_{\text{opt}} = 30.3\%$, respectively [36] (see Fig. 3). Optimal values can also be calculated on the basis of the equations proposed by Hughes [30] and Batchelor and Green [37], leading to $\varphi_{\text{opt}} = 23.6\%$ and $\varphi_{\text{opt}} = 36.3\%$, respectively, and also using other, more complex formulas [36].

The observed HCT values in animal species show a relatively large variance with values from about 20% (crocodile) to about 65% (several seals) with a pronounced peak at 40%–45% (see [8] and Table 1 in [36]). Various factors can explain the deviations from the predicted optimal value of 40% calculated above.

Some diving marine mammals have HCT values that are significantly larger than 40%. For example, average measured values amount to 63.2% for the Weddell seal [40] and 64.5% for the Northern elephant seal [32,41]. This deviation is likely to be due to the oxygen storage capacity necessary for diving. This requires a trade-off between oxygen transport rate and oxygen storage [41]. Since erythrocytes are biconcave discs, the maximum packing density can be approximated by that of circles in the plane, which amounts to $\pi/\sqrt{12} = 90.7\%$ [42].

A first approximative approach to this bicriterion problem is to calculate the mean between the optimal values for oxygen transport rate (40%) and oxygen storage, which amounts to a hypothetical HCT value of 90.7%:

$$(40\% + 90.7\%)/2 = 65.4\%. \quad (18)$$

This theoretical value is in very good agreement with the values observed for the Weddell seal and Northern elephant seal.

Interestingly, not all diving animals show such high HCT values. Several values together with diving depths and durations are given in Table 1. There is a clear correlation between these parameters—high HCT values occur mainly in those marine mammals that dive very long. This is understandable because they need high oxygen storage capacities. The correlation with the diving depth is weaker; the Beluga whale, for example, has a HCT of about 42% although it dives to 647 m. However, its maximal diving time is only 15 min [43]. The main factor requiring high oxygen storage capacity is the diving time rather than depth, although these quantities are correlated to some extent.

Table 1
Hematocrit values, maximum diving time and maximum diving depths of six marine mammals.

Species		Max. duration (min)	Max. depth (m)	Hematocrit (%)	References
Tursiops truncatus	(Bottlenose dolphin)	8	535	48.5	[32,61,62]
Lagenorhynchus obliquidens	(Pacific white-sided dolphin)	6	Not given	53	[32,62]
Delphinapterus leucas	(Beluga whale)	15	647	52.7	[32,40,43,63,64]
Zalophus californianus	(California sea lion)	10	275	43.5	[32,61]
Mirounga angustirostris	(Northern elephant seal)	120	1653	64.5	[32,41,61]
Leptonychotes weddellii	(Weddell seal)	93	741	63.2	[40,61]

Many animals have HCT values in the range from 20% to 40%. There are various factors worth mentioning here. First, poikilothermic animals have to cope with changing temperatures. This is a problem especially when temperature is decreasing, because viscosity is then increasing. To avoid a harmfully viscous blood in the cold, it is probably beneficial for poikilothermic animals to have a somewhat lower HCT at "normal" temperatures. This view is substantiated by the observation that many fish species, especially cartilaginous fish, have rather low HCT values of 20%–30% [44] and that various frogs show HCT values of about 25% (cf. [36]). In contrast, tuna fish, which are warm-blooded [45], show values above 30% [44,46].

Second, many animals show a reduced physical movement, with some short bursts, such as chicken, which can fly only briefly. Another example are crocodiles; they lie quietly in the water over longer periods and only move quickly when catching a prey. The energy metabolism in such animals mainly relies on glycolysis rather than respiration [47,48]. Accordingly, their muscle tissue is brighter, indicating that they contain less mitochondria and myoglobin. As glycolysis does not require oxygen, we can consider the hypothetical extreme case that virtually no oxygen transport is needed. Since blood also transports heat and various substances in the plasma, the viscosity should then be as low as possible. This would be achieved in the hypothetical case where the HCT is zero. Since in some situations, (aerobic) respiration is necessary, a trade-off should be found between minimum viscosity (HCT = 0) and the situation of maximum oxygen transport rate (HCT = 40%). This is expressed mathematically by Eq. (25) in [36], which expresses the transport by the plasma and by erythrocytes. As a very rough approximation, the average between these two values, HCT = 20%, may be taken as the optimal values for these animals. This is in line with the above-mentioned HCT range for many poikilothermic species and, in particular, in very good agreement with the observed values for rainbow trout (23%, [49]), killifish (24%, [50]) and also for estuarine crocodile (19.2%, [51]). One exception worth mentioning is provided by tuna fish. They are not only partially warm-blooded (see above) but also possess a large amount of red muscle tissue, allowing them to maintain physical activity over long periods [52]. Thus, they require more oxygen, leading to higher HCT values.

The fractional contribution of glycolysis and respiration to the energy metabolism can vary continuously. This can clearly be seen in domesticated animals. For example, the wild boar has darker muscle tissue than the pig, due to a larger content of mitochondria and myoglobin.

The HCT value for boar is 44.7% [53], while those for the pig vary at least between 28% [54] and 41% [55].

Since the respiratory pathway is much more efficient in terms of ATP-over-substrate yield, many higher animals mainly rely on this pathway (cf. [48]). Therefore, their HCT is near 40%, so that there is a pronounced peak in the distribution of HCT values across animal species near that value. This can be seen in a diagram of that distribution in Jensen et al. [8] calculated from values compiled in [36].

