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MONOGRAPH SERIES: J.W. - THEORETICAL FOUNDATIONS FOR MODELING OF MEMBRANE TRANSPORT IN MEDICINE AND BIOMEDICAL ENGINEERING

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Introduction

Life is structured in the form of open nonequilibrium systems that continuously exchange matter and energy with the environment to support the internal physical and biochemical processes. Furthermore, matter and energy are also continuously transported inside the organisms and their internal distribution is mostly inhomogenous. Problems, associated with transport, arise at all levels of body organization and at all time scales, characteristic for the living organisms. The present monograph is focused only on a small section of mathematical models, meant to describe transport processes, related to life, at the interface of medicine and biomedical engineering.

The treatment of patients with the end stage renal disease needs the replacement of excretory function of the kidneys by artificial means, being it engineered devices (hemodialysis) or stimulation of blood purification by the dialysis fluid in the peritoneal cavity (peritoneal dialysis). Optimization of the treatment requires a quantitative description of transport of excess water and waste solutes across selectively permeable membranes and/or within the perfused tissue and between the tissue and its environment. Similar problems appear in cell physiology and physiology at the level of organs and the whole body, and in other branches of medicine, like, for example, oncology.

The main objective of the book is to present the mathematical and theoretical models that can be solved, at least approximately, in closed formulas, and relatively easily analyzed. Therefore, various approximations are discussed and applied, although in many cases the obtained solutions are quite precise for the range of conditions that appear in biological and medical applications. The basic physical laws for the transport processes are well known and we show how to apply these laws for different geometries of the system and various treatment conditions.

The simplest transport processes to be described mathematically are the (linear) diffusion of a solute in a fluid, gas or porous medium, driven by solute concentration gradient (described by the Fick law), and fluid transport in a porous medium (Darcy law), or straight cylindrical tube, driven by hydrostatic pressure (Hagen-Poiseuille law). The simplicity of the description of these processes comes from the linearity of the respective equations. More difficult and interesting mathematical problems arise if one needs to address the combined diffusive-convective transport of solutes and fluid flow driven by a combination of hydrostatic and osmotic pressures, the processes that are in general described by non-linear sets of equations for fluid and solute transport and need the concomi-

tant solution of all equations. We discuss in this book several problems of this kind and possible simplifications, especially for the steady states of transport.

The book contains a brief presentation of linear nonequilibrium thermodynamics, constituting the theoretical basis for the description of all phenomena discussed here. It contains also a short account of the models applied in the capillary physiology for the exchange between blood and tissue. The main subject are the transport processes taking place during the exchange of solutes between blood and the surrounding medium across the tissue and the exchange of fluid and solute between blood and dialysis fluid that flow inside and outside, repectively, the capillaries made of an artificial selectively permeable membrane in medical mass exchangers.

The focus at the mathematical aspects of the models demands some level of mathematical fluency, mostly in the methods for solving ordinary and partial differential equations. Furthermore, the reader may need to carry out some simple, but sometimes tiresome, algebraic transformations. The good introduction to the mathematical problems analyzed here is provided by the textbooks (Crank, 1975, Edelstein-Keshet, 1988, Evans, 1998, Keener, Sneyd, 1998, Press et al., 2007). For more information about nonequilibrium thermodynamics one may refer to (Bird et al., 1960, De Groot, Mazur, 1962, Katchalsky, Curran, 1967, Prigogine, 1968, Glansdorff, Prigogine, 1971, Guminski, 1983, Nelson, 2004, Fournier, 2007). Our description of physiological processes and medical procedures, which are analyzed in the book, is brief, and the readers unfamiliar with these problems may consult the medical and physiology textbooks (Gokal et al., 2000, Guyton, Hall, 2000, Drukker et al., 2004). Books and articles specific for each problem are cited in the respective sections.

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The thermodynamic principles of transport processes

The thermodynamic theory of transport is based on two principles: 1) equations of conservation of the transported physical variable (balance equations), and 2) thermodynamic relationships between fluxes and forces driving the movement of the respective quantities. The transported entity may be substance, energy, momentum, entropy, etc. The driving forces may be gradients of pressure, concentration, temperature, etc. We recall in this chapter the basic principles for the linear non-equilibrium thermodynamics that are derived and applied in the book.

While classic, equilibrium thermodynamics was formulated for macroscopic systems, its generalization for nonequilibrium processes, which may take place not far from equilibrium, and therefore may be described by equations linear in thermodynamic forces, require the generalized description in the terms of spatially distributed variables and their gradients. After short introduction to the history of nonequilibrium thermodynamics with the focus on transport of substance, Chapter 1.1, the local in space and time balance equations are presented in Chapter 1.2, whereas the principles of local nonequilibrium thermodynamics are reviewed in Chapter 1.3. The entropy is the key idea for both equilibrium and nonequilibrium thermodynamics. The equations for entropy flux and its local generation during dissipative processes are formulated in Chapter 1.4 with gradients of thermodynamic variables playing the role of thermodynamic forces. Lars Onsager generalized many previous experimental and theoretical results on different simple macroscopic processes, such as diffusion, heat flow, fluid flow, charge flow, etc., and on the cross effects, such as thermal diffusion, Dufour effect, graviosomosis, cross-diffusion in multicomponent systems, Knudsen effect, electrokinesis, etc., in the form of the linear relationships between thermodynamic fluxes and thermodynamic forces, and their general description is presented in Chapter 1.5. Finally, we present the mathematical expression for chemical potential, the key variable for the thermodynamic description of the spatial movement of matter, as a function of temperature, pressure and concentrations, and explain the idea of (ideal) osmotic pressure in a simple experimental setup in Chapter 1.6. A short summary of the presented theory is provided in Chapter 1.7.

1.1 Introduction

The principles of thermodynamics, formulated in the final form during the second half of the 19^{th} century, are focused basically on the equilibrium states of macroscopic matter and may predict only the direction of approach to the equilibrium state for the closed systems (the principle of the non-decreasing entropy). The detailed description of some nonequilibrium processes, like heat transfer, diffusion, gas and fluid flows, was formulated also in the second half of the 19^{th} century, but the integrated, general theory of nonequilibrium processes was developed in the first half of 20^{th} century as the linear nonequilibrium thermodynamics. The first general principles were formulated by Lars Onsager in 1931 (Onsager, 1931), and developed further later on by many investigators. The notion of the reflection coefficient, seminal for the membrane transport theory, was introduced by A. J. Staverman in 1951 (Staverman, 1951), and the general description of the membrane transport in application to the biological processes was developed by O. Kedem and A. Katachalsky in 1958 (Kedem, Katchalsky, 1958), with many later modifications and variants (Katchalsky, Curran, 1967). The important contribution to the final formulation of this theory was provided by K. S. Spiegler and O. Kedem in 1966 (Spiegler, Kedem, 1966).

The linear nonequilibrium thermodynamics provides the description of the processes not far from equilibrium and has a wide range of applications in biological problems. However, it has also many limitations and a lot of effort was made to analyze the open nonlinear systems far from equilibrium (Glansdorff, Prigogine, 1971). However, no theory with such generality as thermodynamics and linear nonequilibrium thermodynamics was formulated, even though some useful principles were found (Nicolis, Prigogine, 1977). Another approach was focused on the extension of the local equilibrium hypothesis and other modifications of the linear irreversible thermodynamics and yielded, for example, the telegraph equation for the spread of solutes within a membrane, instead of the diffusion equation (Lebon et al., 1980, del Castillo, Rodriguez, 1989).

Our presentation is reduced to those elements of the general theory that are necessary for derivation of the basic equations of the membrane transport, discussed and applied in this book. For a more general presentation see (De Groot, Mazur, 1962, Prigogine, 1968, Guminski, 1983, Baranowski, 1991).

1.2 Local balance equation

Let a denote the volume density of an extensive physical variable A. Then the mass balance equation states that the amount of the quantity at point $\mathbf{r}$ and time t may change due to the flux of this quantity $\mathbf{j}_A$ and the contribution from its local source q_A(see (Edelstein-Keshet, 1988) for the derivation of balance equations)

$$\frac{\partial a}{\partial t} = -\mathrm{div}\mathbf{j}_A + q_A. \tag{1.1}$$

Equation (1.1) is the mathematical formulation of the principle of local conservation of quantity A. However, in order to describe the flux and source of A some physical principles must be applied.

1.3 Local nonequilibrium thermodynamics

The macroscopic processes of transport dissipate energy and increase entropy, like, for example, diffusion, heat flow, viscous fluid and gas flows, etc. The general description of fluxes and forces that drive these processes may be derived from the local balance of entropy and the expression for the local source of entropy, related to macroscopic processes, such as movement of matter and chemical reactions. The nonequilibrium thermodynamics of spatially distributed systems assumes that local thermodynamic variables and potentials can be defined in the same way as in the thermodynamics of macroscopic systems. This is a non trivial assumption, because it states that in spite of the general lack of equilibrium from a location to another location in space and from one time moment to another time moment, the local equilibrium is maintained at each position and time and therefore the equilibrium laws can be applied locally. In particular, this means that the changes of thermodynamic quantities in space and time cannot be too fast (De Groot, Mazur, 1962, Prigogine, 1968, Guminski, 1983). Let us define the local extensive thermodynamic variables for an infinitesimal volume v: internal energy u, entropy s, and the number of particles n_i for a finite number of chemical species i, as well as local intensive variables: pressure P, temperature T, and chemical potential of species i, μ_i. Now we assume that the basic thermodynamic laws for the system are valid also for these local quantities (De Groot, Mazur, 1962, Katchalsky, Curran, 1967, Prigogine, 1968, Guminski, 1983):

1. The first law of thermodynamics (energy conservation law): the increase of internal energy is equal to the heat change minus the work performed by the system (the work here is reduced to a simple term related to the change of the volume due to pressure; the work may include many other terms, which are not used in our applications)

$$du = dq - Pdv. \tag{1.2}$$

2. The local generation of entropy, q_S, is always nonnegative, and is zero only for reversible processes. This may be described using the notation of equation (1.1) as

$$q_S \geq 0. \tag{1.3}$$

3. The relationship of the differential of internal energy to other thermodynamic variables

$$du = Tds - Pdv + \sum \mu_i dn_i. \tag{1.4}$$

The chemical potential μ_i is defined as the change of internal energy with the change of the number of molecules of i-th component, $\mu_i = \partial u/\partial n_i$, and is used for the description of systems with variable composition due to, for example, diffusion and/or osmosis; see Chapter 1.6 for its detailed description. Another formulation of equation (1.4) that is known as the Gibbs equation may be proposed

$$Tds = du + Pdv - \sum \mu_i dn_i. \tag{1.5}$$

The Gibbs equation provides a few other important relationships, as for example the Gibbs-Duhem equation

$$sdT - vdP + \sum n_i d\mu_i = 0. \tag{1.6}$$

To prove formula (1.6) we derive at first the integrated form of equation (1.4), i.e.,

$$u = sT - Pv + \sum n_i \mu_i. \tag{1.7}$$

We do not assume that u is a linear function of s, v and n_i, as it might be suggested by equation (1.4), but notice at first that u is a homogeneous function of the first order

$$u(\lambda s, \lambda v, \lambda n_i) = \lambda u(s, v, n_i) \tag{1.8}$$

which means that by increasing the system λ times one increases its internal energy also by λ. The variables s, v and n_i are extensive thermodynamic variables and increase proportionally to the increase in the size of the system, whereas the intensive thermodynamic variables T, P and μ_i do not change if the size of the system change. Upon differentiating equation (1.8) in λ we get

$$\frac{\partial u}{\partial \lambda}(\lambda s, \lambda v, \lambda n_i) = s\frac{\partial u}{\partial(\lambda s)} + v\frac{\partial u}{\partial(\lambda v)} + \sum n_i \frac{\partial u}{\partial(\lambda n_i)} = u(s, v, n_i). \tag{1.9}$$

Therefore, for $\lambda = 1$

$$u = s\frac{\partial u}{\partial s} + v\frac{\partial u}{\partial v} + \sum n_i \frac{\partial u}{\partial n_i}. \tag{1.10}$$

But, from equation (1.4): $\frac{\partial u}{\partial s} = T$, $\frac{\partial u}{\partial v} = P$, and $\frac{\partial u}{\partial n_i} = \mu_i$, and therefore equation (1.10) yields equation (1.7) for u. By calculating the differential of both sides of equation (1.7)

$$\begin{aligned} du = {} & Tds + sdT - Pdv - vdP \\ & + \sum \mu_i dn_i + \sum n_i d\mu_i \end{aligned} \tag{1.11}$$

and comparing with the Gibbs equation (1.5) one obtains the Gibbs-Duhem equation (1.6).

To apply the balance equation (1.1) we need the expression for concentrations of local thermodynamic variables defined as $s_v = s/v$, $u_v = u/v$, $c_i = n_i/v$, $v \neq 0$. For the constant v one obtains directly from the Gibbs equation

$$Tds_v = du_v - \sum \mu_i dc_i. \tag{1.12}$$

Equation (1.12) is also valid for variable v. To prove this, let us notice that the integrated Gibbs equation (1.7) yields

$$Ts_v = u_v + P - \sum c_i \mu_i \tag{1.13}$$

and from the Gibbs equation we get

$$Td\left(vs_v\right) = d\left(vu_v\right) - \sum \mu_i d\left(vc_i\right). \tag{1.14}$$

By differentiating and rearranging the terms of equation (1.14) one obtains

$$\left(Tds_v - du_v + \sum \mu_i dc_i\right) v = \left(-Ts_v + u_v + P - \sum \mu_i c_i\right) dv. \tag{1.15}$$

The expression in the parentheses on the right hand side of equation (1.15) is equal zero because of equation (1.13), and therefore equation (1.12) holds for variable $v \neq 0$.

For the systems with constant volume v, the change in the concentration of internal energy, du_v, is equal to the change in heat per unit volume, $\left(dq\right)_v = dq/v$, where for the open systems $dq = dq' + \sum \bar{H}_i dn_i$, dq' is the change of "pure" heat, and $\bar{H}_i$ is the partial molar enthalpy, defined as $\bar{H}_i = \mu_i + \partial s/\partial n_i$. Note that heat is not a state variable, and therefore we cannot define $q_v = q/v$, but only the heat increment per unit volume, $\left(dq\right)_v = dq/v$. Nevertheless (for the proof see (Katchalsky, Curran, 1967)),

$$du_v = \left(dq\right)_v. \tag{1.16}$$

Thus, we may consider the change of u_v as related to the flux and production of heat.

1.4 Flux and production of entropy

The local balance of internal energy in the system with constant volume is typically related to the transfer and source that are called heat flux $\mathbf{j}_q$ and heat source q_q,

$$\frac{\partial u_v}{\partial t} = -\mathrm{div}\mathbf{j}_q + q_q. \tag{1.17}$$

For the system components the mass balance is

$$\frac{\partial c_i}{\partial t} = -\mathrm{div}\mathbf{j}_i + q_i \tag{1.18}$$

and for entropy

$$\frac{\partial s_v}{\partial t} = -\mathrm{div}\mathbf{j}_s + q_s. \tag{1.19}$$

For the sake of simplicity, we assume now that there are no internal sources of heat and individual components inside the system (like, for example, chemical

reactions), i.e., $q_q = 0$ and $q_i = 0$. To obtain a physical interpretation of entropy flux and source, one may apply equation (1.12) in the form of time derivatives at a fixed point in space

$$\frac{\partial s_v}{\partial t} = \frac{1}{T}\frac{\partial u_v}{\partial t} - \frac{1}{T}\sum \mu_i \frac{\partial c_i}{\partial t}. \tag{1.20}$$

By combining equation (1.20) with equations (1.17) and (1.18), we obtain

$$\frac{\partial s_v}{\partial t} = -\frac{1}{T}\mathrm{div}\mathbf{j}_q - \frac{1}{T}\sum \mu_i \left(-\mathrm{div}\mathbf{j}_i\right). \tag{1.21}$$

Formula (1.21) may be modified using the general rule

$$\mathrm{div}\left(a\mathbf{j}\right) = a\mathrm{div}\mathbf{j} + \mathbf{j}\cdot\mathrm{grad}a \tag{1.22}$$

to obtain the following expression

$$\frac{\partial s_v}{\partial t} = -\mathrm{div}\left(\frac{1}{T}\left(\mathbf{j}_q - \sum \mu_i \mathbf{j}_i\right)\right) + \mathbf{j}_q \cdot \mathrm{grad}\frac{1}{T} + \sum \mathbf{j}_i \cdot \left(-\mathrm{grad}\left(\frac{\mu_i}{T}\right)\right). \tag{1.23}$$

Upon comparing equations (1.23) and (1.19), we get

$$\mathbf{j}_s = \frac{1}{T}\left(\mathbf{j}_q - \sum \mu_i \mathbf{j}_i\right) \tag{1.24}$$

$$q_s = \mathbf{j}_q \cdot \mathrm{grad}\left(\frac{1}{T}\right) + \sum \mathbf{j}_i \cdot \left(-\mathrm{grad}\left(\frac{\mu_i}{T}\right)\right). \tag{1.25}$$

The entropy source q_s may be therefore considered as the sum of products of flows and thermodynamic forces

$$q_s = \sum_m j_m X_m \tag{1.26}$$

where X_m is the thermodynamic force conjugated to flux j_m. In particular,

$$X_q = \mathrm{grad}\left(\frac{1}{T}\right) \tag{1.27}$$

$$X_i = \mathrm{grad}\left(-\frac{\mu_i}{T}\right). \tag{1.28}$$

In general, more external and dissipative forces need to be taken into account with dissipative fluxes that include rates of chemical reactions (scalars), fluxes of substance and heat (vectors), and viscosity effects of momentum flux (second order tensors).

The source of entropy can be presented in a simpler form if one calculates the gradients in equation (1.25) and reduces them to gradients of temperature and chemical potentials, i.e.

$$q_s = \frac{1}{T}\left(\mathbf{j}_s \cdot \mathrm{grad}\left(-T\right) + \sum \mathbf{j}_i \cdot \mathrm{grad}\left(-\mu_i\right)\right), \tag{1.29}$$

where the flux of entropy, equation (1.24), replaces the flux of heat. The function Tq_s is sometimes called the dissipation function. Equation (1.29) is especially convenient for the discussion of isothermic membrane processes, see Chapter 2.

1.5 Onsager principles for fluxes and thermodynamic forces

Although the expression for local production of entropy defines one specific, conjugated thermodynamic force related to each flux, the extensive experimental data, as well as statistical physics, demonstrate that each flux may be induced not only by its conjugated force but also by all other thermodynamic forces, i.e., in general, each flux is a function of all thermodynamic forces active in the system. The simplest assumption, called the Onsager principle, states that flux is a linear function of all thermodynamic forces:

$$J_m = \sum_n L_{mn} X_n \tag{1.30}$$

where L_{mn} are called phenomenological coefficients. The Onsager principle includes many interesting phenomena, such as, for example, thermodiffusion, Dufour effect, and, if we incorporate electromagnetism into the theory, also electrokinetic, thermoelectric, galvanomagnetic and thermomagnetic phenomena, etc.

Phenomenological coefficients. There are some restrictions on the phenomenological coefficient. The second principle of thermodynamics that requires the nonnegativity of q_S yields:

$$q_s = \sum_m j_m X_m = \sum_{m,n} L_{mn} X_n X_m \geq 0 \tag{1.31}$$

and, by the restrictions for coefficients of nonnegative polynomial of the second order,

$$\det(L_{mn}) \neq 0 \tag{1.32}$$

$$L_{mm} \geq 0 \tag{1.33}$$

$$L_{mm} L_{nn} - L_{mn} L_{nm} \geq 0. \tag{1.34}$$

Another restriction comes from the Curie principle that in the *isotropic* medium forbids the cross interactions between forces of different tensor types, i.e., a vector flux may be induced by combination of only vector forces, without interference of scalar and (second order) tensor forces. And finally, the Onsager reciprocity principle states that:

$$L_{mn} = L_{nm} \tag{1.35}$$

(for some coefficients the symmetry conditions must be replaced by antisymmetry, that is, the change of sign, see (Guminski, 1983)). The Onsager reciprocity relationships cannot be obtained from other principles of thermodynamics but, similarly as other laws of thermodynamics, may be derived from statistical physics.

All these restrictions on phenomenological coefficients play an important role in the analysis of specific nonequilibrium thermodynamic systems (Guminski, 1983).

Invariance of entropy production. The presentation of entropy production as the sum of products of fluxes and their respective conjugated forces is not unique. The linear transformation of fluxes may be accompanied by a linear transformation of forces without any change to production of entropy. Let us denote by $\mathbf{j}$ the vector constructed of all fluxes and by $\mathbf{X}$ the vector built of their respective conjugated forces. Now, let us transform the fluxes $\mathbf{j}$ to a new vector $\tilde{\mathbf{j}}$ and the forces $\mathbf{X}$ to a new vector $\tilde{\mathbf{X}}$ using a linear invertible matrix

$$\tilde{\mathbf{j}} = \mathbf{\Omega}\mathbf{j} \tag{1.36}$$

$$\tilde{\mathbf{X}} = \left(\mathbf{\Omega}^T\right)^{-1}\mathbf{X}. \tag{1.37}$$

Then

$$q_s = \tilde{\mathbf{j}}^T \cdot \tilde{\mathbf{X}} = (\mathbf{\Omega}\mathbf{j})^T \cdot \left(\mathbf{\Omega}^T\right)^{-1}\mathbf{X} = \mathbf{j}^T \cdot \mathbf{\Omega}^T \left(\mathbf{\Omega}^T\right)^{-1}\mathbf{X} = \mathbf{j}^T \cdot \mathbf{X}. \tag{1.38}$$

If the relationship between fluxes and forces, equation (1.30), is written in the vector notation,

$$\mathbf{j} = \mathbf{L}\mathbf{X} \tag{1.39}$$

then

$$\tilde{\mathbf{j}} = \tilde{\mathbf{L}}\tilde{\mathbf{X}} \tag{1.40}$$

where

$$\tilde{\mathbf{L}} = \mathbf{\Omega}\mathbf{L}\mathbf{\Omega}^T. \tag{1.41}$$

If $\mathbf{L}$ is a symmetric matrix conforming with the Onsager reciprocity relationships, then $\tilde{\mathbf{L}}$ is also a symmetric matrix.

1.6 Chemical potential and osmotic pressure

Chemical potential describes how the thermodynamic potentials, like, for example, internal energy u, change with the change in number of molecules in the system composed of a few species. More precisely

$$\mu_i = \frac{\partial u}{\partial n_i}, \tag{1.42}$$

compare equation (1.4). Chemical potential is a function of T, P and n_i. We derive now a specific description of this relationship for the systems that are studied in this book, i.e., liquid mixtures. For this purpose we need another thermodynamic potential, called the (Gibbs) free energy, which is defined as

$$g = u - Ts + Pv. \tag{1.43}$$

By differentiating and applying equation (1.4) we get

$$dg = -sdT + vdP + \sum \mu_i dn_i. \tag{1.44}$$

Thus

$$\mu_i = \frac{\partial g}{\partial n_i} \tag{1.45}$$

and

$$\frac{\partial \mu_i}{\partial P} = \frac{\partial}{\partial P}\frac{\partial g}{\partial n_i} = \frac{\partial}{\partial n_i}\frac{\partial g}{\partial P} = \frac{\partial v}{\partial n_i} \tag{1.46}$$

where $\partial g/\partial P = v$ from equation (1.44). By definition,

$$\bar{V}_i = \frac{\partial v}{\partial n_i} \tag{1.47}$$

is the parameter that describes how the volume changes due to the change of the amount of component i and is called the partial molar volume. Let us note that, because v is a homogenous function of the first order of n_i,

$$v = \sum n_i \frac{\partial v}{\partial n_i} = \sum n_i \bar{V}_i \tag{1.48}$$

or

$$\sum c_i \bar{V}_i = 1. \tag{1.49}$$

We assume now that $\bar{V}_i$ is a constant, what is approximately true for many liquid mixtures. Then, from equation (1.46)

$$\frac{\partial \mu_i}{\partial P} = \bar{V}_i \tag{1.50}$$

and, because $\bar{V}_i$ is constant,

$$\mu_i = \bar{V}_i P + \mu_i^c \left(T, c_i\right). \tag{1.51}$$

The Gibbs-Duhem equation (1.6) for constant temperature yields

$$-v dP + \sum n_i d\mu_i = 0 \tag{1.52}$$

and, by equations (1.51) and (1.48),

$$\sum n_i d\mu_i^c = 0. \tag{1.53}$$

To obtain a description of $\mu_i^c\left(T, c_i\right)$ one may consider an osmotic experiment in isothermic conditions with ideal semipermeable membrane (permeable only for a solvent) that separates a pure solvent w in an (formally) infinite container from a solution with a number of solutes in the same solvent in a finite volume container (Katchalsky, Curran, 1967). In the equilibrium state there is no flow of solvent across the membrane and its chemical potential, μ_w, must have the same value on both sides of the membrane. Concomittantly, the pressure of the solution, called osmotic pressure, π, and measured as the increment over the

pressure in the container with pure solvent, increases to an equilibrium value. Thus

$$d\mu_w = \bar{V}_w d\pi + d\mu_w^c = 0 \tag{1.54}$$

and therefore

$$d\mu_w^c = -\bar{V}_w d\pi. \tag{1.55}$$

On the other hand, from equation (1.53),

$$\sum n_i d\mu_i^c = -n_w d\mu_w^c \tag{1.56}$$

where the sum is taken only over all solutes dissolved in the solvent. Now,

$$\sum n_i d\mu_i^c = n_w \bar{V}_w d\pi. \tag{1.57}$$

By denoting the osmotic pressure, exerted by solute i as π_i, we have

$$d\pi_i = n_i d\mu_i^c / \left(n_w \bar{V}_w\right) \tag{1.58}$$

and

$$\sum \pi_i = \pi. \tag{1.59}$$

If we now define

$$\pi_i = \frac{RT}{\bar{V}_i} \frac{n_i \bar{V}_i}{n_w \bar{V}_w} = \frac{RT}{\bar{V}_i} \phi_i \tag{1.60}$$

we get

$$d\mu_i^c = RT d\ln\left(\phi_i\right) \tag{1.61}$$

where

$$\phi_i = \frac{n_i \bar{V}_i}{n_w \bar{V}_w} = \frac{c_i \bar{V}_i}{c_w \bar{V}_w}. \tag{1.62}$$

Equation (1.60), for the negligible volume of solutes, i.e., for $n_w \bar{V}_w \simeq v$, c.f. equation (1.48), is known as the van't Hoff law that describes osmotic pressure of diluted solution

$$\pi_i = RTc_i \tag{1.63}$$

and is used in most applications of transport theory in medicine and physiology (Van't Hoff, 1901, Staub, Taylor, 1984, Guyton, Hall, 2000).

Thus, in general,

$$\mu_w = \bar{V}_w P - \sum \left(\bar{V}_w / \bar{V}_i\right) RT\phi_i + \mu_w^0 \tag{1.64}$$

$$\mu_i = \bar{V}_i P - RT \ln\left(\phi_i\right) + \mu_i^0 \tag{1.65}$$

where constants μ_w^0 and μ_s^0 may depend on temperature. For the diluted (ideal) solutions, the simplified equations

$$\mu_w = \bar{V}_w P - \sum RTc_i + \mu_w^0 \tag{1.66}$$

$$\mu_i = \bar{V}_i P - RT \ln\left(c_i\right) + \mu_i^0 \tag{1.67}$$

are a good approximation and are typically applied for the analysis of biological transport systems.

1.7 Summary

1. Nonequilibrium linear thermodynamics is based on the local principle of conservation of extensive macroscopic variables (such as energy, entropy, number of molecules, etc.) and the extension of macroscopic thermodynamic relationships for the local, spatially distributed intensive variables (such as pressure, temperature, chemical potential) and spatial densities of extensive variables.
2. The local production (source) of entropy can be described as the sum of bilinear terms (the products of the flux of extensive thermodynamic variable and the thermodynamic force that is conjugated to this flux). The thermodynamic force is typically related to the gradient of the conjugated intensive thermodynamic variable. However, each flux can be, in general, induced by any of thermodynamic forces active in the system and its magnitude is proportional to the linear combination of all such forces with the parameters called the phenomenological coefficients.
3. The phenomenological coefficients are restricted by some symmetry conditions (as, for example, the Onsager reciprocity relationships).
4. The production of entropy is invariant with regard to linear transformations of fluxes and the respective linear transformation of thermodynamic forces.
5. The chemical potential, defined as the change of internal energy due to the change of the number of particles, is the key intensive thermodynamic variable for the systems with varying number of molecules. The chemical potential can be expressed, the other variables put apart, by osmotic pressure (equivalent to the hydrostatic pressure in osmotic experiments), and the osmotic pressure, in turn, by solute concentration.
6. The van't Hoff formula for diluted solutions relates osmotic pressure linearly to solute concentration.

2

Transport across permselective membrane

An important example of applications of linear nonequilibrium thermodynamics is constituted by the transport of fluid with diluted solutes across a permselective medium that is differentially permeable for solvent and solute, as, for example, in the transport across a porous membrane with pores permeable for fluid and partially restrictive to solute molecules. If the solute cannot permeate across the membrane permeable for solvent, then the membrane is called (ideally) semipermeable. It is worth remembering that similar problems and similar theoretical description appear also for the transport of a mixture of gases across selectively permeable membranes or media (Mason, Lonsdale, 1990, Taylor, Krishna, 1993, Fournier, 2007).

After a brief introduction in Chapter 2.1, we start with the specification of the general thermodynamic formalism for the case of the solvent and solute transport across semipermeable membrane in Chapter 2.2. Then, another formulation of the transport equations, the "practical" approach, developed initially by Kedem and Katchalsky (Kedem, Katchalsky, 1958, Katchalsky, Curran, 1967), and in its final form by Spiegler and Kedem (Spiegler, Kedem, 1966), is presented in Chapter 2.3. The most important feature of this practical approach is the combination of diffusive transport with the convective transport that depends explicitly on the volumetric (fluid and solutes) flux and avoids the involvement of pressure, the thermodynamic force that is often difficult to measure in biological systems. The important contribution by Spiegler and Kedem was to introduce into the theory the local intramembrane volumetric and solute fluxes and to derive the formulas for these fluxes using the boundary values of pressure and solute concentrations (Spiegler, Kedem, 1966). The Spiegler-Kedem-Katchalsky approach involved an important application of the reflection coefficient, introduced by Staverman on the basis of general thermodynamic considerations concerning the non-ideal permeable (semipermeable) membranes (Staverman, 1951). The local description of membrane transport opened the way to investigations of the relationship between the membrane structure and the net fluxes across it. In Chapter 2.4 we develop the formulas for the case of homogenous, flat or capillary, membrane, and then, in Chapter 2.5, for composite membranes. The nonlinear dependence of solute flux on volumetric flux, developed by Spiegler and Kedem, may be simplified to linear functions in some specific cases, as shown in Chapter 2.6.

An important case of the general theory is the combined diffusive and convective transport of solute across the cylindrical uniform pore perpendicular to the membrane surface, as described in Chapter 2.7. In this theory, hydrody-

namics and microscopic formulas for diffusion and convection within the pore, yield, beside the general formulas in agreement with the linear nonequilibrium thermodynamics, also useful expressions for the relationship between thermodynamic parameters and the size of (spherical) particle and the pore size. A short summary of the respective theory is provided in Chapter 2.8.

2.1 Introduction

The specification of the general linear nonequilibrium thermodynamics for membrane transport of solutes and solvent was an important task for those interested in biological, medical, and industrial applications of the membrane transport. Another branch of the membrane theory deals with the transport of gases and addresses specific problems, related to the separation of gases (Mason, Lonsdale, 1990, Taylor, Krishna, 1993, Fournier, 2007).

The diffusive solute transport in fluids was one of the earliest examples of successful mathematical description of transport processes, this description having been proposed by Adolph Fick in 1855 (Fick, 1855) on the basis of the earlier equation for heat transport. The formulation of the relationship between the ideal osmotic pressure and the concentration of osmotic agent by van't Hoff in 1886 provided the basis for the theoretical description of osmosis (Van't Hoff, 1901). However, only after Staverman had introduced the reflection coefficient, the formulation of general theory for fluid and solute transport in non-ideal membranes, and in particular for the fluid transport driven by combined hydrostatic and effective osmotic pressures, became possible (Kedem, Katchalsky, 1958, Katchalsky, Curran, 1967).

The concept of apparent pore of regular geometry in the capillary wall was introduced in 1951 by Pappenheimer (Pappenheimer et al., 1951). It was proposed to explain mechanistically the experimental data on the transport of fluid and solutes of different sizes. The theory was slowly developed during many years for pores of different geometry until its current formulation in 1980 (Mason et al., 1980); see (Deen, 1987) for the history and different applications of the pore model. Another important mechanistic theory that relates thermodynamic parameters to the structure of the membrane is the fiber matrix theory (Michel, Curry, 1999), which is not discussed in our book.

Besides the linear nonequilibrium thermodynamics, a few other theories were proposed to describe the transport processes in selectively permeable media/membranes, like, for example the formalism of friction coefficients and statistical-mechanical theory of membrane transport (Ogston, Michel, 1978, Mason, Lonsdale, 1990, Tanimura et al., 1993). However, most of the results on liquid phase membrane transport in biology, physiology and medicine were obtained using the practical Spiegler-Kedem-Katchalsky theory (Katchalsky, Curran, 1967, Keener, Sneyd, 1998, Michel, Curry, 1999, Waniewski, 2006, Fournier, 2007, Stamatialis et al., 2008). We present here the thermodynamic theory for non-electrolytes because our applications do not include the transport of charged

molecules and the effect of electromagnetic field; see (Katchalsky, Curran, 1967, Guminski, 1983) for the extension of thermodynamics onto electromagnetic phenomena. The transport processes in industrial systems are discussed in (Bird et al., 1960).

2.2 Fluxes of substance

The isothermic transport of a solvent with a number of dissolved solutes across permselective medium is an important special case of the general thermodynamic approach; most of the results presented in this book are related to this system. According to the general description of entropy production, equation (1.29), for an isothermic system,

$$q_s = \sum \mathbf{j}_i \cdot \frac{1}{T} \mathrm{grad}\,(-\mu_i). \tag{2.1}$$

Thus

$$j_w = L_{ww} \mathrm{grad}\,(-\mu_w) + \sum L_{wi} \mathrm{grad}\,(-\mu_i) \tag{2.2}$$

$$j_i = L_{iw} \mathrm{grad}\,(-\mu_w) + \sum L_{ij} \mathrm{grad}\,(-\mu_j) \tag{2.3}$$

where the coefficients L include the factor $1/T$. However, this representation of the relationships between fluxes and thermodynamic forces is not unique, because the same entropy production can be described as the sum of products of fluxes and conjugated forces in many ways, see Chapter 1.4. To derive an alternative, and more practical, description let us note that flux $\mathbf{j}_i$ of the i-th component is, by definition,

$$\mathbf{j}_i = c_i v_i \tag{2.4}$$

where v_i is the velocity of the i-th component. Therefore,

$$q_s = \sum c_i \mathbf{v}_i \cdot \frac{1}{T} \mathrm{grad}\,(-\mu_i). \tag{2.5}$$

Now, we select one component as the solvent, labelled by the index w, and the other components, labeled by the indexes k, as solutes, and, using the Gibbs-Duhem relationship, equation (1.52), in the form of

$$-dP + \sum c_i d\mu_i = 0 \tag{2.6}$$

we rewrite equation (2.5) as

$$q_s = \mathbf{v}_w \cdot \frac{1}{T} \mathrm{grad}\,(-P) + \sum c_k \left(\mathbf{v}_k - \mathbf{v}_w\right) \cdot \frac{1}{T} \mathrm{grad}\,(-\mu_k). \tag{2.7}$$

In the next step, we take into account the representation of μ_k, given by equation (1.51), which yields

$$\mathrm{grad}\mu_k = \bar{V}_k \mathrm{grad} P + \mathrm{grad}\mu_k^c \tag{2.8}$$

and formula (1.49), to derive

$$q_s = \mathbf{j}_v \cdot \frac{1}{T}\text{grad}\,(-P) + \sum \tilde{\mathbf{j}}_k \cdot c_k \frac{1}{T}\text{grad}\,(-\mu_k^c) \tag{2.9}$$

where

$$\mathbf{j}_v = \sum c_i \bar{V}_i \mathbf{v}_i \tag{2.10}$$

is the volume flux (the summation is over all solutes, including the solvent), and

$$\tilde{\mathbf{j}}_k = \mathbf{v}_k - \mathbf{v}_w \tag{2.11}$$

is the flux of the k-th solute relative to the solvent. The representation of entropy production by equation (2.9) allows us, by using the Onsager principle, to write

$$\mathbf{j}_v = -L_{vv}\text{grad}p - \sum L_{vk} c_k \text{grad}\mu_k^c \tag{2.12}$$

$$\tilde{\mathbf{j}}_k = -L_{kv}\text{grad}p - \sum L_{kj} c_j \text{grad}\mu_j^c \tag{2.13}$$

where the coefficients L include also the factor $1/T$. For dilute liquid solutions one can in many cases neglect the mutual interaction of solutes (thus $L_{kj} = 0$ for $j \neq k$) but their effect on volume flux must, in general, be considered. Therefore, upon neglecting mutual interactions among solutes, we are left with the equation

$$\tilde{\mathbf{j}}_k = -L_{kv}\text{grad}p - L_{kk} c_k \text{grad}\mu_k^c. \tag{2.14}$$

The fluxes have now the units of velocity. The coefficients L in equations (2.12) and (2.14) are, of course, different from those in equations (2.2) and (2.3), and have different units, but they can be related by a linear transformation (not shown here) that involves the state variables (concentrations).

