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A Variable-Volume Kinetic Model to Estimate Absolute Blood Volume in Dialysis Patients Using Dialysate Dilution Protocol

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Abstract

Long- and short-term adverse outcomes in hemodialysis (HD) have been associated with intradialytic hypotension, a common HD complication and significant cause of morbidity. It has been suggested that knowledge of absolute blood volume (ABV) could be used to significantly improve treatment outcomes. Different dilution-based protocols have been proposed for estimating ABV, all relying on the classic mono-exponential back-extrapolation algorithm (BEXP). In this paper, we introduce a dialysate dilution protocol and an estimation algorithm based on a variable volume, two-compartment, intravascular blood water content kinetic model (VVKM). We compare ABV estimates derived using the two algorithms in a dialysate dilution study including 3 arterio-venous (AV) and 3 central-venous (CV) access patients, and multiple bolus injection tests (3–5) within each of several (2–6) HD treatments. The distribution of differences between ABV estimated from the two methods showed negligible systematic difference between the mean values of ABVs estimated from the BEXP and VVKM algorithms, however, the VVKM estimates were 53% and 42% more precise for the CV and AV patients, respectively. Good agreement was observed between measured and VVKM-estimated blood water concentration (BWC) with the root-mean-square error (RMSE) less than 0.02 kg/kg (2%) and 0.03 kg/kg (3%) for AV and CV patients, respectively. The dilution protocol and the new VVKM-based estimation algorithm offer a noninvasive, inexpensive, safe, and practical approach for ABV estimation in routine HD settings.

Keywords

Dialysis; Blood Volume Estimation; Indicator Dilution Protocol; Kinetic Model

1. Introduction:

Volume management plays an important role in renal replacement therapies. Removing too much fluid by ultrafiltration triggers intradialytic hypotension, a significant cause of long-

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and short-term adverse outcomes, while removing too little fluid causes edema, left ventricular hypertrophy and heart failure¹⁻³. Knowing a patient's ABV at the start of ultrafiltration could allow clinicians to better guide fluid balance within an HD treatment and return patients to their dry weight, improving HD outcomes significantly¹⁻³. The gold standard for measuring ABV, isotope dilution, is invasive, expensive, time consuming and impractical for routine clinical application⁴. Therefore, a practical technique for estimating ABV is needed.

Current HD machine technology provides online sensors such as the Crit-Line™ and the blood volume monitor (BVM) to measure the concentration of blood components. The Crit-Line™ sensor (Fresenius Medical Care, Waltham, MA) derives patients' hematocrit and oxygen saturation using photo-optical technology. The BVM (Fresenius Medical Care, Schweinfurt, Germany) derives blood water concentration (BWC) and hematocrit using ultra-sonic technology and temperature measurements. In addition, both sensors provide estimates for the percent *change* in a patient's intravascular blood volume - referred to as relative blood volume (RBV). RBV estimates reported by these sensors are based on a single compartment assumption. However, ABV, the crucial piece of information, cannot be inferred from RBV alone. Patients with differing ABVs can exhibit similar RBVs⁵.

In recent years, in attempting to find a practical approach to translate the RBV information into ABV information, researchers' attention has been directed toward dilution techniques that can use the available measurements by the sensors. A recent study⁶ showed that ultra-pure dialysate, which is readily available in online hemodiafiltration, can be used as a dilution medium to make estimates of ABV⁶. In this technique, a bolus injection of ultra-pure dialysate was administered within the treatment. The online measurement of BWC by the BVM, in conjunction with the back-extrapolation (BEXP) algorithm, was used to estimate the initial BWC at the time of injection. This estimate together with the size of the bolus injection was then used to estimate ABV at the time of injection.

