Report on a problem studied at the UK Mathematics-in-Medicine Study Group Nottingham 2000
< http://www.maths-in-medicine.org/uk/2000/profiled-haemodialysis/ >

Mathematical modelling of profiled haemodialysis

Steve Baigent, UCL
Matt Williams, A&E SHO, UHL (Lewisham)
Alison Marks, Bradford
Mark Penney, Glasgow
Jonathan Wattis, Peter Howell, John King, Nottingham
Jon Chapman, Oxford.

February 2001

1 Background information

In healthy individuals, the removal of fluid and toxic catabolic waste products is a continuous 24 hour process. When the kidneys fail, fluid is retained and the accumulation of some important ions, such as those of potassium and hydrogen, may become life threatening. For many patients with severe loss of kidney function dialysis is the only means of preventing excessive fluid gain and the accumulation of toxic chemicals in the blood (see, for example, [3] for an introduction to treatment of Chronic Renal Failure). Haemodialysis is the transport of water, ions and middle molecules (up to the size of albumin) across the artificial membrane separating the patient plasma volume and the dialysis machine fluid (the dialysate) using both passive diffusion and pressure-driven ultrafiltration. In contrast to healthy kidney function, haemodialysis is an intermittent treatment: patients typically dialyse for 4-6 hours, 3 times a week. During each session, 3-4 litres of fluid is removed along with catabolic end-products, and osmotically active solutes.

The short duration and intermittent nature of haemodialysis means that most patients experience large and acute swings in body fluid volume, ion and solute composition not normally encountered in health. These changes can result in significant intra- and interdialytic morbidity. Indeed, intradialytic morbidity is recorded in around 30% of all haemodialysis treatments. In a significant number of patients, the underlying problem is the rapid removal of water and osmotically active sodium chloride which can lead to severe hypotension or the overhydration and swelling of brain cells. While this is an age-wide problem, it is particularly prevalent in the growing population of elderly haemodialysis patients, many of whom also have impaired cardiac function.

One practice aimed at reducing the incidence of volume-related interdialytic morbidity is *profiled* haemodialysis in which the rate of water removal and/or the dialysis machine sodium concentration are varied with time according to a predetermined profile designed to prevent the wide fluctuations in

plasma osmolarity which cause these volume swings. While some success of profiling has been reported, it is far from standard practice. Machine profiles are determined largely on a trial and error basis for each patient, with the possibility that a new profile may be necessary if patient parameters vary, such as when a patient errs from their strict diet.

2 Problem definition

The problem posed to the study group was to:

> *Build a mathematical model of a typical haemodialysis session that can be used to calculate the result of any pre-determined set of machine profiles for a patient of known 'dry' weight and pre-dialysis blood chemistry. The group was also asked to keep in mind that the longer term aim is to use the model to determine the optimal profiles for a given set of pre-dialysis patient parameters and post-dialysis targets.*

3 Initial discussions

The starting point for discussion was a brief review of existing compartmental models for hameodialysis, including some recent models for profiled hameodialysis [8, 1]. In such models, the patient plus dialysis machine is modelled as a series of membrane-separated fluid-filled compartments. The final compartment is typically a reservoir of dialysate fluid whose composition is unchanged by the removal of water and waste products from the patient, but whose composition can be externally controlled during profiled dialysis. This compartment is separated from the next inner compartment by a membrane whose properties match those of a hollow-fibre dialyser membrane. The remaining compartments represent the various body fluid volumes of the patient[1]. In some models, such as those that focus on urea kinetics, the volumes of the various body compartments are fixed. Such models are inappropriate for studying changes in compartment osmolarity and so we focused on *variable volume* compartmental models.

