A Note on the Kinetics of Oedema Formation and the Paracapillary Transport of Macromolecules

Torsten Teorell
Department of Physiology and Medical Biophysics, University of Uppsala, Sweden

This preliminary note has been prompted by a need of a formal pharmacokinetic model for the distribution of large molecules in a system blood capillaries - interstitial tissue - lymphatics.

Basic considerations - The aim is a simplified compartmental analysis in terms of fluid flows containing dissolved substances (macromolecules) which are subject to "friction" or "retention" located in the capillary walls and in the interstitial matrix. In contrast to earlier work the strict physical "pore" concepts will be circumvented by the introduction of an "admittance" coefficient. Furthermore, bulk flow transport (fluid flow = convection) will be considered as the dominating transport form rather than regular diffusion, because we shall deal with macromolecular solutes of very low diffusibility (as for instance dextran). Finally, time variant "distribution" volumes will be introduced. The model is schematically

It consists of three closed compartments: Number (1) and (2) are connected in series, while number (3) is shunted in parallel between (1) and (2). There are three entries: one Inflow (pressurized) to (1), and one Outflow from (2) and one exit (Lymph flow) from (3). Grossly, it may resemble some technological tank system for liquid mixing. However, an important property is added, namely that the walls of the "tanks" are distensible and react to pressure by volume changes (due to compliance). The mathematics employed is also obviously related to the "clearance" and "extraction" equations which have been presented in the physiological literature.
Many ingredients from the dominating papers in this field have been incor-
porated in the following treatment. In particular, it has certain simi-
larities with the analog simulation model of Wiederhielm (1968) and the work by Aberg et al. (1974-75), but there are also essential differences. A few other papers are listed in the References.

Mathematical Treatment

A. Relation between pressures and bulk flow: — Notations. The symbols are written for computer convenience as capital letters and figures which refer to parameters and locations, according to the scheme above. For example:

I the rate of Inflow. The product of the driving pressure head and the inflow conductance is lumped in the symbol I.

P1 refers to the hydrostatic pressure in compartment (1).

H23 signifies the hydraulic conductance of the boundary or "channel" between (2) and (3), it includes a constant area.

C3 concentration in (3) of the "test" substance.

C1X concentration of non-penetrable "plasma colloids" which exert a colloid osmotic pressure. (C3X) is set to zero.

W2 volume of distribution in (2) at the time t.

v3 the fraction of (W3) available for the test substance.

U3X amount of non-diffusible colloid in (3), the interstitium, dissolved in the distribution volume (W3). The osmolar concentration is approxi-
mated to (U3X)/(W3).

cpl colloid osmotic pressure which is a function of (C1X) and (C2X).

Hence, (cpl) = (r1)(C1X) and (cp2) = (r2)(C2X).

Note that these "oncotic" pressures are time variant.

cp3 is set equal to (U3X)/(W3).

T13 net total pressure difference ("Tension") between (1) and (3), equal to (P1-P3-cpl + cp3).

T23 ditto between (2) and (3), equal to (P2-P3-cp2 + cp3).

F is the instantaneous flow rate of the solvent ("bulk flow"), which transports the test solute. In any particular "channel":

\[
\frac{\text{Rate of bulk flow}}{\text{hydraulic conductance}} = \frac{\text{net total pressure difference (tension)}}{\text{(T)}} \times \frac{\text{hydraulic conductance}}{(H)}.
\]

I = inflow rate, I direction: Inflow \(\rightarrow\) (1)

F12 = (P1-P2) (H12) \(\rightarrow\) (1) \(\rightarrow\) (2)

F13 = (T13)(H13) \(\rightarrow\) (1) \(\leftarrow\) (3)

F23 = (T23)(H23) \(\leftarrow\) (2) \(\leftarrow\) (3)

F24 = (P2)(H24) \(\leftarrow\) (2) \(\rightarrow\) Outflow (4)

F35 = (P3)(H35), if(P3)=0 set (H35)=0/(3) \(\rightarrow\) (3) \(\rightarrow\) Lymph flow (5)

f13 is a factor >1 by which F(13) is multiplied to account for "water" transport, free from the test substance. (f13)=1.2 means that 20 per cent "extra" solvent volume is extruded by the same net driving force (T13), that drives the test solute, cf. /Eqs. 4, 6, 7, 9, 11/.

