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Review

Mathematical modeling of fluid and solute transport in hemodialysis and peritoneal dialysis

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Abstract

Renal replacement therapy involves the control of body pools of water and electrolytes, and removal of small metabolites (urea, creatinine). The correct estimation of "the dose of therapy" and optimization of the procedure needs quantification of fluid and solute transport during dialysis as well as evaluation of the distribution and exchange of water and solutes within the body through a complex system of membranes. Mathematical models can combine the general physiological knowledge with information about individual patients yielded by clinical measurements. Many of these models (urea model, sodium model, models of peritoneal transport) have been presented to the community of clinical nephrologists in the form of computer programs often supplemented with on-line measuring devices. However, the debate about their meaning and the search for better methods of their application are still lively. In this brief review, current approaches to modeling of transport processes in dialysis, including alternative and complementary versions, are described and discussed.

Keywords: Diffusion; Convection; Ultrafiltration; Osmosis; Kinetic models

Contents

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1. Introduction

Over one million patients worldwide can survive due to different forms of kidney replacement therapy, and the increase in the population of patients with end-stage renal disease (ESRD) is by 5–10% per year [1–3]. Treatment of these chronically ill patients requires a huge industrial and medical resources [2,4]. Economical aspects and patient's quality of life need to be adjusted as much as possible to medical indications for the treatment, and the importance of selection of optimal individualized treatment is obvious. Mathematical models are used for evaluation, optimization, and control of various forms of this therapy for both routine clinical applications and investigation of new issues that appear together with advanced technologies. Several sciences – medicine, physiology, biomedical engineering, informatics and mathematics – meet here to provide new solutions and ready-to-use products for physicians and scientists. The therapy induces sometimes dramatic changes in the internal milieu of the body, and this creates interesting (and sometimes troubling) questions about the response of the organism to interventions, which are far from physiological standards. Uremia and some other diseases (cardiovascular problems, diabetes, etc.) may modify this response, and its interpretation may be difficult because of pathological changes in the regulatory mechanisms.

In the present review a brief account of the most popular models is presented with the focus on basic ideas and aims behind the models as well as the relationship between models with different levels of sophistication. In general, there is a continuous search for balance between: (1) simplicity of the model, which is related to the often limited amount of available measurements and (2) its physiological precision and the need for providing more detailed information [5]. Informatics and new technologies may shift this balance towards more sophisticated and realistic models.

2. Fluid and solute transport through semipermeable membranes

The basic, phenomenological description of fluid and solute transport is usually based on linear non-equilibrium thermodynamics [6]. However, a few other approaches, which take into account the structure of membrane, were described [7], including the pore models that are widely used in physiology research and are now applied in peritoneal dialysis modeling [8].

2.1. Thermodynamic model

The fundamental Staverman–Kedem–Katchalsky–Spiegler approach from the 1960s is formulated in its current version as a local (at any point of a flat permselective membrane) set of equations for volume, J_V, and solute, J_S, fluxes (i.e. transport rates per unit area), which for a one-compound solution is as follows:

$$J_V = -l_P \left(\frac{dp}{dx} - \sigma RT \frac{dc}{dx} \right) \quad (1)$$

$$J_S = -p_d \frac{dc}{dx} + (1-\sigma) J_V c \quad (2)$$

where c is the concentration of the solute, p the hydrostatic pressure, l_p the hydraulic permeability of the membrane, σ the Staverman reflection coefficient, R the gas constant, T the absolute temperature, and p_d is the diffusive permeability of the membrane [9]. Eqs. (1) and (2) are formulated here for gradients perpendicular to the membrane surface (x direction), but their generalization is obvious [10].

If the membrane is flat and homogeneous, i.e. the local transport parameters, l_p, σ and p, are independent of the position within the membrane x, and the steady state of transport is assumed, i.e. J_V and J_S are independent of x, then Eqs. (1) and (2) may be integrated yielding [7,9,11]:

$$J_V = L_p(\Delta p - \sigma RT \Delta c) \quad (3)$$

$$J_S = P\Delta c + (1-\sigma) J_V c_m \quad (4)$$

where for a membrane of the width δ, $L_p = l_p/\delta$, $P = p_d/\delta$, Δp and Δc are the transmembrane differences of hydrostatic pressure and solute concentration, respectively, and c_m is the mean intramembrane concentration of the solute described as:

$$c_m = (1-f)c_1 + f c_2 \quad (5)$$

where c_1 and c_2 are the boundary values of the solute concentration, and:

$$f = \frac{1}{\lambda J_V} - \frac{1}{\exp(\lambda J_V) - 1}, \quad \lambda = \frac{1-\sigma}{P} \quad (6)$$

A non-dimensional parameter, $Pe = \lambda |J_V|$ is called the Peclet number and describes the relative importance of the convective versus the diffusive solute transport.

In the "practical" Kedem–Katchalsky approach to the thermodynamic description of solute transport, Eqs. (4)–(6), the solute flux, J_S, is a nonlinear function of volume flux, J_V, and the transport parameters, P and σ, see [11]. Nevertheless, the nonlinear Eq. (4) with f given by Eqs. (5) and (6) may be approximated by its linear analogue with factor f equal to a constant value F, which is selected according to the range of the Peclet number characteristic to the investigated problem [11]. The most widely used approximation is $F = 0.5$ for low values of Pe, $Pe < 1$ [11]. A useful approximation is $F = 0$ (formally for $Pe \gg 1$). For other applications of the linear descriptions J_S, see [11–19].

The original Kedem–Katchalsky formula for c_m with logarithmic mean of c_1 and c_2, $c_m = (c_1 - c_2)/\ln(c_1/c_2)$, was much

discussed and finally abandoned [6,11]; however, its real meaning has not been recognized. As shown in [11], this formula is a particular case of the linear approximations for J_S for the convective transport in the opposite direction than the diffusive transport ($J_V < 0$).

2.2. Pore model

The pore model originated from capillary physiology research in the 1950s, and has been applied in peritoneal dialysis modeling since 1980s [8,20,21]. The parameters used for the current description of the transport through a cylindrical pore are pore radius, r_P, pore length, Δx, Stokes radius of the solute, r_S (calculated from the solute molecular weight), and fluid viscosity, η. The restriction factor for diffusion is presented as the ratio of the effective surface area of the pore cross-section, a_{eff}, over its nominal surface area, $a_0 = \pi r_P^2$ [21]:

$$\frac{a_{eff}}{a_0} = \frac{(1-\alpha)^{9/2}}{1 - 0.395\alpha + 1.0616\alpha^2} \tag{7}$$

where $\alpha = r_S/r_P$. Thus, the pore diffusive permeability is given by the following formula [21]:

$$P = \frac{a_0}{\Delta x}\frac{a_{eff}}{a_0} D_W \tag{8}$$

where D_w is the diffusion coefficient for the solute in water, and a_{eff}/a_0 is given by Eq. (7). The retardation factor for convective solute transport is called the sieving coefficient, S (with $S = I - \sigma$, σ being the Staverman reflection coefficient), and may be calculated as [21]:

$$S = \frac{(1-\alpha)^2[2-(1-\alpha)^2](1-\alpha/3)}{1 - \alpha/3 + 2\alpha^2/3} \tag{9}$$

for $0 \le \alpha \le 1$. The pore hydraulic conductivity, l_P, of the pore is calculated as [21]:

$$l_P = \frac{a_0}{\Delta x}\frac{r_S^2}{8\eta} \tag{10}$$

Note that in the formulas for P, Eq. (8), and for l_P, Eq. (10), there is the same factor $a_0/\Delta x$. Multiplying P and l_P by the number of pores in the whole membrane one gets the global transport coefficients: diffusive mass transport coefficient, PS (permeability–surface area), and hydraulic permeability, L_PS, for the whole membrane. The effectiveness factors, a_{eff}/a_0 for diffusive transport, S for convective transport, and σ for osmotic fluid transport, are shown in Fig. 1.

