Extracorporeal Blood Therapeutic Devices for Renal Replacement: A Review of Current Technologies and Future Directions Toward Microscale-based Devices

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Extracorporeal blood therapeutic devices (ETDs) are medical devices capable of performing treatments outside of the body through an extracorporeal circuit. These devices are widely used in both clinical/hospital settings and at-home care. A prototypical example is the treatment of nephrological diseases through hemodialysis and continuous renal replacement therapy using a hemodialyzer or an artificial kidney. The various applications of ETDs share common limitations such as coagulation, hemolysis, air embolism, and sensitivity reactions, all of which arise from the interactions of human physiology with the treatment mechanisms. Researchers are implementing microscale-based technology to achieve the next-generation ETD that can address persistent problems and improve therapeutic performance.

This review article focuses on the evolution of the structure and development of conventional ETDs towards the miniaturization of the device. We begin with a narrow but common definition of ETDs as well as their current form and uses for renal replacement followed by a review of the importance and progression of microscale-based ETD development together with future directions towards achieving fully functional microscale-based ETDs that reflects contemporary technological and engineering advancements.

Keywords:
blood, extracorporeal, hemodialysis, oxygenation, wearable, renal replacement

Introduction

Extracorporeal treatment is a medical approach designed to support or replace organ function by performing the removal of metabolic wastes or endogenous and exogenous toxins outside the human body[1,2]. In this review, extracorporeal therapeutic devices (ETDs) are referred to medical units designed to perform extracorporeal treatment through an established blood circuit from the patient's body to the device, then returning to the native circulation system. The principle of extracorporeal therapeutic blood processing is the alteration of blood constituents, either via removal (e.g., capture or filtration)[3], through the chemical (e.g., conversion or covalent binding) and mechanical (e.g., diffusion or ultrafiltration) processes performed by a unit or device outside of the body[1]. From this context, devices that administer drugs, either intravenously or subcutaneously, using instruments like drips, needles, or auto-injectors (e.g., EpiPen ®) are not considered ETDs.

A common example of an extracorporeal therapeutic blood-processing device is a hemodialyzer. Due to the growing demands for hemodialysis in everyday medical services, most ETDs serve as blood purification devices for patients with renal diseases. However, extracorporeal blood processing applications are more abundant in the treatment of patients with excessive plasma components (e.g. urea and creatine) and foreign substances such as endotoxins in sepsis or viruses in patients with severe influenza. An extracorporeal circuit can be used for other applications like blood warming in hypothermia[2,4], a support system for the liver failure[5,6] and renal failure[7,8], and blood oxygenation for heart-lung support[9].

The development of contemporary medicine often relies on technological breakthroughs. Chemical, biochemical, and biomedical engineering are at the forefront of enabling various diagnostic and therapeutic medical care treatments. These engineering disciplines contain advanced innovation potentials, spurred by the new radical concept of Process Intensification (PI). Process Intensification introduces new tenets into process design, thus dra-

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matically enhancing our ability to innovate way beyond the completion of laws of transport phenomena and biochemical-kinetics.

Historically, technology played a pivotal role in large-scale, ex vivo, therapeutic blood processing. The earliest ex vivo, large-scale blood oxygenators, and dialyzers were cleverly designed devices implementing the best contemporary understanding of transport phenomena and kinetics. Surprisingly, these design principles did not change substantially for over seventy years, thus having limited persuasion over technological advancement in this field.

Here, we are reviewing the state of clinical large-scale, ex vivo blood processing technologies in light of potential alterations stimulated by advancements in micro-nano-atto-based technologies, process intensification, and digital simulation. We focus on disruptive transformations that will engulf all chemical, biochemical, and biomedical design paradigms. At the end of the paper, we articulate our expert opinion on the progression of biomedical devices for large-scale blood processing. The fundamentals of process intensification and microscale-based design approach are at the root of this progress.

The role of new products of material science and engineering are excluded from consideration. Enabling new materials' properties is certainly important, but minimization of manufacturing costs based on the cost of (new) materials is beyond the scope of this review.

