A simple mathematical model applied to selection of the sodium profile during profiled haemodialysis

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Abstract

Background. Among dialysis patients in the last 10 years the incidence of intradialytic dysequilibrium syndrome and symptomatic hypotension has increased significantly. Profiled haemodialysis (PHD), a new dialysis technique based on intradialytic modulation of the dialysate sodium concentration according to pre-elaborated individual profiles, has been set up to reduce intradialytic imbalances and the incidence of dysequilibrium syndrome and symptomatic hypotension.

The present paper illustrates a new mathematical model for solute kinetics, single-compartment for sodium and two-compartment for urea, aimed at improving the use of PHD. The model allows the sodium profile to be elaborated a priori, before each dialysis session, according to the patient’s clinical needs and respecting the individual sodium mass removal and weight gain.

Method. The mathematical model was first derived and then applied to determining a rational dialysate sodium profile. A procedure which allows the method to be tuned to individual clinical needs on the basis of routine measurements performed before each session is also presented. The proposed method was validated in vivo during seven dialysis sessions, each performed on a different patient.

Results. The comparison between data predicted by the model and those obtained in vivo shows a good correspondence in particular concerning the time pattern of blood urea and sodium. The comparison between the model prediction and in vivo determined sodium and urea plasma curves showed standard deviations (2.25 mEq/l for sodium and 0.87 mmol/l for urea) only slightly higher than those attributable to laboratory measurement errors. Moreover, in vivo implementation of PHD by our model enables one to remove an amount of sodium mass comparable with the a priori quantity predicted by the model.

Key words: haemodialysis; profile elaboration; sodium; sodium balance; sodium kinetic model; urea kinetic model

Introduction

In the last 10 years the dialysis population has greatly changed in age, (40% of patients are older than 65 years), and clinical traits: in particular the incidence of patients with cardiovascular pathology has increased from 25 to 50% both in the USA and in Europe. This qualitative change in the dialysed population has caused a reduction in mean survival rate, an increase in cardiovascular morbidity and a reduction in clinical tolerance to extracorporeal sessions [1]. Consequently the main clinical intradialytical complications, dysequilibrium syndrome and symptomatic hypotension, are now on the increase and their incidence ranges between 5 and 15% for dysequilibrium syndrome and 20 and 35% for hypotension [2–5].

One of the pathophysiological reasons for these complications is the removal of toxins with too fast a reduction in extracellular osmolarity during the first half of the extracorporeal session [6–10]. The main consequences are a loss in fluid refilling from the extracellularly to the intravascular compartment and the fluid shift from extra- to intracellular which, combined with the effects of ultrafiltration, produces an overall reduction in circulating volume [11–14]. As a clinical consequence the reduction in circulating volume causes hypovolaemia with symptomatic hypotension while the intracellular fluid shift causes dysequilibrium syndrome.

The number of patients suffering from symptoms due to dysequilibrium during dialysis, including hypotensive episodes, remains significant, due in part to limited development of dialysis regimes designed to reduce osmotically induced fluid shifts.

Profiled haemodialysis (PHD) aims to reduce dialysis symptoms by varying the dialysate sodium concentration [15]. This is achieved by attenuating plasma
osmolarity losses in the first half of the session, when the osmolarity decrease is higher. To this end, the sodium removal rate is lowered through increasing its dialysate concentration, whilst taking into account the desired individual sodium balance to be reached at the end of the session.

The present work presents a rational new method for computing individual dialysate sodium profiles during PHD, according to the patient’s clinical needs and respecting the individual sodium mass removal and weight decrease [16–19]. We use a new mathematical model for solute kinetics, single-compartment for sodium and two-compartment for urea. The model enables the sodium dialysate profile to be worked out a priori, i.e. before each dialysis session, starting from knowledge of a few patient pre-dialysis individual parameters: timing of the session, body weight to decrease, urea blood concentration, pre-dialysis natremia, sodium mass to be removed. [20,21]

The paper is organized as follows. A simple mathematical model of fluid, sodium, and urea kinetics is first presented, and then applied to calculating of a rational sodium profile in the dialysate. In particular, a procedure is developed which allows the method to be tuned to the individual characteristics of each patient on the basis of routine measurements performed before each session. Finally, in order to validate the proposed method, in vivo data obtained during seven dialysis sessions, each performed on a different patient, are compared with those predicted a priori by the model, and the results thus obtained are critically discussed.

**Model description**

The model entails analysing the fluid balance between the intracellular and extracellular compartments, a single-compartment model for sodium kinetics, and a two-compartment model for urea kinetics. The different subsystems are connected according to the block diagram in Figure 1. A brief qualitative description of the model is presented below without entering into mathemactical details. All equations are reported in Appendix I. A more complete justification of the model biophysical bases and equations can be found in a previous related paper [22].

**Urea and sodium kinetics**

We assume that the urea flow rate from the intracellular to the extracellular pool is proportional to the difference between intracellular and extracellular concentrations, through a constant parameter representing the urea mass-transfer coefficient. By contrast, we assume that the amount of sodium exchanged at the cellular membrane is negligible due to the presence of active pumps [23]. Both sodium and urea are removed from the extracellular pool in the course of dialysis therapy. Solute flow through the dialyser includes both convective and diffusive transport, according to classic equations [24].

**Fluid balance**

The amount of water in the extracellular and intracellular pools (hence their volumes) depends on two factors. First, fluid is removed from the extracellular compartment by ultrafiltration. Second, a water shift occurs at the cellular membrane as a consequence of an osmotic pressure difference. We assume that the latter process takes place almost instantaneously, i.e., with a time constant negligible compared with the time constants of solute kinetics. This assumption is justified since the fluid shift across the cellular membrane is completed within a few seconds of any osmotic pressure change [7], whereas solute dynamics are characterized by time constants of several min. The osmotic pressure difference is determined by the values of sodium concentration in the extracellular pool, urea concentrations in the intracellular and extracellular pools, by the concentration of other cations (mainly K⁺) in the intracellular fluid, and by other less important solutes in both compartments. For the sake of simplicity, the overall mass of these substances (potassium and other solutes) is assumed to remain quite constant during dialysis.

