Navigating the Critical Nexus. Bridging Simulation, Measuring, and Acid-Base diagnosis in ICU and Dialysis

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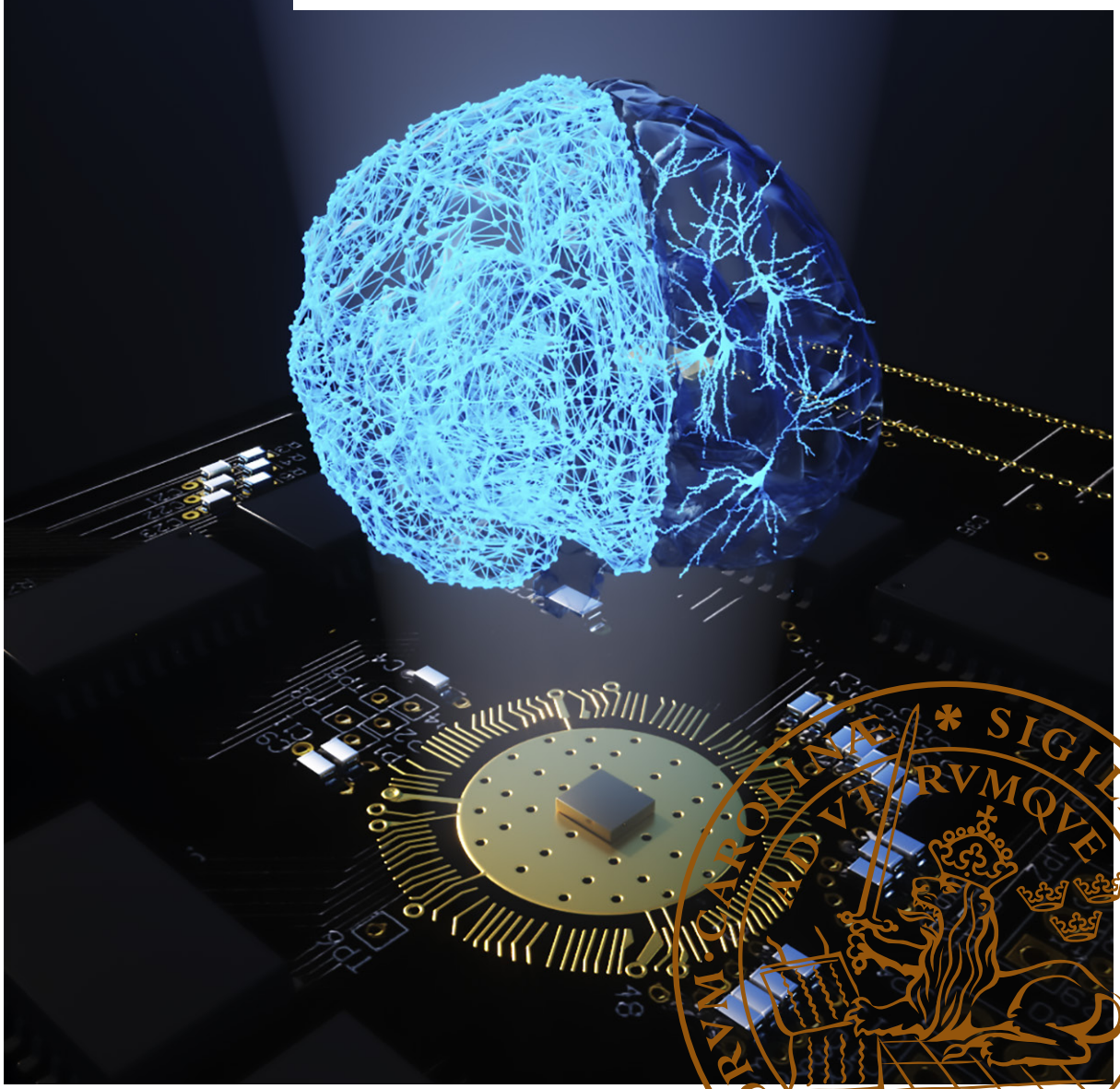

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Navigating the Critical Nexus

Bridging Simulation, Measuring, and Acid-Base diagnosis in ICU and Dialysis

Innas Forsal

DOCTORAL DISSERTATION

Doctoral dissertation for the degree of Doctor of Philosophy (PhD) at the Faculty of Medicine at Lund University to be publicly defended on 16 of April at BMC I1345, Department of Anesthesia and intensive care, Lund

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Title and subtitle: Navigating the Critical Nexus: Bridging Simulation, Measuring, and Acid-base diagnosis in the ICU and Dialysis

Abstract:

Background: Medicine and technology have undergone massive developments and progress during the last decades with digitalization and advancement of medical technology (MedTech). The advancements have resulted in increasing amounts of data being collected for each patient. Today, each specific patient will generate a lot of data that physicians and healthcare personnel need to consider in evaluation of treatment, determining changes in treatment - but also understanding the patient outcome. **Method:** Scripts were developed in MATLAB 2020a/2022a (MathWorks®) for all parts which needed development of scripts.

Results and significance

- Post-filter ionized calcium: Two sets of algorithms were developed to replace blood sample of post-filter ionized calcium. The algorithms were able to estimate in range post-filter ionized calcium values with great trueness (lower mean value) and precision (lower standard deviation).
- Acid-base diagnosis tool: A diagnosis tool was developed for acid base. It works much faster and with greater accuracy than diagnosis by physicians.
- Net buffer load: Net Buffer Load (NBL) can be used to better understand the buffering effect of Regional Citrate Anticoagulated Continuous Renal Replacement Therapy (RCA CRRT). It is important to understand the effect of Continuous Renal Replacement Therapy (CRRT) on acid-base balance. No instances of citrate toxicity or alkalosis could be seen due to RCA CRRT.
- Glucose and sodium levels: We looked at the effect of using correction formula for sodium on intensive care unit (ICU) patients, with often deranged glucose levels, to see the potential change in clinical treatment. A script was created of formulas on an existing clinical phenomenon and included a large amount of patient data in order to see what the formulas can bring forward.

Key words: Algorithms, dialysis, acid-base, software, diagnosis, decision support tool

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None of this would be possible without the support of my mother, brother, and my grandfather Ali Kaoutar. They have been so patient with me during this time and have given me a lot of support.

Power is given only to those who dare to
lower themselves and pick it up.
Only one thing matters, one thing;
to be able to dare!

- Fyodor Dostoevsky

Table of Contents

Abstract

Background

Medicine and technology have undergone massive developments and progress during the last decades with digitalization and advancement of medical technology (MedTech). The advancements have resulted in increasing amounts of data being collected for each patient: The data collected ranges from temperature, ECG, and blood work to settings and information from devices used such as ventilators and dialysis machines. Today, each specific patient will generate a lot of data that physicians and healthcare personnel need to consider in evaluation of treatment, determining changes in treatment - but also understanding the patient outcome.

Method

Scripts were developed in MATLAB 2020a/2022a (MathWorks®) for all parts which needed development of scripts.

Results and significance

1. *Two sets of algorithms were developed to replace blood sample of post-filter ionized calcium.*
   The algorithms were able to estimate in range post-filter ionized calcium values with great trueness (lower mean value) and precision (lower standard deviation).
2. *A diagnosis tool was developed for acid base.*
   Works much faster and with greater accuracy than diagnosis by physicians.
3. *Net Buffer Load*
   It is important to understand the effect of Continuous Renal Replacement Therapy (CRRT) on acid-base balance. Normalized net buffer load (nNBL) is a value that can be used to better understand the buffering effect of Regional Citrate Anticoagulated Continuous Renal Replacement Therapy (RCA CRRT). No instances of citrate toxicity or alkalosis could be seen due to RCA CRRT.
4. *Glucose and sodium levels*
   We looked at the effect of using correction formula for sodium on intensive care unit (ICU) patients, with often deranged glucose levels, to see the potential change in clinical treatment. A script was created of formulas on an existing clinical phenomenon and included a large amount of patient data in order to see what the formulas can bring forward.

Populärvetenskaplig sammanfattning

Intensivvårdsavdelningen (IVA) tar hand om de mest kritiskt sjuka patienterna, ofta med multiorgansvikt. Denna patientgrupp kräver kontinuerlig övervakning av vitala funktioner som blodtryck, EKG och syremättnad. Varje patient på IVA kräver dessutom upprepad provtagning, ibland så ofta som var 15:e min. Denna ständiga övervakning leder till insamling av mycket patientdata som varje läkare/sjukvårdpersonal måste ha i åtanke då beslut skall fattas avseende behandling, men även för uppföljning av patienten efter given behandling. Sjukvårdpersonal måste ständigt kontrollera omfattande mängder data, men den avsatta tiden för att hinna analysera data har med tiden minskat. Det stora informationsflödet kan i sin tur leda till att misstag sker och att viktiga data missas.

Syftet med mitt projekt är att försöka skapa ett beslutsstöd för läkare för att underlätta diagnosticeringen av sjukdomar, i detta fall syrabas-störningar. Detta genom att ersätta ett blodprov med en algoritm, hjälpa till att förstå det sanna natriumvärdet vid avvikande glukosvärden, men även ha ett värde, ”normalized net buffer load”(nNBL), som kan hjälpa till att förstå hur dialys (CRRT, continous renal replacement therapy) påverkar syrabas-balansen. Beslutstödet utgörs av olika algoritmer som utvecklats i MATLAB ®, vilket gjort det möjligt att analysera stora mängder data snabbt och systematiskt på ett sätt som en människa inte hade kunnat göra.

Våra algoritmer har visat att det finns mycket mer att göra inom intensivvården som kan underlätta det dagliga arbetet för sjukvårdspersonal, men även för patienterna. Våra algoritmer har kunnat analysera data som hade tagit år och eventuellt varit omöjligt för den enskilda personen att genomföra.

List of Papers

Paper I

Forsal I, Nilsson A, Bodelsson M, Wieslander A, Broman M. Mathematical modelling of post-filter ionized calcium during citrate anticoagulated continuous renal replacement therapy. PLoS One. 2021 Feb 25;16(2):e0247477. doi: 10.1371/journal.pone.0247477. PMID: 33630962; PMCID: PMC7906315.