The number of body fluid compartments varies from model to model. In [8, 1], the authors use 2 variable-volume fluid compartments, namely an intracellular compartment (IC) and an extracellular compartment (EC). IC constitutes all the fluid inside the patient's cells (i.e. all the cytoplasmic fluid) whereas EC is all the fluid outside the cells and lumps together the plasma and interstitial volumes. The IC and EC volumes are separated by a membrane whose permeability properties match those of a typical cell, i.e. effectively impermeable to sodium, highly permeable to water. This results in a 2-compartment model consisting of the IC separated from the EC by a patient membrane, and the EC separated from the dialysis fluid by an artificial membrane.

The general form for the haemodialysis model is a set of differential equations for the flux of solutes and water between the various fluid compartments. Water is driven from compartments of high osmo-

[1]The accepted convention in the literature is that the number of compartments in a given haemodialysis model is the number of fluid compartments describing the patient, so that the dialysate is not included in the count. We will adopt this convention here.

larity to compartments of lower osmolarity. The flux of a given solute is the sum of passive diffusive and ultrafiltrative components.

Most haemodialysis models focus on a limited number of solutes. Urea kinetics models use urea concentration as an indicator for the removal of nitrogenous middle molecules, but ignore the osmotic effect of ions such as sodium. After discussion it was decided to follow [8, 1] and focus on sodium transport, since sodium with its counterions account for 90% of blood osmolarity, and hence is likely to be the key ion responsible for osmolarity-related interdialytic morbidity. We therefore decided that sodium transport should form the core of the model, and since the transport of osmotically active sodium between compartments induces obligatory water shifts, the model also should couple sodium transport to compartmental volume changes.

During these early discussions, a number of interesting points were raised which helped to shape the model.

P1 *Modelling of intracellular sodium.*
Existing models (e.g. [8, 1]) assume that a cell responds to changes in the extracellular environment in order to maintain its IC sodium mass. The validity of this assumption was questioned. One alternative suggested (based upon Nernst equilbrium arguments) was that it might be IC sodium concentration rather than mass which is maintained constant.

P2 *Modelling of the hollow fibre dialyser.*
The hollow fibre dialyser has a complex geometry of hollow blood-carrying fibres surrounded by dialysate-carrying space. In some systems the blood and dialysate fluid are in counter-flow. What is the concentration profile in the dialyser? How is the concentration profile in the dialyser accounted for in the model?

P3 *Is refilling of the plasma volume from the interstitial space the true rate-limiting process?*
This turned out to be a crucial point. A typical cell membrane is highly permeable to water, so that the IC compartment is always in quasi-osmotic balance with the adjoining compartment. In many existing models, the adjoining compartment is the EC compartment that lumps the interstitial space and the blood plasma. In reality, to pass from the IC space to the blood plasma, water has to 'filter' through the interstitial space.

P4 *What are the other osmotically active solutes in each compartment that help to balance the effect of sodium?*

P5 *How do we include the osmotic pressure due to large proteins in the interstitial space and the plasma volume?*

4 A 3-compartment variable-volume model

4.1 Group response to points raised during initial discussions

R1 *The modelling of intracellular sodium.*

Although the cell membrane is highly impermeable to sodium, there is a small leakage of sodium into the cells. For cell volume regulation, sodium pumps in the cell membranes pump sodium outwards and potassium inwards against their concentration gradients [5]. The efflux of sodium increases as the intracellular concentration of sodium increases, and this feedback mechanism enables the cell to match the passive influx of sodium with its active efflux. This balance of sodium influx with sodium efflux means that to a good approximation the sodium mass remains constant.

R2 *Modelling of the hollow fibre dialyser.*

The classic modelling of haemodialysis by Sargent and Gotch [7] uses the concept of *dialysance* D, which is defined for a dialyser by

$$D = \frac{\text{change in solute content of incoming blood}}{\text{concentration driving force}}$$

This is a constant for a given blood and dialysate flow rate. The flux of solute X out of the plasma compartment B into the dialysate D is (e.g. [7]):

$$J = D\left(1 - \frac{U(t)}{Q_B}\right)([X_B] - [X_D]) + U(t)[X_B]. \tag{1}$$

Since we are only interested in the change in solute content as the blood passes through the dialyser, we do not need to know the concentration profile. However, it was noted that the complex structure of the hollow fibre dialyser makes the efficiency of the dialyser for various counter-flow dialysate and blood flow rates an interesting modelling problem worth further study.

