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A New Approach to Bicarbonate Addition During Hemodialysis: Testing Model Predictions in a Patient Cohort

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This work involved human subjects or animals in its research. Approval of all ethical procedures and protocols was granted by the Ethical Committee of Campania Sud, Italy.

ABSTRACT In this study, we present a new protocol for kidney replacement therapy (hemodialysis), based on an explicitly solvable mathematical model. With current protocols, the high and constant level of bath bicarbonate (HCO_3^-) used to prevent metabolic acidosis leads to very rapid delivery of HCO_3^- into the patient during the first part of the therapy. This rapid alkalinization elicits a robust buffer response that, paradoxically, consumes more HCO_3^- than is added during the remainder of the treatment. In previous studies, we developed an analytical model that allows one to quantify these events and tested alternative protocols manipulating the rate of rise in blood bicarbonate concentration (HCO_3^-). The protocol tested in this paper enforces a more gradual increase in blood HCO_3^-, by means of a model-based staircase adjustment of bath HCO_3^-. Model equations predict a reduction of buffer response and rate of organic acid production. These predictions are tested in 20 stable outpatients receiving hemodialysis. We find that the proposed protocol achieves the desired profile of blood HCO_3^- with good accuracy and reduces the total buffer response by 1/3 and the rate of lactic acid production by at least 1/4, as compared to conventional therapy. Although more studies are needed, we believe that our work will pave the way for a more rational approach to correction of acidosis during hemodialysis.

ARTICLE HIGHLIGHTS

- Our study tests an analytic model designed to enforce a more gradual rate of bicarbonate delivery during hemodialysis.
- Using our model, we show that we can reduce the excessive buffer response and lactic acid production that occur with the conventional approach.
- We demonstrate that our model can provide a rational approach to bicarbonate addition during treatment.

INDEX TERMS Acid-base balance, dialysis protocols, kidney disease, mathematical model of hemodialysis, linear systems.

I. INTRODUCTION

Chronic kidney disease is a serious illness affecting more than 10% of the worldwide population [1], with important social impact. In the USA, Medicare expenditures for the treatment of end stage kidney disease amounted to 49,2 billion dollars in 2018. Extracorporeal hemodialysis is a life-saving therapy for end-stage kidney disease and remains the most expensive Medicare treatment at 93,191 dollars per person annually [2, Chapter 9]. At the end of 2018, there were 554,038 patients undergoing dialysis in the USA [2, Chapter 1]. Hemodialysis therapy is carried out in three sessions per week, each about four hours long. In the interval between treatments, the patient accumulates hydrogen ion (H^+) in excess, which is buffered by HCO_3^-, with consequent pH reduction; in addition, the patient retains fluids and accumulates metabolic end-products and toxins.

At the most basic level, hemodialysis therapy is tasked to replenish blood HCO_3^- in order to maintain a more

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acceptable acid-base homeostasis, and remove the excess of body water and uremic toxins [3]. These tasks are accomplished by linking the patient's blood to an external bath solution separated by a semipermeable membrane. Relevant to our study, the bath solution typically contains bicarbonate at a concentration much higher than the patient's blood, allowing for inward diffusion. The bath solution also contains acetate that is metabolized into bicarbonate. Removal of the excess body fluid is accomplished through removal of a fraction of the liquid component of serum by adjusting the transmembrane hydrostatic pressure. The concentration[1] of HCO_3^- and acetate in the dialysis bath and the ultrafiltration rate are three key variables under the control of the nephrologist. We refer to the selection of these three quantities as a *protocol* and one theme of this paper is how to design a dialysis protocol ensuring slow alkalinization (HCO_3^- restoration), as elaborated below.

To assure that sufficient alkali is added, bath HCO_3^- is typically set 10 to 15 mmol/L higher than the patient's blood level at the initiation of treatment and maintained without change for the duration of therapy (standard protocol) [3]. As a result, blood HCO_3^- and pH rise rapidly during the first 1-2 hours of dialysis [4]–[8]. After this initial surge, however, little additional alkali is added, despite a continued gradient for HCO_3^- and acetate influx. The fall in alkali addition occurs because the initial rapid alkalinization induces a release of H^+ from body buffers and stimulates cellular organic acid production, mainly lactic acid [7].

In our recent studies, we have proposed that this excess buffer response is maladaptive, diverting energy from normal metabolism. To address this issue, our research group has developed a mathematical model for the acid-base events occurring during dialysis therapy [4], [9], [10]. Exploiting the model, we have proposed that H^+ release can be significantly reduced if the bath HCO_3^- is started at a lower level and gradually increased during dialysis [9]. Our proposed change in dialysis prescription should reduce lactic acid production and H^+ release from body stores, and prevent the inefficient loss of HCO_3^- as dialysis progresses. In this paper, we use our model to create a hemodialysis prescription with a staircase increase in bath HCO_3^- to enforce a linear increase in patient blood HCO_3^- and report the results of a clinical study aimed at testing whether this prescription will actually diminish lactic acid production and the release of H^+ from body buffers [10].

A. RELATED WORK AND MOTIVATION

Hemodialysis therapy is, of course, largely investigated from a medical and biochemical perspective. The interested reader is referred to [3], [7], for useful entry-points to such literature. Engineering-oriented studies falling under the wide umbrella of health care applications are reviewed in [11]. Improving risk prediction, diagnosis accuracy and detection rate of chronic kidney disease are the focus of [12], [13]. The analysis and design of the hemodialysis therapy can be traced back to the early seventies, with the first attempts to design optimized dialyzers [14]. Automatic monitoring of the dialysis is the topic considered in [15]. Adaptive control of the dialysis procedure to manage the wide range of patients' clinical conditions is addressed in [16]–[20]. In particular, using an algorithmic approach based on tracking procedures, in [16], [18], the goal is to achieve a target profile of the blood solute concentration by imposing a suitable profile of the ultrafiltration rate and of the solute concentration of the dialysate. In [19], [20], a discrete-time hemodynamic model of the patient response to dialysis is proposed, with ultrafiltration rate and dialysate sodium concentration as input and physiological parameters as output.

Development of efficient circuits and sensors for on-line monitoring of the therapy have recently been considered in [21]. Health-care systems exploiting predictions of the clinical status to optimize the patient management is the issues addressed in [22]–[24]. Management of medical data is considered in [25]. In [26] the design of wearable kidneys is addressed.

