ADVANCED MATERIALS INTERFACES
Open Access
www.advmatinterfaces.de

Development and Evaluation of User-Friendly Modeled Approach for Sustainable Polymer Membranes for Advanced Hemodialysis

*Ahmed Khan, Zaib Jahan, Muhammad Ahsan, Muhammad Bilal Khan Niazi, Muhammad Nouman Aslam Khan, Ahmed Sayed M. Metwally, and Farooq Sher**

Hemodialysis is crucial for patients with end-stage renal disease, yet evaluating its operating parameters often requires complex mathematical models. To simplify this process, user-friendly modules have been developed to accurately assess key parameters with minimal inputs, enabling users to track disease prognosis. These modules incorporate governing equations and allow straightforward analysis. Validation against experimental data from polymer membrane studies demonstrated that at a blood flow rate of 300 mL min^{-1}, the model predicted a clearance of 262 mL min^{-1}, showing 7% difference from the actual value of 281 mL min^{-1}. At a dialysate flow of 400 mL min^{-1}, the model's predicted clearance was 286.47 mL min^{-1}, with only a 1% difference compared to previous model. The module also showed 40% higher clearance in counter-current flow compared to co-current, with a 47% difference at 400 mL min^{-1} dialysate flow. Increasing the hollow fibre length from 27 to 50 cm led to a 4% clearance increase. Additionally, increasing residual renal clearance by 0.5 mL min^{-1} doubled the standard Kt V^{-1} Kt/V, and similar effects were seen by increasing weekly hemodialysis sessions. The app allows simulations, plots, and comparisons with minimal inputs and can be integrated into MATLAB or other platforms, benefiting both patients and researchers in prognosis and treatment analysis.

1. Introduction

End-stage renal disease (ESRD), Kidney failure, is a condition where the glomerular filtration rate (GFR) falls below 15 mL min^{-1}/1.73 m^2. The various stages of ESRD are described based on the value of GFR.[1] Around 89% of patients recommended dialysis undergo hemodialysis.[2] Patients suffering from ESRD have hemodialysis as a last resort, but the mortality and morbidity rates are still considerably high.[3] Hemodialysis is an intermittent therapy performed usually three times a week.[4] Each session is ≈3–5 h, during which the excess solutes and fluids that have been accumulated in the human body throughout a few days need to be removed within a few hours, and this often leads to complications such as dialysis disequilibrium and hemodynamic instability, both of which have unpleasant symptoms.[5] Hemodialysis requires hollow fiber membranes with a surface area of 0.8–2.5 m^2 and a 180–220 µm diameter. This extracorporeal circuit acts as an artificial kidney and mimics the functioning of the glomerulus.[6,7]

Most nitrogenous waste from the human body is removed in the form of Urea. Although Urea itself is mildly toxic, the buildup of Urea represents that other waste compounds are not being eliminated.[8] Urea is generated in the human body by the process of the Urea cycle, mainly in the liver and, to some extent, in other tissues.[9] Urea is a low molecular weight toxin removed via diffusion while middle molecular weight toxins such as β2-microglobulin and complement factor D are removed via convection. The convective and diffusive processes' efficiency depends on factors such as the geometry of hollow fibers, the characteristics of the membrane,

A. Khan, Z. Jahan, M. Ahsan, M. B. K. Niazi, M. N. A. Khan
Department of Chemical Engineering
School of Chemical and Materials Engineering
National University of Science and Technology
Islamabad 44000, Pakistan

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/admi.202400435

DOI: 10.1002/admi.202400435

A. S. M. Metwally
Department of Mathematics
College of Science
King Saud University
Riyadh 11451, Saudi Arabia

F. Sher
Department of Engineering
School of Science and Technology
Nottingham Trent University
Nottingham NG11 8NS, UK
E-mail: Farooq.Sher@ntu.ac.uk

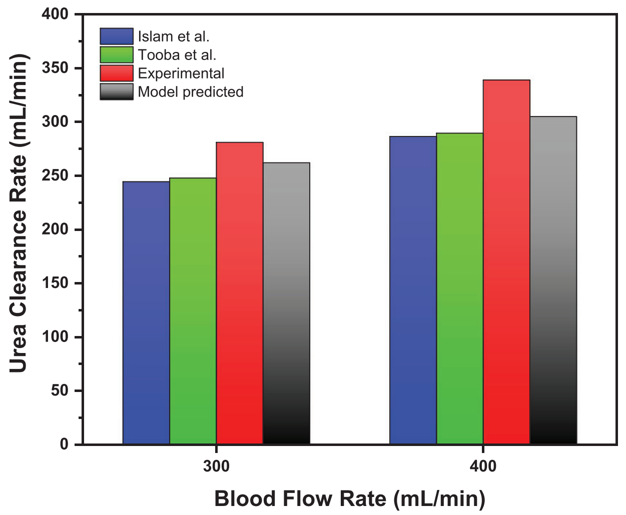

Figure 1. Comparison of urea clearance values for in-vitro and in-silico scenarios with the current module at varying blood flow rate and constant dialysate flow rate (Qd = 500 mL min^{-1}).

and the operating variables.[10] The major challenges related to hemodialysis include the cost and time of the hemodialysis process, as longer session times come with a high cost.[8] A thorough investigation of the process parameters is needed as it can help minimize time and cost while optimizing efficiency.[9]

Several attempts have been made to mimic kidney toxic removal processes using mathematical models that are focused on the operating parameters of the hemodialysis process. Mathematical modeling assists in accurately analyzing the course of treatment and predicting the possible outcomes of treatment undertaken with certain process conditions. It can help physicians develop a prognosis according to patient profile.[11] However, mathematical models for evaluating operating parameters are complex and require solvers and expertise. Also, in computational fluid dynamics (CFD) models, fluid behavior is a challenging part as the exact flow conditions are hard to replicate.[12] Even after the attainment of the required skills in these fields, integrating the background algorithm with the front-end interface of an app requires a certain level of understanding of app development which specifically falls in the realm of software engineering. Furthermore, existing applications are focused on diet and a limited number of parameters. In previous mathematical models related to hemodialysis, the inclusion of the tortuous pore diffusion model caters to the effect of parameters such as tortuosity and porosity to estimate the clearance of Urea across the hemodialysis membrane.[13] Also, the blood and dialysate flow rates play a critical role in determining the adequacy and clearance of the hemodialysis process and prediction of clearance with varying blood and dialysate flow rates can assist in achieving the target adequacy.[14] The existing applications for hemodialysis patients focus on one or the other aspect of the process and do not cater to multiple parameter calculation or their plotting. Lastly, several mobile applications are available for patients to use to keep track of their nutrient intake, assist in meal planning, and also help the patients to meet the target intakes set according to dietary guidelines. Therefore, user-friendly modules can be developed that can evaluate key parameters accurately and can be used by end-users, researchers, and physicians with minimal inputs, also allowing comparisons to be made for certain input values and enabling the prognosis of the disease.

Herein, a combination of modules developed using MATLAB R2022 can carry out calculation and comparison analysis of key parameters. The key parameters particularly related to Urea clearance were shortlisted and the equations governing these parameters were incorporated in MATLAB code that allows the user to enter the value of input parameters.[15] The parameters include blood and dialysate flow rates, flow orientations, overall mass transfer coefficient, and standard adequacy. The modules compare the effect of blood and dialysate flow rates on the clearance, the drop in Urea concentration over time, the impact of flow orientation on clearance, the effect of overall mass transfer area coefficient on clearance, and the effect of hollow fiber dimensions on clearance. The last module plots the influence of residual renal clearance on standard dialysis adequacy with an increasing number of dialysis sessions per week. Blood and dialysate flow rates in hemodialysis are important key factors determining adequacy and clearance.[16] A study also found that blood flow rate values less than 250 mL min^{-1} are associated with higher mortality rates, the underlying reason being dialysis dose inadequacy. The inadequate dose promotes malnutrition and infection which ultimately increases mortality.[16] Another study showed that by increasing the blood flow rate from 300 to 400 mL min^{-1}, the value of clearance increased by 8% while increasing it further from 400 to 500 mL min^{-1} further increases clearance by 18%.[13]

Hemodialysis being the most efficient treatment for hemodialysis, is recommended to most of the patients and its efficiency is dependent on key parameters that are explored using mathematical models. Mathematical models used to evaluate operating parameters in hemodialysis are complex and replicating exact flow conditions in computational fluid dynamics models is challenging.[12] Integrating the algorithm with an app's front-end interface requires software engineering expertise and existing applications in hemodialysis mainly focus on diet and a limited number of parameters and lack comprehensive parameter calculation and plotting. Additionally, mobile apps exist for nutrient