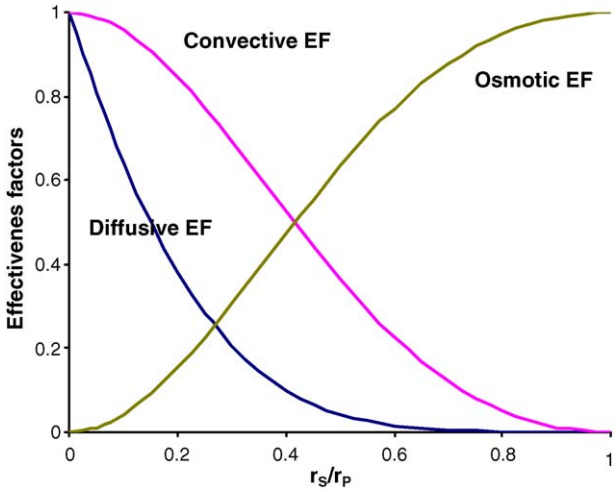

Fig. 1. Effectiveness factors calculated according to the pore model as a function of the ratio of molecular (Stokes) radius r_S to pore radius r_P. Diffusive effectiveness factor is given by a_{eff}/a_0, Eq. (7), convective effectiveness factor is equivalent to sieving coefficient S, Eq. (9), osmotic effectiveness factor is equivalent to Staverman reflection coefficient $\sigma = 1 - S$.

3. One-dimensional theory of hemodialyzer

The one-dimensional theory of solute transport in hemodialyzer was described in 1981 [22], and then applied in many studies [13,15,23–27]. It provides a simplified description of solute flows in blood and dialysate channels, assuming that the average concentration of the solute in any cross-section of the channel, C_B and C_D, respectively, is equal to the concentration of the solute at the surface of the membrane. This theory works well for the transport of small solutes [15,28]. For middle molecules, a more sophisticated theory with the boundary layers close to the membrane, was elaborated and tested [29,30].

3.1. Transport equations

The flows of solute in blood and dialysate channels in the counter-current system are described by ordinary differential equations [31], which may be derived using the mass balance in the infinitesimal slice from x to $x + dx$:

$$\frac{d(Q_B C_B)}{dx} = -J_S A, \qquad \frac{d(Q_D C_D)}{dx} = -J_S A \tag{11}$$

where Q_B and Q_D are the rates of volume flows of blood and dialysate, respectively. The variable x describes the normalized distance from the inlet of blood flow into the part of the hemodialyzer, where effective fluid and solute transmembrane exchange occurs [31], i.e. x is equal to the real distance over the total length of the transport-active part of the hemodialyzer, and A is the total surface area of the permselective membrane. The solute flux, J_S, at x is described by the thermodynamic theory of the membrane transport, cf. Section 2.1:

$$J_S = P(C_B - C_D) + (1-\sigma)J_V C_m \tag{12}$$

and various versions of Eq. (5) for C_m.

The equations of the one-dimensional theory, Eq. (11), depend on only one geometrical parameter of the hemodialyzer—the total surface area of the membrane, A, but not on the length or diameter of its hollow fibers. This feature of the theory is a consequence of the assumptions applied, especially that the distribution of solute concentration in the cross-section of the channels is neglected.

Eqs. (11) and (12) may be solved if the rates of volume flows, Q_B and Q_D, are known as functions of x. Usually, a constant (independent on x) ultrafiltration flux is assumed, and there-

fore, for the counter-current flow system: $Q_B(x) = Q_{Bi} - Q_u x$ and $Q_D(x) = Q_{Di} - Q_u x$ where Q_{Bi} and Q_{Di} are the inlet values of Q_B and Q_D, respectively, and $Q_u = J_V A$ is the rate of ultrafiltration flow [13,15,27]. Nevertheless, Eq. (11) may be solved for any distribution of the ultrafiltration in the dialyzer. The general solution may be presented in an integral form with the integrals calculated numerically, and for special cases analytical solutions may be found [13,15,27]. The mathematical background of the general one-dimensional theory of hemodialyzer is presented in [31]. This theory may be also applied for the description of hemofilters or other devices based on the filtration process, as plasma filters, etc., as described in [32–35].

3.2. Clearance and transmittance coefficient

The concept of clearance, a parameter describing solute removal from the body, originates from renal physiology in the 1950s [36]. The definition of clearance, K, of a solute from blood to dialysate, assuming that its concentration in the inflowing dialysate, C_{Di}, is zero, is:

$$K = \frac{Q_{Bo}C_{Bo} - Q_{Bi}C_{Bi}}{C_{Bi}} \tag{13}$$

where Q_{Bi} and C_{Bi} are Q_B and C_B at the inlet to the hemodialyzer, respectively.

Ultrafiltration from blood to dialysate, Q_u, enhances diffusive solute transport from blood to dialysate and the clearance of the hemodialyzer, K, may be described as:

$$K = K_0 + \mathrm{Tr}\, Q_u \tag{14}$$

where K_0 is the diffusive clearance for $Q_u = 0$ and Tr is the so-called transmittance coefficient [27,37].

The one-dimensional theory yields that:

$$K_0 = Q_B \frac{\exp(\gamma) - 1}{\exp(\gamma) - Q_B/Q_D} \tag{15}$$

for $Q_B \neq Q_D$, where $\gamma = \mathrm{PA}(1/Q_B - 1/Q_D)$.

The total membrane permeability, PA, i.e. the permeability of the membrane together with the boundary fluid layers, may be estimated using a measured value of K_0 and Eq. (15), whereas the Staverman reflection coefficient, σ, is usually assessed assuming that PA is known, for example, from the value of K_0, and using a value of the sieving coefficient of the filter, $S = C_F/C_{Bi}$, where C_F is the solute concentration in filtrate, measured in an isolated ultrafiltration experiment with $Q_{Di} = 0$, and the following equation [15]:

$$S = \frac{1 + (1-\sigma)(1-f)\frac{Q_u}{\mathrm{PA}}}{1 + [1-(1-\sigma)f]\frac{Q_u}{\mathrm{PA}}} \tag{16}$$

where f is the function of the Peclet number, Eq. (6), or a constants F, $0 \le F \le 1$.