The idea of monitoring the patient state by means of an ensemble of sensors can be traced back to the late 1980's. The goal of the authors of [27]–[29] is to avoid patients' hypotension by proper design of the ultrafiltration profile. In [27] the authors propose continuously adapting the main dialysis parameters (ultrafiltration and dialysate sodium concentration) using a dynamic controller. With the recent advances in data storage capacity, cloud storage, and computing, efforts have been made in the direction of using very large datasets of dialysis sessions for the estimation of clinically relevant parameters [30]. All these studies highlight the need for reliable mathematical models of the dialysis process.

In the seventies, researchers started to systematically develop mathematical models of the patients' response to the dialysis treatment [31]. A landmark contribution to such studies was the modeling of urea kinetics in 1985 [32]. In successive years, several models have been developed to improve therapy effectiveness [33], [34] and capture the dynamics of mass exchange during the treatment [35]–[39].

Next, we review the literature more closely related to the present contribution. Multiparametric mono/multicompartmental kinetic models have been studied in a series of works [40]–[44]. The authors of [43] developed mathematical models for the movement of the solutes through the dialyzer membrane. Likewise, mathematical models of solute kinetics and body fluid changes during hemodialysis are addressed in [44]. The HCO_3^- mass transfer between dialysate and patient blood is studied in [45]. We also mention the recent contribution provided in [46] that is directed at profiling ultrafiltration. Most of the cited studies provide mathematical models that can only be solved numerically.

In order to explain the motivation for the present work, let us start by noting that one of the main goals of the dialysis therapy is to replace body HCO_3^- stores lost in the interval

[1]We denote by HCO_3^- the bicarbonate content and by $[HCO_3^-]$ the bicarbonate concentration.

between treatments by dietary acid production. To achieve this goal, standard dialysis protocols maintain bath HCO_3^- high and constant throughout the procedure, in order to replenish HCO_3^- stores, a practice perhaps also influenced by the simplistic model developed in [47]. The therapy goal is not efficiently achieved and therefore we believe that new protocols are needed [4].

Most of the currently available dialysis machines allow for adjusting bath HCO_3^- in a stepwise fashion, and protocols with variable bath HCO_3^- have been developed to exploit this capability, without adhering to rigorous criteria [48]. In recent years, our research group has developed a more reliable mathematical tool, known as the H^+ mobilization model, able to accurately predict the time profile of blood HCO_3^- during hemodialysis [4], [9], [10]. This model is a key enabler in exploiting engineering skills to assess the acid-base events during hemodialysis in a more rational manner and provide the impetus for the present article.

B. CONTRIBUTION

In this paper, we review the model developed in [4], [9], [10] and extend it to include the dynamics of lactic acid production and lactate loss into the bath during hemodialysis. Then, we develop fully the hemodialysis staircase protocol, initially conceived in [10], and test its predictions in hemodialysis patients. The contributions of this paper can be summarized as follows.

- We provide a comprehensive and engineering-oriented review of the H^+ mobilization model, expanding the framework presented in [9], [10]. Simple closed-form analytical solutions of the differential equations are presented and their system-theory interpretation emphasized, providing important insights. This should be contrasted with the state-of-the-art before [4], [9], [10], where the few models developed for specific aspects of acid-base homeostasis are mainly solved numerically.
- Elaborating on the approach originally proposed in [10], in this paper we present a protocol in which the bath HCO_3^- is adjusted in a staircase fashion, with the goal of enforcing a slower alkalinization of the patient, which we propose should improve dialysis therapy protocols.
- We report the novel results of an observational study to test whether the staircase protocol actually achieves the goals of enforcing a linear increase in blood HCO_3^- and whether it reduces the release of H^+ from body buffers and organic acid production. Comparisons with previous studies are also provided to corroborate our findings.

With this paper we hope to stimulate large-scale experimental studies aimed at assessing acid-base homeostasis during hemodialysis. Our vision is that a cross pollination between engineering skills and medical expertise may provide fundamental steps toward safer and more beneficial hemodialysis therapy. In the long term, we envision that the engineering model discussed in this paper has the potential of orienting the design of next-generation dialysis machines. In this respect, our studies indicate the advantage of finely and continuously adjusting bath HCO_3^- during therapy.

The remainder of the paper is organized as follows. In Sect. II the mathematical models of acid-base events during hemodialysis are introduced. Solutions to the differential equations of the H^+ mobilization model are provided in Sec. III. The protocol and details of the patient study are described in Sec. IV. Section V summarizes our findings and discusses the main results of the paper. Final remarks are given in Sec. VI. An appendix contains some mathematical derivations.

II. MODEL FORMULATION

A. ABS MODEL

Before we developed our H^+ mobilization model [4], [9], [10], the time profile of blood HCO_3^- during hemodialysis was explained according to the pharmacokinetic concept of apparent HCO_3^- space (ABS) [47]. The apparent space is not a physical space, which is a model weakness and, more important, it wrongly predicts the dynamic behavior of patient's blood HCO_3^-, providing little insight [4], [7], [49]. In mathematical terms, the ABS model is:

$$V\dot{C}_b(t) = D(C_d - C_b(t)) + J_a, \qquad t \geq 0, \tag{1}$$

where the dot indicates time derivative. In the above: $C_b(t)$ (measured in mmol/L) is the patient's blood HCO_3^-, whose initial value $C_b(0)$ is denoted by C_{b0}; the constant apparent volume V (L) is assumed equal to 50% of the post-dialysis patient's body weight; dialysance D (L/min) is to be interpreted as a "conductance" that determines the rate of passage of HCO_3^- from the bath to the blood through a semipermeable membrane of separation; $t = 0$ is the time at which the dialysis session begins and we also denote by $t = t_{end}$ the time at which it ends; C_d (mmol/L) is the constant bath HCO_3^-; and J_a (mmol/min) is a constant flux assumed equal to the product $C_{da}S_a$, where C_{da} (mmol/L) is the bath acetate concentration and S_a (L/min) is a constant to be introduced shortly. Here, C_d and C_{da} are *effective* values of bath HCO_3^- and acetate concentration. They correspond to 95% of the actual bath concentration, due to the Gibbs-Donnan effect [4].

In system-theory interpretation, dialysis therapy is modeled as a system with constant inputs C_d and C_{da} and time-varying output $C_b(t)$. Starting from a rest equilibrium with $C_b(t) = C_{b0}$ for $t = 0$, when the patient's blood is connected to the dialysis bath through the semipermeable membrane, C_d (typically larger than C_{b0}) and C_{da} act as *forces* in response to which $C_b(t)$ grows from its initial value C_{b0}, tending to restoring a semblance of acid-base homeostasis, which is the main goal of the therapy.

Solution to equation (1) is straightforward [50]:

$$C_b(t) = C_{b0}\, e^{-\frac{D}{V}t} + (C_d + J_a/D)\left(1 - e^{-\frac{D}{V}t}\right), \tag{2}$$

which is the response of a first-order linear time-invariant (LTI) system with time constant V/D (min), see [51].