A similar reasoning about a continuous distribution applies to the upper end of the distribution. When oxygen storage is important, the approximate optimal value is 65.4% (Eq. (18)). Upon a change of importance of that criterion in comparison to the criterion of maximum oxygen transport rate, different HCT values between 40% and 65.4% can be optimal.

3. Discussion

Here, we have presented a simple but satisfactory approach to calculating the theoretical optimal hematocrit in humans achieved during evolution. It is simpler than earlier approaches taking into account the shape and size of erythrocytes [7,19]. The calculated optimal HCT value of 40% is in very good agreement with the pronounced maximum of the distribution of observed HCT values for many animals [8,36]. For example, chimpanzee, gorilla, cat, lion, lemur, antelope and killer whale show HCT values of 40–45% [36].

For complex situations or processes, simple formulas sometimes lead to surprisingly good results. In hemorheology, many effects play a role such as non-Newtonian properties, deformation of erythrocytes and the Fahraeus–Lindquist effect [56], which leads to a dependence on vessel diameter, etc. Here, we have used several approximations to concentrate on the essential properties. In spite of these simplifications, realistic results could be derived.

Einstein's equation does not lead to a realistic optimal HCT value because the function $\frac{\varphi}{1+2.5\varphi}$ is monotonically increasing. This "failure" of the equation is due to the fact that it was derived for dilute suspensions, while blood is a more concentrated suspension. Nevertheless, Einstein's equation can serve as a starting point for calculating realistic optimal HCT values. The most straightforward approach is to replace the linear term by an exponential term. This was suggested by Svante Arrhenius [33] based on empirical data, not considering blood though.

It is an interesting question how the Arrhenius equation can be derived on theoretical grounds. One idea is to assume that the increase in viscosity by a small increase in the volume fraction of suspended particles is proportional to the current viscosity, since the added particles face that viscosity upon moving. This gives the differential equation $\frac{\partial \eta}{\partial \varphi} = k\eta$ which indeed leads to an exponential solution, $\eta = \eta_0 e^{k\varphi}$.

Using Arrhenius' equation for deriving the optimal HCT leads to 40%. In the calculation, the term 1/2.5 occurs, leading to the mentioned value. Since the factor 2.5 occurs in Einstein's equation already, it can be said that the optimal HCT is related to physical relationships derived as early as 1911 by Albert Einstein, although he did not deal with properties of the blood. Thus, it can be said that Einstein's and Arrhenius' work can help us enormously in understanding the optimal flow of our blood.

Moreover, we have here derived a relation saying that the viscosity of the blood in the optimal state is $e = 2.71828$ times higher than the viscosity of blood plasma, with e being the Euler constant, at least at high shear rates. This represents a new, interesting application of this constant of nature. As shown above, this relation is in good agreement with measured values for several (but not all) species (cf. [57]).

Extensions are needed for animal species showing HCT values different from those calculated above. Above, we have proposed a first approximation for calculating the value in deep-diving animals. Oxygen storage might also be an additional criterion in some terrestrial animals, especially when they need short-term, fast physical performance, during which their breathing cannot fully replenish blood oxygen. This might explain the relatively high HCT value of 53% in kangaroos [58].

It is well known that viscosity gets lower as temperature increases. This effect is expressed by a dependence of the viscosity of the solvent (η_0) on temperature. Since η_0 does not depend on the HCT, temperature does not affect the above calculations. However, to avoid a harmfully viscous blood in the cold, it is probably beneficial for poikilothermic animals to have a somewhat lower HCT at "normal" temperatures. Moreover, temperature would become relevant also if complex phenomena such as erythrocyte aggregation were taken into account. Moreover, it may be argued that in those poikilothermic animals for which oxygen storage is important, the two tendencies of decreasing the optimal HCT below 40% and increasing it above 40% approximately compensate each other, leading to a value of about 40%.

Above, we have shown that HCT values below 40% can also occur when the energy metabolism of the species in question mainly relies on glycolysis rather than respiration, because glycolysis does not require oxygen.

In the future, optimal hematocrit theory can be extended in several directions. For example, in very thin capillaries, classical hydrodynamics is not valid, because just one erythrocyte can pass at a time. Then the discrete nature of cells needs to be considered and methods from traffic research might be useful [65]. Second, in thin capillaries, oxygen diffusion should be considered as another transport mechanism in addition to advection flow.

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. Both for perseverant divers and for animals obtaining their ATP mainly by glycolysis, the optimal HCT values can be estimated by taking appropriate mean values between two extremes. Thus, the present approach can be considered as a basis for extensions of optimal hematocrit theory in various directions. The difference in HCT values between women and men can also be analysed on that basis [36]. Menstruation 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 HCT in women is higher after menopause [13,59]. Thus, changes in HCT are related to ageing (Fig. 2). For men, in contrast, no or only a very weak correlation of the HCT with age was found [14], in agreement with the assumed optimality of hematocrit. Bowdler and Foster [18] found a slight but significant decline in HCT with age [18]. Moreover, in some animals, the HCT and blood viscosity appear to vary in early stages of life [60]. Another factor to be considered is the transport of substances (such as carbon dioxide) in the plasma.

Overall, our results are in support of optimal hematocrit theory. The fundamental optimality criterion of maximum oxygen transport rate leads to a HCT value of 40%, which is approximately observed in many species. The deviations in many other species can nicely be explained by additional optimality criteria.

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