2.3 The practical Spiegler-Kedem-Katchalsky equations

The Spiegler-Kedem-Katchalsky approach is based on three principles: 1) the hydrostatic pressure gradient is difficult to measure in biological application and should be avoided, whenever possible, in the transport equations, 2) the volume flux $\mathbf{j}_v$ is, to the contrary, easily measured and should be used in the transport equations whenever possible, and therefore 3) the solute flux $\mathbf{j}_s$ relative to the external, unmoving frame of reference (for example membrane) should be expressed by volume flux and diffusive thermodynamic force. This program can be carried out for dilute solutions and the so called "practical equations" can be derived from equations (2.12) and (2.14). For this purpose, we may assume that for dilute solutions the volume flux is equal to the solvent velocity $\mathbf{j}_v = \mathbf{v}_w$, because all other coefficients in equation (2.10) are negligible compared to $c_w \bar{V}_w$ that is close to one (the volume occupied by solutes in the solution is minor due

to their low concentration). Next, one assumes that, approximately, $\tilde{\mathbf{j}}_k = \mathbf{v}_k - \mathbf{j}_v$, and therefore

$$\mathbf{j}_k = c_k \mathbf{v}_k = c_k \tilde{\mathbf{j}}_k + c_k \mathbf{j}_v. \tag{2.15}$$

Furthermore, from equation (2.12),

$$-\mathrm{grad}p = \frac{1}{L_{vv}} \left(\mathbf{j}_v + \sum L_{vk} c_k \mathrm{grad}\mu_k^c \right) \tag{2.16}$$

and therefore

$$\tilde{\mathbf{j}}_k = \frac{L_{kv}}{L_{vv}} \mathbf{j}_v + \frac{L_{kv}}{L_{vv}} \sum L_{vj} c_j \mathrm{grad}\mu_j^c - L_{kk} c_k \mathrm{grad}\mu_k^c \tag{2.17}$$

or, neglecting again the mutual interactions among different solutes,

$$\tilde{\mathbf{j}}_k = \frac{L_{kv}}{L_{vv}} \mathbf{j}_v - \frac{L_{vv} L_{kk} - L_{kv} L_{vj}}{L_{vv}} c_k \mathrm{grad}\mu_k^c. \tag{2.18}$$

Taking into account that, by equation (1.58), for dilute solution we have

$$c_k \mathrm{grad}\mu_k^c = \mathrm{grad}\pi_k = RT \mathrm{grad}c_k \tag{2.19}$$

we may write

$$\mathbf{j}_k = -\frac{L_{vv} L_{kk} - L_{kv} L_{vj}}{L_{vv}} c_k RT \mathrm{grad}c_k + \left(1 + \frac{L_{kv}}{L_{vv}} \right) c_k \mathbf{j}_v. \tag{2.20}$$

Therefore, from equation (2.12),

$$\mathbf{j}_v = -\lambda_p \left(\mathrm{grad}p - RT \sum \sigma_k \mathrm{grad}c_k \right) \tag{2.21}$$

and, from equation (2.20),

$$\mathbf{j}_k = -\omega \mathrm{grad}c_k + (1 - \sigma)\, c_k \mathbf{j}_v \tag{2.22}$$

where

$$\lambda_p = L_{vv} \tag{2.23}$$

$$\omega_k = RT \frac{L_{vv} L_{kk} - L_{kv} L_{vk}}{L_{vv}} c_k \tag{2.24}$$

$$\sigma = -\frac{L_{kv}}{L_{vv}} = -\frac{L_{vk}}{L_{vv}} \tag{2.25}$$

because, by the Onsager reciprocity law, $L_{kv} = L_{vk}$. The parameter σ is called the Staverman reflection coefficient, ω is the diffusive permeability, and λ_p – the hydraulic conductivity of the membrane. The parameter $S = 1 - \sigma$ is called sieving coefficient. Thus, pressure is explicitly excluded from the solute transport

equation and the solute transport may be analyzed as a combination of diffusive transport and convective transport with volume flux. However, the pressure gradient is still the driving force for volume flux.

The definition of solute concentration within the membrane calls for a comment. The electrochemical potential, which includes electrical, magnetic, pressure, surface tension, and intermolecular forces, is continuous through the boundary of the membrane, however, the solute concentration in free solution, c_∞, is usually not equal to the solute concentration in the water phase inside the membrane, c_m, at the membrane surface (Spiegler, Kedem, 1966). This fact is taken into account by using the partition coefficient, $\Phi = c_m/c_\infty$, which is assumed to be $\Phi = \exp(-\Delta E_i/RT)$, where ΔE_i is the difference in potential energy, other than chemical energy, acting on the solute inside and outside the membrane. However, the solute concentration inside the membrane cannot usually be measured. Therefore, one may rescale the intramembrane concentration as $c = \Phi c_m$, and the so defined concentration c is continuous across the membrane boundary (Spiegler, Kedem, 1966). An equivalent definition of c may be also formulated for flat membrane as follows: $c = c(x)$ is the solute concentration in an aqueous solution that would be at equilibrium with the membrane in an imaginary infinitesimal slit parallel to the membrane surface at point x inside the membrane (Merten, 1969). This definition of solute concentration c is applied in most studies on membrane transport. See Chapters 2.4 and 2.7 for broader discussion and exemplary applications of the partition coefficient, and the analysis of the change of pressure at the membrane boundary.

2.4 The homogeneous permselective membrane

Flat membranes. In the case of transport across a flat permselective membrane of thickness δ, the general transport equations for solvent and one solute, transported in the direction x, perpendicular to the membrane surfaces, are simplified to

$$j_v = -\lambda_p \left(\frac{dP}{dx} - \sigma RT \frac{dc}{dx} \right) \tag{2.26}$$

$$j_s = -\omega \frac{dc}{dx} + (1-\sigma) j_v c \tag{2.27}$$

where c is the concentration of the solute. Note that index "s" denotes now "solute" instead of entropy, as this was the case in previous chapters. If the membrane is also homogeneous, i.e., the local transport parameters, σ, ω and λ_p are independent of x, and we consider the steady state of transport (that means, in particular, that j_v and j_s are independent of x, because only then the inflow and outflow at any point are balanced), then we may describe the fluxes using the constant boundary values of pressure and concentration, i.e., integrate the equations (2.26) and (2.27). The integration of equation (2.26) is straightforward and yields

$$j_v = L_p \left(\Delta P - \sigma RT \Delta c \right) \tag{2.28}$$

where $L_p = \lambda_p / \delta$, $\Delta P = P(0) - P(\delta)$, and $\Delta c = c(0) - c(\delta)$, with P and c denoting, respectively, the pressure and concentrations inside the membrane (see the comments in Chapter 2.3, further on in this Chapter, and in Chapter 7 on the definitions of intramembrane concentration and pressure). A similarly straightforward integration of equation (2.27) yields

$$j_s = P_d \Delta c + (1 - \sigma) j_v \bar{c} \tag{2.29}$$

where $P_d = \omega / \delta$, and $\bar{c} = \int_0^\delta c(x)\, dx / \delta$ is the mean intramembrane concentration. In order to find $c(x)$ let us notice that equation (2.27) is the first order ordinary differential equation for c with constant parameters and its solution for $(1 - \sigma) j_v \neq 0$ is

$$c(x) = \gamma + (c(0) - \gamma) \exp\left((1 - \sigma) j_v x / \omega \right) \tag{2.30}$$

where $\gamma = j_s / \left((1 - \sigma) j_v \right)$. We may now express γ as function of $c(\delta)$ and $c(0)$ using equation (2.30) for $x = \delta$ and present $c(x)$ as

$$c(x) = \frac{1 - \exp\left(Pe \cdot x / \delta \right)}{1 - \exp(Pe)} c(\delta) + \frac{\exp\left(Pe \cdot x / \delta \right) - \exp(Pe)}{1 - \exp(Pe)} c(0) \tag{2.31}$$

where

$$Pe = \frac{(1 - \sigma) j_v}{P_d} \tag{2.32}$$

is the scaling parameter, called Peclet number, describing the relative importance of the convective versus the diffusive transport processes. The mean concentration can now be calculated as

$$\bar{c} = (1 - f) c(0) + f c(\delta) \tag{2.33}$$

where

$$f = \frac{1}{Pe} - \frac{1}{\exp(Pe) - 1}. \tag{2.34}$$

Finally,

$$j_s = P_d \Delta c + (1 - \sigma) j_v \left((1 - f) c(0) + f c(\delta) \right). \tag{2.35}$$

After algebraic transformations, equation (2.35) can be rewritten in another, frequently applied form, namely

$$j_s = (1 - \sigma) j_v c(0) \frac{1 - \left(c(\delta) / c(0) \right) \exp(-Pe)}{1 - \exp(-Pe)} \tag{2.36}$$

which is valid for $j_v \neq 0$. While equation (2.35) makes the diffusion term explicit and then adds the convective term, modified by diffusion (because f depends on diffusive permeability P_d), equation (2.36) stresses the convective transport with

diffusive parameter hidden in Pe. Notice that $j_s = (1-\sigma) j_v c(0)$ for $Pe \to +\infty$, i.e., for the prevailing convective transport.

Whereas P_d can be measured in experiments on pure diffusion, $j_v = 0$, a method for the membrane reflection coefficient σ is called isolated ultrafiltration and consists in collecting on the other side of the membrane $x = \delta$ ultrafiltrate, so that in the steady state $j_s = j_v c(\delta)$. Then, combining this condition with equation (2.36) yields the sieving coefficient of the membrane, S_M,

$$S_M \equiv \frac{c(\delta)}{c(0)} = (1-\sigma)\frac{1-\exp(-Pe)}{1+\exp(-Pe)} \tag{2.37}$$

that can be directly calculated from the measured $c(\delta)$ and $c(0)$. Equation (2.37) is a nonlinear equation for σ, because Pe is proportional to $1-\sigma$, but it can be solved numerically, if S_M is known. Only for high values of Pe, $S_M = (1-\sigma)$. In general, one can define a (local) sieving coefficient for the membrane material as $S = (1-\sigma)$. Then, $0 \le S_M \le S$.

Pure diffusive transport. If $j_v = 0$, then the solute transport equation takes a simple form

$$j_s = P_d \Delta c \tag{2.38}$$

with the linear intramembrane concentration profile

$$c(x) = c(0) - (c(0) - c(\delta))\frac{x}{L} \tag{2.39}$$

and the mean intramembrane concentration

$$\bar{c} = 0.5\,(c(0) + c(\delta)) \tag{2.40}$$

i.e., with $f = 0.5$.

Bulk boundary values. In most applications, the concentrations in the bulk solutions outside the membrane, $c_b = c_\infty$, are measured and applied in the transport equations. To transform our equations, derived for the intramebrane boundary values, into the equations with the boundary values expressed by the bulk concentrations, one has to use the equilibrium distribution (partitioning) coefficient $\Phi = c_m/c_b$, relating the concentration in the membrane c_m to the bulk concentration c_b. It is sometimes assumed that pressure is continuous across the membrane boundary, but this assumption leads to inconsistency in the description of osmotic pressure. Therefore, we assume, following Merten (Merten, 1969), that the pressure at the membrane boundary changes because of osmotic force according to the solute distribution coefficient

$$P_m = P_b - (\pi_b - \pi_m) = P_b - (1-\Phi)\,\pi_b \tag{2.41}$$

for $\pi = RTc$. With this assumption on the effect of boundary distribution coefficients, the transformation of the transport equations (2.28) and (2.35) to the form with the bulk values of pressure and concentration requires only the recalculation of the coefficients, while the form of equations remains intact. In

particular, for homogenous membrane, i.e., the one with the same distribution coefficient at both boundaries, we have

$$j_v = L_p \left(\Delta P_b - \sigma_b RT \Delta c_b \right) \tag{2.42}$$

$$j_s = P_{db} \Delta c_b + S_b j_v \left((1-f)\, c_b\,(0) + f c_b\,(\delta) \right) \tag{2.43}$$

where

$$\sigma_b = 1 - (1-\sigma)\,\Phi \tag{2.44}$$

$$P_{db} = P_d \Phi \tag{2.45}$$

$$S_b = (1-\sigma)\,\Phi \tag{2.46}$$

and L_p is not changed. Notice that $S_b = 1 - \sigma_b$ and therefore it fulfills the thermodynamic relationship $S = 1 - \sigma$, which is demanded by the Onsager reciprocity principle. The description of the ideal semipermeable membrane, which may be interpreted as corresponding to $\Phi = 0$, by the theory, presented here, yields (correctly) $\sigma_b = 1$ (see Chapter 1.7 on osmotic pressure). The applied assumptions allow for smooth transition to the limit of ideal semipermeability as a special case and for consideration of the boundary phenomena consistently for solutes of all sizes. Its applicability can, however, vary for different types of membranes. For other hypotheses about boundary partition phenomenon see (Merten, 1969).

Capillary membranes. For homogenous capillary membranes one may typically assume the cylindrical symmetry of the membrane and boundary conditions (i.e., independence of the angular variable) and then the global description of fluxes across the membrane depends on the internal, r_{in}, and the external, r_{ex}, radii of the capillary. We assume also that there is no flux along the membrane. If j_s and j_v are the radial fluxes at the distance r from the center of the capillary, then

$$j_v = -\lambda_p \left(\frac{dP}{dr} - \sigma RT \frac{dc}{dr} \right) \tag{2.47}$$

$$j_s = -\omega \frac{dc}{dr} + (1-\sigma)\, j_v c. \tag{2.48}$$

By the conservation law, the total flux j_{tot} across the circle of radius r in the steady state must be the same for all $r_{in} \leq r \leq r_{ex}$, and therefore $j_{tot} = 2\pi r j\,(r) = const$; this statement is valid for both volume and solute fluxes. Therefore, the transport equations can be presented as

$$j_{tot,v} = -\lambda_p 2\pi r \frac{d\,(P - \sigma RTc)}{dr} \tag{2.49}$$

$$j_{tot,s} = -\omega 2\pi r \frac{dc}{dr} + (1-\sigma) j_{tot,v} c. \tag{2.50}$$

Equations (2.49) and (2.50) are the linear differential equations with variable coefficients

$$\frac{d\left(P-\sigma RTc\right)}{dr}+\frac{j_{tot,v}}{\lambda_p 2\pi r}=0 \tag{2.51}$$

$$\frac{dc}{dr}-\frac{(1-\sigma)j_{tot,v}}{\omega 2\pi r}c+\frac{1}{\omega 2\pi r}j_{tot,s}=0. \tag{2.52}$$

Let us consider first the equation (2.52) for purely diffusive solute transport, i.e., for $j_v = 0$. Its solution is

$$c\left(r\right)=c\left(r_{in}\right)-\frac{j_{tot,s}}{2\pi\omega}\ln\left(\frac{r}{r_{in}}\right) \tag{2.53}$$

and, for $r = r_{ex}$,

$$j_{tot,s}=2\pi\frac{\omega}{\ln\left(r_{ex}/r_{in}\right)}\left(c_{in}-c_{ex}\right)=2\pi r_m\frac{\omega}{\delta}\left(c_{in}-c_{ex}\right) \tag{2.54}$$

where $\delta = r_{ex} - r_{in}$ is the thickness of the membrane and r_m is the logarithmic mean radius defined as

$$r_m=\frac{r_{ex}-r_{in}}{\ln r_{ex}-\ln r_{in}}. \tag{2.55}$$

Finally,

$$j_{tot,s}=P_{rd}\left(c_{in}-c_{ex}\right) \tag{2.56}$$

where $P_{rd} = 2\pi r_m\omega/\delta = 2\pi\omega/\ln\left(r_{ex}/r_{in}\right)$.

The identical reasoning for equation (2.51) yields

$$\begin{aligned} j_{tot,v} &= 2\pi\frac{\lambda_p}{\ln(r_{ex}/r_{in})}\left(P_{in}-P_{ex}-\sigma RT\left(c_{in}-c_{ex}\right)\right) \\ &= 2\pi r_m\frac{\lambda_p}{\delta}\left(P_{in}-P_{ex}-\sigma RT\left(c_{in}-c_{ex}\right)\right) \end{aligned} \tag{2.57}$$

or

$$j_{tot,v}=L_{rp}\left(P_{in}-P_{ex}-\sigma RT\left(c_{in}-c_{ex}\right)\right) \tag{2.58}$$

where $L_{rp} = 2\pi r_m\lambda_p/\delta$.

The solution of the general transport equation for the solute, equation (2.52) with $(1-\sigma)\, j_v \neq 0$, is

$$c\left(r\right)=\frac{j_{tot,s}}{\left(1-\sigma\right)j_{tot,v}}+\left(c\left(r_{in}\right)-\frac{j_{tot,s}}{\left(1-\sigma\right)j_{tot,v}}\right)\left(\frac{r}{r_{in}}\right)^b \tag{2.59}$$

where

$$b=\frac{\left(1-\sigma\right)j_{\mathrm{tot,v}}}{2\pi\omega}=\frac{\left(1-\sigma\right)j_{\mathrm{v}}}{\omega}r. \tag{2.60}$$

By applying equation (2.59) for $r = r_{ex}$ and using the formula $\left(r/r_{in}\right)^b = \exp\left(b\ln\left(r/r_{in}\right)\right)$, one gets the formula for solute flux

$$j_{tot,s}=\left(1-\sigma\right)j_{tot,v}c_{in}\frac{1-\left(c_{ex}/c_{in}\right)\exp\left(-Pe_c\right)}{1-\exp\left(-Pe_c\right)} \tag{2.61}$$

where

$$Pe_c = b \ln (r_{ex}/r_{in}) = \frac{(1-\sigma)\, j_{tot,v}}{P_{rd}} = \frac{(1-\sigma)\, j_v}{\omega/r} \tag{2.62}$$

which is analogous to formula (2.36) for flat membrane. Note that if $j_{tot,v} \to 0$, then formula (2.61) tends to formula (2.56). If one wants to present explicitly the diffusive component in equation (2.61), then

$$j_{tot,s} = P_{rd}\,(c_{in} - c_{ex}) + (1-\sigma)\, \mathrm{j}_{tot,v}\,((1-f_c)\, c_{in} + f_c c_{ex}) \tag{2.63}$$

where

$$f_c = \frac{1}{Pe_c} - \frac{1}{\exp(-Pe_c) - 1}. \tag{2.64}$$

If the curvature of the capillary circumference is low, i.e., $\delta << r_{in}$, then P_c may be approximated by $P = \omega/\delta$ for flat membrane, see equation (2.29).

2.5 Composite membranes

Artificial permselective membranes may be sometimes considered homogenous, as, for example, the dialysis membranes, but both artificial and biological membranes are more or less heterogeneous. A good example is the distribution of pore size in the membrane, which can sometimes be approximated by a few types of pores (multi-peak distribution with narrow peaks). If, locally, the pores of different size are intermixed, one may assume that the outer concentration is the same for all pores if there is enough mixing in the external solutions. Thus, with such assumptions one can discuss heterogeneous/heteroporous membranes. Another kind of complexity results from different transport characteristics in the layers of the membrane parallel to the membrane surface. Thus, one may discuss also multilayer membranes. Of course, there might be a mixture of heteroporosity and multilayerness, and also some other types of membranes with locally different physical transport mechanisms occur. However, the two basic types of complex membrane, heterogeneous/heteroporous and multilayer, are the most often analyzed examples of composite membranes (Waniewski, 1994b).

a) Heteroporous membranes

If a membrane consists of a number of different local component regions, each occupying the fraction of area α_i, i.e. $\sum \alpha_i = 1$, with fluxes j_{vi} and j_{si} across the i-th component, each set of fluxes being described by equations (2.28) and (2.35) with parameters L_{pi}, P_i and σ_i, then the overall fluxes are, by definition

$$j_v = \sum \alpha_i j_{vi} \tag{2.65}$$

$$j_s = \sum \alpha_i j_{si}. \tag{2.66}$$

Thus, if the boundary values of pressure and solute concentrations are the same at the membrane surface of all its components (patches) then j_v and j_s may be described by equations (2.28) and (2.35) with the following expressions for parameters

$$L_p = \sum \alpha_i L_{pi} \tag{2.67}$$

$$P = \sum \alpha_i P_i \tag{2.68}$$

$$\sigma = \frac{\sum \alpha_i \sigma_i L_{pi}}{L_p} \tag{2.69}$$

$$S = \frac{\sum \alpha_i (1 - \sigma_i) j_{vi}}{j_v} \tag{2.70}$$

$$f = \frac{\sum \alpha_i \left(1 - \sigma_i\right) j_{vi} f_i}{S j_v}. \tag{2.71}$$

Note that $S = 1 - \sigma$ only if $\sigma_i = 0$ for all i, or $\sigma_i = 1$ for all i, and/or if $\Delta c = 0$ (because, if $\Delta c = 0$, then $j_v = L_p \Delta p$ and $j_{vi} = L_{pi} \Delta p$ for all i); however, equation $S = 1 - \sigma$, which is the result of the reciprocity principle for thermodynamic parameters in homogenous membrane, may be violated for heterogeneous membrane. This happens, for example, for a solute with $0 < \sigma < 1$, applied as a (non-ideal) osmotic agent. In general, S depends on j_v and its decomposition into j_{vi} and therefore may change with the change of volume fluxes.

b) Multilayer membrane

Let us consider a membrane that is composed of n layers in stack, each of which is characterized by parameters L_{pi}, P_i and σ_i. In the steady state: $j_s = j_{si}$ and $j_v = j_{vi}$ for all i, and $\Delta p = \sum \Delta p_i$ and $\Delta c = \sum \Delta c_i$ (Sigdell, 1982). We aim at the presentation of the fluxes as functions of the boundary values of variables in formulas similar to those for each homogenous layer separately. A method to solve the problem is to write equations for all layers and try to eliminate the values of variables at the contact between the layers. By proceeding in this way, one can obtain closed formulas for j_v, but only in some special cases:

1. No osmotic force, for example, all $\sigma_i = 0$, or constant concentration of the solute in the whole membrane system. Then

$$j_v = L_p \Delta p \tag{2.72}$$

with

$$\frac{1}{L_p} = \sum \frac{1}{L_{pi}}. \tag{2.73}$$

2. No gradient of hydrostatic pressure, $p = const$, within the membrane system. Then

$$j_v = L_p \sigma \Delta c \tag{2.74}$$

with

$$\frac{1}{L_p\sigma} = \sum \frac{1}{L_{pi}\sigma_i}. \tag{2.75}$$

3. The reflection coefficients are the same for all membrane layers, i.e., all $\sigma_i = \sigma$. Then

$$j_v = L_p \Delta P - \sigma L_p RT \Delta c \tag{2.76}$$

where L_p is described by formula (2.73) and $L_p\sigma$ by formula (2.75).

Unfortunately, in the general case, the system of equations for the layers yields nonlinear equation with the boundary (for the system) values of variables and the nonlinearly combined fluxes j_v and j_s, which can be solved only numerically. However, the solution for j_v depends, besides the system variables, also on the solute flux j_s and is of no practical usefulness. This problem, though, can be resolved to some extent for the solute flux that can be expressed in the closed formula as a function of the boundary solute concentrations and volumetric flux j_v.

It is convenient to present the equation (2.35) for j_{si} using unidirectional clearances k, i.e.

$$j_{si} = k_{1,i}c_{1,i} - k_{2,i}c_{2,i} \tag{2.77}$$

where $c_{1,i} = c_{2,i-1}$ is the solute concentration at the border of layers $i-1$ and i, for $i = 2, ..., n$, $k_{1,i} = P_i + S_i j_V (1 - f_i)$, $k_{2,i} = P_i - S_i j_V f_i$, and f_i is defined by equation (2.34) with the transport parameters for the i-th membrane. In the case of pure diffusive transport, $j_v = 0$, $k_{1,i} = k_{2,i} = P_i$ and overall permeability, P, may be calculated from the formula

$$\frac{1}{P} = \sum \frac{1}{P_i}. \tag{2.78}$$

However, in the general case of $j_v > 0$, both P and S depend on j_v. Note that, for $j_v > 0$, $k_{1,i} > 0$ for all i, but the signs of $k_{2,i}$ may vary depending on the values of the transport parameters and the value of $j_v > 0$. If the equation for j_s as a function of boundary concentrations $c_1 = c_{1,1}$ and $c_2 = c_{2,n}$ is also written using unidirectional clearances

$$j_s = k_1 c_1 - k_2 c_2 \tag{2.79}$$

then, for two layers, $n = 2$,

$$k_1 = \frac{k_{1,1}k_{1,2}}{k_{1,1} + k_{2,2}} \tag{2.80}$$

$$k_2 = \frac{k_{2,1}k_{2,2}}{k_{1,1} + k_{2,2}} \tag{2.81}$$

assuming $k_{1,1} + k_{2,2} \neq 0$. For more than two layers equations (2.80) and (2.81) may be obtained by induction (Sigdell, 1982). If j_s is to be presented in the form of equation (2.35), then one has to express the membrane transport parameters by unidirectional clearances

$$P = \frac{k_1 + k_2}{2} + \frac{k_1 - k_2}{2}(2f - 1) \tag{2.82}$$

$$S = \frac{k_1 - k_2}{j_v} \tag{2.83}$$

where k_1 and k_2 are unidirectional clearances for the whole membrane. Notice that equations (2.82) and (2.83) describe the general relationship between transport parameters and overall unidirectional clearances, and therefore are independent of the number of membranes in the stack. Parameters k_1, k_2, as well as P and S, are functions not only of the transport parameters for all layers, but of j_v as well. The sieving coefficient may be, in principle, anomalous, taking, for example, negative values for some membranes and specific rates of j_v. Note also that the factor f in the formula for P in equation (2.82) may be defined as an independent parameter under the condition that the mean intramembrane concentration is defined as $\bar{c} = (1 - f)\, c_1 + f c_2$. This observation demonstrates some arbitrariness in the definition of P and the mean intramembrane concentration. If factor f is to be defined as for homogeneous membranes, see equations (2.34) and (2.32), then formula (2.82) is actually a nonlinear equation for P. If $f = 0.5$, then $P = (k_1 + k_2)/2$.

The formula (2.79) for j_s as a function of j_v, c_1 and c_2, could be in principle inverted and provide a description of j_v as a function of j_s, c_1 and c_2, but this can be done in general only numerically. This illustrates the problem with the description of the volume flux across the multilayer membrane: we do not have any simple formula for the general case and the system of equations for all layers must be solved numerically, except for some special cases mentioned above.

2.6 Approximations for solute flux through permselective membrane

In the "practical" Spiegler-Kedem-Katchalsky approach to the thermodynamic description of solute transport, given by equations (2.28) and (2.29), the solute flux, j_s, is a nonlinear function of volume flux, j_v, and the transport parameters, P and σ. Nevertheless, the nonlinear equation (2.29), with f given by equations (2.34), may be approximated by its linear analogue with the factor f equal to a constant value F, which is selected according to the range of the Peclet number characteristic for the investigated problem (Waniewski, 1994a). The most widely used approximation is $F = 0.5$ for low values of Pe, $Pe < 1$. Other important cases are: $F = 0$ for large positive volume fluxes with $Pe \to \infty$ (approximation is good practically for $Pe >> 10$), and $F = 1$ for large negative volume fluxes with $Pe \to -\infty$ (approximation is good practically for $Pe << -10$). Another good approximation may be provided by $F = 1/3$ for $0 < Pe < 3$ (Waniewski, 1994a).

The original Kedem-Katchalsky formula for $\bar{c}$ with logarithmic mean of $c(0)$ and $c(\delta)$, $\bar{c} = (c(0) - c(\delta)) / (\ln(c(0)) - \ln(c(\delta)))$, was extensively discussed

and finally abandoned (Katchalsky, Curran, 1967, Bressler, Wendt, 1969); yet, its real meaning has not been recognized for a long time. It is a particular case of the linear approximations for j_s for the convective transport in the opposite direction than the diffusive transport and is strictly valid if $j_s = 0$ (Waniewski, 1994a). It is, however, worth noting that the general formula for $\bar{c}$ may be presented as the generalized logarithmic mean by modifying equation (2.33) to obtain

$$\bar{c} = \gamma + \left(c\left(0\right) - c\left(\delta\right)\right) / \left(\ln\left(c\left(0\right) - \gamma\right) - \ln\left(c\left(\delta\right) - \gamma\right)\right) \tag{2.84}$$

with $\gamma = j_s / \left(\left(1 - \sigma\right) j_v\right)$, c.f. equation (2.30), as shown in (Waniewski, 1994a).

2.7 The pore model

The pore model is based on the concept of a cylindrical uniform pore across the membrane. Solute and fluid transport through the pore is evaluated using the hydrodynamic theory of fluid flow and the theoretical description of diffusion and convective drag of spherical particles along the cylindrical pore (Deen, 1987). The theory incorporates 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 compared to the free transport in an unbound medium. Our presentation of the pore model is based on the review paper by Deen (Deen, 1987).

The parameters used for the description of transport through a pore are the pore radius, r_P, pore length, δ, Stokes radius of the solute, r_S (calculated from the molecular weight of solute), and fluid viscosity, η. It is assumed that the transport of each molecule is not influenced by the presence of other molecules in the pore, which means that the solution is diluted enough to study the transport of one molecule in the pore. The molecule is considered to be a hard sphere. It is assumed also that the pore is wide enough to apply the macroscopic description of fluid transport along the pore and long enough to neglect the entrance effect. Therefore, the viscous flow of pure solvent along a tube is described by the Poiseuille formula

$$v\left(z, \beta\right) = 2\bar{v}\left(1 - \beta^2\right) \tag{2.85}$$

where $\beta = r / r_P$ is the dimensionless radial position and $\bar{v}$ is the mean velocity. For the same reason we discuss only the velocity of the particle along the pore, denoted $u\left(x, \beta\right)$, where x and β describe the position of the center of the hard sphere. The thermodynamic drive for diffusion of the particle may be described as $-kT\partial \ln\left(c\right) / \partial x$, and the resistance of the fluid to the motion of this particle is described as $K 6\pi\eta r_S \left(u - Gv\right)$. The constant K describes the enhancement of the viscous drag on molecule due to the presence of the wall, and G describes the lag of fluid velocity at the longitudinal position of the molecule, compared to the pure solvent velocity. For $G = 0$ and $K = 1$ this equation is the well known description of diffusive movement of a hard sphere in unlimited viscous fluid in

rest with the coefficient $6\pi\eta r_S$, which describes the drag of a hard sphere in the fluid.

With no other forces except for these two, in isothermal conditions and steady state movement, they should be equal

$$-kT\frac{\partial \ln(c)}{\partial x} = K6\pi\eta r_S (u - Gv). \tag{2.86}$$

Because the solute flux is described as $\iota_s = cu$, see Chapter 2.2, therefore, using the formula for u, obtained from equation (2.86),

$$\iota_s = -\frac{D_\infty}{K}\frac{\partial c}{\partial x} + Gcv \tag{2.87}$$

where

$$D_\infty = \frac{kT}{6\pi\eta r_s} \tag{2.88}$$

is the well known Stoke-Einstein formula for solute diffusivity in dilute bulk (unrestricted) solution. In the steady state, the flux ι_s is independent of x, but depends on β. For our purposes we need an expression for the average flow through the pore cross-section, j_s,

$$j_s = \frac{\int_0^1 \iota\beta d\beta}{\int_0^1 \beta d\beta} = 2\int_0^{1-\alpha} \iota\beta d\beta. \tag{2.89}$$

The upper limit of the integration with integrand ι may be reduced to $1-\alpha$, where $\alpha = r_s/r_P$, because the center of hard sphere cannot be closer to the wall than the distance r_s. To proceed further with the theory, one assumes that $c(x,\beta) = g(x) f(\beta)$. It is often assumed that, according to the Boltzmann rule, $f(\beta) = \exp(-E(\beta)/kT)$, where $E(\beta)$ is the potential of long-range forces (for example, electrostatic interactions) between the pore wall and the solute. Then, using expression (2.87) for ι in equation (2.89) and expression (2.85) for v, one may calculate j_s as

$$j_s = 2D_\infty\frac{\partial g}{\partial x}\int_0^{1-\alpha} K^{-1} f\beta d\beta + 4\bar{v}g\int_0^{1-\alpha} Gf\left(1-\beta^2\right)\beta d\beta. \tag{2.90}$$

Defining

$$K_d = \frac{\int_0^{1-\alpha} K^{-1} f\beta d\beta}{\int_0^{1-\alpha} f\beta d\beta} \tag{2.91}$$

$$K_c = \frac{2\int_0^{1-\alpha} Gf\left(1-\beta^2\right)\beta d\beta}{\int_0^{1-\alpha} f\beta d\beta} \tag{2.92}$$

and noting that the average (over the pore cross-section) concentration $\bar{c}$ is defined as

$$\bar{c}(x) = \frac{g(x)\int_0^{1-\alpha} f\beta d\beta}{\int_0^1 \beta d\beta} = 2g(x)\int_0^{1-\alpha} f\beta d\beta \tag{2.93}$$

we get the equation for $\bar{c}$

$$j_s = -K_d D_\infty \frac{\partial \bar{c}}{\partial x} + K_c \bar{c} \cdot \bar{v}. \tag{2.94}$$

This equation may be integrated along the pore length and the solute flow along the pore may be related to the boundary values of concentrations. Furthermore, using the partition coefficient Φ, see Chapter 2.4, one can express j_s by the concentrations in external solutions outside both sides of the pore. The obtained equation is identical with equation (2.43)

$$j_s = P_{db}\Delta c_b + S_b j_v \left((1-f)\, c_b(0) + f c_b(\delta)\right) \tag{2.95}$$

with the parameters

$$P_{db} = \frac{K_d \Phi D_\infty}{\delta} \tag{2.96}$$

$$S_b = K_c \Phi \tag{2.97}$$

where j_v denotes the volume flux along the pore. For very dilute solutions, one may equate the flux of solvent $\bar{v}$ with the volume flux of solution j_v, see Chapter 2.2.

The estimation of the partition factor Φ was proposed to be based on the Boltzmann distribution $f(\beta) = \exp(-E(\beta)/kT)$ for the radius-dependent component of c and on the assumption $g(0) = c_b(0)$ and $g(\delta) = c_b(\delta)$. Then, taking the average concentration at the inlet and outlet of the pore

$$\Phi = \frac{\bar{c}(0)}{c_b(0)} = \frac{\bar{c}(\delta)}{c_b(\delta)} = 2\int_0^{1-\alpha} f\beta d\beta. \tag{2.98}$$

If the long range interactions may be neglected, then $E = 0$ and $f = 1$, and

$$\Phi = (1-\alpha)^2 \tag{2.99}$$

describes the purely steric (i.e. depending only on the geometrical factors) partition factor.

