1

Representations of Peritoneal Tissue – Mathematical Models in Peritoneal Dialysis

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1. Introduction

During peritoneal dialysis solutes and water are transported across the peritoneum, a thin "membrane" lining the abdominal and pelvic cavities. Dialysis fluid containing an "osmotic agent", usually glucose, is infused into the peritoneal space, and solutes and water pass from the blood into the dialysate (and vice versa). The complex physiological mechanisms of fluid and solute transport between blood and peritoneal dialysate are of crucial importance for the efficiency of this treatment (Flessner, 1991; Lysaght &Farrell, 1989).

The major transport barrier is the capillary endothelium, which contains various types of pores. Capillaries are distributed in the tissue. Across the capillary walls, mainly diffusive transport of small solutes between blood and dialysate occurs. As the osmotic agent creates a high osmotic pressure in the dialysis fluid - exceeding substantially the osmotic pressure of blood - water is transported by osmosis from blood to dialysate and removed from the patient with spent dialysis fluid. At the same time the difference in hydrostatic pressures between dialysate (high hydrostatic pressure) and peritoneal tissue interstitium (lower hydrostatic pressure) causes water to be transported from dialysate to blood. In addition, there is a continuous lymphatic transport from dialysate and peritoneal tissue interstitium to blood.

In this chapter a brief characteristic of the two most popular simple models describing transport of fluid and solutes between dialysate and blood during peritoneal dialysis is presented with the focus on their application and techniques for estimation of parameters which may be used to analyze clinically available data on peritoneal transport.

2. Membrane representation of transport barrier

This rather complicated transport system of water and solutes can be described with sufficient accuracy for practical purposes with a simple, membrane model based on thermodynamic principles of fluid and solutes transport across an "apparent"

semipermeable membrane that represents various transport barriers in the tissue (Kedem &Katchalsky, 1958; Lysaght &Farrell, 1989; Waniewski et al., 1992; Waniewski, 1999). In this model no specific structure of the membrane is assumed (the "black box" approach). The membrane model allows an accurate description of diffusive and convective transport of solutes and osmotic transport of water between blood and dialysate, but it must be supplemented by fluid and solute absorption from dialysate to blood.

2.1 Estimation of fluid absorption rate from dialysate to peritoneal tissue and determination of dialysate volume during dialysis

Transport of fluid from blood to dialysate (ultrafiltration) and from dialysate to peritoneal tissue (absorption) occurs at the same time. Estimation of fluid absorption can be done using a so-called "volume marker" - a substance added to the dialysate in low concentration (so that this addition does not influence the transport of other solutes) which might be distinguished from the solutes produced by the body (and transported to dialysis fluid), to calculate its disappearance from dialysis fluid (Waniewski et al., 1994).

Two processes: convection and diffusion take part in the transport of the volume marker from dialysate. The convective transport consists of lymphatic transport and fluid absorption from peritoneal cavity caused by dialysate hydrostatic pressure which is higher than that of interstitium. Because of a high molecular weight of the volume marker, its diffusion is negligible and the determination of its elimination rate, K_E, can serve as an estimation of fluid absorption rate from dialysate to peritoneal tissue, Q_A. However, it should be remembered that even small diffusion of a marker creates an error in determination of K_E (and Q_A). Therefore substantial decrease of marker's diffusive transport is of great importance and can be achieved by selection of macromolecular solutes, as the diffusive transport decreases with increasing molecular weight. For this reason only high molecular weight protein (albumin and hemoglobin) and dextrans of molecular weight from 70000 to 2 millions have been applied as a volume markers (De Paepe et al., 1988; Krediet et al., 1991; Waniewski et al., 1994).

K_E (and consequently Q_A) can be calculated using a simple, one compartment mathematical model representing dialysate of variable volume V_D caused by fluid transport from and to the peritoneal cavity. The applied model is based on the assumption that the rate of decrease of volume marker mass in the peritoneal cavity is proportional to the volume marker concentration in the intraperitoneal dialysis fluid. Applying the mass balance equation one gets (Waniewski et al., 1994):

$$\frac{dM_z}{dt} = -K_E C_z, \tag{1}$$

where M_z is mass and C_z concentration of the volume marker. After integration, Eqn (1) can be presented in the following form:

$$M_z(t_0) - M_z(t_{end}) = -K_E \int_{t_0}^{t_{end}} C_z(t)dt = K_E(t_{end} - t_0)\overline{C}_z(t_{end}), \tag{2}$$

where t_0 and t_{end} denoted the time of the beginning and the end of a peritoneal dialysis dwell, respectively (therefore $t_{end} - t_0$ is the time of dialysis) and $\overline{C}_z(t_{end})$ is an average concentration of volume marker in dialysate during the session, which can be calculated

using frequent measurements of volume marker concentration in dialysate. Measurements should be done more frequently at the beginning of dialysis when concentration changes of the volume marker are more rapid. Mass of volume marker at the beginning of dialysis, $M_z(t_0)$, is equal to the mass in the fresh dialysis fluid in the peritoneal cavity, whereas mass at the end of dialysis, $M_z(t_{end})$, can be calculated knowing dialysate volume and marker concentration at the end of dialysis. It must be also remembered that dialysate volume at the end of dialysis is a sum of the volume removed and the residual volume remaining in the peritoneal cavity, which may be calculated using a short (5 min) rinse dwell just after the end of the dialysis session:

$$V_{res}C_z^{before} = \left(V_{res} + V_{rinse}\right)C_z^{after}, \tag{3}$$

where V_{res} is the sought residual volume, V_{rins} is the rinse volume, C_z^{before} is the concentration of the marker before the rinse and C_z^{after} is the marker concentration after the rinse. Therefore:

$$V_{res} = V_{rinse}C_z^{after} \Big/ \left(C_z^{before} - C_z^{after}\right), \tag{4}$$

Thus, as the other terms in this equation are known, K_E can be calculated from Eqn (2) as follows:

$$K_E = \left(C_z(t_0)V_D(t_0) - C_z(t_{end})\left(V_D(t_{end}) + V_{res}\right)\right) \Big/ \left((t_{end} - t_0)\overline{C}_z(t_{end})\right). \tag{5}$$

Thereafter, knowing K_E and having data concerning marker concentration changes during the session (measured as a radioactivity), using Eqn (2) written not for duration of dialysis, t_{end}, but for a selected time during dialysis, t, dialysate volume during dialysis can be calculated. Expressing the mass of volume marker, $M_z(t)$, as the product of dialysate volume, $V_D(t)$, and marker concentration $C_z(t)$ one gets (Figure 1):

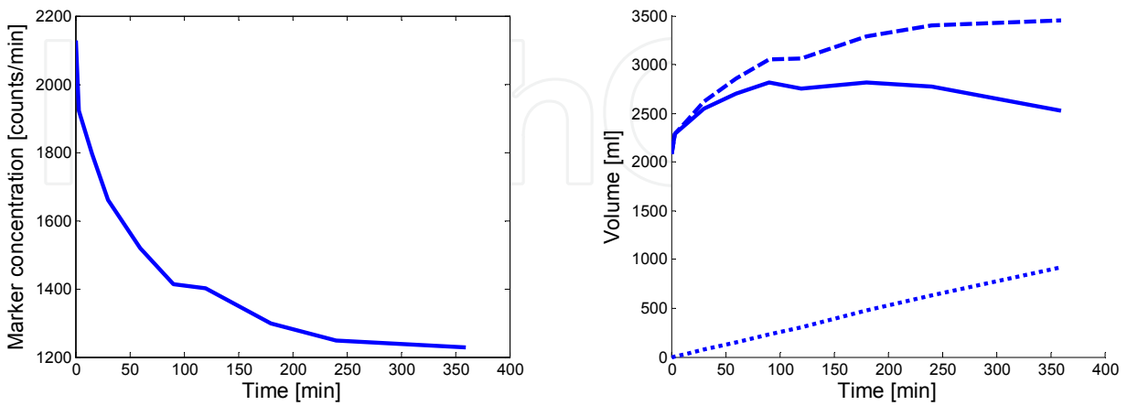

Fig. 1. Marker dialysate concentration during peritoneal dialysis dwell (left panel) and comparison of volumes calculated from marker concentration using Eqn (6) (right panel): dialysate volume (solid line), apparent volume calculated without the correction for the absorption of marker (dashed line) and absorbed volume (K_E = 2.29, dotted line).

$$V_D(t) = \underbrace{\frac{M_z(t_0)}{C_z(t)}}_{\text{APPARENT VOLUME}} \underbrace{- K_E t \frac{\overline{C}_z(t_{end})}{C_z(t)}}_{\text{ABSORPTION}}. \quad (6)$$

It is worth noting that the first part of the right hand side of Eqn (6) is the formula for calculation of dialysate volume using dilution of the volume marker without marker absorption taken into account. The second part is the correction for marker absorption (Figure 2).