The BEXP algorithm, which fits an exponential function to a measured indicator, is a standard pharmacokinetic approach⁷ that assumes that the indicator dynamics can be sufficiently represented by a single-compartment model with constant coefficients. However, studies have shown that the distribution of an indicator is not uniform within the bloodstream especially during the initial phase due to blood flow^{8, 9}, and researchers have considered models consisting of more than one compartment to better reflect such distribution¹⁰⁻¹⁴. Multi-compartment modelling has been studied, including fixed-volume, ¹⁰⁻¹³ variable-volume, ^{14, 15} and parallel and series compartment configurations.¹² Applications of such models include the distribution of indicators in solute kinetics¹⁰⁻¹², hemodialysis¹³, β_2 -microglobulin kinetics¹⁴, indocyanine green distribution in blood¹⁶, and urea kinetics¹⁵. However, application of high-order compartmental models, such as models described in¹⁰⁻¹⁶ involve an increasing number of unknown parameters, resulting in a difficult, if not impossible, estimation problem. Because of such limitations, these algorithms have not been incorporated into day-to-day clinical practice.

In this paper, we present a new, physiologically motivated, variable-volume, two-compartment model as the basis for estimating ABV corresponding to the technique

presented in reference⁶. The model is uniquely configured to achieve a better balance between complexity, identifiability, and precision. Absolute blood volume estimates derived from this model are compared with estimates from the classic mono-exponential back-extrapolation algorithm.

2. Materials & Methods

A Fresenius 4008H-HDF machine equipped with a BVM and dedicated data acquisition software (Fresenius Medical Care, Bad Homburg, Germany)¹⁷ provided hemodiafiltration (HDF) therapy and measurement of hematocrit and BWC, the latter of which was used to calculate RBV changes. Dialysate was delivered at a flow of either 500 or 800 mL/min, and at 36 degrees C. Extracorporeal blood flows, substitution fluid infusion rates, and ultrafiltration rates were maintained constant within each treatment. Dialysate $[Na^+]$ and the HDF pre- or post-dilution configuration were set as previously prescribed⁶. Mean substitution volume was 5 L.

Indicator dilutions were administered using the bolus function in the HDF machine. This function delivers ultrapure dialysate in multiples of 30 mL at a constant infusion rate of approximately 150 mL/min during the HDF session. This bolus volume was delivered with an accuracy of better than $\pm 1.5\%$ ⁶. During infusion lasting about 1 to 2 min depending on the magnitude of the bolus volume, the HDF machine automatically reduced the blood flow rate to prevent an excessive increase in venous line pressure but maintained all ultrafiltration and infusion rates.

Patients

The study included 3 arterio-venous (AV) and 3 central-venous (CV) access patients, and multiple (3–5) indicator dilution experiments within each of several (2–6) HD treatments. Patients consented to participate as approved by the Ethics Committee of the Medical University of Graz, Austria. Table 1 summarizes the patient and treatment data.

Modeling

Following the techniques described in previous studies^{10–16}, we modeled the intravascular circulatory system by two compartments loosely termed central and peripheral, respectively (Figure 1). The water mass and blood mass constituted the state for each compartment.

The following assumptions were used:

- Ultrafiltration removed fluid from the central compartment at the prescribed rate q_{ufr} .
- The indicator fluid was injected into the central compartment at a rate of q_{ind} . Instantaneous mixing was assumed within each compartment. Following the injection, the indicator fluid was assumed to arrive at the measurement site with a fixed time delay after circulating throughout the body.
- Since an accurate model of the inter-compartment flow was beyond the scope of this work, we assumed that, over the time period of interest (20 min), both

$q_1(t)/V_1(t)$ and $q_2(t)/V_2(t)$ were constants. Here q_1 was the blood flow from the central to peripheral compartments, q_2 was the blood flow from peripheral to central compartments and V_1 and V_2 were the fluid volumes for the central and peripheral compartments, respectively.