Many efforts were devoted to the development of description of the restriction factors as functions of α, see the review of these studies in (Deen, 1987). Finally, upon having collected all available theoretical and numerical data, Mason and co-authors proposed simple formulas for the approximate description of the restriction factors (Mason et al., 1980)

$$K_d\Phi = \frac{(1-\alpha)^{9/2}}{1 - 0.3956\alpha + 1.0616\alpha^2} \tag{2.100}$$

$$K_c\Phi = \frac{(1-\alpha)^2\left(2-(1-\alpha)^2\right)(1-\alpha/3)}{1-\alpha/3+2\alpha^2/3}. \tag{2.101}$$

The flux in formula (2.95) is calculated per unit surface area of the pore. In practical applications one needs to calculate the flux per unit surface area of the membrane with many pores, say n pores per unit of membrane surface area. The transformation to this practical description is performed by modifying the equation (2.95) through multiplication of both of its sides by the total surface area of all pores in one unit of membrane surface area. Then, the diffusive permeability of the homoporous membrane may be described using the formula (Mason et al., 1980, Rippe, Haraldsson, 1994)

$$P_m = \frac{a_0}{\delta}\frac{a_{eff}}{a_0}D_\infty \tag{2.102}$$

where $a_0 = n\pi r_P^2$ is the surface area of the total pore cross section in one unit of the membrane surface, and $a_{eff} = nK_d\Phi\pi r_P^2$ is called the effective surface area available for solute diffusion across unit surface area of the membrane. By comparing this representation with the one given in equation (2.96) one obtains $a_{eff}/a_0 = K_d\Phi$. For the sieving coefficient there is no change in the definition and $S_b = K_c\Phi$. Thus, formulas (2.100) and (2.101) may be applied for the description of the solute flux across the membrane. The hydraulic conductivity, L_{pm}, of the porous membrane is described according to the Poiseuille law (Deen, 1987, Rippe, Haraldsson, 1994)

$$L_{Pm} = \frac{a_0}{\delta}\frac{r_s^2}{8\eta}. \tag{2.103}$$

One has, however, to know or be able to estimate, the geometric coefficient a_0/δ. Frequently, the above theoretical description is not related to the real pore structure in biological membranes, but the apparent "ideal" pores are used to correlate the data on fluid and solute transport; then, the parameter a_0/δ is estimated from the data; however, the separation of the pore cross-section, a_0, and the pore length, δ, is typically not possible for such cases (Wolf, 1994, Michel, Curry, 1999, Gokal et al., 2000, Galach et al., 2013).

2.8 Summary

1. The description of fluxes of water (solvent) and dissolved solutes may be transformed to another, equivalent, representation with the flux of volume (of water and solutes together) and solutes. The transformation leaves the source of entropy unchanged. The new representation was found useful in many biological applications. For dilute solutions the interactions between solutes are negligible and not taken into account.

2. Further useful modification of the flux equations is obtained by eliminating the hydrostatic pressure from expressions for solute fluxes (the practical Spiegler-Kedem-Katchalsky approach). This allows for the investigation of solute fluxes as functions of volume flux and solute concentration. However, the transport coefficients in this approach may depend in general on solute concentration. The convective transport component is proportional to the volume flux and solute concentration, and the diffusive transport component is proportional to the gradient of solute concentration.
3. The volume flux is a function of gradients of hydrostatic pressure and effective osmotic pressure of all solutes, and the osmotic pressure of a solute is assumed to be proportional to the gradient of the solute concentration. The set of equations for volume and solute fluxes is nonlinear in solute concentrations and gradients, however, the solute transport is often considered for the known volumetric flux and then its equation is linear in solute variables.
4. The local (in space) equations for volumetric flux across a permselective membrane as a function of gradients of hydrostatic osmotic pressures may be expressed in the steady transport state by the formulae that depend on the differences of boundary (i.e. at the boundaries of the membrane) hydrostatic and osmotic pressures, respectively.
5. The local (in space) equations for solute fluxes across a permselective membrane as functions of solute concentration and its gradient may be expressed in the steady transport state by the formulae that depend on the solute concentrations at the membrane boundary and the (constant) volume flux.
6. The solute flux for the transport across a flat homogenous membrane are linear in boundary solute concentrations but nonlinear in volume flux and the modified transport parameters, some of which depend now on the thickness of the membrane. The diffusive and convective transport processes cannot be unequivocally separated in this global formulation. The nondimensional parameter, the Peclet number, which describes the relative strength of the convective over diffusive transport process, characterizes also the degree of intertwinning between these two components.
7. The transport parameters for the capillary homogeneous membrane depend on the radius of the capillary and the thickness of the membrane. For thin capillary membrane, the theory for flat membrane is a good approximation.
8. The formulas for fluxes across composite membranes as functions of the boundary concentrations may be obtained, however, the transport parameters depend, in general, on volume flux. The Onsager reciprocity relationships are generally not valid for composite membranes.
9. In specific conditions and for specific transport parameters, some approximations for solute flux, which are linear in the transport parameters, can be obtained.
10. The pore model provides an example of a mechanistic microscopic theory that may be expressed at macroscopic level in terms of the thermodynamic theory of membrane transport. In addition, the pore theory provides the

relationships between the geometric characteristics of the pore and solute and the membrane transport parameters. The formulas for the transport parameters include factors that describe how much the solute transport is restricted compared to its transport in a medium without boundaries. A lumped parameter, the ratio of the area of pore cross-section to pore length, appears in these formulas.

3

Transport across the capillary wall

After presenting the ways to describe the transport across permselective membrane, we move to more complex problems with the involvement of this theory. The typical experimental setup for the investigation of the membrane transport is the membrane placed between two well mixed compartments. With this arrangement, one can assume that the solute concentration is the same over the whole membrane surface on both sides of the membrane. The next step is the combination of transport across and along the membrane. Both solute flows, across and along the membrane, contribute to the change of the the solute concentration at the membrane surfaces. The typical and important case is the blood flow in the capillary with permselective walls that enable the fluid and solute flux between blood and tissue outside the capillary. This exchange is vital for all cells in the tissue.

Chapter 3.1 presents the history and the basic structure of the Krogh model and other models for the exchange of solutes and fluid across the capillary wall. The classic model of the capillary exchange comes from Krogh and is presented in Chapter 3.2 for the case of convective solute transport along the capillary, diffusive solute transport across the capillary wall and solute diffusion and metabolism in the tissue. In the Krogh model, the capillary bed of many parallel capillaries (as, for example, in the muscle) is replaced by one capillary surrounded by a tissue cylinder.

The next model describes the transport process for the solution (blood) passing along the capillary and exchanging fluid and solute by combined diffusion and convection with the well mixed compartment outside the capillary, see Chapter 3.3. This model is frequently applied in the capillary physiology for markers, labeled solutes injected to blood, but not present in the tissue; if its concentration in the tissue increases only slightly during the experiment, one may neglect its impact on the transcapillary transport. With the theory developed for such a case, one may define the capillary clearance and extraction coefficients, the basic parameters in the capillary physiology, see Chapter 3.4. These parameters are applied for the description of the solute exchange between blood, tissue and external medium (as in the case of the dialysis fluid in the peritoneal cavity), as expounded in Chapter 4.

Chapter 3.5 containes the basic information about the fluid balance in the tissue and the control of the fluid flow across the capillary wall. This information is applied in Chapter 5, dealing with the modeling of fluid transport during

peritoneal dialysis. A short summary of the presented theory is provided in Chapter 3.6.

3.1 Introduction

The Krogh cylinder is a theoretical model for the exchange of fluid and solutes that was introduced by August Krogh and the mathematician Agner K. Erlang in 1919 (Krogh, 1919). Its original purpose was to describe the exchange of oxygen between the capillary and the surrounding tissue, assumed to form a cylinder along the capillary, and define the saturation of the tissue with oxygen at different sites of the cylinder (Krogh, 1919, Fournier, 2007). The Krogh-Erlang model addresses several problems that are discussed in our book, such as the convective transport of a solute with blood along the capillary, the diffusive exchange of the solute across the membrane (capillary wall), the diffusive transport of the solute across the tissue, and the combination of all these processes. The fourth important ingredient of the model, the utilization of oxygen in the tissue, represents another aspect of mathematical modeling that is not discussed in detail in other parts of the book. The diffusive model in the tissue layer of the Krogh cylinder is an example of the transport equation in cylindrical geometry, analyzed also in Chapter 2.4.

The diffusive-convective model of the capillary exchange between blood flow and well mixed interstitium is a simple example of the approach that is presented in more general formulation for hemodialyzer and hemofilter in Chapter 7 as the one-dimensional theory of these devices. Based on this simple theory, two parameters, important for the capillary physiology are described: the clearance and extraction coefficients. The simple theoretical description of the capillary clearance is the introduction to the more elaborate theory of clearance and dialysance of hemodialyzer and clearance and sieving coefficient of hemofilter, provided in Chapter 7.

A brief description of the rules for the fluid exchange across the capillary wall addresses the problems that are discussed within the theory of the fluid transport during peritoneal dialysis in Chapter 5, and in the hemodialyzer, in Chapter 7.

3.2 The Krogh tissue cylinder

Blood transports to the tissue many solutes that are used by tissue cells and removes their products from the tissue. For solutes that do not participate in metabolism, the steady state consists in the equilibration of the concentration in extracellular fluid with its concentration in blood. More interesting are transport problems related to solutes that are metabolized within the tissue. The exchange of solutes between the blood, passing along the capillary bed, and the tissue that surrounds the capillary, is highly simplified if one considers a single capillary,

surrounded by a concentric layer of tissue, the so called Krogh tissue cylinder, which may be considered as a good approximation for the capillary bed in the muscle (Krogh, 1919), see also (Fournier, 2007). The respective mathematical model ought to describe the transport of the solute in blood, accounting for blood flow, the solute passage across the capillary wall, and finally the flow of solute across the tissue that surrounds the capillary (Fournier, 2007).

Let us denote the radius of the capillary by R_C, the width of the capillary wall by δ, and the radius of the whole cylinder by R_T. The normalized space variable along the cylinder is x, with the cylinder length L, and the radial space variable is r. We assume the cylindrical symmetry of the system. For the sake of mathematical simplicity, we assume also that the solute metabolism is of the zeroth order, i.e., it may be described by a constant χ_{MR} that corresponds to the metabolism rate per unit of tissue volume and is positive, if the solute is produced by tissue cells, or negative, if the solute is utilized by tissue cells (Fournier, 2007). The analysis is focused on the steady state of the transport and metabolism. We assume that the solute concentration in each capillary cross-section is relatively flat so that one can define a uniform solute concentration $C_B(x)$ for the cross-section of the capillary at each x, and also that the solute flow in the capillary is convective (i.e., the diffusion along x is negligible compared to the convection). Denoting the volumetric blood flow by Q_B we may write the equation for solute transport in the capillary as follows:

$$\frac{d(Q_B C_B)}{dx} = -J_S A_C \tag{3.1}$$

where J_S is the solute flux across the capillary wall at x and $A_C = 2\pi R_C L$ is the capillary wall surface area (here we assume that the membrane is thin compared to the capillary radius, $\delta \ll R_C$, and therefore the membrane may be described by the theory for flat membranes; for a more general approach to the transport across capillary membrane see Chapter 2.4). We assume in this chapter that ultrafiltration and convective solute transport in the radial direction inside the membrane are negligible, and so

$$J_S = P_C (C_B - C_T^m) \tag{3.2}$$

where $C_T^m(x) = C_T(x, r = R_C + \delta)$ is the solute concentration at the outer surface of the capillary wall, and P_C is diffusive permeability of the capillary membrane. Finally, for the solute concentration in the tissue we have

$$-D_T \Delta C_T + \chi_{MR} = 0 \tag{3.3}$$

where D_T is the solute diffusivity in the tissue, and Δ denotes the Laplace operator (laplacian), c.f. Chapter 4 for the general, time dependent description of the solute transport in the tissue. If we neglect the diffusion in the tissue along the cylinder axis, the transport equation takes the form

$$-\frac{D_T}{r}\frac{d}{dr}\left(r\frac{dC_T}{dr}\right) + \chi_{MR} = 0. \tag{3.4}$$

The boundary conditions for equation (3.4) are: $C_T\left(r = R_C + \delta\right) = C_T^m\left(x\right)$ at the outer capillary surface and $dC_T/dr\left(r = R_T\right) = 0$ at the outer tissue surface. The later condition expresses the equilibration of the solute at the outer surface, with the concentration on the outer surface of the other, parallel tissue cylinders. With all these assumptions, C_T depends on x only via its boundary value at the capillary surface (where it depends on the concentration in blood, described by equation (3.2)), and therefore one may present the solution to equation (3.4) as

$$C_T\left(x,r\right) = C_T^m\left(x\right) + \frac{\chi_{MR}}{4D_T}\left(r^2 - \left(R_c+\delta\right)^2\right) - \frac{R_T^2\chi_{MR}}{2D_T}\ln\left(\frac{r}{R_c+\delta}\right). \quad (3.5)$$

$C_T^m\left(x\right)$ is involved in equations (3.1) and (3.2), and we need to relate it to $C_B\left(x\right)$. However, instead of solving equation (3.1), we may use the global mass balance for the tissue segment from $x = 0$ to x: the solute delivered to the tissue from the capillary within this segment must be equal in the steady state to the solute utilized by the metabolism in the segment, i.e.

$$Q_B C_{B0} - Q_B C_B\left(x\right) = xA_T\chi_{MR} \quad (3.6)$$

where $A_T = \pi R_T^2 - \pi\left(R_C+\delta\right)^2$ is the surface area of the cross section of the tissue layer in the cylinder, xA_T is the volume of the tissue layer in the segment, and $C_{B0} = C_B\left(0\right)$. Thus

$$C_B\left(x\right) = C_{B0} - \frac{A_T\chi_{MR}}{Q_B}x \quad (3.7)$$

and $dC_B/dx = -A_T\chi_{MR}/Q_B$. Now, one can calculate $C_T^m\left(x\right)$ from equations (3.1) and (3.2) as

$$C_T^m\left(x\right) = C_B\left(x\right) - \frac{A_T\chi_{MR}}{P_C A_C} \quad (3.8)$$

where $V_T = A_T L$ is the volume of tissue layer in the Krogh cylinder. Combining equations (3.5), (3.7) and (3.8), we get

$$\begin{aligned} C_T\left(x,r\right) &= C_{B0} - \tfrac{A_T\chi_{MR}}{Q_B}x - \tfrac{A_T\chi_{MR}}{P_C A_C} + \\ &+ \tfrac{\chi_{MR}}{4D_T}\left(r^2 - \left(R_c+\delta\right)^2\right) - \tfrac{R_T^2\chi_{MR}}{2D_T}\ln\left(\tfrac{r}{R_c+\delta}\right). \end{aligned} \quad (3.9)$$

Equations (3.7) and (3.9) describe the solution of the Krogh cylinder problem for the solutes with characteristics that fulfill all the assumptions admitted in order to obtain the closed formulas.

3.3 Diffusive and convective transport across the capillary wall

Interesting theoretical results may also be obtained for the case of constant external concentration, C_T, and the combined diffusive and convective solute flux

across the capillary wall (compare the one dimensional theory of the hemodialyzer, provided in Chapter 7). The respective mathematical description is

$$\frac{d(Q_B C_B)}{dx} = -J_S A \tag{3.10}$$

$$\frac{dQ_B}{dx} = -J_V A. \tag{3.11}$$

Variable x describes here the normalized distance from the inlet of blood flow to the capillary, where effective fluid and solute exchange with interstitium occurs, i.e., x is equal to the ratio of the real distance to the total length of the capillary. The total surface area of the membrane is denoted by A. The transmembrane volumetric flux, J_V, is considered as a defined function of x. Outside the capillary there is a well mixed compartment with constant concentration C_T.

The solute transport through permselective capillary membrane may be described using the Spiegler-Kedem-Katchalsky equation for solute flux, see equation (2.43), as follows

$$\begin{aligned} J_S &= P\left(C_B - C_T\right) + \left(1-\sigma\right) J_V \left(\left(1-f\right) C_B + f C_T\right) \\ &= p C_B - r C_T \end{aligned} \tag{3.12}$$

where J_V is the rate of local, at the distance x, ultrafiltration flux, and

$$p\left(x\right) = PA + \left(1-\sigma\right)\left(1-f\left(x\right)\right) J_V\left(x\right) A \tag{3.13}$$

$$\begin{aligned} r\left(x\right) &= PA - \left(1-\sigma\right) f\left(x\right) J_V\left(x\right) A \\ &= p(x) - \left(1-\sigma\right) J_V\left(x\right) A \end{aligned}. \tag{3.14}$$

The net rate of ultrafiltration through the capillary wall, Q_U, may be calculated as $Q_U = A \int_0^1 J_V(x)dx$. If $J_V\left(x\right) = const\ (= J_V)$, then $Q_U = J_V A$. The alternative descriptions of the membrane transport may be applied by assuming f to be given by a formula for homogenous membrane, equation (2.32), or a constant, F, with a value between 0 to 1, see Chapter 2.5. The description of J_S for a composite membrane, Chapter 2.4, may also be applied. Thus,

$$\frac{d(Q_B C_B)}{dx} = -\alpha(x) Q_B C_B + r(x) C_T \tag{3.15}$$

where

$$\alpha\left(x\right) = p\left(x\right)/Q_B\left(x\right). \tag{3.16}$$

The solution of equation (3.15) is given by

$$\left(Q_B C_B\right)\left(x\right) = \frac{Q_{Bi} C_{Bi} + R\left(x\right) C_T}{M\left(x\right)} \tag{3.17}$$

where $Q_{Bi} = Q_B\left(0\right)$ and $C_{Bi} = C_B\left(0\right)$ are the flow rate and solute concentration at the inlet to the capillary $x = 0$, and

$$M(x) = \exp\left(\int_0^x \alpha(y)\, dy\right) \tag{3.18}$$

$$R(x) = \int_0^x r(y)\, M(y)\, dy. \tag{3.19}$$

The total removal of the solute from the capillary, Q_S, is equal to

$$\begin{aligned} Q_S &= Q_{Bi}C_{Bi} - Q_{Bo}C_{Bo} = \\ &= Q_{Bi}\left(1 - \tfrac{1}{M_1}\right)C_{Bi} - \tfrac{R_1}{M_1}C_T \end{aligned} \tag{3.20}$$

where $M_1 = M(1)$,$R_1 = R(1)$, and $Q_{Bo} = Q_B(1) = Q_{Bi} - Q_U$ and $C_{Bo} = C_B(1)$ are the flow rate and solute concentration at the outlet of the capillary at $x = 1$.

Another interesting representation of the solution to equation (3.15) may be obtained if this equation is presented as

$$\frac{d(Q_B C_B)}{dx} = -\alpha(x) Q_B (C_B - C_T) - (1-\sigma) J_V A C_T \tag{3.21}$$

or, taking into account equation (3.11),

$$\frac{d\left(Q_B (C_B - C_T)\right)}{dx} = -\alpha(x) Q_B (C_B - C_T) + \sigma J_V A C_T. \tag{3.22}$$

Equation (3.22) has the same structure as equation (3.15) with $\sigma J_V(x) A$ replacing $r(x)$, and therefore the solution is

$$\left(Q_B (C_B - C_T)\right)(x) = \frac{Q_{Bi}(C_{Bi} - C_T) + \tilde{R}(x) C_T}{M(x)} \tag{3.23}$$

or

$$\begin{aligned} (Q_B C_B)(x) &= \frac{Q_{Bi}C_{Bi} - \left(Q_{Bi} - \tilde{R}(x) - Q_B(x)M(x)\right)C_T}{M(x)} \\ &= \frac{Q_{Bi}C_{Bi} - \left(Q_{Bi} - \tilde{R}(x)\right)C_T}{M(x)} + Q_B(x) C_T \end{aligned} \tag{3.24}$$

where

$$\tilde{R}(x) = \sigma \int_0^x J_V(y)\, AM(y)\, dy. \tag{3.25}$$

Thus,

$$\begin{aligned} Q_S &= Q_{Bi}C_{Bi} - Q_{Bo}C_{Bo} \\ &= Q_{Bi}\left(1 - \tfrac{1}{M_1}\right)C_{Bi} - \left(Q_{Bo} - \tfrac{\left(Q_{Bi} - \tilde{R}_1\right)}{M_1}\right)C_T. \\ &= Q_{Bi}\left(1 - \tfrac{1}{M_1}\right)(C_{Bi} - C_T) + \left(Q_U - \tfrac{\tilde{R}_1}{M_1}\right)C_T \end{aligned} \tag{3.26}$$

The problem of solving the second order ordinary differential equation was here reduced to the problem of calculating the respective integrals (the so called "quadrature problem"). Some examples of solutions in the closed formulas for specific parameters are provided in Chapter 3.4.

3.4 The capillary clearance and extraction coefficients

The rate of solute removal from the capillary, $Q_S = J_S A$, may be presented using unidirectional clearances: K_{BT} from blood to tissue and K_{TB} from tissue to blood, as

$$Q_S = K_{BT} C_{Bi} - K_{TB} C_T \tag{3.27}$$

where, by comparison with equation (3.20),

$$K_{BT} = Q_{Bi}\left(1 - \frac{1}{M_1}\right) \tag{3.28}$$

$$K_{TB} = \frac{R_1}{M_1}. \tag{3.29}$$

Another description of Q_S, given by equation (3.26), yields

$$Q_S = K_{BT}\left(C_{Bi} - C_T\right) + \left(Q_U - \frac{\tilde{R}_1}{M_1}\right) C_T. \tag{3.30}$$

An alternative formula for K_{TB} may be derived from equations (3.30) and (3.28):

$$K_{TB} = Q_{Bo} - \frac{\left(Q_{Bi} - \tilde{R}_1\right)}{M_1}. \tag{3.31}$$

Because $\tilde{R}_1 = 0$ for solutes with $\sigma = 0$, hence

$$Q_S = K_{BT}\left(C_{Bi} - C_T\right) + Q_U C_T \tag{3.32}$$

and

$$K_{TB} = K_{BT} - Q_U. \tag{3.33}$$

In the special case of constant ultrafiltration rate, $J_V = const$, i.e., for linear function $Q_B(x) = Q_{Bi} - Q_U x$, one can obtain the closed formulas for K_{BT} and K_{TB}:

$$K_{BT} = Q_{Bi}\left[1 - \left(1 - \frac{Q_U}{Q_{Bi}}\right)^{p/Q_U}\right] \tag{3.34}$$

$$K_{TB} = r\frac{K_{BT} - Q_U}{p - Q_U}. \tag{3.35}$$

The clearance from blood to tissue is often presented as

$$K_{BT} = E Q_{Bi} \tag{3.36}$$

where the parameter E is called the extraction coefficient and, by equation (3.28),

$$E = 1 - M_1^{-1} = 1 - \exp\left(-\int_0^1 \frac{p(x)}{Q_B(x)} dx\right). \tag{3.37}$$

The extraction coefficient E describes the hypothetical portion of blood flow that is cleared from solute if the external solute concentration is zero, i.e. EQ_{Bi} is the effective blood flow cleared from the solute in this condition. The extraction coefficient E is often measured in physiological experiments on organ perfusion with $C_T = 0$. It depends only on the parameters that describe the transport of the solute between capillary and the tissue and not on the tissue transport parameters. For constant ultrafiltration rate we have

$$E = 1 - \left(1 - \frac{Q_U}{Q_{Bi}}\right)^{p/Q_U}. \tag{3.38}$$

If ultrafiltration is negligible and one can assume that $J_V(x) = 0$ for all x, then $p = r = PA$, and

$$E = 1 - \exp(-PA/Q_{Bi}). \tag{3.39}$$

If $PA << Q_{Bi}$, then $K_{BT} \approx PA$, c.f. equation (3.36), and one speaks about the permeability limited transport. On the other hand, if $PA >> Q_{Bi}$, then $K_{\mathrm{BT}} \approx Q_{Bi}$, c.f. equation (3.36), and one speaks about the blood flow limited transport. If the transport is blood flow limited, then E is close to 1, whereas for solutes with permeability limited transport E is close to PA/Q_{Bi}. If ultrafiltration is negligible, the change of the solute concentration in blood between the arterial and the venous parts of the capillary may be calculated, in the general case, using E, as $C_{Bo}/C_{Bi} = 1 - E(1 - C_T/C_{Bi})$, and, for $C_T = 0$, $E = 1 - C_{Bo}/C_{Bi}$.

For the model of the Krogh tissue cylinder with the metabolism of solute, the solute exchange between blood and tissue in the steady state is fully determined by the metabolic rate, compare the equation (3.6),

$$Q_S = V_T \chi_{MR}. \tag{3.40}$$

Therefore, to study the capillary transport of such solutes, one has to apply a tracer, i.e., a labeled solute with zero initial concentration in the tissue, and analyze the experimental data for the time when the tracer concentration in the tissue is still close to zero. Then, using the measurements at the blood outlet in the tissue, one may calculate the diffusive permeability of the solute for the capillary wall, for example from equation (3.39). The solutes that are not metabolized in the tissue, equilibrate in the steady state to their concentrations in blood, and again one has to apply a tracer or induce by other means the difference between solute concentrations in blood and tissue compared to the equilibrium values, for example by arranging the transport across the tissue surface, see Chapter 4.

3.5 Fluid transport across the capillary wall

The fluid flux across the capillary wall passes between plasma (often referred to as blood) and interstitial fluid (often referred to as tissue), and is controlled by two

forces: 1) the difference between hydrostatic pressures in blood and in interstitial fluid, and 2) the difference between osmotic pressures of plasma and interstitial fluid. In normal conditions, the small molecules are quickly equilibrated between plasma water and interstitial fluid water and their osmotic pressure difference is negligible. In contrast, the concentration of macromolecules, mostly proteins, is different in plasma and in interstitial fluid and their reflection coefficient is high. The overall osmotic pressure of proteins can be directly measured and is called oncotic pressure. It correlates in nonlinear fashion with total protein concentration (Staub, Taylor, 1984), but in theoretical considerations this relationship is often replaced by the van't Hoff formula (Chapter 1.6).

The first correct description of the fluid flux across the capillary wall was proposed by Ernest Starling in 1896 (Starling, 1896). It presents the fluid flux as the linear function of the so called Starling forces (hydrostatic pressure and oncotic pressure):

$$j_V = L_p \left(\Delta P - \sigma \Delta \Pi \right) \tag{3.41}$$

where $\Delta P = P_B - P_T$, P_B is the hydrostatic pressure in the capillary, P_T is the hydrostatic pressure of the interstitial fluid, $\Delta \Pi = \Pi_B - \Pi_T$, Π_B is the oncotic pressure of plasma, Π_T is the oncotic pressure of the interstitial fluid, and σ is the overall (effective) reflection coefficient for total protein. Oncotic pressure is exerted by a mixture of large number of proteins of different molecular weight and therefore also different transport characteristics. Theoretically, the effective oncotic pressure should be presented as a sum of the concentration of each individual protein multiplied by its reflection coefficient. Practically, the concentration of "total protein" is measured and an apparent reflection coefficient is attributed to this "solute". In the original Starling formula σ was not used (we may say that σ was equal one), and still many authors use $\sigma = 1$. More precise evaluations give the values of σ between 0.8 and 1.0. The plasma oncotic pressure prevents fast ultrafiltration from the circulation to the tissue that would occur due to high hydrostatic pressure, which in turn is necessary for the support of blood flow in the circulation system.

While the interstitial hydrostatic and oncotic pressures may be considered approximately constant at the scale of the length of the capillary, the hydrostatic pressure in the capillary decreases linearly downstream and the oncotic pressure increases due to the removal of water and substantial sieving of large proteins. The initial considerations suggested that because of the changes in the Starling forces along the capillary, the filtration of fluid occurs at the arterial end of the capillary, whereas at the venular end and in small venules the filtrated fluid is reabsorbed (Landis, Pappenheimer, 1963). This hypothesis was criticized on the basis of the experimental data (Levick, Mortimer, 1999). The most popular approach is to apply the mean capillary pressure and the mean capillary oncotic pressure in the formula (3.41). This assumes, implicitly, that the capillary pressures change linearly along the capillary.

The typical situation in normal physiological conditions is a slight net ultrafiltration from the capillary bed that is reabsorbed by the lymphatic capillaries

in the tissue. Therefore, the balance of fluid volume in the tissue must take into account both flows: 1) from the capillary bed, driven by the Starling forces, and 2) to the lymphatics, driven by hydrostatic pressure of the interstitial fluid. Any disturbance in these flows may lead to overhydration or dehydration of the tissue (Staub, Taylor, 1984, Guyton, Hall, 2000); see Chapters 4 and 5 for the mathematical analysis of the role of lymphatic absorption in fluid and solute transport in the tissue.

The theory of transport across the capillary wall is a good example of application of the pore theory, described in Chapter 2.7. The three types of pores are necessary for the description of the transport of fluid, small and middle molecules and macromolecules: large pores, small pores, and ultrasmall pores. Typically, they are assumed to be cylindrical pores, and their size and abundance in the capillary wall are specific for each type of pore; see (Wolf, 1994, Michel, Curry, 1999) for more information on the pore structure of the capillary wall and the applications in physiological and medical studies. A similar structure of the three types of pores is also applied in the models of peritoneal dialysis (Gokal et al., 2000).

3.6 Summary

1. The simplifications made in the Krogh model (convective solute transport within the capillary with blood flow, diffusive transport across the capillary wall, diffusive transport in the tissue layer along the direction perpendicular to the capillary, simple description of the solute utilization in the tissue) allow for the description of the steady state distribution of the solute within the cylinder in the form of closed formulas.
2. The one dimensional theory of transport from the blood, flowing down the capillary, to the well mixed fluid in its surrounding provides closed formulas for the capillary clearance and the capillary extraction coefficient in the case of combined diffusive-convective transport across the capillary wall and constant ultrafiltration flux.
3. The diffusive extraction coefficient for diffusive transport across the capillary wall depends on the ratio of the capillary permeability times the capillary surface area parameter to the rate of blood flow; this formula is applied in many experimental studies on capillary physiology.
4. The concept of the Starling forces that control the exchange of fluid across the capillary wall is crucial for the description of the fluid balance in the tissue. However, the lymphatic flow needs also to be taken into account in this balance. Together, these factors play the major role in the turnover of fluid in the tissue.

4

Spatially distributed models for solute exchange between the perfused tissue and the external medium

An important biological example of transport systems is constituted by the exchange of fluid and solutes between the blood perfusing the tissue and a medium external to the tissue. The transport involves typically at least two processes: 1) the transport across the capillary wall, and 2) the transport across the tissue between the tissue surface and the internal, perfused layers of the tissue. The solutes may be also metabolized or generated by the tissue cells, see Chapter 3. The pathways of transport in the tissue may include the intracellular space or be restricted to the interstitial space only. A solute at high concentration in the external medium penetrates the tissue, is absorbed by blood and lymphatics and washed away from the tissue to the other parts of the body. Therefore, its penetration into the tissue is limited in depth.

The simplest mathematical description of such a transport system involves passive solutes with only one transport pathway across the tissue (uniformly across the whole tissue or, for example, across the interstitium only), perpendicular to the tissue surface and with the capillary bed uniformly distributed within the tissue. Such models are based on partial differential equations.

After a brief description of the history and applications of the spatially distributed models, provided in Chapter 4.1, a simple model for diffusive-convective solute transport is described in Chapter 4.2. Closed formulas for the solutions of the transport equations can be obtained for the steady state of the transport for different boundary conditions, as shown in Chapter 4.3. An important characteristic of these transport systems is the solute penetration depth and the closed formulas for its description are presented in Chapter 4.4.

Another useful theoretical result deals with the expression for the solute flux across the tissue surface. The measurements of the solute concentrations are typically, especially in clinical studies, possible only in the external medium and then, using these data, the net transport parameters can be estimated. These net parameters can be derived from the local transport parameters for the tissue and the capillary wall, and the general formula for the transport across the tissue surface is similar to the formula for the transport across the homogenous membrane, as described in Chapter 4.5. In the case of pure diffusive transport, a more detailed theoretical analysis can be performed and is presented in Chapter 4.6.

The spatially distributed model allows for a precise definition of effective blood flow, i.e., the blood flow that is involved in the exchange of the solute with the external medium. The model explains how the effective blood flow depends

on the local transport coefficients, as shown in Chapter 4.7. Finally, Chapter 4.8 contains the examples of solutions to the distributed transport equation for the boundary conditions other than in the earlier considerations. A short summary of the presented theory is provided in Chapter 4.9.

4.1 Introduction

Our objective in this chapter is the description of the system of the perfused capillary bed that exchanges fluid and solutes with the tissue and across the permeable tissue surface that is in contact with an external medium (fluid or gas). The external medium may be a source or sink for the transported substances. There are many such systems, like, for example, the penetration of solutes across the skin and their uptake by subcutaneous capillaries, the exchange of solutes between cerebrospinal fluid, brain tissue and blood, the absorption of gases from intraperitoneal or subcutaneous pockets, the exchange of gases in the lung, and the peritoneal dialysis, specifically aimed at the removal of waste solutes and excess water from the body into dialysis fluid in the peritoneal cavity, but also at the delivery of some solutes, as buffers (or, in some specific applications, locally acting chemotherapeutics), from the peritoneal cavity to the body. Also osmotic agents and water are absorbed from the peritoneal cavity to the body, but these are mostly unwanted effects; and exception is the absorption of a mixture of amino acids applied as osmotic agent in malnourished patients.

The mathematical problem here is simplified to uniformly and continuously distributed capillary and lymphatic beds and the transport in the direction perpendicular to the surface. Thus, the basic equations are one dimensional in the space variables. The system is considered homogeneous and time independent, which, in particular, means that the model parameters are constant. Many mathematical results may be obtained for the steady state solutions and we deal with such a theory in this chapter. All these simplifications are aimed at obtaining the theoretical description of the transport processes and relationships between the model parameters and phenomenological transport parameters and indices applied in clinical and animal studies. The transport of solutes is discussed in details at first because of its relative simplicity and wide range of practical applications. The transport of fluid is more difficult as it involves nonlinear equations, see Chapter 5. For extensions of the idealized model, discussed in Chapters 4 and 5, these extensions attempting to take into account many (nonlinear) physiological phenomena, see (Seames et al., 1990, Cherniha, Waniewski, 2005, Stachowska-Pietka et al., 2006, Waniewski et al., 2009, Stachowska-Pietka et al., 2012, Cherniha et al., 2014).

The basic ideas for the distributed modeling of the solute exchange between the perfused tissue and the external medium were discussed initially for the exchange of gases between blood and artificial gas pockets within the body as well as in the general context of the exchange of matter and heat between blood and tissue for the intratissue source of solute or heat (Perl, 1962, Piiper et al., 1962,

Perl, 1963). The first application of the model for the description of the solute transport was proposed for diffusion of solutes with low molecular weight from cerebrospinal fluid to the brain (Patlak, Fenstermacher, 1975). The subsequent applications dealt with gas transport between subcutaneous or intraperitoneal gas pockets and blood (Piiper et al., 1962, Van Liew, 1968, Collins, 1981). The model was applied in the analyses of the solute transport during peritoneal dialysis in patients (Dedrick et al., 1982), and then in a series of theoretical and experimental studies on transport of small, middle and macro-molecular solutes during peritoneal dialysis in rats (Flessner et al., 1984, 1985a, b, Flessner et al., 1985c, Flessner et al., 1985d, Flessner et al., 1997). Other studies dealt with the transport of anticancer or other drugs applied intraperitoneally (Collins et al., 1982, Dedrick et al., 1982), intravesically (Wientjes et al., 1991, Wientjes et al., 1993), or on skin (Gupta et al., 1995). The general theory of transport processes in solid tumors was also formulated (Baxter, Jain, 1989, 1990). While most of these initial studies were focused at diffusive solute transport, the diffusive-convective solute transport was investigated with the distributed model less frequently (Seames et al., 1990, Leypoldt, Henderson, 1992). Only exceptionally some reaction terms were added to the model to describe the interaction of the solute with the tissue (Collins, 1981). More recent studies worked with other practical and theoretical aspects of peritoneal dialysis (Waniewski et al., 1999, Waniewski, 2001, 2002). Different aspects of fluid transport during peritoneal dialysis were also described using the distributed model (Leypoldt, 1993, Stachowska-Pietka et al., 2006, Waniewski et al., 2007, Waniewski et al., 2009, Stachowska-Pietka, Waniewski, 2011, Stachowska-Pietka et al., 2012). Other applications of the distributed model deal with peritoneal chemotherapy and the transport in solid tumors (Baxter, Jain, 1989, Markman, 1999). Peritoneal dialysis is an exceptional opportunity to study the combination of diffusive and convective transport of solutes over a wide range of solute size and osmotically induced fluid flow. The theory here presented is based mostly on the results published in (Waniewski et al., 1999, Waniewski, 2001, 2002); these papers contain also many examples of applications of the theory developed.