\(\frac{\partial}{\partial t}\) is the "admittance" coefficient defined in section B.

\(\partial, P, W\) are the time derivatives \(d(C)/dt, d(P)/dt, d(W)/dt\).
B. Theoretical considerations on the solute flow of macromolecules ("fluxes") -

A generally accepted theory for transport kinetics in a system with simultaneous diffusion and bulk flow is formulated in the well-known Hertz convection-diffusion equation. This reveals the importance of a coupling term between the bulk flow velocity \( V \), the diffusion coefficient \( D \) and the length of the transport path \( L \) as the exponential in the Hertz equation, abbreviated "exp \((- VL/D)\)".

This equation has interesting limiting cases (cf Teorell 1969): at steady states and for very large \( V \)s, the fluxes become \( J = V(C_1) \) and \( J = -V(C_2) \) respectively depending on the bulk flow direction. Note that the diffusion constant \( D \) disappears. The same simple limiting equations apply at moderate or small bulk flow velocities if \( D \) is very small. An extended transport path \( L \) favours also dominance of bulk flow transport, \( J = V \cdot C \), or in the present notation \( J = (F)(C) \). However, "fine pore" theories and experimental evidence show that other factors complicate matters: transport of solutes across a porous membrane involve several frictional interactions and the \( D \) value has to be corrected according to "restricted diffusion" formulas by Renkin-Pappenheimer and others.

These considerations certainly give a pessimistic outlook for an easy pharmacokinetic approach to the "paracapillary" system. In order to resolve the dilemma a very simplified view was adopted. When dissolved macromolecules borne on a solvent stream encounter blood vessel walls or the interstitial structural matrix they get "stranded" or "wrecked" for a longer or shorter time, hence the travel rate, relative to the immobile matrix, will be less for the solute than for the solvent. A proper term would be "retardation" or "sieving". However, these terms have somewhat different significance for different authors. What "happens" is that the solute is impeded i.e. the compartment boundaries offer an "impedance" \((Z)\), for the "current" of the dissolved macromolecules. To pursue this electrical analogy, the use of the term "admittance" is adopted for the inverse of the impedance, \( Y = 1/Z \). "Admittance" has the dimension \( 1/(\text{complex}) \) resistance. The following definition will be used,

Admittance coefficient \( (Y) = 1 \), when the solute travels with the same rate as the solvent, i.e. no retardation with respect to the compartment "channel" wall.

\( (Y) < 1 \), lowered admittance of the solute particles to the transport path, hence lowered transport rate.

\( (Y) > 1 \), enhanced admittance, will not be discussed here ("facilitated" transport).

One can now write: \( \text{(Rate of concentration change)} = (\text{flow rate}) \times \text{admittance} \times \text{(conc.)} = (F) \times (Y) \times (C) \), compare section E.
The admittance concept is, of course, an oversimplification. However, it has obvious relations to gel chromatography and similar procedures. It does not directly include any relation (pore diameter - molecular diameter). The concept is void of preformed pore structures of any dimensions. Nevertheless, it may be interpreted as a symbolic transcription of the Staverman "reflection coefficient" \( \sigma \) as \( 1 - \sigma \). Possible relations between \( \gamma \) and molecular size will be mentioned in section F.

At this point it should be strongly emphasized that the presented theory is not committed beyond the built-in assumptions. Hence, any identification or interpretation in specialized physical or physiological terms should be made with great caution.

Before one can set up the final differential equations (sections D and E) the problem of time variant volumes must be treated in the following section.