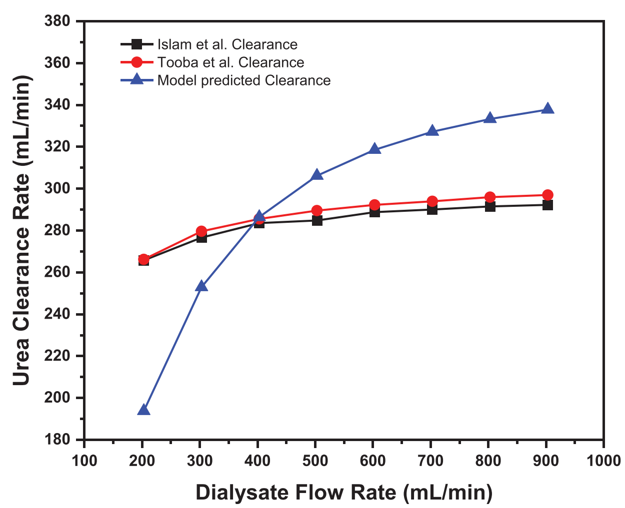

Figure 2. Model predicted Urea clearance versus in silico solute clearances plotted at increasing dialysate flow rate at Qb = 400 mL min^{-1}.

Table 1. Comparison of module results for Urea clearance versus blood flow rate with the previous models.[13,18,67]

Blood flow rate [mL min^{-1}]	Model predicted Urea clearance [mL min^{-1}]	Tooba et al. predicted clearance [mL min^{-1}]	Islam et al. predicted clearance [mL min^{-1}]	Experimental data (Polyflux 210H) [mL min^{-1}]	Percentage difference of Model-predicted and Manufacturer data [%]	Percentage difference of Tooba et al. and Manufacturer data [%]	Percentage difference of Islam et al. and Manufacturer data [%]
300	262	247.77	244.62	281	6.76	11.82	12.94
400	305	289.52	286.40	339	10.03	14.59	15.51

tracking, meal planning, and adhering to dietary guidelines.[17] Therefore, there was a need for an application incorporating key parameters that is convenient to use, allows for analysis, comparisons, tracking prognosis, and is accurate as well.

The current study demonstrates a pioneering MATLAB R2022-based application that has been designed to optimize hemodialysis parameters and its novelty is present in its integration of multiple analytical modules that can compare and assess key factors that influent hemodialysis efficiency which includes dialysate and blood flow rates, flow orientations and mass transfer coefficient. Existing tools are focused on specific aspects which include isolated parameter calculations or dietary management, whereas this application represents a holistic approach by allowing real-time comparison and evaluation of parameters. In addition, the user-friendly interface allows for intuitional input of data and allows for analysis, thus making complex mathematical models accessible to users with the least expertise on the technical side. It allows for making accurate predictions and makes the tracking of the prognosis convenient. The integration of all these features into a singular tool covers the gap between computational modeling and clinical and patient use, presenting significant improvement over current solutions that are used in the management of hemodialysis. This tool not only offers treatment planning and tracking of the prognosis but also reduces the complexity and cost of hemodialysis by crucial decision-making processes.

2. Results and Discussion

2.1. Increasing Urea Clearance with Increase in Blood and Dialysate Flow Rate

The modules developed in MATLAB R2022 app designer were simulated with the values of parameters inserted as mentioned in the previous section of this paper. To validate the module in Experimental Section, the model predicted curves of Islam et al.,[18] Tooba et al.[13] and experimental data from the literature was used as shown in **Figures 1** and **2**. In Figure 1, the dialysate flow rate is kept constant at 500 mL min^{-1}, and the Urea clearance rate is plotted at different values of blood flow rate while in Figure 2, the blood flow rate is kept constant at 400 mL min^{-1} and Urea clearance rate is plotted at varying dialysate flow rates. The module is in agreement with the fact that an increased blood flow rate increases clearance.[19] This is in agreement with previous results as with increasing blood flow rate, the volume of blood flowing through the dialyzer per unit of time increases and as a result, there is an increase in the convective transport of Urea across the dialyzer membrane This convective transport is directly proportional to the value of flow rate of blood. As a consequence, more Urea gets transported from blood to dialysate due to increased mixing and turbulence in the dialyzer.[20] In **Table 1**, the percentage difference between the module's predicted clearance and experimentally found clearance is relatively less as compared to previous works. This can be attributed to the underestimation of diffusivity and friction across the membrane in the case of the current module developed using MATLAB. Previous models incorporate the tortuous pore diffusion model (TPDM), which takes into account all factors that cause hindrance to the movement of molecules across the membrane, such as effective diffusivity and friction coefficient due to which the values for clearance are underestimated as compared to the current module which does not cater for friction that occurs between the pore wall and solute molecules. Furthermore, previous simulations performed using COMSOL can incorporate boundary conditions alongside complex geometries and utilize finite element analysis for solving partial differential equations that describe transport phenomena, fluid dynamics, and more. Alongside, detailed models of Physics such as fluid dynamics, mass transfer, and chemical reactions occurring within a system can be incorporated.[21]

Although the optimal value for blood flow during hemodialysis is not determined and depends on the patient profile and the quality of vascular access of the patient, a study has shown that mortality rates are significantly higher in patients with Blood Flow Rate (BFR) BFR<250 mL min^{-1} than those patients who are treated with BFR>250 mL min^{-1}.[16] TPDM also takes into account the steric hindrance factor that represents the volume fraction available for the solute molecules in cylindrical pores.[22] Therefore, this model overestimates the clearance values compared to the previous works. The inclusion of TPDM in the current module may result in clearance values closer to the previous works. However, that would require the development of a module on computational fluid dynamics software since there are no backend models for solving and converging the system of equations in MATLAB. The models that are developed in MATLAB may lack the spatially resolved phenomena that CFD software can capture and sometimes also lack the details.[23] Since the Polyflux 210H is a high-efficiency hemodialysis membrane (KoA = 1452 mL min^{-1} for Urea), for comparison of the module with it, the value of KoA was considered to be 1000.[24] However, assuming values of the overall mass transfer coefficient closer to 1452 mL min^{-1} brings the model more aligned with experimental data.

The module predicted a trend for an increase in clearance with increasing dialysate flow rate agreed with previous research works.[19] This is in agreement with the fact that as the value of the dialysate flow rate is increased, the stagnant fluid layer adjacent to the dialyzer membrane reduces thus increasing the transfer of Urea from blood to dialysate. This boundary layer is also sometimes referred to as concentration polarization and it can

Table 2. Percentage difference between this model and previous models.[13,18]

Dialysate flow rate [mL min^{-1}]	Tooba et al. clearance [mL min^{-1}]	Islam et al. clearance [mL min^{-1}]	Model predicted clearance [mL min^{-1}]	Percentage difference b/w Model and Tooba et al. [%]	Percentage difference b/w Model and Islam et al. [%]
203	266.23	265.73	193.75	−37.41	−37.15
303	279.61	276.64	252.97	−10.53	−9.35
403	285.56	283.58	286.47	0.32	1.01
503	289.52	284.81	306.21	5.45	6.99
603	292.25	288.78	318.60	8.27	9.36
703	293.98	290.02	327.20	10.15	11.36
803	295.96	291.50	333.30	11.20	12.54
903	296.96	292.25	337.80	12.09	13.48

hinder the transfer of solutes from blood to the dialysate.[25] The module for evaluating the effect of dialysate flow rate on clearance was used for plotting and the model-predicted clearance curves were plotted with Islam et al.[18] and Tooba et al.[13] in silico model results for comparison, as shown in Figure 2. Both the current and previous models depict an increase in clearance with increasing dialysate flow rate as it results in a decrease in the thickness of stagnant fluid layers close to the membrane wall.[26] **Table 2** shows an increase in clearance as the dialysate flow rate increases initially and the model predicted values are much lower than previous in silico models, which can be attributed to the fact that the current module uses Michael's equation for calculating clearance, whereas, previous in-silico models utilize TPDM model and Navier Stokes equation embedded in the CFD software to calculate clearance.[22] In addition, the convergence criteria, initial boundary conditions, and cell zone conditions provided to the CFD solver play a role in calculating clearances using computational software.[27] Moreover, the algebraic equations used in this model developed using MATLAB are not able to capture all the real-time complexities of the process which includes membrane fouling, flow conditions that are nonideal, and dynamics of solute transport.[23] Due to these reasons, the predicted clearance becomes greater after 400 mL min^{-1} dialysate flow rate as the current module is following the trend of an equation, whereas previous models utilize solvers that solve within specified initial boundary conditions and they cater for hindrance factors as well through models embedded in the software.