This review explores the primary therapeutic applications of ETDs including hemodialysis and renal replacement therapy followed by their miniaturized successors. Overviews of their structures, functions, current implementations, emerging technologies, and challenges are discussed. Potential future directions for microscale ETDs are described based on observations of the field and advances in parallel areas: Time-scale analysis, two-dimensional lamina platform, and surface functionalization.

Conventional hemodialysis and renal replacement therapy

Chronic Kidney Disease (CKD) has become one of the most prevalent diseases in end-stage renal disease (ESRD) patients and, in fact, elderly patients in general. Approximately 14 % of the global population is diagnosed with CKD with around 4.902 and 7.083 million require renal replacement therapy[10] or dialysis[11].

The primary purpose of hemodialysis is to perform excretory and filtration functions in place of failed kidneys. The circuit draws blood through central venous catheter access using a peristaltic pump. The hemodialyzer transfers waste components, namely uremic toxins, across a semi-permeable membrane into dialysate[12]. A conventional dialysis circuit operates by flowing blood through a capillary dialyzer column with a membrane. This unit is responsible for the filtration of solutes, effectively the small-molecular-weight water-soluble molecules in the range of less than 500 Daltons such as asymmetric dimethylarginine, creatine, creatinine, hyaluronic acid, guanidine, guanidinoacetate, guanidinosuccinate, oxalate, symmetric dimethylarginine, urea, and uric acid through diffusion[13,14]. Middle and large molecules (500 – 5,000 Daltons) are removed primarily by both diffusion and convection where ultrafiltration occurs[15]. Air trap units are positioned for the deaeration of bubbles generated in the circuit before recirculating back to the patient[16].

Hemodialysis has a range of treatment regimens including short daily dialysis, in-center dialysis, peritoneal dialysis (PD), and home dialysis coming with their advantages and challenges listed in Table 1. Although the process is different in each modality, some mutual limitations are observed such as large fluid volume requirement, inflexibility of schedule, and long duration of the operation. These limitations influence the miniaturization of hemodialyzers in the next-generation devices targeting improvement of quality of life for patients. From 1913 to 1985, various designs of commercial membrane hemodialyzer were developed including the hollow fiber dialyzer, spiral dialyzer, parallel flow dialyzer, sheet dialyzer, capillary dialyzer, and rotating drum dialyzer[17,18]. A hollow fiber dialyzer bundle comprises approximately 1000 semipermeable hollow fibers with typical fibers having an internal diameter of 180–200 microns and wall thickness of 30–40 microns, yielding 1.0–2.5 m^2 of surface area. The fibers can also have structural features, such as undulations, to improve dialysate flow distribution through the fiber bundle[19]. The cartridges range in size from a 20 to 30 cm in length and 5 to 10 cm in diameter depending on the manufacturer.

Hollow fibers (capillary filtration) became the standard design of hemodialyzers due to its cost-effectiveness and mass transport performance[20,21]. Following the widespread adoption of the hollow fiber design in the 1960s, modern hemodialyzer developments were aimed toward the selection of proper membrane material to enhance solute clearance and albumin retention. In 1980, the F60 polysulfone dialyzer/ultrafilter was developed as a high-flux dialyzer with a capability to minimize the diminution of white blood cell count and excellent biocompatibility compared to cellulose membranes with a similar capillary design and later became a