R3 *Is refilling of the plasma volume from the interstitial space the true rate-limiting process?*

A brief investigation of the available literature [6] suggested (at a rough estimate) that the half-time for refilling of the plasma volume from the interstitial space is of the order of 30 minutes. This is to be compared with a half-time of 3 seconds for osmotic equilibriate across a typical cell membrane [5]. Even allowing for significant error in the estimate of the plasma refilling rate, it is clear that the refilling of the plasma volume is the rate-limiting step in the dialysis process. Consequently we decided to split the EC compartment into the plasma volume and the interstitial volume, thus leading us to a 3-compartment model.

R4 *What are the other osmotically active solutes in each compartment that help to balance the effect of sodium?*

The other solutes include, for example, potassium, urea, magnesium, etc. To include these, we introduced a class of 'other solutes' of generic name X and concentration [X]. The relative osmolytic effect of each X was incorporated by introducing a reflection coefficient r_X for each solute

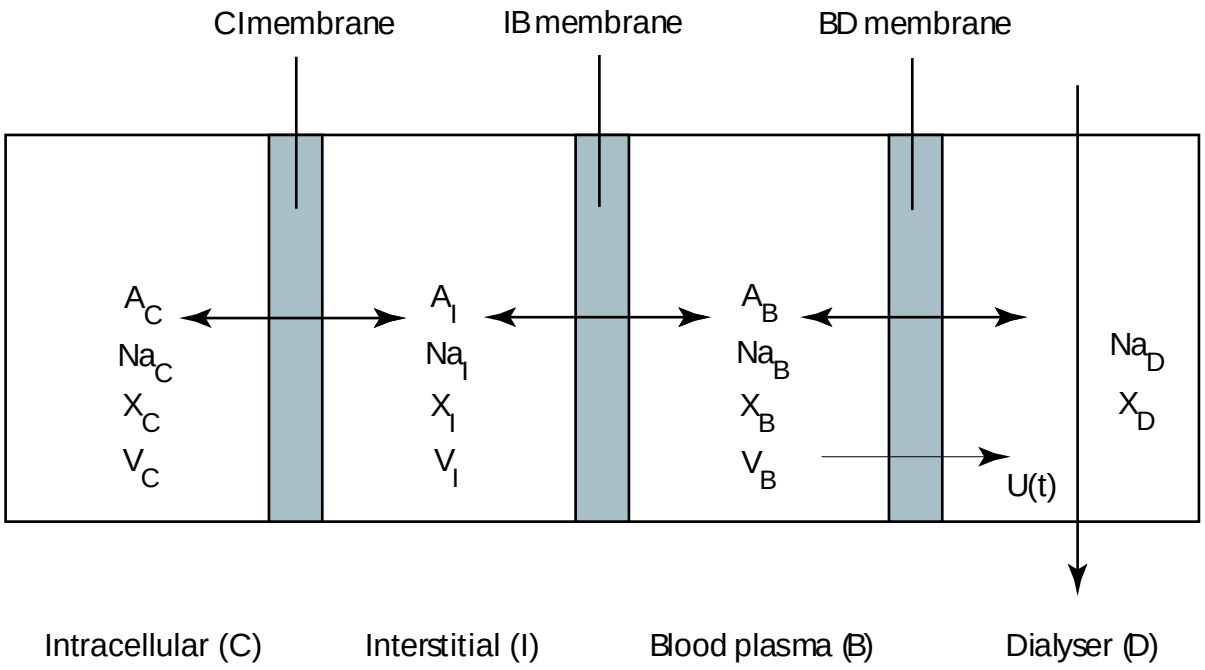

Figure 1: A 3-compartment model

X, where $0 \leq r_X \leq 1$. A completely impermeable solute X has $r_X = 1$, and a solute X' as permeable as water has $r_{X'} = 0$. The van't Hoff formula gives the water flux J across a membrane of hydraulic conductivity L in terms of the transmembrane pressure difference Δp and omsotic pressure difference $\Delta\pi$ (e.g. [5]):