Paper II

Forsal I, Bodelsson M, Wieslander A, Nilsson A, Pouchoulin D, Broman M. Analysis of acid-base disorders in an ICU cohort using a computer script. Intensive Care Med Exp. 2022 Apr 4;10(1):11. doi: 10.1186/s40635-022-00437-8. PMID: 35377054; PMCID: PMC8980140.

Paper III

Forsal I, Pouchoulin D, Roos V, Echeverri J, Broman M. Net buffer load during regional citrate anticoagulated renal replacement therapy. Submitted for publication.

Paper IV

Broman M & Forsal I. Analysis of pseudohyponatremia phenomenon in cohort of critically ill patients. Submitted for publication.

Author's contribution to the papers

Paper I

Analysis and handling of patient data. Writing and reviewing the manuscript. Further development of algorithms.

Paper II

Analysis and handling of patient data. Writing and reviewing the manuscript. Further development of algorithms.

Paper III

Analysis and handling of patient data. Writing and reviewing the manuscript. Further development of algorithms.

Paper IV

Analysis and handling of patient data. Writing and reviewing the manuscript. Further development of algorithms.

Abbreviations

MedTech	Medical technology
CRRT	Continuous renal replacement therapy
nNBL	Normalized net buffer load
RCA	Regional citrate anticoagulation
ICU	Intensive care unit
ECG	Electrocardiogram
EMR	Electronic medical record
ML	Machine learning
AI	Artificial intelligence
Post-filter iCa	Post-filter ionized calcium
NBL	Net buffer load
AKI	Acute kidney injury
ESRD	End-stage renal disease
HD	Hemodialysis
APTT	Activated partial thromboplastin time
CVVH	Continuous venovenous hemofiltration
CVVD	Continuous venovenous hemodialysis
CVVHDF	Continuous venovenous hemodiafiltration
SCUF	Slow continuous ultrafiltration
CDC	Central dialysis catheter
CKD	Chronic kidney disease
ICU	Intensive care unit
MATLAB	Matrix laboratory
ARDS	Acute respiratory distress syndrome
$PaCO_2$	Partial pressure of carbon dioxide
HCO_3^-	Bicarbonate
Q_B	Blood flow rate
Q_d	Dialysate flow rate

Q_{PBP}	Post-blood flow pump (i.e. often citrate containing solution)
C_0	Initial concentration of toxin
Ce	Time dependent concentration of toxin
Kd	Dialyzer clearance
Kc	Intercompartment mass transfer coefficient
V	Volume
Vi	Intracompartment volume
Ve	Extracompartment volume
t	Time
C_T	Toxin concentration
Ci	Toxin concentration in interior water
iCa	Ionized calcium
PF	Post-filter iCa
CDC	Central dialysis catheter
AV fistula	Ateriovenous fistula
BGA	Blood gas analyzer

Introdution

Medicine and technology have undergone great development and progress during the last decades with digitalization and advancement of medical technology (MedTech). MedTech are tools/aids that can be used to support prevention of disease, aiding in diagnosis and treat diseases etc. The advancements have resulted in increasing amounts of data being collected for each patient. The collected data could be everything ranging from body weight, prescriptions, previous medical history (known diseases and family history), allergies, and temperature to ECG (electrocardiogram), and blood work, but also settings and information from devices used such as ventilators and dialysis machines etc. Today each specific patient will generate a large number of data that physicians and healthcare personnel need to consider in the evaluation of treatment, determining changes in treatment - but also to understand the patient outcome.

The large amount of data has resulted in a lot of stress amongst healthcare personnel, but also safety issues due to data being disregarded. The constant stress of feeling that one has not been able to look at all data has also resulted in burnout amongst medical professions, for some so severe that they even consider changing jobs [1].

The decision support tool developed by our group in Lund is a software, that could be integrated to the electronic medical record (EMR), that works in the background and asses large and relevant volumes of data in a fast and secure way. The software can be used on a computer or a smartphone and uses relevant data from the EMR. Specific algorithms, developed to help with decision making, highlight/suggest what laboratory test results should be considered first. The software analyzes the data and points out the areas of possible intervention, e.g., diagnose the acid-base disorder the patient has quickly, and helps with preliminary considerations in regards of the diagnosis. The decision support tool may give healthcare personnel more time for patients and, additionally, it is not affected by fatigue, or stress when handling data hence, it may increase accuracy as well as safety [2].

Introduction to the intersection of medicine and modeling

It has for a long time been discussed that some kind of artificial intelligence/machine learning (AI/ML) will be used in healthcare. Machine learning could be used to help interpret medical scans, pathology slides, skin lesions, retinal images, electrocardiograms, endoscopic examinations, face recognition, and vital signs etc. The AI is typically compared with physicians' assessments and has already been shown to have a place in medical companies such as CellaVision, being able to provide services such as automated and simplified process of performing blood cell differentials that previously was performed manually. CellaVision's technology has been shown to be as good or better than manual microscopy [3]. Deep neural networks have also been used to diagnose and classify skin cancer, and have shown to be very accurate and fast [4].

Different areas in medicine have been faster than others to adapt to the digitalization and at the forefront of this are the radiologists. In radiology, several image-recognition studies have been conducted for different imaging modalities. but also, interpretation of the different organ systems. The accuracy of the interpretations varies; in some areas, deep neural networks have been shown to be faster in interpreting scans and often with higher accuracy than that of clinicians, especially during stressful situations [5].

The intensive care unit (ICU) is a place that takes care of the most critical patients from all specialties with all kinds of medical underlying diseases needing surveillance and meticulous care. Often, the patients need support of multiple organ systems with machines such as ventilators, dialysis machines, or transcutaneous pacing. The data being collected for each patient during their ICU stay is significant and there is always a risk of data being missed. Artificial intelligence has not been developed as much in this specialty compared to other specialties. and there are a lot of things that can be done to improve this field [6].

MATLAB's usage in the medical field with a focus on the ICU

Development of algorithms in the medical field is on the rise and there are many ways to develop algorithms. MATLAB (Matrix Laboratory) has with time become one of the most used software for developing algorithms in different fields, ranging from engineering to medicine. The application of MATLAB in the medical field has emerged as a potential transformative force and could be particularly important in the context of medicine in for example aiding in diagnosis. This powerful

computational platform, known for its versatility and mathematical capabilities, could play a crucial role in bridging the gap between technology and healthcare. With its extensive toolset, MATLAB has made it easy for researchers to develop aids/algorithms to improve patient care and diagnostics of diseases. Open source (source code that freely can be modified and redistributed) has made it easy to access code developed by others, but also to find solutions to problems present in one's own code. MATLAB is a powerful tool with many possibilities and is widely used amongst engineers today already. It is also a tool that easily can be understood and has many good and user-friendly interfaces, but also makes the user being able to create whatever interface they wish and for most applications. The tool is easily available, but at some cost, and to be able to access all the toolsets a substantial fee needs to be paid, which most institutions will assist with. There have been many discussions for several years of the need for algorithms in healthcare and some of the issues hindering the development is, e.g., the legislation that has not made development easy.

The usage of MATLAB can be divided into different areas:

1. Real-Time Data Analysis

   MATLAB's ability to process and analyze vast streams of real-time patient data is invaluable in ICUs. It enables healthcare professionals to monitor a patient's vital signs, such as heart rate, blood pressure, and oxygen saturation, and instantly detect anomalies or trends. This is critical for early intervention and the prevention of life-threatening complications. One example of processing vast amount of patient data is e.g., diagnosis of acid-base disturbances. Managing acid-base balance is critical in the ICU. MATLAB's computational capabilities are particularly useful for analyzing complex acid-base disorders, helping clinicians make precise adjustments to medications and interventions to maintain patient stability [7].

2. Simulation and Modeling

   In the ICU, where patient conditions can change rapidly, MATLAB's simulation and modeling capabilities provide healthcare teams with helpful tools. These models can forecast patient outcomes, assist in treatment planning, and optimize resource allocation. The ability to simulate different scenarios aids in making informed decisions, particularly in complex cases. Physiological modeling has been done previously and has many times been cumbersome, but AI/ML could aid in simplifying the process of developing simulations [8].

3. Image Processing and Analysis:

   ICUs often rely on medical imaging for diagnosis and monitoring. MATLAB's image processing toolbox enhances the interpretation of medical images, such as X-rays, CT scans, and MRIs. Development has already been

done in regards of image interpretation and more can be done since these aids in the timely diagnosis of conditions and the assessment of treatment effectiveness. Different tools are readily available making development of algorithms easier, but also due to a lot of data being available for usage, making progress a bit faster [9].

4. Machine Learning and Artificial Learning:

   The integration of machine learning and artificial intelligence is something that probably will come more in the future in the field of ICU care. MATLAB's extensive support for these technologies allows for the development of predictive algorithms that can anticipate patient deterioration, recommend treatment strategies, and assist in automating routine tasks, thereby reducing the workload on healthcare professionals [10].

Severity scores have for a long time been used to predict outcome, severity of the disease, and also to assess resource use. There are many scoring systems/early warning systems and some can take some effort to use, although online versions are available often manual insertion of data is necessary [11]. Here, AI/ML might present a way to have continuous assessment of the different scores and potentially be able to aid in fast detection of deterioration.

With large amounts of patient data stored for each patient, information might easily be missed. Predictive modelling of medical records to improve healthcare quality has been a topic for a long time. Deep learning has become an important aid in simplifying the analysis of data, reducing the work needed for analysis of raw data but also making it possible to analyze a vast number of data. Studies have shown that deep-learning could achieve high accuracy in predicting in-hospital mortality and find patients with risk for prolonged hospital stay or re-admission. Deep learning can also be used for identification of relevant information from the patient chart/data, which has become important nowadays since large amounts of data are stored for each unique patient [12].

Artificial Intelligence and Machine Learning are not the only efforts in medicine to improve healthcare. Everyday technology, such as mobile devices and tablets, are useful to help patients to adhere to their treatment regimens, for example, tuberculosis treatment where efforts were made to facilitate patient/provider contact and could be seen to improve patient commitment to medication [13].

