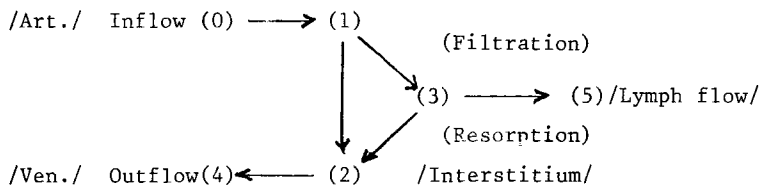# A Note on the Kinetics of Oedema Formation and the Paracapillary Transport of Macromolecules

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This preliminary note has been prompted by a need of a formal pharmaco-kinetic model for the distribution of large molecules in a system blood capil-laries – 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 in-troduced.The model is schematically

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/Art./   Inflow (0)  ──→ (1)
                          │  ╲   (Filtration)
                          │    ╲
                          │     ↘(3) ────→ (5)/Lymph flow/
                          │     ╱
                          ↓   ╱   (Resorption)
  /Ven./  Outflow(4)◄──── (2)      /Interstitium/
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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 vo-lume changes (due to compliance). The mathematics employed is also obviously related to the "clearance" and "extraction" equations which have been presen-ted in the physiological literature.

Many ingredients from the dominating papers in this field have been incorporated in the following treatment. In particular, it has certain similarities with the analog simulation model of Wiederhielm (1968) and the work by Åberg 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.

$C1^X$ concentration of non-penetrable "plasma colloids" which exert a colloid osmotic pressure. $(C3^X)$ is set to zero.

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

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

$U3^X$ amount of non-diffusible colloid in (3), the interstitium, dissolved in the distribution volume (W3). The osmolar concentration is approximated to $(U3^X)/(W3)$.

cp1   colloid osmotic pressure which is a function of $(C1^X)$ and $(C2^X)$. Hence, $(cp1) = (r1)(C1^X)$ and $(cp2) = (r2)(C2^X)$. Note that these "oncotic" pressures are time variant.

cp3   is set equal to $(U3^X)/(W3)$.

T13   net total pressure difference ("Tension") between (1) and (3), equal to $(P1-P3-cp1 + cp3)$.

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":

(Rate of bulk flow) = (net total pressure difference (tension)) x (hydraulic conductance) or (F) = (T)(H).

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I    = inflow rate, I      direction:    Inflow ──────➤ (1)
F12  = (P1-P2)(H12)                       (1) ──────➤ (2)
F13  = (T13)(H13)                         (1) ──────➤ (3)
F23  = (T23)(H23)                         (2) ◄────── (3)
F24  = (P2)(H24)                          (2) ──────➤ Outflow (4)
F35  = (P3)(H35)/If(P3)<0 set (H35)=0/(3) ──────➤ Lymph flow (5)
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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/.

Y   is the "admittance" coefficient defined in section B.

$\dot{C},\dot{P},\dot{W}$ 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 wellknown 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(C1) and J = -V(C2) 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 · 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/(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: (Rate of concentration change)=(flow rate)x(admittance) x(conc.)=(F)x(Y)x(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 con-
cept is void of preformed pore structures of any dimensions. Nevertheless, it
may be intepreted as a symbolic transcription of the Staverman "reflection
coefficient " (σ) as ($1 - \sigma$). Possible relations between Y 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" vo-
lumes.— The basic rate equation in pharmacokinetics of multicompartment sys-
tems is $(dN)/(dt) = k \cdot (x/V_1 - y/V_2)$ 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 cor-
rection" (Teorell 1947). In the essence the modification of a rate equation in-
volving time variant compartment volumes (W) rests on the transformation
$(dN)/(dt) = d(CW)/(dt) = C(dW)/(dt) + W(dC)/(dt)$, here C is the concentration.
Material conservation requires that $(dN)/(dt)$ 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 concen-
tration as

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

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 $Wi(t) = (qi)(Pi) + Wi(t=0)$. Here i is the compartment number and $Wi(t=0)$
the constant volume under zero pressure (referred to the "outside"). The para-
meter (qi) 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)·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:

d(W1)/(dt) = (q1)·d(P1)/(dt) =(I)- (F13)(f13) − F(12)   /Eq.4/
d(W2)/(dt) = (q2)·d(P2)/(dt) = (F12) − (F23) − (F24)   /Eq.5/
d(W3)/(dt) = (q3)·d(P3)/(dt) = (F13)(f13) + (F23) − (F35)   /Eq.6/