premier membrane material[22,23]. The operational blood dialysate flow rates are commonly prescribed in the range of 200 – 300 mL min^{-1} and 500 mL min^{-1}, respectively[24]. Following the popularization of the hollow fiber membrane, the development of nanoporous membranes with solute adsorption ability led to the miniaturization of the dialysis system which significantly reduces the amount of dialysate usage[25]. These nanoporous membranes yield high removal of uremic toxins through adsorptive biomaterials such as charcoal, activated carbon, and zeolites, all playing a crucial part in the regeneration of dialysate. Nanoporous materials are also effective for acute exogenous poisoning and intoxication treatment through hemoperfusion and enhanced membrane permeability. However, membranes like activated carbon have an unselective binding affinity, which can result in the undiscerning adsorption of organic biomolecules. Recently, the invention of silicon nanoporous membranes (SNMs) created a potential combination between dialysis and microfluidic filtration systems with in-vitro experiments showing potential enhancement of therapeutic performance and safety. Johnson *et al*. developed a miniaturized dialyzer utilizing a high throughput membrane capable of filtering middle molecular weight protein toxins while preserving essential blood components like albumin. The silicon-based nanoporous membrane is claimed to be more permeable than conventional membranes by orders of magnitude[26]. The membrane is 75 nm thick with a burst pressure of 3.62 psi, which suggests practicality and survivability inside a hemodialysis system with a transmembrane pressure of 1 to 1.5 psi.

With rapid development of technologies, conventional hemodialysis remains a current epitome of CKD treatment. However, in severe cases of acute kidney injury (AKI), patients may require renal replacement therapy, a modified dialysis approach with additional modalities for critically ill individuals.

Renal replacement therapy incorporates several modalities for renal support including intermittent hemodialysis (IHD), continuous renal replacement therapy (CRRT), and prolonged intermittent renal replacement therapies (PIRRTs). The main differences are the rates of solute clearance and ultrafiltration which govern the duration of treatment. IHD offers ultrafiltration and a high rate of solute clearance which shorten the treatment duration to 3 to 5 hours, whereas CRRT needs up to 24 hours of treatment duration and is prone to interruption by several complications, like system clotting or therapeutic procedures[31]. PIRRTs have a treatment duration range of 8 to 16 hours using the same equipment as IHD but operate at lower blood and dialysate flow rates. CRRT incorporates specific hemodialysis techniques, including continuous venovenous hemodiafiltration (CVVHDF), continuous venovenous hemodialysis (CVVHD) and continuous venovenous hemofiltration (CVVH). The pump-driven venovenous extracorporeal circuit features pressure monitors and air detectors. Due to low solute clearance and blood flow rates, CRRTs are commonly used in patients with AKI, especially those with hemodynamics instability[32] and to prevent shifting of pH, electrolyte and fluid balance which occur in IHD[33]. CVVH relies on a process known as ‘solute drag’, an ultrafiltration using transport from solute convection across a semi-permeable membrane[34]. This method does not require dialysate, instead the filtered fluid is replaced by substitute fluid. CVVHD on the other hand utilizes dialysate to create the concentration gradient across a semi-permeable mem-

Table 1 – *Available dialysis approaches with their advantages and disadvantages*

Approach	Advantage	Limitation	Reference
Conventional short dialysis	Requires a shorter time per session (3–4 h/treatment, three times per week), performed by medical personnel.	The schedule for this approach can be inflexible. The patient is required to travel up to five times per week to the facility. In some patients, the total dialysis duration of 12 hours per week can be insufficient.	27
Home dialysis	Studies revealed that patients’ improved quality of life when performed as prescribed (8–10-hour treatment, three times per week).	The process can be tedious and complicated, since the living quarter must be partially modified into a healthcare facility with water systems for waste disposal installment.	28
Nocturnal dialysis (In-center)	Performed in three 7–9-hour sessions weekly. Proved to yield better-regulated levels of phosphate and blood pressure.	The schedule for this approach can be inflexible. Patients are required to leave home at night, which can be inconvenient.	29
Peritoneal Dialysis (PD)	Patients are not subjected to stay stationary throughout the process. Exchange (Draining and refilling dialysate) is preferably done during the night.	A large volume of fluid is required for this operation. May induce protein loss and leading to malnutrition. Support is limited if being done remotely. Process also requires sufficient training and supply.	30