The dependence of K on Q_u in the one-dimensional theory is slightly nonlinear for the standard hemodialysis conditions, but may be considered as a linear one with high accuracy [27]. This linearity was confirmed experimentally for the hollow fiber hemodialyzers [27]. Therefore, the transmittance coefficients, Tr, may be assumed to be independent of Q_u and depend mainly on the membrane parameters, P, σ and A, and the flow rates Q_{Bi} and Q_{Di}. Tr may be assessed with the measurements of K_0 and K for at least one value of $Q_u > 0$ using the following equation:

$$\mathrm{Tr} = \frac{K - K_0}{Q_u} \tag{17}$$

If K is measured for a few different values of Q_u, then linear regression may be applied for the estimation of Tr [27].

The one-dimensional theory of the hemodialyzer provides the solution in the integral form, but for special cases (e.g. $Q_u = 0$ or $\sigma = 0$) analytical formulae have been found. Some of these formulae may also be used as an approximate description for other parameter values, for example the following approximate formula for K may be applied for any value of $Q_u > 0$ and σ, $0 \le \sigma \le 1$, and for typical conditions of hemodialysis [15,27]:

$$K = Q_{Bi} \frac{1 - \frac{Q_{Do}}{Q_{Di}}\frac{Q_{Bo}}{Q_{Bi}}Z}{1 - \frac{Q_{Bo}}{Q_{Di}}Z} \tag{18}$$

with

$$Z = \left(1 - \frac{Q_u}{Q_{Bi}}\right)^{(p/Q_u)-1} \left(1 - \frac{Q_u}{Q_{Do}}\right)^{-(p/Q_u - 1)} \tag{19}$$

and $p = \mathrm{PA} + (1-\sigma)(1-f)Q_u$, where f is the function of the Peclet number, Eq. (6), or a constant F, $0 \le F \le 1$. Similar formulas may be used for back-clearance and back-transmittance coefficient in the case of solute transport from dialysis fluid to blood against the ultrafiltration flow from blood to dialysis fluid [13].

This theory was extended to include the equations for flow rates of blood and dialysis fluid and the boundary layers for solute transport in blood and dialysis fluid channels [29]. Thus, it can be applied for high ultrafiltration rates. Nevertheless, the accuracy of the extended model was not higher than the presented here one, even for middle molecules [30].

4. Kinetic modeling in hemodialysis

In hemodialysis blood flows through an extracorporeal circuit and is cleaned in dialyzers made of synthetic permselective membrane that separates blood from dialysis fluid [38,39]. The treatment is short, typically 4 h, and has to be repeated every 2 or 3 days. The marked changes of plasma concentration of small metabolites (urea, creatinine), which occur during hemodialysis and inter-dialysis periods are calculated by mathematical modeling and fitted to measured values. This allows for the estimation of adequacy and nutrition indices. The definition and validation of "adequate dialysis dose" (i.e. the amount of these solutes that should be removed during dialysis) are hotly debated [40–47].

4.1. Urea kinetic modeling

Extensive clinical studies on removal of small metabolites during the treatment yielded "urea *KT/V* paradigm"—a method for simple quantification of dialysis dose and guidelines for its

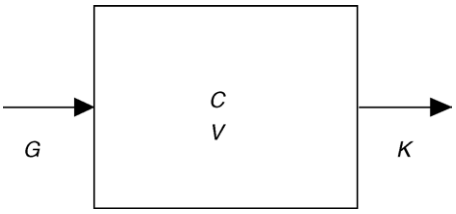

Fig. 2. One compartment urea model. V: total water volume; C: urea concentration; G: rate of urea generation; K: urea clearance.

minimal value. A simple one compartment mathematical model (Fig. 2, Eq. (20)) allows for estimation of KT/V parameter.

For one compartment of urea distribution in total body water volume, V, the mathematical description of the balance of total urea mass is [38,48]:

$$\frac{\mathrm{d}(VC)}{\mathrm{d}t} = G - KC \tag{20}$$

with the following solution:

$$C(t) = C_0\,\mathrm{e}^{-Kt/V} + \frac{G}{K}(1 - \mathrm{e}^{-Kt/V}) \tag{21}$$

The clearance of urea K is equal to dialyzer clearance plus residual renal clearance during dialysis and to the residual renal clearance of the patient between dialyses. The ratio G/K is small during dialysis, and the final urea concentration after dialysis depends basically on one lumped parameter KT/V, see Eq. (21), where T is dialysis time. KT/V was shown to correlate well with morbidity and mortality on the base of extended clinical investigations in USA called National Cooperative Dialysis Study [38,49,50]. However, when the improved equipment allowed for much faster removal of small metabolites, the simple model had to be replaced by a more complex two compartment one (Fig. 3, Eq. (22)) with variable total body water, which could not be easily solved [38]. Its implementation into computers, which at that time started to be used for treatment planning and monitoring of artificial kidney machine, made it possible to continue modeling for all available treatment schedules. "KT/V" is nowadays the basic parameter to prescribe the "dose" of dialysis (clearance K, time of dialysis T) for individual patients (represented by their total body water volume V). The clearance depends on the choice of hemodialyzer and operating conditions of dialysis (blood and dialysate flows, ultrafiltration rate), and it can be predicted on the base of a mathematical model of dialyzer performance, see Section 3.2.

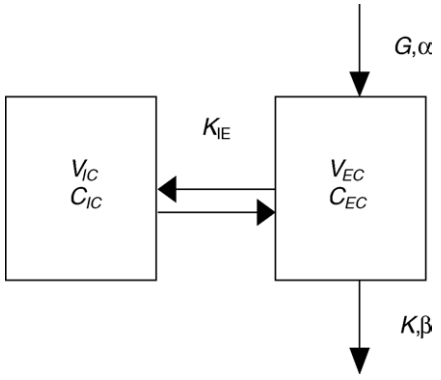

Fig. 3. Two compartment urea model. K_{IE}: diffusive mass transport coefficient for urea, α: rate of fluid intake, β: rate of ultrafiltration during dialysis, other symbols as in Fig. 2; subscripts: IC: intracellular compartment, EC: extracellular compartment.

The equations for the two compartment urea model are [38,51]:

$$\frac{\mathrm{d}(V_{\mathrm{EC}}C_{\mathrm{EC}})}{\mathrm{d}t} = G - KC_{\mathrm{EC}} + K_{\mathrm{IE}}(C_{\mathrm{IC}} - C_{\mathrm{EC}}),$$
$$\frac{\mathrm{d}(V_{\mathrm{IC}}C_{\mathrm{IC}})}{\mathrm{d}t} = -K_{\mathrm{IE}}(C_{\mathrm{IC}} - C_{\mathrm{EC}}) \tag{22}$$

where $V(t) = V(0) + (\alpha - \beta)t$, $V = V_{\mathrm{IC}} + V_{\mathrm{EC}}$. The model is able to describe not only a non-exponential decay of urea concentration during dialysis, but also the phenomenon of urea rebound—the fast increase of urea concentration after dialysis because of disequilibrium between the compartments [38,51]. Both (one and two compartment) models can also provide the urea generation rate G, which is an important indicator of patient's nutritional status [38,51].

The newest studies rose however some problems concerning the interpretation of the model and its clinical significance. In particular, an alternative model was proposed to explain the discrepancies between one compartment urea model and clinical data [52,53]. This new model proposed the discrimination between organs with high and low blood perfusion, and it was shown to yield the same numerical description of urea removal as the standard two compartment urea model. So far, it is not possible to get any definitive answer for the basic physiological mechanisms for urea transport in the body during dialysis.

