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A NON-STEADY COMPARTMENTAL FLOW MODEL OF THE CEREBROVASCULAR SYSTEM

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Abstract—A lumped parameter compartmental model for the cerebrovascular fluid system is constructed and solved for the general linear problem of a nonsteady flow with constant resistances and compliances. The model predicts the intracranial pressure waves in the various compartments of the brain in response to pressure changes in the vascular system.

NOMENCLATURE

$\mathbf{A}^{(*)}$	sensitivity matrix
A	arterial
$\mathbf{B}$	deformational flow
B	brain
$\mathbf{C}$	compliance matrix
C	capillary
$\mathbf{D}$	difference vector
F	cerebrospinal fluid (CSF)
J	jugular bulb
P	pressure
$\mathbf{Q}$	flux vector
R	resistance
S	venous sinus
$(\ )^T$	transpose
t	time
V	venous, volume
$\mathbf{Z}$	fluidity matrix
α	ratio of CSF–brain resistance to vein–venous sinus resistance
β	ratio of CSF–brain resistance to capillary–brain resistance
γ	ratio of capillary–vein resistance to brain–vein resistance
θ	coefficient
κ	$\Delta t \cdot C^{-1}\mathbf{Z}$
Π	n-set pressure matrix

INTRODUCTION

This paper summarizes the first stage of a research aimed at modelling the movement of fluids and chemicals in the cerebrovascular system. Here we present the solution of the non-steady flow with constant resistances and compliances; namely the general linear problem—in its entirety.

The lumped-parameter compartmental model of the cerebrovascular system is the first step towards a more comprehensive modelling of the cerebral content considered as a material continuum both on the macro and on the micro-scales. By the compartmental approach, the intracranial content is divided into a number of subunit compartments the behaviour of each of which is represented by a single pressure parameter and by a single fluid discharge, both functions of time but not of space. The resistance to flow due to a particular vessel type is lumped at the outflow of its compartment. Likewise, the integrated change in volume of each compartment of the system is representable as an overall compartmental property and the functional interaction between the components of the lumped parameter system is assumed to be at the interfaces between adjacent compartments.

Monro's (1783) first model of the intracranial cavity was bi-compartmental: brain and blood as two almost-incompressible phases. Kellie (1824), Monro's pupil, modified this hypothesis by assuming three instead of two material compartments, namely arteries, veins and brain tissue. The Monro–Kellie doctrine prevailed to this century and was only relaxed in stages. The number of fluid compartments was increased to six: arterial, capillary, venous, venous sinus, jugular bulb and cerebrospinal (CSF) (Agarwal, 1971). Yet, the fluid itself remained incompressible. More recent approaches relaxed the latter assumption and the fluid was taken as being linearly compressible, i.e. the change in pressure and the change in volume are proportional to each other and the coefficient of proportionality, the bulk modulus or its inverse—the *compliance*, are constants. As to the brain tissue, in essence a multiphasic material continuum, the experimental results pointed at non-linear elasticity of the tissue or, alternatively, the nonlinearity of the compliance (Marmarou *et al.*, 1975; Miller, 1975; Hakim *et al.*, 1976; Lewer and Bunt, 1978; Chopp and Portnoy, 1980). To overcome the 'non-linearity' of a single coefficient, more complex models of single-phased, multi-parameter viscoelastic materials were introduced such as the one consisting of four viscoelastic coefficients known as the 'three-parameter solid', coupled dynamically with another elastic element (Pamidi and Advani, 1978).

Our model consists of seven compartments, namely the six compartments listed above and the brain tissue compartment (Fig. 1). The lumped resistances are: between the artery (A) and capillary (C) compartments (R_{AC}), the capillary (C) and cerebrospinal fluid (F)

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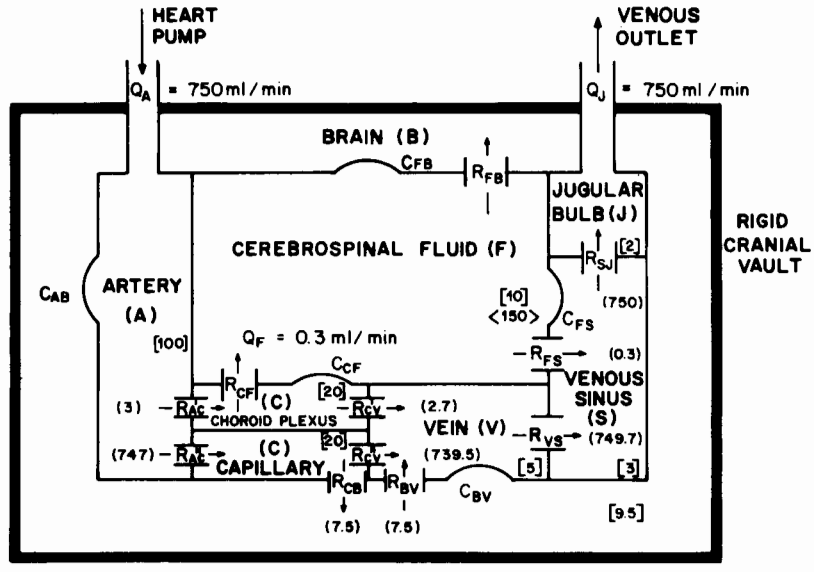

Fig. 1. Lumped-parameter seven-compartmental model of the intracranial cerebrovascular fluid system (R–resistance, C–compliance; [ ] pressure (mmHg); ( ) flow ml min^{-1}); 〈 〉 volume (ml).

compartments (R_{CF}), the capillary (C) and brain tissue (B) compartments (R_{CB}), the capillary (C) and vein (V) compartments (R_{CV}), the brain tissue (B) and vein (V) compartments (R_{BV}). The cerebrospinal fluid (F) and the brain (B) compartments (R_{FB}), the vein (V) and venous sinus (S) compartments (R_{VS}), the cerebrospinal fluid (F) and the venous sinus (S) compartments (R_{FS}) and between the venous sinus (S) and jugular bulb (J) compartments (R_{SJ}); altogether nine resistances. In Fig. 1, the capillary compartment and the R_{AC} resistance are subdivided into the chambers of the choroid plexuses (those tufts of small capillary vessels inside each of the four cerebral ventricles) and the capillary system outside the ventricles. However, in the equations to follow, only the combinations of $R'^{-1}_{AC} + R''^{-1}_{AC} = R^{-1}_{AC}$ and $R'^{-1}_{CV} + R''^{-1}_{CV} = R^{-1}_{CV}$ appear so that the lumped resistances, R_{AC} and R_{CV}, into and out of the capillary compartment prevail. Nevertheless, it is justified to conserve the individual components of R^{-1}_{AC} and R^{-1}_{CV} because the latter relate to anatomically distinct features through which different flows take place. We note that the lumping is a consequence of the fact that the pressure difference across the components is the same.