2.2 Description of fluid transport in peritoneal dialysis

For low molecular weight osmotic agents, as glucose or amino acids, the value of osmotically induced ultrafiltration flow, Q_U, is proportional to the difference of osmotic pressure between dialysate and blood, $\Pi_D - \Pi_B$ (Waniewski et al., 1996b). The coefficient of proportionality, a_{os}, is called osmotic conductance. The mass balance equation for fluid is then as follows (Chen et al., 1991):

$$\frac{dV_D}{dt} = Q_V = Q_U - Q_A = a_{os}(\Pi_D - \Pi_B) - Q_A. \quad (7)$$

where: Q_V is the net rate of peritoneal dialysate volume change, Q_U is the rate of ultrafiltration flow ($Q_U = a_{os}(\Pi_D - \Pi_B)$) and Q_A is the fluid absorption rate.

Since V_D and Q_A (with the assumption that $Q_A = K_E$) can be estimated from Eqns (2) and (6), whereas Π_D and Π_B can be measured, thus Eqn (7) can be used for determination of osmotic conductance (Figure 2, left panel). Note however, that $Q_A = K_E$ is only a simplified assumption. Thus if both parameters (a_{os} as well as Q_A) are fitted, then the fitted Q_A value may not have a value comparable to K_E (Figure 2, right panel). All clinical data shown in this chapter are from Karolinska Institutet, Stockholm, Sweden.

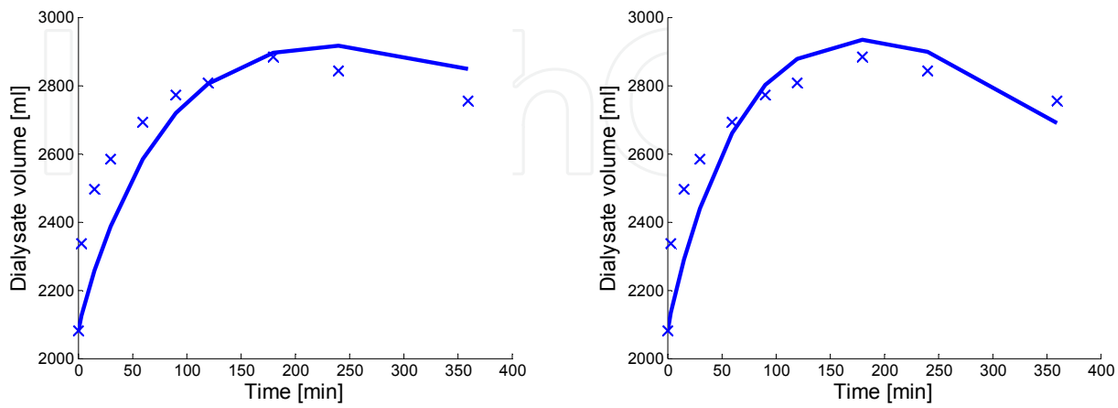

Fig. 2. Dialysate volume (x) calculated from marker concentration using Eqn (6) and osmotic model (solid line) with one fitted parameter and assumption $Q_A = K_E$ (left panel, a_{os} = 0.105, K_E = 1.93), and with two fitted parameters (right panel, a_{os} = 0.134, Q_A = 3.48).

As shown in Figure 2, the osmotic model underestimates dialysate volume during the first phase of dialysis dwell. This is the result of the assumption that osmotic conductance is constant that generally is only a simplification (Stachowska-Pietka et al., 2010; Waniewski et al., 1996a).
The fluid transport may be also described by a simple phenomenological formula proposed by Pyle et al. (Figure 3 shows example of patient with ultrafiltration failure defined as net ultrafiltration volume at 4 hour of the dwell less than 400 ml), and applied also by other investigators (Stelin &Rippe, 1990):

$$Q_V(t) = a_p e^{-k_p(t-t_0)} - b_p, \tag{8}$$

where t_0 is the start time of the dialysis, and a_p, b_p and k_p are the constants.

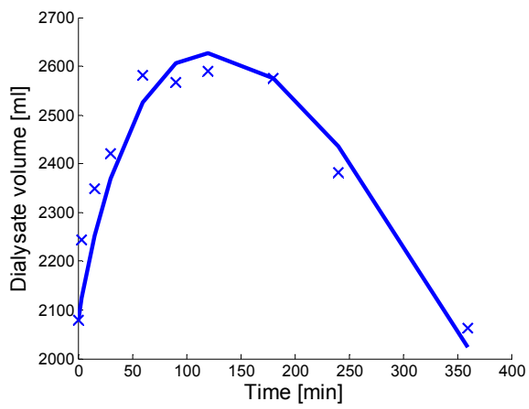

Fig. 3. Dialysate volume: clinical data (x) and Pyle model (solid line, a_p = 19.6, k_p = 0.022, b_p = 2.5).

2.3 Transport of low molecular solutes in peritoneal dialysis

Analysis of transport of low molecular weight solutes, such as urea, creatinine or glucose, from blood to dialysate (or in opposite direction) is of special importance in the evaluation of the quality of dialysis (Lysaght &Farrell, 1989; Waniewski et al., 1995). One of the methods used for assessment of the transport barrier between blood and dialysate is application of the so-called thermodynamic transport parameters. For the estimation of these parameters there is a need for frequent measurement of dialysate volume (i.e. volume marker concentration) during dialysis as well as concentrations of other solutes in the dialysate and blood, and then calculation of the rate of solutes mass change caused by their transport from blood to dialysate (or in opposite direction).
Solute transport occurs in three ways: a) diffusion of solute caused by the differences in solute's concentration in dialysate and blood; b) convective transport with fluid flow from blood to dialysate (ultrafiltration); c) convective transport with fluid absorbed from dialysate to the subperitoneal tissue and lymphatic vessels (absorption). In the description of these processes it is assumed that generation of solutes in the subperitoneal tissue and peritoneal cavity as well as the interaction between solutes are negligibly small.
All of these transport components are governed by specific forces (often described as thermodynamic forces) the effects of which, measured as a rate of solute flow, depends not

only on the value of the force, but also on transport parameters characterizing the environment in which the solute transport occurs. Thus, the rate of diffusive solute transport is proportional to the difference of solute's concentration between blood and dialysate, $C_B - C_D$, with the rate coefficient K_{BD}, called diffusive mass transport coefficient.