$$\begin{aligned} J &= L(\Delta p - \Delta\pi) \\ &= L(\Delta p - RT \sum_X r_X \Delta[X]) \end{aligned} \tag{2}$$

where R is the universal gas constant and T is the temperature.

R5 *How do we include the osmotic pressure due to large proteins in the interstitial space and the plasma volume?*

Typically dialysers are impermable to proteins larger in size than albumin. Thus there will be a permanent population of proteins in the blood plasma. There will also be a population of permanent proteins trapped in the interstitial space.

To model refilling of the plasma volume from the interstitial space we started with a 3-compartment model consisting of intracellular volume, interstitial space and blood plasma volume (see Figure 1). Each patient compartment is separated by a living tissue membrane, whose surface area and permeability can be estimated from data in the literature. The properties of the dialyser artificial membrane are documented by the manufacturer.

Symbol	Description	Symbol	Description
Na_C	IC sodium molar mass	$V(0)$	Total body fluid volume at start of dialysis
Na_I	Interstitial sodium molar mass	V_C	IC volume
Na_B	Plasma sodium molar mass	V_I	Interstitial volume
$[Na_C]$	IC sodium concentration	V_B	Blood plasma volume
$[Na_I]$	Interstitial sodium concentration	d_C^{Na}	permeability of cell membrane to sodium
$[Na_B]$	Blood plasma sodium concentration	d_C^X	permeability of cell membrane to solute X
$[Na_D]$	Dialysate sodium concentration	d_I^{Na}	permeability of interstitial space to sodium
X_α	Molar mass of X in compartment α	d_I^X	permeability of interstitial space to X
$[X_\alpha]$	Concentration of X in compartment α	$D_{Na}*$	Dialysance of dialyser membrane to sodium
A_C	Impermeant cytoplasmic proteins	D_X	Dialysance of dialyser membrane to X
A_I	Total interstitial proteins	L_C	hydraulic conductivity of cell membrane
A_B	Total plasma proteins	L_I	hydraulic conductivity of the interstitial space
$U(t)$	Ultrafiltration rate	Q_B	Blood flow rate
r_X	Reflection coeff. of interstitial space for X		

Table 1: Glossary of symbols used in the 3-compartment model for profiled haemodialysis

4.2 Model equations

See Table 1 for a glossary of the mathematical symbols used.

1. **Intracellular compartment (C)**
   We assumed that the transmembrane transport of the 'other' class of solutes is entirely passive, thus leading to equations (4). Equation (5) is a straight application of (2), and incorporates the intracellular impermeable proteins of molar concentration $[A_C]$.

$$Na_C = Na_C^0, \text{ a constant} \tag{3}$$

$$\frac{dX_C}{dt} = d_C^X \left([X_I] - [X_C]\right), \quad X = \text{K, Urea, Mg, } \ldots \tag{4}$$

$$\frac{dV_C}{dt} = L_C \left\{ \left([A_C] + [Na_C] + \sum_X r_X [X_C] \right) - \left([A_I] + [Na_I] + \sum_X r_X [X_I] \right) \right\} \tag{5}$$

2. **Interstitial compartment (I)**
   Equation (6) says that the molar mass of impermeable proteins residing within the interstitial space remains constant. Equations (7) and (8) state that solute transport across the interstial space is solely due to passive diffusion. Equation (9) is an application of equation (2) to the interstitial space separating the intracellular and blood plasma compartments.