The description of the transport characteristics and the application of various approximations in the mathematical models depend on the physical and geometrical features of the molecules with the size (represented by Stoke radius or molecular weight, MW, shape, electric charge, etc., of the molecule). An aproximate, highly conventional division of solutes according to their molecular weight is sometimes applied: 1) solutes with low molecular weight ("small solutes") below 300 daltons, with such markers as urea (MW = 60) and creatinine (MW = 113) and typically prevailing diffusive mode of transport, 2) solutes of middle molecular weight, 300<MW<15 000, including small proteins as beta2-microglobulin (MW = 11 818), with both, diffusive and convective, transport components typically important, and 3) macromolecules of high molecular weight, MW >15 000, with such marker as albumin (MW about 60 000), for which convection is typically the prevailing transport component (Drukker et al., 2004). Of course, the

transport characteristics change within each subgroup too, and may depend on other features of the molecules than their molecular weight only.

4.2 The spatially distributed model for solute transport

The general local mass balance for the solute "S" is described by equation (1.1) for mass density C_S, which may be expressed in units of mass (like gram) or molar units (like mmol) per unit volume (like mL or L), i.e., for the infinitesimal mass dm in the infinitesimal volume element $dV = dxdydz$, $C_S = dm/dV$. However, if the solute cannot be distributed in the whole element dV, as this is the case, for example, in the porous material with impenetrable wall of the pores, this definition is only formal and C_S does not represent the real concentration of the solute in pores, C, which actually drives diffusive solute transport in pores. To obtain the mass balance equation for C, one need to define the space fraction θ of the solute void volume that is accessible for solute within dV, that is, $dm = C\theta dV$, or $C_S = C\theta$. Therefore, equation (1.1) can be written as follows

$$\frac{\partial(\theta C)}{\partial t} = -\mathrm{div}\mathbf{j}_S + q_S. \tag{4.1}$$

If the solute can fill the entire space element dV, then $\theta = 1$.

In the following, we consider a flat tissue layer, parallel to the plane $Y - Z$ and the transport in the direction perpendicular to the tissue surface, corresponding to the space variable X. Thus, the general expression for solute flux $\mathbf{j} = (j_x, j_y, j_z)$ can be reduced by assuming $j_y = 0$, $j_z = 0$ to

$$\frac{\partial(\theta C)}{\partial t} = -\frac{\partial j_S}{\partial X} + q_S \tag{4.2}$$

where θ is the solute void volume (for example, in many applications of the model, the solute is distributed in the interstitial fluid), j_S is the solute flux across the tissue, q_S is the rate of the net solute flow to the tissue by transcapillary transport and lymphatic absorption, and X is the distance from the tissue surface in contact with fluid (e.g., parietal mesothelium) through the tissue to the external tissue surface (e.g. skin), measured from $X_0 = 0$ to $X_{MAX} = L$, and

$$j_S = -D_T\frac{\partial C}{\partial X} + S_T j_V C \tag{4.3}$$

$$\begin{aligned} q_S = q_{SBTL} &= k_B C_B - k_T C + q_L C \\ &= -(k_T + q_L)(C - \kappa C_B) \end{aligned} \tag{4.4}$$

where: $C = C(X,t)$ is the local solute concentration in the void space, j_V is the volumetric flux across the tissue, D_T is the diffusivity of solute in the void space, S_T is the sieving coefficient of solute in the tissue, C_B is the solute concentration in blood, q_L is the lymphatic absorption from the tissue, k_B and k_T

are unidirectional clearances for solute exchange between blood and tissue across capillary wall, described in detail in Chapter 3, and expressed here (together with q_L) as densities per unit tissue volume. Finally,

$$\kappa = \frac{k_B}{k_T + q_{VL}}. \tag{4.5}$$

The fluxes across the tissue are positive if taking place in the direction from $X = 0$ to $X = L$. The flow densities across the capillary wall are positive if directed from blood to tissue.

Boundary conditions. The tissue layer has two boundaries: the boundary at $X = 0$ is assumed to be in contact with the external medium and fluid and solutes can be exchanged by this boundary (Dirichlet boundary condition), whereas for the boundary at $X = L$ we discuss two types of boundary conditions. The first case deals with the boundary impermeable for fluid and solute (zero Neumann boundary conditions). The second case deals with permeable boundary and external medium having the concentration different from the medium at $X = 0$. If these two concentrations are equal and the tissue is homogenous, then the problem can be reduced to the zero Neumann conditions at $X = L/2$.

4.3 Diffusive and convective solute transport: steady state

In the following, we assume that fluid flux across the tissue, j_{VT}, is known and constant in time and space. This assumption, as we demonstrate, allows for some closed formulas that provide useful relationships between the spatially distributed model and the more often used membrane approximation.

The steady state equation for the solute transport that provides the solute distribution within the tissue is

$$-\frac{dj_{ST}}{dX} + q_{SBTL} = 0 \tag{4.6}$$

with

$$j_{ST}(X) = -D_T \frac{dC_T}{dx}(X) + S_T j_{VT} C_T(X). \tag{4.7}$$

From these two equations and equation (4.4)

$$\frac{d}{dX}\left(-D_T \frac{dC_T}{dx} + S_T j_{VT} C_T\right) = -(k_T + q_{VL})(C_T - \kappa C_B). \tag{4.8}$$

Let us define two non-dimensional variables: $x = X/L$, where L is the width of the tissue layer, and the normalized concentration profile, Γ, defined as

$$\Gamma(x) = \frac{C_T(x) - \kappa C_B}{C_D - \kappa C_B} \tag{4.9}$$

where C_D is the solute concentration in the the external medium, for example in peritoneal dialysis fluid. Here and in the following considerations we assume that $C_D \neq \kappa C_B$. Using these variables one may derive from equation (4.8) the following description of the steady state normalized concentration profiles

$$\frac{d^2\Gamma}{dx^2} - Pe_T \frac{d\Gamma}{dx} - \Phi^2 \Gamma = 0 \tag{4.10}$$

where $Pe_T = S_T j_{VT}/P_T$ is the Peclet number for diffusive-convective transport across the tissue, $P_T = D_T/L$ is the diffusive permeability of the tissue layer, and $\Phi = L/\sqrt{D_T/(k_T + q_{VL})}$.

The solution of equation (4.10) with the boundary conditions $\Gamma(0) = \Gamma_1$, $\Gamma(1) = \Gamma_2$ is

$$\Gamma(x) = \Gamma_1 \frac{\sinh(\Psi(1-x))}{\sinh(\Psi)} \exp\left(\frac{Pe_T x}{2}\right) + \Gamma_2 \frac{\sinh(\Psi x)}{\sinh(\Psi)} \tag{4.11}$$

where

$$\Psi = \sqrt{(Pe_T/2)^2 + \Phi^2}. \tag{4.12}$$

For the boundary conditions of the form $\Gamma(0) = \Gamma_1$ and $(d\Gamma/dx)(1) = 0$, the solution is

$$\Gamma(x) = \Gamma_1 \frac{\Psi \cosh(\Psi(1-x)) + (Pe_T/2)\sinh(\Psi(1-x))}{\Psi \cosh(\Psi) + (Pe_T/2)\sinh(\Psi)} \exp\left(\frac{Pe_T x}{2}\right). \tag{4.13}$$

The typical boundary condition at $x = 0$ is $C_T(0) = C_D$, and therefore in the following $\Gamma_1 = \Gamma(0) = 1$; see (Patlak, Fenstermacher, 1975) for a more general condition.

If the tissue layer is sufficiently wide, so that the solute concentration deep within the tissue is in equilibrium with blood, $C_T(1) = \kappa C_B$, i.e. $\Gamma_2 = \Gamma(1) = 0$ (strictly speaking, this condition may get valid only for $L \to \infty$), then the normalized concentration gradient is described by the following exponential function, c.f. (Patlak, Fenstermacher, 1975),

$$\Gamma(x) = \exp\left(-\left(\Psi - \frac{Pe_T}{2}\right)x\right). \tag{4.14}$$

Because $\Psi \geq Pe_T/2$, equation (4.14) describes the exponential decrease of the normalized concentration gradient, Γ, with the distance from the surface at $x = 0$. Equation (4.14) may be also derived from equations (4.11) and (4.13) for $\Psi >> 1$ and $\Gamma_2 = 0$.

4.4 The depth of solute penetration

A useful parameter that characterizes the depth of penetration of a solute from the surface or, equivalently, the depth of the layer involved in the removal of the

solute from blood, may be defined for the case of wide tissue layers. Its specific components, diffusive and convective penetration depths, can be combined into one net penetration depth. The parameters are, nevertheless, generally useful for the analysis of transport in tissue layers of any width, although their geometric interpretation is not so straightforward.

Using the real distance from the tissue surface, X, equation (4.14) may be rewritten as

$$\Gamma(X) = \exp(-X/\Lambda) \tag{4.15}$$

with the use of the characteristic value for the solute penetration to the tissue, called the penetration depth

$$\Lambda = L/(\Psi - Pe_T/2); \tag{4.16}$$

Λ has the unit of length and describes the rate of decrease of the normalized concentration gradient with increasing X in the case of $\Lambda << L$. The parameter Λ may be expressed as a function of two other parameters, Λ_D, which describes the penetration depth for purely diffusive transport, and Λ_C, which describes the penetration depth for purely convective transport.

For purely diffusive transport, $j_{VT} = 0$, the solution of the reduced equation (4.8) for the boundary conditions $\Gamma(0) = 1$ and $(d\Gamma/dx)(1) = 0$ is (c.f. (Leypoldt, Henderson, 1992))

$$\Gamma(x) = \frac{\cosh(\Phi(1-x))}{\cosh(\Phi)} \tag{4.17}$$

or, for $\Phi >> 1$,

$$\Gamma(X) = \exp(-X/\Lambda_D) \tag{4.18}$$

where

$$\Lambda_D = \sqrt{D_T/(k_T + q_{VL})}. \tag{4.19}$$

Note that $\Phi >> 1$ means that $\Lambda_D << L$, i.e., the penetration depth is much smaller than the tissue width.

For purely convective transport, $D_T = 0$, $j_{VT} > 0$, into the tissue, the solution of the reduced equation (4.8) for the boundary condition $\Gamma(0) = 1$ is

$$\Gamma(X) = \exp(-X/\Lambda_C) \tag{4.20}$$

where the convective penetration depth is

$$\Lambda_C = S_T j_{VT}/(k_T + q_{VL}). \tag{4.21}$$

Now we can note that $Pe_T = L\Lambda_C/\Lambda_D^2$ and

$$\Lambda = \frac{\Lambda_D}{\sqrt{1 + r^2/4} - r/2} \tag{4.22}$$

where $r = \Lambda_C/\Lambda_D$. If $|r| << 1$, then $\Lambda = \Lambda_D + \Lambda_C/2$, whereas if $r >> 1$, then $\Lambda = \Lambda_C$, and, if $r << -1$, then $\Lambda = 0$.

4.5 Transport across tissue surface

The solute flux from the external medium to the tissue across the tissue surface at $X = 0$ is described as

$$j_S = j_{ST}(0) = -D_T \left.\frac{dC_T}{dX}\right|_{X=0^+} + S_T j_{VT} C_T(0). \tag{4.23}$$

For the known solutions (4.11) – (4.14) one can easily calculate j_S as

$$j_S = \frac{D_T}{L}\left(\Psi\varphi(\Phi, Pe_T) - \frac{Pe_T}{2}\right)(C_D - \kappa C_B) + S_T j_{VT} C_D \tag{4.24}$$

where $\varphi(\Psi, Pe_T) = cth(\Psi)$ for solution (4.11) with $C_T(L) = \kappa C_B$,

$$\varphi(\Phi, Pe_T) = \frac{\Psi \sinh(\Psi) + (Pe_T/2)\cosh(\Psi)}{\Psi \cosh(\Psi) + (Pe_T/2)\sinh(\Psi)} \tag{4.25}$$

for solution (4.13), and $\varphi(\Phi, Pe_T) = 1$ for solution (4.14). After algebraic transformations, equation (4.24) can be represented as

$$j_S = k_{BD}(C_D - \kappa C_B) + S j_V((1-F)C_D + F\kappa C_B) \tag{4.26}$$

where we denote $j_V = j_{VT}$, $S = S_T$, and

$$k_{BD} = \frac{D_T}{L}\Phi\varphi = \varphi\sqrt{D_T(k_T + q_{VL})} \tag{4.27}$$

$$F = 0.5 - \alpha \tag{4.28}$$

$$\alpha = \frac{\Psi - \Phi}{Pe_T}\varphi = \frac{\sqrt{1 + \frac{Pe^2}{4}} - 1}{Pe}\varphi \tag{4.29}$$

with $Pe = \frac{\Lambda_C}{\Lambda_D} = \frac{S j_V}{k_{BD}}$ (i.e., $Pe = r$ from formula (4.22)). For the approximation of the thin penetration layer, equation (4.14), $\varphi = 1$ and

$$\alpha = \frac{\sqrt{1 + \frac{Pe^2}{4}} - 1}{Pe}. \tag{4.30}$$

One may obtain the approximate expressions for the function $F(Pe)$ in the spatially distributed model, similar to those proposed in the homogenous membrane theory, see Chapter 2, as follows: 1) if $|Pe| << 1$ then $\alpha = Pe/8$ and $F = 0.5 - Pe/8$, 2) if $Pe >> 1$ then $\alpha = 0.5$ and $F = 0$, and 3) if $Pe << -1$ then $\alpha = -0.5$ and $F = 1$.

The description of j_S by equations (4.26) – (4.30) for the thin penetration layer may be compared to the standard, steady state description of transmembrane flux (see Chapter 2.3) through an apparent membrane between blood and

external medium using membrane parameters and boundary values of concentrations, namely

$$j_S = k_{BD}^m \left(C_D - C_B\right) + S^m j_V \left(\left(1 - F\right) C_D + F C_B\right) \tag{4.31}$$

with F defined by equations (2.34) and (2.32). Equation (4.31) is often used for the assessment of clinical and experimental data and for estimation of the membrane transport coefficients. Both equations (4.26) and (4.31) for j_S use the same formula for Pe. The formulas for F differ, but their values at $Pe = 0$ and asymptotic behaviors for large absolute values of Pe are the same. Actually, the comparison of the functions $F\left(Pe\right)$ demonstrates that their difference at other points is not big (Waniewski, 2001).

An important difference between equations (4.26) and (4.31) is constituted by the presence of coefficient κ in the former equation. In typical physiological conditions of transport through the capillary wall, κ is close to 1 for small and middle molecules, but substantially lower than 1 for macromolecules. Therefore, according to equation (4.26), the equilibration level for macromolecules in dialysate is not their concentration in blood, C_B, but their equilibrium concentration in the tissue $C_{Teq} = \kappa C_B$. In fact, the equilibrium level for total protein, observed in the experiments with dogs under prolonged accumulation of the lost protein in dialysate was five times lower than blood concentration, see (Rubin et al., 1985). Another consequence of the difference between both equations is the value of the estimated sieving coefficient. The sieving coefficient may be measured directly, if convective transport is prevailing, i.e. with very high fluid flow, or in isocratic conditions, i.e. during diffusive equilibrium at both sides of the membrane (Rubin et al., 1982, Park et al., 1995). If the measurement is done using solute concentration in blood as the reference, then the obtained value depends on the direction of fluid flow. If $j_{VT} > 0$ and $Pe >> 1$, i.e., for fluid flow into the tissue, then the measured value of S is equal to S_T, whereas for $j_{VT} < 0$ and $Pe << -1$, i.e., for fluid flow from the tissue, this value is equal to κS_T, c.f. equation (4.26). For high fluid flow through the capillary wall, κ may be lower than one even for small molecule solutes. In contrast, the membrane model, equation (4.31), predicts the estimated values of S as being independent of the fluid flow direction.

4.6 Diffusive solute transport

For the case of negligible fluid flow across the tissue, $j_{VT} = 0$, the solution of transport equation with boundary conditions $\Gamma\left(0\right) = \Gamma_1$ and $\left(d\Gamma/dx\right)\left(1\right) = 0$ is

$$\Gamma\left(x\right) = \Gamma\left(0\right) \frac{\cosh\left(\Phi\left(1 - x\right)\right)}{\cosh\left(\Phi\right)} \tag{4.32}$$

where $\Phi = L/\Lambda_D$, see equation (4.13) for $Pe_T = 0$. For small values of Φ, the normalized gradient may be approximated by a function $\Gamma_a\left(x\right) = 1 - \Phi^2 x\left(2 - x\right)$,

whereas for large values of Φ, $\Gamma(x)$ may be approximated by the exponential function $\Gamma_b(x) = \exp(-\Phi x)$, where we assumed that $\Gamma(0) = 1$. Thus, the flux across the tissue surface is, c.f. equation (4.24),

$$\begin{aligned} j_{ST}(0) &= \frac{D_T}{\Lambda} \tanh\left(\frac{L}{\Lambda}\right)(C_D - \kappa C_B) \\ &= \frac{D_T}{L}\Phi \tanh(\Phi)(C_D - \kappa C_B) \end{aligned} \tag{4.33}$$

or, using the unidirectional clearances

$$j_{ST}(0) = k_{DB}C_D - k_{BD}C_B \tag{4.34}$$

where

$$k_{DB} = \sqrt{D_T(k_T + q_{VL})}\tanh\left(L/\sqrt{D_T/(k_T + q_{VL})}\right) \tag{4.35}$$

or

$$\begin{aligned} k_{DB} &= P_T\Phi\tanh(\Phi) = k_{TBL}\Lambda\tanh(\Phi) \\ &= k_{TBL}L\Phi^{-1}\tanh(\Phi) \end{aligned} \tag{4.36}$$

and

$$\begin{aligned} k_{BD} &= \kappa k_{DB} = \kappa P_T\Phi\tanh(\Phi) \\ &= k_{BT}\Lambda\tanh(\Phi) = k_{BT}L\Phi^{-1}\tanh(\Phi). \end{aligned} \tag{4.37}$$

For the approximation of the thin exchange layer, i.e., for $\Phi >> 1$, $\tanh(\Phi) \sim 1$ and

$$k_{DB} = \sqrt{D_T(k_T + q_{VL})}. \tag{4.38}$$

Global parameters. The parameter $P_T = D_T/L$ is the diffusive permeability of the tissue layer of the thickness L, and furthermore $p_T = P_T/L$ is the local permeability of the tissue layer, i.e. permeability normalized per unit thickness of the membrane. Therefore, Φ may be described by local transport characteristics of the tissue, p_T and k_{TBL}, only: $\Phi = \sqrt{k_{TBL}/p_T}$. Both k_{TBL} and p_T have the dimension of time^{-1}; the parameters $\tau_{TBL} = \theta/k_{TBL}$ and $\tau_T = \theta/k_T$ are characteristic times for the nonstationary redistribution of the solute inside the tissue, see Chapter 6.

By multiplying the local unidirectional clearances and tissue permeability by the surface area, available for the exchange between the tissue and the external medium, A_M, one may obtain total unidirectional clearances K_{BD} and K_{DB} and express their description by the global tissue transport coefficients

$$K_{TBL} = k_{TBL}A_ML \tag{4.39}$$

$$K_{BT} = k_{BT}A_ML \tag{4.40}$$

$$K_T = P_TA_M. \tag{4.41}$$

Note that $\Phi = \sqrt{K_{TBL}/K_T}$. Now, the total flow between the tissue and external medium, $J_S = j_S(0)A_M$ may be described as

$$J_S = K_{DB}C_D - K_{BD}C_B \tag{4.42}$$

where

$$\begin{aligned} K_{DB} &= K_T \Phi \tanh(\Phi) = K_{TBL} \Phi^{-1} \tanh(\Phi) \\ &= \sqrt{K_{TBL} K_T} \tanh\left(\sqrt{K_{TBL}/K_T}\right) \end{aligned} \tag{4.43}$$

and

$$K_{BD} = K_{BT} \Phi^{-1} \tanh(\Phi). \tag{4.44}$$

Because $\Phi^{-1} \tanh(\Phi) \leq 1$, therefore

$$K_{BD} \leq K_{BT}. \tag{4.45}$$

Furthermore, from the fact that $\tanh(\Phi) \leq 1$

$$K_{DB} \leq \sqrt{K_{TBL} K_T}. \tag{4.46}$$

For high values of Φ: $K_{DB} = \sqrt{K_{TBL} K_T}$, i.e. K_{DB} is the geometric mean of K_{TBL} and K_T. For $\kappa = 1$: $K_{BD} = K_{DB}$.

Using the local transport coefficients k_{TBL} and p_T one can rewrite equation (4.43) as

$$K_{DB} = A_M L \sqrt{k_{TBL} p_T} \tanh\left(\sqrt{k_{BT}/p_T}\right). \tag{4.47}$$

Note that, because $A_M L$ is the characteristic volume of the organ, one can define the density k'_{DB} of the diffusive mass transport coefficient per unit tissue volume in terms of the local transport coefficients k_{TBL} and p_T,

$$k'_{DB} = \sqrt{k_{TBL} p_T} \tanh\left(\sqrt{k_{TBL}/p_T}\right). \tag{4.48}$$

Furthermore, the surface density k_{DB} of K_{DB}, i.e., K_{DB} normalized per unit surface area of the peritoneal side of the tissue with the surface area A_M, may be defined as

$$k_{DB} = \sqrt{k_{TBL} D_T} \tanh\left(L \sqrt{k_{TBL}/D_T}\right). \tag{4.49}$$

For high Φ, the density k_{DB} is the geometric mean of k_{TBL} and D_T.

Transport parameters for apparent tissue layers. Still another description of K_{BD} follows from the definitions of clearance for tissue layer of the width Λ,

$$K_{BT\Lambda} = k_{BT} A_M \Lambda = K_{BT} \Phi^{-1} \tag{4.50}$$

$$K_{TBL\Lambda} = k_{TBL} A_M \Lambda = K_{TBL} \Phi^{-1} \tag{4.51}$$

$$K_{T\Lambda} = D_T A_M / \Lambda = K_T \Phi. \tag{4.52}$$

The coefficient $K_{BT\Lambda}$ may be interpreted as the diffusive mass transport coefficient for the solute transport from blood to tissue within the tissue layer of the thickness Λ, and $K_{T\Lambda}$ as the diffusive mass transport coefficient for the transport through the same tissue layer. With these definitions

$$K_{BD} \;=\; K_{BT\Lambda} \tanh(\Phi) = \kappa K_{T\Lambda} \tanh(\Phi) \tag{4.53}$$

$$K_{DB} = K_{TBL\Lambda} \tanh(\Phi) = K_{T\Lambda} \tanh(\Phi). \tag{4.54}$$

Because $\tanh(\Phi)$ is less than 1 for all Φ, equations (4.53) and (4.54) provide estimations of K_{BD} and K_{DB} by capillary and tissue clearances $K_{TBL\Lambda}$, $K_{BT\Lambda}$, and $K_{T\Lambda}$, defined for the tissue layer of thickness Λ.

Furthermore, one can also define two other geometric parameters: $\Lambda_T = \Lambda / \tanh(\Phi)$ and $\Lambda_{TBL} = \Lambda_{BT} = \Lambda \tanh(\Phi)$, and consider two apparent tissue layers of the widths Λ_T and Λ_{TBL} and the same surface area A_M. For the apparent tissue layer of the width Λ_{TBL} one obtains that $K_{DB} = k_{TBL} A_M \Lambda_{TBL}$ and $K_{BD} = k_{BT} A_M \Lambda_{TBL}$, and for the apparent tissue layer of the width Λ_T one obtains that $K_{BD} = D_T A_M / \Lambda_T$. This result means that K_{BD} can be interpreted in two complementary ways: 1) as the transport coefficient between blood, which flows through a hypothetical capillary bed of the size equal to that in the tissue slice of the surface area A_M and the equivalent width Λ_{TBL}, and external medium, which surrounds the capillary bed, or 2) as the transport coefficient for diffusion between compartments of blood and external medium through a hypothetical non-perfused tissue slice of the surface area A_M and the equivalent width Λ_T. In general: $\Lambda_{TBL} < \Lambda < \Lambda_T$, but in the case of the tissue film transport (high Φ), $\tanh(\Phi)$ approaches 1 and all three penetration depths get approximately equal. Thus, for high Φ: $K_{BD} \approx K_{TBL\Lambda} \approx K_{BT\Lambda} \approx K_{T\Lambda}$, and K_{BD} can be interpreted as the transport coefficient between blood and tissue or the transport coefficient through the tissue, with the tissue thickness equal to the penetration depth Λ.

4.7 Effective blood flow

In the context of peritoneal dialysis it is usually assumed that only a relatively thin layer of the tissue that is adjacent to the peritoneal surface participates effectively in the exchange of solutes between dialysate and blood. The rate of blood flow in this layer was called the effective peritoneal blood flow (EPBF). To provide a more precise description of EPBF, or, in general, of effective blood flow (EBF) within the framework of the distributed model, the notion of the extraction coefficient E, defined in Chapter 3.4, may be used,

$$E = \frac{K_{BT}}{Q_B} \tag{4.55}$$

where Q_B is the total blood flow to the tissue and K_{BT} is the mass transport coefficient for the removal of the solute from blood to the tissue, $K_{BT} = A_M L k_{BT}$, c.f. equations (3.36) and (4.40).

Let us define the effective blood flow for the solute transport between tissue and external medium as the value Q_{BEF}, such that the ratio of K_{BD} (i.e. the maximal clearance for peritoneal dialysis) to Q_{BEF} is equal to the extraction coefficient E for the tissue

$$\frac{K_{BD}}{Q_{BEF}} = E. \tag{4.56}$$

Formulae (4.55) and (4.56) yield

$$Q_{BEF} = \frac{K_{BD}}{K_{BT}} Q_B \tag{4.57}$$

and, using equations (4.44), one obtains

$$Q_{BEF} = \Phi^{-1} \tanh(\Phi)\, Q_B \tag{4.58}$$

i.e. $Q_{BEF}/Q_B = \Phi^{-1} \tanh(\Phi)$, which is always less than or equal to 1. For $\Phi << 1$: $Q_{BEF} = Q_B$, whereas for $\Phi > 3$: $Q_{BEF} = Q_B/\Phi$.

Another approach to defining effective blood flow is through the process of absorption of the solute from external medium to the tissue and then from the tissue to blood and lymph. For the local absorption of the solute from tissue (in the absence of any solute exchange between the tissue and external medium) the absorption coefficient, E^a, may be defined in analogy to the extraction coefficient, equation (4.55), as

$$E^a = \frac{K_{TBL}}{Q_B} \tag{4.59}$$

where the total fluid (blood and lymph) outflow from the tissue is equal to $Q_B = Q_{Bin} = Q_{Bout} + Q_L$, because $Q_{Bout} = Q_{Bin} - Q_V$ and $Q_V = Q_L$, according to the assumed steady state of fluid transport within the tissue. Then, the absorptive effective blood flow, Q^a_{BEF}, may be defined as:

$$\frac{K_{DB}}{Q^a_{BEF}} = E^a. \tag{4.60}$$

It is easy to check that Q^a_{BEF} is described by the same formula as Q_{BEF}, i.e. by equation (4.58). Q^a_{BEF} is the effective fluid (blood and lymph) outflow from the tissue, but at the same time it is equal to effective blood inflow to the tissue, as described above, and therefore it may be considered simply as the effective absorptive blood flow. For solutes of low molecular weight with the prevailing diffusive transport through the capillary wall, $\kappa \approx 1$, and the two definitions of effective peritoneal flow yield the same result.

For solutes with high Φ, the following interpretation of the (minimal or absorptive) effective blood flow may be proposed. If equation (4.58) is written for high Φ, i.e. with $\tanh(\Phi) = 1$, then, using the approximation of Φ as $\Phi = L/\Lambda$, one gets:

$$Q_{BEF} = \frac{\Lambda}{L} Q_B \tag{4.61}$$

i.e., Q_{BEF} is the blood flow within the tissue layer of the thickness Λ. Because, for high values of Φ, the solute concentration within the tissue is exponential, it equilibrates to blood concentrations at the distance of about 3Λ from the peritoneal surface, and this means that the blood flow, which participates in the solute exchange with dialysate, is confined within the tissue layer of thickness 3Λ.

The problem of effective blood flow was disputed by many investigators, because the data obtained using different solutes, as, for example, quickly diffusing gases versus typical markers of transport of hydrophilic solutes with low molecular weight, as urea and creatinine, provided significantly different values of EPBF (Aune, 1970, Nolph, Twardowski, 1989, Grzegorzewska, Antosiewicz, 1993, Ronco et al., 1996). Our approach shows that different solutes may have different penetration depths and therefore also different perfused tissue layers participate in the exchange of these solutes. Some examples of the theoretical estimations of EPBF, based on physiological and clinical data may be found in (Waniewski et al., 1999, Waniewski, 2001).

4.8 Distributed model for tissue layer with different boundary concentrations

All the previous considerations concerning the spatially distributed model assumed the Dirichlet boundary condition at $X = 0$, $C_T(0) = C_D$, and Neumann boundary condition at $X = L$, $(dC_T/dX)(0) = 0$, i.e., the impermeable tissue surface at $X = L$, or the same Dirichlet boundary conditions for both surfaces with the tissue width of $2L$ – then by symmetry the Neumann boundary condition is valid at $X = L$. However, another practically important case comprises two different concentrations of solute at the opposite surfaces of the tissue, for example, $C_T(0) = C_D$ and $C_T(L) = C_G$. In peritoneal dialysis this may be valid for the gastrointestinal wall with dialysis fluid (D) at the serosal side of the gut wall and intra-intestinal stuff (G) that fills the lumen of the gut at the mucosal side of the gut wall. The general solution with these boundary conditions was described by equation (4.11); here we discuss this case with purely diffusive transport and derive a formula for clearance across the D surface. For these boundary conditions and the same scaling of the variables as for diffusive equation (4.10), the solution may be presented as

$$\Gamma(x) = \Gamma(0)\frac{\sinh(\Phi(1-x))}{\sinh(\Phi)} + \Gamma(1)\frac{\sinh(\Phi x)}{\sinh(\Phi)} \tag{4.62}$$

where $\Gamma(0) = 1$, and $\Gamma(1) = (C_G - \kappa C_B)/(C_D - \kappa C_B)$. For $C_G = C_D$, equation (4.62) describes the same Γ profile for the whole tissue width as equation (4.32) does for the half of the tissue width. The solute flux from dialysis solution to tissue across the surface D, $J_{SD} = A_M j_{ST}(0)$, is then described as

$$J_{SD} = K_T \Phi \coth(\Phi)(C_D - C_{EQD}) \tag{4.63}$$

where

$$C_{EQD} = \left(1 - \frac{1}{\cosh(\Phi)}\right)\kappa C_B + \frac{1}{\cosh(\Phi)} C_G \tag{4.64}$$

is the apparent equilibrium concentration for the transport between D fluid and the tissue and is expressed in the form of a weighted average of κC_B and C_G.

C_{EQD} is close to κC_B for $\Phi >> 1$ (i.e. for the tissue film approximation), and to C_G for $\Phi << 1$, i.e. for the case of easy penetration of the solute to the whole tissue.

The unidirectional clearance from external medium (D) to tissue is described as

$$K_{DB} = K_T \Phi \coth(\Phi) \tag{4.65}$$

but it represents the net transport only if $C_B = 0$ and $C_G = 0$. Another useful expression for K_{DB} is

$$K_{DB} = \sqrt{K_{TBL} K_T} \coth(\Phi). \tag{4.66}$$

Because $\coth(\Phi) \geq 1$, so $K_{DB} \geq \sqrt{K_{TBL} K_T}$. This restriction expresses the transport from D not only to blood but also to G fluid. For low values of Φ, i.e., for deep penetration of solute to the tissue: $K_{DB} = K_T$.

The solute flow from the tissue to D fluid,

$$J_{STD} = K_T \Phi \coth(\Phi) \left(\left(1 - \frac{1}{\cosh(\Phi)} \right) \kappa C_B + \frac{1}{\cosh(\Phi)} C_G \right) \tag{4.67}$$

for high Φ is reduced to

$$J_{STD} = K_{BT} \frac{\Lambda}{L} C_B \tag{4.68}$$

i.e., it may be considered as the flow from blood in the tissue layer of width Λ. The whole tissue layer is, however, permeable at both sides, and the solute flow from the G fluid at the other side of the tissue (e.g. in the gut lumen) to tissue, $J_{SGT} = -A_M j_{ST}(1)$ (here we assume that the tissue layer has the same surface area at both sides; however, the case with different surface areas may be easily incorporated into our theory), need also be taken into account

$$J_{SG} = K_T \Phi \coth(\Phi) (C_G - C_{EQG}) \tag{4.69}$$

where

$$C_{EQG} = \left(1 - \frac{1}{\cosh(\Phi)} \right) \kappa C_B + \frac{1}{\cosh(\Phi)} C_D \tag{4.70}$$

is the equilibrium concentration for the transport between G fluid and the tissue. The diffusive mass transport coefficient for the unidirectional transport from G fluid to tissue, K_{GB}, is given by the same formula as for K_{DB}, equation (4.65).

For high Φ ($\Phi >> 1$) the solute exchange through each surface is independent of the conditions at the other surface, i.e. $K_{DT} = K_{GT} = \sqrt{K_{TBL} K_T}$ and $C_{EQD} = C_{EQG} = \kappa C_B$, but for small Φ ($\Phi << 1$): $J_{SD} = -J_{SG} = K_T (C_D - C_G)$, i.e., the perfusion of the tissue has negligible impact on steady state solute transport.

The overall flow of solute from blood to both fluids (D and G), $J_{SFB} = -(J_{SGT} + J_{SDT})$, is

$$J_{SBF} = 2\sqrt{K_{TBL} K_T} \coth(\Phi) \left(1 - \frac{1}{\cosh(\Phi)} \right) \left(\kappa C_B - \frac{C_D + C_G}{2} \right). \tag{4.71}$$

Thus, the unidirectional clearance from blood to both fluids, K_{BF}, may be described as

$$K_{BF} = 2K_{BT}\Phi^{-1}\coth(\Phi)\left(1 - \frac{1}{\cosh(\Phi)}\right). \tag{4.72}$$

For $\Lambda << L$, and therefore high Φ, $K_{BF} = 2K_{BT}\Lambda/L = 2k_{BT}A_M\Lambda$, i.e., the two thin boundary layers at both boundary surfaces of the tissue layer contribute independently to the total clearance, whereas for $\Lambda >> L$, and therefore low Φ, K_{BF} tends to K_{BT}. The effective blood flow for the exchange of solute between blood and a hypothetical fluid with the same (average) solute concentration at both sides of the tissue may be defined using equation (4.71) and the methods described in Chapter 4.7.

4.9 Summary

1. The balance equation for solute transport in the tissue needs to include the fractional volume available for the solute distribution.
2. The steady state of the linear system of the solute transport equations (in particular, the transport parameters, including volumetric flux across the tissue and fluid exchange between the tissue, blood and lymph, are assumed to be constant in time and space) has solutions in terms of closed formulas.
3. The steady state profiles of solute concentration in the tissue may be characterized by solute penetration depth, which is a function of solute diffusivity in the tissue, convective component (sieving coefficient times volumetric flux across the tissue), solute permeability across the capillary wall, convective component of solute transport across the capillary wall, and lymphatic uptake. The components of the overall penetration depth for diffusive and convective transport separately can also be defined.
4. The equation for diffusive–convective solute transport across the peritoneal surface is similar to the standard equation for the transport across permselective membrane. However, there are two important differences:
   (a) The distributed model predicts, in agreement with experimental data, that solutes in dialysate equilibrate to their physiological concentration in the tissue, not in blood as it was assumed in the standard membrane model. This observation is of special importance for macromolecules, which have different concentrations in blood and interstitial fluid in physiological conditions, and for small and middle molecules if ultrafiltration from blood is high.
   (b) The distributed model yields the formula for the mean weighted intramembrane concentration of the solute in the convective component, described by a different function of the Peclet number than that for the membrane model. However, numerical difference between these formulas is not high and they have the same asymptotic limits for high Peclet numbers and the same value for $Pe = 0$.