The other two transport components are convective. The fluid flux, caused by the difference of osmotic pressures and the difference of hydrostatic pressures, carries solutes across the membrane characterized by its sieving coefficient. Sieving coefficient, S, determines the selectivity of this process: a sieving coefficient of 1 indicates an unrestricted solute transport while for S equal 0 there is no transport. Note also, that for a given membrane each solute has its specific sieving coefficient. Therefore, for the second transport component, the rate of convective flow is proportional to the rate of water flow (ultrafiltration), Q_U, to the average solute concentration in blood and dialysate C_R, and to sieving coefficient S. For the membrane model of peritoneal tissue C_R is expressed as follows:

$$C_R = (1 - F)C_B + FC_D, \tag{9}$$

where C_B and C_D are concentrations in blood plasma and dialysate, respectively, and F is:

$$F = \frac{1}{Pe} - \frac{1}{e^{Pe} - 1}, \tag{10}$$

where Pe is Peclet number which is the ratio of terms characterizing the convective and diffusive transport:

$$Pe = \frac{SQ_U}{K_{BD}}. \tag{11}$$

In clinical investigations it has been demonstrated that for low molecular weight solutes it can be assumed that $F \approx 0.5$ and for proteins $F = 1$. The illustration of this estimation of F can be done using clinical data concerning the dwell study with 1.36% glucose solution published in (Olszowska et al., 2007). In this paper the values of K_{BD} for small solutes were found to be between 8 ml/min (glucose) and 25 ml/min (urea) and S of 0.68. Using these data it is possible to calculate F, yielding the values between 0.46 (for K_{BD} = 8 ml/min) and 0.65 (for K_{BD} = 25 ml/min).

For the third component, the rate of solutes absorption is proportional to the rate of fluid absorption rate, Q_A, and the solute concentration in dialysate. In this case the sieving coefficient is taken as equal to one. It is justified by experimental investigations in which no sieving effect (even for proteins) was demonstrated.

The total solute flow between blood and dialysate is the sum of all the described components. Thus, using the thermodynamic description, the following mass balance equation can be written (Waniewski et al., 1995):

$$\frac{dV_D C_D}{dt} = -K_{BD}(C_B - C_D) + SQ_U C_R - Q_A C_D. \tag{12}$$

In this equation there are two transport coefficients: diffusive mass transport coefficient, K_{BD}, and sieving coefficient, S, which characterize membrane properties of peritoneal tissue. All other variables in Eqn (12) can be measured or calculated from the measured values. In

principle Eqn (12) can be used for estimation of S and K_{BD}. For practical reasons (decrease of the impact of measurement errors on parameters estimation) it is better to use Eqn (12) in its integral form (Waniewski et al., 1995):

$$V_D(t)C_D(t) = V_D(t_0)C_D(t_0) + K_{BD}(\overline{C}_B - \overline{C}_D)\Delta t + S\overline{Q_U C_R}\Delta t - Q_A\overline{C}_D\Delta t, \tag{13}$$

where the bar above symbols denotes averaged values for the time period from t_0 to t and $\Delta t = t - t_0$. The parameters K_{BD} and S can be estimated from Eqn (13) using two dimensional linear regression. The theoretical curves for solute concentrations that can be obtained by this procedure are compared to the measured concentrations in dialysis fluid in Figure 4.

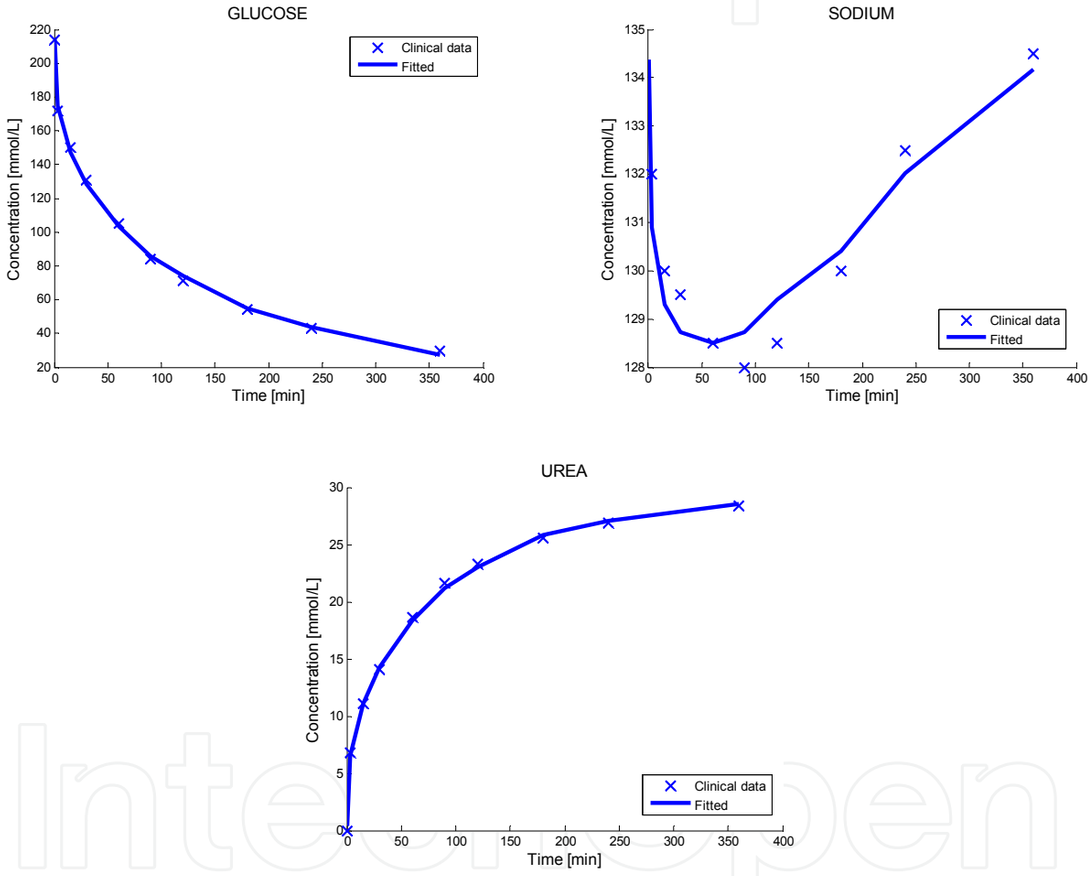

Fig. 4. Solute concentrations during peritoneal dialysis: clinical data vs. fitting curve (Eqn (13)) for: glucose (K_{BD} = 10.2 , S = -0.62), sodium (K_{BD} = 11.6, S = 0.73) and urea (K_{BD} = 14.0, S = 1.82)

It must be remembered that there are following limitations for the values of estimated parameters:

$$0 \le K_{BD} \text{ and } 0 \le S \le 1 . \tag{14}$$

The estimated values of K_{BD} are typically positive, but the limitations for S are often violated in experimental investigations (Waniewski et al., 1996d), as for the case depicted in Figure 4.

The reason for the problem with estimation of S is the assumption used in the estimation procedure that the transport parameters (K_{BD} and S) are constant during the whole dwell time (Imholz et al., 1994; Krediet et al., 2000; Waniewski et al., 1996c). Additionally, in normal condition of peritoneal dialysis the convective transport is much smaller than the diffusive one. In experimental conditions this problem can be overcome by choosing the concentration of the investigated solute in dialysate close to that in blood. In this way the diffusive transport component is substantially decreased and is similar to the convective component. In these conditions application of two-dimensional linear regression results in estimation of K_{BD} and S which are within the theoretical limits. The other advantages of this approach is the possibility of simplification of expression for convective transport in which the average value of substance concentration C_R can be substituted with solute blood plasma concentration and in this way, the problem of estimation of F can be eliminated.