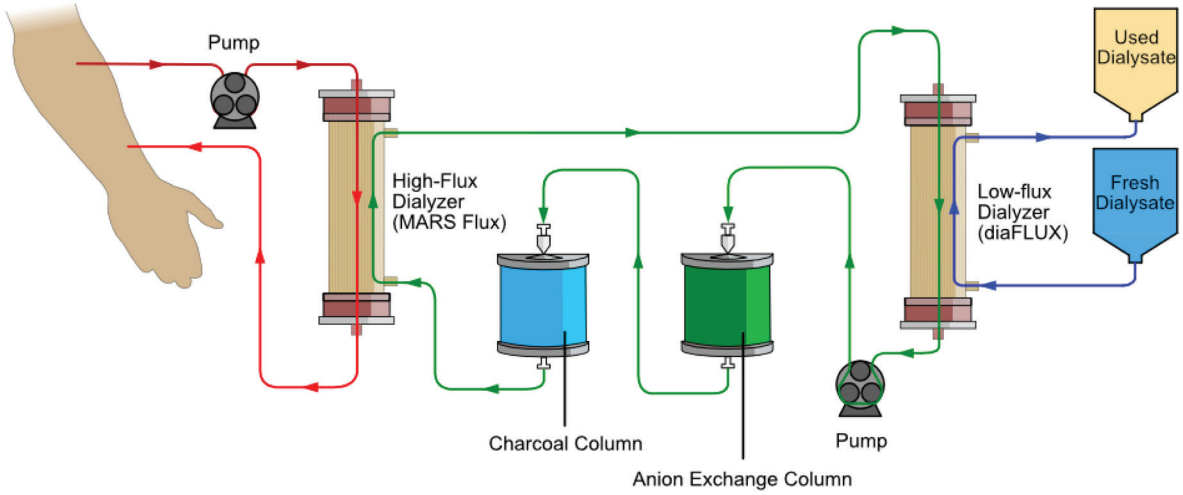


Fig. 1 – *Process flow diagram of the Molecular Adsorbent Recirculating System (MARS) circuit incorporating a low-flux dialyzer with adsorption columns to regenerate the circulating albumin-rich liquid*

brane for solute diffusion, pertinent for the clearance of small molecular weight solutes like potassium, urea, or creatinine[35]. CVVHDF combines the two modalities for the removal of fluid and solutes[36] featuring both high ultrafiltration rate and substitute fluid.

RRT is also effective for the removal of small, nonprotein-bound toxin molecules. A renowned extracorporeal unit for sepsis and blood toxification treatment in intensive care units is the Molecular Adsorbent Recirculating System (MARS). MARS operates with the same principles as a hemodialyzer but with renewable albumin-rich liquid instead of a dialysate solution. Toxins are transported across a high-flux membrane through diffusion with albumin as a toxin-binding conveyer in the dialysate phase. Albumin-bound substances are then cleansed using activated charcoal and anion exchange columns, as depicted in Fig. 1[37].

Miniaturization of dialyzers

Conventional renal replacement modalities like IHD, CVVH, and hemodialysis are not entirely appropriate for handling renal disorders in small patients, neonates and infants. The main reasons behind this impediment are the large priming volume requirement, high risk of excessive fluid removal, and large catheter size[38]. A high mortality rate (>50 %) is observed in pediatric patients weighing less than 3 kg treated with conventional CRRT modalities including CVVH and CVVHD.

Prominent miniaturized extracorporeal devices designed specifically for smaller patients have been developed and tested. Notable machines for pediatric renal replacement therapies are Cardio-Renal Pediatric Dialysis Emergency Machine (CARPEDIEM), the Newcastle Infant Dialysis and Ultrafiltration System (NIDUS), and the Aquadex Flex flow Ultrafiltration system.