Dialysis in the ICU

Continuous renal replacement therapy (CRRT) is a dialysis modality used in the intensive care setting and is the most common renal support modality in the intensive care unit (ICU) [14]. It is often used to treat patients with acute kidney injury (AKI) with hemodynamic instability. The indications for CRRT are many and examples are correction of acid-base disturbances [15, 16], removal of toxic substances in the patient [16], sepsis, correction of electrolyte imbalance [17], and removal of excess fluid in hypervolemic patients. [18]. Continuous renal replacement therapy provides continuous solute clearance and fluid removal, during long periods, often days to weeks and presents a slower form of dialysis compared to, e.g., intermittent hemodialysis with a typical treatment period of 3 to 5 hours triweekly [19]. Continuous renal replacement therapy requires vascular access (central dialysis catheter), pumps to pump the blood and solutions used in the circuit, permeable membrane to filter the plasma water (part of the plasma not containing proteins/other big substances that cannot pass the filter) and solutions [20].

Anticoagulation is very important during CRRT for the patency of the extracorporeal circuit. As soon as blood touches the tubing/circuit, a coagulation cascade will be triggered that will result in clotting and reduction of filter life [21]. Commonly, either heparin or citrate is used as an anticoagulant to avoid clotting of the dialysis circuit; however, in patients with a high risk of bleeding or other contraindications to anticoagulation CRRT may be conducted without anticoagulation. Anticoagulation-free CRRT procedures are generally less effective due to higher risk of filter clotting entailing increased down time [22].

For a long time, unfractionated heparin was the first-hand choice anticoagulant for CRRT worldwide [23]. Critically ill patients admitted to the ICU most often have impaired coagulation and an increased risk of bleeding [24]. Studies have shown that as many as 12-15% of the ICU patients will have a platelet count of $<50 \times 10^9$/L and prolonged activated partial thromboplastin time (APTT) in 14-28% [25]. Due to the increased bleeding risk seen in ICU patients, the usage of heparin as an anticoagulation method is frequently limited. Heparin anticoagulated CRRT has a bleeding incidence ranging from 4-25% [26, 27].

Regional citrate anticoagulation (RCA) has gained popularity in recent years due an anticoagulant effect which is limited to the dialysis circuit without affecting the patient's coagulation [28]. Due to the benefit of citrate the KDIGO guidelines recommend RCA as the preferred anticoagulation method during CRRT in ICU patients that do not have contradictions to usage of citrate such as liver failure and shock with muscle hypoperfusion [24]. For patients having contradictions for both heparin and citrate then the only option is anticoagulation-free CRRT, and globally 33-50% of patients do not receive anticoagulation [29-31]. Continuous renal

replacement therapy is often cumbersome and time-consuming, but also takes a lot of focus from the nurse due to circuit changes/change of solutions [20].

There are different settings for CRRT treatment depending on treatment goal:

Solutes will be removed from the patient with dialysis and the efficiency of the solute removal will be based on the molecular size of the solute compared to the filter pore size. Molecules can be divided into three sizes: small (<500 Da, e.g., electrolytes), middle (<60 kDa, most medication and vitamins), and large molecules (>60 kDa, e.g., albumin and Beta2-microglobulin) [32].

Continuous venovenous hemofiltration (CVVH): This method uses hydrostatic pressure across a semipermeable membrane/filter to remove solutes using convection. Plasma water can move across the filter, i.e., no blood components or proteins since they are too large to move across the pores of the filter (the cut-off of the size of the molecules being able to pass the filter is dependent on the internal diameter of used filter). Solutes of different sizes are initially transported with equal efficacy until the radius of the molecule/solute exceeds the membrane poor size, e.g., albumin, which is a large solute that has a radius larger than the conventional membranes and will not be removed during dialysis. Since solutes will be removed by convection, substitute fluid is introduced to combat the increased hemoconcentration occurring during filtration, which can result in sludging and occlusion of fibers. The convection rate is determined by the fluid removal rate.

Continuous venovenous hemodialysis (CVVD): This method uses diffusion via a transmembrane concentration gradient across the filter. The concentration gradient is created with a dialysate solution. The smaller the solute the faster and easier it will be transferred across the membrane compared to larger solutes. The larger the molecule is, the longer time it will take for it to be removed, a hindrance for CRRT is removal of large molecules due to the limitation in pore size compared to hemodialysis. This method is not dependent on high ultrafiltration (patient fluid removal) rates. This dialysis method is used more for removal of middle-sized solutes [33].

Continuous venovenous hemodiafiltration (CVVHDF): Combines both convention and diffusion. Dialysate is used in combination with high ultrafiltration rates and usage of replacement solution. In this case both small and middle molecules are removed efficiently. In some cases, no substitute solution is used, e.g., when the focus is volume management, and in this case the treatment is called slow continuous ultrafiltration (SCUF) [34].

Good vascular access is necessary for efficient CRRT treatment. There are different placements of a central dialysis catheter (CDC) and the most common and favorable is inserting a CDC in the right internal jugular vein due to it having a more direct pathway to the superior vena cava. In some cases, internal jugular vein access is not possible due to known underlying problems such as thrombosis. In this case the

femoral vein can be used as an alternative access site. In some cases, none of the previously mentioned sites can be cannulated which leaves the subclavian vein as a third but less preferable option due to a higher risk of stenosis of this vessel (a statement that is under discussion). The preferred location of the tip of the CDC inserted in the jugular or subclavian vein is at the junction of the superior vena cava and right atrium. It is important to test the flow in the CDC, since it needs to be able to meet minimum blood flow rates of 200-300 ml/min [33].

Citrate works by binding free calcium, which is needed in many steps of the anticoagulation cascade (intrinsic and extrinsic), hence hindering the clotting process in the circuit. Since it binds calcium, it is important to control ionized calcium levels in the patient to not risk hypocalcemia, post-filter ionized calcium levels to control at the amount of citrate dosed is sufficient to reach adequate anticoagulation in the circuit but also does not risk the patient developing hypocalcemia. Citrate is not perfect and has side-effects, these include hypocalcemia, metabolic alkalosis, citrate toxicity etc. [35].

The disturbances mentioned previously have been significantly reduced with meticulous monitoring of laboratory values, but also usage of structured protocols, such as the Flexicitrate protocol, in which one measures ionized calcium (iCa), post-filter iCa, and systemic total calcium [36, 37]. Post-filter iCa ensures the efficiency of the anticoagulation of the extracorporeal circuit, i.e., that the circuit is anticoagulated enough and hence ensuring a longer dialysis filter life. Post-filter iCa together with systemic iCa ensures the safety of the patient, i.e., reducing risk of hypocalcemia in the patient and making sure the patients stay normocalcemic [38-40]. A point of care blood gas analyzer (BGA) is commonly used for the measurement of post-filter iCa and systemic iCa, while the systemic calcium is measured in a clinical chemistry laboratory in or affiliated with the hospital. Sometimes systemic iCa can also be measured in the chemistry laboratory, but most often it is analyzed with BGA.

Table 1: The Flexicitrate protocol. PF is post-filter iCa measuremnt. Patient Ca^{2+} is systemic iCa.

	High PF-Ca^{2+} >0.50 mmol/l	**Normal PF-Ca^{2+} 0.25-0.50 mmol/l**	**Low PF-Ca^{2+} <0.25mol/l**
Low patient Ca^{2+} <1.0 mmol/l	Increase citrate dose by 0.5 mmol/l and calcium infusion by 5-10%	Increase calcium infusion by 5-10%	Decrease citrate dose by 0.5 mmol/l
Normal patient Ca^{2+} 1.0-1.2 mmol/l	Increase citrate dose by 0.5 mmol/l	No change	Decrease citrate dose by 0.5 mmol/l
High patient Ca^{2+} >1.2 mmol/l	Decrease calcium infusion by 5-10%	Decrease calcium infusion by 5-10%	Decrease citrate dose by 0.5 mmol/l and calcium infusion by 5-10%

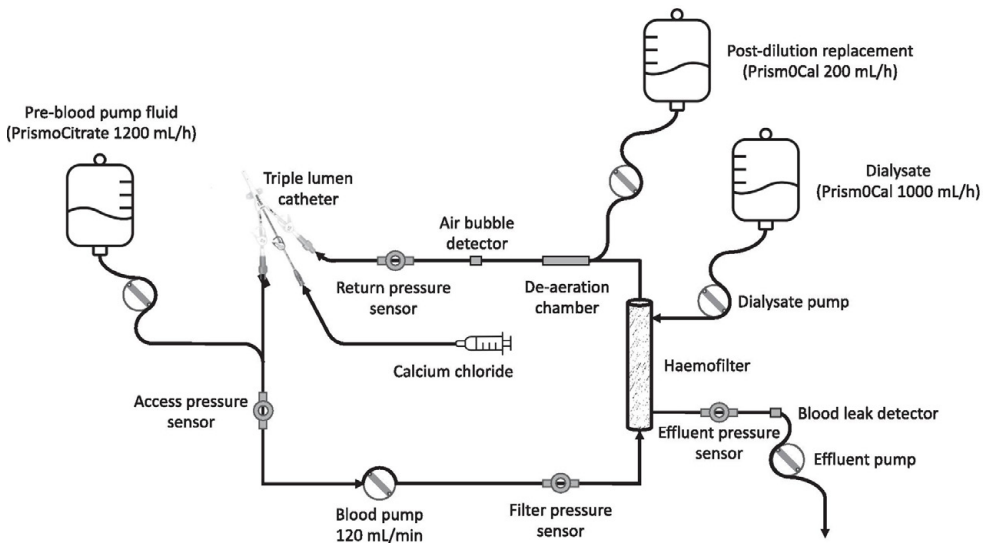

Figure 1: Common CRRT setup with the different fluids used during RCA CRRT and with examples of realistic flows. The pre-blood pump fluid (Q_{PBP}) is the citrate containing fluid [41].

Efforts to model the effects of CRRT have been done but is not as established as for hemodialysis or peritoneal dialysis.

Dialysis modelling

Dialysis is a treatment used to replace the kidney function in patients with oftentimes end-stage renal disease (ESRD). Peritoneal dialysis, in which one uses the peritoneal membrane as a physiological semipermeable membrane, presents an alternative form of dialysis to the extracorporeal hemodialysis techniques described above [42].

