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Letter to the Editor

The hyperbolic function: a mathematical solution of the protein flux/CSF flow model for blood–CSF barrier function
A reply to the letter by S. Öhman (*J. Neurol. Sci.*, 126 (1994) 240–242)

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Sir,

Perhaps my paper (Reiber 1994) is not easy to understand, but all five "flaws" suggested by Prof. Öhman are misunderstandings. There are some demanding mathematical and physical-chemical differential equations involved, which are not easy for the reader untrained in biophysics to understand. I will present a background discussion and then comment on the "flaws".

There is disagreement about the best method to discriminate between the blood- and brain-derived protein fractions in cerebrospinal fluid. There are many reports about evaluations of data from rather small groups of patients, often also restricted to a small range of blood–CSF barrier dysfunctions. In the absence of a physiologically relevant theory it is possible to fit all types of linear and nonlinear functions to describe the discrimination function, in particular for a very restricted range. My paper (Reiber 1994) reports for the first time a consistent theory to explain quantitatively the changing ratio of protein concentrations in CSF of patients with neurological diseases. Additionally, the set of CSF/serum quotient data reported from 4400 patients is the largest collection of data ever published in the field. The range of blood–CSF barrier dysfunction is from albumin quotients Q_{Alb}=0.001–0.700 (theoretical upper limit 1.0).

With the hyperbolic function in Eq. (1), I describe a mathematical solution of a diffusion model with well defined boundary conditions. This equation is derived as an implicit solution for the differential equation of Fick's second law of diffusion which has no explicit but only implicit solutions which refer to specific initial or boundary conditions (references in Carslaw and Jaeger 1959).

Regarding the diffusion of proteins from blood into CSF, the following boundary conditions are suggested:

(1) The protein concentration of a single protein at one side of the barrier (e.g. in the blood) remains constant, i.e. the reservoir of proteins is infinite.

(2) Proteins diffuse through tissue, which does not need to be characterized with its very different structures like endothelial cell layer with tight junctions, fenestrated capillaries, intercellular fluid, ependymal cell layer with and without tight junctions. This simplification is possible as the theory only compares the relation of proteins of different size, diffusing through the same tissue structures at the same time. It is reasonable to suggest that the ratio of diffusion coefficients is not changed in spite of different values of the single diffusion coefficient in different tissue structures.

(3) Proteins diffusing from blood through the tissue enter the cerebrospinal fluid along its way in the subarachnoidal space. The theory does not need to state a laminar flow or CSF flow rate unique for the whole subarachnoidal space.

This Eq. (1) which was not reported in the literature so far can be applied to any biological system fulfilling the above mentioned boundary conditions.

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$$Q_B = \frac{erfc\,(z \cdot \sqrt{D_B/D_A})}{erfc\ z} \cdot Q_A \qquad (1)$$

$$Q_B = a/b\sqrt{Q_A^2 + b^2} - c \qquad (2)$$

Eq. (1) could not be transformed into a hyperbolic function of the usually known form in Eq. (2), as *erfc z* is a trigonometrical series type of solution. But, for values of *z*, tabulated values of *erfc z* have been available for 150 years (Table 5 in Reiber 1994; Carslaw and Jaeger 1959). With an arbitrary ratio of the diffusion coefficients D_B/D_A, I compared the values for Q_B obtained from Eq. (1) and Eq. (2) numerically. Covering three orders of magnitude for the values of Q_B there was shown to be an excellent fit between Eq. (1) and Eq. (2) (Table 5 in Reiber 1994) . The values for the parameters *a*, *b*, *c* in this comparison are calculated and fitted by iteration for the arbitrary ratio of diffusion coefficients in this example. The conclusion that Eq. (1) represents a hyperbolic function is so far independent of any patient data. As shown in Fig. 1 the shape of the hyperbolic function depends only on the ratio of the diffusion coefficients, different for different pairs of molecules (e.g., like IgG/albumin or IgM/albumin). Instead of this indirect way to show that Eq. (1) represents a hyperbolic function, it might be possible to find a direct transformation of Eq. (1) into the form of Eq. (2) using Laplace transforms (Carslaw and Jaeger 1959).

So, the diffusion model and the mathematical solution in itself is not influenced by any criticism about experimental approaches and applications to the patient data. This is not the place to discuss the unrelated suggestions of Prof. Öhman about ultrafiltration, which is not a separate theory as stated by him, but an application of the laws of diffusion under certain boundary conditions. The same is true for Öhman's irrelevant view of tight junctions which are structural restrictions to a diffusion process, too. This as answer to the first and fifth "flaw".