Furthermore, although the National Cooperative Dialysis Study helped to establish the minimum value of the adequacy parameter KT/V, the new studies on the problem of dialysis dose did not find any benefit from increased level of KT/V over the currently accepted minimal value for patients on hemodialysis or peritoneal dialysis [54,55]. These observations have increased interest in alternative dialysis adequacy parameters, as fractional solute removal and equivalent renal clearance [42,56]. The search for new adequacy parameters is motivated also by the need to compare the adequacy of different treatment modalities and schedules [47].

4.2. Sodium modelling

One important aim of the artificial kidney is the removal of excess of water and regulation of the ion content of the body [38,57,58]. Overhydration was recently shown to correlate negatively with patient survival [59], and the adequacy of ultrafiltration is therefore an important topic in dialysis treatment. The fast short hemodialysis treatments, and the high rate of water removal, increase the prevalence of adverse reactions in patients (nausea, headache, muscle cramps), which are, at least in part, caused by the lack of similarly fast refilling of plasma volume from other fluid compartments in the body and inter compartment osmotic disequilibrium [60]. Sodium is a potent osmotic regulator of water distribution within the body [57,61].

Therefore, a method of sodium load into the extracellular compartment at the beginning of dialysis and its increased removal at the end was proposed with the aim to increase the initial refilling rate from the intracellular compartment and keep the sodium concentration low after the treatment (to avoid thirst). Mathematical modeling was necessary to guarantee the appropriate manipulations of sodium concentration [62]. The basic idea is to make use of high osmotic effectiveness of sodium and load it from dialysis fluid to blood by diffusion due to increased sodium concentration in dialysis fluid. Then, sodium induces water flow from intracellular to extracellular compartment, and therefore inflow of water to blood, which counteracts fast decrease of blood volume due to ultrafiltration in hemodialyzer.

However, the final sodium concentration in plasma has to be reduced to a physiological level, and therefore the sodium concentration in dialysis fluid has to be low during the last period of hemodialysis. Some kidney machines are now equipped with computer controlled ultrafiltration and sodium profiling based on the mathematical model of fluid and sodium transport and distribution. Although a few clinical studies demonstrated the usefulness of the sodium model in reducing hypotension related morbidity, there has not been any large scale clinical evaluation of the model yet.

The control of intercompartmental water flow and sodium concentration enables a simple mathematical model, called "sodium model" [62–66].

4.3. Sodium distribution in the body

The kinetics of water and sodium transport in the body should be described by a two compartment model for the compartments of extracellular water (with volume V_{EC}) and intracellular water (with volume V_{IC}) [67] (Fig. 4).

In typical problems, the small change of small amount of intracellular sodium may be neglected. Therefore, the extracellular water may be considered as a representative compartment of interchangeable sodium. On the other hand, the removal of water by ultrafiltration comes from the total water space $V = V_{IC} + V_{EC}$. Thus, the equations for the removal of water and sodium are:

$$\frac{dV}{dt} = -Q_F \tag{23}$$

$$\frac{d(C_{NaEC} V_{EC})}{dt} = -Q_{Na} \tag{24}$$

where Q_F is the ultrafiltration flow, C_{NaEC} the sodium concentration in extracellular water (equal to sodium concentration in plasma water), and Q_{Na} is the flow of sodium removed from blood in dialyzer.

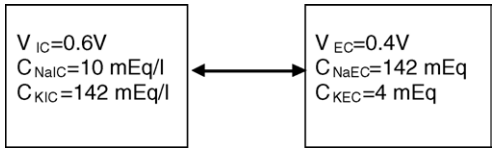

Fig. 4. Typical values of volumes and concentrations of sodium (Na) and potassium (K) for compartments of intra (IC) – and extra (EC) – cellular water.

The three variables V, V_{EC}, C in two Eqs. (23) and (24) need to be related by an additional constraint.

4.4. Theoretical foundations of one compartment sodium model

The modeling of water and sodium kinetics is much simplified because of an empirical fact that the change of sodium amount in the body $Na = C_{NaEC} V_{EC}$ (see above) is approximately equal to the change of the sodium concentration in plasma water multiplied by the total water volume in the body, i.e.:

$$\Delta(C_{NaCE} V_{EC}) = \Delta(C_{NaCE} V) \tag{25}$$

This rule may be derived from the following assumptions, which provide a simplified description of the osmotic water equilibrium in the body [38,68–70]:

(A1) The only osmotically active cation in extracellular water is sodium, whereas in intracellular water–potassium.
(A2) Water transport through the cell membrane is very fast, and therefore the osmotic equilibrium in the body is maintained continuously. Net transport of sodium and potassium through the cell membrane is negligible.
(A3) The change of potassium amount in the body during dialysis is negligible.

Thus, assumptions (Al) and (A2) yield that in the osmotic equilibrium sodium concentration in extracellular water C_{NaEC} and potassium concentration in intracellular water are equal C_{KIC}:

$$C_{NaEC} = \frac{Na}{V_{EC}} = \frac{K}{V_{IC}} = C_{KIC} \tag{26}$$

It follows from Eq. (26) that:

$$Na V_{IC} = K V_{EC} \tag{27}$$

and, from Eq. (27):

$$\frac{Na}{V_{EC}} = \frac{Na}{V_{EC}} \frac{V_{EC} + V_{IC}}{V} = \frac{Na V_{EC} + Na V_{IC}}{V_{EC} V} = \frac{Na V_{EC} + K V_{EC}}{V_{EC} V} = \frac{Na + K}{V} \tag{28}$$

where the one but last equality comes from Eq. (27). Eq. (28) states that sodium concentration in extracellular water is equal to the total amount of osmotically active cations divided by the total water volume. This is an important physiological fact confirmed by clinical studies [38,68].

Eq. (28) yields:

$$C_{NaEC} V = Na + K \tag{29}$$

and, from assumption (A3):

$$\Delta(C_{NaEC} V_{EC}) = \Delta Na = \Delta(C_{NaEC} V) \tag{30}$$

i.e. Eq. (25). Thus, Eq. (24) may be written as:

$$\frac{\mathrm{d}(C_{\mathrm{NaEC}}V)}{\mathrm{d}t} = -Q_{\mathrm{Na}} \tag{31}$$

The system of two Eqs. (23) and (31) allows for modeling of water and sodium transport during dialysis.

Note also that from definition of concentration C_{NaEC} and Eq. (27) it follows that:

$$C_{\mathrm{NaEC}}V_{\mathrm{IC}} = \frac{\mathrm{Na}}{V_{\mathrm{EC}}}V_{\mathrm{IC}} = K \tag{32}$$

and, by assumption (Z3), that $C_{\mathrm{NaEC}}V_{\mathrm{IC}}$ = const during dialysis. This law was confirmed by Kimura et al. [68], and may be used for estimation of the change of intracellular water volume using measured sodium concentration in plasma water:

$$\frac{V_{\mathrm{IC}}(t)}{V_{\mathrm{IC}}(0)} = \frac{C_{\mathrm{NaEC}}(0)}{C_{\mathrm{NaEC}}(t)} \tag{33}$$

In particular, to remove water from intracellular space one needs to increase sodium concentration in extracellular space, and vice versa, the decrease of sodium concentration in extracellular space results in decrease of extracellular water volume due to water flow to intracellular space.