Hemodialysis modelling has been available and known for a long time compared to modelling of CRRT. Modelling is needed to understand the effects of flows/solutions on blood composition. For a long time, modelling was used to mainly understand how solutions and filters should be manufactured to give the most optimal treatment without risking the patient trough unfavorable events, such as removal of e.g., large molecules needed in the body or having fluid composition that in turn would lead to unfavorable composition in the blood. With time, the need for modelling for everyday use has increased both in clinical work, but also in research. It is difficult to, in an intuitive way, understand how changes in flows or changes in solutions used during dialysis will affect the patient, and this leads to many changes in settings according to lab data, which can be reduced by using a model. The number of unnecessary changes in therapy and also number of blood samples taken could be reduced by using a dialysis model which can predict how the changes would affect the patient and how one should decide which setting is optimal for the patient's blood composition and treatment goal.

For modelling, clearance of toxins is used as a measure of efficiency and in the dialysis; urea is seen as a good measure of treatment effectiveness. Removal of unfavorable substances, such as uremic toxins and inflammatory mediators, are seen as waste products that if removed could improve outcome. Continuous renal replacement therapy dose today relates to measured removal of the small sized solute urea [43]. Urea is a preferable measure of efficiency of dialysis treatment due to it having a sieving coefficient (SC) close to 1, which indicate the potential of a solute to be able to pass across a semipermeable membrane [44]. Compared to urea, myoglobin has a value of 0.58 (indicating less removal), and albumin (large sized molecule) has a SC of <0.01 indicating almost no removal [44, 45].

Development of one- and two-compartment models of hemodialysis treatment makes it possible to have continuous information about the progress of treatment and predict the effect of the prescribed dialysis. The benefit of modelling is that it assists physicians in personalizing the dialysis therapy with greater precision to the patients' needs. Dialysis kinetics and dialyzer clearance have been described for the first time over 70 years ago [46]. Over the last seven decades, the modelling of dialysis has been improved and with greater computational powers the precision has increased. The first time a dialysis model has been used in clinical practice was already in the late 1970s, but unfortunately, since then progress has been slow [47].

In recent years, several clinical and theoretical articles discussing the benefit and risk of usage of dialysis models have been published [48-50].

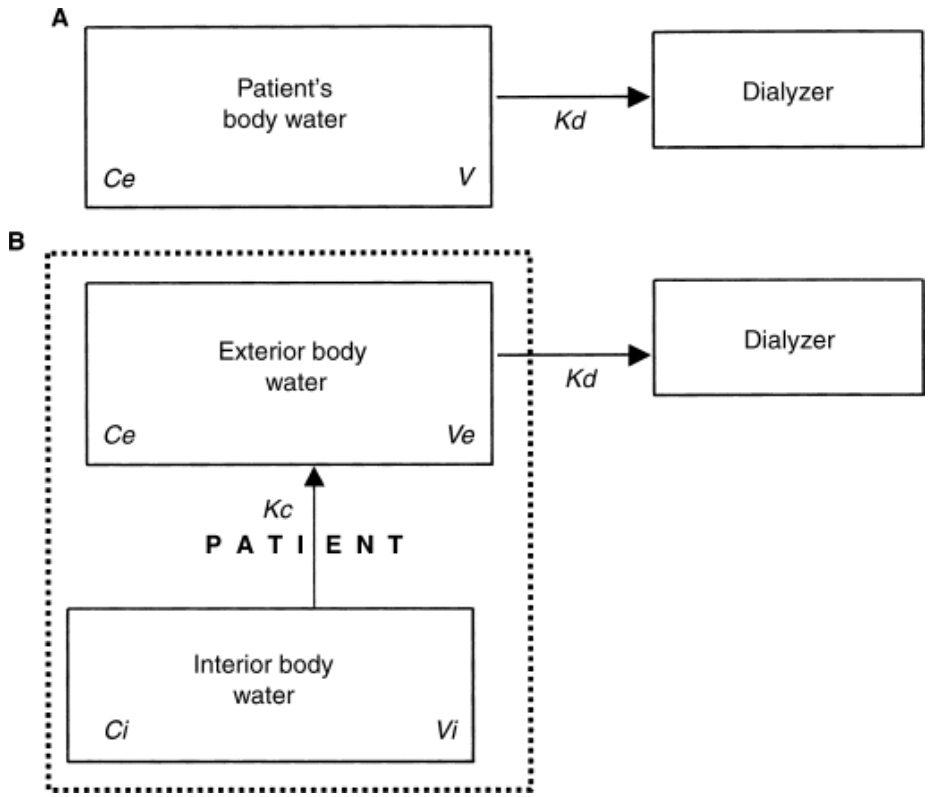

Figure 2: Dialysis toxin flow according to (A) one-compartment model vs (B) two-compartment model [46].

Figure 2A shows the flows of the waste products during dialysis treatment according to a one-compartment model. All fluids and plasma water (i.e., the part of the blood that can pass through the semipermeable membrane, everything smaller than the pore size of the filter) are considered as one volume of distribution [47]. This is a simplified dialysis model, assuming that the change of volume (V) during HD has little influence on modeling efficiency (how accurately a model can predict reality), and hence was neglected (simulations and verifications have shown it has little effect on improving the accuracy of the modeling). Another assumption is that urea generation and residual urea removal by the kidneys are very low/insignificant compared to dialyzer clearance (Kd). The one-compartment modeling only takes into account the most important phenomena and assumes that other less important

phenomena would cancel each other out. The one-compartment dialysis model can easily be described in the form of a differential equation.

$$\frac{dCe}{dt} = -\frac{Kd}{V}Ce \quad (1)$$

A simplified interpretation is that the rate of toxin concentration is decreasing with time, and the time variable toxin concentration (Ce) is negatively proportional to constant dialyzer clearance (Kd), distribution/compartment volume (V), and time (t), see **equation 1**.

$$Ce(t) = C_0 e^{-tKd/V} \quad (2)$$

Ce described the decrease of toxin concentration during hemodialysis. C0 is the initial toxin concentration, see **equation 2**.

To be able to decide the optimal dialysis time a formula was developed, optimizes use of available resources for dialysis and adapts to each patient. Dialysis time calculation requires for volume distribution (V) to be known. The formula can be used for both deciding the optimal dialysis time, but also to calculate dialyzer clearance (Kd).

$$T = \frac{V}{Kd}\ln\frac{C_0}{C_T} \quad (3)$$

T is the dialysis time, C_T is the toxin concentration at the end of dialysis, and ln is the natural logarithm. As previously defined, C_0 is the initial concentration of the toxin. Formula (**equation 3**) introduced the factor T (time), T is the time needed to be able to go from C_0 (initial concentration of toxin) to C_T (final concentration of toxin after time T). The above formula can be of great clinical impact if the data for V, Kd, and C_0 is available and unaffected by significant errors, which has been proved by simulation and testing.

In the two-compartment model some new assumptions are made, and new aspects considered - the main consideration is the shift of molecules from the extracellular space to the intracellular space. In the two-compartment model, the main assumption is that body fluids are divided into two parts: one directly accessible to the dialyzer and the other indirectly assessable. The blood is directly accessible due to the direct contact with the semipermeable membrane, hence direct removal of

toxins via the blood. Removal of toxin from the blood pool will result in gradual solute transfer from interior body water (i.e., the second and indirectly accessible compartment), due to both fluid and solute shift.

$$\frac{dCe}{dt} = -\frac{K_C(Ci-Cd)}{Ve} - \frac{KdCe}{Ve} \quad (4)$$

$$\frac{dCi}{dt} = -\frac{K_C(Ce-Ci)}{Vi} \quad (5)$$

Ce is the toxin concentration in blood, Ci is the toxin concentration in the interior water, Ve extracompartment volume, Vi intracompartment volume, and Kc is the intercompartment mass transfer coefficient, see **equations 4-5**.

As previously described in the one-compartment model, the rate of toxin removal from the dialyzer is a linear function of the concentration of Ce. In the one-compartment modeling formula, Ce is the toxin concentration value in the bloodstream entering the dialyzer; Ci is the toxin concentration value localized at a non-defined location in the patient's body (but not in the intravascular compartment) that cannot be measured due to its inaccessibility.

The initial concentration of the toxin C_0 can be measured in the blood of the patient and constitutes the initial condition. Equation 6 describes the time-dependent function of Ce.

$$Ce(t) = 0.5C_0e^{ta1}[(1+a_3)e^{-ta2} + (1-a_3)e^{ta_2}] \quad (6)$$

The dialysis clearance (Kd) is based on data from the manufacturer and is dependent on blood flow rate (Q_B) and dialysis flow rate (Q_d) (set of formulas for instances of different conditions in regards of the relationship between Q_B and Q_d is available). Kd can be simplified to rate of solute removal [46].

Dialysis modelling in regards of post-filter iCa

Calculation of post-dialyzer iCa requires a model simulating the interactions of calcium with other substances in the blood. These interactions are defined by chemical reactions. The outcome is determined by the local concentration of the reactants, chemical equilibrium constants, and the total amounts of calcium and other participating substances. The total of a certain substance is the sum of all its forms, in other words both the substance in its free form and in its bound form (often

bound to albumin). The local concentrations depend on the composition of the blood that is pumped out of the patient and the fluids that are mixed into the extracorporeal circuit and transported over the dialyzer membrane [51].

The blood-chemistry includes free and bound calcium and, in our model, for calculation of post-filter ionized calcium, calcium bound to citrate, albumin, bicarbonate, phosphate, and carbonate are considered. Magnesium, sodium, and hydrogen are competition to calcium in regards of binding sites. The patient's systemic concentration of calcium is measured either as a total concentration or as ionized (free) concentration. The other modelled substances are assumed to be at a constant level over time, with the exception of citrate, which is modelled over treatment time based on the supplied citrate for anticoagulation, which imposes a strong effect on the balance between free and bound calcium and is therefore important to the model. The body always tries to keep the ionized calcium as constant as possible, and it should be noted that normal equilibrium of calcium concentration is not reached during RCA CRRT due to the constant addition of citrate, the removal of substances, and addition of solutions during the dialysis itself. Addition of citrate into the dialysis solutions causes the equilibrium between bound and free calcium to change. The mass flow of each substance into the mixing point is simulated and gives the final concentration. Calculation of post-filter calcium is dependent on the amount of the total calcium which is free for transport over the dialyzer and protein-bound calcium which cannot pass the dialyzer. A large portion (30-70%) of the free calcium will bind citrate and citrate-calcium complexes and will be lost through the dialyzer [52]. In order to be able to derive the clearance, i.e., how much of a solute will be removed, the flow rates and the concentrations of the solute at the inlets of the dialyzer must be known [53].