Furthermore, the meshing of the geometry, its sizing, and quality are important considerations when it comes to developing a computational model. Incorporating all of these factors in the current computational tool can result in clearance values in closer agreement with previous models. In COMSOL simulations, factors such as membrane characteristics, detailed fluid dynamics, and turbulence modeling are also captured.[13] However, it would require a complex system of equations to be solved in the backend of the module and would require several different input parameters that the user would have to provide.[28] Therefore, the current module can be utilized for predicting the clearance with increasing dialysate flow rates within acceptable dialysate flow rates but a coefficient value can be introduced to cater to the differences between the current and the previous models. However, blood and dialysate flow rate values are kept between specific ranges in clinical practices.[29] For example, the average variation range is from 250 to 300 mL min^{-1} depending on the patient profile and quality of vascular access. An increase of 30% in the value of blood flow rate results in ≈ a 23% increase in Urea clearance, provided that all other parameters are kept constant.[30]

However, lesser blood flow rates could lead to reduced adequacy that promotes atherosclerosis, infection, and, ultimately, mortality. In addition, increasing value beyond this range can cause complications related to cardiovascular function in the human body.[30] Similarly, in clinical arrangements, the dialysate flow values are kept between 500 and 800 mL min^{-1}. A higher dialysate flow rate increases adequacy and clearance. However, it could increase the amount of dialysate utilized in a dialysis session, increasing the overall cost of a dialysis session.[16] A study showed that increasing the dialysate flow rate from 500 to 800 mL mi^{-1}n increased the Urea KoA by an average of 14 ± 7% as it decreases the thickness of a stagnant fluid layer on the dialysate side.[13] It could be suggested that it is due to improved flow distribution of dialysate.

2.2. Decrease in Urea Concentration with Time

The backend equation governing the drop of Urea concentration with time is the one-compartmental model equation where all the body fluids and plasma water are considered a single volume while the dialyzer is considered another volume where the transfer occurs from blood to dialysate.[11] The plotted change in the concentration of Urea over time showed that a single pool model predicts an exponential decrease in the toxin concentration over time, as shown in **Figure 3**. A single pool model considers the whole patient's body into a single compartment and the extracorporeal circuit or dialyzer into a separate pool. For calculating the time required to reduce toxin concentration to a certain level, the single pool model first calculates a dialyzer's clearance value. Here it must be noted that an advantage of using this module is that it allows the calculation of dialyzer clearance before the single pool equation is solved.[31] The model also relies on first-order kinetics according to which the rate at which Urea is removed is proportional to the concentration of Urea in the blood. As the process progresses, the value of the concentration gradient present between blood and dialysate lowers due to which the rate of Urea removal slows down. Consequently, we can observe an exponential curve indicating the proportional nature of solute removal as it is described by this model.[32] Based on the blood, dialysate flow rates, and initial and final concentrations of the toxin in the

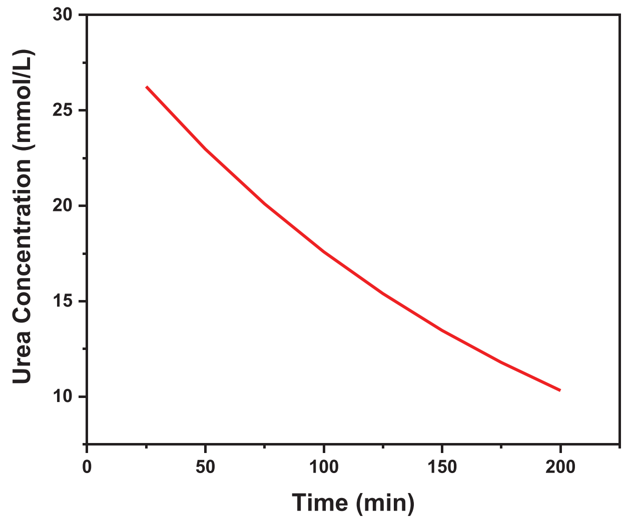

Figure 3. Graph showing the decrease in urea concentration with respect to time.

patient's blood, it calculates clearance which in the given scenario was calculated to be 216 mL min^{-1}.

Furthermore, the module calculates the toxin distribution volume that was assumed to be a 70 kg male patient in our case. Finally, the incorporation of the dialyzer clearance and the toxin distribution volume was done to find the Urea concentration at a specific time during the hemodialysis session. Table ST7 (Supporting Information) shows the decrease in toxin concentration with time quantitatively. This exponential drop in Urea concentration was experimentally confirmed by Ziolko,[11] where a patient was dialyzed for 3 h and 30 min thrice a week using a Polysuflone F-6 dialyzer with a blood flow rate 250 mL min^{-1} and dialysate flow rate 500 mL min^{-1}. The current module allows users to determine the drop in Urea concentration keeping under consideration the initial concentration of Urea in blood along with the desired concentration at the end of the dialysis session and calculates the clearance as well. Finally, it incorporates the distribution volume and calculates the drop in Urea concentration.

2.3. Comparison Effect of Flow Orientation on Urea Clearance

The effect of flow direction is always substantial in case fluids come into contact with one another, whether directly or through a semipermeable barrier– for example, blood and dialysate contact counter-currently across a hollow fiber module in clinical arrangements. The rationale behind this flow arrangement is that counter-current flow assists in maintaining a constant concentration gradient because fresh dialysate keeps coming in contact with blood containing sufficient solutes.[33] The module calculates the change in clearance for co and counter-current flow arrangements. The change in urea clearance rate for both orientations is negligible initially as the dialysate flow rate increases. At the dialysate flow rate of 100 mL min^{-1}, the difference between the clearance of both flow orientations is less and as the dialysate flow rate is increased, the difference in clearance starts to increase as shown in **Figure 4**. The underlying reason behind the similar clearances for both flow orientations initially is the negligible convective mass transfer when the dialysate flow rate is less. However, as the value for the dialysate flow rate increases, the convective transport starts adding to the diffusive mass transfer.[13] It becomes the dominant mass transfer phenomenon at a higher dialysate flow rate when the fresh dialysate is constantly exposed to blood. This is also in agreement with the fact that in counter-current flow arrangement, the highest concentration of Urea in the bloodstream comes in contact with the lowest concentration of dialysate and as a result, more efficient transfer of Urea is observed from blood to dialysate in this flow arrangement.[13]

On the other hand, as dialysate flow rates are increased for co-current flow, the concentration gradient approaches a constant value, after which it does not alter further and clearance becomes constant since the concentration gradient is the primary driving force in hemodialysis.[26] In clinical practices, the counter-current arrangement is utilized since it enables exposing fresh dialysate to blood to maintain a high concentration gradient. A study showed that the removal of small solutes is ≈20% greater when the dialysate flow rate is made to flow counter-currently for the blood flow rate.[34] In the current study, the values for clearance in both flow orientations increased with increasing dialysate flow rate. This difference was maximum at a dialysate flow rate of 200 mL min^{-1} where the counter-current flow arrangement had 37% more clearance than the co-current flow arrangement. This difference can be explained by the fact that at lower values of flow rates, the efficiency of the countercurrent system is higher since slower flow rates allow more time for diffusion to take place. With increasing dialysate flow rate, the gradient tends to become more and more balanced.[35]

Once the dialysate flow rate is increased beyond 800 mL min^{-1}, the difference in clearance values becomes constant. **Table 3** also shows that as dialysate flow rates 500 mL min^{-1} value, the percentage difference between clearance starts changing with a constant rate since at higher dialysate flow rates, the maximum concentration gradient is approached and clearance varies very to a

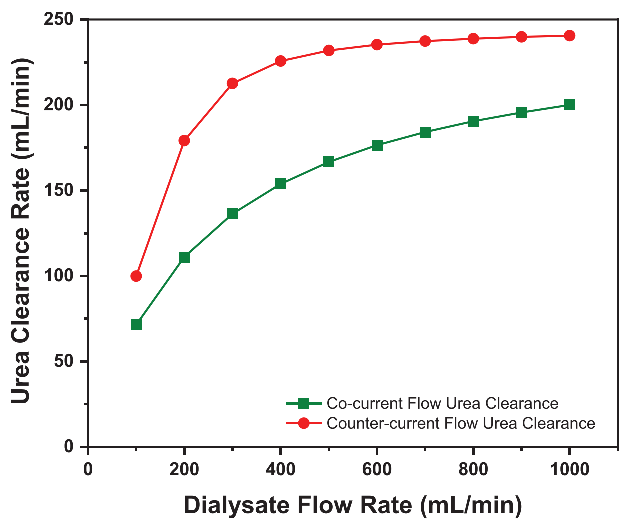

Figure 4. Difference in urea clearance with change in flow orientation at different dialysate flow rates.