- We assumed that the fluid exchange between the interstitial and intravascular spaces, referred to as refilling/filtration, occurred between the interstitial and peripheral compartments. For simplicity, we took this nonlinear exchange q_f as an affine function of the central volume as in

$$q = q_{f0} + \alpha V. \quad \text{Eq. 1}$$

Here we assumed that q_f depended only on the central volume since the interstitial volume was much larger than the volume of fluid removed by ultrafiltration within the simulation time period. The coefficient α modeled the sensitivity of q_f to the lymphatic flow rate and the nonlinear Starling mechanism describing microvascular refilling/filtration flow into the peripheral compartment^{18, 19}.

- The water content W_{ind} and density of dilution ρ_{ind} were 0.991 kg/kg and 1.0 kg/L⁶, respectively. We assumed that the same water content and density as the diluted indicator (i.e. ultra-pure dialysate) for the fluid removed from intravascular space by ultrafiltration (denoted by W_{ufr} and ρ_{ufr}) and filtration (denoted by W_f and ρ_f).²⁰.

Under these assumptions, we can write mass balance equations for the indicator fluid (water) and blood in each compartment in our model:

Central compartment:

Indicator mass balance:

$$\frac{dm_{w,1}(t)}{dt} = -\frac{q_1(t)}{V_1(t)}m_{w,1} + \frac{q_2(t)}{V_2(t)}m_{w,2} + W_{ind}\rho_{ind}q_{ind}(t) - W_{ufr}\rho_{ufr}q_{ufr}(t), \quad \text{Eq. 2}$$

Blood mass balance:

$$\frac{d}{dt}(\rho_1 V_1) = -\rho_1 q_1(t) + \rho_2 q_2(t) + \rho_{ind} q_{ind}(t) - \rho_{ufr} q_{ufr}(t). \quad \text{Eq. 3}$$

Peripheral compartment:**Indicator mass balance:**

$$\frac{dm_{w,2}(t)}{dt} = \frac{q_1(t)}{V_1(t)}m_{w,1} - \frac{q_2(t)}{V_2(t)}m_{w,2} + W_f\rho_fq_f(t), \quad \text{Eq. 4}$$

Blood mass balance:

$$\frac{d}{dt}(\rho_2V_2) = \rho_1q_1(t) - \rho_2q_2(t) + \rho_fq_f(t). \quad \text{Eq. 5}$$

where $m_{w,i}$ denotes water mass, V_i denotes fluid volume, $W_i=m_{w,i}/\rho_iV_i$ is the water content, ρ_i is fluid density calculated from W_i and temperature as described elsewhere^{6, 21}. Blood mass and water mass define the state for each compartment. Subscript $i=1,2$ denotes central compartment and peripheral compartment, respectively, and subscripts *ufr* and *ind* denote ultrafiltration and indicator dilution, respectively. For example, W_{ind} denotes the water content of the indicator injection and W_{ufr} is the water content of fluid removed by ultrafiltration. In the above equations, $W_{ind}\rho_{ind}q_{ind}$ and $W_f\rho_fq_f$ equal the rate of water mass added by indicator dilution and refilling/filtration, respectively, and $W_{ufr}\rho_{ufr}q_{ufr}$ is the rate of water mass removed by ultrafiltration. $\frac{q_2(t)}{V_2(t)}m_{w,2}$ and $\frac{q_1(t)}{V_1(t)}m_{w,1}$ denote the convective inflow between compartments. Other terms can be interpreted in a similar manner.

The output is the measured water content defined as water mass over blood mass. In this study, we measure water content of blood W_m in the arterial line of extracorporeal circulation. Subscript *m* refers to the measurement. In AV patients, arterial blood from the fistula/graft enters the extracorporeal circulation with high flow rate before equilibrating with the peripheral compartment because of so-called cardio-pulmonary recirculation.²⁰ We therefore assumed that W_m measures the central compartment's water content ($W_m=W_I=m_{w,1}/\rho_I V_I$). For CV patients, venous blood from the superior vena cava, a mix of blood from both compartments, enters the extracorporeal circulation. Therefore, W_m comprises an almost half-and-half mix of water contents from each compartment ($W_m=0.5[W_I+W_2]=0.5[m_{w,1}/\rho_I V_I + m_{w,2}/\rho_2 V_2]$). The variation in blood water content due to indicator dilution appears at the measurement site with a time delay after circulating the body, and is modeled using a Heaviside function, $H(t-t_{delay})$.