The predictions of (2) are in contrast with experimental evidences and are inconsistent [4], [7], [49]. For instance, the steady-state level of blood HCO_3^-, $\lim_{t\to\infty} C_b(t)$, is equal to $C_d + J_a/D$, which is not physically possible because it is larger than C_d.

B. H^+ MOBILIZATION MODEL

Our model considers a physical space, the extracellular fluid (ECF) volume in place of the ABS and we make the point that the HCO_3^- removal from ECF can occur by two different mechanisms. The first efflux is HCO_3^- itself flowing across the dialysis membrane due to ultrafiltration, and the second efflux is due do the addition of H^+ to the ECF from extracellular and intracellular buffers and also from organic acid production. Addition of H^+ to the ECF from any source consumes HCO_3^- by converting it to CO_2 and water. Addition of H^+ is a physiological response that protects the patient from the effects of acute alkalinization, but which can also be maladaptive, preventing the patient from restoring their body HCO_3^- stores and diverting energy from normal metabolism [4]. These considerations can be summarized by the following master equations. For $t \geq 0$:

$$\frac{d}{dt}\left[C_b(t)V(t)\right] = J_b^+(t) + J_b^-(t) + J_a(t) + J_m(t), \quad \text{(3a)}$$

$$V_a \dot{C}_{ba}(t) = D_a(C_{da} - C_{ba}(t)) - K_a C_{ba}(t), \quad \text{(3b)}$$

with the initial conditions $C_b(0) = C_{b0}$ and $C_{ba}(0) = 0$, respectively, with $C_{ba}(t)$ (mmol/L) being the blood acetate concentration. Differential equation (3a) is derived in [9], [10]. Differential equation (3b) accounts for the acetate contribution to blood HCO_3^- $C_b(t)$. The four fluxes appearing at the right-hand side (RHS) of (3a), namely

$$J_b^+(t) = D(C_d(t) - C_b(t)), \quad \text{(4a)}$$

$$J_b^-(t) = \frac{1}{2}\dot{V}(t)(C_b(t) + C_d(t)), \quad \text{(4b)}$$

$$J_a(t) = K_a C_{ba}(t), \quad \text{(4c)}$$

$$J_m(t) = -M(C_b(t) - C_{b0}), \quad \text{(4d)}$$

are measured in mmol/min and have the following interpretation:

- $J_b^+(t)$ is analogous to the first addend at the RHS of (1) with the important difference that here we allow the bath HCO_3^- $C_d(t)$ to be time-varying;
- $J_b^-(t)$ appears as a consequence of the assumed time-variability of the physical ECF volume

$$V(t) = V_0 - Q_f t, \quad \text{(5)}$$

  wherein V_0 is the volume at time 0 and Q_f (L/min) is the ultrafiltration rate;
- $J_a(t) = K_a C_{ba}(t)$ is the component corresponding to the second addend at the RHS of (1), taking into account the *dynamics* of acetate diffusion into the patient, metabolized into HCO_3^-, with K_a (L/min) being the constant ruling the metabolic conversion of acetate into HCO_3^- [4];
- a distinctive feature of the model is the negative flux $J_m(t)$ in (4d) that models the response of the organism to the external stimulus, counteracting the increase in HCO_3^- elicited by the therapy; flux $J_m(t)$ is characterized by the *mobilization constant* M (L/min), which is a key model parameter.

Hydrogen ion release into the ECF, modeled by flux $J_m(t)$, is in part physiological and in part maladaptive. The physiological component is the necessary back-titration of body buffers. The maladaptive part is due both to the release of H^+ from buffers to prevent excessive acute alkalinization and to stimulation of lactic acid production by cellular metabolism, which is instantly dissociated into H^+ and lactate. Hydrogen ion addition to the ECF from lactic acid production is only sustained when the lactate anions produced are also lost into the dialysis bath. If they remain in the ECF, they are eventually metabolized removing H^+ and regenerating HCO_3^-.

Consider next (3b), wherein D_a (L/min) and V_a (L) are the "acetate counterpart" of the HCO_3^- dialysance D and volume $V(t)$, respectively; note that V_a is assumed constant [4]; Solving (3b) is straightforward and gives:

$$C_{ba}(t) = C_{da}\, S_a \left(1 - e^{-t/\tau_a}\right), \quad \text{(6)}$$

where $S_a = \frac{D_a K_a}{D_a + K_a}$ (L/min), and

$$\tau_a = \frac{V_a}{D_a + K_a} \qquad \text{(min)} \quad \text{(7)}$$

is a time constant. This provides an explicit expression for the flux $J_a(t)$ at the RHS of (3a).

We enrich the model developed in [4], [9], [10] with a differential equation for lactate dynamics during hemodialysis. Lactate generation and loss are calculated from the change in measured blood lactate concentration during dialysis using an equation that assumes first order kinetics [52]. The physical basis for the concentration of lactate in the patient's blood, denoted by $C_\ell(t)$ (mmol/L), consists of internal (cellular) production P_ℓ (mmol/min) of lactic acid (instantly converted into lactate) and a loss from a fixed volume V_ℓ (L), through a membrane of "conductance" D_ℓ (L/min) that connects the volume with an external void compartment (dialysis bath). We assume that internal production of lactic acid is constant. Let the initial concentration of lactic acid in the volume be $C_\ell(0) = C_{\ell 0}$. This gives the following differential equation, for $t \geq 0$:

$$\underbrace{V_\ell\, \dot{C}_\ell(t)}_{\substack{\text{lactate variation}\\ \text{per unit time}}} = \underbrace{P_\ell}_{\substack{\text{production}\\ \text{per unit time}}} - \underbrace{D_\ell\, C_\ell(t)}_{\substack{\text{loss per}\\ \text{unit time}}} \quad \text{(mmol/min)} \quad \text{(8)}$$

with initial condition $C_\ell(0) = C_{\ell 0}$.

Lactic acid production P_ℓ diverts energy from normal metabolism and should be minimized. We propose that the time profile of $C_b(t)$ has an effect on P_ℓ. In particular, if the therapy restores blood HCO_3^- too rapidly, i.e. the derivative

$\dot{C}_b(t)$ is too large, especially during the initial stages of the treatment, the internal production of lactic acid P_ℓ tends to be higher. This means that the response of the organism elicited by the therapy, $J_m(t)$, is sustained by a larger maladaptive component.