Of course, urea does not contribute to the osmotic pressure difference in steady-state conditions, since it can freely diffuse through the membrane. Hence at equilibrium we have \( C_{u,i} = C_{u,e} \) (where \( C_{u,i} \) and \( C_{u,e} \) are the extra-and intracellular urea concentrations respectively). However, during haemodialysis, a small urea concentration gradient results at the cellular membrane, which transiently forces water into the intracellular pool.

In steady state conditions, sodium is in equilibrium with intracellular K⁺. During haemodialysis, excessive sodium removal may induce a significant drop in extracellular osmolarity, which may drive water into

![Block diagram describing the main mathematical relationships among solute masses and volumes used in the model.](image_url)
the intracellular compartment, worsening arterial hypotension and causing dysequilibrium syndrome.

By way of example, Figure 2 shows the changes in the intracellular and extracellular volumes simulated by the model during three different standard haemodialyses (i.e. performed at a constant dialysate sodium concentration, \( C_{Na,d}(t) \) using ‘medium’, ‘low’ or ‘high’ values of sodium in the dialysate. In the first simulation, sodium in the dialysate was maintained at the same concentration as in the extracellular pool (140 mEq/l). In this case, the fall in extracellular osmolarity can only be ascribed to urea removal, which causes a small increase in the intracellular volume during the first h. By contrast, in low-sodium dialysis (\( C_{Na,d}=130 \) mEq/l), a large fall in extracellular osmolarity takes place as a consequence of excessive sodium depletion, resulting in a significant water shift into the intracellular compartment. In this case, the extracellular volume decreases dramatically. Finally, if sodium concentration in the dialysate is set to a value a little higher than in the extracellular fluid (\( C_{Na,d}=145 \) mEq/l), the fall in osmolarity due to urea removal can be completely balanced. Hence, the intracellular volume remains quite constant during the first hour.

By way of comparison in Figure 2 we also present a simulation performed by increasing the initial urea concentration level from 25 mmol/l to 35 mmol/l and using a ‘medium’ sodium concentration in the dialysate (that is, one equal to that in the extracellular fluid, 140 mEq/l). As is clear from the previous curves, urea contributes to the overall fluid shift by less than 10% compared with sodium, if an equivalent decrease of osmotic concentrations by both solutes is simulated. Hence, dysequilibrium syndrome may be caused mainly by excessive sodium removal, while urea plays a minor role.

In conclusion, model simulations confirm that excessive sodium withdrawal may favour hypotension and may cause dysequilibrium syndrome. However, the use of a high sodium concentration in the dialysate may result in insufficient sodium loss and hypernatraemia.

The method presented below aspires at avoiding these imbalances, by establishing a criterion for a priori evaluation of sodium loss during treatment.

**Subjects and methods**

**Method**

The model presented above can be run on a computer via two distinct algorithms, which solve the ‘direct’ and ‘inverse’ simulation problems, respectively.

In the direct problem we use the model to make predictions about the time pattern of intra- and extracellular volumes (Figure 2), and of solute concentrations in the intra- and extracellular fluids, starting from knowledge of model parameters, of the patient’s initial status, and of dialysis operating conditions.

In this study, however, we are especially interested in determining a ‘rational’ sodium profile in the dialysate, \( C_{Na,d}(t) \), which meets some haemodialysis requirements whilst at the same time reducing the risk of intradialytic dysequilibrium syndrome and hypotension. This problem is ‘inverse’ in that we are looking for the best input quantity to be used, given a desired or target output quantity.

In what follows, an algorithm will be described which is designed to optimise haemodialysis so that the likelihood of dysequilibrium syndrome and hypotension is minimised.

When implementing the inverse algorithm, some constraints must be taken into account. In this work the constraints are:

1. The duration of haemodialysis, \( t_{nd} \).
2. The total fluid volume to be removed during one session, \( \Delta V_f \).
3. The total sodium mass to be removed during one session, \( \Delta M_{Na} \).

The presence of the third constraint constitutes an important feature of this algorithm, and may contribute to improving dialysis therapy. In fact, without this constraint, profiled haemodialysis might lead to an unwanted sodium load, with the risk of long-term disturbances (hypertension, pulmonary edema, etc.).

Since in this work we shall only be considering haemodialysis with a constant ultrafiltration rate, \( Q_f \), the first and second constraints imply:

\[
\Delta V_f = \frac{\Delta M_{Na}}{Q_f}.
\]

Moreover, as a consequence of the third constraint, the initial and final values of sodium mass, \( M_{Na,0}(t_{nd}) \) and \( M_{Na,0} \), are assigned, and only the way one can move from the first to the second of these values during the session can actually be chosen.
The target of the inverse problem is to maintain a high extracellular volume during the session, in order to improve vascular refilling and reduce the risk of symptomatic hypoten-
sion. The extracellular volume is significantly affected by the
osmotic concentration in the extracellular fluid (see Eq. 8 in
Appendix I). Clinical considerations (extensively reported in
the Introduction and also justified by the theoretical work
of Thews et al. [25]) suggest that in order to counteract the
rapid solute removal occurring in the first phase of the
dialysis, the sodium mass should be maintained fairly con-
stant during the first hour, and then significantly decreased
at the end of the treatment.

To simplify the solution of the inverse problem, we adopted
a polynomial approximation to describe the time pattern of
sodium mass during dialysis. We found that a third-order
polynomial is general enough for our purpose; hence
\[ M_{Na,d}(t) = M_{Na,d0}(t) + a_1 t + a_2 t^2 + a_3 t^3 \]
(1)
where \(a_1, a_2, a_3\) are constant parameters, to be individu-
ally estimated on the basis of the patient’s data. Eq. 1 fulfills
two main requisites: it is general enough to permit reproduc-
tion of most patterns of practical interest; it is simple enough
to be easily implemented on a computer, avoiding excessive
mathematical intricacy.