$$A_I* = A_I^0, \text{ a constant} \tag{6}$$

$$\frac{dNa_I}{dt} = d_I^{Na}\left([Na_B] - [Na_I]\right) \quad (7)$$

$$\frac{dX_I}{dt} = d_I^{X}\left([X_B] - [X_I]\right) - \frac{dX_C}{dt}, \;\; X = \text{K, Urea, Mg, } \ldots \quad (8)$$

$$\frac{dV_I}{dt}* = L_I\left\{\left([Na_I] + \sum_X r_X * [X_I] + \frac{A_I*}{V_I}\right) - \left([Na_B] + \sum_X r_X * [X_B] + \frac{A_B*}{V_B}*\right)\right\} \quad (9)$$

3. **Blood plasma compartment (B)**
   Equation (10) says that the molar mass of proteins larger in size than albumin (i.e. those that do not permeate the dialyser membrane) in the blood plasma remains constant. Equations (11) and (12) are an application of (1) to the blood plasma compartment. Finally, (13) expresses overall water conservation.

$$A_B* = A_B^0, \text{ a constant} \quad (10)$$

$$\frac{dNa_B}{dt} = -\frac{dNa_I}{dt} - D_{Na} * * \left(1 - \frac{U(t)}{Q_B}\right)\left([Na_B] - [Na_D]\right) - U(t)[Na_B] * \quad (11)$$

$$\frac{dX_B}{dt} = -\frac{dX_I}{dt} - D_X * \left(1 - \frac{U(t)}{Q_B}\right)\left([X_B] - [X_D]\right) - U(t)[X_B], \;\; X = \text{K, Urea, Mg, } \ldots \quad (12)$$

$$\frac{dV_B}{dt} = -\frac{dV_C}{dt} - \frac{dV_I}{dt} - U(t) \quad (13)$$

In line with [1], we note that $\alpha = 1 - U(t)/Q_B \approx 0.95$ and so we may set $\alpha = 1.0$ as a first approximation. Since we wish to elucidate the various time scales of the dialysis process, we next non-dimensionalise the model.

5 Model non-dimensionalisation

We let T be the typical dialysis session duration, N be the average plasma sodium concentration in millimoles in a healthy individual and $V^0 = 2$ litres, the typical quantity of water to be removed during a dialysis session. Define dimensionless variables:

$$Na_C^* = \frac{Na_C^0}{N}, \; [X_\alpha]^* = \frac{[X_\alpha]}{N}, [A_C^*] = \frac{[A_C]}{N}, \; [A_I^*] = \frac{[A_I]}{N}, \; [A_B^*] = \frac{[A_B]}{N}, \; V_\alpha^* * = \frac{V_\alpha}{V^0{}_*}, \; X_\alpha^* = [X_\alpha]^* V^*, \; t^* = \frac{t}{T}*$$

and dimensionless parameters

$$(d_C^{Na})^* = \frac{T d_C^{Na}}{V^0}, \; (d_I^{Na})^* = \frac{T d_I^{Na}}{V^0}, \; (d_I^X)^* = \frac{T d_I^X}{V^0}, \; L_C^* = \frac{TNL_C}{V^0}, \; L_I^* = \frac{TNL_I}{V^0}$$

$$D_{Na}^* = \frac{TD_{Na}}{V^0}, \; D_X^* = \frac{TD_X}{V^0}, \; U^*(t^*) = \frac{TU(Tt^*)}{V^0}*$$

to obtain:

1. **Intracellular compartment**

$$Na_C^* * = Na_C^0/N, \text{ a constant} \quad (14)$$

$$\frac{dX_C^**}{dt^**} = (d_C^{Na})^* \left([X_I]^* * - [X_C]^**\right), \quad X = \text{K, Urea, Mg,} \ldots \tag{15}$$

$$\frac{dV_C^**}{dt^**} = L_C^** \left\{ \left([A_C]^* * + [Na_C]^* * + \sum_X r_X [X_C]^** \right) \right. \tag{16}$$

$$\left. - \left([A_I]^* + * * [Na_I]^* * + \sum_X r_X [X_I]^** \right) \right\} \tag{17}$$