2.4 Parameter estimation: An example

In the paper by Olszowska et al (Olszowska et al., 2007), data from a clinical study on dwells lasting 4 hours with glucose based (1.36%) and amino acids based (1.1%) solutions in 20 clinically stable patients on peritoneal dialysis are presented. With frequent sampling of dialysate, three samples of blood and with dialysate volume and fluid absorption rate obtained using macromolecular volume marker (RISA, radioiodinated serum albumin) it was possible to apply Eqn (13) and two-dimensional linear regression for estimation of diffusive mass transport coefficient, K_{BD}, and sieving coefficient, S, for glucose, potassium, creatinine, urea and total protein. The results demonstrate slightly higher values of K_{BD} obtained for dwells with amino acid solution as compared with glucose based solution (e.g. for glucose K_{BD} = 8.3 ml/min, S = 0.62 vs. K_{BD} 8.1 ml/min, S = 0.21 and for urea K_{BD} = 28.2 ml/min, S = 0.48 vs. K_{BD} 25.3 ml/min, S = 0.39). It seems that the amino acid based solution exerts a specific impact on peritoneal tissue which causes slight increases of diffusive and convective transport. It is worth to note that, for substances specified above, values of K_{BD} and S, estimated using two-dimensional linear regression, were in acceptable range ($K_{BD}>0$, $0 \le S \le 1$). However, for amino acids themselves estimation of S failed and the estimation of K_{BD} was performed with assumption that for these solutes S was 0.55 and therefore one-dimensional linear regression was applied. In this condition the estimated averaged values of K_{BD} for essential amino acids was 10.32±0.51 ml/min and for nonessential amino acids was 10.6±1.33 ml/min. Similar results was also described in (Douma et al., 1996).

In contrast to this assumption, the estimation of parameters performed for shorter periods of time demonstrated that estimated parameters have higher values at the beginning of the dwells than at the end (Waniewski, 2004), and it was proposed that the parameters values estimated for dwell time change with time as described by the function $f(t) = 1 + 0.6875e^{-t/50}$ (t is time in minutes). A more detailed evaluation of this variability (vasoactive effect) can be found in (Imholz et al., 1994; Waniewski, 2004; Douma et al., 1996).

3. Pore representation of peritoneal transport barrier

In the membrane model of the peritoneal barrier, no structure of this barrier is considered. It is simply assumed that blood and dialysate are separated by a semipermeable membrane and that the transport phenomena can be described using the thermodynamic theory of the transport processes. The pore model is more complex and derived from the field of capillary

physiology. The basic idea of this model is the assumption that the capillary wall in the subperitoneal tissue is heteroporous and that the transport through the pores may be evaluated using the hydrodynamic theory of transport along a cylindrical pipe (Deen, 1987) which describes how much the solute and fluid transport is affected due to presence of the pores comparing to a uniform, semipermeable membrane.

In 1987, Rippe et al proposed the so-called two-pore model to describe solute and fluid transport during peritoneal dialysis (Rippe &Haraldsson, 1987; Rippe &Stelin, 1989; Rippe et al., 1991b; Rippe &Haraldsson, 1994). According to this model, the membrane is heteroporous with two size of pores: large pores (radius 250 Å), and small pores (radius 43 Å). A large number of small pores makes the membrane permeable to most small solutes, whereas a very small number of large pores allows for the transport of macromolecules (proteins) from blood to peritoneal cavity. However, this model could not describe the phenomenon of sieving of small solutes, such as sodium, for which one observes a marked decline of dialysate concentration, reflecting a water-only (free of solutes) pathway. After discovery of the existence of aquaporins, the model was extended with a third type of pore, the ultrasmall pore, allowing an accurate description of the low sieving coefficients of small solutes (Figure 5). As it has been shown by Ni et al. (Ni et al., 2006) the ultrasmall pores are an analog of aquaporin-1 in endothelial cells of peritoneal capillaries and venules.

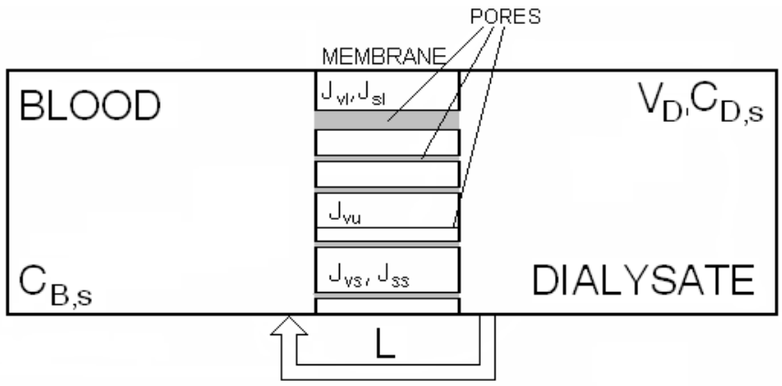

Fig. 5. Scheme of the three-pore model: J – flow of the fluid (subscript 'v') or solute (subscript 's') through the pore (subscript 's' – small pore, 'l' – large pore or 'u' – ultrasmall pore), L – lymphatic absorption from the peritoneal cavity, C_B – blood concentration. C_D – dialysate concentration, V_D – dialysate volume.

3.1 Three-pore model

According to the three-pore model (Figure 5), the change of the peritoneal volume (V_D) depends on the sum of the fluid flows through the three types of pores (J_{Vpore} , *pore*: u - ultrasmall, s – small, l - large) and the peritoneal lymph flow, L, (Rippe &Levin, 2000). Thus (Rippe &Stelin, 1989; Rippe et al., 1991a; Rippe et al., 1991b; Rippe &Levin, 2000):

$$\frac{dV_D}{dt} = J_{V_U} + J_{V_S} + J_{V_L} - L, \tag{15}$$

and J_{Vpore} is governed by the hydrostatic and osmotic pressures as follows (Rippe &Levin, 2000):

$$J_{V_{pore}} = a_{pore} L_p S \left[\Delta P(V_D) - \sum_{solute} \sigma_{solute,pore} \Delta\pi_{solute}(t) \right], \tag{16}$$

where: L_pS is the membrane ultrafiltration coefficient, α_{pore} is the part of L_pS accounted for the specific type of pore, ΔP is the hydrostatic pressure difference between the blood capillaries and the peritoneal cavity (which depends on the fluid volume in the peritoneal cavity: $\Delta P(V_D) = \Delta P(V_0) - {V_D(t) - V_0}/{490}$, V_0 is the initial dialysate volume, 490 is an empirical coefficient, (Twardowski et al., 1983)), $\sigma_{solute,pore}$ is the *solute* osmotic reflection coefficient describing osmotic efficiency of the *solute* in the *pore*, and $\Delta\pi_{solute}$ is the *solute* crystalloid osmotic pressure gradient ($\Delta\pi_{solute}(t) = RT[C_{solute,B} - C_{solute,D}]$, R – gas constant, T – absolute temperature, $C_{solute,B}$ and $C_{solute,D}$ - *solute* concentration in blood and dialysate, respectively).
Solutes are transported only through the large and small pores and by the lymphatic flow, and therefore the solute mass change in the peritoneal cavity ($M_{solute,D}$) is described by the following mass balance equation (Rippe &Levin, 2000):

$$\frac{dM_{solute,D}}{dt} = J_{S_{solute,S}} + J_{S_{solute,L}} - LC_{solute,D}. \tag{17}$$

where $J_{S_{solute,pore}}$ - *solute* flow through the *pore*

The solute flow, $J_{S_{solute,pore}}$, is by diffusion and convection, and is defined as:

$$J_{S_{solute,pore}} = \underbrace{-PS_{solute,pore}(C_{solute,D} - C_{solute,B})}_{\text{diffusion}} + \underbrace{J_{v_{pore}}(1 - \sigma_{solute,pore})\bar{C}_{solute}}_{\text{convection}}, \tag{18}$$

where: $PS_{solute,pore}$ is a *solute* permeability surface area for the specific type of pore, $\bar{C}_{solute}$ is the mean membrane solute concentration, $\bar{C}_{solute} = (1 - F_{solute})C_{solute,B} + FC_{solute,D}$, and $F_{solute} = 1 / Pe_{solute,pore} - 1/(e^{Pe_{solute,pore}} - 1)$ is a function of the ratio of convective to diffusive transport given by the Peclet number $Pe_{pore,solute}$ (Rippe &Levin, 2000):