The resistances R_{CB}, R_{CF} and R_{FB} are identified as the blood–brain barrier; the blood–cerebrospinal fluid barrier and the cerebrospinal fluid–brain barrier respectively.

The compliance elements C_{ij} indicate that an increase in volume of one compartment equals the volume of the cup formed by the deformed membrane. This volume in turn equals the volume displaced from the neighboring compartments, all this within the overall rigid container of the skull (the Monro–Kellie doctrine).

In the non-steady state the deformability of the compartments due to the pulsatory motion of the arteries is taken into account. Thus, first we introduce a compliance element C_{AB} between the artery and the brain tissue compartments. Next, the capillary system is considered non-deformable so we do not insert compliances between this compartment and any of its neighbours. The choroid plexuses, however, although being capillary in character, possess other material properties and can—and in fact, do—convey pulsations to the CSF system (Bering, 1955) so that a compliance element C_{CF} is introduced between them. Further, the CSF system and the brain tissue share common boundaries at the ventricles and along the sub-arachnoidal space which are mechanically deformable. A compliance element C_{FB} is therefore inserted between the two. Finally, additional compliance elements C_{BV} and C_{FS} are introduced respectively between the brain tissue and venous compartments and between the CSF and venous sinus compartments, to account for possible changes in fluid accumulation between the considered compartments and in order to reduce the high pressure in the cardiovascular passage. There is no compliance element between the sinuses and the large jugular veins because the jugular bulb is assumed rigid, with very small storage changes. Altogether, in our presentation, we assume five compliance elements between the cerebrovascular elements.

The mechanical properties of 'resistances' and 'compliances' are 'symmetric' with respect to the inter-

change of direction between one compartment and another. These are outcomes of the law of action and reaction. In general formulae,

$$R_{AC} = R_{CA} \qquad R_{CF} = R_{FC} \quad \text{etc.}$$
$$C_{AB} = C_{BA} \qquad C_{CF} = C_{FC} \quad \text{etc.} \tag{1}$$

Three results obtained by running the model presented here for cases of interest indicate that the model, even in its present form, can simulate certain features actually observed clinically. The first relates to the observed displacement of the main ventricle peripheral boundary. By computing the value of the compliance between the F-compartment and the brain tissue one, approximating the configuration of the F-compartment to a sphere, Karni *et al.* (1987) showed that this displacement is of the order of magnitude actually observed by Lewer and Bunt (1978).

The second indication relates to the pressure variations in the jugular bulb. Sorek *et al.* (1988a), by employing the model presented here, predict that a negative pressure appears during certain portions of the pressure cycle in the jugular bulb compartment. Such negative pressure is indeed observed in reality. Also the model predicts zero pressure in the sinus during certain portions of the cycle, a fact that is also accounted for the action of the heart.

Finally, as shown in this paper, the model predicts the excessive accumulation of CSF in the F-compartment (known as Normal Pressure Hydrocephalus), as a result of clogging of the passage between the capillaries and the brain tissue compartments. Sorek *et al.* (1988b) report observing this relation and discuss the use of it in relieving the pressure by transplanting a shunt.

COMPARTMENTAL MODEL EQUATIONS

The assumptions underlying the hydrodynamical model of the circulatory cerebrovascular system may now be summarized as follows.

(1) Functional brain elements, represented by compartments, are characterized by 'mean' or 'lumped parameter' quantities. Pressure and fluid flux are of interest to us here.

(2) The fluid is single phased, incompressible and Newtonian. From the physical point of view, there is no differentiation between blood and CSF.

(3) The flow is laminar and the relation between the flow rate and pressure drop is linear, i.e.

$$Q = \frac{\Delta P}{R} \tag{2}$$

where R is the resistance.

(4) For the distensibility (elasticity) of the element of brain, a linear function holds between the volume change ΔV and the pressure drop ΔP namely

$$\Delta V = C \cdot \Delta P \tag{3}$$

where the coefficient of proportionality, C, is the compliance.

(5) The system is isothermal and thermodynamically stable.

The explicit continuity equations for the balance of mass for the various compartments now read

For the artery (A) compartment

$$Q_A = \frac{P_A - P_C}{R_{AC}} + C_{AB}\frac{\mathrm{d}}{\mathrm{d}t}(P_A - P_B). \tag{4}$$

For the brain tissue (B) compartment

$$\frac{P_C - P_B}{R_{CB}} + \frac{P_F - P_B}{R_{FB}} = \frac{P_B - P_V}{R_{BV}} + C_{BA}\frac{\mathrm{d}}{\mathrm{d}t}(P_B - P_A) + C_{BV}\frac{\mathrm{d}}{\mathrm{d}t}(P_B - P_V) + C_{BF}\frac{\mathrm{d}}{\mathrm{d}t}(P_B - P_F). \tag{5}$$

For the capillary (C) compartment

$$\frac{P_A - P_C}{R_{AC}} = \frac{P_C - P_F}{R_{CF}} + \frac{P_C - P_B}{R_{CB}} + \frac{P_C - P_V}{R_{CV}} + C_{CF}\frac{\mathrm{d}}{\mathrm{d}t}(P_C - P_F). \tag{6}$$

For the cerebrospinal fluid (F) compartment

$$\frac{P_C - P_F}{R_{CF}} = \frac{P_F - P_S}{R_{FS}} + \frac{P_F - P_B}{R_{FB}} + C_{FB}\frac{\mathrm{d}}{\mathrm{d}t}(P_F - P_B) + C_{FS}\frac{\mathrm{d}}{\mathrm{d}t}(P_F - P_S) + C_{FC}\frac{\mathrm{d}}{\mathrm{d}t}(P_F - P_C). \tag{7}$$

For the vein (V) compartment

$$\frac{P_C - P_V}{R_{CV}} + \frac{P_B - P_V}{R_{BV}} = \frac{P_V - P_S}{R_{VS}} + C_{VB}\frac{\mathrm{d}}{\mathrm{d}t}(P_V - P_B). \tag{8}$$

For the venous–sinus (S) compartment

$$\frac{P_V - P_S}{R_{VS}} + \frac{P_F - P_S}{R_{FS}} = \frac{P_S - P_J}{R_{SJ}} + C_{SF}\frac{\mathrm{d}}{\mathrm{d}t}(P_S - P_F). \tag{9}$$

For the jugular bulb (J) compartment

$$\frac{P_S - P_J}{R_{SJ}} = Q_J. \tag{10}$$

Adding (4–10), making use of (1), yields

$$Q_A = Q_J \tag{11}$$

which is a remanifestation of the Monro–Kellie doctrine.