Of course, since the final value of sodium mass is assigned,
only two parameters in Eq. 1 (say \(a_2\) and \(a_3\)) can be chosen
freely. For instance, by arbitrarily choosing parameters \(a_2\)
and \(a_3\), we must have
\[ a_1 = \frac{\Delta M_{Na} - a_2 t_{end}^2 - a_3 t_{end}^3}{t_{end}} \]
(2)
Let us now assume that a certain value for parameters \(a_2\)
and \(a_3\) (hence, of parameter \(a_1\) too) has been given. The
inverse algorithm yields the sodium profile in the dialysate,
\(C_{Na,d}(t)\), which gives rise to the same pattern of sodium mass
in the extracellular fluid as in Eq. 1. Of course, this solution
depends on the free parameters \(a_2\) and \(a_3\).

A complete description of the algorithm can be found in
Appendix II, where some details for computer implementa-
tion are also given.

To determine a rational sodium profile in the dialysate,
the inverse algorithm described in Appendix II must be run
several times iteratively with different choices for parameters
\(a_2\) and \(a_3\) (iterative procedure). In this way, we can simulate
various dialyses of equal duration, equal ultrafiltration rate
and an equivalent elimination of sodium mass, but with
different profiles for sodium concentration in the dialysate
during different time courses of the extra- to intracellular
volume ratio.

An example of the iterative procedure is presented in
Figure 3. If parameters \(a_2\) and \(a_3\) are set to zero in Eq. 1, the
total sodium mass decreases linearly throughout the session.
In this case, the inverse algorithm provides a pattern of
sodium concentration in the dialysate which warrants
approximately uniform sodium extraction. This is the starting
point of the iterative procedure. By contrast, with a suitable
choice of \(a_2\) and \(a_3\), the time pattern of sodium mass can be
forced to conform with a smaller sodium extraction during
the first hour, but very rapid sodium removal toward the
end of treatment, according to clinical prescriptions.

The aim of the iterative procedure is to vary parameters
\(a_2\) and \(a_3\) automatically, in order to maintain sodium mass
as high as possible during the first 2 h of dialysis, and
decrease it progressively during the last 2 h. In particular,
parameters \(a_2\) and \(a_3\) have been chosen to have a function
\(M_{Na,d}(t)\) with zero curvature and an assigned slope at the
beginning of haemodialysis (i.e., \(t = 0\)). At the first step
of the algorithm we assumed \(a_2 = a_3 = 0\), which corresponds
to having a negative initial slope \(\Delta M_{Na,d1}t_{end}\) with no concavity
in the sodium mass relationship. The initial slope is then
slightly increased at each step of the algorithm, thus imposing
a more negative concavity of the sodium mass relationship.

As is clear from Figure 3, increasing the initial slope of
the sodium mass time pattern results in a greater extra-
to intracellular volume ratio during the first hour of treatment.
High values of extracellular volume, in turn, favour vascular
refilling, improve the patient’s cardiovascular stability and
reduce dysequilibrium syndrome. The iterative procedure is
completed when the time pattern of sodium concentration in
the dialysate, predicted by the algorithm, exceeds a range of
values established a priori; i.e. we require to have:
\[ C_{Na,d,min} \leq C_{Na,d}(t) \leq C_{Na,d,max} \]
With this additional constraint, the final pattern of \(C_{Na,d}(t)\)
exhibits a maximum at approximately 1 h, and then progress-
ively declines.

It is worth noting that at the end of the iterative procedure
the pattern of \(C_{Na,d}(t)\) obtained is continuous in type, whereas
only discrete integer values of sodium concentration can be
set on the dialyser every 15 min. For this reason, the final
sodium profile has been approximated with the closest integer
values, thus obtaining a stepwise integer function (Figure 3).

The values of all constant parameters in the model (i.e.
parameters which do not depend on the individual patient)
are reported in Table 1.

Materials
Seven uraemic patients on dialysis treatment in the dialysis
unit of the S. Orsola University Hospital were chosen for
the study. All patients selected suffered from hypotension in
the inter- and intradialytic period; inclusion criteria were the
presence of hypotension at the beginning of standard haemo-
dialysis treatment (mean blood pressure <80 mmHg) and
the appearance of at least one dysequilibrium syndrome
symptom (headache, muscle cramp, hypertensive crises)
per session. In all patients vascular access recirculation was
less than 10%.

In vivo tests for model validation were performed in the
dialysis unit of the S Orsola University Hospital over seven
PHD sessions (one per patient) using a patient-specific profile
for the dialysate sodium concentration. The sodium profile
was elaborated at the beginning of the session utilizing the
algorithm described in the previous paragraph on the basis
of the following parameters: timing of the session, body
weight to be lost, pre-dialysis plasma urea and plasma
sodium concentration, sodium mass to be removed.

The sodium mass to be removed was calculated for each
patient by applying the principle of mass balance between
dietary input and physiological loss of sodium (renal if there
is some residual function, as well as gastrointestinal and
cutaneous). Evaluation of this mass balance leads to know-
ledge of the amount of sodium accumulated by the patient
in the period between the end of one session and the start
of the next. This quantity represents the amount which must
be removed during haemodialysis to restore the overall
sodium pool to the basal, end-dialysis, clinical state. In
this way the extracorporeal session may diminish the sodium
pool in the case of a positive interdialytic sodium balance or
replenish it if the balance is negative.