Parameter estimation, observability, and identifiability

The feasibility of obtaining reasonable estimates depends on several factors including model structure and model complexity relative to what is measured. A dynamic system is said to be observable if the initial states can be determined from system's measured outputs²². Observability is a necessary condition for parameter identification, but is not a sufficient condition for identifiability^{23–25}. Our analysis based on linearization (see Appendix) shows

that the two-compartment model described by Eqs. (2)–(4) is unobservable when the output measures mixed venous blood water content sampled from a central venous access.

In the Appendix, we show that parameters of our two-compartment model for CV patients are not identifiable because the measurement W_m is an unknown function of $W_1=m_{w,1}/\rho_1 V_1$ and $W_2=m_{w,2}/\rho_2 V_2$. To overcome this limitation, we assume that the states of central compartment and peripheral compartment are equal to each other (i.e. $m_{w,1} = m_{w,2}$ and $\rho_1 V_1 = \rho_2 V_2$). Using this assumption, the mass balance equations for the central and peripheral compartments can be combined to define a new set of mass balance equations consisting of two equations that include the both compartments. In other words, this assumption transforms the unobservable two-compartment model into an observable, single-compartment model. This assumption is supported by the fact that the post-dilution slope of the measured BWC in CV patients depicts a single exponential decay suggesting an observable single compartment behavior. A list of model estimated parameters is given in Table 2.

The parameter estimation is conducted using the nonlinear least squares with the “trust-region-reflective” algorithm²⁶ in MATLAB, in which the parameters are identified to minimize the root-mean-square error (RMSE) between the water content measurements W_m and the water content estimates $W_{estimates}$ obtained by our algorithm

$$RMSE = \sqrt{\frac{\sum_{k=1}^N (W_{estimates} - W_m)^2}{N}}. \quad \text{Eq. 6}$$

Parameter estimation is conducted 5 min prior to and 10 min after indicator injection time, by taking 15 min samples of W_m .

Figure 2 summarizes estimation results for an AV patient. The left panel shows the variation of BWC in each compartment throughout the indicator dilution protocol and the right panel shows the variation in flow rates between compartments within the dilution protocol⁶. The spike in the measured variation of BWC occurring at $t=74$ min is due to automatic transmembrane pressure tests (TMP) from the Fresenius on-line HD/HDF machines. These spikes are repeated every 15 min and each spike affects measurements for about 3 min. Since dilution starts immediately after these TMP tests, a 5 min period prior to dilution ensures that 2 min of spike-free data were collected prior to dilution. Since the two-compartment model equilibrated after an injection in about 10 min, we found a 15 min sampling period was a good compromise between practicality and the model’s approximation of the actual nonlinear and time-varying phenomena.

Finally, the estimate of ABV at any time of interest $V(t)$ is derived from the sum of the two estimated compartments (central and peripheral $V(t_0)=V_1(t_0)+V_2(t_0)$) at time of start of dilution t_0 and measured relative blood volume ($RBV(t)$, vol/vol) at injection time and at time of interest⁶:

$$\frac{RBV(t_0)}{RBV(t)} = \frac{V(t_0)}{V(t)}. \quad \text{Eq. 7}$$

Note that at the start of the HD treatment $RBV(0)=1$.

In the next section, we discuss and compare ABV estimates from our model with ABVs estimates obtained using the classic back-extrapolation algorithm. In obtaining ABV estimates using BEXP we followed the technique described in reference⁶. We found this estimation is very sensitive to the period of time used for back-extrapolation. For consistency with previous results⁶, in all cases we used the time period of 4 to 10 min after the injection to estimate ABV.