5. The effective diffusive mass transport parameter for the system is a function of solute diffusivity in the tissue, solute permeability of the capillary wall, sieving coefficient of the capillary in the capillary wall, volumetric flux across the capillary wall, and lymphatic flux from the tissue.
6. The effective sieving coefficient is equal, according to the distributed model, to the tissue sieving coefficient of the solute. However, its measured values may depend on the direction of the solute transport (i.e., for different boundary conditions) because of the dependence of the mean solute concentration on the ratio of the equilibrium solute concentration in the tissue to its concentration in plasma.
7. In the case of purely diffusive transport of solute across the tissue, the two complementary interpretations of the effective diffusive mass transport parameter are valid:
   (a) The effective mass transport parameter is equal to the diffusive permeability coefficient for the nonperfused tissue layer of the width equal to the solute penetration depth.
   (b) The effective mass transport parameter for the transport from blood to external medium is equal to the unidirectional clearance from blood to tissue for the perfused capillary bed in the tissue layer of the width equal to the solute penetration depth. The effective mass transport parameter for the transport from external medium to blood is equal to the unidirectional clearance from tissue to blood and lymphatics for the perfused capillary bed in the tissue layer of the width equal to the solute penetration depth.
8. Effective blood flow that participates in the diffusive transport of the solute may be defined as such blood flow that the effective diffusive mass transport parameter is equal to the extraction coefficient multiplied by the effective blood flow. The effective blood flow depends on the transport characteristics of the solute. For solutes with low diffusive penetration depth, the effective blood flow is equal to the blood flow in the tissue layer of the width equal to the penetration depth.

5

Spatially distributed models for fluid exchange between perfused tissue and external medium

Fluid transport in biological systems is typically driven by hydraulic pressure, as in the cardiovascular system, or by a combination of hydrostatic and osmotic pressures, as in the transport across the capillary wall, induced by the Starling forces and across the cell membrane, induced by the pressure and overall osmotic pressure differences across the cell membrane with most important player being sodium and potassium. Within the tissue, both fluid driving forces are typically operating with the prevalence of hydraulic pressure during the physiological circulation of interstitial fluid between the capillary and lymphatic vessel or therapeutically applied osmotic pressure in peritoneal dialysis. The mathematical description of osmotically driven flow is intrinsically nonlinear and therefore more sophisticated than the linear model for purely hydraulic pressure. Actually, the model for the hydraulic-osmotic driving forces needs to include also the description of the transport of the osmotic agent (or agents) that is, the solutes, which exert osmotic pressure. These solutes might be macromolecules (mostly plasma proteins, then their overall osmotic pressure is called oncotic pressure) or low molecular weight (small) solutes, as, for example, glucose, which is used as osmotic agent in peritoneal dialysis.

The spatially distributed model of fluid transport was developed much later than the model for diffusive and diffusive-convective solute transport, mostly for the applications in modeling of cancer therapy and peritoneal dialysis (Gokal et al., 2000). After a short introduction, in Chapter 5.1, the general mass balance for water (solvent) mass is simplified using the approximate description of the change of the fluid void fraction (fraction of tissue volume available for fluid) and the application of the Spiegler-Kedem-Katchalsky approach based on fluid volume flux, in Chapter 5.2. Because the fluid flux driven by osmotic pressure is important in many applications, the system of equations for volumetric fluid and solute (osmotic agent) transport is described in Chapter 5.3. The rest of the chapter deals with the steady state solutions. The simplest steady state case of fluid flux, driven only by hydraulic pressure, allows for the closed formula description similar to the solutions of distributed diffusive equation, as shown in Chapter 5.4. However, the general case of fluid flow, driven by combined hydraulic and osmotic pressure leads to the nonlinear problem of fluid and osmotic agent transport that allows only for approximate solution with additional assumptions, see Chapter 5.5. Another special, approximated case of prevailing osmotic pressure is discussed in Chapter 5.6. The summary of the results is presented in Chapter 5.7.

5.1 Introduction

The spatially distributed modeling of fluid transport was initiated much later than the spatially distributed modeling of (diffusional) solute transport, with the first fluid transport model formulated (and analyzed numerically) for solid tumors in (Baxter, Jain, 1989), and for peritoneal dialysis in 1990 (Seames et al., 1990). The selection of the parameters for this model yielded a disagreement between the predicted and measured values of the hydrostatic pressure in the tissue (Flessner, 1994). There were several other versions of the model proposed for the osmotically driven fluid flow in peritoneal dialysis and for the hydrostatic pressure driven absorption of fluid from the peritoneal cavity to the tissue and blood (Leypoldt, Henderson, 1992, Leypoldt, 1993, Flessner, 1996, Cherniha, Waniewski, 2005, Stachowska-Pietka et al., 2006, Cherniha et al., 2007, Stachowska-Pietka et al., 2012, Cherniha et al., 2014). Some of these models included several nonlinear functions for the description of various physiological phenomena and were studied by numerical simulations. Another problem of fluid exchange in the solid tumour and between the tumour and the surrounding tissue, with the focus on the hydrostatic and oncotic pressures as the main driving forces was discussed in (Baxter, Jain, 1989, 1990, Pozrikidis, Farrow, 2003). Our theoretical discussion of the simple versions of the spatially distributed model for fluid transport is based on (Waniewski, 2009, Waniewski et al., 2009).

5.2 Spatially distributed model for volumetric transport

As for any other solute, the mass balance for water, c.f. equation (1.1), is

$$\frac{\partial C_w}{\partial t} = -\mathrm{div}\mathbf{j}_w + q_w. \tag{5.1}$$

To model the exchange of fluid that is a dilute solution, one considers the general expression for water (solvent) flux $j_w = C_w v_w$, Chapter 2.1, and assumes that water velocity in the dilute solution is equal to the volumetric flux, $v_w = j_V$, see Chapter 2.2. By the same reasoning, the source/sink term for fluid may be described as $q_w = C_w q_V$, where q_V is the volumetric source/sink flow density. As we are interested in the description of water mass balance in some specific local subspace, as the space available for water inside the pores (or, for example, in the interstitium in biological applications), we have to assume that $C_w = \theta C$, where θ is the space fraction for the fluid void volume that is accessible for fluid within the space element dV, and C is the water concentration expressed per real water distribution space θdV, see Chapter 4.2. Moreover, we have to define the fluxes j_V and q_V to pass across or to/from the fluid void volume. Thus, the water fluxes related to the fluid void volume are $j_w = C j_V$ and $q_w = C q_V$, and equation (5.1) may be approximately presented as

$$\frac{\partial (\theta C)}{\partial t} = -\mathrm{div}\,(C\mathbf{j}_V) + C q_V. \tag{5.2}$$

Because water is the dominant substance in the dilute solution and therefore its concentration changes only slightly if the concentrations of the dissolved solutes change, we consider C as a constant, and from (5.2) we obtain the equation for the changes in the interstitial fluid void volume fraction, θ,

$$\frac{\partial \theta}{\partial t} = -\mathrm{div}\mathbf{j}_V + q_V. \tag{5.3}$$

For flat tissue and the fluid transport perpendicular to the surface, see Chapter 4.2,

$$\frac{\partial \theta}{\partial t} = -\frac{\partial j_V}{\partial X} + q_V \tag{5.4}$$

wherej_V is now the X-component of volumetric flux across the tissue.

5.3 The fluid and solute transport across the perfused tissue

By specifying the model for fluid transport across the tissue and adding an equation for the transport of one solute (osmotic agent) one gets the distributed model of fluid transport induced by hydrostatic and osmotic pressures and diffusive-convective solute transport in the general form of fluid volume and solute mass balances

$$\frac{\partial \theta_V}{\partial t} = -\frac{\partial j_V}{\partial X} + q_V \tag{5.5}$$

$$\frac{\partial \left(\theta_S C\right)}{\partial t} = -\frac{\partial j_S}{\partial X} + q_S \tag{5.6}$$

where θ_V is the fluid void volume, θ_S is the solute void volume, j_V is the volumetric flux across the tissue, q_V is the rate of the net fluid flow to the tissue by the transcapillary ultrafiltration and lymphatic absorption, j_S is the solute flux across the tissue, q_S is the rate of the net solute flow to the tissue by the transcapillary transport and lymphatic absorption, X is the distance measured from the tissue surface in contact with fluid (e.g., at the parietal mesothelium) at $X_0 = 0$ through the tissue to the external tissue surface (e.g., skin) at $X_{MAX} = L$, and

$$j_V = -K\left(\frac{\partial P}{\partial X} - \sigma_T RT\frac{\partial C}{\partial X}\right) \tag{5.7}$$

$$q_V = L_P a\left[\left(P_B - P\right) - \sigma_C RT\left(C_B - C\right)\right] - q_L \tag{5.8}$$

$$j_S = -D_T\frac{\partial C}{\partial X} + S_T j_V C \tag{5.9}$$

$$\begin{aligned} q_S = q_{SBTL} &= k_B C_B - k_T C + q_L C \\ &= -\left(k_T + q_L\right)\left(C - \kappa C_B\right) \end{aligned} \tag{5.10}$$

where $P = P\left(X,t\right)$ is the local tissue hydrostatic pressure, $C = C\left(X,t\right)$ is the local tissue solute concentration, K is the hydraulic permeability of the tissue,

σ_T is the Staverman reflection coefficient for the solute in the tissue, R is the gas constant, T is the temperature, $L_p a$ is the capillary wall hydraulic conductivity times capillary surface area of the capillary wall per unit tissue volume, P_B and C_B are hydrostatic pressure and solute concentration in blood, respectively, σ_C is the Staverman reflection coefficient for the solute in the capillary wall, q_L is the rate of lymphatic absorption from the tissue per unit volume, D_T is the diffusivity of solute in the tissue, S_T is the sieving coefficient of solute in the tissue, k_B and k_T are unidirectional clearances for solute exchange between blood and tissue across capillary wall described in detail in Chapter 3, expressed as the densities per unit tissue volume. Finally,

$$\kappa = \frac{k_B}{k_T + q_{VL}}. \tag{5.11}$$

The fluxes across the tissue are positive if directed from $X = 0$ to $X = L$. The flow densities across the capillary wall are positive if directed from blood to the tissue. Equations (5.5) and (5.6) need also a description of the relationship between θ_{V} and P, as well as θ_{V} and θ_S, and then the system may be considered, alternatively, as having two variables, P and C, see (Stachowska-Pietka et al., 2006, 2012). However, the steady states of this system, under some simplifying assumptions, can be studied directly using the equations presented.

The model of fluid transport, driven by the combined effect of hydrostatic and osmotic pressures, is nonlinear because of coupling of solute flow to convective fluid flow and the dependence of osmotic pressure on solute concentration. Therefore, its closed solutions may be only approximate and need numerical simulations in the general case. Nevertheless, the theoretical analysis of this model provides valuable insights into its structure and relevant parameters. Before attacking the nonlinear model, we discuss a simpler case of fluid flow driven only by the hydrostatic pressure gradient.

5.4 Distributed model of fluid transport driven by hydrostatic pressure

Let us discuss two cases of the hydrostatic pressure driven fluid flow across the perfused tissue: 1) without, $q_L = 0$, and 2) with lymphatic absorption, $q_L > 0$, from the tissue. In the case of the lack of osmotic agent, $C \equiv 0$, one can derive from equations (5.5) and (5.7) the steady state equation for hydrostatic pressure, P,

$$K\frac{d^2P}{dX^2} + q_V = 0. \tag{5.12}$$

In the first case, by equation (5.8),

$$q_V = L_P a\,(P_B - P) \tag{5.13}$$

whereas in the second case

$$q_V = L_P a\,(P_B - P) - q_L. \tag{5.14}$$

In the physiological equilibrium, $q_V = 0$, which implies, in the first case, that $P_0 = P_B$, and in the second case, that $q_L = L_P a\,(P_B - P_0)$, where P_0 denotes the pressure in the physiological equilibrium, obtained without fluid exchange with external medium. Thus, if we assume that the lymphatic flow is not changed during fluid exchange, compared to the physiological equilibrium, and we may combine equation (5.14) with the equilibrium expression for q_L, then during the external exchange

$$q_V = L_P a\,(P_0 - P) \tag{5.15}$$

and we have similar equations for q_V in both cases, except that P_B in equation (5.13) is exchanged with P_0 in equation (5.15).

Assuming the boundary conditions

$$P(0) = P_D \quad (P_D \neq P_{eq}) \tag{5.16}$$

$$(dP/dx)\,P\,(L) = 0 \tag{5.17}$$

and denoting $\Lambda_F = \sqrt{K/L_P a}$, $\varphi = L/\Lambda_F$, $x = X/L$, and scaled hydrostatic pressure $p\,(x) = (P\,(Lx) - P_{eq})\,/\,(P_D - P_{eq})$ with $P_{eq} = P_B$ for the first case or $P_{eq} = P_0$ for the second case, we get the same normalized transport equation

$$-\frac{d\iota}{dx} - \varphi p = 0 \tag{5.18}$$

where

$$\iota = -\frac{1}{\varphi}\frac{dp}{dx} \tag{5.19}$$

Note that $\iota\,(1) = 0$ by the boundary condition (5.17). The integration of equations (5.18) – (5.19) gives

$$p\,(x) = \frac{e^{\varphi(1-x)} + e^{-\varphi(1-x)}}{e^{\varphi} + e^{-\varphi}} = \frac{\cosh\,(\varphi\,(1-x))}{\cosh\,(\varphi)} \tag{5.20}$$

$$\iota\,(x) = \frac{e^{\varphi(1-x)} - e^{-\varphi(1-x)}}{e^{\varphi} + e^{-\varphi}} = \frac{\sinh\,(\varphi\,(1-x))}{\cosh\,(\varphi)}. \tag{5.21}$$

Therefore, using the formula $j_V\,(X) = k\iota\,(X/L)\,(P_D - P_{eq})$ with $k = \sqrt{K \cdot L_P a}$,

$$j_V\,(0) = k\iota\,(0)\,(P_D - P_{eq}) = k\tanh\,(\varphi)\,(P_D - P_{eq}) \tag{5.22}$$

with $k\tanh\,(\varphi)$ being the effective hydraulic conductance of the system. Assuming that $\varphi >> 1$, i.e. $\Lambda_F << L$, we get the approximate solutions

$$p\,(x) = e^{-\varphi x} \tag{5.23}$$

$$\iota\,(0) = 1 \tag{5.24}$$

or

$$j_V(0) = k(P_D - P_{eq}) \tag{5.25}$$

for $k = \sqrt{K \cdot L_P a}$. Note that the transport equation and its solution in the here considered fluid transport, driven only by hydrostatic pressure, are analogous to the transport equation and its solution, respectively, for the purely diffusive solute transport, discussed in Chapter 4.6.

5.5 Distributed model of fluid transport driven by combined hydrostatic and osmotic pressures

We shall now consider the steady state solutions of the full system of equations (5.5) and (5.6). The condition of zero q_V in the physiological equilibrium yields

$$q_L = L_P a[(P_B - P_0) - \sigma_C RT(C_B - C_0)] \tag{5.26}$$

where, as we know already, $C_0 = \kappa C_B$ is the equilibrium solute concentration in the tissue in the presence of lymphatic absorption, see Chapter 4.2, and P_0 is the equilibrium tissue pressure, see Chapter 5.4. Assuming that q_L is constant and equal to the equilibrium value also during exchange with the external medium, we get from equation (5.8) that

$$q_V = L_P a[(P_0 - P) - \sigma_C RT(C_0 - C)]. \tag{5.27}$$

Thus,

$$K\left(\frac{d^2P}{dX^2} - \sigma_T RT\frac{d^2C}{dX^2}\right) + L_P a[(P_0 - P) - \sigma_C RT(C_0 - C)] = 0. \tag{5.28}$$

The boundary conditions are

$$P(0) = P_D \quad (P_D \neq P_0) \tag{5.29}$$

$$j_V(L) = 0. \tag{5.30}$$

If $(dC/dx)(L) = 0$, as for the solution of the full system of equations (5.5) and (5.6), then the boundary condition (5.30) is equivalent to $(dP/dX)(L) = 0$.

Let us denote $\Lambda_F = \sqrt{K/L_P a}$, $\varphi = L/\Lambda_F$, and change the variable X to $x = X/L$, as it was done in Chapter 5.3. Furthermore, let us denote $c(x) = (C(Lx) - C_0)/(C_D - C_0)$, $p(x) = (P(Lx) - P_0)/(P_D - P_0)$, where $C_D = C(0) \neq C_0$ and $P_D = P(0) \neq P_0$. Then, equation (5.28) may be rewritten as two equations

$$-\frac{1}{\varphi}\frac{d\iota}{dx} - (\varepsilon p - \sigma_C c) = 0 \tag{5.31}$$

$$\iota = -\frac{1}{\varphi}\left(\varepsilon\frac{dp}{dx} - \sigma_T\frac{dc}{dx}\right) \tag{5.32}$$

with $\varepsilon = (P_D - P_0) / (RT (C_D - C_0))$. Note that $\iota (1) = 0$. The integration of equation (5.31) from 1 to x gives

$$\iota (x) = -\varphi \left(\varepsilon \int_1^x p (s)\, ds - \sigma_C \int_1^x c (s)\, ds \right). \tag{5.33}$$

Thus,

$$j_V (0) = k\iota (0)\, RT (C_D - C_0) = k \left(\int_0^1 p (s)\, ds \cdot (P_D - P_0) - \sigma_C \int_0^1 c (s)\, ds \cdot RT (C_D - C_0) \right). \tag{5.34}$$

The equation for p may be written, see equation (5.28), as

$$\frac{1}{\varphi^2} \frac{d^2 p}{dx^2} - \left(p + \frac{1}{\varepsilon} f(x) \right) = 0 \tag{5.35}$$

where:

$$f = \frac{\sigma_T}{\varphi^2} \frac{d^2 c}{dx^2} - \sigma_C c. \tag{5.36}$$

The solution to equation (5.35) with the boundary conditions $p(0) = 1$ and $(dp/dx)(1) = 0$ is

$$p (x) = \frac{\cosh (\varphi (1 - x))}{\cosh \varphi} - \frac{u' (1)}{\varepsilon \varphi} \frac{\sinh \varphi x}{\cosh \varphi} + \frac{u (x)}{\varepsilon} \tag{5.37}$$

where:

$$u (x) = \frac{\varphi}{2} \left[e^{\varphi x} \int_0^x f (s)\, e^{-\varphi s} ds - e^{-\varphi x} \int_0^x f (s)\, e^{\varphi s} ds \right] \tag{5.38}$$

and

$$u' (x) = \frac{du}{dx} (x) = \frac{\varphi^2}{2} \left[e^{\varphi x} \int_0^x f (s)\, e^{-\varphi s} ds + e^{-\varphi x} \int_0^x f (s)\, e^{\varphi s} ds \right]. \tag{5.39}$$

The calculation of $u(x)$ may be reduced, using formula (5.36) and integration by parts, to the calculation of integrals that involve function c only

$$u (x) = \sigma_T \left[c (x) - \frac{c' (0)}{\varphi} \sinh \varphi x - \cosh \varphi x \right] + (\sigma_T - \sigma_C)\, v (x) \tag{5.40}$$

where

$$v (x) = \frac{\varphi}{2} \left[e^{\varphi x} \int_0^x c (s)\, e^{-\varphi s} ds - e^{-\varphi x} \int_0^x c (s)\, e^{\varphi s} ds \right] \tag{5.41}$$

and $c'(0) = (dc/dx)(0)$. In the following, we investigate the consequences of equations (5.37) – (5.39), assuming that the profile of normalized solute concentration in the tissue may be approximately described by the exponential function

$$c(x) = \exp(-\psi x) \tag{5.42}$$

where $\psi = \alpha\varphi = L/\Lambda_S$. Note that the boundary condition for $c'(1) = 0$ can be fulfilled only approximately for $\psi >> 1$. Using the exponential function (5.42) we can calculate the integrals in formulas (5.38) and (5.39), and get

$$u(x) = \left(\sigma_T - \frac{\sigma_C}{\alpha^2}\right) \frac{\alpha^2}{\alpha^2 - 1} \left(\alpha \sinh \varphi x - \cosh \varphi x + e^{-\psi x}\right) \tag{5.43}$$

$$\frac{du}{dx}(x) = \left(\sigma_T - \frac{\sigma_C}{\alpha^2}\right) \frac{\alpha^2}{\alpha^2 - 1} \left(\alpha \cosh \varphi x - \sinh \varphi x - \alpha e^{-\psi x}\right) \varphi. \tag{5.44}$$

Now, from equation (5.32),

$$\begin{aligned} \iota(0) &= -\tfrac{1}{\varphi}\left(\varepsilon \tfrac{dp}{dx}(0) + \sigma_T \psi\right) \\ &= \left[\varepsilon \tanh \varphi + \left(\sigma_T - \tfrac{\sigma_C}{\alpha^2}\right) \tfrac{\alpha^2}{\alpha^2 - 1} \left(\alpha - \tanh \varphi - \alpha \tfrac{e^{-\psi}}{\cosh \varphi}\right) - \sigma_T \alpha\right]. \\ &= \left[\varepsilon \tanh \varphi - \tfrac{\sigma_C}{\alpha} \tfrac{\alpha^2}{\alpha^2 - 1} - \left(\sigma_T - \tfrac{\sigma_C}{\alpha^2}\right) \tfrac{\alpha^2}{\alpha^2 - 1} \left(\tanh \varphi + \alpha \tfrac{e^{-\psi}}{\cosh \varphi}\right)\right] \end{aligned} \tag{5.45}$$

For $\varphi >> 1$ (i.e. $L >> \Lambda_F$) and $\psi = \alpha\varphi >> 1$ (i.e. $L >> \Lambda_S$)

$$\iota(0) = \left[\varepsilon - \frac{\sigma_C}{\alpha} \frac{\alpha^2}{\alpha^2 - 1} - \left(\sigma_T - \frac{\sigma_C}{\alpha^2}\right) \frac{\alpha^2}{\alpha^2 - 1}\right]. \tag{5.46}$$

Thus, the expression for fluid flow across the surface $x = 0$ is

$$j_V(0) = k\left[(P - P_0) - \left(\frac{\sigma_C}{\alpha} \frac{\alpha^2}{\alpha^2 - 1} + \left(\sigma_T - \frac{\sigma_C}{\alpha^2}\right) \frac{\alpha^2}{\alpha^2 - 1}\right) RT(C - C_0)\right] \tag{5.47}$$

and the effective reflection coefficient of osmotic agent, defined as

$$j_V(0) = k\left[(P - P_0) - \sigma_{eff} RT(C - C_0)\right] \tag{5.48}$$

is given by the formula

$$\sigma_{eff} = \frac{\sigma_C}{\alpha} \frac{\alpha^2}{\alpha^2 - 1} + \left(\sigma_T - \frac{\sigma_C}{\alpha^2}\right) \frac{\alpha^2}{\alpha^2 - 1}. \tag{5.49}$$

Furthermore, we can calculate the pressure at $x = 1$, i.e., at the non-permeable side of the tissue layer,

$$\begin{aligned} p(1) &= \tfrac{1}{\cosh \varphi} - \tfrac{u'(1)}{\varepsilon\varphi} \tanh \varphi + \tfrac{u(1)}{\varepsilon} \\ &= (1 - \delta) \tfrac{1}{\cosh \varphi} + \tfrac{\delta}{\varepsilon} (\alpha \tanh \varphi + 1) e^{-\psi} \end{aligned} \tag{5.50}$$

where

$$\delta = \left(\sigma_T - \frac{\sigma_C}{\alpha^2}\right)\frac{\alpha^2}{\alpha^2 - 1}. \tag{5.51}$$

Equation (5.50) can be applied for the estimation of the tissue reflection coefficient as a function of other parameters if $p(1)$ is known for the particular ε

$$\sigma_T = \frac{\sigma_C}{\alpha^2} - \frac{\alpha^2 - 1}{\alpha^2}\frac{\varepsilon\cosh\varphi}{\varepsilon - (\alpha\tanh\varphi + 1)\,e^{-\psi}\cosh\varphi}\left(p(1) - \frac{1}{\cosh\varphi}\right). \tag{5.52}$$

The obtained formulas are cumbersome for direct analysis and therefore we consider separately an important approximation for the general model to provide an insight into its interpretation.

5.6 Approximation for prevailing osmotic pressure

We simplify the general description of the transcapillary transport by assuming that osmotic pressure difference is much higher than hydrostatic pressure difference between blood and tissue, and the transcapillary flux may be described as

$$q_V = L_P a \cdot \sigma_C RT\,(C - C_B). \tag{5.53}$$

Thus, from equation (5.28),

$$K\left(\frac{d^2P}{dX^2} - \sigma_T RT\frac{d^2C}{dX^2}\right) + L_P a \cdot \sigma_C RT\,(C - C_0) = 0. \tag{5.54}$$

For the same boundary conditions and the scaling system as in Chapter 5.4 one has

$$-\frac{1}{\varphi}\frac{d\iota}{dx} + \sigma_C c = 0 \tag{5.55}$$

where

$$\iota = -\frac{1}{\varphi}\left(\varepsilon\frac{dp}{dx} - \sigma_T\frac{dc}{dx}\right) \tag{5.56}$$

and $\varepsilon = P_D/\left(RT\,(C_D - C_B)\right)$, whereas the non-scaled fluid flux across the tissue is related to ι as

$$j_V(X) = k\iota(X/L)\,RT\,(C_D - C_B) \tag{5.57}$$

where $k = \sqrt{K \cdot L_P a}$. Note that $\iota(1) = 0$ by the boundary condition at $X = L$. The integration of equation (5.55) from 1 to x yields

$$\iota(x) = \sigma_C\varphi\int_1^x c(s)\,ds. \tag{5.58}$$

With our approximation we do not need to solve the second order ordinary differential equation (5.54) for p, but, instead, we can integrate the first order

differential equation (5.56) with the left hand side described by equation (5.58), and get

$$p(x) = p_0 - \frac{1}{\varepsilon}\left[\sigma_T\left(c_0 - c(x)\right) + \sigma_C\varphi^2 \int_0^x \left(\int_1^z c(s)\,ds\right) dz\right] \tag{5.59}$$

where $p_0 = p(0) = 1$ and $c_0 = c(0) = 1$. Note also that

$$\iota(0) = -\sigma_C\varphi \int_0^1 c(s)\,ds \tag{5.60}$$

or

$$j_V(0) = k\iota(0)\,RT\left(C_D - C_B\right) = -k\sigma_C\varphi \int_0^1 c(s)\,ds\,RT\left(C_D - C_B\right). \tag{5.61}$$

Furthermore, if we apply equation (5.59) for $x = 1$ and demand that $p(1) = 0$, then we obtain an additional condition for the parameters of the model, which may be presented as the condition for the Staverman reflection coefficient of the tissue:

$$\sigma_T = \frac{\varepsilon + \sigma_C\varphi^2 \int_0^1 \left(\int_z^1 c(s)\,ds\right) dz}{1 - c(1)}. \tag{5.62}$$

In the following, we investigate the consequences of equations (5.58) - (5.62), assuming that the solute (e.g. glucose) penetrates only a thin layer of the tissue and the profile of its concentration in the tissue may be approximately described by the exponential function

$$\begin{aligned} C(X) &= \exp\left(-X/\Lambda_S\right) \\ c(x) &= \exp\left(-\psi x\right) \end{aligned} \tag{5.63}$$

where $\psi = L/\Lambda_S$, $x = X/L$. Let $\alpha = \Lambda_F/\Lambda_S = \psi/\varphi$, see Chapter 5.4. Note that with this assumption, the boundary condition $(dC/dx)(L) = 0$ can be fulfilled only approximately. Using the exponential function for $c(x)$, we can calculate the integrals in equations (5.59) and (5.60), and get

$$p(x) = 1 + \frac{1}{\varepsilon}\left[\left(\frac{\sigma_C}{\alpha^2} - \sigma_T\right)\left(1 - e^{-\psi x}\right) - \frac{\sigma_C}{\alpha}\varphi x e^{-\psi}\right] \tag{5.64}$$

$$\iota(x) = -\frac{\sigma_C}{\alpha}\left(e^{-\psi x} - e^{-\psi}\right) \tag{5.65}$$

or

$$j_V(0) = k\iota(0)\,RT\left(C_D - C_B\right) = -k\frac{\sigma_C}{\alpha}\left(1 - e^{-\psi}\right) RT\left(C_D - C_B\right) \tag{5.66}$$

where $k = \sqrt{K \cdot L_P a}$ is the effective hydraulic conductance of the system, and the effective reflection coefficient is described as $\sigma_{eff} = \sigma_C \left(1 - e^{-\psi}\right)/\alpha$. Furthermore,

$$\sigma_T = \frac{\sigma_C}{\alpha^2} - \frac{\varepsilon\left(p\left(1\right) - 1\right) + \frac{\sigma_C}{\alpha}\varphi e^{-\psi}}{1 - e^{-\psi}}. \tag{5.67}$$

Assuming that $\alpha\varphi = \psi >> 1$, one may simplify the formulas to

$$\iota\left(0\right) = -\frac{\sigma_C}{\alpha} \tag{5.68}$$

$$\frac{dp}{dx}\left(0\right) = \frac{\psi}{\varepsilon}\left(\frac{\sigma_C}{\alpha^2} - \sigma_T\right) \tag{5.69}$$

$$\sigma_T = \varepsilon\left(1 - p\left(1\right)\right) + \frac{\sigma_C}{\alpha^2} \tag{5.70}$$

and

$$j_V\left(0\right) = -k\frac{\sigma_C}{\alpha}RT\left(C_D - C_B\right). \tag{5.71}$$

The effective reflection coefficient may be therefore described as $\sigma_{eff} = \sigma_C/\alpha$, and the tissue reflection coefficient σ_T may be expected to be of the order of σ_C/α^2, because ε is negligible for this approximation with the prevailing osmotic pressure.

There are many interesting conclusions from these formulas. In particular, α may be calculated from equation (5.71) if $j_V\left(0\right)$ is known from computer simulations. Otherwise, α may be estimated after obtaining Λ_S by fitting the exponential curve to the concentration profile obtained from computer simulations (Waniewski et al., 2009).

5.7 Summary

1. The model of fluid transport across the perfused tissue can be derived from the standard transport equation for water using typical approximations for dilute solutions.
2. The steady state equation for the case of fluid flow, driven by hydrostatic pressure only, is the equation for intratissue hydrostatic pressure, analogous to the diffusion equation with sink/source in the tissue. The pressure profile in the tissue can be characterized by the fluid/pressure penetration depth. The penetration depth and the effective hydraulic permeability are the functions of the hydraulic conductivity of the tissue and the hydraulic permeability of the capillary wall.
3. The presence of lymphatics within the tissue changes the equilibrium hydrostatic pressure at the permeable tissue boundary from that equal to blood pressure to the equilibrium hydrostatic pressure for the tissue with lymphatics, which is typically lower than the hydrostatic pressure of blood.

4. The steady state equation for the intratissue hydrostatic pressure in the case of fluid flow, driven by the combined hydrostatic and osmotic pressures, can be solved if the steady state profile of osmotic pressure is assumed to be known.
5. The effective (net) osmotic reflection coefficient for the distributed system depends on the reflection coefficients for the capillary wall and for the tissue as well as on the ratio of fluid to solute (osmotic agent) penetration depth. It can be approximately estimated as the capillary reflection coefficient divided by the ratio of the fluid to solute penetration depth.
6. The reflection coefficient for the tissue can be estimated, assuming all other parameters of the system known, from the value of hydrostatic pressure at the impermeable surface of the tissue.

6

Transit times and transient states of the linear distributed model

The problem of finding the transient solutions of a mathematical model is typically more difficult than the investigation of the steady state solutions, which were presented for the spatially distributed model of fluid and solute transport in the tissue and between the perfused tissue and the external medium in Chapters 3, 4 and 5. For linear diffusion-reaction-convection systems of partial differential equations with constant parameters, the transient solutions may be derived in closed formulas in the form of infinite series, see, for example, (Waniewski, 2002). However, these formulas are nowadays of limited applicability, because of the frequent slow convergence of the infinite series, and because of that, numerical solutions are often applied even in simple practical problems.

There are, however, some interesting aspects of the time scales characteristics for a transport process. They are related to the theory of random walk and might be reduced in the simplest cases to the investigation of the steady state solutions of the diffusion equation. The mean transit time for the particles crossing the system can be characterized in this manner and estimated by a simpler method of mean residence time during the steady state conditions (Segel, 1980). The theory, typically described for two extreme cases – the purely diffusive or the purely convective transport, can be extended for combined diffusive and convective transport and for systems with distributed source/sink.

The general ideas related to transit time in various types of biological problems are presented in Chapter 6.1, and the definitions of mean transit time and mean residence time are given in Chapter 6.2. The application of these ideas to the convective transport of solutes across the tissue with the solute exchange between blood and tissue is described in Chapter 6.3, whereas the classical theorem of the equality of the mean transit and the mean residence times for diffusive transport is quoted in Chapter 6.4. The general theorem is proved in Chapter 6.5. Some application for the mean transit time for the system with the impulse injection of a solute are reported in Chapter 6.6, whereas the mean residence times for such systems are discussed in Chapter 6.7. The mean characteristic times are defined as the first moment of the respective exit function; the theorem on the relationship between the mean transit and the residence times may be generalized for higher moments as the variation of transit time, see Chapter 6.8. Some examples of closed formulas are shown in Chapter 6.9. The two subsequent chapters deal with the exemplary applications of the here developed theory for peritoneal dialysis, as the solute mean transit time during dialysis (Chapter 6.10), and the solute mean residence time during dialysis (Chapter

6.11). The rate of approach to the steady state of solute transport is considered in Chapter 6.12. A brief summary is given in Chapter 6.13.

6.1 Introduction

We review here a couple of typical systems with transient behaviour that are often analyzed using the characteristic times of passage through the system. For example, transport processes in various structures are investigated by the injection of a bolus amount of a marker at the inlet to the system and the measurement of the fraction of injected marker at the outlet from the system as a function of time. In particular, physiological experiments are carried out for the whole isolated organs, in which the exchange of water and solutes between blood, lymphatics and the tissue involves a complex network of membranes and distributed transport barriers (Bassingthwaighte, Goresky, 1984, Roberts, Rowland, 1986, Swartz et al., 1996, Audi et al., 1998, Beard, Bassingthwaighte, 2000, Weiss et al., 2006).

Mean transit time (MTT) is usually defined for experiments with a momentary input to the system of a known amount of substance, M_0 (often a small amount of a labelled form of the investigated substance), and the recording of its concentration, C, at the outlet from the system as a function of time. MTT may then be calculated as $\int_0^\infty tC(t)dt/\int_0^\infty C(t)dt$ (Bassingthwaighte, Goresky, 1984). The theoretical evaluation of MTT requires having a solution to the model equations for the system, which is generally described by ordinary differential equations (compartment systems) or partial differential equations (distributed systems). The transport may be convective, diffusive or combined. It was shown that for pure diffusive or pure convective transport in some simple transport system this definition of MTT is equivalent to another one that is formulated for the steady state of the system (Meier, Zierler, 1954, Segel, 1980, Hardt, 1981). In this case, for a steady input of the solute, the system reaches after some time a steady state of the concentration distribution and the constant output of the substance. Under these conditions one can calculate the mean residence time, MRT, as MRT $= M_S/J_{Sin}$, where M_S is the amount of the substance in the system and J_{Sin} is the rate of the substance input to the system. For pure convective transport and pure diffusive transport in the system, MRT is equal to MTT calculated for the transient passage of the substance through the system (Meier, Zierler, 1954, Hardt, 1981).

The typical biological applications that involve the estimation of MTT arise in medicine, physiology, cell biology, and pharmacokinetics. The experiments with the in-vivo perfused organs are based on the convective transport of the (labelled) solute to the organ by a bolus infusion to the organ artery and the measurements of the solute concentration in blood leaving the organ via its vein (Bassingthwaighte, Goresky, 1984). The transport of the solute from blood to the tissue and back may be diffusive or combined, diffusive–convective. An example of such investigation may be found in the studies of the transport in the liver

using, among other data, MTT and the variance of the distribution of transit times (Roberts, Rowland, 1986, Mellick et al., 1997, Roberts, Anissimov, 1999). Another problem, diffusion of a substrate from the cell surface to the site inside the cell, where the enzyme that consumes the substrate is located, is a template for the consideration of MTT and MRT for the diffusive transport by Hardt (Hardt, 1981).