III. SOLUTION TO THE H^+ MOBILIZATION MODEL

The H^+ mobilization model considered in this paper is completely described by equations (3) and (8). We now solve the model, starting from considering the lactate dynamic defined by (8). It is well-known that the unique solution[2] to (8) with initial condition $C_\ell(0)$ is:

$$C_\ell(t) = C_\ell(0)e^{-t/\tau_\ell} + \frac{P_\ell}{D_\ell}\left(1 - e^{-t/\tau_\ell}\right), \tag{9}$$

where

$$\tau_\ell = \frac{V_\ell}{D_\ell} \qquad \text{(min)} \tag{10}$$

is the time constant. Let

$$\mathrm{u}(t) = \begin{cases} 1, & t \geq 0, \\ 0, & t < 0, \end{cases} \tag{11}$$

denote the unit step signal. Expression (9) is the output of a standard first-order LTI filter with impulse response $e^{-t/\tau_\ell}\,\mathrm{u}(t)$. The output is composed of the sum of two contributions: the system free response due to the non-zero initial condition $C_\ell(0)$, plus the response of the LTI system at rest forced by the input $\frac{P_\ell}{V_\ell}\,\mathrm{u}(t)$ [51]. Equivalently, we can define the input and the output with respect to the reference level of lactate concentration $C_\ell(0)$. Let

$$h_\ell(t) = \frac{1}{\tau_\ell} e^{-t/\tau_\ell}\,\mathrm{u}(t) \qquad \text{(1/min)} \tag{12}$$

be the system input response, and let $\left(P_\ell/D_\ell - C_\ell(0)\right)\mathrm{u}(t)$ be the input signal. For $t \geq 0$:

$$\begin{aligned} C_\ell(t) - C_\ell(0) &= \left(\frac{P_\ell}{D_\ell} - C_\ell(0)\right)\mathrm{u}(t) \star h_\ell(t) \\ &= \left(\frac{P_\ell}{D_\ell} - C_\ell(0)\right)\left(1 - e^{-t/\tau_\ell}\right), \end{aligned} \tag{13}$$

where $\star$ denotes convolution [51]. Expression (13) is the same as (9). For $t \gg \tau_\ell$, expression (13) reduces to

$$D_\ell\, C_\ell(t) \approx P_\ell \qquad \text{(mmol/min)}. \tag{14}$$

After a sufficiently long time, the lactate lost through the membrane per unit time is constant and equal to the lactic acid production per unit time. This is an obvious consequence of (8): at equilibrium the left-hand side (LHS) of (8) is zero and the differential equation reduces to (14).

Recall from Sec. II-B that only the lactate lost into the bath is responsible for HCO_3^- consumption and therefore contributes to the potentially maladaptive component of flux $J_m(t)$. Let LOSS (mmol) denote the total amount of lactate lost into the bath during the whole course of the therapy. From (9):

$$\begin{aligned} \text{LOSS} &= \int_0^{t_{end}} D_\ell\, C_\ell(\xi)\, d\xi \\ &= V_\ell(C_\ell(0) - C_\ell(t_{end})) \\ &\quad + D_\ell\, t_{end}\, \frac{C_\ell(t_{end}) - C_\ell(0)\, e^{-t_{end}/\tau_\ell}}{1 - e^{-t_{end}/\tau_\ell}}. \end{aligned} \tag{15}$$

For $t_{end} \gg \tau_\ell$, the above simplifies to:

$$\text{LOSS} \approx V_\ell(C_\ell(0) - C_\ell(t_{end})) + D_\ell C_\ell(t_{end}) t_{end}. \tag{16}$$

Next, let us consider the solution to (3a) that describes the HCO_3^- dynamics. In the assumption $|\dot{V}(t)| = Q_f \ll 2D$ for $0 \leq t \leq t_{end}$, which is usually verified in practice, straightforward algebraic manipulations yield the following differential equation:

$$\dot{C}_b(t) + C_b(t)\frac{D+M}{V(t)} = \frac{DC_d(t) + MC_{b0} + J_a(t)}{V(t)}. \tag{17}$$

The standard therapy protocol assumes that the bath HCO_3^- is constant, $C_d(t) = C_d$, in which case an approximate closed-form expression for $C_b(t)$ can be derived [10, Eq. (16)]:

$$\begin{aligned} C_b(t) - C_{b0} \approx{}& \frac{D(C_d - C_{b0})}{D+M}\left(1 - e^{-t/\tau}\right) \\ &+ \frac{C_{da}S_a}{D+M}\,\frac{\tau\left(1 - e^{-t/\tau}\right) - \tau_a\left(1 - e^{-t/\tau_a}\right)}{\tau - \tau_a}, \end{aligned} \tag{18}$$

where

$$\tau = \frac{V_0}{D+M} \tag{19}$$

is the HCO_3^- time constant measured in minutes, and τ_a has been defined in (7). From a system theory perspective, we see that (18) describes the output $C_b(t) - C_{b0}$ of a LTI filter with two input signals

$$\begin{cases} \left(C_d - C_{b0}\right)\mathrm{u}(t), & HCO_3^- \text{ input}, \\ C_{da}\,\mathrm{u}(t), & \text{acetate input}, \end{cases} \tag{20}$$

respectively. Note that the blood and bath HCO_3^- are measured with respect to C_{b0}, which can be interpreted as a *reference* HCO_3^-. The LTI filter is then described by two impulse responses

$$\begin{cases} h(t) = \dfrac{D}{V_0} e^{-t/\tau}\,\mathrm{u}(t), & HCO_3^- \text{ filter}, \\ h_a(t) = \dfrac{K_a D_a}{V_a D} e^{-t/\tau_a}\,\mathrm{u}(t), & \text{acetate filter}, \end{cases} \tag{21}$$

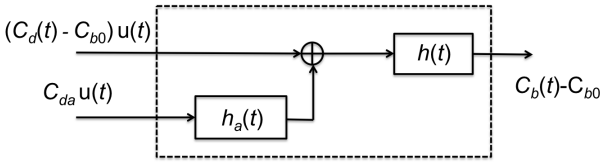

FIGURE 1. System model representation of the hemodialysis therapy, see (20) and (21).

[2]For instance, this can be regarded as a special case of [50, Th. 8.3].

TABLE 1. Clinical parameters of the patients involved in the study.