C. The kinetics of solute transport with time variant "distribution" volumes.— The basic rate equation in pharmacokinetics of multicompartment systems is

\[
\frac{dN}{dt} = k \cdot \left( \frac{x}{V_1} - \frac{y}{V_2} \right)
\]

where \( N, x \) and \( y \) are amounts, \( V_1 \) and \( V_2 \) time invariant distribution volumes and \( k \) a rate constant (cf. Teorell 1937). In "mixing" kinetics the \( k \) includes the rate of bulk flow. Diffusion kinetics with a time-dependent volume can be solved by the introduction of a "dilution correction" (Teorell 1947). In the essence the modification of a rate equation involving time variant compartment volumes \( W \) rests on the transformation

\[
\frac{dN}{dt} = d(CW)/(dt) = C(dW)/(dt) + W(dC)/(dt),
\]

here \( C \) is the concentration.

Material conservation requires that \( \frac{dN}{dt} \) should be equal to the net sum of all "ingoing" and "outgoing" rates of "amount" transport (= "sum of fluxes"). After rearrangement of the terms one obtains the rate of change of the concentration as

\[
\frac{dC}{dt} = (\text{sum of fluxes})/(W) - (C)(dW)/(dt)/(W)
\]

The second term is the "dilution term" (positive or negative). In the present problem \( (dW)/(dt) \) is directly accessible from Eqs. 4-6 below. The solute "flux" will be described in section E.

D. The differential equations for bulk flows:— The initial conditions refer to the assumption that the compartment walls are reversibly distensible under varying internal pressures obeying linear relation that the instantaneous volume \( W_i(t) = (q_i)(P_i) + W_i(t=0) \). Here \( i \) is the compartment number and \( W_i(t=0) \) the constant volume under zero pressure (referred to the "outside"). The parameter \( q_i \) is a constant compliance coefficient. As \( i = 3 \) three volume-pressure equations (= Eq. 1 - Eq. 3) are needed which should be solved in an auxiliary subroutine to be run in parallel with the final computer integration procedure.
The rate of volume change is \( dW/dt = (q) \cdot dP/dt \), hence one needs to employ only one set of differential equations either in \( W(t) \) or \( P(t) \). In any compartment the following equation is obeyed:

**Rate of change of volume = sum of ingoing and outgoing volume rates**

Using the bulk flow definitions of the previous section A one can now formulate the first set of differential equations necessary to solve the kinetic problem in question:

\[
\begin{align*}
\frac{d(W1)}{dt} &= (q1) \cdot \frac{d(P1)}{dt} - (I) - (F13)(f13) - F(12) \quad \text{/Eq.4/} \\
\frac{d(W2)}{dt} &= (q2) \cdot \frac{d(P2)}{dt} = (F12) - (F23) - (F24) \quad \text{/Eq.5/} \\
\frac{d(W3)}{dt} &= (q3) \cdot \frac{d(P3)}{dt} = (F13)(f13) + (F23) - (F35) \quad \text{/Eq.6/}
\end{align*}
\]

As pointed out above Eqs. 1-3 should be run, together with Eqs. 4-6, as subroutines.

**E. The solute flux differential equations:** Using the notation and definitions of section A and section C a second set of differential equations, now in terms of concentration changes, is

\[
\begin{align*}
(C1^X) &= \frac{((I)(CO^X) - (F13)(Y13^X)(C1^X) - (C1^X)(I) + (C1^X)(F13)(f13))/(W1)} \quad \text{/Eq.7/} \\
(C2^X) &= \frac{((F12)(C1^X) - (C2^X)(F12) + (C2^X)(F23))/(W2)} \quad \text{/Eq.8/} \\
(C1) &= \frac{((I)(C0) - (F13)(Y13)(C1) - (C1)(I) + (C1)(F13)(f13))/(W1)} \quad \text{/Eq.9/} \\
(C2) &= \frac{((F12)(C1) - (F23)(Y23)(C3) - (C2)(F12) + (C2)(F23))/(W2)} \quad \text{/Eq.10/} \\
(C3) &= \frac{((F13)(Y13)(C1) + (F23)(Y23)(C3) - (F35)(Y35)(C3) - (C3)(F13)(f13) - (C3)(F23) + (C3)(F35))/(W3)(v3))}{(W3)(v3))} \quad \text{/Eq.11/}
\end{align*}
\]

Eq. 7 and 8 apply to the "plasma colloids", Eqs. 9 through Eq.11 to the "test" substance.