The algorithms for dialyzer transport were based on the previous work done by *Sternby et al.* presenting mathematical models of the diffusive-convective mass transfer rates in dialyzers for solutes present on both sides of the membrane for uncharged solutes. In the report, the mass transport rate is assumed to be linear in both inlet concentrations, since the driving forces for diffusion and convection are linear [51].

Normally the systemic citrate (Csys) in the patient is low, 0.13 mmol/l, and during RCA CRRT the systemic citrate will increase to between 0.3–0.6 mmol/l or even higher, since some of the citrate given during the treatment will not be removed through the dialyzer and will be returned to the patient [37, 39].

Acid-base disturbance and CRRT

It is of great importance in clinical practice to diagnose the patients with the correct acid-base disorders, since it is not only the key for correct treatment but also for monitoring the progress of the given treatment [54]. In the ICU, the correct diagnosis of acid-base disorders is of outmost importance, since it can be a key for determining the next intervention i.e., should the patient be intubated or even should CRRT be started, nevertheless, the investigation of acid-base disorders in the ICU is often intricate and time consuming.

The human body is striving towards homeostasis and pH is tightly controlled within defined limits, like other physiological parameters in the body such as temperature, blood pressure, and osmolality [55]. In the intensive care unit, the most critically ill patients are taken care of. Frequently these patients have complex acid-base and electrolyte disorders [56]. In most cases, the acid-base disorders are mild and self-limiting; however, rapid changes may occur resulting in extreme blood pH with possibly detrimental effects on the patient's organ function and health. As mentioned above, in these cases the correct diagnosis is of great importance for adequate treatment. There has been a lot of work in evaluating acid-base balance, and all this work has resulted in greater understanding of the impact of e.g., fluids on the disturbances and also on the critically ill patients [57].

$$pH = pK_a + \log_{10}\frac{[HCO_3^-]}{\alpha\, pCO2} \tag{7}$$

$$Where\ pK_a = -\log_{10} K_a = \log_{10}\frac{[HA]}{[A^-][H^+]}\ (where\ HA \rightleftharpoons A^- + H^+)$$

$$and\ \ HCO_3 = (10^{pH-pK_a}) * \alpha\, pCO2 \tag{8}$$

The Henderson-Hasselbalch equation will give the formula for pH. The formula consists of various factors: pKa is the dissociation constant of carbonic acid, plasma concentration of bicarbonate ($[HCO_3]$), pCO_2 is partial pressure of carbon dioxide, and α is solubility of carbon dioxide in blood at 37°C. The above equation relates pH with ratio of concentration of undissociated acid HA to the concentration of conjugate anion A^- (see **equations 7-8**) [58].

Buffer is a solution that resists changes in pH, i.e., counteracts acidity or alkalinity. There are many buffer systems in the body (such as plasma proteins, hemoglobin, phosphate etc.), but most often one is seen as key and that is bicarbonate (HCO_3) when wanting to understand acid-base disturbances.

$$H^+ + HCO_3^- \rightleftharpoons H_2CO_3 \rightleftharpoons H_2O + CO_2 \tag{9}$$

The acidity of a solution is determined by the concentration of hydrogen ions (H^+). There are several disorders that can result in an increase of hydrogen ions, resulting in the body becoming more acidic, such as increase in lactate, ketones, and kidney failure. The bicarbonate buffer system will resist this unfavorable change in pH [59-63]. It does so by driving the above reaction to the right (**equation 9**), i.e., hydrogen ions will react with bicarbonate (thereby being consumed) to minimize the acidity in the body. Since bicarbonate is "consumed", a supply of bicarbonate is needed. The kidneys are vital organs when it comes to maintaining acid-base balance and can both generate bicarbonate and resorb filtered bicarbonate in the proximal tubules [61, 64].

$$H^+ is\ propotional\ to\ \frac{PaCO_2}{HCO_3^-} \qquad (10)$$

Equation 10 is a simplified version of the acid-base reaction presented equation 9, illustrating the relationship between the hydrogen ion concentration in the body and the ratio of $PaCO_2$ to bicarbonate. Ventilation controls $PaCO_2$ levels (increase if hydrogen ions stimulate the respiratory center to increase the respiratory rate and hence decreasing $PaCO_2$), and the kidneys regulate the bicarbonate level. This relationship explains that hydrogen ions can increase under conditions, firstly, in an increase in $PaCO_2$ and secondly, if bicarbonate is reduced [54].

Acid-base disorders can broadly be divided into problems involving metabolic or respiratory processes, or a combination of both. Simplifications of acid base disorders have been sought after, and one of these simplifications is that metabolic disorders can be seen as process effecting the bicarbonate levels and respiratory disorders as changes in $PaCO_2$. The body will try to adapt and compensate for the acid-base disturbance in order to reach and maintain homeostasis. If the main problem is metabolic, then the compensation will be respiratory; this process can start within minutes. When the main issue is respiratory then the compensation will be metabolic, this process usually takes place over several days and will result in increase in bicarbonate levels [65].

Table 2: Some important definitions regarding acid-base [54].

Acidaemia	An arterial pH below the normal range (pH<7.35).
Alkalaemia	An arterial pH above the normal range (pH>7.45).
Acidosis	A process lowering pH. This may be caused by a fall in serum bicarbonate and/or a rise in the partial pressure of carbon dioxide ($PaCO_2$).
Alkalosis	A process raising pH. This may be caused by a rise in serum bicarbonate and/or a fall in $PaCO_2$.

The different acid-base disorders:

Metabolic acid-base disorders:

- Metabolic acidosis: Arise due to increase of organic anions (e.g., lactate), loss of bicarbonate or gain of exogenous anions.
- Metabolic alkalosis: Arise due to loss of strong anions or administration of strong cations [48].

Respiratory acid-base disorder:

- Respiratory acidosis: Increase of PaCO2 (partial pressure of carbon dioxide).
- Respiratory alkalosis: Decrease of PaCO2 [66].

Acid-base disorders can be occurring simultaneously, i.e., a patient can have a combination of more than one acid-base diagnosis, and this is why good understanding of the diagnosis and disturbances is important for determining the correct treatment.

The different components for diagnosis of acid-base disorders such as $PaCO_2$, bicarbonate, pH, and base excess (BE) are measured by a blood gas analyzer (BGA). It is important to know that BGA measures two substances, which are hydrogen ion (from which pH is calculated), and $PaCO_2$. From these two the rest of the parts needed for diagnosis of acid-base disorders will be calculated [54]. BE is defined as the amount of strong acid [mmol/l] needed to be added to blood sample to return the sample to pH 7.40 after equilibration while maintaining a $PaCO_2$ of 40 mmHg, and at this condition BE will be 0 mmol/l [67].

For a long time people have been looking at new approaches for acid-base diagnosis, and Stewart introduced a new way to see acid-base physiology and disorders [68]. Stewart introduced a method combining several principles of physical chemistry such as electroneutrality, conservation of mass, and dissociation of electrolytes. This was a reaction to the bicarbonate-centered approach, which is still one of the most used methods, that was seen as inadequate due to simplifications, but also confusing. In the model developed by Stewart, three variables are important: SID (strong ion difference, see **equation 11**), $PaCO_2$, and total weak-acid concentration. The two most important ions in plasma are sodium and chloride. Stewart suggested that bicarbonate and BE can be used for determination of how deranged an acid-base disorder is rather than trying to understand the mechanism behind the disorder [68-70].

$$SID = [Na^+] + [K^+] + [Mg^{2+}] - Cl— [other\ strong\ ions] \qquad (11)$$

The Stewart approach can be used for not only understanding the mechanism behind acid-base disorder, but also management strategies which also include fluid management [71-73].

There are many different approaches in regards of diagnosis of acid-base disorders. and there are still discussions about which one is the correct one. No consensus is present to this day and every approach is able to showcase their clinical benefit [74].

Buffering effect of RCA CRRT and effect on acid-base disturbances

One of the most common disturbances seen in ICU patients is respiratory disturbances. A possible indication for CRRT is amongst other things the correction of acid-base disorders. Commonly, the buffering effect of dialysis due to the bicarbonate content of the dialysis fluids is of interest. Today most physicians will try to evaluate the underlying acid-base disturbance by interpreting parameters derived from a blood-gas analysis and subsequently prescribe a, for the patient suitable, CRRT treatment.

As mentioned previously, some kind of anticoagulation is needed during dialysis due to the clotting process being triggered in the blood as soon as it touches foreign material, i.e., the tubing/filter of the dialysis circuit. The most used anticoagulation method is citrate. Citrate binds calcium and inhibits several steps of the coagulation cascade, hence resulting in hindering the clotting process and prolonging the filter life. The citrate-calcium complex will be mostly removed through the membrane filter, resulting in risk for hypocalcemia in the patient. Systemic control of systemic ionized calcium is vital together with post-filter iCa to make sure the patient is not at risk of hypocalcemia but also to make sure the filter is coagulated enough. A fraction of the citrate-calcium complexes will reach the patient, and constitute a citrate load, citrate will be metabolized to bicarbonate by the liver, kidneys, and skeletal muscles. One citrate molecule will yield three bicarbonate molecules when metabolized [75].

In addition to hypocalcemia, citrate toxicity is a possible detrimental side effect of RCA CRRT. To avoid citrate toxicity and hypocalcemia, monitoring the systemic total calcium and systemic ionized calcium ratio, as well as using a structured protocol during RCA CRRT treatment is of importance. A ratio over >2.5 is suggestive of citrate toxicity. Mainly, citrate toxicity occurs due to two reasons: 1. Excessive citrate reaches the patient and is then metabolized to bicarbonate leading to metabolic alkalosis, or 2. Citrate that reaches patient surpasses the metabolic capacity and leads to accumulation of citrate and metabolic acidosis [76].

The effect of RCA CRRT on systemic acid-base balance (i.e., total buffer load) can be impacted by several factors such as: 1. Citrate load, 2. Citrate metabolic capacity of the patient, 3. Bicarbonate from CRRT fluids, 4. Buffer from other sources, and 5. Underlying disturbances from the patient's underlying disease.

CRRT has bicarbonate containing solutions (in dialysate and replacement), ranging from 22 to 30 mmol/l depending on manufacturer. Depending on the flow rates used during therapy; but also depending on specific solutions used, the concentration of bicarbonate can differ. The variability in the solutions used but also flows will lead to different amounts of bicarbonate reaching and entering the blood stream, which needs to be accounted for when looking at the total buffer load.