ID	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20
age (years)	76	61	48	49	31	57	67	50	60	54	82	53	70	51	90	78	78	64	69	57
gender	m	f	f	f	m	m	m	f	f	m	m	m	f	m	m	m	m	m	m	m
height (cm)	160	160	167	153	184	176	175	160	157	166	166	175	155	172	173	167	185	172	181	175
vintage (months)	184	69	434	590	21	74	284	115	240	402	88	11	70	377	69	180	372	30	70	39
pre-BW (Kg)	67.4	102	53.9	85.5	106	83.2	96.5	61.9	103	91	60.5	85.4	68	82	62.3	100	96.3	90.7	84	97.3
post-BW (Kg)	65.7	99.2	52.4	83	104	80.3	93	59	103	87.2	59.1	82.3	65.8	79	60.6	99.2	93.2	86.9	82.4	94.3
pre-BUN (mg/dl)	68.6	54.1	79.3	68.1	65.3	78.4	65.8	73.3	97.1	93.8	73.7	80.3	82.6	55.1	75.1	77.9	45.7	82.6	54.6	65.3
post-BUN (mg/dl)	18.2	14.5	15.4	12.6	18.2	15.4	17.3	15.4	33.6	26.1	14.9	25.7	14.9	10.7	19.1	24.7	11.2	28	12.1	21
pre-pH	7.39	7.42	7.33	7.40	7.36	7.37	7.40	7.38	7.35	7.35	7.43	7.35	7.36	7.39	7.41	7.30	7.42	7.44	7.46	7.43
pre-pCO_2 (mmHg)	36	35	36	39	37	36	35	41	39	43	39	32	42	39	40	38	40	30	34	32
pre-[HCO_3^-] (mmol/L)	21.4	21.9	18.4	23.5	20.4	20.4	20.9	23.8	20.7	23	25.6	17.2	23	22.7	24.5	18.1	25.3	19.8	23.7	21.1
pre-lactate (mmol/L)	0.83	1.09	0.65	1.21	1.02	1.26	1.35	0.51	0.54	1.38	0.56	0.55	0.92	0.95	0.6	0.79	1.53	0.56	0.84	0.98

ID = patient identifier; pre = pre-dialysis; post = post-dialysis; BW = body weight; BUN = blood urea nitrogen.

measured in (L/min). The system-theory interpretation is schematically summarized in Fig. 1.

As pointed out at the end of Sec. II, dialysis therapy can be substantially improved if the nephrologist has the opportunity to adjust the time profile of blood HCO_3^-. One way to shape the $C_b(t)$ profile is to modify the force C_d acting on it.[3] Namely, we seek for the filter input C_d such that a desired output $C_b(t)$ is obtained. To this aim we now consider a time-varying bath HCO_3^- $C_d(t)$. Many of the currently available dialysis machines allow one to adjust bath HCO_3^- in steps, facilitating our investigation of what is called a *staircase* protocol:

$$C_d(t) = C_{di}, \qquad \text{for } t_{i-1} \le t < t_i, \tag{22}$$

where $t_0 = 0$, and $C_{d1}, \ldots, C_{d\kappa}$, are values of bath HCO_3^- set on the machines at times $i = 1, \ldots, \kappa$. The staircase protocol (22) offers a formidable flexibility and allows the nephrologist to obtain virtually any desired time-profile of $C_b(t)$ [10]. The input signal $C_d(t)$ in (22) can be written as a superposition of delayed unit-step signals and therefore the solution to (3a) follows by the superposition principle. After some algebraic manipulations, the following approximate solution is obtained [10]:

$$\begin{aligned} C_b(t) \approx C_{b0} + \frac{D}{D+M}\Bigg[& C_{dj(t)}\left(1 - e^{-(t-t_{j(t)-1})/\tau}\right) \\ & + \sum_{i=1}^{j(t)-1} C_{di}\left(e^{-(t-t_i)/\tau} - e^{-(t-t_{i-1})/\tau}\right) \\ & - C_{b0}\left(1 - e^{-t/\tau}\right) \\ & + \frac{C_{da}S_a}{D}\,\frac{\tau\left(1-e^{-t/\tau}\right) - \tau_a\left(1-e^{-t/\tau_a}\right)}{\tau - \tau_a}\Bigg], \end{aligned} \tag{23}$$

where, for $t \in (0, t_{end})$, $j(t) \in \{1, \ldots, \kappa\}$ is the integer such that $t_{j(t)-1} \le t \le t_{j(t)}$. The availability of such a closed-form for $C_b(t)$ is important because, given a sequence $\{C_b(t_i)\}$ of desired values of blood HCO_3^- at specific times $\{t_i\}$, expression (23) can be easily solved sequentially for obtaining the corresponding bath HCO_3^- sequence $C_{d1}, \ldots, C_{d\kappa}$, to be set on the dialysis machine. The explicit expression for this sequence is given in Appendix.

[3]There is debate about possible adverse effects of changing C_{da}, and modifying Q_f within a reasonable range has little effect on the profile of $C_b(t)$. Thus, changing the bath HCO_3^- C_d appears to be the best option.

IV. MATERIAL

In this section, we provide the details of the study we have conducted to test our staircase model predictions in dialysis patients. The study was formally approved by the Ethical Committee of Campania Sud, Italy (item No. 10 dated 01/28/2020). Stable patients receiving outpatient hemodialysis treatments for longer than 3 months at the Maria Rosaria Clinic, Pompeii, Italy, were invited to participate. Only adult patients having a native arteriovenous fistula for dialysis access and having a urea exchange ratio (Kt/V) greater than 1.2 were included. Patients with acute illness, congestive heart failure, liver failure, lung failure and those hospitalized in the 3 months preceding the study were excluded. Twenty patients (14 men and 6 women) were enrolled after giving informed consent. Table 1 summarizes the relevant patient data, collected on the day of study.

The study patients underwent standard dialysis treatments shaped by their clinical needs. Blood and dialysate flow rates were set to 400 (ml/min) and 500 (ml/min) in all cases. Ultrafiltration rates were set by clinical judgment. All treatments were carried out on Nipro Surdial X monitors. ELISIO™ Polynephron dialyzers with surface area 1.9 m^2 (5 instances) or 2.1 m^2 (15 instances) were used. The characteristics of the dialyzer determine the dialysances (D, D_a and D_ℓ) of the solutes (respectively: HCO_3^-, acetate and lactate). The therapy duration was decided by the patients' clinical needs and ranged from 204 to 240 minutes, with an average value $t_{end} = 224$ min.

The bath solution was obtained by mixing an acid concentrate (Diasol, Baxter Healthcare SA, Switzerland) with a sodium bicarbonate cartridge (Niprocart A2F 750, Nipro Europe NV, Belgium). The final dialysate bath contains, in mmol/L, K 2 or 3, Ca 1.5, Mg 0.5, Cl 109 or 110, acetate 3 and Glucose 5.55. Bath Na was set according to patient's usual prescription with levels ranging between 136 and 140 mmol/L. Bath HCO_3^- was adjusted at 30-min intervals, according to the staircase protocol, as described below.