$$Pe_{solute,pore} = J_{V_{pore}} \frac{1 - \sigma_{solute,pore}}{PS_{solute,pore}}, \tag{19}$$

compare to Eqns (9)-(12). Note that $1 - \sigma_{solute,pore}$ is sieving coefficient for these particular *pore* and *solute*.
In the previous approach based on the membrane model, there were two transport coefficients: diffusive mass transport coefficient (K_{BD}) and sieving coefficient (S) which both characterize membrane properties of peritoneal tissue and can be estimated from clinical or experimental data. The analogues of these parameters in the three-pore model are, respectively, the permeability surface area coefficient ($PS_{solute,pore}$) and the solute's osmotic reflection coefficient ($\sigma_{solute,pore}$) which may be calculated using the following formulas (Rippe &Levin, 2000):

$$PS_{solute,pore} = D_{solute} \left(\frac{A_0}{\Delta x} \right)_{pore} \left(\frac{A}{A_0} \right)_{solute,pore}, \tag{20}$$

$$\sigma_{solute,pore} = 1 - \frac{(1-\lambda)^2[2-(1-\lambda)^2](1-\lambda/3)}{1-\lambda/3+2/3\lambda^2}, \tag{21}$$

where: D_{solute} represents the free solute diffusion coefficient, $A_0/\Delta x$ is the unrestricted (nominal) pore area over unit diffusion distance, A/A_0 is the restriction factor for diffusion defined as the ratio of the effective surface pore area over unrestricted (nominal) pore area, and λ = solute radius/pore radius.

3.2 Parameter estimation: Problems and pitfalls

The three-pore model is more complicated than the membrane model and it is not possible to find analytical or integrated solutions and to estimate parameter values using linear regression. Therefore the model has to be solved numerically using a computer software with ODE (ordinary differential equation) solver (e.g. Matlab®, Berkeley-Madonna or JSim) and with some parameter estimation techniques (Freida et al., 2007; Galach et al., 2009; Galach et al., 2010). For example, in Matlab the estimation of parameters may be done using function *fminsearch* (Nelder-Mead type simplex search method) with the aim to minimize the difference between numerical predictions and clinical data (usually, absolute difference or the squared difference). Therefore, the aim is to find the global minimum of the error function, and, thus, the values of parameters that describe the predicted curves as close to the clinical data as possible (Freida et al., 2007; Galach et al., 2009; Galach et al., 2010).

It should however be noted that, with the increasing number of estimated parameters or decreasing number of data points, the chance that not global but local minimum is attained is growing (Juillet et al., 2009). The results are often strongly dependent on starting values of the fitted parameters (in particular on their difference from those that describe the global minimum (Juillet et al., 2009)), see an example in Section 3.3. To deal with these problems, one can lower the number of fitted parameters using the sensitivity analysis to find parameters with the highest influence on numerical results, and use not one but many initial sets of parameter values to check parameter space extensively, avoid local minima and hit the global minimum. Additionally, to avoid calculation problems when fitted parameters have different order of magnitude (i.e. in chosen set of parameters there are very small as well as large values), it is to be preferred to fit not the parameter itself but its multiplier:

$$Par_{fitted} = x \cdot Par_{initial}, \tag{22}$$

where Par_{fitted} is the sought value of the parameter, $Par_{initial}$ is a basal value of the parameter and x is the fitted coefficient. Then all fitted coefficients (x) have a similar order of magnitude.

Another important issue is an appropriate selection of parameters set, because it is often possible to obtain similar predictions with much different sets of fitted parameters (see an example in Section 3.3). Therefore, any final conclusions should be drawn with the utmost caution.

3.3 Parameter estimation: An example

Clinical data of patients on six hour peritoneal dialysis dwell with glucose 3.86% solution (Karolinska Institutet, Stockholm, Sweden) were used to estimate the parameters of the three-pore model. More detailed description of the clinical data can be found in (Galach et al., 2010). The model was solved using *ode45* solver of Matlab® v. R2010b software

(MathWorks Inc., USA) based on an explicit 4th and 5th order Runge-Kutta formula. The data of each patient separately were used as target values for estimation of the model parameters done using Matlab® function *fminsearch* (Nelder-Mead type simplex search method) with the aim to minimize the function f_{min} that described the sum of fractional absolute differences between theoretical predictions and clinical data scaled to the experimental values:

$$f_{\min} = \sum_i \frac{|V_D^{\exp}(T_i) - V_D^{sim}(T_i)|}{V_D^{\exp}(T_i)} + \sum_i \frac{|C_{U,D}^{\exp}(T_i) - C_{U,D}^{sim}(T_i)|}{C_{U,D}^{\exp}(T_i)} + \sum_i \frac{|C_{Na,D}^{\exp}(T_i) - C_{Na,D}^{sim}(T_i)|}{C_{Na,D}^{\exp}(T_i)} + \ldots$$
$$\ldots + \sum_i \frac{|C_{G,D}^{\exp}(T_i) - C_{G,D}^{sim}(T_i)|}{C_{G,D}^{\exp}(T_i)} \quad , \quad (23)$$

where $V_D(T_i)$ is dialysate volume at time T_i, $C_{s,D}(T_i)$ is dialysate solute concentration at time T_i ('s': 'G' – glucose, 'Na' - sodium), '*exp*' stands for clinical data, and '*sim*' stands for simulation results. The chosen f_{min} function depends, of course, on dialysate volume and on glucose, urea and sodium as a representative of small solutes: glucose is an osmotic agent, urea is a marker of uremia, and sodium is a solute for which the so-called "sodium dip" (indicating sodium sieving as water passes the ultra-small pores) is observed during the peritoneal dwell. The influence of the other substances is taken into account only through their impact on dialysate volume.

Six parameters were estimated by fitting the three-pore model to clinical data: *LpS* (membrane UF-coefficient), *L* (peritoneal lymph flow), *PS* (permeability surface area coefficient) for glucose, sodium and urea and, alternatively, r_{small} (small pore radius, Set 1), or α_{small} (the part of L_pS accounted for the small pores, Eqn (16), Set 2), see Table 1. Other parameters were calculated from the estimated ones or their values were assumed based on previous investigations (Rippe &Levin, 2000), Table 1. The choice between two different sets

Three-pore model parameters	
Set 1	Set 2
Fitted parameters	
LpS, *L*, $PS_{small,G}$, $PS_{small,Na}$, $PS_{small,U}$, r_{small}	*LpS*, *L*, $PS_{small,G}$, $PS_{small,Na}$, $PS_{small,U}$, α_{small}
Assumed parameters (Rippe &Levin, 2000)	
$\alpha_{ultrasmall}$ α_{small} α_{large}, r_{large}, r_{solute}	α_{large}, r_{small}, r_{large}, r_{solute}, $\sigma_{solute,\,small}$
Parameters calculated from the fitted values	
$PS_{large,solute}$, in proportion to the fitted values for small pores, $\sigma_{solute,\,small}$ (dependent on r_{small})	$PS_{large,solute}$ in proportion to the fitted values for small pores, $\alpha_{ultrasmall}$ to achieve $\sum_{pore} \alpha_{pore} = 1$

Table 1. Division of the three-pore model parameters according to the source of their values.

of parameters that describe the three pore structure of the transport barrier used in estimation procedure is the choice between two different hypotheses about the variation of this structure among patients. The first hypothesis (Set 1) is based on the assumption that the radius of the small pore may vary from patient to patient but the fractional contribution of these pores to the hydraulic permeability, α_{small}, is the same in all patients. The other alternative with α_{small} varying between patients but the size of small pores being the same is investigated when Set 2 is selected. In general, both parameters may be expected to vary among patients, and, moreover, a similar variability may be considered for the remaining types of pores (large and ultrasmall). However, one cannot estimate all the parameters from the limited data and therefore, based on the previous experience with the model, the values of some of them need to be selected before the estimation procedure starts. The impact of the assumptions on the large pores on the simulations is less than those on the small pores. Thus, it was assumed that the radii of large and ultrasmall pores as well as the percentage input of large pores to the hydraulic permeability were constant. Note that the fraction of ultrasmall pores was related to the fraction of small and large pores by the condition that the sum of all coefficients α should be one.

