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MATHEMATICAL MODELS FOR EVALUATION, OPTIMIZATION, AND CONTROL OF ARTIFICIAL KIDNEY THERAPY

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 optimisation 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. 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 vivid.

1. INTRODUCTION

Over one million patients worldwide can live due to different forms of kidney replacement therapy. Continuous treatment of these chronically ill patients needs a huge industrial and medical support. 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, optimisation, 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 simplicity of the model and limited amount of available measurements on the one hand and its physiological

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precision and the amount of the information provided on the other hand. Informatics and new technologies may shift this balance towards more sophisticated and realistic models.

2. 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 [32,49]. The treatment is short, typically 4 hours, and has to be repeated every two or three days. The changes of plasma concentration of small metabolites (urea, creatinine) during hemodialysis and inter-dialysis periods are subjected to mathematical modeling. The problem of adequate "dialysis dose" (i.e. the amount of these solutes that should be removed during dialysis) is hotly debated at medical meetings [3,9,16,18,22,36,41].

2.1. 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 minimal value. A simple one compartment mathematical model (Figure 1, equations 1 and 2) allows for estimation of *KT/V* parameter.
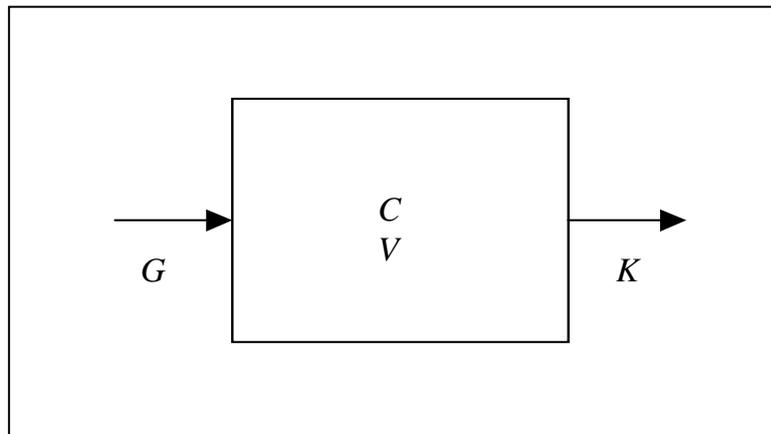

Fig.1. One compartment urea model. *V* – total water volume, *C* – urea concentration,
G – rate of urea generation, *K* – urea clearance.

For one compartment of urea distribution – total body volume V – the mathematical description of the balance of total urea mass is [4,32]:

$$\frac{d(VC)}{dt} = G - KC \qquad (1)$$

with the following solution:

$$C(t) = C_0 e^{-Kt/V} + \frac{G}{K}\left(1 - e^{-Kt/V}\right) \tag{2}$$

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 equation (2), 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 [10,31,32]. 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 (Figure 2, equation 3) with variable total body water, which could not be easily solved [32]. 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 [4,44,49].
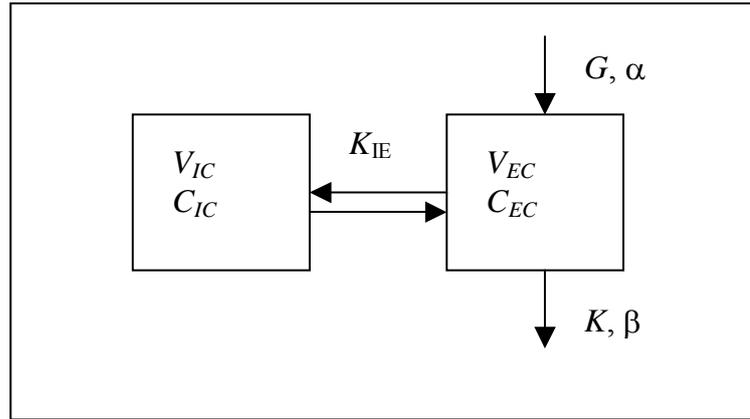

Fig.2. Two compartment urea model. K_{IE} – diffusive mass transport coefficient for urea, α – rate of fluid intake, β – rate of ultrafiltration during dialysis, other symbols as in Figure 1; subscripts: IC – intracellular compartment, EC – extracellular compartment.

The equations for the two compartment urea model are [32,51]:

$$\frac{d(V_{EC}C_{EC})}{dt} = G - KC_{EC} + K_{IE}(C_{IC} - C_{EC})$$
$$\frac{d(V_{IC}C_{IC})}{dt} = -K_{IE}(C_{IC} - C_{EC}) \tag{3}$$

where $V(t) = V(0) + (\alpha - \beta)t$, $V = V_{IC} + V_{EC}$. 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 [15,32,51]. Both (one and two compartment) models can also provide the urea generation rate G, which is an important indicator of patient's nutritional status [32,33].

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 [34,35]. 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.