Blood samples were taken in vivo during the session every
15 min on the arterial line and were analysed for sodium by
Fig. 3. An example of how the iterative procedure can actually work. The figure shows the time pattern of sodium mass in the extracellular fluid, sodium concentration in the dialysate, sodium concentration in plasma, and extra- to intracellular volume ratio, simulated by the inverse algorithm in patient no. 6, starting from different possible patterns of sodium mass. Dotted lines were obtained by assuming a constant sodium removal (i.e. $a_2=a_3=0$ in Eq. 1). The other curves were obtained by changing the values of parameters $a_2$ and $a_3$ in Eq. 1, so as to have a lesser sodium removal during the first phase of dialysis, and very rapid sodium removal at the terminal phase. The final pattern of sodium concentration in the dialysate (continuous line) was approximated by an integer step function, and the latter was installed on the dialyser.

Table 1. Model parameters

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Values</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K_u$ (l/min)</td>
<td>0.77</td>
<td>[26]</td>
</tr>
<tr>
<td>$V_i(0)/V_e(0)$</td>
<td>5/3</td>
<td>[7]</td>
</tr>
<tr>
<td>$C_{Na_d}(0)$ (mEq/l)</td>
<td>45</td>
<td>[7,10]</td>
</tr>
<tr>
<td>$D$ (l/min)</td>
<td>0.241</td>
<td>d.o.c.</td>
</tr>
<tr>
<td>$C_{Na_e}$ (l/min)</td>
<td>0.241</td>
<td>d.o.c.</td>
</tr>
<tr>
<td>$Q_d$ (l/min)</td>
<td>0.3</td>
<td>d.o.c.</td>
</tr>
</tbody>
</table>

Values of model parameters chosen $a$ priori on the basis of dialysis operating conditions [d.o.c.] and data taken from the physiological literature [7,10 and 26].

The ISE (ion-selective electrode) potentiometer method and for urea by enzyme (urease) testing using ultraviolet rays. The range error was estimated by the laboratory as $CV=1.3\%$ for sodium and $CV=1.1\%$ for urea (where $CV$ denotes the coefficient of variation, that is the percentage standard deviation of measurement errors).

The main characteristics of the patients selected for the study were: men 5, women 2, mean age $62.2\pm9.0$ years, residual renal function $0 \text{ ml/min}$, residual diuresis $0 \text{ ml/24 h}$, dry body weight $76.5\pm6.4$ kg, body weight decrease $3.5\pm0.4$ Kg, haematocrit $30.1\pm2.5\%$, total protein $6.30\pm0.2 \text{ g/l}$, systolic pressure $100\pm5 \text{ mmHg}$ at the beginning of the session.

Dialysis sessions were performed in each case by Bellco NT 1508 dialyser, cuprophane membrane, $1.5 \text{ m}^2$ surface area, $Kuf 7.4 \text{ ml/h mmHg TMP}$, for which the sodium mass transfer coefficient and urea clearance had previously been calculated. Bicarbonate buffer; $Q_b 300 \text{ ml/min}$ and $Q_d 500 \text{ ml/min}$ were maintained the same in every session. The dialysis machine, Althin System 1000, was an automatic ultrafiltration control monitor able to be programmed for haemodialysis with variable sodium dialysate concentration.

During dialysis sessions no solid or fluid dietary intake and no therapy or parenteral fluids were administered to patients and the sessions were performed without any clinical complications such as dysequilibrium syndrome or symptomatic hypotension.

In order to assess the agreement between model and $in$ vivo data, we computed the average deviations of plasma sodium and urea concentrations in each patient, according to the following formula

$$AD \equiv \left[ \frac{\sum\limits_{n=1}^{N} \left(C_{model} - C_{experimental} \right)^2}{n-1} \right]^{1/2}$$

where $n$ is the number of determinations of solute concentration during the dialysis session, and $C$ represents sodium or urea extracellular concentration.

We can expect that, due to intrinsic measurement errors, the value of $AD$ should be no less than $0.3-0.4 \text{ mmol/l}$ as to sodium, and no less than $1.5 \text{ mEq/l}$ as to sodium. Values of $AD$ significantly greater than these lower bounds denote some inaccuracy either in the model structure or in the parameter numerical values.

**Results**

As stated, the algorithm presented above was used to design the pattern of sodium concentration in the
Sodium profile elaboration in PHD 409 dialysate during seven profiled haemodialyses. The patients’ data used to compute a priori values of model parameters are reported in Table 2. The data concerning patient no. 4 deserve a few comments. In this patient, a greater amount of fluid volume was removed (4.2 litres), thus requiring an unnaturally high ultrafiltration rate (1.05 l/h). As a consequence of the large amount of sodium removed by convection, the required sodium balance in this patient (∼300 mEq) could only be fulfilled by adopting a higher range for sodium concentration in the dialysate (up to 155 mEq).

In each patient, a rational sodium profile in the dialysate was determined just before starting the session, and the dialysis machine was set to this value. A detailed description of a single case, including sodium profile in the dialysate, sodium and urea blood concentrations (both in vivo and in the model) and the simulated extra- to intracellular volume ratio is shown in Figure 4.

A comparison between in vivo sodium and urea blood concentrations, and the same curves simulated a priori, is presented in Figures 5 and 6 for the other six sessions. The ability of the model to fit the in vivo data, as assessed by means of the average deviation (AD), is reported in Table 3.