Equations (4–10) can be grouped into a single matrix equation of the form

$$\mathbf{C}\frac{\mathrm{d}\mathbf{P}}{\mathrm{d}t} + \mathbf{Z}\mathbf{P} = \mathbf{Q} \tag{12}$$

where $\mathbf{P}$ is the pressure column vector

$$\mathbf{P} = \{P_A, P_B, P_C, P_F, P_V, P_S\}, \tag{13}$$

$\mathbf{Z}$ is the fluidity (inverse of resistivity) matrix

$$\mathbf{Z} = [Z_{ij}] \equiv \left[\frac{1}{R_{ij}}\right] = \begin{bmatrix} Z_{AC} & 0 & -Z_{AC} & 0 & 0 & 0 \\ 0 & [Z_{CB}+Z_{FB}+Z_{BV}] & -Z_{CB} & -Z_{FB} & -Z_{BV} & 0 \\ -Z_{AC} & -Z_{CB} & [Z_{AC}+Z_{CF}+Z_{CB}+Z_{CV}] & -Z_{CF} & -Z_{CV} & 0 \\ 0 & -Z_{FB} & -Z_{CF} & [Z_{CF}+Z_{FS}+Z_{FB}] & 0 & -Z_{FS} \\ 0 & -Z_{BV} & -Z_{CV} & 0 & [Z_{CV}+Z_{VS}+Z_{BV}] & -Z_{VS} \\ 0 & 0 & 0 & -Z_{FS} & -Z_{VS} & [Z_{VS}+Z_{ES}] \end{bmatrix}, \tag{14}$$

$\mathbf{C}$ is the symmetric compliance matrix

$$\mathbf{C} = [C_{ij}] = [C_{ji}] = \begin{bmatrix} C_{AB} & -C_{AB} & 0 & 0 & 0 & 0 \\ -C_{AB} & [C_{AB}+C_{FB}+C_{BV}] & 0 & -C_{FB} & -C_{BV} & 0 \\ 0 & 0 & C_{CF} & -C_{CF} & 0 & 0 \\ 0 & -C_{FB} & -C_{CF} & [C_{CF}+C_{FS}+C_{FB}] & 0 & -C_{FS} \\ 0 & -C_{BV} & 0 & 0 & C_{BV} & 0 \\ 0 & 0 & 0 & -C_{FS} & 0 & C_{FS} \end{bmatrix} \tag{15}$$

and $\mathbf{Q}$ is the flux column vector

$$\mathbf{Q} = \{Q_A, 0, 0, 0, 0, -Q_j\}. \tag{16}$$

The resistance R_{SJ} deos not appear in equation (14) as it is readily obtainable from equation (10).

The matrix equation (12) comprises nine resistances and five compliances listed in equation (1). Even for the steady state, whereby all the derivatives with respect to time vanish identically and equation (12) reduces to

$$\mathbf{Z}\,\mathbf{P} = \mathbf{Q} \tag{17}$$

we are left with the eight resistances (as R_{SJ} is determined separately) against six *independent* balance conditions for the various compartments of the cerebrovascular model, excluding the jugular bulb. However, by virtue of the Monro–Kellie doctrine which assumes an absolute rigidity of the cranial vault, only five equations of the six are actually independent. Thus, the redundancy of the system (17) is three, and three additional conditions are needed to solve the set. One of them is the flux $Q_F = 0.3$ ml min^{-1} which can be taken as pivot value with high credibility from the literature (Cutalar, 1968). Two more conditions have to be stipulated by physiological data. They, however, do not assume specific values; instead they are known to be within certain limits. We shall have, therefore, to accompany their determination by a sensitivity analysis, sweeping the entire range of variation of possible values, as discussed in the following section.

EVALUATION OF THE FLUIDITY MATRIX

The intracranial, compartmental flow problem of the cerebrovascular system lies in the solution of the set (12) in its entirety. This is an inhomogeneous, first-order, ordinary differential matrix equation with respect to time. In the previous section, we chose to refer to the matrices C and Z as constant, a fact that made (12) a set of linear equations. The respective mean values were taken as these constants, as a first approximation. However, in principle, the coefficient matrices $\mathbf{C}$ and $\mathbf{Z}$ could be functions of the dependent vector parameter $\mathbf{P}$ which, in turn, depend on the time, t. Thus, basically the problem is *non-linear*. There are, however, some passive cases which can be approximated by the linear problem namely, when $\mathbf{C}$ and $\mathbf{Z}$ assume constant values. At any event, even while dealing with the non-linear problem, we shall have to pass through the linear case. To the latter, therefore, our attention is now focused.

The procedure of solution of the linear case is as follows

(a) Given information about fluxes and pressures, equation (12) can be solved to yield values for resistances and compliances. This is often referred to as *parameter identification* or *model calibration*.

(b) When the R_{ij}s and C_{ij}s have been evaluated, the changes in pressures and rates of fluid flow can be determined for variations in the rate of fluid discharge from the heart pump and from the venous outlet.

(c) With the pressures and compliances already solved, information about the volume changes and also of the displacements of the compartments under certain assumptions, can be obtained.

Here, we confine the attention to the parameter identification and proceed in two stages.

(1) *The steady state*

For constant pressures, the governing equation is the particular integral of (12). The matrix equation to be solved is (17).

The chart of mean pressure variations along the cerebrovascular fluid system conforms with the press-

ure profile of the cardiovascular system cited in the literature (e.g. Guyton, 1969, Ch. 14). In the arteries, the average pressure—between systole and diastole—is 100 mmHg. It drops to 20 mmHg in the capillaries including the choroid plexuses; 10 mmHg in the CSF system, 9.5 mmHg in the brain tissue, 5 mmHg in the venous system, 2 mmHg in the sinuses and 1–2 mmHg in the larger veins—jugular and spinal—leading into the vena cava (Fig. 1). Volumes of the compartments are also recorded in Fig. 1 as much as they are documented in the literature.