It may happen that each single run of the fitting procedure (*fminsearch* function) for different starting parameter values yields different final sets of parameters and also different predictions for the simulated curves (Figure 6), which not necessarily are good approximations of the clinical data (Figure 6, right middle panel). It is also worth to mention that, usually, the fitting procedure is not sensitive to single data errors and may yield a smooth curve based on the other points (Figure 6, left panels).

As in the previous studies (Galach et al., 2009; Waniewski et al., 2008), the results of the simulations and estimations show that the three-pore model with fitted parameters is capable of reproducing clinical data concerning peritoneal dialysis with glucose solution rather well (Figures 6-9), but the parameter values are substantially different for different patients (Tables 2-3).

Parameters	Initial 2 hour	Dwell 6 hour	
	Set 1	Set 1	Set 2
LpS	0.0610	0.0870	0.0890
L	0.1624	2.9127	3.7367
PS_G	12.53	10.45	9.76
PS_{Na}	9.77	15.21	12.78
PS_U	23.05	31.83	31.37
r_{small}	43.8	48.5	43.0 (not estimated)
α_{small}	0.90 (not estimated)	0.90 (not estimated)	0.9799

Table 2. Values of estimated parameter for patient No 1; Estimation procedure: data concerning initial 2 hours of the dwell and Set 1 of the estimated parameters (Table 1), data concerning the whole dwell and Set 1 of the estimated parameters, data concerning the whole dwell and Set 2 of the estimated parameters

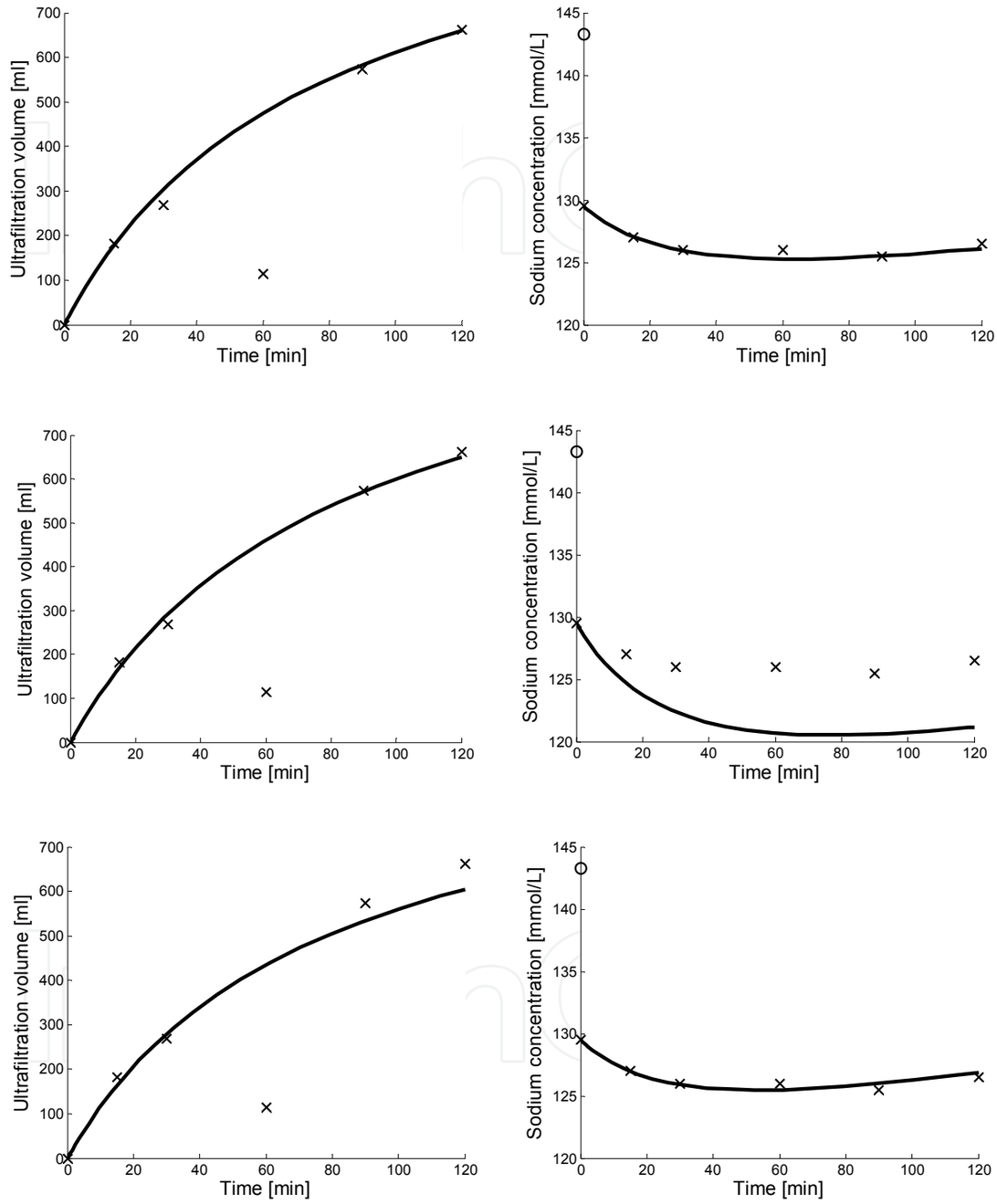

Fig. 6. Ultrafiltration volume and sodium concentration during initial 2 hours of the session for the patient No 1 and following starting points (x values) in the fitting procedure (*fminsearch*): [0.95,0.74,1.10,1.14,1.35,1.52] (top), [1.24,2.48,0.59,2.27,2.33,2.09] (middle) and [0.71,1.03,1.18,1.86,0.78,1.95] (bottom).