4.5. Practical applications of sodium modeling

The rate of sodium transport in dialyzer, Q_{Na}, may described as follows:

$$Q_{\mathrm{Na}} = D(\alpha C_{\mathrm{Bin}} - C_{\mathrm{Din}}) + C_{\mathrm{Bin}}Q_{\mathrm{F}} \tag{34}$$

where D is the sodium dialyzans, α the Donnan factor for sodium, and C_{Bin} denotes sodium concentration in plasma water. Assuming a linear function for the change of body water (i.e. constant Q_{F}), solution of Eqs. (23), (31) and (34), can be derived

$$C(t) = \frac{1}{\alpha}C_{\mathrm{Din}} + \left(C_0 - \frac{1}{\alpha}C_{\mathrm{Din}}\right)F(t)^{\alpha D/Q_{\mathrm{F}}} \tag{35}$$

with $F(t)$ defined as:

$$F(t) = 1 + \frac{Q_{\mathrm{F}}}{V_0}t \tag{36}$$

Eq. (35) may be used for calculation of sodium concentration in dialysis fluid, C_{Din}, to change the known sodium concentration in plasma water, C_0, at some time denoted $t = 0$, to a desired concentration C_T, at some time denoted $t = T$:

$$C_{\mathrm{Din}} = \alpha\frac{C_T - C_0F(T)^{\alpha D/Q_{\mathrm{F}}}}{1 - F(T)^{\alpha D/Q_{\mathrm{F}}}} \tag{37}$$

Thus, during the initial phase of dialysis, sodium concentration in dialysis fluid may be increased to accelerate the removal of water from intracellular compartment and decrease the rate of blood volume change. Next, during the final phase of dialysis, sodium concentration in dialysis fluid may be decreased to avoid hypernatremia after dialysis.

4.6. Two compartment model for water transport during hemodialysis

The model presented above (Sections 4.1–4.3) was based on simplifying assumptions. A more sophisticated model was also formulated for the application in hemodialysis with the finite rate of water transport through the cell wall and possible osmotically active solutes other than sodium, for example urea, which is removed at high rate during dialysis, or mannitol, which may be infused to a vein to decrease side effects of fast dialysis [38]. Thus, the equations describe sodium and some other osmotic agent with concentration C_{In}:

$$\begin{aligned}\frac{\mathrm{d}V_{\mathrm{EC}}}{\mathrm{d}t} &= K_{\mathrm{F}}(C_{\mathrm{OsIE}} - C_{\mathrm{OsEC}}) + Q_{\mathrm{F}},\\ \frac{\mathrm{d}V_{\mathrm{IC}}}{\mathrm{d}t} &= K_{\mathrm{F}}(C_{\mathrm{OsIC}} - C_{\mathrm{OsEC}})\end{aligned} \tag{38}$$

$$\frac{\mathrm{d}(C_{\mathrm{Na}}V_{\mathrm{EC}})}{\mathrm{d}t} = -Q_{\mathrm{Na}} \tag{39}$$

$$\begin{aligned}&\frac{\mathrm{d}(V_{\mathrm{EC}}C_{\mathrm{InEC}})}{\mathrm{d}t}\\ &\quad = G - K_{\mathrm{R}}C_{\mathrm{InEC}} + K_{\mathrm{IE}}(C_{\mathrm{InIC}} - C_{\mathrm{InEC}}) - K_{\mathrm{D}}C_{\mathrm{InEC}},\\ &\frac{\mathrm{d}(V_{\mathrm{IC}}C_{\mathrm{InIC}})}{\mathrm{d}t} = -K_{\mathrm{IE}}(C_{\mathrm{InIC}} - C_{\mathrm{InEC}})\end{aligned} \tag{40}$$

where K_{F} is the water transport parameter for water transport through the cell membrane, C_{Os} is the average concentration of all osmotically active solutes, Q_{Na} is described by formula (34), C_{Na} and C_{In} are the concentrations of sodium and the additional osmotic agent, respectively.

5. Models of peritoneal transport

Peritoneal dialysis is a modality of the renal replacement therapy that uses physiological mechanisms of solute and fluid transport between blood in abdominal organs and dialysis fluid infused through a catheter into the peritoneal cavity [71]. The most popular form of peritoneal dialysis is continuous ambulatory peritoneal dialysis (CAPD), with consecutive four exchanges of dialysis fluid per day and about 6-h dwell time each, carried out by patients themselves. The removal of water is achieved by the application of an osmotic agent (a solute, typically glucose, added at high concentration to dialysis fluid) that creates high osmotic pressure in the peritoneal cavity and the inflow of water from blood. The problems of the quantification of dialysis dose and the distribution and transport of water and various solutes in the body are as important for peritoneal dialysis as for hemodialysis. However, at least in CAPD with its continuous treatment, the system is close to the steady state and therefore the quantification of water and solute removal is rather simple. In contrast to hemodialysis, where the removal occurs in artificially constructed filter with well known and practically constant characteristics that may be investigated in vitro, the transport of water and solutes during peritoneal dialysis occurs within the highly

dynamical system of blood capillaries and tissue of abdominal organs [71,72]. Here, the investigation of the transport system and its changes during the therapy is carried out with the application of mathematical models and clinically available methods of measurements. Again, widely available computer programs based on mathematical models have made such studies possible for many clinical investigators [73,74].

The transport of fluid and solutes during peritoneal dialysis is complicated due to several different transport processes occurring simultaneously and driven by different thermodynamic forces within the complex structure that consists of blood capillaries, cells and interstitium [21,71,75,76]. Simple clinical methods allow for evaluation of the overall result of all these processes. However, to separate and study the role of individual transport components and specific structural elements of the system one needs mathematical models combined with clinical studies that are more sophisticated than routine evaluation. Some problems in peritoneal transport may be studied only using animal experiments. Mathematical modeling may help in analyzing peritoneal transport in four respects [76]: (1) separation of peritoneal transport components, as water ultrafiltration from blood and absorption to tissue in fluid transport, and diffusion, convective transport with ultrafiltrate, and bulk absorption with absorbed fluid, for solute transport, (2) quantitative correlation between flows and their driving forces, which are: osmotic pressure for fluid ultrafiltration, hydrostatic pressure for fluid absorption, concentration gradient for solute diffusion, ultrafiltrate flow for convective solute transport, and absorptive fluid flow for solute absorption; the correlations are described by the so called transport parameters, (3) quantitative relationship between the transport parameters for various solutes and between fluid and solute transport parameters, and (4) quantitative relationship between the structure and physiological state of peritoneal tissue and its transport characteristics. According to these four aspects of modeling the three main models are applied for the evaluation of peritoneal transport: the membrane model for objectives 1 and 2, the three-pore model for objective 3, and the distributed model for objective 4. Below we discuss briefly these models. They are of more or less phenomenological character and attempt to provide an effective mathematical description of experimental data rather than theoretical derivation of the description from detailed structure of the system.