2.2. SODIUM MODELING

Another aim of the artificial kidney is the removal of excess of water and regulation of ion content of the body [14,32,37]. The fast (and therefore short) treatments, which involve a 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 osmotic disequilibrium [52]. Sodium is a potent osmotic regulator of water distribution within the body [11,14]. 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 [27]. 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 physiological one, 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.

3. 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 [23]. The most popular form of peritoneal dialysis is continuous ambulatory peritoneal dialysis (CAPD), with consecutive four exchanges of dialysis fluid per day with about six hour 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 however, 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 [23]. 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 [13,42].

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 [5,23,29,45]. 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 more sophisticated than routine measurements. Some problems in peritoneal transport may be studied only using animal experiments. Mathematical modeling may help in analyzing peritoneal transport in four respects [45]: 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, 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 1 and 2, the three-pore model for 3, and the distributed model for 4. Below we discuss briefly these models. They are of more or less phenomenological character and attempt to provide effective mathematical description of experimental data rather than theoretical derivation of the description from detailed structure of the system.

3.1. 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 [23,29,43,45]:

$$\frac{dV_D}{dt} = Q_V$$

$$\frac{d(V_D C_D)}{dt} = Q_S$$

(4)

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.

3.2. 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 Figure 3.
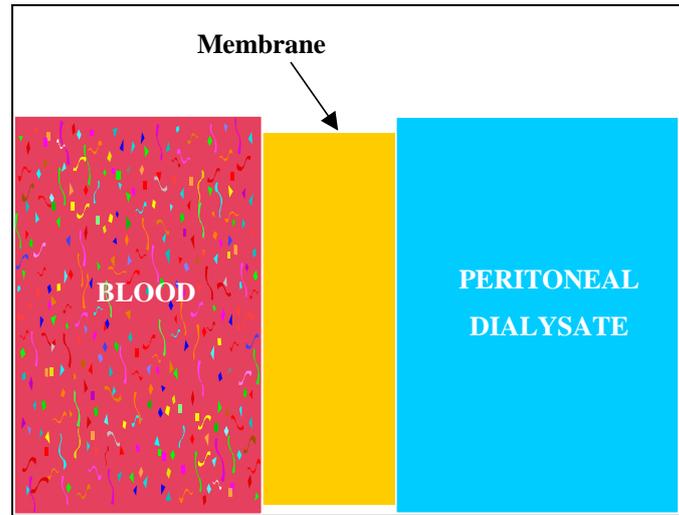

Fig.3. Schematic presentation of the assumptions for the membrane model that describes diffusive and convective transport processes through a permselective membrane between two well-mixed compartments for blood and peritoneal dialysate.

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 [45,47]:

$$Q_V = L_{PA}(\Delta P - \sum_i \sigma_i \Delta \Pi_i) - Q_A \qquad (5)$$

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 i-th 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 [47].

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 [12,29,42-45]:

$$Q_S = K_{BD}(C_B - C_D) + SQ_U C_M - Q_A C_D \qquad (6)$$

There are alternative versions of the model, which differ mainly in the description of the convective transport component [12,29,42-45].

To estimate the transport parameters for the mebrane model using equations 5 and 6 one needs to know the dialysis fluid volume and solute concnetrations 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 [21]. However, because markers are radioactively labelled (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 [29,44].

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.

3.3. THREE PORE MODEL

The pore model is based on a concept of the transport through a cylindrical uniform pore across the membrane [12,29]. 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 (Figure 4). The equations for water and solute transport are the same as for the membrane model (equations 5 and 6) 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 [12,29,45]: 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 Figure 5. 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 – Personal Dialysis Capacity – has been designed on the base of the three pore model and a set of data selected because of their clinical availability [12,29]. 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.
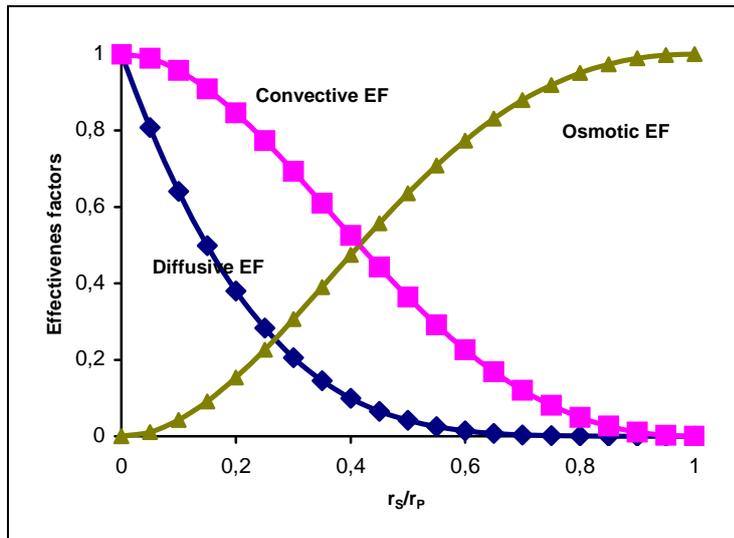