Given the compartmental mean pressures P_i^* ($i = A, B, C, F, V, S, J$), also introducing the abbreviations P_{ij}^* for the difference in mean pressure between two adjacent interacting compartments, $P_{ij}^* \equiv P_i^* - P_j^*$; similarly, $Q_{ij}^* \equiv Q_i^* - Q_j^*$ represents the difference between the mean fluxes in compartments i and j. Because Q_A^*, Q_J^* and Q_F^* are *a priori* known, and the mean pressure values P_{AC}^*, P_{CF}^* and P_{SJ}^* (as all other mean pressures) are also known, the following elements of $\mathbf{Z}$ are immediately solved:

$$Z_{AC} = \frac{Q_A^*}{P_{AC}^*} \quad Z_{CF} = \frac{Q_F^*}{P_{CF}^*} \quad Z_{SJ} = \frac{Q_J^*}{P_{SJ}^*}. \tag{18}$$

This leaves us with six elements of $\mathbf{Z}$ against five equations for the remaining compartments, four of which are independent.

To account for the double redundancy, we introduce the scalar coefficients

$$\alpha \equiv \frac{R_{FB}}{R_{VS}} = \frac{Z_{VS}}{Z_{FB}} \qquad (\alpha > 0) \tag{19}$$

$$\beta \equiv \frac{R_{FB}}{R_{CB}} = \frac{Z_{CB}}{Z_{FB}} (0 \leqslant \beta < \infty). \tag{20}$$

Here, α indicates the ratio of the cerebrospinal fluid–brain barrier to the vein–venous sinus resistance, whereas β is the ratio of the cerebrospinal fluid–brain barrier to the blood–brain barrier.

Let us now examine the following cases:

(i) $0 \leqslant \beta < \infty$. Based on equation (20), solution of equation (17) leads to

$$Z_{AC} = \frac{Q_A^*}{P_{AC}^*} \quad Z_{CF} = \frac{Q_F^*}{P_{CF}^*} \quad Z_{SJ} = \frac{Q_J^*}{P_{SJ}^*} \tag{21.1}$$

$$Z_{FB} = \frac{1}{\alpha P_{VS}^* - P_{FB}^*} Q_{AF}^* \tag{21.2}$$

$$Z_{VS} = \frac{\alpha}{\alpha P_{VS}^* - P_{FB}^*} Q_{AF}^* \tag{21.3}$$

$$Z_{FS} = \frac{1}{\alpha P_{VS}^* - P_{FB}^*} \cdot \frac{1}{P_{FS}^*} (\alpha P_{VS}^* Q_F^* - P_{FB}^* Q_A^*) \tag{21.4}$$

$$Z_{CV} = \frac{\alpha P_{VS}^* - P_{FB}^* - \beta P_{CB}^*}{\alpha P_{VS}^* - P_{FB}^*} \cdot \frac{1}{P_{CV}^*} Q_{AF}^* \tag{21.5}$$

$$Z_{CB} = \frac{\beta}{\alpha P_{VS}^* - P_{FB}} Q_{AF}^* \tag{21.6}$$

$$Z_{BV} = \frac{1+\beta}{\alpha P_{VS}^* - P_{FB}^*} \cdot \frac{P_{FB}^*}{P_{BV}^*} Q_{AF}^*. \tag{21.7}$$

The lower extreme value of $\beta = 0$ is noteworthy of mention. From the definition of β [equation (20)], it can assume a zero value in two cases. First, $R_{FB} = 0$, indicating a complete rupture of the cerebrospinal–brain barrier. Here, $\alpha = 0$ also prevails and the only consistent condition for equation (21.3) to exist is $P_F^* = P_B^*$, which means that there is hydrodynamical equilibrium and absolute stagnancy of flow between the CSF compartment and the brain tissue compartment. To avoid this, the pressures at the CSF compartment and the brain tissue compartment ought to differ by some amount, $P_F^* \neq P_B^*$. In the literature, it is customary to assume that both are in the order of 10 mmHg. In our calculations, we arbitrarily used the mean values of $P_F^* = 10$ mmHg and $P_B^* = 9.5$ mmHg (Fig. 1) to enable flow from the F to the B compartment.

The second possibility for the vanishing of β is $R_{CB} \to \infty$. Physiologically, this means that there is a complete blockage of the blood–brain barrier; there is no transmission of blood nutritiants from the capillaries to the interstitial fluid of the brain tissue, in short—a total collapse of the brain. We, therefore, rule this case out.

There is, however, one more case of an admissible non-singular solution of the hydrodynamical problem for $\beta = 0$. It occurs when $Z_{FS} = 1/R_{FS} = 0$ or, alternatively, from equation (21.4), when $\alpha = Q_A^* P_{FB}^* / Q_F^* P_{VS}^*$. This (if $P_F > P_B$) indicates that there is no direct drainage of the CSF into the sinuses through the arachnoidal granulations (the pacchionian bodies), the CSF compartment considerably increases its size and the symptoms are those of hydrocephalus.

There is little, indeed almost no data about the physiological or pathological ranges of α and β. By trial and error however, we could assume β to be in the range of 1/1000. This value led to results that have actually been observed in the clinic. At the same time, the values of the compliances and resistances obtained were found to be insensitive to the value of β, (see Sorek *et al.*, 1986). To convert this into corresponding ratios of fluxes designated by a bar instead of ratios of reesistances, we have by definition,

$$\bar{\beta} \equiv \frac{Q_{CB}}{Q_{FB}} \qquad \bar{\alpha} \equiv \frac{Q_{VS}}{Q_{FB}} \tag{22}$$

so that

$$\bar{\alpha} = \frac{P_{VS} Z_{VS}}{P_{FB} Z_{FB}} = \frac{P_{VS}}{P_{FB}} \frac{R_{FB}}{R_{VS}} = \frac{P_{VS}}{P_{FB}} \alpha$$

$$\bar{\beta} = \frac{P_{CB} Z_{CB}}{P_{FB} Z_{FB}} = \frac{P_{CB}}{P_{FB}} \frac{R_{FB}}{R_{CB}} = \frac{P_{CB}}{P_{FB}} \beta. \tag{23}$$