Sodium and glucose, the need for correction

Deranged sodium levels are commonly seen- at either side of the physiological range (normal range is 135-145 mmol/l) and is one of the most common electrolyte imbalance disorders seen in healthcare [77]. Hyperglycemia is associated with decreased serum sodium level concentration. Water homeostasis is mediated by thirst, arginine vasopressin, and the kidneys [78]. Glucose creates an osmotic gradient that will result in movement of water from the intracellular compartment to the extracellular compartment, resulting in the reduction of serum sodium levels. This is why most hyperglycemic patients are mildly hyponatremic [79]. However, there are instances where patients present with normal or sometimes even elevated serum sodium levels due to development of osmotic diuresis without fluid replacement. Commonly, this is the case in the elderly population with impaired thirst mechanism or no access to enough fluids [80].

Hypo- and hypernatremia have both been associated with increased mortality in hospitalized patients. This is why correct understanding of the potential underlying reasons for deranged sodium levels are of outmost importance [81, 82]. Deranged sodium levels are also a negative prognostic factor in e.g., patients with CKD (chronic kidney disease), heart failure, liver disease, and even intracerebral hemorrhage. Due to sodium imbalance being a negative prognosis predictor, close monitoring of the shifts has been strongly recommended [83-87].

It is known that hyperglycemia can depress sodium concentration, and in some cases patients with hyponatremia can be overlooked during episodes of severe hyperglycemia. Previous research in patients with hyperglycemia has shown that the corrected sodium level is a better indicator of prognosis compared to measured sodium, hence a correction formula should be used when treating these patients [88].

The correction formula has been available for a long time and the usage of the formula clinically has varied. A study by *Chuang et al.* showed that if one only uses

measured sodium levels to predict clinical outcomes one may overlook the clinical impact of true hypernatremia (i.e., not having correct sodium levels due to not using correction formulas). In this study, they showed a higher risk of 90-day mortality irrespective of underlying disease when taking the true sodium levels in extremely hyperglycemic patients into account [88]. A further study by *Anthanont et al.,* showed that hypernatremia on admission is as a strong predictor for mortality in patients with hyperglycemic crisis [89]. A reason for hypernatremia is lack of ability to compensate for osmolality and severe dehydration, especially in patients with osmotic diuresis and in combination with inadequate fluid replacement [90]. It is also important to note that dehydration by itself is a prognostic factor in mortality [89, 91].

$$Corrected\ Sodium = Measured\ Na + \frac{1.6\ x\ (glucose - 5.6)}{5.6} \qquad (12)$$

Katz' formula considers only the increase in extra-cellular glucose and dismisses changes in body water and other monovalent ions, i.e., it characterizes only a closed system [92]. Patients with normal renal function and with free water intake governed by thirst represent an "open system", where additional parameters such as osmotic diuresis and dilution will count.

The measured, actual sodium level will be falsely low in hyperglycemia, and the true corrected, calculated sodium level is always higher (see **equation 12**). The greatest impact is seen in patients with hyperglycemic crises. However, in critically ill patients, blood glucose levels can also be elevated due to other circumstances. In addition, many critically ill patients have other sodium disturbances, as well as potassium imbalances, which are two of the most common electrolyte disturbances seen in the ICU. The measured, actual sodium level might be outside the normal range, making the correction calculation even more important [93-95].

Method

The main program used for development of algorithms, drawing figures, analysis of data, and most other aspects of the PhD project was done in MATLAB 2019b/2022b. Updates were continuously performed as soon as a new version was available, and different available packages in MATLAB were used that fitted the specific projects. Some pictures were developed in collaboration with experts in the area and Baxter employees, i.e., some pictures in the nNBL (normalized net buffer load) project were done in Minitab.

Baxter international provided the main versions of some of the algorithms that were used and that were significantly developed during the course of this PhD project. For nNBL, no major changes were done to the actual original code since the purpose was more testing of the accuracy of the code on actual patient data.

Patient data was extracted from the electronic medical records (EMR) in two parts, one used for the acid-base and sodium/glucose project, and the other part contained dialysis data and was used for development of post-filter iCa algorithm and nNBL. The data was analyzed to find outliers and out-range-data, but also to get a better understanding of the collected data and patient clientele in the ICU in Lund. Data of 120 patients treated in the ICU at Skåne University Hospital in Lund during 2010-2017 was extracted from the EMR (Philips ICCA system), this data was used for the post-filter iCa and nNBL projects.

Ethical approval was received from the Regional Ethics Board of southern Sweden (Dnr 2017/618), used for post-filter iCa and nNBL. Another ethical application was sent for acid-base diagnosis and sodium/glucose projects, in which data was extracted for patients being admitted to the ICU at Skåne University Hospital in Lund during 2011-2021 for a large number of data (>300k unique data points). The second ethical permission was accepted by the Swedish Ethical Review Authority (Dnr 2020-04642).

Post-filter ionized calcium

Two algorithms were developed in MATLAB to calculate post-filter iCa and were compared to real blood gas analysis from patients. 57 patients were finally included after exclusion of patients due to, e.g., missing data or being part of another study. The total number of measurements compared was 1,034.

The difference between the two algorithms is that in one systemic calcium used as an input comes directly from a measurement made in a chemistry laboratory, while in the second algorithm it is converted from a formula from measured systemic iCa from a point-of-care blood gas analyzer. The reason for having two formulas is due to systemic calcium analyzed by a chemistry laboratory can be measured from once every 24 hours to every 72 hours, while systemic iCa needs to be measured much more often.

$$Post-filter\ iCa = \beta_0 + \beta_1 * \left(Ca_{PD} - Ca_{ref}\right) + \beta_2 * (Cit_{PD} - iCit) \qquad (13)$$

The linearized formula for post-filter iCa calculation (see **equation 13**), where β_0 and β_1 and β_2 are constants given by the linearization of the full model.

Table 3: Algorithm 1 used systemic total calcium and Algorithm 2 used an initial blood gas as input.

	Algorithm 1	**Algorithm 2**
Patient parameter inputs	The most recent measured systemic total calcium value from hospital laboratory	Systemic iCa from BGA pH from BGA Bicarbonate from BGA Albumin (fixed or from laboratory)
Machine parameter inputs	Blood flow, Dialysis fluid flow Post-filter replacement fluid flow Calcium replacement flow Patient fluid removal rate Pre-filter replacement fluid flow Citrate dose Composition of solutions used (i.e. concentration of calcium, bicarbonate, citrate, hydrogen phosphate, sodium, magnesium, potassium) Filter Elapsed treatment duration (blood pump running time)	

Acid-base diagnosis

A tool to diagnose acid-base disturbances was developed in MATLAB in 2020. The theories applied were the Boston and Copenhagen approach, while the Stewart approach was in this version disregarded. The analysis was done on 8,875 initial blood gases of patients admitted in the ICU.

The model can be divided into four parts:

1. Initial input variables are pCO_2 and pH. Based on those two variables a primary disturbance will be determined.

Table 4: Flow sheet for determination of the most likely primary disturbance in the first evaluation level.

pCO_2	pH	Outcome
⇩	⇩	Metabolic acidosis
⇩	⇧	Respiratory alkalosis
⇧	⇩	Respiratory acidosis
⇧	⇧	Metabolic alkalosis

2. Compensation will be determined based on the primary diagnosis. Compensation variables: pCO_2 for metabolic and HCO_3 for respiratory disorders are determined. Compensation is defined according to the Boston formulas. If compensation is partial, then a secondary disturbance is present.
3. If the diagnosis is metabolic acidosis than the script will calculate the anion gap (AG) and delta ratio (DR) (**equations 14-15**) to determine the presence of a tertiary disturbance. For instances in which AG > 16, then a Delta ratio was calculated to determine potential tertiary disturbance present. Normal AG was defined as 12 and normal bicarbonate as 24 mmol/l.

$$Anion\ gap\ (AG) = [Na^+] - [Cl^- + HCO_3^-] \quad (14)$$

$$Delta\ ratio = \frac{\Delta AG}{\Delta HCO_3^-} \quad (15)$$

Where $\Delta AG = Measured\ AG - Normal\ AG$ *and*

$\Delta HCO_3^- = Normal\ HCO3 — Measured\ HOC_3^-$

4. The fourth and final level is an evaluation filter that will present the final results in written graphical form. It will combine the results from all the previously

mentioned layers and provide a final output. The final level is not fully developed, and many features are in need of improvement. A graph will be drawn, where pH is placed on the X-axis, bicarbonate in the Y-axis. The graph has a superficial layer consisting of pCO2 isopleths, created using Henderson-Hasselbach equation solved for bicarbonate. The isopleths will be drawn by having the Henderson-Hasselbach formula have pCO2 as a constant input (e.g., 20, 40, 60, and 80) and solving it for bicarbonate instead of pH, see formula 8.

Net buffer load

60 patients were left after application of inclusion and exclusion criteria from the 120 patients extracted. The algorithm for net buffer load was developed in MATLAB 2022b. Prismaflex dialysis machines equipped with ST-150 filters were used for all patients with the modality of CVVHDF. The Flexicitrate protocol was used for all patients.

Some definitions are introduced in the development of the algorithm for nNBL, such as steady state which is assumed to be reached after 48 hours. Steady state needs a time period to reach equilibrium, i.e., effect of bicarbonate to alter the metabolic component of an acid-base disturbance needs time, the body needs time for compensation. Time is also needed due to the low intensity of CRRT therapy compared to, e.g., hemodialysis.

Net buffer load (NBL_{25}) was determined as a function dependent on concentration of bicarbonate and/or bicarbonate precursors generated from the citrate metabolism (J_{metcit}), bicarbonate infused from CRRT solutions during therapy ($J_{HCO3bal}$) according to **equation 16**, but also CRRT treatment settings. The citrate load is multiplied by three since citrate will be metabolized to three bicarbonate and this will provide the value for J_{metcit}.

$$NBL_{25} = J_{metcit} + J_{HCO3bal} = 3\,x\,J_{citrateload} + (J_{HCO3inf} - J_{HCO3eff}) \qquad (16)$$

The bicarbonate concentration at the filter inlet is a result of patient HCO_3^- (assumed venous blood values of 25 mmol/l in the model, hence NBL_{25}), and the predilution from the prefilter replacement solution. The citrate concentration of the prefilter replacement solution is dependent on the prefilter replacement solution dilution.