Statistical Analysis

We assessed the differences between the algorithms with an approach motivated by Bland and Altman²⁷, namely, using a two-sided 95% statistical tolerance interval (TI) (confidence level 95%)²⁸ for a population of differences having a normal distribution with unknown variability. Nested one-way analysis of variance (ANOVA)²⁹ was used to compute and compare the intratreatment variability of estimates in the two algorithms. ANOVA provided a more sophisticated comparison between the variabilities of the BEXP and VVKM algorithms. Patients were chosen as the main factor while treatments (within patients) were taken as the nested factor. Normally distributed results were reported using mean (SD), otherwise, median [first quartile-third quartile]. Shapiro–Wilk test was used to test normality.

3. Results

A total of 85 bolus dilution tests (60 to 210 mL) of ultrapure dialysate were performed over 21 HD treatments in 6 patients using multiple indicator dilutions within each treatment. The descriptive statistics of the estimation results are given in Table 3. Figure 3 shows measured water content and the estimation using the VVKM algorithm for AV patient AF300 and CV patient ST011. Good agreement was observed between measured and estimated BWC with RMSE less than 0.02 kg/kg (2%) and 0.03 kg/kg (3%) for AV and CV patients, respectively. The largest RMSE values were at the fourth indicator dilution of KH110 (RMSE=0.03 kg/kg) for AV patients and at the second indicator dilution of FR170 (RMSE=0.05 kg/kg) for CV patients (Figure 4).

A normal probability plot (not shown) and a Shapiro-Wilk test for AV patients indicated that the differences between the ABV estimates of the BEXP and VVKM algorithms were normally distributed with mean of 0.02L, standard deviation (SD) of 0.52L, and with a 95% tolerance interval from -1.27L to 1.32L. For CV patients, the differences were also normally distributed with mean of -0.09L, SD of 0.42L, and with 95% tolerance interval from -1.10L to 0.91L. Thus, the systematic difference between the two algorithms was negligible.

Since a patient could have different blood volumes on different treatment days, it is appropriate to compare the results of the two algorithms at each treatment day (intratreatment variability). Figure 5 provides such a comparison. Within each treatment, three to five indicator dilutions were administered. The ABV estimates at the start of HD treatment obtained from dilutions within the same treatment are summarized as mean $\pm$ SD. Results showed that our algorithm had much better reproducibility by virtue of lower SD in all 11 treatments in CV patients, and in 8 out of 9 instances in AV patients. The smallest value for ABV was observed in the case of a patient with bilateral leg amputation (FR). The lower blood volume estimates in case of patient SW can be explained by the clinical condition (hypoalbuminemia) of the patient.

The results of nested one-way analysis of variance are presented in Table 4. Intratreatment SDs for the BEXP estimates were 0.51L and 0.47L for CV and AV patients respectively; and the corresponding SDs for VVKM estimates were 0.24L and 0.27L for CV and AV patients, indicating significant reductions in variability by 53% and 42% respectively. The AV and CV intratreatment coefficients of variation were 0.080 and 0.128 for BEXP, and 0.046 and 0.062 for VVKM.

4. Discussion

This study shows that ABV during an HD treatment can be successfully estimated using an indicator dilution protocol and a new physiologically-motivated compartmental model. The dilution protocol delivers boluses of ultra-pure dialysate using the bolus function of a modern HDF dialysis machine. When compared to other solutions such as normal saline, this ultra-pure dialysate has the advantage of being readily available at the proper temperature and osmotic concentration. Though not shown here, the VVKM algorithm can be extended for hemoglobin and hematocrit measurements available within almost all HD machines.

In this study, our central compartment was assumed to model central parts of the intravascular volume including the heart, central veins and arteries, and lungs¹⁰. This compartment is where the dilution indicator mixes with blood at a high rate. Estimated central volume (2.83 ± 0.66 L) was larger and estimated intercompartmental flow rate (1.64 ± 0.39 L/min) was lower than typical central blood volume and cardiac output, respectively, which can be explained by the remote location of the BVM sensor in the extracorporeal system³⁰. It appears that without additional experimental information it will not be possible to evaluate the accuracy of estimated individual parameters except for ABV. The potential of faster sampling rates to allow estimation of these parameters is a topic for future research.