For our choice of $\beta = 1/1000$, $\bar{\beta} = 0.021$ (cf. Fig. 1). As illustrations, Figs 2 and 3 present the computer solution of the set (21) for $R_{CB}(\alpha)$ and $R_{FS}(\alpha)$ respectively in the particular case of $\bar{\beta} = 0.021$ ($\beta = 1/1000$). The functional dependence of R_{CB} on α is linear,

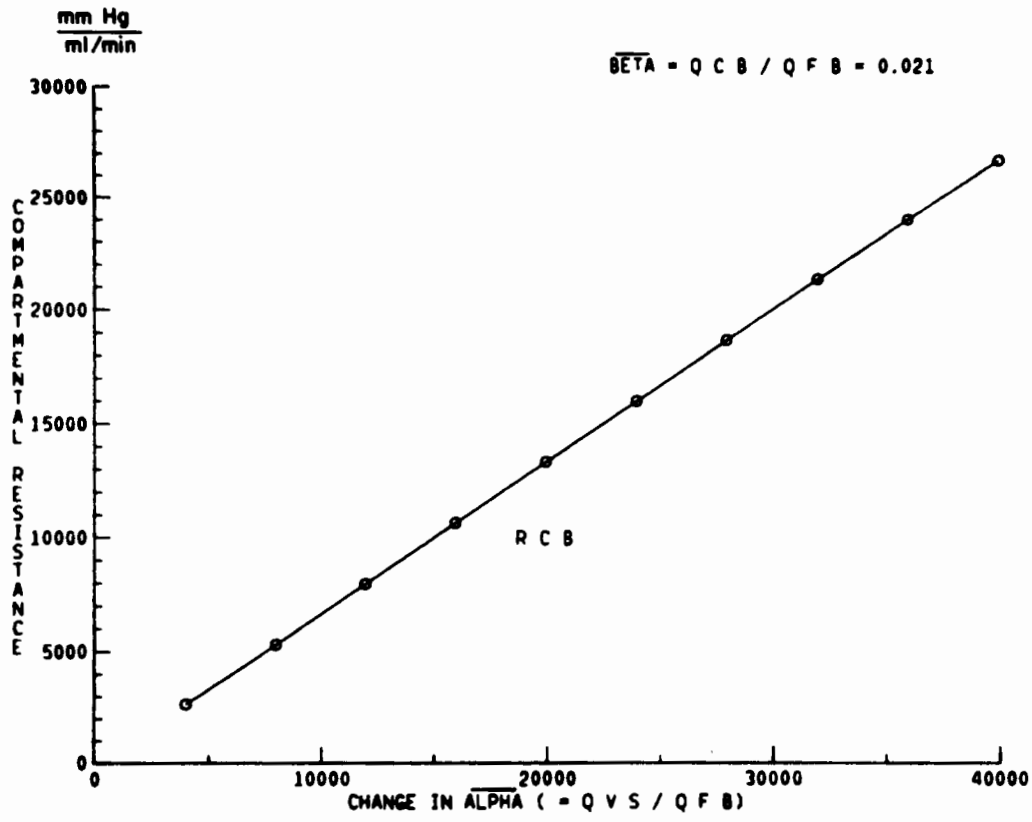

Fig. 2. The lumped blood–brain barrier R_{CB}.

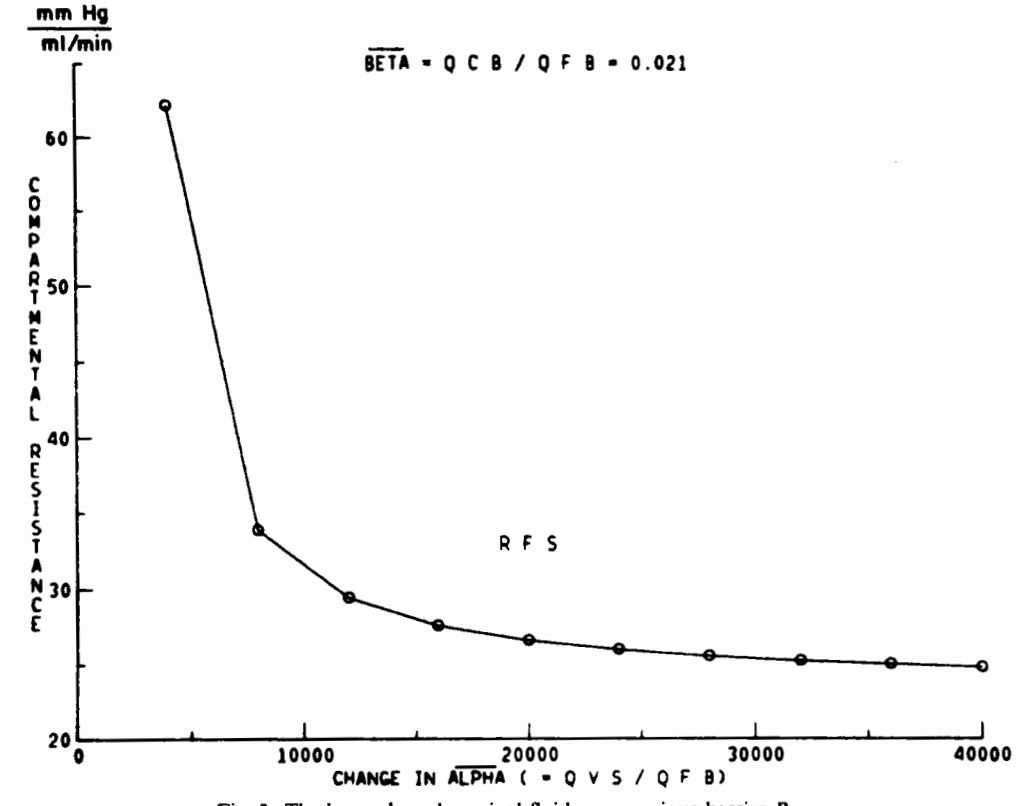

Fig. 3. The lumped cerebrospinal fluid–venous sinus barrier R_{FS}.

whereas that of $R_{FS}(\alpha)$ is hyperbolic.