Fig.4. Effectivness factors calculated according to the pore model as a function of the ratio of molecular (Stokes) radius r_S to pore radius r_p. Diffusive effectiveness factor multiplied by solute diffusivity in water yields diffusive permebility of the pore, osmotic effectiveness factor is equivalent to Staverman reflection coefficient σ in equation 5, convective effectiveness factor is equivalent to sieving coefficient S in equation 6.
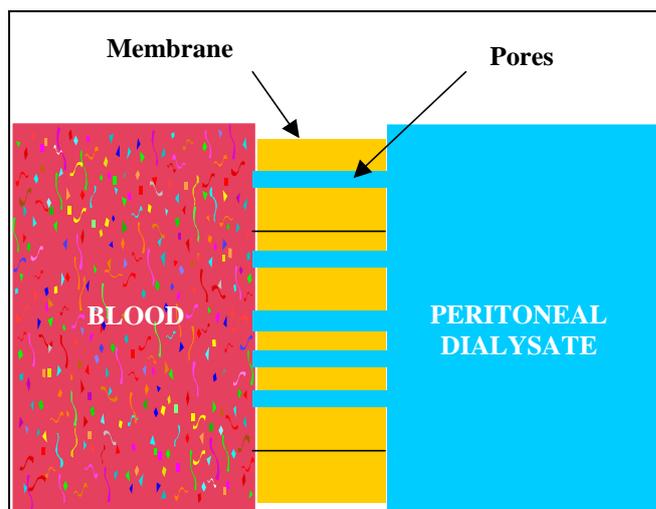

Fig.5. Schematic presentation of the three pore model for the membrane separating blood and dialysis fluid compartments with pores of different cross-section surface area.

3.4. DISTRIBUTED MODEL

Blood capillaries are placed within the tissue at different distance from the peritoneal surface (Figure 6). 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 three pore model [5,8,43,45]. 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 [45,46,48].
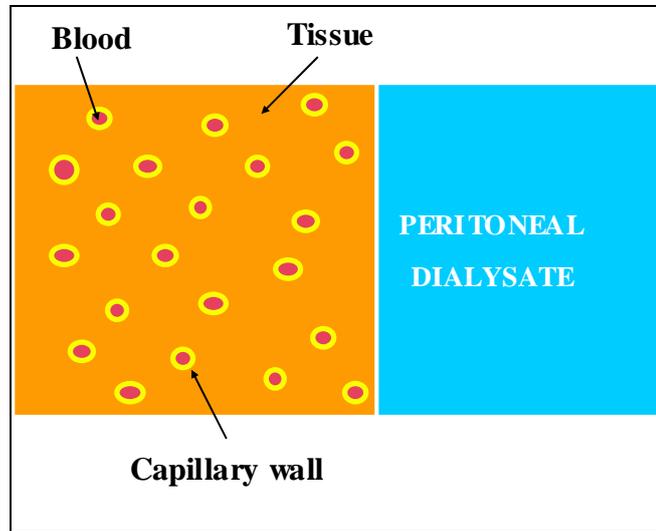

Fig.6. Schematic presentation of the distributed model for peritoneal transport with capillaries distributed within the tissue at different distances from the tissue surface.

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) [5,8,43,45,46,48]:

$$\frac{\partial(\theta C_T)}{\partial t} = -\frac{\partial j_{ST}}{\partial x} + q_{SBTL} \tag{7}$$

where θ is the void fraction, i.e. the fraction of tissue volume effectively available to the solute, C_T is solute concentration in the tissue, x is the distance from the tissue surface,

$$j_{ST}(x,t) = -D_T \frac{\partial C_T}{\partial x}(x,t) + S_T j_{VT} C_T(x,t) \tag{8}$$

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 fluid volumetric flux through the tissue, and:

$$q_{SBTL}(x,t) = k_B C_B - k_T C_T(x,t) - q_{VL} C_T(x,t) \qquad (9)$$

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 $K_{BD} = A\sqrt{D_T(k_T + q_{VL})}$, $S = S_T$, $Q_U = Aj_{VT}(x=0)$, where A is the tissue surface area [45,46]. C_B in this formula however has to be replaced, according to the distributed model, by the equilibrium concnetration of the solute in the tissue $C_{Teq} = \kappa C_B$, where $\kappa = k_B/(k_T + q_{VL})$; for macromolecules κ is substantially lower than 1.

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 [45] for more information).

4. 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 [1,2,32,38,50]. 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 ten years many new modalities for hemodialysis and peritoneal dialysis were introduced to clinical practice or are under investigation [19,30]. 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 [7,31]. 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

[6,15,17,24-26,28,50]. 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 [1,2,28,39,40,51]. 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 [1,2,3,16,18,20,22]. 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 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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