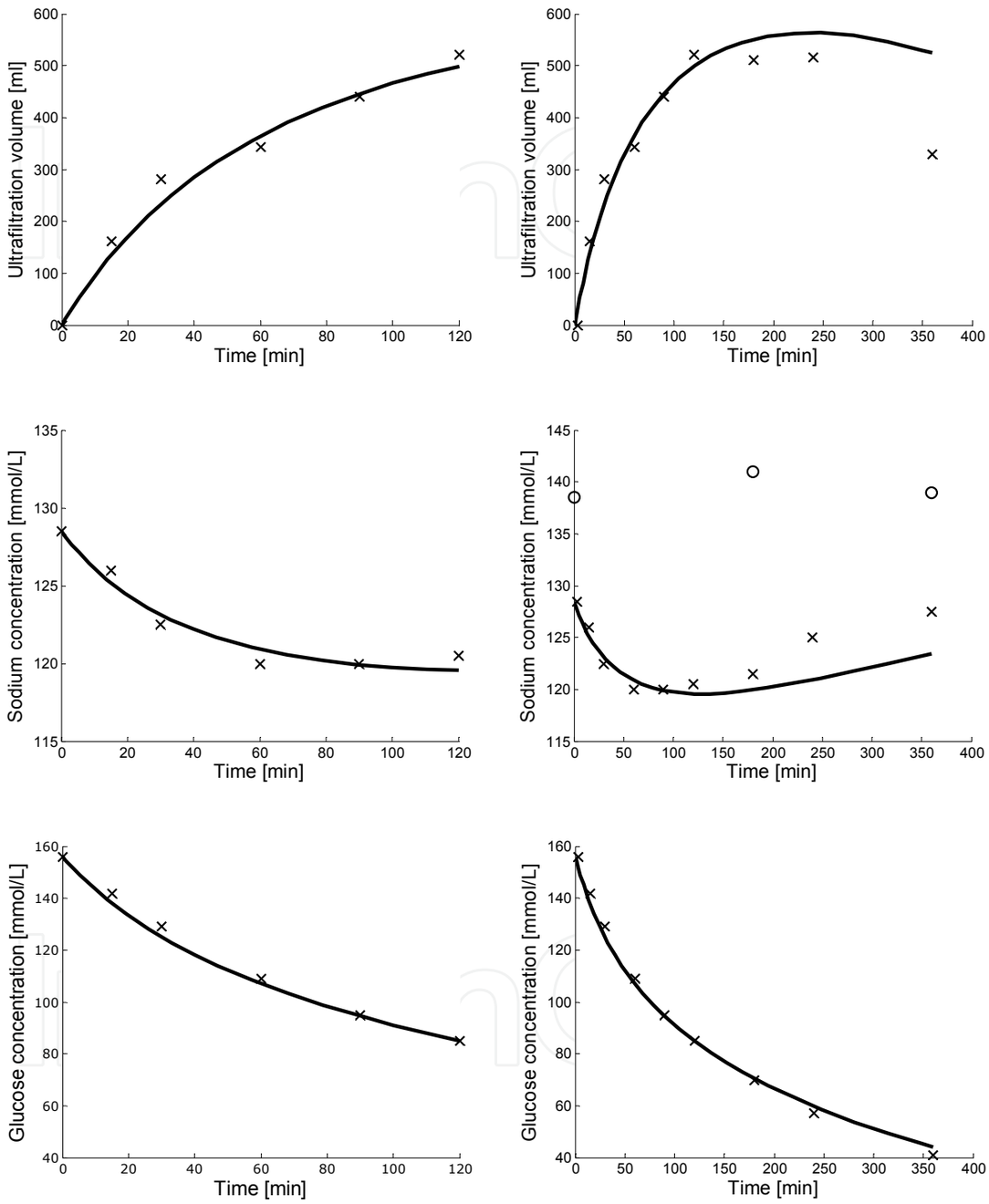

Fig. 7. Ultrafiltration volume, sodium concentration and glucose dialysate concentration during initial 2 hours of the session (left panel) and during the whole dwell (right panel) for the patient No 2 and for the same parameter values estimated from the initial 2 hours of the dwell; — - simulation result, x - dialysate data, o - blood data.

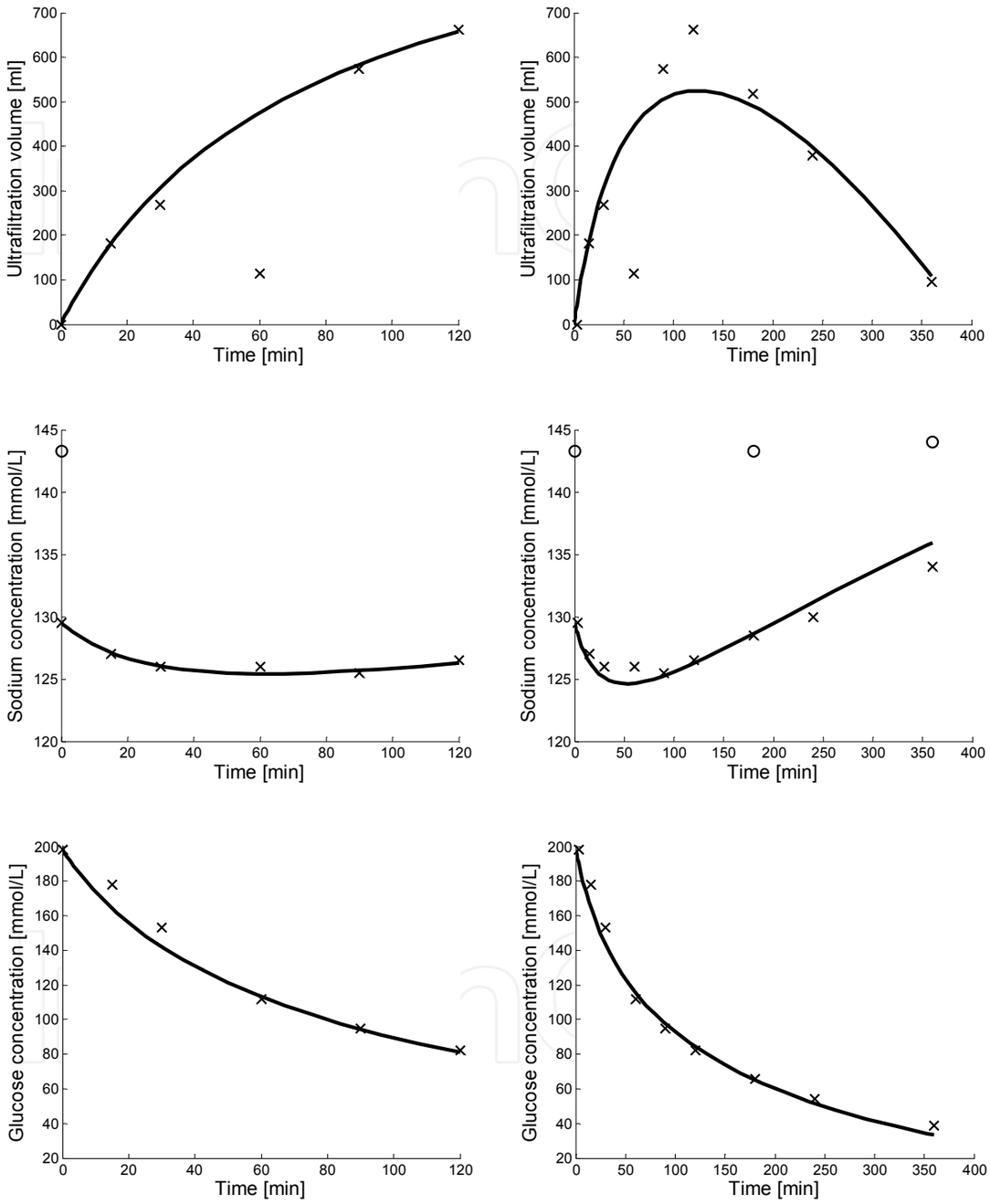

Fig. 8. Ultrafiltration volume, sodium concentration and glucose dialysate concentration during initial 2 hours of the session (left panel) and during the whole peritoneal dialysis dwell (right panel) for the patient No 1 and Set 1 of the estimated parameters (parameters from Table 2, column 1 and 2); —- simulation result, x - dialysate data, o - blood data