The second row in an equation contains the noncancelling parts of the "dilution correction".

**Comments to section D and E:** Eqs. (1-3),(4-6) provide the basis for the kinetics of oedema formation, but they require also Eq.7 and Eq.8 to generate the colloid osmotic pressure contributions \( (cp) \). The concentration scale of \( (C) \) is sufficiently small to give negligible \( (cp) \)'s. The total system, Eqs.1 through Eq.11, describes pharmacokinetics of "test" macromolecules in the given compartment system, which mimics the "paracapillary" dynamics. Grossly the treatment can conform with the Landis-Starling's concept as will be shown in the next section F.
F. A numerical example: The Runga-Kutta-Gill integration method was used for solution of the system of simultaneous differential equations derived in sections D and E, i.e. Eqs (4 through 11). Arbitrary values for constants were \((H12)=0.5, (H13)=2, (H23)=1, (H24)=2\) (at "venous congestion" = 0.5), \(H(35)=0.5\), \((f13) = 1.2\), \((U3^2) = 0.5\) and \((r1) = (r2) = 0.5\). Initial conditions were \((W10)=(W20)=(W30)=1\) with corresponding constant compliances \(q1=0.5\), \(q(2)=q(3)=1\), the \((P)s\) about 0.01 - 1 and finally the concentrations \((C0X)=3\) and \((C0)=3\).

The "Inflow" \(I = 3\) ("continuous injection").

The assignment of numerical admittance values \((Y)\) is difficult. A pure ad hoc assumption is that the admittance is proportional to some power of the solute molecular surface area. In order to obtain a reasonable fit with the experiments of Grotte (1956) on dextrans of different mol.wts. it was empirically found that \(Y = 12 \cdot (MW \cdot 10^{-3})^{-3/2}\) was satisfactory for \(MW \geq 5200\) to \(300 \cdot 10^{3}\). In Tables I and II the \(Y\)-value becomes 0.23 for \(MW = 14 \cdot 10^{3}\).

This formula yields \(Y = 1\) for a \(MW\) of 5200, meaning full, unrestricted admittance, i.e. a solute transport velocity equal to the solvent flow velocity. For larger \(MW\)'s the \(Y\) becomes increasingly smaller (for \(MW = 70 \cdot 10^{3}\), \(Y = 0.02\)). The \(Y\) formula is primarily assigned to the (1-3) compartment barrier (the arteriole capillary wall) as \((Y13) = 0.002\).

It is conceivable that further impedance will be encountered by the molecules, which have been admitted to the interstitium during the ensuing solvent drift towards the venous part (2) and the lymph vessels (5). To describe the coercion and crowding of the macromolecules "in transit" in (3) the following empirical expressions were used: \((Y23) = 1/(1+a/(Y13)),\) respectively \((Y35) = 1/(1+b/(Y13))\) with the value of \(a = 0.3\) and \(b = 0.01\). The factor \((v3)\) was equal to \(Y(35)\).

Results. A comprehensive presentation is assembled in the Tables I and II. A diagram of comparisons with Grotte's material (loc.cit.1956, Table 17,p.58 and Table 18,p.62) is shown in Figure 1.

CONCLUSIONS: The "ultra"-filtration in (1) leads to an appreciable concentration augmentation of both the "plasma" colloids and the test substance, which is greatly compensated in (2) by "resorption". Only about 50 per cent of the test "macrosolute" \((M=14 \cdot 10^3)\) resides in (3), the interstitium. The \(C_L/C_P\) ratio declines to a level of about 0.05 - 0.1 at large molecular sizes in reasonable agreement with Grotte's observations (cf. Figure 1).