Developed at the Department of Nephrology and International Renal Research Institute of the San Bortolo Hospital in Vicenza, CARPEDIEM is a miniaturized CRRT machine tailored to treat newborn children weighing less than 10 kg[39]. CARPEDIEM incorporates a low priming volume at around 27 mL, miniaturized roller pumps capable of running at the flow rate of 5 – 50 mL min^{-1}, and highly accurate ultrafiltration control. The machine is capable of various therapeutic modalities namely, plasma exchange, blood exchange, and CVVH. The first operation was recorded in 2013, in 2.9 kg female neonate with an underlying hemorrhagic complication. During the process, the patient experienced hyperbilirubinemia (*i.e.,* excess concentration of plasma bilirubin) due to liver impairment. Physicians performed rapid blood exchange, single-pass albumin dialysis, and plasma exchange to maintain the physiological stability. Hemofiltration was discontinued after 400 hours of operation, and stable hemodynamic and respiratory statuses were observed in the patient[40]. Even though CARPEDIEM is a promising pediatric dialysis machine, more extensive research is needed to ensure safety in patients, especially those with underlying disorders incapable of being treated with PD.

Initially developed in 1995 by a research team in Newcastle, England, NIDUS is a miniaturized dialysis machine capable of treating patients weighing between 0.8 to 8 kg. The extracorporeal circuit operates by withdrawing a blood aliquot of 5 to 12.5 mL to pass through a 0.045 m^2 high-flux polysulfone membrane using two syringe pumps to perform dialysis and ultrafiltration at a 20 mL min^{-1} flowrate[41]. The machine is recognized for its preprogrammed pressure control, which allows for pre-

cise dialysis and safety from needle dislodgement and air leakage with only a minimum amount of anti-coagulant requirement. A study was conducted assessing the efficiency of NIDUS compared to PD and HD, and showed the miniaturized unit performed exceptionally precise ultrafiltration by maintaining minimal standard deviation of ± 17 g in fluid mass compared to HD with standard deviation of ± 96 g [41].

Aquadex was developed by Baxter Corporation (Minneapolis, Minnesota, USA) as a low-extracorporeal-volume (ECV) CRRT unit. The US Food and Drug Administration (FDA) approved the device in 2007 for plasma volume ultrafiltration in adults with heart failure. The machine was later adapted by Askenazi *et al.*[42] to perform CVVH in 12 critically ill infants with weight less than 15 kg. The adapted extracorporeal circuit is 33 mL in volume incorporating a 0.12 m^2 polysulfone filter. Ultrafiltration can be performed up to a maximum rate of 500 mL h^{-1} in CVVH mode with an accuracy of ±10 %. The results showed an improved 86 % survival rate compared to 33 % for the prospective pediatric CRRT registry[43].

Apart from the miniaturization of ETDs for small patients, the visions of next-generation renal replacement therapy involve the development of portable and wearable operational units. The development of portable artificial kidneys started around 1960, by Longmore and colleagues, focused on the fabrication of a portable artificial kidney claimed to require less dialysate solution only at around 10 L compared to conventional intermittent dialysis. A model with higher clearance was later developed requiring almost 50 L of dialysate and too cumbersome to be considered portable[44]. Suitcase dialyzers, invented during the 1970's by Friedman and colleagues, with components including pumps, monitors, and a dialysate reservoir performed acceptable creatinine and urea clearance rates in three patients while traveling. The group concluded that the dialyzer is a safe device for treating individuals with acute kidney disease needing constant blood dialysis. However, users were required to have access to clean water and an electrical outlet for the operation[45].

Certain portable dialyzer designs utilize a regenerative dialysate (REDY) sorbent system to minimize the frequency of dialysate exchange. Visualized in Fig. 2, the system features sorbent cartridges that accommodate zirconium phosphate, hydrated zirconium oxide, and carbon-urease complex responsible for breaking down urea into ammonia and carbon dioxide[46]. The REDY sorbent system was popularly employed in the miniaturized dialysis designs owing to its ability to reduce the amount of required dialysate[47]. Several downsides of REDY appeared during the first year of manufacturing including urease dislocation, unrinsed dialyzers causing deafness, and the deactivation of urease by copper from the water source[46]. Some technical issues like ammonia leakage after the saturation of the cation exchange column into the regenerated dialysate and the generation of carbon dioxide bubbles from the binding of free hydrogen and carbonate also persist[48]. The high cost of manufacturing disposable