5.1. Kinetics of fluid and solute transport during peritoneal dialysis

The common basis for all models of peritoneal transport is the fluid volume and solute mass balance in the peritoneal cavity [21,31,71,76]:

$$\frac{dV_D}{dt} = Q_V, \qquad \frac{d(V_D C_D)}{dt} = Q_S \tag{41}$$

where V_D and C_D are the volume of dialysis fluid and solute concentration in the peritoneal cavity, respectively, and Q_V and Q_S are fluid and solute flows through the tissue surface to the peritoneal cavity. The description of these flows depends on the choice of the model of peritoneal transport.

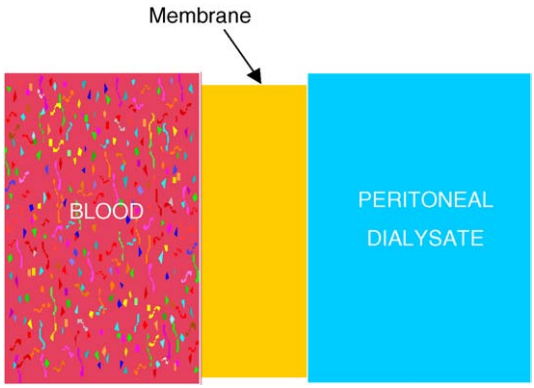

Fig. 5. Schematic presentation of the assumptions for the membrane model that describes diffusive and convective transport processes through a permselective membrane between two well-mixed compartments for blood and peritoneal dialysate.

5.2. Membrane model

The membrane model provides a simple relationship between the rates of fluid and solute flows and their respective driving forces. It is derived from linear non-equilibrium thermodynamics for the case of two well-mixed compartments, blood and dialysis fluid, separated by a permselective membrane, see Fig. 5.

The net rate of fluid transport to the peritoneal cavity depends basically on three factors: (1) osmotic pressure difference between dialysis fluid and blood plasma, (2) hydrostatic pressure difference between dialysis fluid and blood plasma, and (3) absorption of dialysis fluid to the tissue and lymphatic vessels. The net rate of peritoneal dialysate volume change, Q_V, may be described according to the thermodynamically based membrane model by the following equation [76,77]:

$$Q_V = L_{PA}\left(\Delta P - \sum_i \sigma_i \Delta \Pi_i\right) - Q_A \tag{42}$$

where L_{PA} is the total hydraulic permeability of the membrane; $\Delta P = P_B - P_D$ is the difference between blood hydrostatic pressure, P_B, and peritoneal dialysate hydrostatic pressure, P_D; $\Delta \Pi_i$ is the osmotic pressure difference between blood and dialysis fluid for ith solute, the subscript "i" denotes various osmotically active solutes in blood and peritoneal dialysate, C_{iB} and C_{iD} are the plasma and the dialysate concentrations of the ith solute, respectively; σ_i is the Staverman reflection coefficient for ith solute; and, Q_A is the rate of peritoneal absorptive flow of dialysis fluid. For practical applications a few simplified formulae for fluid flow have been proposed [77].

The rate of solute flow between blood and dialysis fluid may be described as the sum of three terms: (1) the rate of diffusive flow, which is proportional to the difference of solute concentration in blood and dialysis fluid, $C_B - C_D$, with the coefficient of proportionality called the diffusive mass transport coefficient, K_{BD}, (2) the rate of convective solute flow due to ultrafiltration, which is proportional to the rate of ultrafiltration, Q_U, and a weighted mean of solute concentrations in blood and in dialysis fluid C_M, with the coefficient of proportionality S called the sieving coefficient, and (3) the rate of bulk absorption together

with absorbed fluid, which is equal to the rate of fluid absorption, Q_A, times solute concentration in dialysis fluid, C_D. Thus, the solute flow rate, Q_S, is described as [31,73,76,78]:

$$Q_S = K_{BD}(C_B - C_D) + SQ_U C_M - Q_A C_D \quad (43)$$

There are alternative versions of the model, which differ mainly in the description of the convective transport component [31,73,76,78].

To estimate the transport parameters for the membrane model using Eqs. (41)–(43) one needs to know the dialysis fluid volume and solute concentrations in dialysis fluid and blood versus dwell time. Sampling of dialysis fluid through the catheter is used for the assessment of solute concentration. The estimation of dialysis fluid volume needs a more sophisticated method. The application of a macromolecular volume marker and the dilution principle with a correction for absorption the marker was proposed for this purpose [79]. However, because markers are radioactively labeled (albumin) or difficult to measure (dextran) the evaluation of dialysate volume kinetics is carried out in a few research centers only. Therefore, some approximate methods for estimation of solute transport parameters were also applied [21,31].

The transport parameters are usually assumed to be constant during a dwell study. However, at least for some of dialysis fluids, as for example for the standard glucose-based fluids, the values of K_{BD} for small solutes were found to be higher at the beginning of the dwell than during its later part [78,80]. A typical function may be described as:

$$\frac{K_{BD}(t)}{K_{BDS}} = 1 + 0.6875 \exp\left(-\frac{t}{50}\right) \quad (44)$$

where K_{BDS} is the steady state value of K_{BD} reached after about 4 h of the peritoneal dwell [81]. A possible reason for this inflation of K_{BD} may be a vasodilation of the vascular bed by vasoactive factors in dialysis fluid [81,82].

Using the membrane model one may estimate transport parameters separately for water and each solute of interest. However, a relationship between these parameters for different solutes and water should exist and be derivable from the solute size and the structure of the tissues involved in the transport processes. A simple example of such correlations is provided by the pore model.

5.3. Three-pore model

The pore model is based on a concept of the transport through a cylindrical uniform pore across the membrane [21,83]. Solute and fluid transport through the pore is evaluated using the hydrodynamic theory of fluid flow along a cylindrical pipe and diffusion and convective drag of spherical molecules along the pore. The theory provides algebraic, simplified formulae for the so called restriction factors for diffusive and convective solute transport, which describe how much the solute transport is retarded due to the presence of the pore wall comparing to free transport in unrestricted medium. The equations for water and solute transport are the same as for the membrane model,

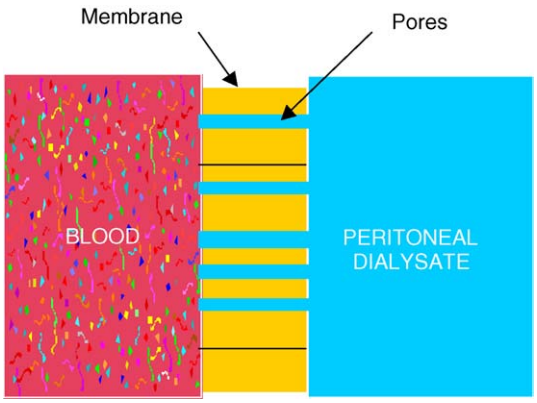

Fig. 6. Schematic presentation of the three-pore model for the membrane separating blood and dialysis fluid compartments with pores of different cross-section surface area.

Eqs. (41)–(43), with the transport parameters calculated from the number and size of the pores.

To describe the peritoneal transport it was necessary to consider a heteroporous structure of the peritoneal membrane with three types of pores [21,76,83]: large pores of radius about 250–300 Å, small pores of radius about 40–50 Å, and ultrasmall pores of radius about 2–4 Å, see Fig. 6. Ultrasmall pores are not permeable for any solutes except water. Hydraulic conductivity of the ultrasmall pores is about 1–2% of the total hydraulic conductivity. Large pores play an important role in the transport of macromolecules (of the size of albumin and larger) mainly by convective flow. Small pores are the main routes for the exchange of small and middle molecules by diffusion and convection. Osmotically driven water flow passes small and ultrasmall pores. The number of large pores is about 12 500 times lower than the number of small pores.