The transport system involved in the peritoneal dialysis and the local drug delivery is more complex (Flessner, 2005). It comprises the transport (diffusive or diffusive–convective) through the organ surface and the distributed internal source or sink (depending on the direction of the solute transport, which may be regulated by imposing different boundary conditions) within the tissue. The flow through the surface and the capillary wall is, in general, bi-directional, but one may select some special boundary conditions, which make the transport unidirectional, and in this way simplify the interpretation of the results. Furthermore, the combined diffusive and convective transport is typical for peritoneal dialysis, although, for solutes of low molecular weight, diffusion prevails, and one may approximately neglect the convective transport (Waniewski, 2001). The status of microcirculation may also contribute to the efficiency of the peritoneal therapy (Bassingthwaighte, Goresky, 1984, Waniewski et al., 1999, Waniewski, 2002).

Transit time for infrared photons injected into the tissue, scattered there, and recorded at a different site on the tissue surface are used for obtaining information about the tissue and its microcirculation (Arridge, Schweiger, 1995). In particular, the first moment of the distribution of time of photon flights can be used for the analysis of changes in the absorptive characteristics of the tissue, and the inclusion of the second moment improves the analysis (Liebert et al., 2003).

Our theoretical analyses, Chapters 6.5 – 6.12, are based on the results presented in (Waniewski, 2007, 2008).

6.2 Mean transit and residence times: definitions

Mean transit time, called also mean first passage time, is usually defined for a system that can comprise a solute of some total mass M, which may be a function of time, t, and the solute may flow into the system at the rate F_{in} and flow at the rate F_{out} out of the system, the rates being defined at the inlet to and the outlet from the system, respectively, as functions of time (Hardt, 1981, Bassingthwaighte, Goresky). Under the assumptions that: 1) there is no solute in the system before the experiment (for example, the solute is labelled); 2) the initial bolus load of solute mass M_0 is injected at the inlet to the system; 3) there is no other solute inflow to the system; and 4) there is no back-flow of the solute molecules that leave the system through the inlet, one defines the mean transit time MTT, denoted in the following considerations by τ, as

$$\tau = \int_0^\infty th\,(t)\,dt \tag{6.1}$$

where $h\,(t)$ is the distribution of times for molecules to reach the exit from the system, and is given by the formula

$$h\,(t) = \frac{F_{out}\,(t)}{\int_0^\infty F_{out}\,(t)\,dt}. \tag{6.2}$$

Taking into account the fact that under the stated assumptions we have $F_{out}\,(t) = -dM\,(t)\,/dt$, $M\,(t) \to 0$ for $t \to \infty$, and therefore $\int_0^\infty F_{out}\,(t)\,dt = M_0$, one obtains

$$h\,(t) = -\frac{1}{M_0}\frac{dM}{dt} \tag{6.3}$$

and, using formula (6.1),

$$\tau \ = \frac{1}{M_0}\int_0^\infty M\,(t)\,dt \tag{6.4}$$

where it was assumed that $tM\,(t) \to 0$ if $t \to \infty$.

If the initial load M_0 is spatially distributed, for example – at the inlet to the system or within the sytem, or both, with the concentration $C_0\,(x)$, then one may define the distribution of exit time for the molecules that are at point x at time $t = 0$ to leave the system with the time distribution function $\tilde{h}\,(x,t)$ and the initial bolus mass $M_0 = \int_V C_0\,(x)\,dx$. Then, the overall distribution function may be defined by the summation of these partial functions

$$h\,(t) = \int_V \frac{C_0(x)}{M_0}\tilde{h}\,(x,t)\,dx. \tag{6.5}$$

In the general case one needs also to take into account the source and sink flow densities within the system, $f_{in}\,(x,t)$ and $f_{out}\,(x,t)$, and consider the flows through the boundary and through the system's interior with the total inflow and outflow $F_{in} = F_{bound,in} + F_{tissue,in}$ and $F_{out} = F_{bound,out} + F_{tissue,out}$, respectively, where $F_{bound,in}$ and $F_{bound,out}$ are the total inflow and outflow, respectively, through the boundary, and $F_{tissue,in} = \int_V f_{in}\,(x,t)\,dx$ and $F_{tissue,out} = \int_V f_{out}\,(x,t)\,dx$ are the total inflow and outflow, respectively, within the tissue.

If the system is in the steady state, then the solute concentration within the system, C_S, the solute mass in the system, M_S, and the solute inflow to the system, F_{Sin}, are constant. The mean residence time MRT, denoted in the

following considerations by τ_{res}, is the mean time that the particle, which enters the system, spends in it (Hardt, 1981). It can be calculated as

$$\tau_{res} = \frac{M_S}{F_{Sin}}. \tag{6.6}$$

The equivalence of τ and τ_{res}, $\tau = \tau_{res}$, was initially shown for the convective transport of a flow indicator for measurements of blood flow and volume (Meier, Zierler, 1954). Next, the Hardt theorem was established, stating that for the systems with pure diffusion and the inflow and outflow only through the boundary, $\tau = \tau_{res}$ (Hardt, 1981). It was mentioned by Hardt that this theorem is also valid for the systems with the distributed source/sink of the solute (Hardt, 1981). It can be shown that this result is valid for a general linear diffusion–convection reaction system (described by the elliptic differential operator), and that higher moments of the transit time distribution function may also be calculated using a steady state solution for the system.

6.3 Blood flow, blood volume and transit time

This example consists of the blood vessel network with one inflow and one outflow vessel and a branching tree of vessels from the entrance artery to the capillaries and back to the exit vein. The injection of a solute called "indicator" into the circulation allows for the measurements of blood flow and blood volume and the method is called the indicator dilution method. The experiment may be performed in two ways: 1) bolus injection, and 2) constant injection.

Let F be the solute flow of the indicator, the volumetric flow F_v through the network be constant, and mass M_0 of the indicator be injected at the entrance at time $t = 0$ (bolus injection). One can measure the concentration of the indicator $C(t)$ at the exit for $t \geq 0$. Then, $dM/dt = -F_v C$ and, because $M(0) = 0$,

$$M_0 = F_v \int_0^\infty C(t)\, dt \tag{6.7}$$

and F_v may be estimated as

$$F_v = M_0 / \int_0^\infty C(t)\, dt. \tag{6.8}$$

Furthermore,

$$h(t) = \frac{F_v C(t)}{M_0} \tag{6.9}$$

$$\tau = \frac{F_v}{M_o} \int_0^\infty tC(t)\, dt. \tag{6.10}$$

To calculate the volume of blood in the network, let us assume also that the average velocity of the indicator in the blood vessels is the same as the average velocity of blood. The total blood volume V at each time moment may be

divided into volumes dV^t of blood that will leave the system after time t, and $V = \int_0^\infty dV^t$. In turn, dV^t is composed of pieces $dV^{t,s}$ that entered the system at times s to $s+ds$, $0 \le s \le t$, and will leave at time t to $t+dt$. Each such piece $dV^{t,s}$ is a fraction $h(t)\,dt$of a volume $F_v ds$ that entered during time s to $s+ds$: $dV^{t,s} = h(t)\,dtF_v ds$. Here we use the assumption about equal velocities of blood and the indicator, allowing to estimate the fractions of volume by the respective fractions of the indicator mass. Now, $dV^t = h(t)\,dt \int_0^t F_v ds = F_v t h(t)\,dt$ and

$$V = F_v \int_0^\infty t h(t)\,dt = F_v \tau. \tag{6.11}$$

This rule states that blood volume is equal to blood flow (estimated from (6.8)) multiplied by mean transit time of the indicator (estimated from (6.10)). Thus, both F_v and V can be estimated from the bolus injection experiment with the mean transit time measured for the indicator.

Another approach is based on a continuous infusion of indicator with the constant mass flow rate F to the entrance artery starting with time $t = 0$ and the measurements of indicator concentration $C(t)$ at the exit for $t \ge 0$. We assume that blood flow F_v through the system is also constant. The indicator fills the whole blood volume in the system and finally reaches the maximum value of concentration $C_{\max} = \lim\limits_{t\to\infty} C(t)$. But, by the design of the experiment, $C_{\max} = F/F_v$. Then

$$F_v = \frac{F}{C_{\max}}. \tag{6.12}$$

The concentration may be related to the exit time distribution by comparison of two measured indicator outflows: 1) $F_v C(t)$ at time t, with 2) the outflow, predicted by summing up the fractions of the input indicator flow at time s that leave the system at time t, i.e., after time interval $t-s$, which can be calculated as

$$F \int_0^t h(t-s)ds = F \int_0^t h(s)ds \tag{6.13}$$

(hint: change the integration variable in the left hand integral $t-s \to z$). Therefore,

$$C(t) = \frac{F}{F_v} H(t) = C_{\max} H(t) \tag{6.14}$$

where $H(t) = \int_0^t h(s)ds$. Because $dM/dt = F - F_v C$ (i.e., inflow minus outflow), then

$$\begin{aligned} M(t) = Ft - F_v \int_0^t C(s)\,ds &= F \int_0^t (1 - H(s))\,ds \\ &= \frac{F}{C_{\max}} \int_0^t (C_{\max} - C(s))\,ds. \end{aligned} \tag{6.15}$$

Upon defining $M_\infty = \lim\limits_{t\to\infty} M(t)$,

$$M_\infty = \frac{F}{C_{\max}} \int_0^\infty (C_{\max} - C(s))\, ds = F_v \int_0^\infty (C_{\max} - C(s))\, ds \tag{6.16}$$

and, because $M_\infty = C_{\max} V$,

$$V = \frac{F_v}{C_{\max}} \int_0^\infty (C_{\max} - C(s))\, ds. \tag{6.17}$$

Thus, F_v can be calculated using formula (6.12) and V – using formula (6.17). By definition of the residence time τ_{res}, equation (6.6), $\tau_{res} = \int_0^\infty (1 - H(s))\, ds$. We show now that $\tau_{res} = \tau$. To prove this, we integrate by parts

$$\int_0^t (1 - H(s))\, ds = t(1 - H(t)) + \int_0^t sh(s)\, ds. \tag{6.18}$$

Taking the limit at $t \to \infty$ and noting that, by definition, $H(t) \to 1$ if $t \to \infty$, one gets

$$\tau_{res} = \int_0^\infty (1 - H(s))\, ds = \int_0^\infty sh(s)\, ds = \tau \tag{6.19}$$

if $H(t) \to 1$ faster than t^{-1}, which should be the case if both τ_{res} and τ have finite values.

6.4 Diffusive mean transit time: the Hardt theorem

Linear diffusive transport is related to Brownian motion with its own problem of mean first passage time (Hardt, 1981). Assuming that diffusive particles do not interact, the problem may be reduced to the solution of diffusion equation that is often a simpler task than following the Brownian motion of one particle. Moreover, solutions of the diffusion equation are known for many geometries of the space available for diffusion (Crank, 1975). Hardt analysed the relationships between those two theories, admitting definite assumptions (Hardt, 1981). A known mass M_0 of the solute is placed on a part of the boundary, denoted R_S, and the particles may leave the system across a different part of the boundary, R_T, of a bounded region of volume V. If there is only one particle, then the time the particle spends in the system, having been released from R_S at $t = 0$, until it leaves, without return, through R_T, is called the first passage time. After many such experiments one can find the distribution of first passage times $h(t)$ and the mean first passage time $\tau = \int_0^\infty th(t)dt$, see equation (6.1), which is also called mean transit time. Next, assuming that many particles in our system move independently, one may use an experimental definition of $h(t)$, by defining $F_{out} = -D \int_{R_T} \mathrm{grad} c dR_T$, where D is particle diffusivity parameter, and $M(t) = \int_V c dV$, compare our definitions (6.2) and (6.3), and

$$h(t) = \frac{-D \int_{R_T} \mathrm{grad} c dR_T}{M_0} = \frac{-\frac{d}{dt} \int_V c dV}{M_0} \tag{6.20}$$

where $c(x,t)$ is the solution of the diffusion equation

$$\frac{\partial c}{\partial t} = D\Delta c \tag{6.21}$$

with the initial condition $c(x,0) = 0$ everywhere, except for R_S, where $c(x \in R_S, 0) = M_0/R_S$, and the boundary condition of impermeable (reflecting) boundary with the normal flux equal to zero everywhere, except for R_T, where $c(x \in R_T, t) = 0$ (absorbing boundary, here it is assumed that the particles, which leave the system, do not reenter it).

The definition of the residence time requires the assumption of the steady inflow of particles that in the limit of $t \to \infty$ is balanced by the outflow, $F_{Sin} = F_{out,\infty}$, and a constant amount of particles in the system, M_∞, is attained. For this conditions, the standard definition of the residence time (although this name is not used by Hardt) $\tau_{res} = M_\infty/F_{Sin}$, compare equation (6.6), may be applied. Then it is observed that, in the steady state of the system, the number of particles that leave at t and stay in the system during time shorter than t is $F_{Sin}dt\int_0^t h(t-s)ds = F_{Sin}dt\int_0^t h(s)ds$, compare equation (6.13), and the number of particles that leave at t and stay in the system during time longer than t is $F_{Sin}dt - F_{Sin}dt\int_0^t h(s)ds$. To obtain all particles that were present in the system at $t = 0$, one needs to sum up this number from $t = 0$ to $t = \infty$

$$M_\infty = F_{Sin}\int_0^\infty \left(1 - \int_0^t h(s)\,ds\right)dt \tag{6.22}$$

Integrating by parts, compare equation (6.16), one obtains

$$\tau_{res} = \frac{M_\infty}{F_{Sin}} = \int_0^\infty sh(s)\,ds = \tau \tag{6.23}$$

The convergence of the integrals is guaranteed by the characteristics of the Brownian motion, as noted by Hardt (Hardt, 1981). Thus, the mean first passage time may be assessed by the solution of the steady state solution for diffusion in the system with constant inflow.

6.5 General linear transport model

Basic equation for $C(x,t)$ in a connected bounded region V of n-dimensional Euclidean space R^n, $n \geq 1$, is

$$\frac{\partial C}{\partial t} = LC + S \tag{6.24}$$

where L is a linear operator defined as

$$LC = -\mathrm{div}\mathbf{F} - AC \tag{6.25}$$

and

$$\mathbf{F} = -\mathbf{D}\text{grad}C + \mathbf{J}C \tag{6.26}$$

for $\mathbf{D} = (D_{ij})(x)$, $\mathbf{J} = (J_i)(x)$, $A = A(x) \geq 0$, and $S = S(x) \geq 0$, $i,j = 1,\ldots n$, and symbols in bold describe the $\mathbf{n}$-dimensional vectors or $n \times n$ matrices. Furthermore, it is assumed that the diffusivity matrix is symmetric, $D_{ij} = D_{ji}$, and that $\xi \cdot \mathbf{D}(x)\xi \geq \theta\xi \cdot \xi$ for some $\theta > 0$, almost all $x \in V$, and all $\xi \in \mathrm{R}^n$, where R^n is the n-dimensional Euclidean space, and $\mathrm{R} = \mathrm{R}^1$ is the set of real numbers. The last condition states that L is an elliptic operator, and guarantees that diffusion goes along the concentration gradient (Evans, 1998).

Boundary conditions. The boundary ∂V of the region V can be split into three parts, $\partial V = \partial V_W \cup \partial V_D \cup \partial V_N$, with the following characteristics:

1. "no-flux" Robin boundary condition (impermeable wall) on ∂V_W: $F_n(x,t) = 0$ for $x \in \partial V_W$, $t > 0$,
2. Dirichlet boundary condition for ∂V_D: $C(x,t) = \varphi(x)$ for $x \in \partial V_D$, $t > 0$,
3. Robin boundary condition for ∂V_N: $F_n(x,t) = -\psi(x)$ for $x \in \partial V_N$, $t > 0$,

where subscript n denotes the component normal to the boundary in the direction outward from V, and ψ is the normal component of inflow.

The third boundary condition, known also as the Danckwerts condition (Danckwerts, 1953, Roberts, Rowland, 1986, Mellick et al., 1997, Roberts, Anissimov, 1999), includes an important case, in practical terms, of purely convective flow at the boundary: $\frac{\partial C}{\partial n}(x,t) = 0$ and $C(x,t) = \phi(x)$ for $x \in \partial V_N$, $t > 0$.

The typical initial condition is $C(x,0) = C_0(x)$ for $x \in V \backslash \partial V$.

All functions of x and t that appear in our considerations need to be sufficiently smooth for the correctness of the mathematical formulas and proofs, but these conditions are not described here for the sake of simplicity and focus on the physical interpretation.

The Green function $G(x,y,t)$ for equation (6.24) is defined, assuming x as a parameter and y and t as variables, as the solution of the following equation for any $x \in V$

$$\frac{\partial G}{\partial t} = L_y^* G \tag{6.27}$$

where the linear operator L_y^* is defined as

$$L_y^* G = -\text{div}(\mathbf{F}^*) - (\text{div}\mathbf{J} + A)G \tag{6.28}$$

and

$$\mathbf{F}^* = -\mathbf{D}\text{grad}G - \mathbf{J}G \tag{6.29}$$

for the same parameters that appear in equation (6.24), and all spatial derivatives taken in variable y.

Boundary conditions for G in variable y for any $x \in V \backslash \partial V$ are

1. "no diffusive flux" Neumann boundary condition on $\partial V_W \cup \partial V_N$: $(\mathbf{D}\text{grad}G)_n(x,y,t) = 0$ for $y \in \partial V_W \cup \partial V_N$, $t > 0$,

2. Dirichlet boundary condition for ∂V_D: $G(x,y,t)=0$ for $y\in\partial V_D,\ t>0$,

Initial condition for G: $G(x,y,0)=\delta(x-y)$ for x and y in $V\backslash\partial V$.

One can show that $C(x,t)$ can be expressed by G, S, φ, ψ, and $C(x,s)$, $s<t$, as follows

$$C(x,t)=\int_V G(x,y,t-s)\,C(y,s)\,dy+\int_s^t\int_V G(x,y,t-u)\,S(y)\,dydu$$
$$-\int_s^t\int_{\partial V_D}(\mathbf{D}(y)\,\mathrm{grad}G(x,y,t-u))_n\,\varphi(y)\,dydu-\int_s^t\int_{\partial V_N}G(x,y,t-u)\,\psi(y)\,dydu \tag{6.30}$$

where $s\in[0,t]$.

In order to prove formula (6.30) let us define

$$A(x,t)=\int_s^t\int_V G(x,y,t-u)\left(\frac{\partial C}{\partial u}-L_yC\right)(y,u)$$
$$+\left(\frac{\partial G}{\partial u}+L_y^*G\right)(x,y,t-u)\,C(y,u)\,dydu. \tag{6.31}$$

Because $\frac{\partial G}{\partial u}(x,y,t-u)=-\frac{\partial G}{\partial t}(x,y,t-u)=-L_y^*G(x,y,t-u)$, then, using equation (6.24),

$$A(x,t)=\int_s^t\int_V G(x,y,t-u)\,S(y)dydu. \tag{6.32}$$

On the other hand, equation (6.30) may be rearranged as follows

$$\begin{aligned}A(x,t)\ &=C(x,t)-\int_V G(x,y,t-s)\,C(y,s)dy\\&+\int_s^t\int_{\partial V}G(x,y,t-u)\,\mathbf{F}_n(y,u)dydu\\&+\int_s^t\int_{\partial V}(\mathbf{D}(y)\,\mathrm{grad}G(x,y,t-u))_nC(y,u)\,dydu\end{aligned} \tag{6.33}$$

using the Gauss–Ostrogradski theorem, $\int_V \mathrm{div}\mathbf{B}dy=\int_{\partial V}\mathbf{B}_n dy$, and the identity $\mathrm{div}(A\mathbf{B})=A\mathrm{div}\mathbf{B}+\mathbf{B}\cdot\mathrm{grad}A$ for the scalar function $A(y)$ and the vector function $\mathbf{B}(y)$. The application of the boundary conditions for C to the integrals over ∂V in equation (6.33) and the comparison of equations (6.32) and (6.33) yield formula (6.30).

6.6 Mean transit time for impulse input

We assume that the system has a (stable) steady state $C_\infty(x)$ with total mass $M_\infty=\int_V C_\infty(x)\,dx$, and this state is disturbed at $t=0$ by a pulse function,

concentrated at $x = z$: $M_0\delta(x-z)\,\delta(t)$. Let $C(x,t;z)$ be the solution of equation (6.24) with the initial condition $C_0(x;z) = C_\infty(x) + M_0\delta(x-z)$, and denote $M(z,t) = \int\limits_V C(x,t;z)\,dx$ and $m(z,t) = M(z,t) - M_\infty$. The solution $C(x,t;z)$ may be found using formula (6.30) for the initial state $C_0(x;z)$

$$\begin{aligned} C(x,t;z) = {} & M_0 G(x,z,t) + \int\limits_V G(x,y,t-s)\,C_\infty(y)\,dy \\ & + \int\limits_s^t \int\limits_V G(x,y,t-u)\,S(y)\,dydu \\ & - \int\limits_s^t \int\limits_{\partial V_D} \left(\mathbf{D}(y)\,\mathrm{grad}G(x,y,t-u)\right)_n \varphi(y)\,dydu \\ & - \int\limits_s^t \int\limits_{\partial V_N} G(x,y,t-u)\,\psi(y)\,dydu \end{aligned} \tag{6.34}$$

for any $s \in [0,t]$. Formula (6.30), applied for the steady state $C_\infty(x)$, implies

$$\begin{aligned} C_\infty(x) = {} & \int\limits_V G(x,y,t-s)\,C_\infty(y)\,dy + \int\limits_s^t \int\limits_V G(x,y,t-u)\,S(y)\,dydu \\ & - \int\limits_s^t \int\limits_{\partial V_D} \left(\mathbf{D}(y)\,\mathrm{grad}G(x,y,t-u)\right)_n \varphi(y)\,dydu - \int\limits_s^t \int\limits_{\partial V_N} G(x,y,t-u)\,\psi(y)\,dydu \end{aligned} \tag{6.35}$$

and, by comparing equations (6.34) and (6.35), we get

$$C(x,t;z) = M_0 G(x,z,t) + C_\infty(x) \tag{6.36}$$

and

$$m(z,t) = M_0 \int\limits_V G(x,z,t)\,dx. \tag{6.37}$$

Therefore, using equation (6.27),

$$\frac{\partial m}{\partial t}(z,t) = \left(L_z^* m\right)(z,t) \tag{6.38}$$

with

1. "no diffusive flux" Neumann boundary condition on $\partial V_W \cup \partial V_N$: $\left(\mathbf{D}\mathrm{grad}m\right)_n(z,t) = 0$ for $z \in \partial V_W \cup \partial V_N,\ t > 0$,
2. Dirichlet boundary condition for ∂V_D: $m(z,t) = 0$ for $z \in \partial V_D,\ t > 0$,
3. Initial condition for m: $m(z,0) = M_0$ for z in $V \backslash \partial V$.

The mean transit time in this case is defined as (see equation (6.4)):

$$\tau(z) = \frac{1}{M_0} \int\limits_0^\infty m(z,t)\,dt. \tag{6.39}$$

We now show that $\tau(z)$ is the solution of equation

$$\left(L_z^*\tau\right)(z) + 1 = 0 \tag{6.40}$$

with the boundary conditions of the same type as for $G(x,z,t)$

1. $\frac{\partial\tau}{\partial n}(z) = 0$ for $z \in \partial V_W \cup \partial V_N$,
2. $\tau(z) = 0$ for $z \in \partial V_D$.

To prove this conjecture, one may calculate

$$\begin{aligned} L_z^*\tau(z) &= \tfrac{1}{M_0}\int_0^\infty L_z^* m(z,t)\,dt = \tfrac{1}{M_0}\int_0^\infty \tfrac{\partial}{\partial t} m(z,t)\,dt \\ &= \tfrac{1}{M_0}\left(m(z,\infty) - m(z,0)\right) = -1 \end{aligned} \tag{6.41}$$

Because, due to our assumptions, $m(z,\infty) - m(z,0) = M_0$.

6.7 Mean residence time

Let $\bar{C}(x)$ be a steady state solution for equation (6.24) for the boundary conditions, c.f. (Hardt, 1981),

1. $\bar{F}_n(z) = 0$ for $z \in \partial V_W$,
2. $\bar{F}_n(z) = -\bar{\psi}(z)$, $\bar{\psi}(z) \geq 0$ for $z \in \partial V_N$, with ∂V_N considered as the inlet to the system,
3. $\bar{C}(z) = \bar{\varphi}(z)$, $\bar{\varphi}(z) \geq 0$ for $z \in \partial V_D$, with ∂V_D considered as the outlet from the system.

Then, the total inflow through the boundary, $\bar{F}_{inlet}$, is

$$\bar{F}_{inlet} = \int_{\partial V_N} \bar{\psi}(z)\,dz \tag{6.42}$$

and the inflow-averaged mean time τ_{inlet} for the solute entering the system through ∂V_N is defined as

$$\tau_{inlet} = \frac{1}{\bar{F}_{inlet}} \int_{\partial V_N} \left(\tau\bar{\psi}\right)(z)\,dz. \tag{6.43}$$

The total inflow from the source is $F_{source} = \int_V S(z)\,dz$, and the inflow-averaged mean time τ_{source} for the solute entering the system from the source is defined as

$$\tau_{source} = \frac{1}{F_{source}} \int_V (\tau S)(z)\,dz. \tag{6.44}$$

Let us define the overall mean transit time, τ_{tot}, for both inflow pathways

$$\tau_{tot} = \frac{\bar{F}_{inlet}}{\bar{F}_{inlet} + F_{source}}\tau_{inlet} + \frac{F_{source}}{\bar{F}_{inlet} + F_{source}}\tau_{source}. \tag{6.45}$$

To derive a formula for τ_{tot} let us note that using equation (6.40), one obtains

$$\int_V \bar{C}(z)\left(L_z^*\tau\right)(z)\,dz = -\bar{M} \tag{6.46}$$

where

$$\bar{M} = \int_V \bar{C}(z)\,dz. \tag{6.47}$$

On the other hand

$$\int_V \bar{C}(z)\left(L_z^*\tau\right)(z)\,dz = \int_V \left(L_z\bar{C}\right)(z)\,\tau(z)\,dz + \int_{\partial V} \left(\bar{C}\left(\mathbf{D}\mathrm{grad}\tau\right)_n + \tau\bar{F}_n\right)(z)\,dz. \tag{6.48}$$

Because $\left(L_z\bar{C}\right)(z) = -S(z)$ by the definition of the stationary state, one gets, upon comparing equations (6.46) and (6.48), and using the boundary conditions for τ,

$$\bar{M} = -\int_{\partial V_D} \left(\bar{C}\left(\mathbf{D}\mathrm{grad}\tau\right)_n\right)(z)\,dz - \int_{\partial V_N} \left(\tau\bar{\mathbf{F}}_n\right)(z)\,dz + \int_V S(z)\,\tau(z)\,dz. \tag{6.49}$$

Equations (6.45) - (6.49), together with the boundary conditions for $\bar{C}$, yield the formula

$$\tau_{tot} - \int_{\partial V_D} \left(\bar{\varphi}\left(\mathbf{D}\mathrm{grad}\tau\right)_n\right)(z)\,dz = \frac{\bar{M}}{\bar{F}_{inlet} + F_{source}} \tag{6.50}$$

where $\bar{M}$ and $\bar{F}_{inlet}$ are calculated for the steady state $\bar{C}$.

The residence time, τ_{res}, for this system is defined as

$$\tau_{res} = \frac{\bar{M}}{\bar{F}_{inlet} + F_{source}} \tag{6.51}$$

see equation (6.6), and therefore

$$\tau_{tot} - \int_{\partial V_D} \left(\bar{\varphi}\left(\mathbf{D}\mathrm{grad}\tau\right)_n\right)(z)\,dz = \tau_{res}. \tag{6.52}$$

Thus, for $\bar{\varphi} \equiv 0$ one obtains from equation (6.52) that

$$\tau_{tot} = \tau_{res} \tag{6.53}$$

i.e. the Hardt theorem (Hardt, 1981). Formula (6.50) may be therefore considered as a generalization of the Hardt theorem for arbitrary Dirichlet boundary conditions at the outlet from the system.

The inflow-averaged mean time τ_{inlet} for the solute entering the system through ∂V_N depends on the boundary condition $\bar{\psi}(z)$ at the inlet. However, if $\bar{\psi}(z)$ does not depend on $z \in \partial V_N$, then

$$\tau_{inlet} = \frac{1}{|\partial V_N|} \int\limits_{\partial V_N} \tau(z)\, dz \tag{6.54}$$

may be calculated directly, if equation (6.40) is solved.

6.8 Higher moments of the exit function

By using similar methods we can derive recursive equations and formulas for higher moments of the exit time distribution function, defined as

$$\tau_k(z) = -\frac{1}{M_0} \int\limits_0^\infty t^k dm(t;z) \tag{6.55}$$

for integers $k \geq 0$. Note that $\tau_0(z) = 1$. In the following, we assume that $t^k m(t;z) \to 0$ and $t^{k-1} G(x,z,t) \to 0$ for $t \to \infty$, $z \in V \setminus \{\partial V_W \cap \partial V_D\}$, and all integers are higher than 1, $k \geq 1$. Then, for $k \geq 1$,

$$\tau_k(z) = \frac{k}{M_0} \int\limits_0^\infty t^{k-1} m(t;z)\, dt = k \int\limits_0^\infty \int\limits_V t^{k-1} G(x,z,t)\, dtdx \tag{6.56}$$

see equations (6.4), (6.39) and (6.37) and their derivations. The partial differential equation for $\tau_k(z)$ is obtained in the same way as equation (6.40),

$$\left(L_z^* \tau_k\right)(z) = -k\tau_{k-1}(z) \tag{6.57}$$

and the boundary conditions are the same as those for equation (6.40).

The Hardt theorem about the description of mean transit time by mean residence time (Hardt, 1981), described in Chapter 6.4, may be generalized for higher moments of exit functions. Let us define the following parameters

$$\tau_{k,source} = \frac{1}{F_{source}} \int\limits_V (\tau_k S)(z)\, dz \tag{6.58}$$

$$\tau_{k,inlet} = \frac{1}{\bar{F}_{inlet}} \int\limits_{\partial V_N} \left(\tau_k \bar{\psi}\right)(z)\, dz \tag{6.59}$$

$$\bar{\tau}_k = \frac{1}{\bar{M}} \int\limits_V \left(\bar{C}\tau_k\right)(z)\, dz \tag{6.60}$$

for the steady state $\bar{C}$. Then

$$\tau_{k,tot} - \int\limits_{\partial V_D} \left(\bar{\varphi}\left(\mathbf{D}\mathrm{grad}\tau_k\right)_n\right)(z) = \frac{k\bar{M}\bar{\tau}_{k-1}}{\bar{F}_{inlet} + F_{source}} \tag{6.61}$$

where $\bar{M}$ and $\bar{F}_{inlet}$ are calculated for the steady state $\bar{C}$, and $\tau_{k,tot}$ is defined as

$$\tau_{k,tot} = \frac{\bar{F}_{inlet}}{\bar{F}_{inlet} + F_{source}} \tau_{k,inlet} + \frac{F_{source}}{\bar{F}_{inlet} + F_{source}} \tau_{k,source}. \tag{6.62}$$

For $k = 1$, formulae (6.58) - (6.62) reduce to the relation, described by equation (6.45).

6.9 Examples

Let us consider transport equation with constant coefficients on interval $[0, L]$

$$\frac{\partial C}{\partial T} = D\frac{\partial^2 C}{\partial X^2} - J\frac{\partial C}{\partial X} - AC + S. \tag{6.63}$$

After rescaling to $x = X/L$ and $t = DT/L^2$, we get

$$\frac{\partial C}{\partial t} = \frac{\partial^2 C}{\partial x^2} - j\frac{\partial C}{\partial x} - aC + s \tag{6.64}$$

with the coefficients $j = JL/D$, $a = AL^2/D$, $s = SL^2/D$. Equation (6.40) is now

$$\frac{\partial^2 \tau}{\partial z^2} + j\frac{\partial \tau}{\partial z} - a\tau = -1 \tag{6.65}$$

with $\frac{\partial \tau}{\partial z}(0) = 0$ and $\tau(1) = 0$. The solution of equation (6.65) for $j, a \neq 0$ is

$$\tau(z) = \frac{1}{a}\left(1 - \exp(j(1-z)/2)\frac{u\cosh(uz/2) + j\sinh(uz/2)}{u\cosh(u/2) + j\sinh(u/2)}\right) \tag{6.66}$$

for $u = \sqrt{j^2 + 4a} \neq 0$.

Important special cases of solution (6.66) are

1. for $j \neq 0$, $a = 0$:

$$\tau(z) = \frac{1}{j}\left(1 - z - \frac{\exp(-j)}{j}(\exp(j(1-z)) - 1)\right) \tag{6.67}$$

2. for $j = 0$, $a > 0$:

$$\tau(z) = \frac{1}{a}\left(1 - \frac{\cosh(\sqrt{a}z)}{\cosh(\sqrt{a})}\right) \tag{6.68}$$

3. for $j = 0$, $a = 0$:

$$\tau(z) = \frac{1}{2}\left(1 - z^2\right) \tag{6.69}$$

$$\tau_2(z) = \frac{1}{2}\left(\frac{5}{6} - z^2\left(1 - \frac{z^2}{6}\right)\right) \tag{6.70}$$

and, for $var(z) = -\frac{1}{M_0}\int_0^\infty (t-\tau)^2\, dm(t;z) = \tau_2 - \tau^2$,

$$var(z) = \frac{1}{6}\left(1 - z^4\right). \tag{6.71}$$

For the Dirichlet boundary conditions at both boundaries regarding the main equation (6.65) one has the boundary conditions on τ: $\tau(0) = 0$ and $\tau(1) = 0$. Then, the solution of equation (6.65) for $j, a \neq 0$ is

$$\tau(z) = \frac{1}{a}\left(1 - e^{(u-j)z/2} + \left(e^{u/2} - e^{j/2}\right) e^{-jz/2}\frac{\sinh(uz/2)}{\sinh(u/2)}\right) \tag{6.72}$$

where $u = \sqrt{j^2 + 4a}$.

Some special cases of the solution (6.72) are

1. for $j \neq 0$, $a = 0$:
$$\tau(z) = \frac{1}{j}\left(\frac{1 - \exp(-jz)}{1 - \exp(-j)} - z\right) \tag{6.73}$$
2. for $j = 0$, $a > 0$:
$$\tau(z) = \frac{1}{a}\left(1 - \exp\left(\sqrt{a}z\right) + \left(\exp\left(\sqrt{a}\right) - 1\right)\frac{\sinh\left(\sqrt{a}z\right)}{\sinh\left(\sqrt{a}\right)}\right) \tag{6.74}$$
3. for $j = 0$, $a = 0$:
$$\tau(z) = \frac{1}{2}z(1 - z). \tag{6.75}$$

For the Neumann boundary conditions at both boundaries of the main system with equation (6.65) one has the boundary conditions on τ: $\frac{d\tau}{dz}(0) = 0$ and $\frac{d\tau}{dz}(1) = 0$. Then, the solution of equation (6.65) for $a \neq 0$ is

$$\tau(z) = \frac{1}{a}. \tag{6.76}$$

However, there is no solution if $a = 0$.

6.10 Mean transit time in peritoneal dialysis

Let us consider the solute transport model for the peritoneal dialysis, equations (4.2), (4.3) and (4.4), for the tissue of width L and the area A of the surface of contact with the dialysis fluid. The integration of these equations over the whole tissue layer yields the global mass balance

$$\frac{dM}{dt} = J_0 - J_L + \frac{k_{BT}}{\theta}M_B - \frac{k_{TBL}}{\theta}M \tag{6.77}$$

where $M(t) = A\int_0^L \theta C(x,t)\,dx$ is the solute mass in the tissue, $M_B = AL\theta C_B$ is the solute mass in the tissue if the solute in the tissue is in the equilibrium with the solute in blood, J_0 is the solute inflow through the tissue surface at $x = 0$, J_L is the solute outflow through the tissue surface at $x = L$. Equation (6.77) may be also written in another form:

$$\frac{dM}{dt} = J_{in} - J_{out} + F_{Tin} - F_{Tout} \tag{6.78}$$

where $J_{in}$is the solute inflow through tissue surface, $J_{out}$is the solute outflow through tissue surface, $F_{Tin} = \frac{k_{BT}}{\theta} M_B$ is the inflow of the solute from blood to the tissue, and $F_{Tout} = \frac{k_{TBL}}{\theta} M$ is the outflow of the solute from the tissue to blood and lymph. Note that $J_{in} - J_{out} = J_0 - J_L$.