The results in Figures 4–6 and in Table 3 indicate that the model is able to reproduce the progressive decrease in urea concentration of the extracellular fluid quite well in all the patients examined. Only in patients no. 3 and no. 7 can small differences between in vivo and model data be seen. In general, the AD for urea is a little higher than that expected on the basis of measurement errors. Hence the AD values obtained are probably attributable to little measurement errors in the initial urea concentration value (which affect the entire simulation curve) and/or to small differences in urea clearance between subjects. Clearance, in fact, may depend not only on the dialyser, but also on

Table 2. Patients’ data

<table>
<thead>
<tr>
<th>Patients</th>
<th>$W_{\text{start}}$ (kg)</th>
<th>$\Delta V_T$ (l)</th>
<th>$t_{\text{out}}$ (min)</th>
<th>$\Delta M_{\text{Na}}$ (mEq)</th>
<th>$C_{U,0}=C_{U,e}(0)$ (mmol/l)</th>
<th>$C_{\text{Na,pl}}(0)$ (mEq/l)</th>
<th>$C_{\text{Na,d}}(\text{mEq/l})$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72.0</td>
<td>3.7</td>
<td>210</td>
<td>300</td>
<td>24.5</td>
<td>140</td>
<td>143–152</td>
</tr>
<tr>
<td>2</td>
<td>74.6</td>
<td>3.0</td>
<td>240</td>
<td>240</td>
<td>210</td>
<td>140</td>
<td>147–152</td>
</tr>
<tr>
<td>3</td>
<td>90.3</td>
<td>3.0</td>
<td>240</td>
<td>240</td>
<td>26.8</td>
<td>140</td>
<td>145–152</td>
</tr>
<tr>
<td>4</td>
<td>70.8</td>
<td>4.2</td>
<td>240</td>
<td>240</td>
<td>200</td>
<td>140</td>
<td>148–155</td>
</tr>
<tr>
<td>5</td>
<td>76.0</td>
<td>3.5</td>
<td>240</td>
<td>250</td>
<td>26.8</td>
<td>140</td>
<td>140–149</td>
</tr>
<tr>
<td>6</td>
<td>75.8</td>
<td>3.3</td>
<td>240</td>
<td>240</td>
<td>29.5</td>
<td>140</td>
<td>145–152</td>
</tr>
<tr>
<td>7</td>
<td>76.4</td>
<td>3.9</td>
<td>240</td>
<td>240</td>
<td>200</td>
<td>140</td>
<td>144–153</td>
</tr>
</tbody>
</table>

Individual patient data. The last column denotes the range of sodium concentration in the dialysate used for profiled haemodialysis.

Fig. 4. Time pattern of plasma sodium concentration, plasma urea concentration, sodium concentration in the dialysate and extra- to intracellular volume ratio simulated in patient no. 7 starting from a priori knowledge of all model parameters (continuous line). Asterisks connected through dashed lines denote in vivo results.
individual biorheological parameters, such as vascular access, cardiopulmonary recirculation, haematocrit, plasma protein and others. These factors have a certain, but not statistically measurable, *in vivo* effect on all the parameters considered. They do not cause any alteration of the *in vivo* recorded values compared with the predictions of the model. The incidence of such factors may thus be taken to lie within the limits of
Table 3. A priori validation

<table>
<thead>
<tr>
<th>Patients</th>
<th>AD Na (mEq/l)</th>
<th>AD Urea (mmol/l)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.59</td>
<td>0.31</td>
</tr>
<tr>
<td>2</td>
<td>3.04</td>
<td>0.95</td>
</tr>
<tr>
<td>3</td>
<td>1.29</td>
<td>1.27</td>
</tr>
<tr>
<td>4</td>
<td>3.88</td>
<td>0.45</td>
</tr>
<tr>
<td>5</td>
<td>2.06</td>
<td>0.82</td>
</tr>
<tr>
<td>6</td>
<td>1.45</td>
<td>0.96</td>
</tr>
<tr>
<td>7</td>
<td>1.46</td>
<td>1.33</td>
</tr>
<tr>
<td>Average</td>
<td>2.25</td>
<td>0.87</td>
</tr>
</tbody>
</table>

Comparisons between model prediction and in vivo determined sodium and urea plasma curves, with all model parameters given a priori: analysis of variance.

standard error [22]. Of course, a best fit between in vivo and model urea data could be achieved by performing an a posteriori individual estimation for parameter CL. However, this was scarcely influential for the purposes of this work.

Looking at the pattern of sodium concentration in the blood (Figures 4–6) one can note that, although the trends of the model and in vivo curves are ordinarily quite similar, some meaningful differences can occasionally be seen. These differences are not systematic, but may vary from one case to the next. For instance, while in certain trials the sodium concentration increases much more rapidly during the first hour in the model than in vivo (patients no. 2 and no. 7), in other cases the initial rise in sodium concentration is higher in vivo than in the model (patients no. 1 and no. 4). On the whole the AD for sodium (2.25 mEq/l) is higher than the standard errors of sodium concentration measurement (deemed to be about 1–1.5 mEq/l), suggesting the presence of some error in the model.

Finally, in order to emphasize the advantages of the new technique, it is useful to compare the main features of profiled and standard haemodialysis at the same sodium removal. To this end, Figure 7 shows the time pattern of sodium concentration in the dialysate, the sodium mass in the extracellular fluid, the extracellular to intracellular volume ratio and the sodium concentration in the blood; the parameters refer to patient no. 7, for both a priori profiled haemodialysis and standard haemodialysis. The standard haemodialysis in Figure 7 was simulated by using a constant $C_{Na,d}(t)$, chosen so as to have exactly the same overall sodium loss as in profiled haemodialysis. As is clear from Figure 7, the ratio $V_e/V_i$ remains significantly higher during profiled than standard haemodialysis over most of the session. Only at the terminal phase of the treatment does the volume ratio become equivalent in the two techniques, as imposed by the constancy of sodium removal.

Discussion

In the present work, the mathematical model of solute kinetics and fluid balance, originally presented in a previous paper [22], is used to achieve a rational choice of sodium concentration in the dialysate. The single equations of this model resemble those presented in previous modelling studies (for instance, in Peticlerc et al. [23] as to sodium kinetics, Thews et al. to urea kinetics [25,27], Sargent and Gotch [24], and Gotch [28] as to osmotic balance). The main new contributions of our approach lie in the way the equations are combined together to produce the entire dynamics and, above all, in the algorithm proposed to solve these equations in an inverse manner, where the dialysate sodium profile is calculated as a possible output for the model. There are two main advantages of this method.