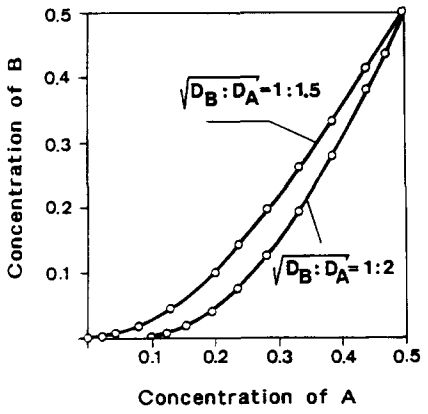

Fig. 1. Concentration ratio of two pairs of diffusing molecules at *z* (effective diffusion path length). The concentrations Q_A and Q_B are calculated from tabulated values for the error function complement *erfc z* (Reiber 1994; Carslaw and Jaeger 1959) with $Q_A = 0.5\ erfc\ z$ and $Q_B = 0.5\ erfc\ z \times \sqrt{D_A/D_B}$. The two hyperbolic curves (according to Eq. 1 in the text) are defined by arbitrary ratios of the diffusion coefficients D_B/D_A = 1:2.25 and D_B/D_A = 1:4.

The second part of my paper refers to an improved experimental fit to patient data. Compared to the earlier paper (Reiber and Felgenhauer, 1987) the set of data was extended from 340 patients to 4400 patients. In addition to the upper discrimination line, in the paper I characterized the mean and the lower discrimination function, too. On the basis of this huge number of patient data I introduced a "population variation coefficient" to characterize the biological variation of IgG, IgA, IgM quotients for a subgroup of patients with the same albumin quotient. With these data and the kinetics of protein transfer from blood into CSF in single patients, I concluded that a decreased CSF flow rate is sufficient to explain quantitatively the increased protein content in CSF in neurological diseases.

Several misunderstandings of Prof. Öhman refer to the method of fitting the hyperbolic function to the data. Fig. 3 in Reiber and Felgenhauer (1987), to which Öhman refers, gives the definition of the parameters *a, b, c*, for the mathematically untrained reader, but not the procedure of fitting the curves.

The upper and lower discrimination curve is fitted graphically for the complete range between Q_{Alb}=0.001 and 0.150, excluding 1% of the data. The variables *a, b, c* are fitted together not independently for extreme values as suggested by Öhman. If one parameter was changed all would be changed in the fitting procedure. So, I made no extrapolation beyond the range of the empirical data. And, in particular, the hyperbolic function for the mean has been obtained independently by calculating the mean value of subgroups of the patients over small intervals of albumin quotients. The hyperbolic function was then fitted to these mean values (shown in Fig. 3, Reiber 1994), independent of the graphically fitted curves for the upper and lower discrimination function. This mean is almost identical with the mean values between the upper and lower border lines. Table 2 and Figs. 1 and 2 report information about this symmetrical distribution of the populations with a large number of IgG, IgA, or IgM quotients.

It might be that for some other reason Prof. Öhman does not like the empirical results, but they do clearly confirm a symmetrical distribution, which should not occur according to his obviously incorrect suggestions. So, there is still no reason which contradicts the introduction of the "population variation coefficient". A restricted symmetrical distribution in the IgM quotient diagram for low albumin quotients has been taken into account and in-

terpreted (Reiber 1994).

The requested coefficients of variation for our detection of the single proteins in CSF and serum were CV = 2–4% for albumin and IgG in CSF and serum, and CV=7–9% for IgA and IgM in CSF and serum.

With respect to the difference between molecular size of IgA and IgG, I would like to refer to the excellent paper of Felgenhauer (1974), where he reports the different hydrodynamic radii of IgA and IgG.

A correlation between the albumin quotient and the serum values of albumin reported by Prof. Öhman can be confirmed, but, again it should be a nonlinear function too (e.g., a hyperbolic function?).

I wonder about the relevance of the correlation between the hyperbolic function and Öhman' s extended index for an arbitrary set of data (Fig. 1 in Öhman's letter, 1994) referring to the parameters reported several years ago (Reiber and Felgenhauer 1987), but not to the improved parameters in my paper.

I hope my reply helps readers to better understand my paper. I would like to take this opportunity to correct some printing errors.

- The dimensions of the values for the parameters a/b, b^2, and c in Table 1 have to be added: values of b^2 have to be multiplied by 10^{-6} and values of c have to be multiplied by 10^{-3}. As an example the upper discrimination limit for IgG has the parameters $a/b=0.93$; $b^2=6\times10^{-6}$; $c=1.7\times10^{-3}$.
- The trigonometric series in Eq. (5b) have to start in brackets with $1/z$ instead of $1/2$.
- The empirical approach to characterize the changes in CSF flow rate according to Eq. (15) should be $\Delta r \sim 1/\sqrt{\Delta Q_{Alb}}$.

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