TABLE 2. Average values ± standard deviations for bath HCO_3^- during hemodialysis. Values refer to the HCO_3^- set on the dialysis machine, as detailed in the main text.

time interval min	bath $[HCO_3^-]$ (set on the machine) mmol/L
0-30	25.0 ± 0.9
30-60	25.5 ± 0.7
60-90	26.8 ± 0.5
90-120	28.2 ± 1.0
120-150	29.8 ± 1.6
150-180	31.3 ± 2.1
180-210	32.7 ± 2.9
210-end	31.2 ± 2.1

Bath HCO_3^- was changed in eight steps during hemodialysis: C_{di}, $i = 1, \ldots, 8$, at times $t = 0, 30, 60, 90, 120, 150, 180, 210$ minutes. The values were obtained by (A.4) in Appendix. After computing C_{di} $i = 1, \ldots, 8$, by (A.4), the result is corrected for the Gibbs-Donnan effect (i.e., divided by 0.95) and then rounded to the nearest integer or set to the minimum value available on the machine (24 mmol/L). Table 2 shows the average values and standard deviations for bath HCO_3^- set on the machine in each of the eight time intervals. This staircase protocol was designed to enforce a linear increase in blood HCO_3^- $C_b(t)$ from the pre-dialysis value C_{b0} to a value of 27 mmol/L at 210 minutes and to maintain this value until the end of the treatment. We choose this value because it is similar to the end-dialysis value achieved in our patients studied several years earlier [4].

To test our model, blood samples (< 1 ml) were obtained from arterial fistula needle immediately before the treatment and subsequently from the sample port on the arterial line of the extracorporeal circuit at 30, 60, 90, 120, 150 minutes, and at the end of treatment.[4] Blood flow rate was reduced to 100 ml/min for 1 minute before each blood withdrawal. Blood analysis was performed by using an onsite OPTI CCA-TS gas and electrolyte analyzer and OPTI CCA-TS B-Lac cassettes (OPTI Medical System, Inc, USA) that provide measurements of pH, partial pressure of carbon dioxide (pCO_2), and lactate in 180 seconds. Blood HCO_3^- was calculated from the measured pH and pCO_2 using the Henderson equation. A summary of the measurements is given in Table 3.

Based on previous studies [9], [10], the H^+ mobilization parameter (M) is initially set to 0.182 L/min, when using our equations to obtain the eight values of bath HCO_3^- by means of (A.4). After obtaining these values, we adjusted the value of M to find the best fit (least-square methodology) of the theoretical curve obtained by our equations to the curve defined by experimental data. The best fit value for M (0.189 L/min) was very close to our assumed value (0.182). C_{b0} is the average of the pre-dialysis values of HCO_3^- shown in Table 1. Likewise, $C_{\ell 0}$ is the average of the pre-dialysis values of lactate. Total body water was calculated to be 51% of post-dialysis weight and ECF volume was taken as 1/3 of this value. The initial ECF volume is obtained as $V_0 = V_{end} + Q_f t_{end}$, see (5). Note that, for acetate and lactate, the volume is considered to be constant and equal to V_{end}. In addition to the sequence $\{C_{di}\}$, the other two main inputs under the control of the nephrologist are the ultrafiltration rate appearing in (5), which we set equal to the average value in the twenty patients studied, $Q_f = 1.06\ 10^{-2}$ L/min, and the bath acetate concentration, set to $C_{da} = 2.86$ mmol/L, which is the bath concentration (3 mmol/L) corrected for Gibbs-Donnan equilibrium. The internal production of lactate is computed by setting $t = t_{end}$ in (9) and solving for P_ℓ. Table 4 summarizes the model parameters for our study.

[4]Two additional blood withdrawals have been performed at the beginning and the end of the dialysis to measure blood urea nitrogen (BUN), as reported in Table 1. The values of BUN are used to check dialysis adequacy.

TABLE 3. Average values ± standard deviations for measured blood acid-base parameters and lactate level during hemodialysis.

time min	$C_b(t)$ mmol/L	pH	pCO_2 mmHg	$C_\ell(t)$ [a] mmol/L
0[b]	21.8 ± 2.4	7.39 ± 0.04	37.2 ± 3.5	0.91 ± 0.32
30	22.9 ± 2.1	7.39 ± 0.03	38.5 ± 3.5	0.63 ± 0.31
60	22.9 ± 2.0	7.40 ± 0.03	38.0 ± 3.8	0.57 ± 0.22
90	23.7 ± 1.6	7.41 ± 0.03	38.5 ± 2.9	0.70 ± 0.29
120	24.3 ± 1.5	7.42 ± 0.03	37.9 ± 3.2	0.68 ± 0.29
150	25.1 ± 1.2	7.44 ± 0.04	38.0 ± 3.7	0.67 ± 0.35
224	27.7 ± 2.0	7.48 ± 0.04	38.1 ± 3.6	0.71 ± 0.34

[a] Measured values below the instrument sensitivity (0.4 mmol/L) are arbitrarily set to 0.3 mmol/L.
[b] Time $t = 0$ refers to pre-dialysis measurements.

TABLE 4. Summary of the model parameters used in the study.

param.	value	meas. unit	param.	value	unit
C_{b0}	21.8	mmol/L	D_a	0.170	L/min
C_d	variable	mmol/L	D_ℓ	0.170	L/min
C_{da}	2.86	mmol/L	K_a	0.65	L/min
Q_f	$1.06\ 10^{-2}$	L/min	S_a	0.135	L/min
M	0.189	L/min	τ	40.37	min
D	0.213	L/min	τ_a	16.89	min
V_0	16.23	L	τ_ℓ	81.47	min
V_ℓ	13.85	L	t_{end}	224	min
V_a	13.85	L	P_ℓ	0.118	mmol/min

V. RESULTS AND DISCUSSION

Our results indicate that the model equations we developed successfully achieved our goal of inducing a linear increase in blood HCO_3^- over the course of a hemodialysis treatment in patients with kidney failure. The results are summarized in Tables 2 and 3, and in Figures 2 and 3. Table 2 shows the average values for bath HCO_3^- (C_d) chosen in the 20 patients we studied, based on the solution to our equation for each of the staircase "steps". Table 3 shows the average blood HCO_3^- measurements ($C_b(t)$) that resulted from these changes in bath HCO_3^-. Figure 2 shows the same average blood measurements (black circles) plotted against the average time on dialysis, along with the curve predicted by our equations (black line). As can be seen, the increase was roughly linear over the course of treatment.