The effect of venous congestion is a marked pressure increase in all compartments, particularly of (2), and corresponding volume increases. The total volume increase results in a "swelling" or "oedema" to about twice the normal
Table I. Values of parameters in normal conditions and venous congestion (parenthesis). M = 14·10³. Steady state. \((C_0^X) = 3, (CO) = 3. \\

<table>
<thead>
<tr>
<th>Compartment</th>
<th>(1) Art.</th>
<th>(2) Ven.</th>
<th>(3) Interstit.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pressure ((P))</td>
<td>4.26 (6.32)</td>
<td>1.28 (3.79)</td>
<td>0.87 (2.21)</td>
</tr>
<tr>
<td>Colloid (\text{cp})</td>
<td>3.02 (3.54)</td>
<td>1.75 (2.36)</td>
<td>0.26 (0.16)</td>
</tr>
<tr>
<td>Volume ((W))</td>
<td>3.13 (4.16)</td>
<td>2.28 (4.79)</td>
<td>1.87 (3.20)</td>
</tr>
<tr>
<td>Conc.((\text{coll.})) (\text{coll.}(X))</td>
<td>6.04 (7.08)</td>
<td>3.50 (4.72)</td>
<td>neglected</td>
</tr>
<tr>
<td>(\text{conc.}(\text{test})) ((C))</td>
<td>5.07 (5.63)</td>
<td>3.24 (3.96)</td>
<td>1.65 (1.40)</td>
</tr>
</tbody>
</table>

Sum of volumes 7.28 (12.16 = oedema)

Lymph flow 0.44 (1.11)

\(\frac{C_1}{C_p}, \frac{(C_3)}{(CO)}\) 0.55 (0.47)
Table II. Rates of bulk flow and solute transport (amount) in normal conditions and venous congestion (parenthesis). $M = 14.10^3$. Steady state.

<table>
<thead>
<tr>
<th>Channel</th>
<th>Bulk flow</th>
<th>Solute flux</th>
<th>Process</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inflow</td>
<td>3.0 (3.0)</td>
<td>9.0 (9.0)</td>
<td>Arter. input</td>
</tr>
<tr>
<td>(1) - (2)</td>
<td>1.49 (1.27)</td>
<td>7.54 (7.13)</td>
<td>Art. - ven.</td>
</tr>
<tr>
<td>(1) - (3)</td>
<td>1.51 (1.73)</td>
<td>1.46 (1.86)</td>
<td>Filtration</td>
</tr>
<tr>
<td>(2) - (3)</td>
<td>-1.08 (-0.63)</td>
<td>-0.77 (-0.38)</td>
<td>Resorption</td>
</tr>
<tr>
<td>(3) - (5)</td>
<td>0.44 (1.11)</td>
<td>0.69 (1.48)</td>
<td>Lymph</td>
</tr>
<tr>
<td>(2) - (4)</td>
<td>2.56 (1.89)</td>
<td>8.31 (7.51)</td>
<td>venous output</td>
</tr>
<tr>
<td>Sum (Out)</td>
<td>3.0 (3.0)</td>
<td>9.00 (8.99)</td>
<td>(3) → (5) + (2) → (4)</td>
</tr>
</tbody>
</table>

volume. The macrosolute concentration in (3) decreases by about 15 per cent and the lymph flow rate becomes approximately doubled, also in good agreement with Grotte's data.

In spite of the unphysiological arrangement and scaling one may conclude that the proposed model can serve to reproduce essential properties of the Landis-Starling paracapillary circulation. The results have been confined to steady state, but preliminary work has shown that the transient time course, i.e. the actual kinetics, has many interesting features which will be discussed in other publications. It is obvious that the model lends itself to studies on the "single injection" technique, or other problems dealing with the circulation.

ACKNOWLEDGEMENTS

This research was supported by the Swedish Medical Research Council (14X-629) and was partially conducted while the author was Scholar-in-Residence at the Fogarty International Center, National Inst. Health (Bethesda, USA) in 1972-1973.

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Received April 2, 1979

Address for reprints:

Professor Torsten Teorell 
Department of Physiology and Medical Biophysics 
University of Uppsala 
Box 572, S-751 23 Uppsala, Sweden