The data about the structure and number of equivalent pores may be obtained by the analysis of fluid and solute transport in peritoneal dialysis. An interesting method for evaluation of patient's peritoneal membrane – Peritoreal Dialysis Capacity – has been designed on the base of the three-pore model and a set of data selected because of their clinical availability [74,83]. Although the three-pore model is currently widely used it misses one important feature of the peritoneal transport system: blood does not form a compartment but flows in capillaries.

The estimation of transport parameters for small solutes, including sodium, may be performed using the called membrane model of peritoneal transport [12]. The membrane model is a "black box" model, which may provide information about the transport of fluid and each solute separately, but the interpretation of transport parameters needs a more sophisticated description, as the three-pore model and the distributed model [21,84]. An illustration of such relationships between the parameters of different models of the same phenomenon can be found in the problem of free water transport and the interpretation of sieving coefficient, estimated by the membrane model, using the three-pore model.

According to the three-pore model, the transport of fluid through the peritoneal transport barrier can be described as a flow through a heteroporous membrane with three types of

pores: (1) large pores, (2) small pores, and (3) ultrasmall pores, arranged in parallel pathways. For our discussion it is important that ultrasmall pores are permeable only for water molecules, and therefore sieving coefficient for any, even small solutes as sodium, is zero. On the other hand, large and small pores permit the almost unrestricted passage of small molecules, as sodium ions, and the sieving coefficient for sodium in large and small pores is close to one. Thus, the fluid flow rate, Q_V, may be described as:

$$Q_V = Q_{V,large} + Q_{V,small} + Q_{V,ultrasmall} \quad (45)$$

and the rate of convective component of sodium transport, Q_{conv}, as:

$$Q_{conv} = S_{large} Q_{V,large} C_B + S_{small} Q_{V,small} C_B + S_{ultrasmall} Q_{V,ultrasmall} C_B \quad (46)$$

where the subscripts large, small and ultrasmall refer to the characteristics of the large, small and ultrasmall pores, respectively, and C_B is the concentration of sodium in plasma water. For sodium, $S_{large} \cong S_{small} \cong 1$, $S_{ultrasmall} = 0$.

Sieving coefficient, S, in the membrane model is defined by the equation:

$$Q_{conv} = S Q_V C_B \quad (47)$$

Thus, for sodium:

$$S = \frac{Q_{V,large} + Q_{V,small}}{Q_V} \quad (48)$$

The interpretation of sieving coefficient for sodium by the three-pore model is that S is a fraction of water flow that passes through small and large pores. Furthermore:

$$1 - S = \frac{Q_{V,ultrasmall}}{Q_V} \quad (49)$$

The quotient $Q_{V,ultrasmall}/Q_V$ describes the fraction of flow that passes through the ultrasmall pores and does not carry any solutes, i.e. is free of solutes. Therefore, this fraction may be called the free water fraction, FWF, and:

$$FWF = 1 - S \quad (50)$$

Thus, the estimation of sieving coefficient for sodium using the membrane model allows, according to the three-pore model, for the calculation of the free water fraction. Recently, some new modified methods for the assessment of FWF were also proposed [85,86].

Using the previous data about the transport parameters for sodium [12,14,87], we find the respective values of FWF, see Table 1. The values of S shown in Table 1 were obtained by the concomitant estimation of the diffusive mass transport parameters, K_{BD}, and sieving coefficient, S, using a mathematical model of solute transport in peritoneal dialysis, Eq. (43) with $C_M = C_B$, and two parameter linear regression [12]. Next, FWF was calculated using Eq. (50). The results demonstrate that FWF does not depend on the (crystalloid) osmotic agent used in dialysis fluid, at least if the high (equivalent to glucose 3.86%) concentration is used (Table 1). For glucose-based dialysis fluids no dependence of FWF on glucose concentration was found; nevertheless, there is some tendency for lower FWF if the initial glucose concentration is lower (Table 1). FWF, estimated for different time intervals within one dwell study, was found substantially lower during the final 4 h than during the initial 2 h of the dwell study (Table 1).

Table 1
Sieving coefficient, S, for sodium, estimated using the modified Babb–Randerson–Farrell model, and free water fraction, FWF, for different dialysis fluid tonicities, osmotic agents, and dwell periods

	Sieving coefficient, S	Free water fraction FWF = 1 − S
Tonicity [12]		
Glucose 1.36%, $n = 9$	0.71 ± 0.12	0.29 ± 0.12
Glucose 2.27%, $n = 9$	0.61 ± 0.11	0.39 ± 0.11
Glucose 3.86%, $n = 20$	0.57 ± 0.10	0.43 ± 0.10
Osmotic agent[a] [14]		
Glycerol 2.50%, $n = 4$	0.50 ± 0.11	0.50 ± 0.11
Amino acids, 2.70%, $n = 9$	0.59 ± 0.14	0.41 ± 0.14
Glucose 3.86%, $n = 20$	0.58 ± 0.10	0.43 ± 0.10
Estimation period [12]		
3–360 min	0.57 ± 0.12	0.43 ± 0.12
3–120 min	0.53 ± 0.18	0.47 ± 0.18
120–360 min	0.87 ± 0.24[b]	0.13 ± 0.24[b]

[a] Estimated using the Babb–Randerson–Farrell model.
[b] $p < 0.05$, compared with 3–120 and 3–360 min.

5.4. Distributed model

Blood capillaries are placed within the tissue at different distance from the peritoneal surface (Fig. 7). The difference in solute concentration between blood and dialysis fluid induces a continuous concentration profile within the tissue, which changes from the value equal to dialysate concentration at the tissue surface (C_D) to the value approaching blood concentration (C_B) inside the tissue. Therefore the concentration of the solute outside a capillary depends on the distance of this capillary from the peritoneal surface. This fact has been taken into account in the so-called distributed model of peritoneal transport, but neglected in other mathematical models, as the membrane model and the

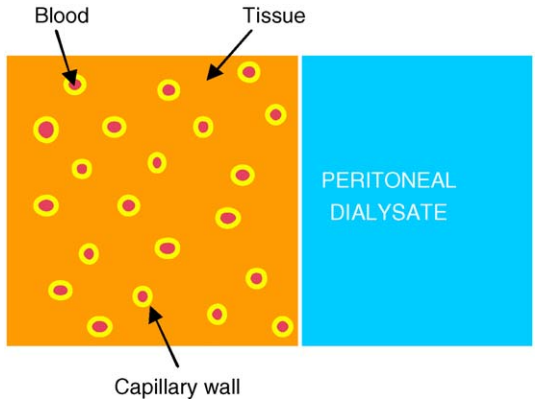

Fig. 7. Schematic presentation of the distributed model for peritoneal transport with capillaries distributed within the tissue at different distances from the tissue surface.

three-pore model [75,76,78,88]. A new version of the distributed model takes into account the rate of blood flow within the capillaries in the tissue, the heteroporous structure of the capillary wall, and the lymphatic absorption from the tissue [78,82,84,89].