The fidelity of our parameter estimation scheme was studied by analyzing the sensitivity of the model's output to changes in the model parameters. To this end, we used forward sensitivity analysis (FSA) to compare sensitivities at each sampled point in time^{31, 32}. It is convenient to multiply the forward sensitivity function by the model parameter to define the unnormalized forward sensitivity function with respect to a parameter in cases where the

magnitudes of the parameters differ considerably. The unnormalized forward sensitivity function with respect to a model parameter p_i is given by³³

$$S_i = p_i \frac{\partial W_m}{\partial p_i}(t, \mathbf{p}), \quad \text{Eq. 8}$$

where $\mathbf{p}$ is the vector of model parameters p_i . Knowledge of how the model output changes with respect to changes in model parameters is crucial for experimental design, and sampling of data for the purpose of optimal parameter estimation³². Figure 6 shows an example of this sensitivity analysis for AV patient AF300. The plot is divided into three regions: region I captures dynamics prior to dilution, region II captures dynamics immediately after dilution which is dominated by mixing between compartments, and region III captures post-mixing dynamics referred to as the elimination phase, starting 4 min after dilution. Figure 6 shows that the model output W_m has much lower sensitivity to model parameters in region I compared to the other regions. The output is dominated by refilling/filtration prior to dilution in region I, by time delay and compartmental volumes during mixing in region II, and by central compartment volume and refilling/filtration during the elimination phase (region III). The output is most sensitive to the central compartment's volume in region II with sensitivity dropping significantly in region III. We observe that the shape of curves becomes similar to each other moving from region II to region III. Since the BEXP algorithm is limited to modelling only the elimination phase (region III), it is less likely to uniquely identify parameters.

Figure 6 shows that our model has a higher sensitivity for estimates of central compartment volume $V_1(t_0)$ compared to peripheral compartment volume $V_2(t_0)$, and lower sensitivities for other model parameters such as blood exchange between compartments. Sensitivity analysis would suggest higher variabilities in the estimates of these parameters which is consistent with actual estimation results. These low sensitivities are consistent with the results reported in reference¹³ where some of the estimated parameters are different from expected value. Separate sensitivity analysis using a modified model which has ABV as a state (work not shown here for brevity) showed good $ABV(t_0)$ sensitivity. Indeed, for example, for our AV patients, intratreatment SD of estimates for $V_1(t_0)$ and $V_2(t_0)$ is 0.23L and 0.32L, while the SD of $ABV(t_0) = V_1(t_0) + V_2(t_0)$ is only 0.27L.

It is worth noting that the forward sensitivity function is a function of time that indicates the sensitivity of the model's output at any time to changes in the parameters. Therefore, it indirectly indicates how to select sample points in time to enhance information provided by the measurement, as more information can be extracted from a sample point with high sensitivity. This becomes crucial when only a limited number of measurements can be recorded. Also note that ABV estimates in this study, similar to ABV reported in reference⁶, include the added extracorporeal circulation volume, estimated to be around 300 ± 10 mL⁶. This volume needs to be subtracted from our estimates to obtain actual absolute blood volume.

Study limitations include small patients sample size, lack of validation against gold-standard methods, and the assumption that the so-called F-cell ratio³⁴ is fixed. However, the variation in F-cell ratio during HD may not be as large as previously assumed³⁴. The current model is expressed in terms of blood water concentration. This measure is not uncommon in hemodialysis research. Measurement of BWC has been suggested to quantify ultrafiltration-induced blood volume changes before³⁵ and is also relevant for urea kinetic modeling³⁶. BWC varies in parallel with volume expansion and volume contraction and is therefore more intuitively related to blood volume issues compared to hemoglobin concentration or hematocrit showing an inverse relationship. Also, since BWC is related to hematocrit, mean cellular hemoglobin, and plasma protein concentration, the model can – in principle – be expressed in these variables, as well. This is beyond the scope of this study.