ADVANCED MATERIALS INTERFACES Open Access
www.advmatinterfaces.de

Table 3. Percentage difference in clearance rate with increasing dialysate flow rates for Co and Counter-current flow arrangements.

Dialysate flow rate [mL min^{-1}]	Co-current flow Urea clearance [mL min^{-1}]	Counter-current flow Urea clearance [mL min^{-1}]	Percentage difference between co and counter-current clearance [%]
100	71.43	99.85	28.46
200	111.11	179.15	37.98
300	136.36	212.61	35.86
400	153.85	225.69	31.83
500	166.67	231.86	28.12
600	176.47	235.26	24.99
700	184.21	237.37	22.40
800	190.48	238.79	20.23
900	195.65	239.80	18.41
1000	200.00	240.55	16.86

minimal extent with further increasing dialysate flow rate. Further extending these curves gives plateaus for both flow arrangements as the effect of the dialysate flow rate becomes constant. This can also be understood from the fact that as the dialysate flow rate approaches higher values, concentration polarization starts to diminish due to which the concentration of Urea present near the surface of the membrane decreases, and as a result, the clearance curves start forming a plateau. Furthermore, at higher dialysate flow rates, the performance of the hemodialysis system becomes less sensitive to the flow direction because the dialysate flow rate significantly boosts the overall transfer rate.[36] Therefore, the results obtained by utilizing equation equation-based modules are in agreement with the literature. Counter-current flow maximizes the concentration gradient throughout the length of the dialyzer and is the most commonly used clinical arrangement.[37] The current module allows users and potentially new researchers to hemodialysis to evaluate the effect flow orientation has on the clearance by providing as little as three inputs only since this area of flow orientation in hemodialysis is usually not explored thoroughly.

2.4. Increase in Urea Clearance with Overall Mass Transfer Coefficient

Dialyzers with KoA up to 600 mL min^{-1} represent moderate efficiency, while those above 600 mL min^{-1} are considered high-efficiency dialyzers.[25] The effect of changing values of KoA on clearance is negligible until it becomes prominent at a dialysate flow rate of 100 mL min^{-1}, as shown in **Figure 5**. The underlying reason behind this trend is that at lower values of dialysate flow rates, the influence of KoA on Urea clearance is more prominent as clearance is very sensitive to changes in values of the mass transfer coefficient. Lower values of dialysate flow rates result in a stagnant boundary layer formation that is thicker which has a profound effect on the mass transfer efficiency.[38] This effect on clearance keeps on becoming prominent until ≈300 mL min^{-1}, after which both the curves start forming plateaus and the percentage difference between both clearance rates becomes stable. The reason behind the formation of plateaus is that beyond a certain value of dialysate flow rate, the Urea removal rate is also limited by factors other than KoA which includes the intrinsic properties of membrane and blood flow rate. Further, increasing the dialysate flow rate produces no change in the clearance of Urea for both cases as shown in values in **Table 4**. The stabilization of clearance can be attributed to the fact that at very high dialysate flow rates, the system approaches maximum efficiency and mass transfer limitations are minimal.[38] For both scenarios, the concertation gradient reaches a maximum value and any further increase in dialysate flow rate causes no assistance in incrementing the concentration gradient. Furthermore, for initial similar clearance patterns, the rationale is that at low dialysate flow rates, diffusion is the dominant mass transport phenomenon and diffusion rate is dependent on the dialysate flow rate to a considerable extent at lower dialysate flow rates.[39]

The increase in Urea clearances for both values of KoA is because fluid mixing is good at higher dialysate flow rates and reduces the film resistance for smaller molecules. The solute clearing efficiency of a dialyzer is quantified by KoA which is the overall mass transfer coefficient and is often referred to as the efficiency of the dialyzer.[25] The manufacturers mention the values for KoA under specific blood and dialysate flows. Initially, the value of KoA was supposed to be constant for a certain

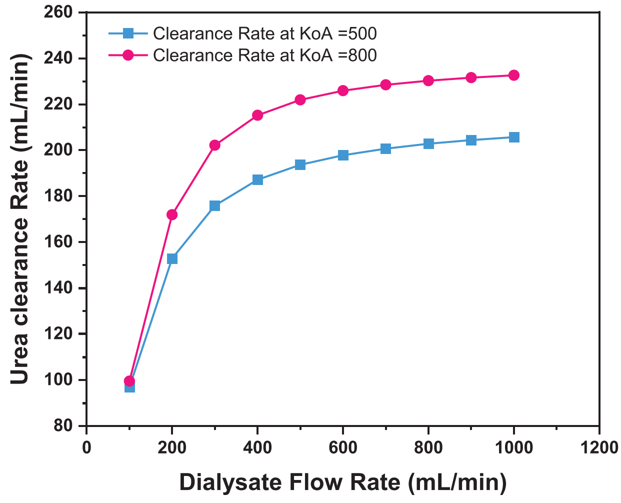

Figure 5. Effect of overall mass transfer area coefficient on clearance with changing dialysate flow rates.

ADVANCED MATERIALS INTERFACES Open Access
www.advmatinterfaces.de

Table 4. Percentage difference in clearance of dialyzers with low and high overall mass transfer area coefficient.

Dialysate flow rate [mL min^{-1}]	Clearance rate at KoA = 500 [mL min^{-1}]	Clearance rate at KoA = 800 [mL min^{-1}]	Percentage difference in clearance with low and high KoA [%]
100	96.95	99.50	2.57
200	152.87	171.94	11.09
300	175.90	202.18	13.00
400	187.16	215.21	13.03
500	193.65	221.93	12.74
600	197.82	225.90	12.43
700	200.70	228.48	12.16
800	202.81	230.27	11.92
900	204.42	231.59	11.73
1000	205.69	232.60	11.57

dialyzer; however, investigations have refuted this supposition as with increasing dialysate flow rates, flow distribution within the fiber bundle enhances, thus enhancing the overall mass transfer coefficient. Classification of dialyzers is also often done based on this parameter, with low-efficiency dialyzers having KoA less than 500 mL min^{-1}, moderate-efficiency dialyzers having 500 to 600 mL min^{-1}, and high-efficiency dialyzers having KoA greater than 600 mL min^{-1}.[40] Several researchers have theoretically predicted the effects of increasing dialysate flow rates on the KoA. The module allows the user to quantitatively carry out a comparison and plot the comparison curves between high and low-value overall mass transfer coefficient dialyzers. It also enables to evaluation of the effect of the overall mass transfer coefficient on clearance and how with increasing flow rates, it influences the clearance.

2.5. Increase in Urea Clearance with Hollow Fiber Length

Hollow fiber modules are preferred over others as capillary dialyzers offer minimal overall resistance to transfer.[41] As the length of the dialyzer fiber increases, there is an increase in the value of the Urea clearance rate, as shown in **Figure 6**. Increasing the length could add to the dialyzer cost, ultimately increasing the cost of the process for patients. Previous studies have shown an increase in the clearance with the increasing length of hollow fibers.[13] Previous models have shown that as the length of hollow fibers is increased from 27 cm with an increment of 3 cm, the increase in clearance is ≈4% and this increase becomes minute as the length of fibers approaches 50 cm as clearance becomes constant.[13] In this study, the clearance rate throughout the curve is higher for the current module than the previous ones. This difference is because the current models incorporate radius, fiber length, dialyzer's KoA, and blood and dialysate flow rates. In contrast, previous in-silico models utilize TPDM and Navier Stokes equation embedded in the CFD software to calculate clearance, and the convergence criteria, initial boundary conditions and cell zone conditions provided to the CFD solver are important in calculating clearances using computational software.[42] In addition, flow patterns are assumed to be idealized, and certain resistances that are present within the hemodialysis system are neglected due to which clearance values obtained are higher. The influence of steric effects, turbulent flows, secondary currents, and eddies is not accounted for and solute-membrane interactions are also not incorporated.[13]