First, the use of the mathematical model allows us to get an approximate estimation for the amount of sodium which is actually removed during haemodialysis. The correct choice of dialysate concentration profile, able to remove a given amount of sodium per session, is a difficult problem, solution of which depends on several different simultaneous factors: mainly the initial concentration of sodium and of other solutes in the blood and in the extracellular pool, the ultrafiltration rate, the dialysis operating conditions, the duration of the session [21,29]. All these factors interact in complex non-linear ways during treatment, thus making qualitative predictions of sodium extraction unreliable.

Accordingly, the model suggests that the use of a single value for $C_{Na,d}$, equal for all patients, would result in the total sodium extraction being uncorrelated with the actual patient’s need. Hence, the possibility of an individual choice of sodium in the dialysate becomes a fundamental target to improve the long-term clinical benefits of haemodialysis.

A second important point is that the algorithm proposed allows us to reduce some negative intradialytic consequences of extracorporeal depuration, namely symptomatic hypotension and dysaequilibrium syndrome. In this regard, the model theoretically supports the observations of previous clinical experience. The use of a dialysate sodium concentration profile which exhibits a maximum at about 1 h, and then progressively declines toward the end of the treatment, enables quite a constant extra- to intracellular volume ratio to be maintained during the second and the third hour. This has obvious benefits on vascular refilling and intracellular fluid distribution.

Another important prerogative of the proposed method is that it requires only knowledge of a few a priori measurements on the patients, which can be performed routinely before starting the session. Furthermore, the entire optimisation procedure for computation of the sodium profile takes no more than a few minutes to perform on a 486 MS-DOS personal computer, hence can easily be introduced at low cost in any routine clinical setting with current computer technology.

Model validation performed on seven patients suggests that the time pattern of urea concentration in the blood can be reproduced quite well using only a priori knowledge. By contrast, some discrepancies were
Fig. 7. Comparison between the characteristics of standard and profiled hemodialysis in patient 7 (continuous line, profiled hemodialysis; dashed lines, standard hemodialysis). The figures represent the simulated time pattern of sodium concentration in the dialysate, sodium mass in the extracellular fluid, plasma sodium concentration, and extra- to intracellular volume ratio. Profiled hemodialysis was simulated using the sodium profile in the dialysate obtained by the inverse algorithm. Standard hemodialysis was simulated using a constant sodium concentration in the dialysate, chosen to have the same total sodium loss as in profiled hemodialysis. Worth noting are the differences in the extra- to intracellular volume ratio between the two techniques, especially evident at the second and third hour of treatment.

observed during the first hour of treatment between the model and in vivo time patterns of sodium concentration in the blood. Such discrepancies might be partly attributed to a different fluid shift between the intracellular and extracellular pools, occurring during the first hour as a consequence of diffusion of other solutes (K⁺, Mg²⁺, HCO₃⁻, etc.). During dialysis some of these solutes (such as K⁺ or Mg²⁺) do in fact have a higher concentration in the blood than in the dialysate, and hence are removed by diffusion, whereas other solutes (mainly HCO₃⁻) are at higher values in the dialysate, and are supplied to the patient to compensate for the decline occurring during the interdialytic phase. As a result, the overall mass of these solutes in the extracellular space, $M_{eq,e}(t)$, may increase, decrease, or remain unchanged during treatment. A decrease in $M_{eq,e}(t)$, of course, contributes to the osmotic fluid shift from the extra- to the intracellular pool, thus causing a rise in sodium concentration. The opposite effects occur if $M_{eq,e}(t)$ increases during treatment.

Despite the acceptable results obtained in this preliminary study, various refinements and improvements on the method can be suggested, which may become the subject of future works.

An obvious improvement to this technique may consist in the inclusion of other solute kinetics in the model, and in measuring their concentration in the blood before the session. While extension of the model to include these substances does not present any significant theoretical problems, it has the shortcoming of increasing the computational cost of the algorithm and, above all, requiring additional measurements before the session starts. As a result, the method may become more difficult to apply in today’s routine clinical settings.

A second possible improvement derives from the observation that the main differences between model estimation and in vivo results occur during the first hour. Hence the technique may be improved by providing a correction for the sodium profile after about 1 h, on the basis of the values of natraemia up to that moment. To this end, at about 1 h from the beginning of treatment a modified version of the algorithm may be run to compute a correction factor for $C_{Na,d}(t)$, taking into account the difference between the amount of sodium actually measured in the patient and that predicted a priori. Of course, this method requires real-time measurement of sodium in the blood, which is becoming rapidly possible with advances in dialysis technology.

In a longer perspective, the algorithm should be applied continuously on line, to provide frequent real-time adjustments of sodium in the dialysate and, maybe, of ultrafiltration rate too. This might be the final target of the proposed procedure.

Appendix I

In the following, all model equations are separately presented and justified. A more complete description can be found in a previous related paper [22].
Fluid balance

During haemodialysis, the total fluid volume, $V_T$, varies continuously due to ultrafiltration through the dialyser. Calling the ultrafiltration rate $Q_f$, the fluid mass balance allows us to write:

$$\frac{dV_T(t)}{dt} = -Q_f(t)$$  \hspace{1cm} (3)

In this work we consider only the case of a constant ultrafiltration rate. Hence, Eq. 3 can be reduced to

$$V_T(t) = V_T(0) - Q_f t$$  \hspace{1cm} (4)

where $t=0$ is the dialysis starting time.