In conclusion, the dilution protocol and the new VVKM-based estimation algorithm offer a noninvasive, inexpensive, safe, and practical approach for ABV estimation in routine HD settings. The estimation of ABV estimates is significantly more precise when compared with estimates derived from the classical BEXP algorithm. This ABV information can be the basis for hypothesis generating studies aimed at achieving better fluid balance management resulting in improved HD outcomes.

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Appendix

Analysis of observability in nonlinear systems requires detailed theoretical considerations which are beyond the scope of this work³⁷. However, we can discuss this important issue which affects identifiability by using a linearized version of the model. A general linear (time-invariant) two-compartment model can be described in state-space form as

$$\begin{aligned}\dot{x} &= Ax + Bu \\ y &= Cx,\end{aligned}\quad \text{Eq. 9}$$

where x , u , y are respectively the state, input and output vectors. A , B and C denote the state matrix, input matrix, and output matrix, respectively. The second row of the state matrix of a two-compartment model is the negative of the first row as follows:

$$A = \begin{bmatrix} a_{11} & a_{12} \\ -a_{11} & -a_{12} \end{bmatrix}. \quad \text{Eq. 10}$$

The linear two-compartment model is said to be *observable* if and only if the observability matrix is full rank²²:

$$\text{rank} \begin{bmatrix} C \\ CA \end{bmatrix} = 2 \quad \text{Eq. 11}$$

$$C = \begin{bmatrix} c_{11} & c_{12} \\ c_{21} & c_{22} \end{bmatrix}.$$

Application to the linearized model with y_I being the output, results in the following condition for observability:

$$\det \begin{bmatrix} c_{11} & c_{12} \\ a_{11}(c_{11} - c_{12}) & a_{12}(c_{11} - c_{12}) \end{bmatrix} \neq 0 \rightarrow c_{11} \neq c_{12} \quad \text{Eq. 12}$$

When $c_{11}=c_{12}$, we have a situation where the output is an equal (half-and half) mixture of the states of both compartments and the system is not observable. In such cases, since the states are unobservable, the model parameters become unidentifiable^{23–25}. Our numerical simulations suggested that a similar loss of observability also occurs in the nonlinear model.

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Figure 1:
Schematic diagram of the variable volume two-compartment, intravascular blood-water model. $q_{ufr}(t)$, ultrafiltration rate; $q_{ind}(t)$, indicator infusion rate rate; $q_f(t)$, refiling/filtration rate; $q_1(t)$ and $q_2(t)$, blood exchange between compartments

Figure 2:

Estimation details for patient AF300 at the first injection (RMSE=0.02 kg/kg). Left panel shows estimated blood water content of central compartment (dashed line), peripheral compartment (dashed-dot line) and measurement (solid line). The variation in blood water content due to the indicator dilution shows up at measurement site with a time delay, t_{delay} . Right panel shows administered indicator dilution profile (solid line), and inter-compartment flows $q_1(t)$ (dashed line) and $q_2(t)$ (dashed-dot line).

Figure 3:
Overview of measured water content (dashed line with circle symbol) and model estimation (solid line) during HDF session for arterio-venous (AV) access patient AF300 and central-venous (CV) access patient ST011

Figure 4:
Overview of measured water content (dashed line with circle symbol) and model estimation (solid line) for arterio-venous (AV) access patient KH110 and central-venous (CV) access patient FR170

Figure 5:

Intratreatment variability of ABV estimates (mean $\pm$ SD) in arterio-venous (AV) and central-venous (CV) access patients. Our physiologically motivated kinetic model (line with the circle for mean), classic mono back-extrapolation method (dashed line with triangle for mean)

Figure 6:

Forward sensitivity analysis for five model parameters for arterio-venous (AV) access patient AF300 at first dilution experiment before (Region I), during (Region II), and after the perturbation (Region III); central compartment volume $V_f(t_0)$ (solid line), peripheral compartment volume $V_f(t_0)$ (dashed line), blood exchange between compartments $q_f(0)$ (dashed-dotted line), refilling/filtration $q_f(0)$ and α (triangle, dotted line), time delay t_{delay} (rectangle, dashed line)

Table 1

Patient and treatment data

Variable (unit)	Values*
Age (year)	61 [54–73]
Body height (m)	1.70 [1.64–1.85]
Body mass at dry weight (kg)	69 [58.5–80]
Anthropometric blood volume estimated at dry weight (L)	4.50 (0.82)
Specific blood volume based on anthropometric estimates (kg/mL)	67.53 (4.59)
Ultrafiltration volume (L)	3.1 [1.8–4]
Ultrafiltration rate (mL/min)	13.35 [7.50–18.00]
Extracorporeal blood flow (mL/min)	250**
Dialysate flow (mL/min)	500 or 800***
Infusion flow rate of the HDF substitution fluid (mL/min)	23 [21–35]

* Normal distributed results are reported using mean(SD), otherwise, median [first quartile-third quartile]. Shapiro–Wilk test is used to test normality.

** All treatments at 250 mL/min

*** 500mL/min for 5 patients (18 treatments) and 800mL/min for 1 patient (3 treatments)

Table 2

Parameters to be estimated

Parameter (units)	
Central Compartment's volume at start of analysis (L)	$V_f(t_0)$
Peripheral Compartment's volume at start of analysis (L)	$V_p(t_0)$
Blood exchange between compartments (L/min)	$q_f(t_0)$
Fluid exchange with interstitial space (L/min and L/min ²)	q_{f0} and α
Time delay (min)	t_{delay}

Table 3

Descriptive statistics of estimates *

Variable (unit)	
Central compartment blood volume at $t=0$, $V_1(0)$ ** (L)	2.83 (0.66)
Peripheral compartment blood volume at $t=0$, $V_2(0)$ ** (L)	2.98 (0.66)
Intravascular blood volume at $t=0$, $V(0)$ *** (L)	4.16 [3.80–5.59]
Specific blood volume (kg/mL)	71.94 [51.40–79.97]
Blood exchange between compartments, $q_1(t_0)$ (L/min)	1.64 (0.39)
Fluid exchange with interstitial space, q_{10} (mL/min)	10.26 (5.62)
Fluid exchange with interstitial space, α (mL/min ²)	21.12 (21.94)
Time delay, t_{delay} (min)	0.68 [0.56–0.84]
RMSE (kg/kg)	0.02 [0.02–0.03]

* Normal distributed results are reported using mean(SD), otherwise, median [first quartile-third quartile]. Shapiro–Wilk test is used to test normality.

** only includes AV patient results as the parameter is not available (identifiable) in CV patient.

*** includes both AV and CV patient results

Table 4

Nested one-way ANOVA of absolute blood volume

		Intravascular blood water content kinetic model (VVKM) (L)				Back-extrapolation algorithm (BEXP) algorithm (L)		
		Degree of freedom	Sum of Squares	Mean square	Standard deviation	Sum of Squares	Mean square	Standard deviation
Arterio-venous (AV) access Patients	Interpatient	2	8.81	4.41	2.08	9.07	4.53	2.13
	Intertreatment	6	3.29	0.55	0.73	1.84	0.31	0.54
	Intratreatment	26	1.80	0.07	0.27	5.10	0.22	0.47
central-venous (CV) access Patients	Interpatient	2	0.95	0.48	0.69	2.07	1.04	1.01
	Intertreatment	9	1.40	0.15	0.39	3.17	0.35	0.59
	Intratreatment	39	2.33	0.06	0.24	10.31	0.26	0.51