2. **Interstitial compartment**

$$A_I^** = A_I^0/N, \text{ a constant} \tag{18}$$

$$\frac{dNa_I^**}{dt^**} = (d_I^{Na})^* * \left([Na_B]^* * - [Na_I]^**\right) \tag{19}$$

$$\frac{dX_I^**}{dt^**} = (d_I^X)^* * \left([X_B]^* * - [X_I]^**\right) - \frac{dX_C^**}{dt^**}, \quad X = \text{K, Urea, Mg,} \ldots \tag{20}$$

$$\frac{dV_I^**}{dt^**}* = L_I^** \left\{ \left([Na_I]^* * + \sum_X r_X * [X_I]^* * + \frac{A_I^* *}{V^0 * V_I^**} \right) \right. \tag{21}$$

$$\left. - \left([Na_B]^* * + \sum_X r_X * [X_B]^* * + \frac{A_B^* *}{V^0 * V_B^**}* \right) \right\} \tag{22}$$

3. **Blood plasma compartment**

$$A_B^* = A_B^0/N, \text{ a constant} \tag{23}$$

$$\frac{dNa_B^**}{dt^**} = -\frac{dNa_I^**}{dt^**} - D_{Na}^* * * \left([Na_B]^* * - [Na_D]^**\right) - U^*(t^**)[Na_B]^* * \tag{24}$$

$$\frac{dX_B^**}{dt^**} = -\frac{dX_I^**}{dt^**} - D_X^* *([X_B]^* * - [X_D]^**) - U^*(t^**)[X_B]^**, \quad X = \text{K, Urea, Mg,} \ldots \tag{25}$$

$$\frac{dV_B^**}{dt^**} = -\frac{dV_C^**}{dt^**} - \frac{dV_I^**}{dt^**} - U^*(t^*) \tag{26}$$

6 Reductions using timescale differences

As mentioned in item R3 above, the osmotic equilibriation across the cell membranes is several magnitudes faster than the refilling of the blood plasma volume from the interstitial space. This suggests, as a first approximation, that we can reduce the model by setting the righthand side of equation (17) to be zero (i.e. assume osmotic quasi-equilibrium across the cell membranes).

Since we did not have access to a complete set of parameter values, to make further progress we assumed that the refilling timescale is sufficently dominant that the intracellular compartment C and interstitial compartment are in quasi-equilibrium. From (14) to (26) we have, for quasi-equilibrium,

$$[X_I]^* = [X_C]^*, \quad X = \text{K, Urea, Mg} \ldots \tag{27}$$

$$[Na_I]^* = [Na_B]^* \tag{28}$$

$$[X_I]^* * \quad = \quad [X_B]^* * \tag{29}$$

$$[A_C]^* + [Na_C]^* \quad = \quad [A_I]^* + [Na_I]^* \tag{30}$$

together with the slower timescale equations derived using these relations. Of these remaining equations, the flux of X_B, given by*

$$\frac{dX_B^**}{dt^**} = -(d_I^X)^* * ([X_B]^* * - [X_I]^**) - D_X^*([X_B]^* * - [X_D]^**) - U^*(t^**)**[X_B]^**, \quad X = \text{K, Urea, Mg, } \ldots \tag{31}$$

is essentially decoupled, since once V_B^** is known, X_B^** and $[X_B]^*$ follow by time integration of (31). This leaves

$$\frac{dV_I^**}{dt^**}* \quad = \quad L_I^** * \left\{ \left(\frac{A_I^** **}{V^0 * V_I^** *} \right) - \left(\frac{A_B^** *}{V^0 * V_B^**} * \right) \right\} \tag{32}$$

$$\frac{dNa_B^**}{dt^**} \quad = \quad -(d_I^{Na})^* * \left([Na_B]^* + [A_I]^* - (A_C^* + Na_C^*) \frac{V_I^*}{V_C^*} \right) \tag{33}$$

$$-D_{Na}^** * * ([Na_B]^* * - [Na_D]^**) - U^*(t^**) * *[Na_B]^* * * \tag{34}$$

$$\frac{dV_B^**}{dt^**} \quad = \quad -\frac{dV_I^**}{dt^**} - U^*(t^*) \tag{35}$$