A general sensitivity analysis for the variation of the resistances R_{ij} in the present case (i) of $0 \leqslant \beta < \infty$ may follow the same procedure as for case (ii) ($\beta \to \infty$) discussed below. This was not carried out numerically because, at a later stage, due to the vagueness of the assumptions about β, the complete solution for the resistances $R_{ij}(\alpha, \beta)$, rather than the limited solution of $R_{ij}(\alpha)$ for the above values of β, has been obtained. The three-dimensional plottings for the compartmental resistances $R_{ij}(\alpha, \beta)$; later also those for the compliances $C_{ij}(\alpha, \beta)$, will be reported separately.

(ii) $\beta \to \infty$. In addition to equation (18), the remaining elements of the matrix $\mathbf{Z}$ read

$$Z_{FB} = 0; \quad Z_{FS} = \frac{Q^*_F}{P^*_{FS}}; \quad Z_{VS} = \frac{Q^*_{AF}}{P^*_{VS}}$$

$$Z_{CV} = \frac{1}{P^*_{CV} + \gamma P^*_{BV}} Q^*_{AF}; \quad Z_{BV} = \gamma Z_{CV} \tag{24}$$

$$Z_{CB} = \frac{\gamma}{P^*_{CV} + \gamma P^*_{BV}} \frac{P^*_{BV}}{P^*_{CB}} Q^*_{AF}$$

Here, for the sake of a smoother solution, a new parameter γ instead of α has been introduced as the ratio of the resistances R_{CV} and R_{BV}, namely

$$\gamma \equiv \frac{R_{CV}}{R_{BV}}. \tag{25}$$

Strictly, the exact value of the ratio γ, as much as those of α and β, is not known. However, we can still pursue with the sensitivity assessment of the $\mathbf{Z}$ elements against a variation in γ, P^*_{CV} and P^*_{BV}. Let Δ denote a deviation from the mean value, then

$$\Delta P^*_{CV} = \Delta P^*_{BV} + \Delta P^*_{CB}. \tag{26}$$

It follows from equations (24, 25) that

$$\mathbf{D}_Z = \mathbf{A}\mathbf{D}_F \tag{27}$$

where

$$\mathbf{D}_Z = [\Delta Z_{CV}, \Delta Z_{CB}, \Delta Z_{BV}]$$
$$\mathbf{D}_F = [\Delta\gamma, \Delta P^*_{CB}, \Delta P^*_{BV}] \tag{28}$$

are the difference vectors of the $\mathbf{Z}$ elements and of their arguments respectively and $\mathbf{A}$ is the square matrix

$$\mathbf{A} = \frac{Q^*_{AF}}{(P^*_{CV} + \gamma P^*_{BV})^2} \times \begin{bmatrix} -P^*_{BV} & -1 & -(1+\gamma) \\ \dfrac{P^*_{BV}}{P^*_{CB}} P^*_{CV} & \dfrac{-P^*_{BV}}{P^*_{CB}} \left(\dfrac{P^*_{CV}}{P^*_{CB}} + \gamma \dfrac{P^*_{BV}}{P^*_{CB}} + 1 \right) \gamma & \gamma \\ P^*_{CV} & -\gamma & -\gamma(1+\gamma) \end{bmatrix}. \tag{29}$$

The extreme case of $\beta \to \infty$ corresponds to a complete rupture of the blood–brain barrier ($R_{CB} = 0$) causing haemorrhage to the entire brain tissue. This is bound to change the compartmental pressure distribution contrary to our assumption of a steady state. Use of equations (27–29) is, therefore, confined to the onset of the occurrence only.

(2) *Non-steady flow*

An interim solution of the matrix equation (12) for $\mathbf{P} = \mathbf{P}(t)$ and $\mathbf{Q} = \mathbf{Q}(t)$ when the effect of $\mathbf{C}$ is negligible but not zero, has been discussed elsewhere (Karni *et al.*, 1987). As an example, for a given arterial excitation wave $P_A = P_A(t)$, the venous–sinus wave $P_S(t)$ was calculated and checked against the measured $P_S(t)$ wave recorded by Hamit *et al.*, 1965, showing a good matching in wave form, amplitude and frequency. In this way, after the model is calibrated and the resistances R_{ij} solved, the complete evaluation of the pulse wave vector $\mathbf{P}(t)$ can be obtained.

EVALUATION OF THE COMPLIANCE MATRIX

We now proceed to the complete solution of the non-steady flow problem for the compartmental model with constant coefficients, namely the general linear problem.

Equation (12) is rearranged to read

$$\mathbf{C}\frac{\mathrm{d}\mathbf{P}(t)}{\mathrm{d}t} = \mathbf{Q}(t) - \mathbf{Z}\mathbf{P}(t) = \mathbf{B}(t) \quad (\mathbf{C}, \mathbf{Z} = \text{constants}). \tag{30}$$

Information scarcely exists about the time dependency of the vector $\mathbf{Q}(t)$ at all compartments. We, therefore, begin with the average pressure vector $\mathbf{P}^*$ and the average flux vector $\mathbf{Q}^*$ and solve for the matrix $\mathbf{Z}$, which by our assumption is now time-independent from equation (30), namely

$$\mathbf{B}^* = \mathbf{Q}^* - \mathbf{Z}\mathbf{P} = 0.$$

That describes the steady state flow discussed above. We then derive information about the values of $\mathbf{P}(t)$ and $\dot{\mathbf{P}}(t) \equiv \mathrm{d}\mathbf{P}(t)/\mathrm{d}t$ at various times t from clinical data of simultaneous pulse wave recordings at the different compartments (such as from Hamit *et al.*, 1965). Equation (30) now yields an n-set of relations for the compliances for each time value t which is of the form

$$^n\dot{\mathbf{P}}C = {}^n\mathbf{b} \tag{31}$$

$$\frac{\mathrm{d}^n\mathbf{p}}{\mathrm{d}t} \equiv {}^n\dot{\mathbf{p}} = \begin{bmatrix} {}^n\dot{p}_{AB} & & & & \\ & {}^n\dot{p}_{CF} & & & \\ & & {}^n\dot{p}_{BV} & & \\ & & & {}^n\dot{p}_{FS} & \\ & & & & {}^n\dot{p}_{FB} \end{bmatrix}_{5\times 5} \tag{32}$$

$$\mathbf{C} = \{C_{AB}, C_{CF}, C_{BV}, C_{FS}, C_{FB}\}_{5\times 1} \tag{33}$$

$$
{}^{n}b = \begin{bmatrix}
Z_{SJ}{}^{n}P_{SH} - Z_{AC}{}^{n}P_{AC} \\
Z_{AC}{}^{n}P_{AC} - Z_{CV}{}^{n}P_{CV} - Z_{CF}{}^{n}P_{CF} - Z_{CB}{}^{n}P_{CB} \\
Z_{VS}{}^{n}P_{VS} - Z_{CV}{}^{n}P_{CV} - Z_{BV}{}^{n}P_{BV} \\
Z_{SJ}{}^{n}P_{SJ} - Z_{VS}{}^{n}P_{VS} - Z_{FS}{}^{n}P_{FS} \\
-Z_{SJ}{}^{n}P_{SJ} + Z_{AC}{}^{n}P_{AC} + Z_{VS}{}^{n}P_{VS} - Z_{CV}{}^{n}P_{CV} - Z_{CB}{}^{n}P_{CB} - Z_{FB}{}^{n}P_{FB}
\end{bmatrix}_{5\times 1} \tag{34}
$$