Due to these reasons, the module calculated clearance values as shown in **Table 5** with increasing dimensions are higher as the current module is following the trend of Michael's equation in which the values of the area are being varied further influencing the values of final clearance. Whereas previous models utilize solvers that solve equations within specified initial boundary conditions and they cater for hindrance factors as well through models embedded in the software. Furthermore, the meshing of the geometry, its sizing, and quality are important considerations when it comes to developing a computational model. Incorporating all of these factors in the current computational tool can result in clearance values in closer agreement with previous models. However, it would make the model challenging to use by users as it would require a complex system of equations to be solved in the backend of the module and would require a number of different input parameters that the user would have to provide.[42] Increasing the length of hollow fibers can increase the clearance

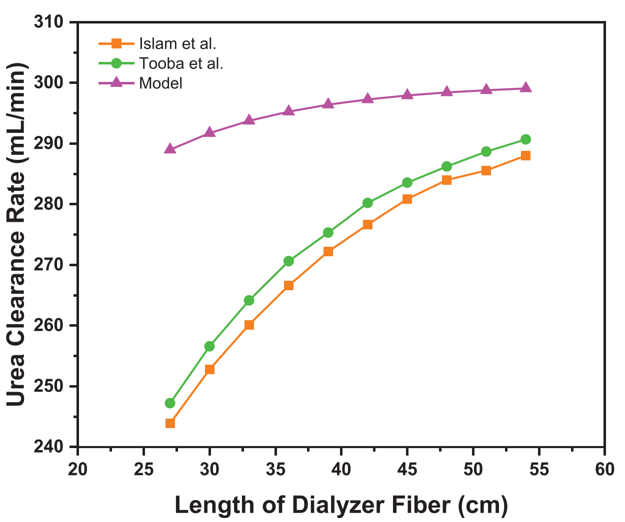

Figure 6. Change in Urea clearance rate with change in length of hollow dialyzer fiber.

Table 5. Percentage difference between models showing a change in urea clearance with a change in the length of the fiber.

Length of dialyzer fiber [cm]	Islam et al. Urea clearance rate [mL min^{-1}]	Tooba et al. Urea clearance rate [mL min^{-1}]	Model Predicted Urea clearance rate [mL min^{-1}]	Percentage difference b/w model and Islam et al. [%]	Percentage difference b/w model and Tooba et al. [%]
27	243.89	247.23	289.00	15.61	14.45
30	252.80	256.59	291.72	13.34	12.04
33	260.16	264.17	293.75	11.44	10.07
36	266.62	270.64	295.27	9.70	8.34
39	272.20	275.32	296.42	8.17	7.12
42	276.66	280.22	297.28	6.94	5.74
45	280.89	283.57	297.93	5.72	4.82
48	284.01	286.24	298.43	4.83	4.08
51	285.57	288.69	298.80	4.43	3.38
54	288.03	290.70	299.09	3.70	2.80

and this has been proven by a recent study by Goodrazi[43] as well. The module developed also resulting an increase in the value of Urea clearance with an increasing length of hollow fiber which is in agreement with a previous study conducted by Goodrazi.[43] However, the length of hollow fibers can only be increased to a certain extent, the reason being the higher cost associated also, over the length of hollow fibers, the concentration gradient keeps decreasing thus reducing the driving force for diffusion. Furthermore, the membrane has a certain capacity to transfer solutes and once this capacity is fulfilled, further increasing the length of fibers does not improve the clearance as sufficient solutes have been removed till the point they reach the end of the fibers. Pressure drop across the length of the dialyzer and issues in flow distribution are other factors that limit the length of hollow fibers.[44] Therefore, the current module can be utilized for predicting the clearance with increasing hollow fiber dimensions but within a certain range and a coefficient value can be introduced to cater for the differences between the current and the previous models.

2.6. Increase in Standard Hemodialysis Adequacy with Residual Renal Clearance

As per various guidelines, an acceptable value of hemodialysis session adequacy is ≥1.2. The single pool Urea kinetic model considers the uniform distribution of Urea within the body having a certain concentration in a certain volume.[45] The single pool Urea kinetic model is based on the assumption that Urea concentration is distributed uniformly in a volume V and it is used to explain the clearance during and after the hemodialysis process has been carried out. The transport of toxins across the membrane occurs due to diffusion and convection.[46] A single pool model further has the following assumptions there is a constant generation of Urea within the body, there is a constant rate with which interdialytic weight gain occurs, and there is instantaneous mixing occurring within the pool. For assessing adequacy, an equation based on a single pool kinetic model is commonly used.[47] However, the single pool adequacy equation slightly overestimates clearance and consequently, adequacy as it does not take into account the Urea rebound that occurs after 30 min of a hemodialysis session. The Urea rebound can be catered by the equilibrated adequacy equation, which gives a more accurate adequacy value.[48] With the increasing number of hemodialysis sessions per week and the improvement of residual renal function, the values of std KT/V could improve, as shown in **Figure 7**. This improvement in std KT/V becomes more prominent with the improvement in residual renal clearance.

Besides, with an increasing number of dialysis sessions per week, with some residual renal clearance, it can be seen that the increase in std KT/V is two times the initial value, as shown in **Table 6**. The reason behind the increase in std KT/V is that with more dialysis sessions per week, the toxins that are present in the blood are removed more frequently and as a consequence, the buildup of toxins does not occur and solute removal efficiency is higher.[49] This validates that improved residual renal clearance plays a vital role in dialysis patients.[50] With increasing the number of sessions per week by one and with a 0.5 mL increase in residual renal clearance, std Kt/V increases by a value of 0.85 initially but as residual renal clearance approaches 5 mL min^{-1}, increasing the number of sessions per week has a minute effect on std Kt/V. This can be explained by the fact that as residual renal clearance approaches a value of 5 mL min^{-1}, the contribution

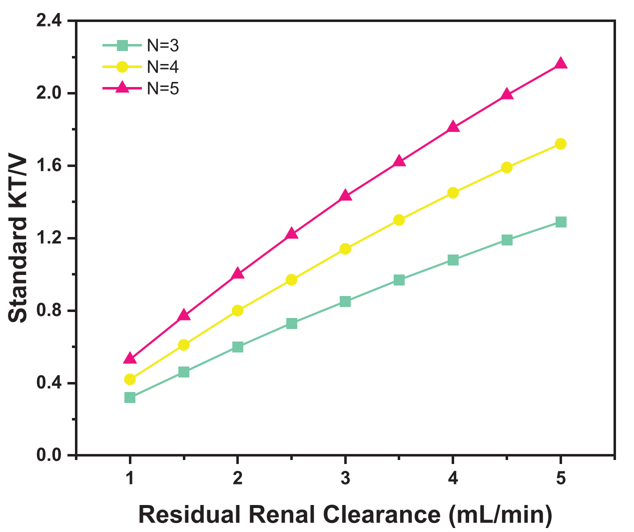

Figure 7. Change in standard KT/V with increasing residual renal function at different numbers of hemodialysis sessions per week.

ADVANCED MATERIALS INTERFACES Open Access
www.advmatinterfaces.de

Table 6. Increase in standard KT/V with an increase in the number of hemodialysis sessions per week.

Residual renal clearance [mL min^{-1}]	std KT/V at N = 3	std KT/V at N = 4	std KT/V at N = 5	Change in std KT/V when N = 3→4	Change in std KT/V when N = 4→5
1	0.32	0.42	0.53	0.1	0.21
1.5	0.46	0.61	0.77	0.15	0.31
2	0.6	0.8	1	0.2	0.4
2.5	0.73	0.97	1.22	0.24	0.49
3	0.85	1.14	1.43	0.29	0.58
3.5	0.97	1.3	1.62	0.33	0.65
4	1.08	1.45	1.81	0.37	0.73
4.5	1.19	1.59	1.99	0.4	0.8
5	1.29	1.72	2.16	0.43	0.87

of kidneys in removing the toxins is more and the relative contribution of hemodialysis sessions becomes smaller ultimately leading to a minimal effect on std KT/V with each session. Since kidneys are doing the major part of clearance work, therefore, the influence of extra dialysis becomes less prominent. The formation of the plateau with increasing residual renal function can be attributed to the fact that kidneys are functioning better and minimal benefits can be obtained in terms of KT/V.[51] A study showed that patients on hemodialysis therapy had preserved residual renal function one year after dialysis initiation had a 30% lower mortality risk and a 31% lesser risk of cardiovascular death. This relation between residual renal function and mortality indicates that residual clearance plays a vital role in the excretion of uremic toxins.[52] Patients suffering from ESRD have a minimal value of residual renal clearance if they have any at all. However, dialysis is usually recommended for patients with residual clearance of less than 15 mL min^{-1}. For patients having minimal residual clearance, an acceptable value of std KT/V can be achieved by increasing the number of sessions per week. The module allows users to have an estimate of their std Kt/V by providing three basic input values of which every patient undergoing hemodialysis sessions is aware. In addition, it depicts the influence of residual renal clearance on adequacy and the important role it plays. Another important factor deduced from the plot is the effect of the number of hemodialysis sessions per week on adequacy.