Citrate load is defined as infusion rate of citrate to the patient, this is calculated by the difference between citrate infusion rate from citrate containing fluid in the prefilter replacement solution (J_{citPBP}) and the removal rate to the effluent (J_{citeff}), see **equation 17**.

$$J_{citrateload} = J_{citPBP} - J_{citeff} \quad (17)$$

Bicarbonate balance ($J_{HCO3bal}$) is dependent on the net infusion/loss of bicarbonate in the extracorporeal circuit, a product of infusion of bicarbonate (dialysate and/or replacement fluids, i.e. $J_{HCO3inf}$) containing solution and bicarbonate removal rate through effluent ($J_{HCO3eff}$), according to **equation 18**.

$$J_{HCO3bal} = J_{HCO3inf} - J_{HCO3eff} \quad (18)$$

The following important assumptions were made: 1. Citrate metabolism is proportional to the body weight, and patient citrate concentration is computed at steady state, with a typical metabolic clearance of 700 ml/min; 2. A constant bicarbonate concentration of 25 mmol/l was assumed to be present in the patient when steady state was reached; and 3. Lactate was ignored.

The computed NBL_{25} does not match to the actual balance of running therapy, but instead to steady state, when patient venous bicarbonate is assumed to stabilize at 25 mmol/l, which is seen after 48 hours of uninterrupted therapy. These 48 hours were not only needed for compensation of the acid-base disorder, but also the high distribution volume of bicarbonate and the low intensity of the CRRT therapy.

Sodium/glucose correction

297,714 simultaneous sodium and glucose measurements were obtained from 9,863 ICU patients measured from a blood gas analyzer. A script was developed in MATLAB 2022a for correction of sodium based on most recent glucose levels.

Our cohort consists only of critical care patients with no free oral intake and tightly controlled fluid balance, and thus represent a "closed system". Subsequent mathematical models in outpatients have confirmed that Katz' formula is very exact [96, 97].

Data was sorted to form simultaneous sodium-glucose pairs according to the timestamp from when the analysis was done. A maximum of 2 minutes time difference between sodium and glucose measurement was allowed (although in most of the instances the measurements were performed simultaneously).

The correction formula used is:

$$Corrected\ Sodium = Measured\ Na + \frac{1.6\ x\ (glucose - 5.6)}{5.6}$$

Results

The general result is that a lot more can be done in the area of algorithm development in the ICU. Promising results were seen from each project, and as most times some more work is needed but the work has shown potential in improving healthcare. My PhD work can be just a beginning in the development of tools to improve and simplify everyday life for physicians/healthcare personnel.

Post-filter ionized calcium

The algorithms were able to estimate in range postfilter iCa values with great trueness and precision. However, there were difficulties to estimate out-of-range postfilter iCa values. More work is needed to improve the algorithms especially in citrate-modelling.

Algorithm 1's deviation from the BGA was 0.0079 ± 0.0709 mmol/l and for Algorithm 2's deviation was -0,0351 ± 0.0727 mmol/l. Algorithm 1 had better trueness (lower mean value) and better precision (lower standard deviation). Algorithm 2 had a tendency to underestimate post-filter iCa compared to Algorithm 1.

Both algorithms had issues detecting the 5 instances of too high post-filter iCa values (i.e., >0.5 mmol/l) and missed the intervention that should have followed. All the 3 instances of low post-filter iCa (< 0.25 mmol/l) were correctly detected.

Acid-base disorder diagnosis

Theories are developed on ideal models and are always approximations. Critically ill patients experience significant disturbances in the blood homeostasis and are thus far from an ideal situation with many unfavorable changes occurring in the body having negative effects on the patient. All exact inputs for the models are not available in real life.

On our cohort it is difficult to develop a working script based on Stewart (SID method), whereas Boston (bicarbonate method) and Copenhagen (base excess

method) work better. Some scenarios are impossible to describe using only one theory, due to the complexity in the patients, but also since not all underlying diseases effect on acid-base disorders can be taken into account. Blood in normal state is already alkalotic and there is more room for acidosis to deviate compared to alkalosis. The first version of the script worked well, gave reasonable output and also understandable output for all blood gases calculated.

The script calculated a single blood gas instantly, compared to manual calculating which required 1–10 min for a simple and a complicated disturbance, respectively. The time frame for the script to calculate all 8,875 blood gases in the cohort was 30.3 s. The script contains ~500 rows, there is 1 calculation per row, giving 8,875 × 500 = 4,437,500 calculations for the complete cohort. To do the same calculation maneuver manually is almost impossible.

Of the 8,875 blood gases analyzed 4,111 (46.3%) were considered normal. Respiratory acidosis was the primary disturbance in 2,753 (31.0%) patients and metabolic acidosis in 464 (5.2%) patients. Respiratory alkalosis was the primary disturbance in 1,501 (17.0%) patients and metabolic alkalosis in 46 (0.5%) patients.

4,764 (53.7%) blood gases showed an acid–base disturbance. Of these a majority presented a mixed disturbance; 3,558/4,764 (74.7%) patients had a primary + secondary disturbance and 100/4,764 (2.1%) patients had a mixed situation with a primary + secondary + tertiary disturbance.

The result of all the calculations resulted in graphical representation of the acid-base disorder, see **figure 3**.

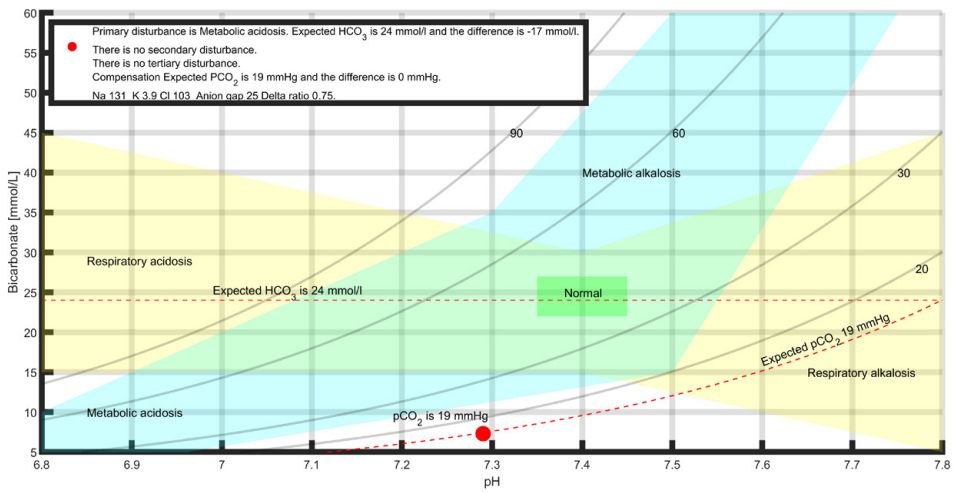

Figure 3: The graphical illustration of the results with a text part placed in a box at the left corner.

Net Buffer Load

The $nNBL_{25}$ is a useful static safety parameter which can alert the operator about the impact of the CRRT circuit on the patient's acid base status. During the period of the first 72 hours of CRRT treatment the mean of all $nNBL_{25}$ values was 0.09 ± 0.04 mmol/h/kg (comparable with previously studies) [75, 98, 99].

In the present study we could not show correlation between $nNBL_{25}$ and steady state bicarbonate. The element with highest impact on $nNBL_{25}$ is citrate containing pre-blood pump (PBP) replacement fluid infusion rate (Q_{PBP}). No citrate toxicity was seen amongst the 60 included patients, the total calcium/ionized calcium ratios were kept within the normal range (< 2.5). No severe instances of metabolic alkalosis (pH > 7.6) were seen amongst the study population.

Table 4. Suggested normal range for $nNBL_{25}$ and high/low deviations including suggestions how to manage a $nNBL_{25}$ deviation.

Normalized net buffer load ($nNBL_{25}$) [mmol/h/kg]	**Status of patient and CRRT**	**Suggested action**
< 0 mmol/h/kg	Predicted net removal of HCO_3 of the CRRT therapy. Patient's HCO_3 state is expected to be less than 25 mmol/l. Moving towards acidosis.	Revise the prescription: increase Q_B or D_{cit}, decrease CRRT dose.
0.1-0.2 mmol/h/kg	Predicted net infusion of HCO_3 of the CRRT treatment. A positive net infusion (when patient is at 25 mmol/l) exists, which balances proton generation rate from patient's metabolism.	No changes needed.
> 0.3 mmol/h/kg	Predicted positive net HCO_3 infusion surpassing the proton generation of the CRRT treatment. Patient's HCO_3 is expected to be greater than 25 mmol/l. Moving towards alkalosis.	Revise the prescription: decrease Q_B or D_{cit}, increase CRRT dose.

Sodium/glucose correction

Correction should be mandatory for higher glucose values (>10 mmol/l) in order to make decisions on true sodium levels. A significant number of Na^+ measurements in a large ICU cohort from the ICU in Skåne University hospital at Lund required correction.

We wanted to use the computational capacities of MATLAB to better understand the effect of glucose on sodium levels in a systemic way but also for the first time ever to evaluate the correction formula for such a large cohort. Patients with deranged glucose levels are commonly seen in the ICU and often sodium is evaluated by looking at the measured value.

Correction formulas taking deranged glucose into account when evaluating sodium is not often done, resulting in physicians only looking at measured values of sodium which would give a wrong picture of the patient's state. The goal of the study is to understand the effect of using a correction formula for sodium for ICU patients, something that has not been used in the ICU, or as systemically before.

In our study, we found that 33 patients were wrongly treated due to them having deranged glucose levels and the treating physician only looking at the measured sodium level from the blood-gas analyzer, showcasing that mistreated occurred when not using correction formula for sodium.

Correction of sodium is evaluated during 24 hours and is defined as increase/decrease of sodium no more than 8 mmol/l during that time period. ΔNa^+ is Corrected Na – Measured Na. $\Delta Na^+ > 8$ mmol/l for 24 hours is seen as unfavorable. We identified 602 patients that showed a $\Delta Na > 8$ mmol/l over 24 h when looking at actual measured Na and 635 instances when using the correction formula for sodium. This means that 33 patients were missed and overcorrected when only looking at measured sodium and not using the correction formula for sodium.