The total fluid volume is naturally the sum of an intracellular and an extracellular volume ($V_i$ and $V_e$ respectively). Hence:

$$V_T(t) = V_i(t) + V_e(t)$$  \hspace{1cm} (5)

The distribution of volume between the intracellular and extracellular compartments is affected not only by the ultrafiltration rate through the dialyser, but also by water movement across the cellular membrane, caused by the osmotic concentration gradient. We assume that the latter process occurs with a time constant much smaller than that of the other dynamic processes in the model. Hence, the intracellular and extracellular osmotic concentrations can be assumed to be always in equilibrium without any appreciable errors. We obtain

$$M_{U,i}(t) + M_{Cl,i}(t) + M_{eq,i} = \frac{V_i(t)}{V_T(t)} M_{Na,i}(t) + M_{U,e}(t) + M_{Cl,e}(t) + M_{eq,e}(t)$$  \hspace{1cm} (6)

where $M_{U,i}$ and $M_{U,e}$ represent the amount of urea in the intracellular and extracellular pool, respectively, $M_{Cl,i}$ and $M_{Cl,e}$ are the amount of chloride ion in the same compartments, $M_{Na,i}$ is the amount of dissociated sodium ion in the extracellular pool, $M_{eq,i}$ and $M_{eq,e}$ are other solutes (K⁺, Mg²⁺, PO₄⁻, HCO₃⁻, etc.) which contribute to osmolarity across the cellular membrane. Furthermore, $M_{eq}$ also includes the amount of non-dissociated ions (i.e. ions bound with solutes) and is corrected for the presence of substances with an osmotic coefficients less than 1. In particular, the values of $M_{eq,i}$ and $M_{eq,e}$ have been given to obtain physiological levels of osmolarity in the two pools. In writing Eq. 6 we have taken the amount of sodium in the intracellular fluid to be negligible, i.e. $M_{Na,i} \approx 0$. The use of an osmotic coefficient equal to 1 for urea and dissociated Na⁺ agrees with Sargent and Gotch [24] and Gotch [28].

In what follows we shall presume that the extracellular Cl⁻ is always very close to equilibrium with the intracellular Cl⁻ and with another intracellular anion, $M_{eq,i}$; i.e. we have: $M_{Cl,e}(t)/V_e(t) \approx (M_{Cl,i}(t) + M_{eq,i})/V_i(t)$. For the sake of simplicity, we also assume that the amounts of other solutes in the intracellular space ($M_{eq,i}$, with $M_{eq,i} = M_{eq,i} + M_{eq,e}$) and in the extracellular space ($M_{eq,e}$) do not change appreciably during dialysis. This is the same as considering that the net quantity of these solutes exchanged at the dialyser or at the cellular membrane is always negligible compared with Na⁺ and urea changes. The possible consequences of this choice on model results are commented on in the discussion.

According to the previous assumptions and simplifications, Eq. 6 can be rewritten as follows

$$M_{U,i}(t) + M_{eq,i} = \frac{M_{Na,i}(t) + M_{U,e}(t) + M_{eq,e}}{V_i(t)}$$  \hspace{1cm} (7)

Eq. 7 is important, since it determines the extra- to intracellular volume ratio during haemodialysis. Rearranging Eq. 7, and taking Eq. 5 into account, we can write the following expression linking the extracellular and total fluid volumes

$$V_i(t) = V_T(t)/\left[1 + \frac{M_{U,i}(t) + M_{eq,i}}{M_{Na,i}(t) + M_{U,e}(t) + M_{eq,e}}\right]$$  \hspace{1cm} (8)

Urea kinetics

The dynamics of urea are described by means of a double-pool model, representing the intracellular and extracellular compartments. The volume of both pools is calculated through the fluid balance equations presented above.

The amount of urea in the intracellular compartment can vary only as a consequence of solute flow across the cellular membrane. As in most previous models [25,27,30,31] the latter phenomenon is described by a linear function of the concentration difference. Hence we can write

$$\frac{dM_{U,i}(t)}{dt} = -K_U(C_{U,i}(t) - C_{U,e}(t))$$  \hspace{1cm} (9)

where $K_U$ is a constant parameter representing the urea mass-transfer coefficient of the cellular membrane, and $C_{U,i}, C_{U,e}$ are the urea concentrations in the extra- and intracellular pools, defined as

$$C_{U,e}(t) = \frac{M_{U,e}(t)}{V_e(t)}$$  \hspace{1cm} (10)

$$C_{U,i}(t) = \frac{M_{U,i}(t)}{V_i(t)}$$  \hspace{1cm} (11)

Two other phenomena affect the amount of urea in the extracellular space: the urea generation rate, and the elimination of urea across the dialyser, $J_U$. In this work we focus the attention only on the intradialytic phase; hence, we assume that urea generation is negligible compared with the amount of urea exchanged across the cellular membrane and the dialyser. The following differential equation can thus be used to describe urea variations in the extracellular pool:

$$\frac{dM_{U,e}(t)}{dt} = K_U(C_{U,i}(t) - C_{U,e}(t)) - J_U(t)$$  \hspace{1cm} (12)
The urea flux across the dialyser is a linear function of urea concentration in the extracellular fluid, according to the following well-known equation [24]

\[ J_U(t) = Q_F C_{U,e}(t) + CL \left( 1 - \frac{Q_F}{Q_B} \right) C_{U,e}(t) \]  

(13)

where \( CL \) is the dialyser urea clearance at \( Q_F = 0 \), and \( Q_B \) is the blood flow rate at the dialyser inlet.

**Sodium kinetics**

The dynamics of sodium are described by means of a single-pool model. Due to the presence of the active pumps, the net sodium exchange between the intra- and the extracellular pools is actually negligible. Hence, we can write a single mass preservation equation, which relates the amount of sodium in the extracellular space with the sodium elimination rate through the dialyser, \( J_{Na} \). We obtain

\[ \frac{dM_{Na,e}(t)}{dt} = -J_{Na}(t) \]  

(14)

In writing Eq. 14 we did not consider the sodium intake, since it is negligible during the simulation period.