The distributed model describes the solute profiles within the tissue using a partial differential equation for local solute balance assuming smooth distribution of solute source and sink (blood capillaries, lymphatic vessels) [75,78,82,84,88–90]:

$$\frac{\partial(\theta C_{\mathrm{T}})}{\partial t} = -\frac{\partial j_{\mathrm{ST}}}{\partial x} + q_{\mathrm{SBTL}} \tag{51}$$

where θ is the void fraction, i.e. the fraction of tissue volume effectively available to the solute, C_{T} the solute concentration in the tissue, and x is the distance from the tissue surface:

$$j_{\mathrm{ST}}(x,t) = -D_{\mathrm{T}}\frac{\partial C_{\mathrm{T}}}{\partial x}(x,t) + S_{\mathrm{T}} j_{\mathrm{VT}} C_{\mathrm{T}}(x,t) \tag{52}$$

is the solute flux across the tissue, where D_{T} and S_{T} are the solute diffusivity and sieving coefficient in the tissue, j_{VT} is the fluid volumetric flux through the tissue, and

$$q_{\mathrm{SBTL}}(x,t) = k_{\mathrm{B}}C_{\mathrm{B}} - k_{\mathrm{T}}C_{\mathrm{T}}(x,t) - q_{\mathrm{VL}}C_{\mathrm{T}}(x,t) \tag{53}$$

is the solute flow density between blood, tissue and lymph, where k_{B} and k_{T} are transport parameters through the capillary wall from blood to tissue and from tissue to blood, respectively, and q_{VL} is the lymph flow density.

It was shown that in the steady state of transport the distributed model yields formula (6) for the solute flow through the tissue surface with $K_{\mathrm{BD}} = A\sqrt{D_{\mathrm{T}}(k_{\mathrm{T}} + q_{\mathrm{VL}})}$, $S = S_{\mathrm{T}}$, $Q_{\mathrm{U}} = Aj_{\mathrm{VT}}(x = 0)$, where A is the tissue surface area [76,84]. C_{B} in this formula however has to be replaced, according to the distributed model, by the equilibrium concentration of the solute in the tissue $C_{\mathrm{Teq}} = \kappa C_{\mathrm{B}}$, where $\kappa = k_{\mathrm{B}}/(k_{\mathrm{T}} + q_{\mathrm{VL}})$; for macromolecules κ is substantially lower than 1. Furthermore:

$$f = 0.5 - \alpha \tag{54}$$

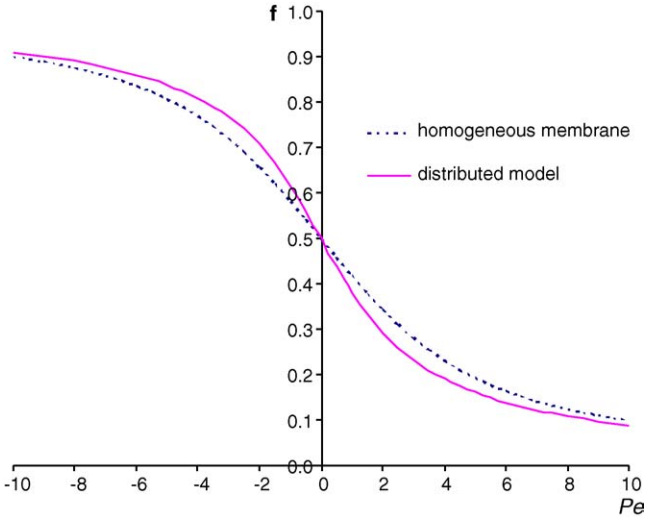

Fig. 8. Function $f(Pe)$ for the membrane model, Eq. (6), and the distributed model, Eqs. (54) and (55).

$$\alpha = \frac{\sqrt{1 + \frac{Pe^2}{4}} - 1}{Pe} \tag{55}$$

with $Pe = Sj_{\mathrm{V}}/k_{\mathrm{BD}}$. Note that Pe is the same in formulae (6), (54) and (55). The comparison of the functions $f(Pe)$ provided by the distributed model and by the theory for homogeneous permselective membranes is shown in Fig. 8. Approximated expressions for $f(Pe)$ in the distributed model are the same as for the membrane model.

The distributed model has been verified in animal experiments with peritoneal dialysis and also for other transport systems, as, for example, local anticancer drug delivery (see [76] for more information).

6. Summary

The renal replacement therapy with its different modalities attracts investigators with clinical, biological, engineering and mathematical background. Difficulties in obtaining a detailed knowledge about individual patient characteristics makes this area of research and medical care an interesting field for applied mathematical modeling that can help to reveal an otherwise unobtainable information hidden in clinical data. The applications of mathematical modeling in the kidney replacement therapy are far richer than those presented here [38,63,67,91,92]. The clinical importance of many other solutes beside urea and sodium evoked interest in their distribution and transport during dialysis sessions and between them. These include various electrolytes, gases, phosphorus, proteins (especially b2-microglobulin and albumin), etc. The models are typically compartmental, but each solute needs specific adjustments. A similar situation occurs in the investigation of the transport within the peritoneal tissue.

During the last 10 years many new modalities for hemodialysis and peritoneal dialysis were introduced to clinical practice or are under investigation [93,94]. They are based on different protocols than traditional methods, as short daily or long nocturnal hemodialysis or automated peritoneal dialysis with frequent nocturnal exchanges of dialysis fluid. Therefore the precise characteristics of the patient's water and solute distribution and transport within the body and transport characteristics of "peritoneal membrane" for peritoneal dialysis patients are nowadays even of more importance than before.

The current and future progress in the monitoring and optimization of renal replacement therapy must take into account a few different aspects. First of all, formal models that are based on fitting of parameters need to be discriminated from realistic description of physiological and pathophysiological processes of water and solutes transport and distribution within the body [38,72]. Many new measurement techniques allow currently for, often noninvasive, monitoring of many variables important for the success of dialysis therapy, and for careful verification of the models [65,66,92,95–99]. For popular simple, but often much simplified, models the limits for their applications should be defined, and their success within their proper range of application should be explained on the

base of general physiological knowledge and modeling. Furthermore, attempts have been undertaken to model and monitor several solutes and body compartments concomitantly [51,63,67,99–101]. Although such integrative approach is nowadays restricted to selected research centers, the progress in technology may allow extending it to other clinical centers in the near future. However, before that more precise targets of dialysis adequacy have to be defined based on many new clinical studies from different regions of the world with different approaches to prescription of dialysis dose and stimulate the search for other markers and indicators of patient status and dialysis adequacy [40,42–44,63,67,102]. These new studies have considerably increased the clinical knowledge about outcome of dialysis therapy and *KT*/*V* paradigm, which was initially based on one U.S. multicenter study. Here, however, the lack of understanding of the bases of uremic toxicity does not allow for easy answer, and more clinical, experimental, and theoretical research is necessary. Thus, although the current standards are criticized no new ones have been accepted yet, and combined effort of clinical and theoretical scientists in their formulation may be expected to dominate during the next years.

Computer based programs and new measurement methods and devices substantially increase the range of application of the models. However, as good their results are, they should be considered only as auxiliary tools in the hand of physicians who decide about the course of the therapy for their patients.

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