Here in equation (34) we have used equation (30) to eliminate $[Na_I]^*$, and we note that on this timescale V_C^* is constant, thus leading to a well-posed system of 3 equations for the 3 unknowns $[Na_B]^*$, V_I^* and V_B^*. Given initial values $[Na_B]^*(0)*$, $V_I^*(0)*$ and $V_B^*(0)$, equations (32), (34) and (35) can be solved for predefined profiles $[Na_D]^*$ and U^*.

7 Conclusions and further work

The identifcation of plasma refilling from the interstitial space as the rate-limiting process is an important improvement upon other recent models for profiled haemodialysis (e.g. [8, 1]). There are some indications that longer dialysis sessions with low filtration rates are better tolerated than short sessions with high ultrafiltration rates. The slowness of the refilling process offers a possible explanation for this observation. Hopefully, the model and its future refinements will enable us to determine how optimal profiling can be achieved in the presence of the refilling constraint.

The model developed during the study group now needs to be fitted with parameter values and compared with actual data from profiled haemodialysis sessions. It will be necessary to liaise with haemodialysis practioners to identify typical values for each of the model parameters. We anticipate that this will lead correctly and rigorously to the reduced model that we proposed here. The parameter values can then be built into a computer model for both the full and reduced models, so that the accuracy of the approximation can be tested, and model simulations compared with actual profiled haemodialysis sessions. It should also be possible to use the reduced model to explicitly identify limits on sodium dialysate and ultrafiltration profiles within which there is minimal risk of intradialytic morbidity. Finally, a longer-term aim is to design a control for the profiling which selects the optimal profiles. Such a control will need to select a profile that leads to successful control of plasma volume, while maintaining the blood concentrations of important electrolytes within safe ranges.

References

[1] S. Baigent, R. Unwin & C. C. Yeng (2000) Modelling of profiled haemodialysis: a simplified approach. *J. Theor. Med.* (In press).

[2] A. K. Cheung. Stages of future technological developments in haemodialysis. *Nephrol. Dial. Transplant.*, 11 [Suppl. 8]:52–58, 1996.

[3] M. G. Cogan and P. Schoenfield, (eds). *Introduction to dialysis*. Churchill Livingstone, New York, 1991.

[4] M. Coli, M. Ursino, V. Dalmastri, F. Volpe, G. La Manna, G. Avanzaloni, S. Stefoni and V. Bonomini. A simple mathematical model applied to selection of the sodium profile during profiled haemodialysis. *Nephrol. Dial. Transplant.* **13**: 39-41, 1998.

[5] K. R. Hallows and P. A. Knauf. *Principles of Cell Volume Regulation*, CRC Press, 1994

[6] H. A. Koomans, A. B. Geers & E. J. Dourhout Mees. Plasma volume recovery after ultrafiltration in patients with chronic renal failure. *Kid. Int.*, **26**: 848-854, 1984.

[7] J. A. Sargent and F. A. Gotch. Mathematical modelling of dialysis therapy. *Kidney Int.* **18**: [Suppl 10]: 2-10, 1980.

[8] M. Ursino, L. Coli, M. Grilli Ciciloni, V. Dalmastri, A. Guidicissi, P. Masotti, G. Avanzolini, S. Stefoni, and V. Bonomini. A single mathematical model of intradialytic sodium kinetics: '*in vivo*' validation during hemodialysis with constant or variable sodium. *Int. J. Artif. Organs*, 19, (6):393–403, 1996.