In accordance with the general definition of MTT, we assume that there is no solute inflow to the system: $J_{in} = 0$, $F_{Tin} = 0$, i.e. $C_B = 0$, $C_D = 0$, but the solute outflow is possible through the surface, $J_{out} \geq 0$, and from the tissue to blood and lymph, and that the initial load of mass in the tissue is M_0. By integrating equation (6.78) from 0 to infinity, one obtains

$$-M_0 = -\int_0^\infty J_{out}(t)\,dt - \frac{k_{TBL}}{\theta}\int_0^\infty M(t)\,dt \tag{6.79}$$

because $M(t) \to 0$ if $t \to \infty$. In another form

$$\int_0^\infty M(t)\,dt = \frac{\theta}{k_{TBL}}\left(M_0 - \int_0^\infty J_{out}(t)\,dt\right). \tag{6.80}$$

From the equation (6.4) for mean transit time τ and equation (6.80) one obtains

$$\tau = \frac{\theta}{k_{TBL}}\left(1 - \frac{\int_0^\infty J_{out}(t)\,dt}{M_0}\right). \tag{6.81}$$

Let us consider two important, special cases of the general formula (6.81):

Case A.

The transport through the peritoneal surface is not possible, e.g. there is no fluid in the peritoneal cavity. Thus, $J_{out} = 0$, and, from equation (6.81), MTT for the solute uptake from the tissue by blood and lymph (as in the wash-out experiments) is

$$\tau^{TBL} = \frac{\theta}{k_{TBL}}. \tag{6.82}$$

Case B.

The transport through the peritoneal surface is possible, e.g. dialysis fluid is present in the peritoneal cavity (however, the build-up of solute concentration in dialysis fluid is negligible). Thus $J_{out} > 0$, and, after the loading of the solute mass M_0 into the tissue, MTT for the solute transport from the tissue to blood, lymph and dialysis fluid is:

$$\tau^{TBLD} = \tau^{TBL} \left(1 - \frac{\int_0^\infty J_{out}(t)\, dt}{M_0} \right). \tag{6.83}$$

Therefore, $\tau^{TBLD} < \tau^{TBL}$, as expected.

6.11 Mean residence time in tissue during peritoneal dialysis

Using the definition of MRT, given by equation (6.6), and the general mass balance, equation (6.78), applied for the steady state of transport, $\frac{dM}{dt} = 0$, $M = M_S$, $J_{in} = J_{Sin}$, $\quad J_{out} = J_{Sout}$, one obtains

$$M_S = \frac{\theta}{k_{TBL}} \left(\frac{k_{BT}}{\theta} M_B + J_{Sin} - J_{Sout} \right). \tag{6.84}$$

The total solute inflow in the steady state, F_{Sin}, is defined as

$$F_{Sin} = J_{Sin} + \frac{k_{BT}}{\theta} M_B. \tag{6.85}$$

Finally, from equation (6.6),

$$\tau_{res} = \frac{\theta}{k_{TBL}} \left(1 - \frac{J_{Sout}}{\frac{k_{BT}}{\theta} M_B + J_{Sin}} \right). \tag{6.86}$$

Note that for wide tissue layers, i.e. for high values of L, $\tau \to \theta / k_{TBL}$, because $M_B \to \infty$ if $L \to \infty$. Two special cases of the net solute flow between blood and dialysis fluid need to be discussed separately:

Case A.

If $C_D > 0$, $C_B = 0$, then $J_{Sout} = 0$, and MRT for the unidirectional transport from dialysis fluid to blood and lymph is

$$\tau_{res}^{DBL} = \frac{\theta}{k_{TBL}}. \tag{6.87}$$

Thus, $\tau^{TBL} = \tau_{res}^{DBL}$. This equality is predicted by the Hardt theorem for purely diffusive transport, but our derivation shows that it holds also for the combined diffusive and convective transport.

Case B.

If $C_D = 0,\ C_B > 0$, then $J_{Sin} = 0$, and MRT for the unidirectional transport from blood to dialysis fluid and lymph is

$$\tau_{res}^{BDL} = \tau_{res}^{DBL}\left(1 - \frac{J_{Sout}}{\frac{k_{BT}}{\theta}M_B}\right). \tag{6.88}$$

Thus, $\tau_{res}^{BDL} < \tau_{res}^{DBL}$ if J_{Sout}. τ^{BDL} may be explicitly calculated for two special cases with the known solution of the transport equation (4.8).

Example 1.

Let us assume pure diffusive transport of a solute through the tissue in the steady state, i.e. the solute flux of the form $j_S = -D_T\frac{dC_S}{dX}$, and the boundary conditions: $C_S(0) = C_D$ and $j_S(L) = 0$. Then

$$C_S(X) = \kappa C_B + (C_D - \kappa C_B)\frac{\cosh\left(\Phi\left(1 - \frac{X}{L}\right)\right)}{\cosh(\Phi)} \tag{6.89}$$

where $\kappa = \frac{k_{BT}}{k_{TBL}},\ \Phi = \frac{L}{\Lambda},\ \Lambda = \sqrt{\frac{D_T}{k_{TBL}}}$, compare equation (4.32). Using formula (6.88) one obtains the following expression for MRT:

$$\tau_{res}^{BDL} = \left(1 - \frac{\kappa C_B \Phi^{-1}\tanh(\Phi)}{\kappa C_B + C_D\Phi^{-1}\tanh(\Phi)}\right)\frac{\theta}{k_{TBL}}. \tag{6.90}$$

In particular, for $C_D = 0$:

$$\tau_{res}^{BDL} = \left(1 - \Phi^{-1}\tanh(\Phi)\right)\tau_{res}^{DBL} \tag{6.91}$$

where $\tau_{res}^{DBL} = \theta/k_{TBL}$, see equation (6.87). If the tissue width, L, increases, and therefore the number Φ increases, then $\tau_{res}^{BDL} \to \tau_{res}^{DBL}$, because $\Phi^{-1}\tanh(\Phi) \to 0$.

Example 2.

For combined diffusive and convective solute transport through the tissue in the steady state, the solute flux is $j_S = -D_T\frac{dC_S}{dX} + S_T j_V C_S$, and the boundary conditions are $C_S(0) = C_D$, $C_S(L) = C_L$ (such boundary conditions may be of interest for the gut wall). Assuming constant volumetric flux, j_V, through the tissue, one gets the solute concentration profile

$$C_S(X) = \kappa C_B + (C_D - \kappa C_B)\frac{\sinh\left(\Psi\left(1 - \frac{X}{L}\right)\right)}{\sinh(\Psi)}\exp\left(\frac{Pe_T\frac{X}{L}}{2}\right) + (C_L - \kappa C_B)\frac{\sinh\left(\Psi\frac{X}{L}\right)}{\sinh(\Psi)} \tag{6.92}$$

where $\kappa = \frac{k_{BT}}{k_{TBL}}$, $\Psi = \sqrt{Pe_T^2 + \Phi^2}$, $Pe_T = \frac{S_T|j_V|}{D_T/L}$, $\Phi = \frac{L}{\Lambda}$, $\Lambda = \sqrt{\frac{D_T}{k_{TBL}}}$, compare equation (4.11). Then

$$\tau_{res}^{BDL} = \left(1 - \frac{2\Psi \frac{\cosh(\Psi)-1}{\sinh(\Psi)} \kappa C_B + Pe_T C_L}{\Phi^2 \kappa C_B + \Psi \frac{\cosh(\Psi)-1}{\sinh(\Psi)} (C_D + C_L) + Pe_T C_D}\right) \frac{\theta}{k_{TBL}}. \tag{6.93}$$

In particular, if $C_D = 0$, $C_L = 0$:

$$\tau_{res}^{BDL} = \left(1 - \frac{\Psi^2}{\Phi^2} \frac{\tanh(\Psi/2)}{\Psi/2}\right) \tau_{res}^{DBL}. \tag{6.94}$$

Numerical examples of peritoneal dialysis transit times for different solutes may be found in (Waniewski, 2008).

6.12 Rate of approach to steady state during peritoneal dialysis

Let us assume that before dialysis the solute in the tissue is in equilibrium ($\mathrm{d}M/\mathrm{d}t = 0$), and there is no transport through the tissue surface ($J_0 = J_L = 0$). Then, from equation (6.77),

$$M_{eq} = \frac{k_{BT}}{k_{TBL}} M_B \tag{6.95}$$

where M_{eq} denotes the solute mass in the tissue in the equilibrium. After the initiation of dialysis, the system tends to a *new steady state* with $J_0 \neq 0$, and the steady state solute flow, J_S, is

$$J_S = k_{TBL} M_S - k_{TB} M_B = \frac{k_{TBL}}{\theta} (M_S - M_{eq}). \tag{6.96}$$

The rate of approach to this new steady state may be evaluated using the equation for the change of the total solute mass in the tissue,

$$\frac{dM}{dt} = J - \frac{k_{TBL}}{\theta} (M - M_{eq}) \tag{6.97}$$

where J is the transient component of solute flow through the tissue surface. The solution of equation (6.97) is

$$M(t) = M_{eq} + e^{-\frac{k_{TBL}}{\theta} t} \int_0^t J(u)\, e^{\frac{k_{TBL}}{\theta} u} du. \tag{6.98}$$

Two special cases are of particular interest.

Case A.

If $J(t) > J_S > 0$ for all $t > 0$ (i.e. the solute is being absorbed to the tissue from dialysis fluid), then

$$M_S - M(t) < \frac{\theta J_S}{k_{TBL}} e^{-\frac{k_{TBL}}{\theta}t} = (M_S - M_{eq})\, e^{-\frac{k_{TBL}}{\theta}t}. \tag{6.99}$$

Case B.

If $J(t) < J_S < 0$ (i.e. the solute is being removed from the tissue to dialysis fluid) for all $t > 0$, then

$$M(t) - M_S < \frac{\theta\,|J_S|}{k_{TBL}} e^{-\frac{k_{TBL}}{\theta}t} = (M_{eq} - M_S)\, e^{-\frac{k_{TBL}}{\theta}t}. \tag{6.100}$$

In both cases, the relative change of the solute mass is

$$\frac{M(t) - M_S}{M_{eq} - M_S} < e^{-\frac{k_{TBL}}{\theta}t} = e^{-t/\tau^{DBL}} \tag{6.101}$$

Transient solutions for diffusion in peritoneal dialysis. The solution of the transport equation (4.2) for diffusive solute transport in the tissue may be obtained using the Laplace transformation or the Fourier series methods (Crank, 1975, Press et al., 2007). For the Dirichlet boundary conditions at $x = 0$ and Neumann boundary condition at $x = L$ for each t, see Chapter 4 or Example 1 in Chapter 6.11, and the initial condition $C_T(x, 0) = \kappa C_B$, i.e. the equilibrium between blood and tissue, the solution may be presented as

$$\Gamma(x,t) = \Gamma_\infty(x) - 2\sum_{k=0}^{\infty} \frac{a_k}{\Phi^2 + a_k} \cos(a_k(1-x))\, e^{-\left(1/\tau^{TBL} + a_k^2/\tau_T\right)t} \tag{6.102}$$

where $x = X/L$, $\Gamma(x,t) = (C_T(x,t) - \kappa C_B)/(C_D - \kappa C_B)$ is the time dependent normalized concentration gradient, $\Gamma_\infty(x)$ is the steady state normalized concentration gradient, i.e. the limit of $\Gamma(x,\mathrm{t})$ for $\mathrm{t} \to \infty$ (see equation (4.32)), $a_k = (2k+1)\,\pi/2$, $k = 0,\ 1,\ 2,\ 3,\ \ldots$, $\tau_T = \theta L^2/D_T$ is the characteristic time for diffusion across the tissue of width L, $\tau^{TBL} = \theta/k_{TBL}$, $\Phi = L\sqrt{k_{TBL}/D_T}$. Note that $\tau^{TBL} = \tau^{DBL}_{res} = \tau^{DBL}$. Thus, the slowest approach to the steady state is for the component with time constant $\left(1/\tau^{TBL} + \pi^2/(4\tau_T)\right)^{-1}$.

6.13 Summary

1. Molecules injected into an open spatially distributed system may take different routes to the exit from the system, and therefore they appear at the exit at different times. The distribution of the exit times depends on the structure and transport characteristics of the system.

2. The moments of the exit time distribution are applied in the investigations of biological transport systems, especially the first moment, called the transit time. For example, in the flow systems (like organs, perfused by blood), the transit time of a marker is related to the volume of the system that typically cannot be directly measured.
3. The mean residence time is the time the molecules spent in the open system in its steady transport state. It can be estimated from the rate of inflow of molecules and the total mass of the solute in the system.
4. The equality of the mean residence and mean transit times was shown initially for the flow system, for the systems with diffusive transport, and later on for the general linear systems with diffusive–convective transport and the inlet and exit at the boundary and/or within the system. General relationships exist also for higher moments of the exit time distributions and steady state data.
5. The mean transit time can be found by solving the steady state (conjugated) transport equation for the mean transit time with appropriate boundary conditions.
6. The mean transit time can be easily estimated for simple system with diffusive–convective transport by reducing the problem to the solution of the steady state transport equation.
7. For peritoneal dialysis, the mean residence time for the transit from blood to dialysis fluid is different from the mean residence time for the transit from dialysis fluid to blood.

7

Transport in dialyzers and filters

Another interesting example of application of the membrane transport theory is the case of a membrane with the solutions flowing along its surfaces. In general, such theory, besides the description of the transport processes inside the membrane, requires also the theory of the flow distribution and transport processes in the flow channels/chambers on both sides of the membrane. This problem may demand an application of the Navier–Stokes equations, together with the spatially distributed diffusion-convection equation in the flow channels (Sigdell, 1974). However, in some specific cases the description of fluid and solute transport in the channels can be simplified, like, for example, for the typical flows and transport of solutes in the dialyzers and filters, applied for the purification of blood during hemodialysis, or related blood purification procedures, such as hemodiafiltration, hemofiltration, plasma separation and fractionation (Werynski, Waniewski, 1995). The modern dialyzers and filters are built from the capillary membranes. In these devices, blood flows typically within the capillary (blood channel), and dialysis fluid (or filtrate) flows along the outer surface of the capillary. The flows run in the opposite directions (counter-currently). For the typical size of the capillary and the flow rates, some important theoretical simplifications can be assumed that yield the one dimensional theory of hemodialyzer.

After a short introduction in Chapter 7.1, the one-dimensional theory of hemodialyzer is presented in Chapter 7.2 for the counter-current flow system together with the discussion of its theoretical analysis, whereas Chapter 7.3 contains the analogous theory for co-current flow system. The definitions of basic parameters that characterize the performance of membrane devices, dialysance, clearance, transmittance coefficient, are provided in Chapter 7.4, together with some formulas for their calculation as functions of the transport parameters and flow patterns. Here, we discuss the basic operative mode of the dialyzer, the concomitant solute removal by diffusion and convection that are both directed from blood to dialysate, and also another important case with diffusive transport from dialysate to blood, that is against ultrafiltration flow (back-transport). The latter case may be of interest for buffer solutes and possible contaminations, having concentrations higher in the dialysis fluid than in blood. The one-dimensional theory of hemofilter, but also of other devices for separation procedures by filtration, is presented in Chapter 7.5. This chapter includes also the definition and formulas for the basic parameter that characterizes filtration devices, the sieving coefficient of device. Based on the obtained results, different approximations for

the transmittance coefficient are described in Chapter 7.6. The one dimensional theory of ultrafiltration in hemodialyzer is developed in Chapter 7.7 for counter-current and co-current flow systems. The summary of the theoretical results is provided in Chapter 7.8.

7.1 Introduction

Mathematical modeling of fluid and solute transport in hemodialyzer involves two steps: 1) transport in blood and dialysate channels, and 2) transport through a permselective membrane between blood and dialysis fluid. Transport through the membrane depends on the local concentrations of the solute at both sides of the membrane and the values of the transport parameters of the membrane. The theoretical description of this transport is based on the thermodynamic theory, see Chapter 2. In typical cases, only the transport in the direction perpendicular to the membrane is considered. Diffusion is the main transport component for solutes of low molecular weight, however, convective transport is also important, especially for medium sized molecules and small proteins in hemodialyzers with highly permeable membranes. The convective mode dominates the solute transport in blood purification procedures based on filtration across the selectively permeable membrane, such as hemofiltration, plasma separation and plasma fractionation (Drukker et al., 2004). A strong convective transport component is involved in hemodialfiltration (Drukker et al., 2004). The transport inside the channels is a combined diffusive and convective process. The diffusive component of the transport along the membrane may be usually neglected for typical solutes of interest and typical flow rates applied in hemodialysis, but diffusive and convective components may be comparable for the transport perpendicular to the membrane.

In general, the mathematical description of this transport involves three-dimensional equations for diffusion and convection; for hollow fiber dialyzers two-dimensional equations are used because of the cylindrical symmetry of hollow fibers (Sigdell, 1974). The idea of the Krogh cylinder is often applied with the dialysis flow in the outer layer of the cylinder, see Chapter 3.2. Nevertheless, the transport component in the channels perpendicular to the membrane may be often neglected and for practical purposes one may apply one-dimensional equations for the convective transport along the membrane. This approach, described for the first time in 1981, and called the one-dimensional theory of hemodialyzer (Jaffrin et al., 1981), is discussed in this chapter. The one-dimensional theory may be extended by adding the boundary transport layers (Bird et al., 1960); however, at least for the standard operating conditions this extension is as precise as the one-dimensional model itself (Galach et al., 2003).

For the solutes that are to be removed from the body during hemodialysis (i.e., they are not present in dialysis fluid at the inlet to dialyzer) the most important parameter that describes the efficiency of the hemodialyzer is called

clearance, in the analogy of the clearance of the kidney, a widely applied parameter in physiology and nephrology (Guyton, Hall, 2000, Drukker et al., 2004). Again by analogy, one may define the back-clearance for the solutes that are present in the inflowing dialysis fluid but absent in blood and are absorbed to blood during hemodialysis. Finally, the parameter called dialysance describes the removal/absorption of solutes that are both in blood and in the fresh dialysis fluid (Drukker et al., 2004). The theoretically simplest case of hemodialysis is the pure diffusive transport of solutes, without the removal of water. The one dimensional theory provides the closed formulas for diffusive clearance/back-clearance/dialysance as functions of the diffusive transport parameter, membrane surface area, and blood and dialysis fluid flow rates; these formulas are nowadays described in medical textbooks (Drukker et al., 2004). The important feature of clearance is its independence of the solute concentration in blood and therefore it describes the dialysis efficiency independently of the current phase of dialysis.

Traditionally, the effectiveness of ultrafiltration (the rate of water removal in dialyzer) is included into the clearance as an additive term, proportional to ultrafiltration with the parameter called the transmittance coefficient. The clearance of the filtration procedures (hemofilter) is described using sieving coefficient. The one-dimensional theory provides theoretical description of these parameters, related to convective solute transport, although the theory can yield closed formulas only in some special cases.

The distribution of transmembrane fluid flux along the dialyzer is often assumed uniform, but the one-dimensional theory of ultrafiltration predicts in general the non-uniform profiles, as discussed in Chapter 7.7.

Our discussion of the theoretical results on the one-dimensional theory of devices applied for blood purification is based on previous publications (Werynski et al., 1985, Waniewski et al., 1991, Waniewski et al., 1993, Waniewski, 1994, Waniewski et al., 1994, Werynski, Waniewski, 1995, Galach et al., 2003).

7.2 The one-dimensional theory of the dialyzer: counter-current flows

The one-dimensional theory of hemodialyzer simplifies the description of solute concentration inside the blood and dialysate channels of hemodialyzer, assuming homogeneous concentration, C_B and C_D, respectively, in any cross-section of the channel. The flows of solute in blood and dialysate channels in the steady state are described by ordinary differential equations, which are based on the mass balance in the infinitesimal slice from x to $x + dx$; for the counter-current flows

$$\frac{d\left(Q_B C_B\right)}{dx} = -J_S A \tag{7.1}$$

$$\frac{d\left(Q_D C_D\right)}{dx} = -J_S A \tag{7.2}$$

$$\frac{dQ_B}{dx} = -J_V A \tag{7.3}$$

$$\frac{dQ_D}{dx} = -J_V A. \tag{7.4}$$

The variable x describes the normalized distance from the inlet of blood flow to this part of hemodialyzer, where effective fluid and solute transmembrane exchange occurs, i.e., x is equal to the real distance along the channel over the total length of the transport-active part of the hemodialyzer. The total surface area of the membrane is denoted by A. J_S is the transmembrane solute flux, and the transmembrane volumetric flux, J_V, is considered as a defined function of x.

Solute transport through the permselective membrane between the channels is described using the modified Spiegler-Kedem-Katchalsky equation for solute flux

$$J_S = P\left(C_B - C_D\right) + \left(1 - \sigma\right) J_V C_M \tag{7.5}$$

where C_M is the mean intramembrane concentration of the solute, and J_V is the rate of local, at the distance x, ultrafiltration flux, see Chapter 2.2. The net rate of ultrafiltration flow in dialyzer, Q_U, may be calculated as $Q_U = A\int\limits_0^1 J_V\left(x\right) dx$. If $J_V\left(x\right)$ is independent of x, then $Q_U = J_V A$. For homogeneous membranes C_M is described as (see Chapter 2)

$$C_M = \left(1 - f\right) C_B + f C_D \tag{7.6}$$

where

$$f = \frac{1}{\lambda J_v} - \frac{1}{\exp\left(\lambda J_v\right) - 1} \tag{7.7}$$

$$\lambda = \frac{\left(1 - \sigma\right)}{P}. \tag{7.8}$$

Alternative descriptions of the membrane transport may assume function f to be a constant, F, with a value between 0 to 1, see Chapter 2.5.

In the countercurrent system, the known values of variables are those at the inlet of blood flow to dialyzer, i.e., C_B and Q_B for $x = 0$, and at the inlet of dialysis fluid to dialyzer, i.e., C_D and Q_D for $x = 1$. Therefore, the solution of equations (7.1) - (7.4) should be presented as a function of these boundary values. We do not deal here with the solution of the typical initial value problem for ordinary differential equations. For the numerical solution, additional algorithms need to be applied, such as, for example, the shooting method, in addition to a standard ordinary differential equation solver (Press et al., 2007). Fortunately, the overall mass balance in the dialyzer can help in solving the equations with the countercurrent flows in the closed form.

Solution of the dialyzer equations. The difference between the equations (7.1) and (7.2) is equal to zero, and this observation expresses the local principle of mass conservation that can be described as

$$(Q_B C_B - \ Q_D C_D)(x) = H \tag{7.9}$$

where H is a constant, which, for the counter-current flow system, may be presented as the function of inlet and outlet values

$$H = Q_{Bi} C_{Bi} - \ Q_{Do} C_{Do} \tag{7.10}$$

or

$$H = Q_{Bo} C_{Bo} - \ Q_{Di} C_{Di} \tag{7.11}$$

if equation (7.9) is applied for $x = 0$ or $x = 1$, respectively; Q_{Bi} and C_{Bi} are Q_B and C_B at the inlet to the hemodialyzer, respectively, Q_{Do} and C_{Do} are Q_D and C_D at the outlet from the hemodialyzer, respectively, Q_{Bo} and C_{Bo} are Q_B and C_B at the outlet from the hemodialyzer, respectively, and Q_{Di} and C_{Di} are Q_D and C_D at the inlet to the hemodialyzer, respectively.

Thus, $(Q_D C_D)(x)$ may be presented as a function of $(Q_B C_B)(x)$ and H using equation (7.9), and the system of two equations (7.1) may be reduced to one equation

$$\frac{d(Q_B C_B)}{dx} = -\alpha(x) Q_B C_B - \beta(x) H \tag{7.12}$$

where

$$\alpha(x) = p(x)/Q_B(x) - r(x)/Q_D(x) \tag{7.13}$$

$$\beta(x) = r(x)/Q_D(x) \tag{7.14}$$

$$p(x) = PA + (1-\sigma)(1-f)(x) J_v(x) A \tag{7.15}$$

$$r(x) = PA - (1-\sigma) f(x) J_v(x) A. \tag{7.16}$$

The solution of equation (7.12) is

$$(Q_B C_B)(x) = \frac{Q_{Bi} C_{Bi} - H N(x)}{M(x)} \tag{7.17}$$

where

$$M(x) = \exp\left(\int_0^x \alpha(x)\, dx\right) \tag{7.18}$$

$$M(x) = \exp\left(\int_0^x \beta(x) M(x)\, dx\right). \tag{7.19}$$

Now, combining equations (7.11) and (7.17), applied for $x = 1$, we get

$$H = Q_{Bi} c_{Bi} \frac{1}{W_1} - Q_{Di} C_{Di} \frac{M_1}{W_1} \tag{7.20}$$

where $M_1 = M(1)$, $N_1 = N(1)$ and $W_1 = M_1 + N_1$. Thus, combining equations (7.17) and (7.20), yields

$$(Q_B C_B)(x) = Q_{Bi} C_{Bi} \frac{1}{M(x)} \left(1 - \frac{N(x)}{W_1}\right) + Q_{Di} C_{Di} \frac{N(x)}{M(x)} \frac{M_1}{W_1}. \tag{7.21}$$

In particular, for $x = 1$

$$(Q_{Bo} C_{Bo})(x) = Q_{Bi} C_{Bi} \frac{1}{W_1} + Q_{Di} C_{Di} \frac{N_1}{W_1}. \tag{7.22}$$

Furthermore, from equations (7.9) and (7.21),

$$(Q_D C_D)(x) = Q_{Bi} C_{Bi} \frac{1}{M(x)} \left(1 - \frac{N(x) + M(x)}{W_1}\right) + Q_{Di} C_{Di} \frac{M_1}{W_1} \left(1 + \frac{N(x)}{M(x)}\right). \tag{7.23}$$

And, for $x = 0$,

$$Q_{Do} C_{Do} = Q_{Bi} C_{Bi} \left(1 - \frac{1}{W_1}\right) + Q_{Di} C_{Di} \frac{M_1}{W_1} \tag{7.24}$$

because $M(0) = 1$ and $N(0) = 0$.

An interesting and important specific solution may be found for $\sigma = 0$. Let us denote

$$\mu(x) = PA - f(x) J_V(x) A. \tag{7.25}$$

Then, $p(x) = \mu(x) + J_V(x)A$ and $r(x) = \mu(x)$, and M can be expressed as

$$M(x) = m(x) \frac{Q_{Bi}}{Q_B(x)} \tag{7.26}$$

$$m(x) = \exp\left(\int_0^x \mu(x) \left(\frac{1}{Q_B(x)} - \frac{1}{Q_D(x)}\right) dx\right) \tag{7.27}$$

whereas N as

$$\begin{aligned} N(x) &= Q_{Bi} \int_0^x m(x)\, \mu(x)\, \tfrac{1}{Q_B(x) Q_D(x)} dx \\ &= \tfrac{Q_{Bi}}{Q_{Do} - Q_{Bi}} \int_0^x m(x)\, \mu(x) \left(\tfrac{1}{Q_B(x)} - \tfrac{1}{Q_D(x)}\right) dx \\ &= \tfrac{Q_{Bi}}{Q_{Do} - Q_{Bi}} \int_0^x dm(x) dx = \tfrac{Q_{Bi}}{Q_{Do} - Q_{Bi}} (m(x) - 1) \end{aligned} \tag{7.28}$$

Thus, for $\sigma = 0$ the problem is reduced to the calculation of integral $m(x)$, equation (7.27).

The functions (7.21) and (7.23) provide solutions to equations (7.1), expressed by the integrals of functions of the parameters of these equations without any additional assumptions. Now, assuming that J_V is independent of x, one can calculate $M(x)$ for $Q_B(x) = Q_{Bi} - Q_U x$ and $Q_D(x) = Q_{Do} - Q_U x$, $Q_U = J_V A$,

$$M(x) = \left(1 - \frac{Q_U}{Q_{Bi}} x\right)^{-p/Q_U} \left(1 - \frac{Q_U}{Q_{Do}} x\right)^{r/Q_U}. \tag{7.29}$$

Then,

$$\begin{aligned} N(x) &= \frac{r}{Q_{Do}} \int_0^x \left(M(x) / \left(1 - \frac{Q_U}{Q_{Do}} x \right) \right) dx \\ &= \frac{r}{Q_{Do}} \int_0^x \left(1 - \frac{Q_U}{Q_{Bi}} x \right)^{-p/Q_U} \left(1 - \frac{Q_U}{Q_{Do}} x \right)^{r/Q_U - 1} dx \end{aligned} . \tag{7.30}$$

The calculation of N, equation (7.30), requires, in general, a numerical method. However, for specific values of parameters Q_U and σ, closed solutions of equations (7.1) may be provided and these closed solutions may also be used for other values of Q_U and σ as approximate descriptions.

A particular closed solution may be found for pure diffusive exchange in dialyzer, i.e., for $J_V = 0$ and $Q_B \neq Q_D$. Then, from equations (7.18) and (7.19),

$$M(x) = \exp(\gamma x) \tag{7.31}$$

$$\gamma = PA(1/Q_B - 1/Q_D) \tag{7.32}$$

$$N(x) = Q_B(\exp(\gamma x) - 1)(Q_D - Q_B) \tag{7.33}$$

and the solution (7.21) has the form

$$C_B(x) = \left(1 - \frac{1 - \exp(-\gamma x)}{1 - \frac{Q_B}{Q_D} \exp(-\gamma)} \right) C_{Bi} + \frac{1 - \exp(-\gamma x)}{1 - \frac{Q_B}{Q_D} \exp(-\gamma)} C_{Di} \tag{7.34}$$

i.e., $C_B(x)$ is the weighted mean of C_{Bi} and C_{Di}.

For $J_V = 0$ and $Q_B = Q_D$,

$$M(x) = 1 \tag{7.35}$$

$$N(x) = (PA/Q_B)\, x \tag{7.36}$$

and from equation (7.21)

$$C_B(x) = C_{Bi} \left(1 - \frac{PA}{Q_B + PA} x \right) + C_{Di} \frac{PA}{Q_B + PA} x \tag{7.37}$$

i.e., $C_B(x)$ is another weighted mean of C_{Bi} and C_{Di}.

By combining the assumptions of $\sigma = 0$ and $J_V = \text{const}$ one can obtain yet another closed solution using

$$m(\mathrm{x}) = \left(1 - \frac{Q_U}{Q_{Bi}} x \right)^{-\mu/Q_U - 1} \left(1 - \frac{Q_U}{Q_{Do}} x \right)^{\mu/Q_U} . \tag{7.38}$$

Instead of writing the explicit solution for this case, let us note that it can be expressed as

$$C_B(x) = m(x) \left(C_{Bi} - \frac{H}{G} \right) + \frac{H}{G} \tag{7.39}$$

where H is given by formula (7.20), and $G = Q_{Do} - Q_{Bi}$, and we assume $G \neq 0$.

7.3 The one-dimensional theory of the dialyzer: co-current flows

In the case of co-current flows one has the following equations

$$\frac{d\left(Q_B C_B\right)}{dx} = -J_S A \tag{7.40}$$

$$\frac{d\left(Q_D C_D\right)}{dx} = +J_S A \tag{7.41}$$

$$\frac{dQ_B}{dx} = -J_V A \tag{7.42}$$

$$\frac{dQ_D}{dx} = +J_V A \tag{7.43}$$

where we assume that positive flow rates in both channels are in the positive x-direction. The equations for the transmembrane transport are the same as for the counter-current flows, equations (7.5) – (7.7)

Solution of the dialyzer equations. The sum of the equations (7.40) and (7.41) is equal to zero, and this observation expresses the local principle of mass conservation that can be described as

$$\left(Q_B C_B + \ Q_D C_D\right)(x) = \tilde{H} \tag{7.44}$$

where $\tilde{H}$ is a constant, which, for the co-current flow system, is the function of inlet values

$$\tilde{H} = Q_{Bi} C_{Bi} + Q_{Di} C_{Di}. \tag{7.45}$$

Thus, $\left(Q_D C_D\right)(x)$ may be presented as a function of $\left(Q_B C_B\right)(x)$ and $\tilde{H}$ using equation (7.44), and the system of two equations (7.40) may be reduced to one equation

$$\frac{d\left(Q_B C_B\right)}{dx} = -\tilde{\alpha}\left(x\right) Q_B C_B + \beta\left(x\right) \tilde{H} \tag{7.46}$$

where

$$\tilde{\alpha}\left(x\right) = p\left(x\right) / Q_B\left(x\right) + r\left(x\right) / Q_D\left(x\right) \tag{7.47}$$

and other parameters are defined as for the counter-current system, equations (7.14) – (7.16).

The solution of equation (7.46) is

$$\left(Q_B C_B\right)(x) = \frac{Q_{Bi} C_{Bi} + \tilde{H} \tilde{N}\left(x\right)}{\tilde{M}\left(x\right)} \tag{7.48}$$

where

$$\tilde{M}\left(x\right) = \exp\left(\int_0^x \tilde{\alpha}\left(x\right) dx\right) \tag{7.49}$$

$$\tilde{N}(x) = \int_0^x \beta(x)\,\tilde{M}(x)\,dx. \tag{7.50}$$

Thus, using equation (7.45), we get

$$(Q_B C_B)(x) = Q_{Bi}C_{Bi}\frac{\left(1+\tilde{N}(x)\right)}{\tilde{M}(x)} + Q_{Di}C_{Di}\frac{\tilde{N}(x)}{\tilde{M}(x)}. \tag{7.51}$$

In particular, for $x = 1$,

$$Q_{Bo}C_{Bo} = Q_{Bi}C_{Bi}\frac{\left(1+\tilde{N}_1\right)}{\tilde{M}_1} + Q_{Di}C_{Di}\frac{\tilde{N}_1}{\tilde{M}_1}. \tag{7.52}$$

We do not discuss the theory of co-current dialyzers in details because it was found that they are less efficient than the counter-current dialyzers. This can be easily demonstrated for the case of pure diffusive transport, i.e., for $J_V = 0$. In this case, from equations (7.49) and (7.50),

$$\tilde{M}(x) = M(x) = \exp(\gamma x) \tag{7.53}$$

$$\gamma = PA\,(1/Q_B - 1/Q_D) \tag{7.54}$$

$$\tilde{N}(x) = N(x) = Q_B\,(\exp(\gamma x) - 1)\,(Q_D - Q_B) \tag{7.55}$$

and the solution (7.51) has the form

$$C_B(x) = \left(1 - \frac{1-\exp(-\gamma x)}{1+\frac{Q_B}{Q_D}}\right) C_{Bi} + \frac{1-\exp(-\gamma x)}{1+\frac{Q_B}{Q_D}} C_{Di} \tag{7.56}$$

i.e., $C_B(x)$ is a weighted mean of C_{Bi} and C_{Di}, but the weight is different from that for the counter-current system, equation (7.34). In general, we present the profile of solute concentration in blood as

$$C_B(x) = (1 - F(x))\,C_{Bi} + F(x)\,C_{Di} = C_{Bi} - F(x)\,(C_{Bi} - C_{Di}) \tag{7.57}$$

with

$$F^{co}(x) = \frac{1-\exp(-\gamma x)}{1+\frac{Q_B}{Q_D}} \tag{7.58}$$

for the co-current system, and

$$F^{counter}(x) = \frac{1-\exp(-\gamma x)}{1-\frac{Q_B}{Q_D}\exp(-\gamma)}. \tag{7.59}$$

for the counter-current system. Note that

$$F^{co} < F^{counter} \tag{7.60}$$

for all x. Because

$$C_B^{co}(x) - C_B^{counter}(x) = \left(F_B^{counter}(x) - F_B^{co}(x)\right)(C_{Bi} - C_{Di}), \tag{7.61}$$

therefore

$$C_B^{co}(x) > C_B^{counter}(x) \tag{7.62}$$

for all x and $C_{Bi} > C_{Di}$, due to inequality (7.60). Thus, the concentration of the solute to be removed from blood is always higher in blood in the co-current system than in the counter-current system, assuming the same flow rates and dialyzer characteristics.