3. Conclusion

In this study, a user-friendly application containing modules for evaluating, comparing, and analyzing hemodialysis parameters was developed. The modules show good agreement with experimental data and previous models, with a ≤10% difference for the blood flow rate module and a <2% difference for the lower dialysate flow rate module. It was observed that a 0.5 mL min^{-1} increase in residual renal clearance doubles the std KT/V, and increasing the number of weekly sessions has a similar effect. The accuracy of the flow orientations module was verified by the fact that at high dialysate flow, the percentage difference in clearance value decreases, which was found to be 16% at 1000 mL min^{-1} and 31% at 400 mL min^{-1}. It was found that with an increase in the value of KoA of 300 mL min^{-1}, the Urea clearance was incremented by 12%. With increasing hollow-fiber length, model-predicted clearances had a high percentage difference with previous models that reduce if the dimensions are incremented further. The results of the modules developed are in agreement to a certain degree with the previous studies and models but a major factor behind the difference in results is that previous models utilized CFD solvers to solve a complex system of equations and they required a number of inputs whereas current modules solve much simpler equations with minimal inputs. The modules allow for simulations, plots, and comparisons with minimal inputs, providing accurate prognosis, and can be easily integrated into MATLAB or other platforms, benefiting patients and researchers.

4. Experimental Section

Module Development: For hemodialysis, hollow fiber membrane modules are used commercially and are widely studied in silico studies. A collection of ≈12 000 hollow fibers is present in a hollow fiber membrane module casing.[53] Blood is made to flow through the cavity of hollow fibers while dialysate, a solution of various electrolytes, moves counter currently on the external side of the fibers.[54] When the process begins, the uremic toxins and electrolytes such as Sodium present in the blood start to move toward the dialysate side as they are usually present in higher concentrations in blood while at the same time, electrolytes present in dialysate such as bicarbonates move into the bloodstream which helps in maintaining homeostasis and electrolyte balance.[26] The transport occurs through diffusion for molecules with less molecular weight, such as Urea. In contrast, for larger molecular weight molecules, such as Albumin and β2-microglobulins, convection is responsible for transport across the membrane.[55] The designing of the modules was based on the standard procedures as outlined in the literature. Specifically, the modules were developed based on methodologies presented in the study of Clark et al.[7] and Chang et al.[16] Furthermore, the standardized principles of design used for hollow fiber dialysis membranes, including flow dynamics and a number of fibers, were utilized to ensure the relevance and accuracy of the simulations. The model analyzes the transport of Urea and further assumes that fibers are uniformly spaced in hexagonal order, as uneven spacing of fibers leads to a decrease in dialyzer efficiency.[56] It is further assumed that the transport is occurring under isothermal conditions (T = 37 °C) with a steady–state and laminar flow is present on both sides of hollow fibers. The value of the overall mass transfer area coefficient (KoA) was kept fixed at 1000 mL min^{-1} except in one of the models. As for high-efficiency dialyzers, KoA is equal to or close to this.[25] Moreover, the number of hollow fibers was assumed to be 12 000, and 24 cm was the length of each fiber since commonly available dialyzers have this number and length of hollow fibers.[7]

Change in Clearance Concerning Blood and Dialysate Flow Rates: The module allows the user to input values; however, for the curves plotted, commonly utilized values for these parameters are used as demonstrated in the study of Clark et al.[7] and Chang et al.[16] For evaluating the change in clearance of Urea with varying values of blood flow rates, Michaels' equation was used (Equation 1).[25] Where Qd is dialysate and Qb is blood flow rate, both in mL min^{-1} and Kd represents the clearance. The value for Qd was kept constant at 500 mL min^{-1} while the blood flow rate value was initially kept at 300 mL min^{-1} and later at 400 mL min^{-1}. The results were compared with experimental data and in silico Islam et al. and Tooba et al.'s findings.[13] The value of KoA was kept to 1000 mL min^{-1} to assume a high-efficiency dialyzer.[25] Table ST1 (Supporting Information) shows the values of parameters that were used in the model. The change in urea clearance rate with increasing dialysate flow rate can be found using the above equation in which the dialysate flow rate was varied from 200 to 1000 mL min^{-1}, and the resulting plot was compared with the previous in silico investigations.

$$Kd = \frac{QbQd\left(e^{\frac{KA}{Qb}} - e^{\frac{KA}{Qd}}\right)}{Qde^{\frac{KA}{Qb}} - Qbe^{\frac{KA}{Qd}}} \tag{1}$$

Effect on Urea Concentration with Time: The module plots the drop in Urea concentration with time and it allows the user to enter input values of dialysate flow rate along with initial and targeted Urea concentration at the end of a dialysis session. For this module, a single-compartment model Equation (2) was utilized.[11] Where Ce is the Final Urea concentration in a blood sample in the blood exiting the dialyzer, and Co is the toxin concentration in the blood entering the dialyzer, both in mmol L^{-1}. Initially, the clearance of the dialyzer is calculated using Michael's equation with input parameters as blood, dialysate flow rates in mL min^{-1}, initial concentration of Urea in a blood sample, and the final desired concentration of Urea in the blood, and finally, the drop in Urea concentration with time is calculated. Further input parameters include the patient's weight based on gender. Based on the patient's dry weight and gender, the value of Urea distribution volume is calculated using Equations (3) and (4).[11]

$$Ce\ \ (t) = C_o\, e^{-\frac{tKd}{V}} \tag{2}$$

$$V_{\text{male}} = 0.58DW \tag{3}$$

$$V_{\text{female}} = 0.55DW \tag{4}$$

In the above equations, V_{male} and V_{female} are urea distribution volumes in the case of male and female patients respectively. DW is the dry weight of the patient in kilograms. Distribution volume is a pharmacokinetic parameter representing the distribution of Urea within the human body.[57] Finally, Equation (2) incorporates all the above-calculated parameters and plots changes in concentration over time in minutes. Larger reductions in uremic solute concentrations may not be achieved due to non–dialytic solute clearances or due to variations in solute production.[58] Figure SF1 (Supporting Information) shows the user interface of the MATLAB app module developed to find the change in the concentration of Urea with respect to time. The values of inputs are mentioned in Table ST2 (Supporting Information). The app takes dialysate flow rate, initial and final Urea concentrations, and patient's weight as input to plot the curve.

Influence of Flow Direction on Urea Clearance: The module evaluating the effect of flow orientation on clearance uses Michale's equation and its rearranged form. For comparing the effect of the overall mass transfer coefficient on clearance, Michale's equation is utilized where a user is allowed to input the values of blood, dialysate flow rate, and lower and higher-end values of K_oA.[25] However, how much is the quantitive effect of this difference of directions upon the clearance of Urea was explored in this study. For counter-current flow, the clearance of Urea was evaluated using Equation (1), while for co-current flow, clearance was calculated using the following.[59] Where D is the clearance of Urea for co-current flow arrangement. The model required blood flow rate, the concentration of Urea in blood, and dialysate sample as inputs. The overall mass transfer area coefficient is calculated through concentration values, which are further used in both co and counter-current clearance equations. The values of the parameters that are used are shown in Table ST3 (Supporting Information). Furthermore, Figure SF2 (Supporting Information) shows the interface of the module to evaluate the change in the clearance rate of Urea with co and counter-current flow orientation over a range of dialysate flow rates.

$$D = Qb\frac{1 - e^{-\left(\frac{KA\left(1+\frac{Qb}{Qd}\right)}{Qb}\right)}}{1 + \frac{Qb}{Qd}} \tag{5}$$

Overall Mass Transfer Area Coefficient and Urea Clearance: The overall mass transfer coefficient values are always mentioned in the specification manual of each commercially available hemodialyzer. The manufacturer calculates these values of overall mass transfer coefficients under specific blood and dialysate flow rates.[60] Here, KoA was initially considered constant for a certain dialyzer, but varying dialysate flow rates result in varying its values. As varying dialysate flow rates vary the values of KoA, the changes in values of KoA produce a change in the value of clearance. For finding the effect of changing KoA values on clearance, Equation (1) was used with different values of KoA. Dialyzers with KoA up to 600 mL min^{-1} represent moderate efficiency, while those above 600 mL min^{-1} are considered high-efficiency dialyzers.[25] Other than the input values of KoA, the value for blood flow rate was provided. Table ST4 (Supporting Information) shows the values of parameters that were used to form the plots. The user interface of this module is shown in Figure SF3 (Supporting Information), where blood flow rate and mass transfer area coefficient values are provided as inputs to plot the comparison curve.