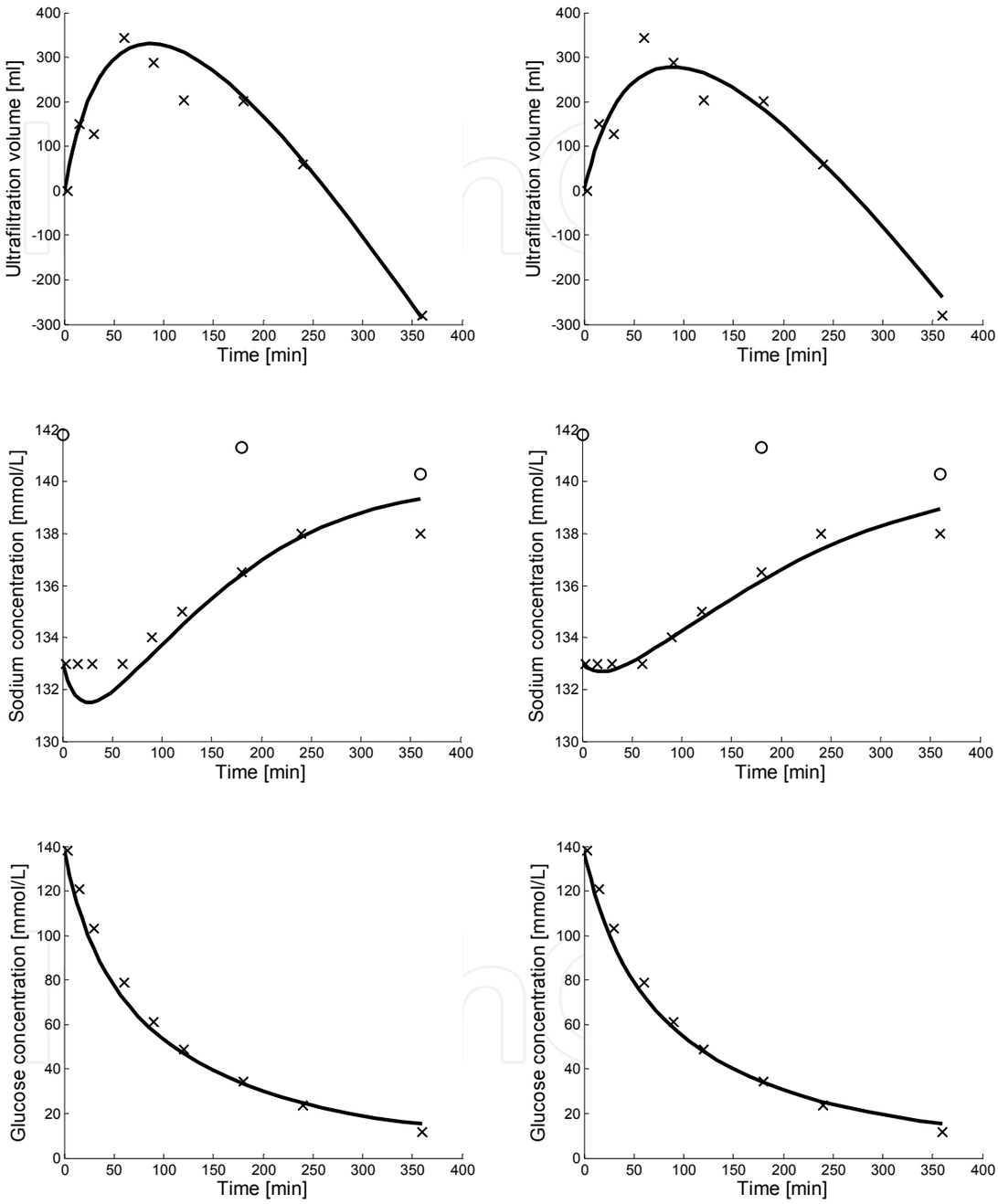

Fig. 9. Ultrafiltration volume, sodium and glucose concentration during 6 hour peritoneal dialysis dwell for the patient No 3 and Set 1 (left panel) or Set 2 (right panel) in fitting procedure; —- simulation result, x - dialysate data, o - blood data.

The assumption that the parameter values are constant during the whole dwell is only a simplification (Imholz et al., 1994; Krediet et al., 2000; Stachowska-Pietka et al., 2010; Waniewski et al., 1996a, 1996d). The transport processes occurring during the first part of dialysis dwell are much more rapid than in the later part, and therefore the parameters estimated using data from the first part of the dwell only may not be correct for the whole dwell (Figure 6); thus, the values of parameters estimated from the partial data and the whole set of data may differ (Figures 7-8, Table 2).

It is also worth noting that the selection of the assumptions, and consequently selection of the proper set of parameters for estimation procedure, is of high importance and has influence on all fitted parameters values and simulation results (Figure 9, Tables 2 and 3). The results of the simulations for different sets of estimated parameters may all give a good approximation of clinical data (Figure 9, results of the simulations for Set 1 and 2), however the fitted parameter values in these sets are different (Tables 3). But it may vary according to the patient. For example: for the patient No 1 the differences between fitted values of the parameters for Set 1 and 2 do not exceed 30% (Figure 8, Table 2), whereas for the patient No 3 the differences for 2 parameters were greater than 60% and for one parameter even than 100% (Figure 9, Table 3). Thus it is always very important to compare parameters fitted with the same assumptions or to discuss the differences in assumed hypotheses.

Parameters	Dwell 6 hour	
	Set 1	Set 2
LpS	0.0371	0.0862
L	2.5976	2.5026
PS_G	16.8806	17.05821
PS_{Na}	16.6024	27.5764
PS_U	30.2129	24.1114
r_{small}	26.7370	43 (not estimated)
α_{small}	0.9 (not estimated)	0.9799

Table 3. Values of estimated parameter for patient No 3 using data for whole dwell with two sets of the estimated parameters (Table 1).

4. Conclusions

Peritoneal dialysis is an interesting and important area for mathematical modeling. In fact peritoneal dialysis treatment as we know it today is the result of kinetic modeling leading to the concept of continuous ambulatory peritoneal dialysis. The first mathematical models describing peritoneal dialysis were based on a simple idea of a semipermeable peritoneal barrier between blood and dialysate allowing solute and fluid transport characterized by the so-called transport parameters (Imholz et al., 1994; Krediet et al., 2000; Waniewski et al., 1995; Waniewski, 1999). Such models were – and still are - useful in evaluation of peritoneal dwell studies and their various versions have been widely applied especially for analysis of solute transport (Heimburger et al., 1992; Pannekeet et al., 1995; Smit et al., 2005; Waniewski et al., 1991, 1992). Despite the fact that they were used to demonstrate and interpret new

transport phenomena, many questions concerning the mechanisms for the transport process could not be answered using this simple mathematical modeling because, although such models can be well fitted to the data and used to estimate transport parameters separately for fluid and each solute, however they cannot reliably predict the results of dialysis session and indicate the relationship between the parameters for different solutes and fluid. Therefore, another type of model, with additional and more physiological assumptions about the structure of the peritoneal membrane, was proposed (Rippe &Haraldsson, 1987; Rippe et al., 1991a; Rippe &Haraldsson, 1994). The pore model derived the description and relationships between the transport parameters from the solute size and the structure of the transport barrier (size of pores, number of pores etc.). The mentioned models of peritoneal transport were included into practical methods and computer programs for the evaluation of the efficacy and adequacy of peritoneal dialysis (Haraldsson, 2001; Van Biesen et al., 2003; Van Biesen et al., 2006; Vonesh et al., 1991; Vonesh &Keshaviah, 1997; Vonesh et al., 1999).
In this chapter these two most popular models describing peritoneal transport of fluid and solutes were presented and compared as regards their basic ideas and aims as well as their applicability. The membrane model provides a simple relationship between the rates of fluid and solute flows and their respective driving forces, whereas the three-pore model gives a quantitative relationship between the transport coefficients for various solutes and between fluid and solute transport coefficients. Additionally, the parameters estimation techniques and the possible problems with parameter estimation were discussed.

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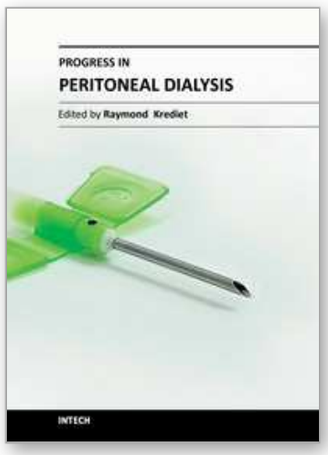

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Progress in Peritoneal Dialysis is based on judgement of a number of abstracts, submitted by interested people involved in various aspects of peritoneal dialysis. The book has a wide scope, ranging from in-vitro experiments, mathematical modelling, and clinical studies. The interested reader will find state of the art essays on various aspects of peritoneal dialysis relevant to expand their knowledge on this underused modality of renal replacement therapy.

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