The expression for sodium elimination across the dialyser is [24]

\[ J_{Na}(t) = Q_F C_{Na,e}(t) + D \left( 1 - \frac{Q_F}{Q_B} \right) (C_{Na,d}(t) - C_{Na,e}(t)) \]  

(15)

where \( D \) is sodium dialysance, \( C_{Na,d} \) is sodium concentration in the dialysate, and \( C_{Na,e} \) is sodium concentration in the extracellular fluid, computed by means of the following equation:

\[ C_{Na,e}(t) = \frac{M_{Na,e}(t)}{V_e(t)} \]  

(16)

It is worth noting that the value of sodium concentration measured in plasma, \( C_{Na,pl} \), is slightly different from the sodium concentration in the extracellular fluid. In fact, the following relationship holds:

\[ C_{Na,e} = \frac{F_p}{\alpha_{Na}} C_{Na,pl} \]  

(17)

where \( \alpha_{Na} \) is the Gibbs–Donnan ratio of sodium and \( F_p \) is the plasma water fraction. Since a typical value for \( \alpha_{Na} \) is 0.95, while \( F_p \) is about 0.94 [10,24,32], the ratio \( \alpha_{Na}/F_p \) is close to 1, which justifies the use of a single-compartment model for sodium. However, Eq. 17 is used as the model output instead of Eq. 16 to provide better model validation starting from data on sodium concentration measured in plasma.

**Appendix II**

In what follows we describe the main aspects of an inverse algorithm for computing the sodium profile in the dialysate, starting from knowledge of sodium mass time pattern in the extracellular fluid (Eq. 1).

**Initialization of the algorithm**

In order to start the algorithm, one must know the value of variables \( M_{U,e}(0) \), \( M_{U,i}(0) \) and \( M_{Na,e}(0) \), at the dialysis starting time. Moreover, a value must be given to all constant parameters in the model.

The values of sodium dialysance and urea clearance were determined during a series of previous dialysis sessions [22]. The blood flow rate in the extracorporeal circuit, \( Q_B \), was set at 300 ml/min in all trials. The transmembrane mass transfer coefficient for urea, \( K_U \), agrees with that commonly reported in the literature [26,33].

The initial value of total fluid volume is estimated assuming that, at the end of the session, the patient’s fluid volume distribution per unit weight will be the same as in normal subjects. In normal adults, total fluid weight is approximately 58% of total weight [7]. Hence, we can assume

\[ V_T(t_{end}) = 0.58 \cdot W_{end} / \rho \]  

(18)

where \( \rho \) is the fluid density (approximately 1.0 g/ml) and \( W_{end} = W_{start} - \Delta V_T \cdot \rho \).

From Eq. 18 the total fluid volume at the beginning of haemodialysis is then computed as

\[ V_T(0) = V_T(t_{end}) + \Delta V_T \]

The intra and extracellular volumes at \( t = 0 \) are determined assuming that the intra- to extracellular volume ratio is 5:3 [7]. Hence

\[ V_i(0) = \frac{5}{8} V_T(0) \quad V_e(0) = \frac{3}{8} V_T(0) \]

A starting value for the sodium and urea masses can be computed from knowledge of the initial urea and sodium concentrations in the blood, and assuming that urea is initially at an equilibrium between the intracellular and extracellular compartments; i.e.: \( C_{U,e}(0) = C_{U,i}(0) \). We obtain

\[ M_{Na,e}(0) = \frac{Z_{Na}}{F_p} C_{Na,pl}(0) V_T(0) \]

\[ M_{U,e}(0) = C_{U,i}(0) V_T(0) \]

\[ M_{U,i}(0) = C_{U,i}(0) V_T(0) \]

The value of \( M_{eq,e} \) has been estimated from data reported in Guyton ([7] page 456) with reference to a typical uraemic patient. We have:

\[ C_{eq,e}(0) = \frac{M_{eq,e}}{V_T(0)} \approx 45 \text{ mEq/l} \]

Finally, the value of \( M'_{eq,i} \) was computed by assuming that the intra- and extracellular pools are in osmotic equilibrium at the instant \( t = 0 \). We obtain:

\[ M'_{eq,i} = \frac{V_T(0)}{V_e(0)} \left[ M_{Na,e}(0) + M_{eq,e} \right] \]

**Body of the algorithm**

Let us now assume that the variables, \( M_{U,e}(t) \) and \( M_{U,i}(t) \), are known at the instant \( t \), together with the
ultrafiltration rate, $Q_F$, and sodium mass, $M_{Na,e}(t)$. The latter is provided by Eqs. 1 and 2, with assumed values for parameters $a_2$ and $a_3$. The algorithm permits computation of all other quantities, particularly $C_{Na,e}(t)$, at the same instant, and of the time derivatives for the urea and sodium masses. This can be done through the following steps:

- the instant value of total fluid volume is provided by Eq. 4;
- the extracellular and intracellular fluid volumes are provided by Eq. 8 and 5;
- equations 10, 11 and 16 provide the values of urea concentrations in the intracellular and extracellular spaces, and of sodium concentration in the extracellular space;
- Eq. 14 is used to estimate the rate of sodium elimination through the dialyser. In fact, by computing the time derivative of Eq. 1, we can write

$$J_{Na}(t) = -\frac{dM_{Na,e}(t)}{dt} = -(a_1 + 2a_2f + 3a_3f^2)$$

- The value of sodium concentration in the dialysate, which is the aim of the inverse algorithm, can be obtained by rearranging Eq. 15. We obtain:

$$C_{Na,e}(t) = \frac{Q_F C_{Na,e}(t) - J_{Na}(t)}{D(1 - Q_F/Q_B)} + C_{Na,e}(t)$$

- Finally, the time derivatives of urea mass in the extra- and intracellular fluid are computed through Eqs. 9, 13 and 12. These enable the same variables to be computed at the next step (i.e. at $t = t + dt$, where $dt$ denotes the integration step).

The above method for solving the system of differential equations was implemented by means of the 5th order Runge–Kutta method with adjustable step length [34]. The maximum allowed time step was 1 min, while the maximum acceptable error was set at $1 \times 10^{-8}$.

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Received for publication: 12.2.97
Accepted in revised form: 5.9.97