Applying the Gauss–Markov theorem, the **C** values are obtained by an assortment of the set of informations at all (n) given time observations, namely

$$\mathbf{C} = (\dot{\Pi}^T \dot{\Pi})^{-1} \dot{\Pi}^T \mathbf{B} \tag{35}$$

$$\dot{\Pi} = \begin{bmatrix} {}^{1}\dot{\mathbf{p}} \\ {}^{2}\dot{\mathbf{p}} \\ \vdots \\ {}^{n}\dot{\mathbf{p}} \end{bmatrix}_{n\times 5} \tag{36}$$

$$\mathbf{B} = [{}^{1}\mathbf{b}, {}^{2}\mathbf{b}, \ldots {}^{n}\mathbf{b}]_{n\times 1} \tag{37}$$

$$C_{AB} = \frac{\sum_{k=1}^{n} {}^{k}\dot{P}_{AB}(Z_{SJ}{}^{k}P_{SJ} - Z_{AC}{}^{k}P_{AC})}{\sum_{k=1}^{n} ({}^{k}\dot{P}_{AB})^2} \tag{38.1}$$

$$C_{CF} = \frac{\sum_{k=1}^{n} {}^{k}\dot{P}_{CF}(Z_{AC}{}^{k}P_{AC} - Z_{CV}{}^{k}P_{CV} - Z_{CF}{}^{k}P_{CF} - Z_{CB}{}^{k}P_{CB})}{\sum_{k=1}^{n} ({}^{k}\dot{P}_{CF})^2} \tag{38.2}$$

$$C_{BV} = \frac{\sum_{k=1}^{n} {}^{k}\dot{P}_{BV}(Z_{VS}{}^{k}P_{VS} - Z_{CV}{}^{k}P_{CV} - Z_{BV}{}^{k}P_{BV})}{\sum_{k=1}^{n} ({}^{k}\dot{P}_{BV})^2} \tag{38.3}$$

$$C_{FS} = \frac{\sum_{k=1}^{n} \dot{P}_{FS}(Z_{SJ}{}^{k}P_{SJ} - Z_{VS}{}^{k}P_{VS} - Z_{FS}{}^{k}P_{FS})}{\sum_{k=1}^{n} ({}^{k}\dot{P}_{FS})^2} \tag{38.4}$$

$$C_{FB} = \frac{\sum_{k=1}^{n} {}^{k}\dot{P}_{FB}(Z_{AC}{}^{k}P_{AC} + Z_{VS}{}^{k}P_{VS} - Z_{SJ}{}^{k}P_{SJ} - Z_{CV}{}^{k}P_{CV} - Z_{CB}{}^{k}P_{CB} - Z_{FB}{}^{k}P_{FB})}{\sum_{k=1}^{n} ({}^{k}\dot{P}_{FB})^2}. \tag{38.5}$$

From the clinical measurements of Hamit *et al.* (1965), the five compartmental compliances listed in equation (33) have been calculated for the values $\alpha = 1000$, $\beta = 1/1000$. They are

$C_{AB} = 0.0155$ ml mmHg^{-1} (constant for α, β)
$C_{CF} = 0.0364$ ml mmHg^{-1}
$C_{BV} = 0.3180$ ml mmHg^{-1}
$C_{FS} = 0.0334$ ml mmHg^{-1} (constant for β)
$C_{FB} = 0.1830$ ml mmHg^{-1}.

At a later stage, the numerical solution has been extended to include the general case of $C_{ij} = C_{ij}(\alpha, \beta)$. The three dimensional $C_{ij}(\alpha, \beta)$ plottings will be reported separately. This concludes the calibration of the compartmental model for the cerebrovascular flow system.

EVALUATION OF THE COMPARTMENTAL PULSE WAVE FORMS

Within the framework of this work, which discusses the compartmental cerebrovascular flow problem with constant resistance R_{ij} and compliances C_{ij} namely the general linear problem, once the model has been calibrated, it is possible to obtain solutions for the pressure–time variations $\mathbf{P}(t)$ at all the compartments.

Solution of the matrix equation (12) in incremental form is given by

$$P_{(t+\Delta t)} = \exp(-\kappa)[\mathbf{P}_{(t)} - \mathbf{Z}^{-1}\mathbf{Q}] + \mathbf{Z}^{-1}\mathbf{Q} \tag{39}$$

Here, $\Delta t = t_{k+1} - t_k$ denotes a time step between the frontier time level t_{k+1} and backtime level t_k. The

matrix κ equals

$$\kappa = \Delta t \cdot \mathbf{C}^{-1}\mathbf{Z} \tag{40}$$

The rational expansion of $\exp(-\kappa)$ leads to the following formula

$$\frac{\mathbf{I}-(1-\theta)\kappa}{\mathbf{I}-\theta\kappa} \quad (0 \leqslant \theta \leqslant 1) \tag{41}$$

where $\mathbf{I}$ is the 6×6 unit matrix. A substitution of equation (41) into equation (40) now reads

$$\mathbf{P}_{(t+\Delta t)} \simeq (\mathbf{I}+\theta\kappa)^{-1}[\mathbf{I}-(1-\theta)\kappa] \times [\mathbf{P}_{(t)} - \mathbf{Z}^{-1}\mathbf{Q}] + \mathbf{Z}^{-1}\mathbf{Q}. \tag{42}$$

The coefficient θ controls the type of solution which evolves in time. When $\theta = 0$, we have an explicit scheme; when $\theta = 1$ we have an implicit scheme and when $0 < \theta < 1$ we have a mixed scheme. Thus, with the choice of θ, equations (18, 21) or (24, 38 and 42) constitute the complete solution of the non-steady, compartmental cerebrovascular flow problem with constant resistances and compliances. In addition, being phrased as a first-order differential matrix equation [equation (12)] sufficient boundary conditions ought to be given to enable us derive complete expressions for the compartmental pressure waves. Unfortunately, because of lack of clinical data, rigour has to give way to speculations from this stage onward. We can only express the hope that the information gap will close itself before long.