7.4 The dialysance, clearance, transmittance coefficient

The rate of the removal of mass from blood in the dialyzer at the steady state of transport in the counter-current hemodialyzer may be calculated as

$$\begin{aligned} Q_{DS} &= Q_{Bi}C_{Bi} - Q_{Bo}C_{Bo} \\ &= Q_{Do}C_{Do} - Q_{Di}C_{Di} \end{aligned}. \tag{7.63}$$

Thus, by equation (7.22),

$$Q_{DS} = Q_{Bi}C_{Bi}\left(1 - \frac{1}{W_1}\right) - Q_{Di}C_{Di}\frac{N_1}{W_1}. \tag{7.64}$$

For purely diffusive transport, i.e., for $J_V = 0$, and for $Q_B \neq Q_D$, Q_{DS} may be evaluated explicitly

$$Q_{DS0} = Q_B \frac{\exp(\gamma) - 1}{\exp(\gamma) - Q_B/Q_D}(C_{Bi} - C_{Di}). \tag{7.65}$$

Therefore, if $C_{Bi} \neq C_{Di}$, one may define a coefficient, called diffusive dialysance

$$D_0 = \frac{Q_{DS0}}{C_{Bi} - C_{Di}} = Q_B \frac{\exp(\gamma) - 1}{\exp(\gamma) - Q_B Q_D}. \tag{7.66}$$

Diffusive dialysance depends only on the dialyzer characteristics and the treatment-related parameters: P, A, Q_B, and Q_D. The generalization of the definition (7.66) of dialysance for non-zero Q_U is, however, not straightforward. Let us first note that equation (7.64) for Q_{DS} can be presented as

$$Q_{DS} = KC_{Bi} - bKC_{Di} \tag{7.67}$$

where K and bK may be considered as two important special cases of the general notion of dialysance. The first case, K, is valid for many solutes that have to be removed from blood during dialysis, and therefore their concentration in the inflowing dialysate, C_{Di}, is zero. Then, dialysance is called clearance and is defined as

$$K = \frac{Q_{Bi}C_{Bi} - Q_{Bo}C_{Bo}}{C_{Bi}} = Q_{Bi}\left(1 - \frac{1}{W_1}\right). \tag{7.68}$$

If solute concentration in the inflowing blood, C_{Bi}, is zero, one may speak about back-clearance, bK, of the solute from dialysate to blood

$$bK = \frac{Q_{Do}C_{Do} - Q_{Di}C_{Di}}{C_{Di}} = \frac{Q_{Bo}C_{Bo}}{C_{Di}} = Q_{Di}\frac{N_1}{W_1}. \tag{7.69}$$

In the case of pure diffusive transport, $J_V = 0$,

$$K_0 = bK_0 = D_0 \tag{7.70}$$

where K_0 and bK_0 are the diffusive clearance and the diffusive back-clearance, 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 given as

$$K = K_0 + \ Tr \ Q_U \tag{7.71}$$

where Tr is the transmittance coefficient. In contrast, diffusive solute transport from dialysate to blood is decreased by ultrafiltration from blood to dialysate, and back-clearance, bK, may be expressed as

$$bK = bK_0 - bTr \ Q_U \tag{7.72}$$

where bTr is the back-transmittance coefficient, defined here for the net ultrafiltration from blood to dialysate. The general expression for Q_{DS}, equation (7.67), cannot be reduced to the form similar to equation (7.65) for Q_{DS0}, i.e., Q_{DS} cannot be presented as a constant multiplied by the difference of C_{Bi} and C_{Di}. This can be checked analytically for the case of $\sigma = 0$. Algebraic transformations of equations (7.68) and (7.69), using equations (7.26) and (7.28), for $x = 1$ yield

$$K = bK + Q_U \tag{7.73}$$

and

$$Q_{DS} = K\left(C_{Bi} - C_{Di}\right) + Q_U C_{Di}. \tag{7.74}$$

So, $D(= K)$ may be calculated as

$$D = \frac{Q_{DS} - C_{Di}Q_U}{C_{Bi} - C_{Di}}. \tag{7.75}$$

Thus, Q_{DS} may be presented as a sum of two terms, equation (7.74): 1) the first term includes the diffusive-convective clearance of dialyzer multiplied by the difference of inlet concentrations of the solute in both channels, and 2) the second term that depends only on ultrafiltration and the inlet concentration of the solute in dialysis fluid. If the concentrations at the inlets are equal, then only the second term contributes to the transport in dialyzer. Equation (7.74), which

was derived for $\sigma = 0$, may be applied also as an approximation for the transport of small molecules with the size not much different from water molecule, i.e., for $\sigma << 1$. For higher σ, the general formula (7.67) has to be used, necessitating the estimation of K and bK, or alternatively K_0, Tr and bTr,

$$Q_{DS} = K_0 \left(C_{Bi} - C_{Di}\right) + \left(TrC_{Bi} + bTrC_{Di}\right) Q_U. \tag{7.76}$$

The one dimensional theory provides the formula for K_0, equation (7.66), but the estimation of the transmittance coefficients requires, in general, numerical calculation of integrals in formulas (7.26) and (7.28).

Extending the solution obtained for $\sigma = 0$ in order for it to be applied also as an approximation for $\sigma > 0$, one may propose the following formula

$$K = Q_{Bi} \frac{1 - \frac{Q_{Do}}{Q_{Di}} \frac{Q_{Bo}}{Q_{Bi}} Z}{1 - \frac{Q_{Bo}}{Q_{Di}} Z} \tag{7.77}$$

with

$$Z = \left(\frac{Q_{Bo}}{Q_{Bi}}\right)^{(p/Q_u)-1} \left(\frac{Q_{Di}}{Q_{Do}}\right)^{-(p/Q_u-1)} \tag{7.78}$$

for $Q_U > 0$ and $p = PA + (1 - \sigma)(1 - f) Q_U$. An analogous formula may be derived for bK,

$$bK = Q_{Bo} \frac{1 - Z}{1 - \frac{Q_{Bo}}{Q_{Di}}}. \tag{7.79}$$

Equations (7.77) and (7.79) are closed solutions for constant nonzero J_V and $\sigma = 0$. Formula (7.77) for K appears to be also a good approximation for $0 < \sigma < 1$ in the typical conditions of hemodialysis (Waniewski et al., 1991), but the formula (7.79) is a good approximation only for small values of σ; it should be noted however that it does not provide any accurate description of bK for σ close to one during the typical conditions of hemodialysis.

7.5 The one-dimensional theory of hemofilter, the sieving coefficient

The one-dimensional theory of hemofilter (and any other membrane module designed for transmembrane filtration) is based on the same assumption as the one-dimensional theory of hemodialyzer. The only difference is that there is no inflow of dialysis fluid and in the dialysate channel of the module there is only the flow of filtrate (fluid that is filtered through the membrane from the blood channel). With Q_F denoting the flow rate of the filtrate and C_F denoting the solute concentration in filtrate, and for the counter-current flows, we have

$$\frac{d\left(Q_B C_B\right)}{dx} = -J_S A \tag{7.80}$$

$$\frac{d\left(Q_F C_F\right)}{dx} = -J_S A \tag{7.81}$$

$$\frac{dQ_B}{dx} = -J_V A \tag{7.82}$$

$$\frac{dQ_F}{dx} = -J_V A \tag{7.83}$$

with other symbols as in Chapter 7.2. Note that $Q_{Fi} = Q_F(1) = 0$ and $Q_{Fo} = Q_F(0) = Q_{Bi} - Q_{Bo}$ is the total filtration flow in the hemofilter.

Solute transport through the permselective membrane between the channels is described using the same modified Spiegler-Kedem-Katchalsky equation for solute flux as in the theory of hemodialyzer, but presented in the form convenient for the description of filtration process, see equation (2.36),

$$J_S = S J_V \left(a C_B - b C_F\right) \tag{7.84}$$

where $S = 1 - \sigma$ is the local membrane sieving coefficient, see Chapter 2.3, and

$$a = 1/\left(1 - \exp\left(-Pe\right)\right) \tag{7.85}$$

$$b = a - 1 = \exp\left(-Pe\right)/\left(1 - \exp\left(-Pe\right)\right). \tag{7.86}$$

The net rate of ultrafiltration flow in dialyzer, Q_U, may be calculated as $Q_U = A \int_0^1 J_V(x)\, dx$. If $J_V A$ is independent of x, then $Q_U = J_V A$. Note that $Q_U = Q_{Fo}$.

Solution of the hemofilter equations. The solution of equations for the hemofilter is obtained through the same steps as for the equations for the hemodialyzer, Chapter 7.2, with

$$\left(Q_B C_B - \ Q_F C_F\right)(x) = H \tag{7.87}$$

where H is a constant, which, for the counter-current flow system, may be presented as the function of inlet and outlet values

$$H = Q_{Bi} C_{Bi} - \ Q_{Fo} C_{Fo} = Q_{Bo} C_{Bo}. \tag{7.88}$$

Thus, $\left(Q_F C_F\right)(x)$ may be presented as a function of $\left(Q_B C_B\right)(x)$ and H using equation (7.87), and the system of two equations (7.80) may be reduced to one equation

$$\frac{d\left(Q_B C_B\right)}{dx} = -\alpha(x)\, Q_B C_B - \beta(x)\, H \tag{7.89}$$

where

$$\alpha(x) = S J_V(x)\, A\left(a(x)/Q_B(x) - b(x)/Q_F(x)\right) \tag{7.90}$$

$$\beta(x) = S J_V(x)\, A b(x)/Q_F(x). \tag{7.91}$$

The solution of equation (7.12) is

$$(Q_B C_B)(x) = \frac{Q_{Bi} C_{Bi} - HN(x)}{M(x)} \tag{7.92}$$

where

$$M(x) = \exp\left(\int_0^x \alpha(x)\, dx\right) \tag{7.93}$$

$$N(x) = \int_0^x \beta(x) M(x)\, dx. \tag{7.94}$$

After eliminating H from equation (7.92), see Chapter 7.2, one gets the solution in the form

$$(Q_B C_B)(x) = Q_{Bi} C_{Bi} \frac{1}{M(x)} \left(1 - \frac{N(x)}{W_1}\right) \tag{7.95}$$

where $W_1 = M_1 + N_1$, $M_1 = M(1)$, $N_1 = N(1)$. In particular, for $x = 1$,

$$Q_{Bo} C_{Bo} = Q_{Bi} C_{Bi} \frac{1}{W_1}. \tag{7.96}$$

Furthermore,

$$(Q_F C_F)(x) = Q_{Bi} C_{Bi} \frac{1}{M(x)} \left(1 - \frac{N(x) + M(x)}{W_1}\right) \tag{7.97}$$

and for $x = 0$

$$Q_{Fo} C_{Fo} = Q_{Bi} C_{Bi} \left(1 - \frac{1}{W_1}\right) \tag{7.98}$$

because $M(0) = 1$ and $N(0) = 0$.

The general definition of clearance, equation (7.68), can be presented for the hemofilter in a different form, based on the total mass balance, $Q_{Fo} C_{Fo} = Q_{Bi} C_{Bi} - Q_{Bo} C_{Bo}$, as

$$K_{HF} = \frac{Q_{Fo} C_{Fo}}{C_{Bi}} = S_{HF} \mathrm{Q}_{Fo} \tag{7.99}$$

where the sieving coefficient of hemofilter, S_{HF}, is

$$S_{HF} = \frac{C_{Fo}}{C_{Bi}} = \frac{Q_{Bi}}{Q_{Fo}} \left(1 - \frac{1}{W_1}\right). \tag{7.100}$$

The equation (7.100) describes the (implicit, unless the integral in W_1 can be solved to a closed formula) relationship between the sieving coefficient of the device, S_{HF}, and the local sieving coefficient of the membrane, $S = 1 - \sigma$. This relationship may be compared to that for the membrane sieving coefficient S_M and the local sieving coefficient S for the membrane material, equation (2.37).

Because $Q_F(1) = 0$, the integrands in formulas (7.93) for M and (7.94) for N are singular at $x = 1$. Nevertheless, they are integrable for particular profiles

of $Q_F(x)$. For example, assuming constant ultrafiltration flux, $J_V(x) = const$, one may calculate $M(\mathrm{x})$ for $Q_B(x) = Q_{Bi} - Q_{Fo}x = Q_{Bi}(1-qx)$ and $Q_F(x) = Q_{Fo}(1-x)$, when $Q_{Fo} = J_V A$ and $q = Q_{Fo}/Q_{Bi}$, as

$$M(x) = (1-qx)^{-Sa}(1-x)^{Sb}. \tag{7.101}$$

Then

$$\begin{aligned} N(x) &= \beta \int_0^x (M(x)/(1-x))\,dx \\ &= Sb \int_0^x (1-qx)^{-Sa}(1-x)^{Sb-1}\,dx \end{aligned}. \tag{7.102}$$

The calculation of N, equation (7.30), requires, in general, a numerical method. Note that the integrand in formula (7.102) is regular for $Sb > 1$, singular, but integrable, for $Sb < 1$, and if $Sb = 1$, then one can get the explicit formula for $N(x)$:

$$N(x) = \left((1-qx)^{-S} - 1\right)/(qS). \tag{7.103}$$

If $S = 1$, i.e., $\sigma = 0$, then, by repeating the calculations from Chapter 7.2, one can get the general solution $C_B(x) = C_F(x) = C_{Bi}$. This is intuitively obvious and may be proved formally by considering equations (7.80) in the form

$$\frac{dC_B}{dx} = -\frac{J_V Ab(C_B - C_F)}{Q_B} \tag{7.104}$$

$$\frac{dC_F}{dx} = -\frac{J_V Aa(C_B - C_F)}{Q_F} \tag{7.105}$$

and

$$\frac{d(C_B - C_F)}{dx} = -J_V A\left(\frac{b}{Q_B} - \frac{a}{Q_F}\right)(C_B - C_F) \tag{7.106}$$

and the solution $(C_B - C_F)(x)$ of equation (7.106) is proportional to $(C_{Bi} - C_{Fo})$. Therefore, it is enough to prove that $C_{Bi} = C_{Fo}$. This, is turn, can be demonstrated by noticing that $W_1 = Q_{Bi}/Q_{Bo}$, by using the definition of $W_1 = M_1 + N_1$ and equations (7.26) for M and (7.28) for N. Then, equation (7.98) yields $C_{Bi} = C_{Fo}$ because $Q_{Bi} = Q_{Fo} + Q_{Bo}$.

Dead-end filtration. An interesting example of the filtration process is the dead-end filtration, that is, the filtration procedure with the whole inflow Q_{Bi} passing across the membrane $Q_{Fo} = Q_{Bi}$, $Q_{Bo} = 0$. Such a process cannot be performed for the entirety of blood, but may be of interest in plasma fractionation or some industrial filtration processes. Note that in this case $H = 0$, equation (7.88), and, because $Q_{Fo} = Q_{Bi}$, $C_{Fo} = C_{Bi}$; therefore $S_{HD} = 1$ and $K_{HD} = Q_{Bi}$. This results is independent of the transport characteristics of the solute, in particular S, and is valid for the steady state, which may be sometimes difficult to obtain because of the clotting of the filter. If we assume, additionally, constant J_V, one has then $J_V A = Q_{Fo} = Q_{Bi}$ and

$Q_F(x) = Q_B(x) = Q_{Bi}(1-x)$, and the solution of equation (7.89) for $H = 0$ can be obtained explicitly as

$$(Q_B C_B)(x) = Q_{Bi} C_{Bi} (1-x)^S \tag{7.107}$$

where we used equations (7.92) and (7.101). Thus, for the solute concentration,

$$C_B(x) = C_{Bi}(1-x)^{S-1}. \tag{7.108}$$

For $S < 1$, $C_B(x) \to \infty$ if $x \to 1$, and the same limit is obtained for $C_F(x)$. This demonstrates some limitations of the one-dimensional theory of the dead-end filter. Nevertheless, the flows of solute are well defined, $(Q_B C_B)(1) = (Q_F C_F)(1) = 0$.

7.6 Approximations for the transmittance coefficient

Transmittance coefficient, Tr, and back transmittance coefficient, bTr, are defined as

$$Tr = \frac{K - K_0}{Q_U} \tag{7.109}$$

$$bTr = \frac{bK_0 - bK}{Q_U} \tag{7.110}$$

where K and bK are clearance and back-clearance, respectively, measured for the total ultrafiltration rate Q_U. By applying the definition of clearance, equation (7.68), one gets

$$Tr = 1 - \frac{K_0}{Q_{Bi}} - \frac{\Delta C_{Bo}}{C_{Bi}} \frac{Q_{Bo}}{Q_U} \tag{7.111}$$

where $\Delta C_{Bo} = C_{Bo} - C^0_{Bo}$, with C_{Bo} and C^0_{Bo} being the concentrations of the solute in blood at the outlet from the hemodialyzer in dialysis with and without ultrafiltration, respectively. Similarly,

$$bTr = \frac{K_0}{Q_{Bi}} + \frac{\Delta C_{Bo}}{C_{Bi}} \frac{Q_{Bo}}{Q_U} \tag{7.112}$$

where ΔC_{Bo} is assessed for the case of back-diffusion and therefore is numerically different from the same variable in equation (7.111). A crude approximation for the transmittance coefficients can be obtained by assuming that the difference in the outflow concentrations is small, i.e., $\Delta C_{Bo} \sim 0$; then

$$Tr = 1 - \frac{K_0}{Q_{Bi}} \tag{7.113}$$

$$bTr = \frac{K_0}{Q_{Bi}}. \tag{7.114}$$

However, according to these formulas, Tr and bTr depend only on the diffusive permeability and surface area of the membrane, as described by equation (7.66), and no impact of the sieving coefficient on the transmittance coefficient is predicted. A more elaborate approximation is obtained if one assumes that the combined diffusive-convective transport in dialyzer is replaced by the serially connected two dialyzers and in the first one diffusive dialysis without ultrafiltration is performed, whereas in the second module only ultrafiltration is carried out without any flow of dialysis fluid (hemofiltration, or ultrafiltration, mode). Note that C^0_{Bo} corresponds now to the solute concentration in blood that leaves dialyzer and enters hemofilter. Then

$$\begin{aligned} Tr &= 1 - \frac{K_0}{Q_{Bi}} - \frac{C_{Bo} - C^0_{Bo}}{C_{Bi}} \frac{Q_{Bo}}{Q_U} \\ &= 1 - \frac{K_0}{Q_{Bi}} - \frac{C^0_{Bo}}{C_{Bi}} \left(\frac{C_{Bo}}{C^0_{Bo}} - 1 \right) \frac{Q_{Bo}}{Q_U} . \end{aligned} \tag{7.115}$$

But, by the definition of K_0,

$$\frac{C^0_{Bo}}{C_{Bi}} = 1 - \frac{K_0}{Q_{Bi}} \tag{7.116}$$

and

$$\frac{C_{Bo}}{C^0_{Bo}} = 1 + \frac{Q_U}{Q_{Bi}} (1 - S_{HF}) \tag{7.117}$$

by the definition of the sieving coefficient of hemofilter, S_{HF}, equation (7.100). Thus,

$$Tr = S_{HF} \left(1 - \frac{K_0}{Q_{Bi}} \right) . \tag{7.118}$$

For the back transmittance coefficient

$$bTr = S_{HF} \frac{bK_0}{Q_{Bi}} . \tag{7.119}$$

Equations (7.118) and (7.119) are correct only if diffusion and ultrafiltration are separated among two different units of the hemodialyzer. The general theoretical estimation of Tr and bTr requires numerical solutions of the transport equations for the dialyzer. Numerical simulations demonstrated that Tr is a nonlinear function of Q_U, but for the values of Q_U, which are applied during hemodialysis, it can be approximated by a constant (Waniewski et al., 1991).

7.7 The one-dimensional theory of ultrafiltration in hemodialyzer

The theory of fluid transport in hemodialyzers is based on the equations for the decrease in pressure along the counter-current flows

$$\frac{dP_B}{dx} = -R_B Q_B \tag{7.120}$$

$$\frac{dP_D}{dx} = R_D Q_D \tag{7.121}$$

and the description of the change of the flow rates, due to the ultrafiltration across the membrane

$$\frac{dQ_B}{dx} = -J_V A \tag{7.122}$$

$$\frac{dQ_D}{dx} = -J_V A \tag{7.123}$$

where P_B and P_D are the pressures in the blood and dialysis fluid channels, respectively, and R_B and R_D are the hydraulic resistances in the blood and dialysis fluid channels, respectively; see (Legallais et al., 2000) and (Galach et al., 2003) for the description of the resistances in the flow channels. The ultrafiltration rate is controlled by the difference of hydrostatic and osmotic pressures across the membrane,

$$J_V A = L_p A \left(P_B - P_D - \sigma \left(\Pi_B - \Pi_D\right)\right). \tag{7.124}$$

We discuss here the case of one solute, but the generalization for many solutes is obvious. The oncotic pressure Π depends on the solute concentration C, and therefore the system of equations (7.120) - (7.124) must be solved together with equations (7.1) and (7.2). As the whole system for the description of fluid and solute transport in dialyzers is nonlinear if $\sigma \neq 0$, the numerical solutions and computer simulations need to be applied. However, the system of equations for fluid transport, equations (7.120) - (7.124), may be solved in closed formulas for pure water (solvent) and for a solute with $\sigma = 0$. For such a case, the system of equations may be reduced to one second order ordinary differential equation for the difference of hydrostatic pressures, i.e.

$$\frac{d^2 \left(P_B - P_D\right)}{dx^2} = L_p A \left(R_B + R_D\right) \left(P_B - P_D\right). \tag{7.125}$$

The solution of equation (7.125) has the general form

$$\left(P_B - P_D\right)(x) = a e^{\alpha x} + b e^{-\alpha x} \tag{7.126}$$

where

$$\alpha = \sqrt{L_p A \left(R_B + R_D\right)}. \tag{7.127}$$

The unknown parameters a and b may be calculated from the differences in hydrostatic pressures $(P_B - P_D)$ at the two sides of the hemodialyzer. However, the prescription of the dialysis treatment includes typically the flow rates Q_{Bi}, Q_{Di}, and the total ultrafiltration rate $Q_U = \int_0^1 J_V A dx$, and therefore we express the solution of equation (7.125) through these parameters. For this purpose we use two additional equations. The first one describes the total ultrafiltration rate

$$Q_U = \frac{L_p A}{\alpha}\left(ae^{\alpha x} - be^{-\alpha x} - a + b\right). \tag{7.128}$$

The second equation can be derived from equations (7.120) and (7.121) as

$$\frac{d\left(P_B - P_D\right)}{dx} = -\left(R_B Q_B + R_D Q_D\right). \tag{7.129}$$

Upon calculating the derivative of function described by equation (7.126) at $x = 0$, one gets

$$b - a = RQ + R_D Q_U \tag{7.130}$$

where the parameter RQ is defined as

$$RQ = R_{Bi} Q_{Bi} + R_{Di} Q_{Di}. \tag{7.131}$$

The equations (7.128) and (7.130) may be solved for a and b as functions of other parameters and, after some algebraic transformations, one gets

$$J_V(x)\, A = \left(Q_U\left(\alpha - R_D\beta\right) - RQ\beta\right)\frac{\cosh(\alpha x)}{\sinh(\alpha)} + \left(Q_U R_D + RQ\right)\beta\frac{\cosh\left(\alpha\left(1-x\right)\right)}{\sinh(\alpha)} \tag{7.132}$$

where $\beta = L_p A/\alpha$. Using formula (7.132) for $J_V(x)\, A$ one can easily derive the formulas for other variables, $Q_B(x)$, $Q_D(x)$, $P_B(x)$, and $P_D(x)$, using equations (7.120) - (7.124).

It is worth noticing that even if there is no net total ultrafiltration, $Q_U = 0$, there is some ultrafiltration flux from blood to dialysis fluid at the inlet of blood to hemodialyzer and back-filtration from dialysis fluid at the outlet of blood from hemodialyzer. To prove this, let us calculate for $Q_U = 0$

$$J_V(0)\, A = RQ\beta\frac{\cosh(\alpha) - 1}{\sinh(\alpha)} > 0 \tag{7.133}$$

$$J_V(1)\, A = -RQ\beta\frac{\cosh(\alpha) - 1}{\sinh(\alpha)} < 0. \tag{7.134}$$

The back-filtration is an unwanted phenomenon, because it decreases the effectiveness of the removal of solutes from blood and may contribute to the transport of some toxic solutes from dialysis fluid to blood. To estimate the minimal total ultrafiltration, $Q_{U\,\min}$, that prevents the occurrence of back-filtration one needs to solve equation $J_V(1)\, A = 0$ for Q_U. As a result

$$Q_{U\,\min} = \frac{RQ\left(\cosh(\alpha) - 1\right)}{R_B + R_D\cosh(\alpha)}. \tag{7.135}$$

Using the solution of the equations for the ultrafiltration of pure water (or a solvent and solute with $\sigma = 0$), we may now discuss also the problem of ultrafiltration driven by both Starling forces, and hydrostatic and osmotic pressures. Equation (7.125), in this general case, takes the form

$$\frac{d^2\left(P_B - P_D\right)}{dx^2} = L_p A\left(R_B + R_D\right)\left(\left(P_B - P_D\right) - \sigma\left(\Pi_B - \Pi_D\right)\right). \tag{7.136}$$

To obtain some information about the contribution of osmotic pressure to the general solution (which requires the equations for solute transport to be solved), we assume that the difference of osmotic pressure may be approximately described by a linear function

$$\Delta\Pi\left(x\right) = \left(\Pi_B - \Pi_D\right)\left(x\right) = \Delta\Pi_i + D\Pi x \tag{7.137}$$

where $\Delta\Pi_i = \Delta\Pi\left(0\right)$, $D\Pi = \Delta\Pi_o - \Delta\Pi_i$, and $\Delta\Pi_o = \Delta\Pi\left(1\right)$; the coefficients in this equation may be expressed by the osmotic pressures measured at the inlets and outlets of the channels.

The solution of equations (7.136) – (7.137) is

$$\begin{aligned}\left(P_B - P_D\right)\left(x\right) &= \left(P_B - P_D\right)^0\left(x\right) + \sigma\Delta\Pi\left(x\right)\\ &= ae^{\alpha x} + be^{-\alpha x} + \sigma\Delta\Pi\left(x\right)\end{aligned} \tag{7.138}$$

where $\left(P_B - P_D\right)^0\left(x\right)$ is the solution (7.126) of equation (7.125). The parameters a and b may be calculated in a similar way, using equation (7.128), applied here without any change, and equation (7.130) in the modified form

$$b - a = RQ + R_D Q_U + \sigma D\Pi. \tag{7.139}$$

Finally

$$\begin{aligned}J_V\left(x\right)A = &\left(Q_U\left(\alpha - R_D\beta\right) - \left(RQ + \sigma D\Pi\right)\beta\right)\frac{\cosh(\alpha x)}{\sinh(\alpha)}\\ &+ \left(Q_U R_D + RQ + \sigma D\Pi\right)\beta\frac{\cosh(\alpha(1-x))}{\sinh(\alpha)}\end{aligned}. \tag{7.140}$$

Let us analyze this new, approximate formula for $J_V\left(x\right)A$ in the case of $Q_U = 0$,

$$J_V\left(0\right)A = \left(RQ + \sigma D\Pi\right)\beta\frac{\cosh\left(\alpha\right) - 1}{\sinh\left(\alpha\right)} > 0 \tag{7.141}$$

$$J_V\left(1\right)A = -\left(RQ + \sigma D\Pi\right)\beta\frac{\cosh\left(\alpha\right) - 1}{\sinh\left(\alpha\right)} < 0. \tag{7.142}$$

Furthermore, the calculation of $Q_{U\,\min}$ yields

$$Q_{U\,\min} = \frac{\left(RQ + \sigma D\Pi\right)\left(\cosh\left(\alpha\right) - 1\right)}{R_B + R_D\cosh\left(\alpha\right)}. \tag{7.143}$$

The sign of $D\Pi$ may depend on the transport parameters of the solute and the conditions of dialysis (such as flow rates). In the important case of hemodialysis and the oncotic pressure of plasma one may derive more precise conclusions. The membrane in hemodialyzer is not permeable for proteins and therefore $\sigma = 1$. Moreover, there are no proteins in the dialysis fluid and $P_D\left(x\right) \equiv 0$. Furthermore, the mass balance for proteins in the blood channel yields $C_B\left(1\right) =$

$C_B(0)\,Q_{Bi}/(Q_{Bi}-Q_U)$. Assuming that the change in oncotic pressure along the blood channel is approximately proportional to the change in protein concentrations, one can derive the formula for $D\Pi = \Pi_{Bi}Q_U/(Q_{Bi}-Q_U)$. Thus, for oncotic pressure $D\Pi > 0$, and therefore the oncotic pressure exaggerates the problem of back-filtration and increases $Q_{U\,\min}$. However, because ultrafiltration / back-filtration rate during hemodialysis is much lower than the blood flow rate, the effect of the change in the oncotic pressure is low. It is worth noting that the oncotic pressure increases the hydrostatic pressure difference, necessary for producing the fixed rate of ultrafiltration (compared to the filtration of pure water). However, interestingly, again within the limits of our approximation, only the change in the oncotic pressure modifies the ultrafiltration profile within the dialyzer.

The parameter RQ is positive and therefore the phenomenon of back filtration for low Q_U is unavoidable in standard counter-current dialyzers. The situation is, however, different for the co-current dialyzer.

Co-current hemodialyzers. The equation for fluid transport in the co-current hemodialyzer differs from those for counter-current dialyzers only by the signs of some derivatives

$$\frac{dP_B}{dx} = -R_B Q_B \tag{7.144}$$

$$\frac{dP_D}{dx} = -R_D Q_D \tag{7.145}$$

$$\frac{dQ_B}{dx} = -J_V A \tag{7.146}$$

$$\frac{dQ_D}{dx} = +J_V A. \tag{7.147}$$

Therefore, equation (7.125) for $(P_B - P_D)(x)$ in the counter-current flow system is exactly the same for the co-current flow system. The solution of this equation for $\sigma = 0$ has also the same general form and one can proceed here in the same way, except for the condition (7.129) that is different for the co-current system; the new equation is

$$\frac{d(P_B - P_D)}{dx} = -(R_B Q_B - R_D Q_D) \tag{7.148}$$

and

$$b - a = RQ^{co} \tag{7.149}$$

where the parameter RQ^{co} is defined as

$$RQ^{co} = R_{Bi}Q_{Bi} - R_{Di}Q_{Di}. \tag{7.150}$$

Finally,

$$J_V(x)\,A = (Q_U\alpha - RQ^{co}\beta)\,\frac{\cosh(\alpha x)}{\sinh(\alpha)} + RQ^{co}\beta\frac{\cosh(\alpha(1-x))}{\sinh(\alpha)}. \tag{7.151}$$

The distribution of ultrafiltration flux $J_V(0)A$ for the zero total ultrafiltration $Q_U = 0$ is given by

$$J_V(x)A = RQ^{co}\beta\left(\frac{\cosh(\alpha(1-x))}{\sinh(\alpha)} - \frac{\cosh(\alpha x)}{\sinh(\alpha)}\right) \tag{7.152}$$

and may be zero for $RQ^{co} = 0$, or it may be positive or negative at any point x depending on the sign of RQ^{co}. This sign actually describes the difference of slopes of hydrostatic pressures at the entrance to the dialyzer, equation (7.148).

The general theory of the co-current system with the hydrostatic and osmotic pressures can be solved using the same linear approximation for the change in osmotic pressure gradient as for the counter-current system, and the solution reads as

$$\begin{aligned} J_V(x)A = {} & (Q_U\alpha - (RQ^{co} + \sigma D\Pi)\beta)\,\tfrac{\cosh(\alpha x)}{\sinh(\alpha)} \\ & + (RQ^{co} + \sigma D\Pi)\,\beta\tfrac{\cosh(\alpha(1-x))}{\sinh(\alpha)} \end{aligned} \tag{7.153}$$

see equation (7.140).

7.8 Summary

1. The equations of the one-dimensional theory of the hemodialyzer depend on one geometrical parameter of the hemodialyzer only, the total surface area of the membrane, A, but not on the length, diameter and number of the hollow fibers. This feature of the theory is the consequence of the assumptions applied, especially that the non-homogeneous distribution of solute concentration in the cross-section of the channels is neglected.
2. The solution of the set of ordinary differential equations of the one-dimensional theory can be reduced to the calculation of the integrals, but they cannot be, in general, presented in closed formulas. The exceptions are pure diffusive transport (no ultrafiltration) and combined diffusive-convective transport without solute reflection ($\sigma = 0$) and constant ultrafiltration flux.
3. The (diffusive) removal of solutes is more efficient if the dialyzer is applied in the counter-current flow system than in the co-current flow system.
4. The one-dimensional theory of the hemofilter can be presented by regular integrals in spite of the singularity in the solute concentration at the closed end of the filtrate channel for some operating conditions.
5. The dialysance, clearance, transmittance and sieving coefficients are functions of the transport parameters of the membrane, its surface area, flow rates of blood and dialysis fluid, and ultrafiltration rate. Closed formulas and closed approximations can be obtained for special cases.
6. The distribution of ultrafiltrate flux along the dialyzer can be described in closed formulas if it is driven only by the transmembrane difference in hydrostatic pressure, and some approximated solution can be provided if the ultrafiltration is driven by the combination of hydrostatic and osmotic pressure difference.

7. For zero or sufficiently low total ultrafiltration, the back-filtration is always present in the counter-current system, whereas it can be absent for specific flow rates in the co-current system.

Summary

Theoretical analysis of mathematical models can provide important clues for the understanding of the relationships between parameters of the models and the parameters that are assessed and applied in clinical and experimental studies, as well as in prescriptions of medical procedures. The examples of such relationships are described in our book mostly for dialysis, and include clearance and dialysance of hemodialyzer and hemofilter, and the transport parameters, estimated in clinical studies for patients on peritoneal dialysis. In both cases, the mathematical models of the transport processes that take into account the geometry of the transport system, yield the descriptions of practical parameters by the parameters that describe model geometry, transport characteristics of its components, and conditions of treatment.

Physiological phenomena are in most cases intrinsically complex, multifactorial and nonlinear. The mathematical description that aims at theoretical analysis needs to be simplified so as to be analytically tractable and still preserve the most important features of the described structures and processes. Sometimes, as in the case of the one-dimensional theory of hemodialyzers (Chapter 7), the simplifications yield the final description, which is accurate enough for practical applications (Waniewski et al., 1991, Waniewski et al., 1993, 1994, Galach et al., 2003). Other models, like the distributed description of peritoneal transport (Chapter 4 – 6), should be, after the initial theoretical analysis of the simplified versions, extended, in order to take into account many nonlinear phenomena, such as vasodilatation, elastic and expandable interstitium, lymphatic absorption from the tissue depending on the interstitial fluid hydrostatic pressure, etc. In this general form the models must be analyzed through numerical simulations (Flessner et al., 1984, Flessner et al., 1985, Baxter, Jain, 1989, 1990, Seames et al., 1990, Flessner et al., 1992, Flessner et al., 1997, Waniewski et al., 1999, Stachowska-Pietka et al., 2006, Waniewski et al., 2009, Stachowska-Pietka, Waniewski, 2011, Stachowska-Pietka et al., 2012). Nevertheless, the theoretical relationships between the model parameters and the practical parameters that can be assessed in clinical and experimental studies, are frequently helpful because of the non-intuitive nature of these relationships. They can be adequately explained in the general and qualitative terms with good agreement regarding the measured characteristics. Furthermore, theory can propose an explanation for some puzzling results and provide the precise methods for the description of the observed phenomena, like, for example, the effective peritoneal blood flow (Chapter 4).

The reading of this book may be supplemented by the analysis of the experimental and clinical studies of the phenomena that are described here from a theoretical point of view. Numerous such results and indications for further reading may be found in the articles referred to in the respective chapters. To quote some of them: 1) for the studies on peritoneal dialysis: (Dedrick et al., 1982, Seames et al., 1990, Waniewski et al., 1999, Stachowska-Pietka et al., 2006, Waniewski, 2008, Waniewski et al., 2009, Stachowska-Pietka et al., 2012, Waniewski, 2013), 2) for the studies on tissue transport and the transport in solid tumor: (Dedrick et al., 1982, Baxter, Jain, 1989, 1990, Flessner, 1996, Flessner et al., 2003, Flessner, 2005, Flessner et al., 2006, Waniewski, 2006, Flessner, 2009, Galach, Waniewski, 2012, Waniewski, 2013).

The spatially distributed model of peritoneal transport is the most advanced approach to the quantitative description of transport processes during peritoneal dialysis. However, a couple of other models that are based on the assumption of the "black box" barrier between blood and the peritoneal cavity were also formulated and are widely applied in clinical and experimental studies. Several clinical tests were proposed to assess the transport characteristics of the "peritoneal transport barrier". For the reviews of different tests and alternative models of peritoneal transport see (Krediet, 2000, Krediet et al., 2000, Heimbürger, 2005, Waniewski, 2006, La Milia, 2010, Waniewski, 2013).

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