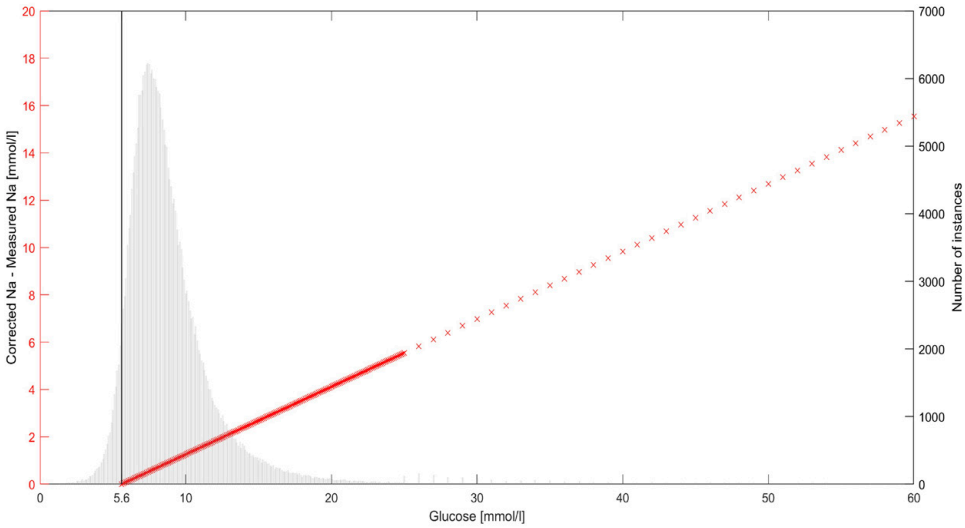

Figure 4: The red linear graph shows the difference [corrected Na] – [measured Na] with increasing glucose level. A histogram of all the 297,714 glucose values is inserted in a graph. For a majority (95.3%) of the glucose values (hyperglycemia > 5.6 mmol/l) need a correction.

Discussion

Post-filter ionized calcium

Both algorithms could predict a single unique value well with high trueness (mean difference) and precision (standard deviation) compared to a measured blood gas analysis as a reference.

Algorithm 1 showed better trueness and precision compared to Algorithm 2. Algorithm 1 did a better overall estimation compared to Algorithm 2. Most likely a systemic confounding factor in the mathematics, predicting the citrate concentration in the patient could explain our systematic difference to the measured post-filter iCa values. The citrate model was modeled after previous work done [38, 39] and the trueness of that model can be discussed especially since the model is based on healthy individuals and not ICU patients that may experience deranged physiological processes. Testing of the citrate model would be preferable and possibilities of eventually measuring citrate concentration in the patient to be able to have better understanding.

Correct conclusions are also limited due to the lack of many instances of out-of-range post-filter iCa values. In this study, there were only five instances of high post-filter iCa and only three instances of low post-filter iCa values measured. More out-of-range data would be preferable, at least 10 of each when doing power calculations. It is also important to note that the high instances of post-filter iCa were all seen at the start of dialysis/soon after start of dialysis and none were seen in, e.g., the middle of CRRT treatment.

It is also important to note that comparison is made to a blood gas analyzer which is unsuitable to measure very low calcium levels or analysis of samples with very high citrate levels. BGAs are not approved for ionized calcium levels 0.2-0.5 mmol/l. BGAs have a typical deviation range of ± 7.5%, however, the deviation can be larger in certain models [39, 40, 100]. Studies have showed that BGAs have a great distribution range, reflecting in uncertainty in BGA measurements [100]. The outliers seen could be a result of the sample being outside the approved range, or sampling error. A study by *Schwarzer et. al.* indicated that as many as 70% of the post-filter samples could lead to incorrect therapy interventions due to measurement errors caused by the BGA [40].

Improvements to the script could be better if increases in the resolution of the data was done, since our extracted data had a resolution of updates once every hour, and a lot of information about interruptions in the CRRT treatment were lacking. It is known that interruptions in CRRT for as long as 18 min would lead to 50% drop of citrate concentration in the patient due to the high metabolization rate [53].

Acid-base disorder diagnosis

We created a mathematical script that can interpret blood gas results on an individual as well as on a cohort level, using all the available theory, and delivered a clinically meaningful result.We argue that a physician in a clinical situation does rarely have the time to manually calculate complex acid–base disturbances, and the risk that the result is not correct is considerable.

A total of 8,875 blood gases were included. The script was evaluated by comparing 100 randomly chosen blood gases calculated and determined by two experienced intensivists, to the output of the script, and the diagnoses were the same in all instances. The script was stable and could easily calculate 8,875 blood gases. In fact, it was tested successfully on 300k blood gases.

Net Buffer Load

In this study we introduced the parameter normalized net buffer load ($nNBL_{25}$) and computed it during 60 CRRT treatments for the first time. The $nNBL_{25}$ will also be included in PrisMax V3 (software version 3, Baxter, Deerfield, USA).

Review of published data revealed that the most optimal (normal) range is 0.1-0.2 mmol/h/kg, i.e., a slight positive net bicarbonate balance opposing the metabolic acidosis originating from the acute kidney injury state. $nNBL_{25}$ values >0.3 mmol/h/kg imply a risk of developing metabolic alkalosis, whereas negative values imply a risk of developing metabolic acidosis [75, 98, 99].

The top underlying problems affecting the $nNBL_{25}$ to steady state acid-base balance correlation in the present cohort were sepsis, cardiac arrest, ARDS (Acute respiratory distress syndome), and high ketones and/or lactate. In a critically ill patient, the acid-base status is complex and multifactorial, and the impact of the CRRT circuit comes on top of existing disturbances, a phenomenon also described by *Lee et al.* [101]. The outliers were often seen in non-surviving patients, where CRRT could not correct the acid-base disturbances, and these patients showed deranged underlying acid-base statuses.

The net infusion of buffer is expected to neutralize the proton (H+) generation rate GH+ from the metabolism. According to literature, GH+ is 0.04 mmol/h/kg for an average human. The production of protons from the metabolism is strongly dependent on the patient´s protein catabolism, and it is 2-3 times less than the optimal $nNBL_{25}$ steady state of 0.1-0.2 mmol/h/kg. Critically ill patients most probably will have a higher proton generation rate, and a greater variability [55, 102].

Arterial blood samples are used in this study, while the net buffer load equations are based on venous samples. There might be a slight difference of 1 mmol/l in bicarbonate level between arterial (lower) and venous blood [103].

If $nNBL_{25}$ surpasses the proton generation rate ($nNBL_{25}$> GH+), steady state equilibrium above venous HCO_3^- 25 mmol/l will occur and thus result in alkalosis. If $nNBL_{25}$ < GH+ the patient will become acidotic since the buffer infusion cannot compensate for the GH+ at steady state [104].

The range of $nNBL_{25}$ was relatively narrow in the cohort, due to the strict prescription protocol in use, compared with $nNBL_{25}$ values calculated in the historic cohorts.

Sodium/glucose correction

In our analysis we show that the error in the measured sodium value can lead to potential iatrogenic and even dangerous over-substitution of sodium. If no correction calculation is carried out, several erroneous sodium values on a time scale will be decided on for the same patient. Even if the correction factor is small, repeated errors on a timescale can accumulate. Normally a safety level for sodium concentration normalization in a patient is maximum 0,5 mmol/L per hour or maximum 8 mmol/L per 24 hours [105-107].

Hyperglycemia itself will also be corrected during the treatment and the requirement of a correction factor of the sodium level will change. In our cohort we could show that 5.0 % ($p=0.02$) of the patients had too fast sodium corrections per 24 hours (the normal change is set to increase/decrease no more than 8 mmol/L in sodium). In these 5% the correct intervention will be missed due to the lack of usage of correction formula for sodium during the evaluation time.

Limitations of this study were possibly inaccurate measurements of the blood gas analyzer; however, the device is accredited for clinical use in Sweden. Also, the analysis of the enormous data amount could include erroneous values. Finally, the Katz' formula itself is an approximation [92].

Conclusion and future

With the increased burden on healthcare and on healthcare staff, the need for simplification/reduction of workload will be needed.

My PhD work is focused on developing a software that will help with analysis of all the patient data for admitted patients and with the aim to reduced workload and have more time for physicians to take care of the patients. The need for a tool that can reduce the workload has been confirmed repeatedly. Especially, during the Covid-19 pandemic, physicians did not have time to look at all the massive patient data due to large numbers of patients and the high complexity of disorders the patients presented with. The lack of time to consider all the available data and possibly also exhaustion may have led to avoidable mistakes. There is a need to make healthcare more effective but also reduce the workload to prevent burnout. The societal impact may be significant, since it will result in increased patient safety, but also improvement of the period of stay for the patient. Patients could benefit from having more time to connect with the treating doctor, instead of the physician only being focused on the patient data. The goal is to create a software that accesses all the data and analyzes it and prioritizes it. The benefit would be increased effectivity but also safety. The further benefit might also result in healthcare personnel that will feel more fulfilled in their ability to do their work without unnecessary stress and reduce risk for burnout. The competition is quite large due to many companies/researchers aiming at developing tools to automate work in medicine and increase efficiency. Machine learning/artificial intelligence is a growing field with a lot of possibilities. The issue today that limits the possibilities to reach further in the development of such tools is the acceptance amongst healthcare personnel, but also the laws that have yet to be adapted to the fast development of these tools.

The sustainable development goals of relevance for my PhD are good health and wellbeing, quality education, gender equality, decent work, economic growth, and reduced inequalities. A software will be able to reduce the inequality on several aspects since a software should not have any kind of biases in regards of gender, religion etc. A tool can improve the education and giving physicians time to learn and develop their skills. Workload will be reduced, and economic growth can be achieved since efficiency can be increased, reduced risk for mistakes, and achieving better care. Reducing the workload may also result in reduction of long-term sick leave.

There are many possibilities for collaboration with both hospitals, other researchers, and also companies. The limitations of developing a product in the hospital is the need for funding, but also having means to further develop the product. The benefits of developing a tool in the hospital/with other researchers is that one will be close to the end user, and also closer to those benefiting from the products. Collaboration with a company will lead to a greater reach for the tool but the limitation is of course that a company will have the commercial benefit in mind and might put pressure on protecting IP.

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