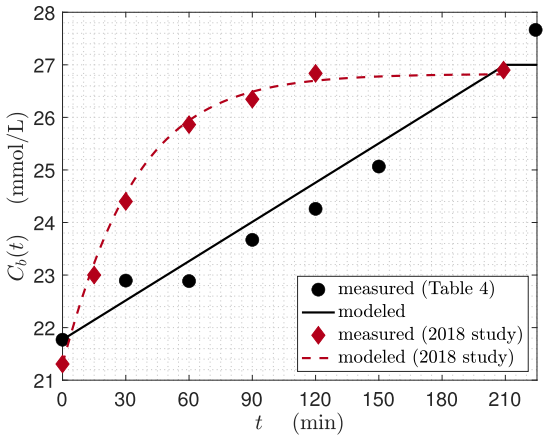

FIGURE 2. Blood bicarbonate concentration $C_b(t)$ during the course of hemodialysis. The circles and diamonds are the measured values of $C_b(t)$, and the dashed and solid lines are the curves generated by the analytical model. The diamonds and dashed red line are from our study published in 2018 [4]. The circles and solid black line are from the present study. Circles correspond to the average measured values of blood HCO_3^- given in Table 3.

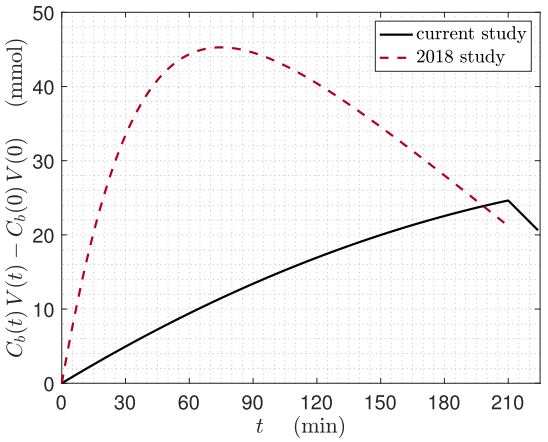

FIGURE 3. Change in ECF HCO_3^- content during the course of hemodialysis. The dashed red line is the curve generated by the model from our study published in 2018 [4]. The solid black line is the curve generated by the model in the present study, see (23).

In contrast to this study, we show the pattern of blood HCO_3^- seen in patients undergoing treatment using a standard hemodialysis protocol, in this instance with the bath HCO_3^- kept stable at 32 mmol/L. These measurements were obtained from an earlier study we carried out in a separate group of patients from the same dialysis unit [4]. In the figure the average blood measurements in that study are designated by red diamonds, and the theoretical curve given by (18) is shown by the dashed red line. In contrast to the staircase protocol used in this study, blood HCO_3^- using the standard protocol rose rapidly in the first 2 hours of treatment and then leveled off, consistent with prior studies using standard protocols [5]–[8].

Figure 3 shows the theoretical curves generated by our analysis of changes in ECF bicarbonate content $(C_b(t)V(t) - C_b(0)V(0))$ during the study hemodialysis treatment. Using the standard protocol, our analysis showed that bicarbonate content rose rapidly in the first 90 minutes and then fell continuously for the remainder of the hemodialysis treatment (red dashed line). The value for bicarbonate content at the end of dialysis, $C_b(t_{end})V(t_{end})$, 374 mmol, was only 20 mmol higher than the value at the beginning of the treatment $(C_b(0)V(0))$. Thus, according to this analysis, almost 90% of the HCO_3^- added during treatment was removed from the ECF by H^+ released from body buffers and newly produced organic acids.

By using the staircase protocol (solid black line), by contrast, ECF HCO_3^- content rose in a linear fashion for virtually all of the treatment, eliciting a much lower buffer response. Because by design we achieved a similar end-dialysis blood HCO_3^- $(C_b(t_{end}))$ in the two studies, net HCO_3^- addition to the ECF was the same in both studies.

By slowing the rate of bicarbonate influx, our staircase approach also increases the contribution of acetate to total alkali addition, without altering the bath acetate C_{da}. To show this, let us compute the individual contributions (all measured in mmol):

$$I_b = \int_0^{t_{end}} \left(J_b^+(\xi) + J_b^-(\xi)\right) \quad d\xi = 64.6, \tag{24a}$$

$$I_a = \int_0^{t_{end}} J_a(\xi) \quad d\xi = 80.1, \tag{24b}$$

$$I = I_b + I_a = 144.7, \tag{24c}$$

$$I_m = \int_0^{t_{end}} J_m(\xi) \quad d\xi = 121.1. \tag{24d}$$

With our protocol, we see that I_a is about 55% of the total alkali addition I, whereas in our prior study this percentage was only of 35%. This is a substantial improvement [4], [52]. Our novel bath prescription also reduces HCO_3^- consumption due to the flux $J_m(t)$: we have $I_m = 121$ mmol, compared to 183 mmol in our previous study [4]. Thus, the total buffer response is reduced by 1/3. We believe that a reduction of I_m is beneficial and, presumably, is associated to a reduction of the maladaptive component of I_m related to the loss of lactate into bath. All the above improvements are obtained despite achieving essentially the same end-dialysis blood HCO_3^- of 27 mmol/L and without impairing dialysis adequacy, as confirmed by inspection of the post-BUN values with respect to the pre-dialysis ones,[5] see Table 1.

Using the measured values of $C_\ell(0)$ and $C_\ell(t_{end})$ to calculate loss of lactate into the bath (LOSS) by equation (15) in our study, we get LOSS = 29.3 mmol. We have used the same equation (15) to compute the loss in two studies in which lactate loss was calculated by the difference between inlet and outlet measured blood concentrations, obtaining a substantial match between their results and ours (Table 5). In the present study lactate loss is only 64.5% of that observed using a constant bath HCO_3^- of 37 mmol/L, and 71.5% when the bath HCO_3^- is reduced to 27 mmol/L. Using the measured concentrations of lactate $C_\ell(0)$ and $C_\ell(t_{end})$, the values of lactic acid production P_ℓ computed by (9) are reported in the

[5]In order to achieve the desired therapy goals, the reduction of post-dialysis BUNs with respect to the pre-dialysis values should exceed 65%.

TABLE 5. Lactate loss into the bath as a measure of H^+ retention due to lactic acid generation during hemodialysis analyzed from pre- and post-dialysis measured blood lactate concentration. The first column gives the number of patients: 10 from [6] and 20 from the present study.