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

$(\overset{\circ}{C1}^X)$ = ((I)(CO^X)− (F13)(Y13^X)(C1^X) −
                            −(C1^X)(I)+(C1^X)(F13)(f13))/(W1)   /Eq.7/

$(\overset{\circ}{C2}^X)$ = ((F12)(C1^X) −
                            −(C2^X)(F12) + (C2^X)(F23))/(W2)   /Eq.8/

$(\overset{\circ}{C1})$ = ((I)(CO) − (F13)(Y13)(C1) −
                            −(C1)(I) + (C1)(F13)(f13))/(W1)   /Eq.9/

$(\overset{\circ}{C2})$ = ((F12)(C1) − (F23)(Y23)(C3) −
                            − (C2)(F12) + (C2)(F23))/(W2)   /Eq.10/

$(\overset{\circ}{C3})$ = ((F13)(Y13)(C1) + (F23)(Y23)(C3)−(F35)(Y35)(C3) −
                            −(C3)(F13)(f13)−(C3)(F23)+(C3)(F35))/((W3)(v3))
                                                                /Eq.11/

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^X) = 0.5 and (r1) = (r2) = 0.5. Initial conditions were (W10)=(W20)=(W30)= 1 with corresponding constant compliances (q1) = 0.5, q(2)= =(q3)=1,the (P)s about 0.01 - 1 and finally the concentrations (CO^X)=3 and (CO)= 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 · (MW ·10^{-3})$^{-3/2}$ was satisfactory for MW $\gtrless$ (5200 to 300·10^3).In Tables I and II the Y-value becomes 0.23 for MW= 14·10^3.

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 = 70·10^3 , Y= 0.02). The Y formula is primarily assigned to the (1-3) compartment barrier (the arteriole capillary wall) as (Y13). (Y13^X) = 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= 14·10^3) 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
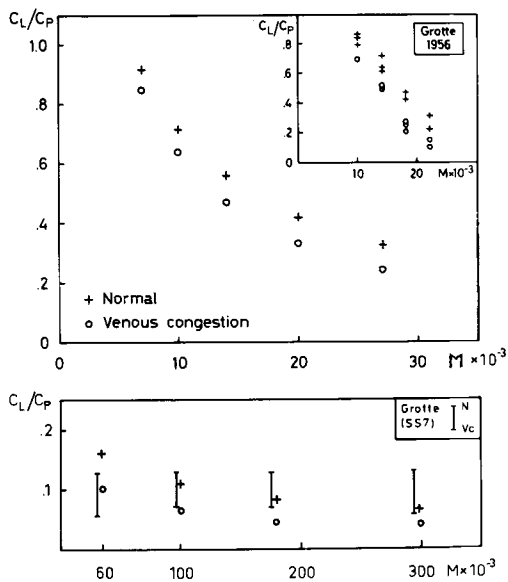
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Fig. 1

Table I. Values of parameters in normal conditions and venous congestion (parenthesis). M = $14 \cdot 10^3$. Steady state. $(CO^x)=3$, $(CO) = 3$.

Compartment →		(1) Art.		(2) Ven.		(3) Interstit.	
Pressure	(P)	4.26	(6.32)	1.28	(3.79)	0.87	(2.21)
Colloid -"-	(cp)	3.02	(3.54)	1.75	(2.36)	0.26	(0.16)
Volume	(W)	3.13	(4.16)	2.28	(4.79)	1.87	(3.20)
Conc.(coll.)	(C^x)	6.04	(7.08)	3.50	(4.72)	neglected	
-"- (test)	(C)	5.07	(5.63)	3.24	(3.96)	1.65	(1.40)

Sum of volumes	7.28	(12.16 = oedema)
Lymph flow	0.44	(1.11)
"C_L/C_p",(C3)/(CO)	0.55	(0.47)

Table II. Rates of bulk flow and solute transport (amount),"flux" in normal conditions and venous congestion (parenthesis).M= $14 \cdot 10^3$. Steady state.

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

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

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