Urea Clearance and Hollow Fiber Dimensions: For finding the effect of hollow fiber dimensions, the value of the area in Michael's equation is calculated based on the input value provided by the user, and this area is used in clearance calculations. For investigating the effect of change in hollow fiber dimensions on Urea clearance, Equation (6) was used to find the area of hollow fibers in which r is the radius and l represents the length of an individual fiber.[7] In Equation (7), N_o is the number of hollow fibers present in the module while A_{fiber} is the area of a single fiber.[7] At the same time, the value of one of the parameters between length and radius was kept constant. From the area value of a single fiber, Equation (7) was used to find out the total area of the membrane (A_{dialyzer}).[7]

$$A_{\text{fiber}} = (2\pi)\ \ (r)\ (l) \tag{6}$$

$$A_{\text{dialyzer}} = \left(A_{fiber}\right)(N_o) \tag{7}$$

Finally, the membrane area was used in Equation (1) to determine the change in Urea clearance over a certain range of changes in specific fiber dimensions. The user will enter these dimensions to evaluate the clearance value over a specific fiber length range. In addition, as the program aims to compare the effect of change in fiber dimensions, blood, and dialysate flow rates are kept constant. Table ST5 (Supporting Information) illustrates the parameters that were used along with their respective values. Figure SF4 (Supporting Information) shows the interface of the module to find the change in Urea clearance with a change in the dimensions of the hollow fibers of the membrane.

Effect of Residual Renal Clearance on Standard Hemodialysis Adequacy: There have been multiple attempts to find the most accurate dialysis dose equation. The significant difference lies in the variables required to calculate adequacy using a particular equation. Residual renal clearance is strongly linked with the survival of patients on hemodialysis. A study found that patients with preserved residual renal function had a 30% lower mortality risk than patients with poor renal function.[61] Residual renal clearance increases equilibrated Kt/V by ≈0.15 units per 1 mL min^{-1} of residual renal Urea clearance in an average person.[62] A critical parameter determining adequacy is the residual renal clearance (Kru), which indicates any remaining kidney function in patients receiving hemodialysis.[63] Preserving a healthy Kru has been related to reduced morbidity and mortality in hemodialysis patients. The relationship between residual renal function and std KT/V has been explored by initially calculating the single pool adequacy using Daugirdas's second-generation logarithmic equation.[26] The values obtained are then used to calculate weekly adequacy (nKt/V), which was found using Depner and Bhatt's[64] equation, the results of which are used to find equilibrated adequacy (eKt/V). Once eKT/V values were obtained, they were substituted in the standard adequacy (std KT/V) equation by Leypoldt.[65] Following Equation (8) shows the relation between residual renal clearance and equilibrated Kt/V (eKt/V). In the equation, V is the Urea distribution volume, and Kru is the residual renal clearance in mL min^{-1}. eKT/V is related to standard Kt/V (stdKT/V) through Equation (9).[66]

$$\frac{eKt}{V} = 4.5 \times \frac{Kru}{V} \quad (8)$$

$$\frac{stdKT}{V} = \frac{10,080\,\frac{1-e^{-eKt/V}}{t}}{\frac{1-e^{-eKt/V}}{eKt/V} + \frac{10,080}{Ft} - 1} \quad (9)$$

where F is the number of weekly hemodialysis sessions and t is the duration of each session. The most commonly used equations are of a single pool, equilibrated, and standard KT/V. Here, standard KT/V and equilibrated KT/V as both of these equations incorporate residual renal function, which plays a vital role in assessing morbidity and mortality of ESRD patients, have been analyzed. Therefore, Equation (8) was used to calculate eKT/V with varying residual renal function, and the values obtained for eKT/V were used to find out stdKT/V. Additionally, the change in values of stdKT/V with varying numbers of sessions per week was evaluated and analyzed. Table ST6 (Supporting Information) shows the values used for parameters to form the plot. Figure SF5 (Supporting Information) below shows the module's user interface, which takes time, dialysis sessions per week, and post-dialysis weight as input to plot the change occurring in standard KT/V with changing residual clearance.

Supporting Information

Supporting Information is available from the Wiley Online Library or from the author.

Acknowledgements

The authors are grateful for the financial support from the International Society of Engineering Science and Technology (ISEST), UK. The authors are thankful for the financial support from the National University of Sciences and Technology (NUST), Pakistan. The authors are also thankful to the Researchers Supporting Project Number (RSP2024R363), King Saud University, Riyadh, Saudi Arabia for the financial support.

Conflict of Interest

The authors declare no conflict of interest.

Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Keywords

dialysis management, hemodialysis, nanomolecules and user-centered design, polymer membranes, renal replacement therapy, sustainability

Received: May 17, 2024
Revised: October 4, 2024
Published online: November 15, 2024

[1] G. Decreased, *Kidney Int. Suppl.* **2013**, *3*, 19.
[2] D. R. P. A. Cohen, *Kidney Int. Suppl.* **2023**, *13*, 1.
[3] M. Lunney, R. Lee, K. Tang, N. Wiebe, A. K. Bello, C. Thomas, D. Rabi, M. Tonelli, M. T. James, *Am. J. Kidney Diseases* **2018**, *72*, 592.
[4] A. S. You, K. Kalantar-Zadeh, E. Streja, C. Park, J. J. Sim, E. Tantisattamo, J. T. Hsiung, Y. Obi, P. K. Potukuchi, A. N. Amin, D. V. Nguyen, C. P. Kovesdy, C. M. Rhee, *Am. J. Nephrol.* **2020**, *51*, 715.
[5] M. Bossola, S. S. Hedayati, A. D. H. Brys, L. P. Gregg, *Am. J. Kidney Diseases* **2023**, *82*, 464.
[6] N. M. Tomas, S. A. Mortensen, M. Wilmanns, T. B. Huber, *Kidney Int.* **2021**, *100*, 281.
[7] W. Clark, D. Gao, *Semin. Dial* **2002**, *15*, 191.
[8] M.-Y. Chuang, C.-C. Chen, H.-W. Zan, H.-F. Meng, C.-J. Lu, *ACS Sens.* **2017**, *2*, 1788.
[9] M. R. Späth, K. J. R. Hoyer-Allo, L. Seufert, M. Höhne, C. Lucas, T. Bock, L. Isermann, S. Brodesser, J.-W. Lackmann, K. Kiefer, F. C. Koehler, K. Bohl, M. Ignarski, P. Schiller, M. Johnsen, T. Kubacki, F. Grundmann, T. Benzing, A. Trifunovic, M. Krüger, B. Schermer, V. Burst, R.-U. Müller, *J. Am. Soc. Nephrol.* **2023**, *34*, 772.
[10] Q. Chen, M. Kou, Y. He, Y. Zhao, L. Chen, *J. Membr. Sci.* **2022**, *657*, 120700.
[11] M. Ziolko, J. A. Pietrzyk, J. Grabska-Chrzastowska, *Kidney Int.* **2000**, *57*, 1152.
[12] D. Mourtzis, J. Angelopoulos, N. Panopoulos, *Proc. CIRP* **2022**, *106*, 215.
[13] T. Yaqoob, M. Ahsan, A. Hussain, I. Ahmad, *Membranes* **2020**, *10*, 139.
[14] K. François, D. De Clerck, A. Tonnelier, M.-L. Cambier, C. Orlando, K. Jochmans, W. Cools, K. M. Wissing, *Am. J. Kidney Diseases* **2022**, *79*, 79.
[15] A. I. Chin, V. Sheth, J. Kim, H. Bang, *Kidney Med.* **2019**, *1*, 376.
[16] K. Y. Chang, S. H. Kim, Y. O. Kim, D. C. Jin, H. C. Song, E. J. Choi, Y. L. Kim, Y. S. Kim, S. W. Kang, N. H. Kim, C. W. Yang, Y. K. Kim, *Korean J. Intern. Med.* **2016**, *31*, 1131.
[17] A. Kowal, M. Wojczuk, M. Grabowska, J. Szaran, M. Kowal, E. Pawłowicz-Szlarska, K. Pęczek-Bartyzel, M. Nowicki, *J. Renal Nutrition* **2023**, *33*, 592.
[18] M. Islam, J. Szpunar, *Open J. Nephrol.* **2013**, *03*, 161.
[19] J. T. Daugirdas, *Kidney Int.* **2015**, *88*, 466.
[20] D. Kassinos, *J. Membr. Sci.* **2021**, *629*, 119234.
[21] X. W. Zhao, L. Zhang, *Comput. Biol. Med.* **2018**, *95*, 1.
[22] C. M. Öberg, B. Rippe, *Kidney Int. Rep.* **2017**, *2*, 943.
[23] R. Halicioglu, L. Dülger, A. T. Bozdana, *J. Phys.: Conf. Ser.* **2014**, *490*, 012053.
[24] J. Grace, *Chem. Eng. Sci.* **1990**, *45*, 1953.
[25] A. T. Azar, in *Modeling Techniques of Hemodialysis Systems*, Vol. *1*, 1st Edition, (Ed.: A.T. Azar), Springer, Berlin, Heidelberg **2013**, p. 379.
[26] J. T. Daugirdas, P. G. Blake, T. S. Ing, in *Lippincott Williams and Wilkins handbook*, 5th Edition, Wolters Kluwer Health, Philadelphia **2015**, p. 660.
[27] S. Madhavan, E. M. C. Kemmerling, *Bio. Medical Engineering* **2018**, *17*, 66.
[28] M. Ghasemian, E. Rahimpour, M. R. Rahimpour, in *Current Trends and Future Developments on Bio Membranes*, (Eds.: A. Basile, K. Ghasemzadeh), Elsevier, Amsterdam, Netherlands **2022**, p. 209.
[29] J. Park, C. M. Rhee, J. J. Sim, Y.-L. Kim, J. Ricks, E. Streja, T. Vashistha, R. Tolouian, C. P. Kovesdy, K. Kalantar-Zadeh, *Kidney Int.* **2013**, *84*, 795.