No.	bath $[HCO_3^-]^{(a)}$	$C_\ell(0)$	$C_\ell(t_{end})$	LOSS		P_ℓ
				by (15)	measured	by (9)
	mmol/L	mmol/L	mmol/L	mmol	mmol	mmol/min
10	37	1.18	1.20	45.4	46.0	0.204
10	27	1.38	0.95	41.0	44.3	0.157
20	variable	0.91	0.71	29.3	—	0.118

(a) After Gibbs-Donnan correction this yields C_d.

last column of Table 5. With our protocol, we see that the lactic acid production P_ℓ is reduced by 42% with respect to the study with bath HCO_3^- set to 37 mmol/L and by 25% when it is set to 27 mmol/L.

These results support our view that by beginning treatment with a lower bath HCO_3^- and gradually increasing it during the course of the treatment, lactic acid production and lactate loss can be notably reduced [7], [53]. With the described staircase protocol, we not only prevent the futile cycle of excess bicarbonate addition at the beginning of treatment, but also can reduce the large outpouring of H^+ caused by rapid and excessive alkalemia that occurs at the onset of treatment.

The descriptive nature of our model is a powerful tool that allows us to predict the effect of bath prescription on the patient acid-base response to alkali addition and on the acid-base outcome of hemodialysis therapy. However, the model can be improved. One limitation is that the current formulation does not explain the almost flat (or even decreasing) shape of $C_b(t)$ in protocols[6] using very low bath HCO_3^-. This could be due to a threshold effect for which the organism responds only when the external stimulus exceeds some minimum level. Including this threshold effect would require a non-linear model that is perhaps less easy to handle with analytically, but would improve prediction accuracy in these special situations.

Another limitation is the lack of a mathematical description for the relationship between the $C_b(t)$ profile and acid production. In the present study, lactic acid production is assumed to be constant and is indirectly measured by blood lactate concentration. As discussed at the end of Sec. II-B, the time profile of $C_b(t)$ has an effect on lactic acid production that in turn determines the maladaptive portion of flux $J_m(t)$, although the global flux $J_m(t)$ remains unaffected. A deeper understanding of the precise mechanisms ruling the production of lactic acid would shed light on the nature of the mobilization constant M, with possible impact on the total flux $J_m(t)$. Mathematically, this would yield a connection between the system equations (3) and (8), leading to a more complete model of acid-base events occurring during the hemodialysis therapy.

Our measurements only involve small sample size and single treatment analysis. Further studies are needed to determine whether our unique staircase protocol is completely safe and whether it will reduce patient morbidity and mortality. Answering these questions is beyond the scope of this contribution and will require large-scale clinical studies with patients observed over long periods. Such studies are very difficult to carry out, as witnessed by the fact that studies similar to ours only involve approximately the same number of patients, see e.g., [6]. We are not aware of experiments with larger numbers of patients but we hope that the insights provided by our mathematical model will encourage researchers to find the financial support needed to carry out larger and longer-term studies to answer the questions raised in our paper.

[6]We have some preliminary experimental evidence of this effect, not reported here for the sake of brevity.

VI. CONCLUSION

Developing tractable and reliable mathematical models of physiological processes is notoriously challenging. Nevertheless, the predictive capabilities of these models have the potential of substantially advancing knowledge and practical skills. In this paper, we present a mathematical model of hemodialysis and test the model by making measurements in dialysis patients. Using our model, we predict the appropriate change in bath HCO_3^- $C_d(t)$ to achieve our goal of a linear rise in blood HCO_3^- $C_b(t)$. Our study demonstrates that adjusting $C_d(t)$ in a staircase fashion during hemodialysis results in a more gradual increase in $C_b(t)$ and pH, achieving the same end-dialysis blood HCO_3^- $C_b(t_{end})$ with less buffer response and less lactic acid production. Our novel bath prescription is clearly beneficial from an acid-base perspective, an advance in therapy in its own right. Although large-scale studies are needed, we believe our new protocol will also be beneficial in the long term with regard to patient morbidity.

APPENDIX
STAIRCASE PROTOCOL

Expression (23) for $t = t_1$ reads:

$$C_b(t_1) = C_{b0} + \frac{D}{D+M}\left[C_{d1}\left(1-e^{-t_1/\tau}\right) - C_{b0}\left(1-e^{-t_1/\tau}\right) + \frac{C_{da}S_a}{D}\,\frac{\tau\left(1-e^{-t_1/\tau}\right) - \tau_a\left(1-e^{-t_1/\tau_a}\right)}{\tau-\tau_a}\right], \quad \text{(A.1)}$$

which, solved for C_{d1} yields

$$C_{d1} = C_{b0} + (C_b(t_1) - C_{b0})\frac{D+M}{D\left(1-e^{-t_1/\tau}\right)} - \frac{C_{da}S_a}{D\left(1-e^{-t_1/\tau}\right)}\,\frac{\tau\left(1-e^{-t_1/\tau}\right) - \tau_a\left(1-e^{-t_1/\tau_a}\right)}{\tau-\tau_a}. \quad \text{(A.2)}$$

Likewise, knowing C_{d1}, specializing expression (23) for $t = t_2$ and solving in C_{d2}, we obtain:

$$C_{d2} = \frac{C_b(t_2) - C_{b0}}{1-e^{-(t_2-t_1)/\tau}}\,\frac{D+M}{D} - \frac{C_{d1}\left(e^{t_1/\tau}-1\right) - C_{b0}\left(e^{t_2/\tau}-1\right)}{e^{t_2/\tau}-e^{t_1/\tau}}$$

$$-\frac{C_{da}S_a}{D}\frac{\tau\left(1-e^{-t_2/\tau}\right)-\tau_a\left(1-e^{-t_2/\tau_a}\right)}{(\tau-\tau_a)\left(1-e^{-(t_2-t_1)/\tau}\right)}. \quad \text{(A.3)}$$

In general, for $k = 1, 2, \ldots,$ given $C_{d1}, C_{d2}, \ldots, C_{d(k-1)}$, we have:

$$\begin{aligned} C_{dk} = {} & \frac{C_b(t_k)-C_{b0}}{1-e^{-(t_k-t_{k-1})/\tau}}\frac{D+M}{D} \\ & -\sum_{i=1}^{k-1} C_{di}\frac{e^{t_i/\tau}-e^{t_{i-1}/\tau}}{e^{t_k/\tau}-e^{t_{k-1}/\tau}} + C_{b0}\frac{e^{t_k/\tau}-1}{e^{t_k/\tau}-e^{t_{k-1}/\tau}} \\ & -\frac{C_{da}S_a}{D}\frac{\tau\left(1-e^{-t_k/\tau}\right)-\tau_a\left(1-e^{-t_k/\tau_a}\right)}{(\tau-\tau_a)\left(1-e^{-(t_k-t_{k-1})/\tau}\right)}, \end{aligned} \quad \text{(A.4)}$$

where, by convention, a void sum is equal to zero and $t_0 = 0$.

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