CONCLUSION

A compartmental model to investigate the non steady flow of the cerebrovascular system was developed. This model is an extension to a quasi steady flow model published earlier (Karni *et al.*, 1987).

In vivo quantitative measurements of mechanical properties (e.g. fluid's phasic pressure and flux, tissue deformation and stress as a function of time), in the various vessels, ventricles and brain tissues of the cerebral system are rare. Those measurements are unique for every human being undergoing changes while maturing and may also be affected by disease.

The model presents a methodology that can be applied to any specific case given its input of phasic pressure and flux curves in the internal common carotid artery. Thus if those inputs are attained say by noninvasive measurements, the model yields pressure mapping of the lumped cerebrovascular system.

Predictions are well within the range of available clinical observations regarding (1) degree of deformation of the ventricles [evaluated by Karni *et al.* (1987) and Sorek *et al.*, (1986) and measured by Lewer *et al.*, (1983)], (2) appearance of suction pressure in the jugular bulb during some interval of the pressure period (Sorek *et al.*, 1988a) (3) occurrence of normal pressure hydrocephalus when flow passage between capillaries and brain tissue is occluded. This prediction was confirmed by an actual head surgery reported by Sorek *et al.* (1988b).

The present lumped parameter model is based on discretizing the cerebral system into seven characteristic compartments with fluidities (reciprocal of resistances) and compliances both assumed as step functions in time. Hence in prolonged excitations such as diseases, a different set of mean fluidity and compliance coefficients is determined to describe a new linear system. This set of coefficients is evaluated by an inverse procedure and by minimal sensitivity of the fluidities and compliances with respect to changes in resistance ratios of cerebrospinal fluid–brain barrier to the vein–venous sinus and the blood–brain barrier one. A detailed explanation of the involved inverse and sensitivity procedures is reported separately (Sorek *et al.*, 1986).

The cerebral system is a complex continuum medium where a saturated solid phase matrix (brain tissue) interacts with fluid phases in the vessels and in the ventricles. Yet the present compartmental model enables a prediction of averaged trends and response of the system when subject to pressure and flux excitations.

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REFERENCES

Agarwal, C. G. (1971) Fluid flow—a special case. *Biomed. Engng* (Edited by Brown, J. H. V., Jacobs, J. E. and Stark, L.). F. A. Davis, Philadelphia.

Bering, E. A. Jr (1955) Choroid plexus and arterial pulsation of cerebrospinal fluid. Demonstration of the choroid plexus as a cerebrospinal fluid pump. *Arch. Neurol. Psych.* **73**, 165–172.

Cutalar, R. W. P. (1968) Formation and observation of CSF in man, *Brain* **9**, 70.

Chopp, M. and Portnoy, H. D. (1980) System analysis of intracranial pressure. *J. Neurosurg.* **53**, 516–527.

Davson, H. (1960) Intracranial and intraocular fluids. *Handbook of Physiology*—1. *Neurophysiology* Vol. 3. American Physiological Society, Washington DC.

Guyton, A. C. (1969) *Function of the Human Body*, 3rd edn. W. B. Saunders, Philadelphia.

Hakim, S., Venegas, J. G. and Burton, J. D. (1976) The physics of the cranial cavity, hydrocephlus and normal pressure: mechanical interpretation and mathematical models. *Surg. Neurol* **5**, 187–210.

Hamit, H. F., Beall, A. C. Jr. and DeBakey, M. E. (1965) Hemodynamic influences upon brain and cerebrospinal fluid pulsation and pressures. *J. Trauma* **5**, 174–184.

Karni, Z., Bear, J., Sorek, S. and Pinczewski, Z. (1987) A quasi steady state compartmental model of intracranial fluid dynamics. *Med. Biol. Engng Comput.* **25**, 167–172.

Kellie, G. (1824) An account . . . . . with some reflections on the pathology of the brain. *Edin. Med. Chir. Soc. Trans.* **1**, 84–169.

Lewer, A. K. and Bunt, E. A. (1978) Dysfunction of the fluid mechanical carniospinal systems as revealed by stress/strain diagrams. *S. Afr. Mech. Engng* **28**, 159–166.

Lewer, A. K., Bunt, E. A. and Poldas, H. (1983) Slow rythmic ventricular oscillations and parenchymal density variations shown by sequential CT scanning. Report No. 83. University of Witwatersand, Johannesburg, S. Africa. p. 36.

Marmarou, A., Shulman, K. and LaMorges, J. (1975) Compartmental analysis of compliance and outflow resistance of the cerebrospinal fluid system. *J. Neurosurg.* **43,** 523–534.

Miller, J. D. (1975) Volume and pressure in the craniospinal axis. *Clin. Neurosurg.* **22,** 76–105.

Monro, J. (1783) *Observations on the Structure and Functions of the Nervous System.* W. Creech. Edinburgh.

Pamidi, M. R. and Advani, S. H. (1978) Nonlinear constitutive relations for human brain tissue. *Am. Soc. mech. Engr* **100,** 44–48.

Rashevsky, N. (1963) Mathematical theory of the effects of cell structure and of diffusion processes on the homeostasis and kinetics of the endocrine system with special reference to some periodic psychoses. *Progress in Brain Research. Vol. 2—Nerve. Brain and Memory Models* (Edited by Wiener, N. and Schafe, J. P.). Elsevier, Amsterdam.

Sorek, S., Bear, J. and Karni, Z. (1988a) Intracranial compartmental pulse wave simulation. *Mathl Biosci.* (in press).

Sorek, S., Bear, J. and Karni, Z. (1986) Compartmental resistances and compliances of the cerebrovascular fluid system. (Submitted for publication).

Sorek, S., Feinsod, M. and Bear, J. (1988b) Can N.P.H. be caused by cerebral small vessel disease? A new look based on a mathematical model. *Med. Biol. Engng Comput.* **26,** 310–313.