ADVANCED MATERIALS INTERFACES
Open Access
www.advmatinterfaces.de

[30] A. Abumoawad, A. Saad, C. M. Ferguson, A. Eirin, S. M. Herrmann, L. J. Hickson, B. B. Goksu, E. Bendel, S. Misra, J. Glockner, A. B. Dietz, L. O. Lerman, S. C. Textor, *Kidney Int.* **2020**, *97*, 793.
[31] J. T. Daugirdas, *J. Renal Nutrition* **2017**, *27*, 256.
[32] S. L. Goldstein, A. Brem, B. A. Warady, B. Fivush, D. Frankenfield, *Pediatric Nephrol.* **2006**, *21*, 1161.
[33] C. J. Yehl, M. G. Jabra, A. L. Zydney, *Biotechnol. Prog.* **2019**, *35*, e2763.
[34] I. Baldwin, M. Baldwin, N. Fealy, M. Neri, F. Garzotto, J. C. Kim, A. Giuliani, F. Basso, F. Nalesso, A. Brendolan, C. Ronco, *Blood Purif.* **2016**, *41*, 171.
[35] D. Physiology, "Diffusion in the Counter-Current Dialysis Circuit", in Deranged Physiology, **2024**, https://derangedphysiology.com/main/cicm-primary-exam/Chapter%20112/diffusion-counter-current-dialysis-circuit.
[36] B. H. Ozer, P. C. Brazy, in *Pathophysiology of Kidney Disease and Hypertension*, Elsevier, xx xx(Eds.: A. V. Moorthy, W.B. Saunders), **2009**, p. 17.
[37] J. Y. Yeun, T. A. Depner, S. Ananthakrishnan, in *Chronic Kidney Disease, Dialysis, and Transplantation*, 4th Edition, (Eds.: J. Himmelfarb, T. A. Ikizler), Elsevier, Philadelphia **2019**, p. 339.
[38] J. K. Leypoldt, A. K. Cheung, L. Y. Agodoa, J. T. Daugirdas, T. Greene, P. R. Keshaviah, *Kidney Int.* **1997**, *51*, 2013.
[39] J. Abdulla, J. Shakor, A. Shallal, *EurAsia J. Biosci.* **2020**, *14*, p1039.
[40] M. Abe, I. Masakane, A. Wada, S. Nakai, K. Nitta, H. Nakamoto, *Front. Med.* **2021**, *8*, 740461.
[41] O. E. M. ter Beek, D. Pavlenko, D. Stamatialis, *J. Membr. Sci.* **2020**, *604*, 118068.
[42] J. Ren, M. R. Chowdhury, L. Xia, C. Ma, G. M. Bollas, J. R. McCutcheon, *J. Membr. Sci.* **2020**, *603*, 117973.
[43] M. R. Goodarzi, D. Mohebbi-Kalhori, *South African J. Chem. Eng.* **2022**, *42*, 1.
[44] J. Yu, V. C. Chitalia, O. O. Akintewe, A. Edwards, J. Y. Wong, *Regen. Eng. Transl. Med.* **2021**, *7*, 291.
[45] C. Geradin, C. Debiais, C. Vinsonneau, in *Critical Care Nephrology*, 3rd Edition, (Eds.: C. Ronco, R. Bellomo, J. A. Kellum, Z. Ricci), Elsevier, Philadelphia **2019**, p. 905.
[46] J. G. Raimann, X. Ye, P. Kotanko, J. T. Daugirdas, *Am. J. Kidney Diseases* **2020**, *76*, 22.
[47] D. D. Franz, W. F. Hussein, G. Abra, C. D. Diskin, V. Duggal, J. J. Teuteberg, T. I. Chang, B. Schiller, *Am. J. Kidney Diseases* **2021**, *77*, 226.
[48] A. Davenport, *Am. J. Kidney Diseases* **2020**, *76*, 10.
[49] R. Chauhan, S. Mendonca, *Indian J. Nephrol.* **2015**, *25*, 329.
[50] T. Li, C. S. Wilcox, M. S. Lipkowitz, J. Gordon-Cappitelli, S. Dragoi, *Am. J. Nephrol.* **2019**, *50*, 411.
[51] J. Tattersall, *J. Clin. Kidney* **2018**, *11*, 853.
[52] L. A. Inker, S. Titan, *Am. J. Kidney Diseases* **2021**, *78*, 736.
[53] H. Ji, Y. Li, B. Su, W. Zhao, N. Jayachandran, C. Zhao, *Adv. Fiber Mater.* **2023**, *5*, 1198.
[54] H. Ji, Y. Li, B. Su, W. Zhao, J. N., C. Zhao, *Adv. Fiber Mater.* **2023**, *5*, 1198.
[55] K. M. Hill Gallant, E. R. Stremke, L. L. Trevino, R. N. Moorthi, S. Doshi, M. E. Wastney, N. Hisada, J. Sato, Y. Ogita, N. Fujii, Y. Matsuda, T. Kake, S. M. Moe, *Kidney Int.* **2021**, *99*, 1225.
[56] Y. Zhou, S. Wang, Z. Zheng, X. Zhao, L. Wang, *J. Membr. Sci.* **2023**, 674.
[57] D. Donato, M. Storr, B. Krause, *J. of Membrane Sci.* **2020**, *598*, 117690.
[58] T. L. Sirich, K. Fong, B. Larive, G. J. Beck, G. M. Chertow, N. W. Levin, A. S. Kliger, N. S. Plummer, T. W. Meyer, *Kidney Int.* **2017**, *91*, 1186.
[59] B. F. Prowant, *ANNA J.* **1997**, *24*, 369.
[60] Y. Liang, A. V. Dudchenko, M. S. Mauter, *J. Membr. Sci.* **2023**, *679*, 121686.
[61] T. Shafi, A. S. Levey, *Adv. Chronic Kidney Disease* **2018**, *25*, 93.
[62] J. Pinto, M. Debowska, R. Gomez, J. Waniewski, B. Lindholm, *Sci. Rep.* **2022**, *12*, 18755.
[63] S. S. Liew, Z. Zeng, P. Cheng, S. He, C. Zhang, K. Pu, *J. Am. Chem. Soc.* **2021**, *143*, 18827.
[64] T. A. Depner, A. Bhat, *Semin. Dial* **2004**, *17*, 79.
[65] J. T. Daugirdas, T. A. Depner, T. Greene, N. W. Levin, G. M. Chertow, M. V. Rocco, *Kidney Int.* **2010**, *77*, 637.
[66] J. K. Leypoldt, *Hemodial. Int.* **2004**, *8*, 193.
[67] D. Donato, A. Boschetti-de-Fierro, C. Zweigart, M. Kolb, S. Eloot, M. Storr, B. Krause, K. Leypoldt, P. Segers, *J. Membr. Sci.* **2017**, *541*, 519.