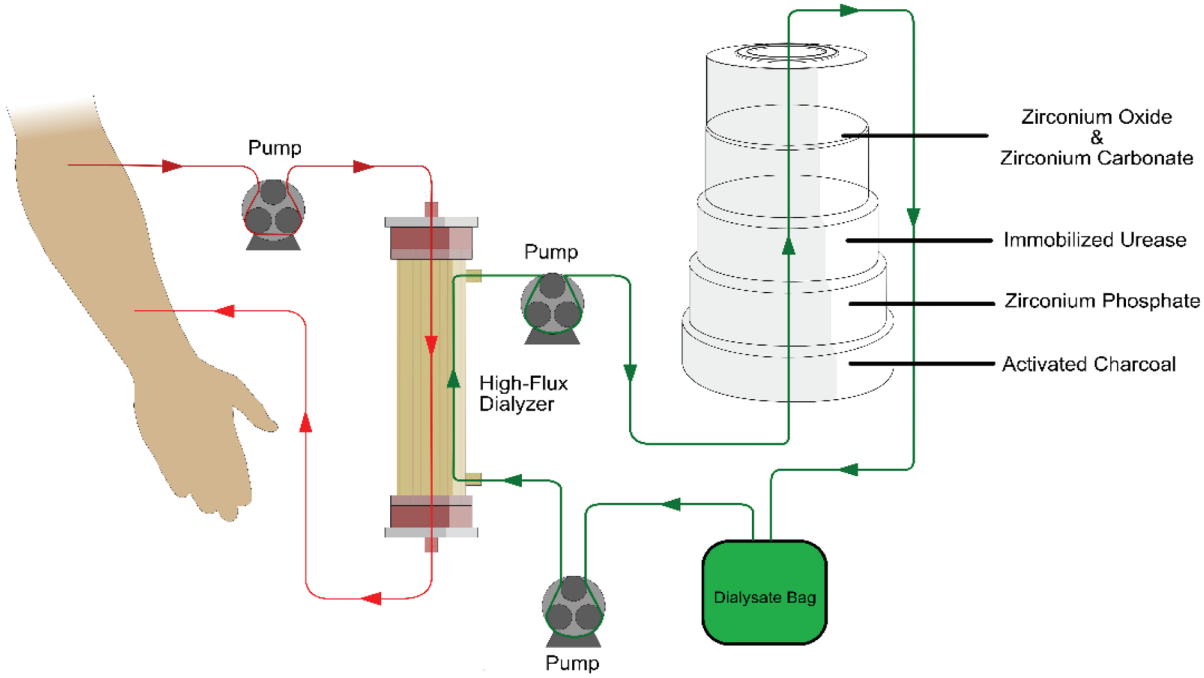


Fig. 2 – *Process flow diagram of a REDY sorbent system integrated with dialysis, with the primary component being the sorbent cartridge containing active compounds*

sorbent cartridges renders this treatment inadequate compared to single-pass dialysis like PD[49]. Despite several limitations, this system inspired the development of wearable dialyzers with ideas revolving around minimizing the required amount of working fluid through regenerative systems.

Though the idea of wearable dialyzers is not novel, alternative designs for an artificial kidney in recent years are needed due to clinical, technical, and socioeconomic drivers. Many limitations found in conventional hemodialysis, especially movement restrictions and insufficient treatment time, are aimed to be resolved through a wearable artificial kidney (WAK) while also reducing the occurrence rate of potential impediments including anemia, hypertension, psychological symptoms, hospitalizations, and need for medications[50,51].

The first-generation WAK was considered a successful design of an extracorporeal device worn around the patient's waist with a blood flow rate of 100 mL min^{-1} [52]. The device weighed approximately 5 kg and ran solely on batteries without water and power access requirements. The components included a membrane, dialysate regeneration system, vascular access, batteries, pumps, monitoring display, and vascular access. Several complications occurred during operation, including the generation of carbon dioxide gas bubbles, clotting despite the administration of anticoagulants, and in some cases, needle dislodgement[53]. Although the system was claimed to be compact and required only a small amount of clean water, it was not commercially accepted, as the machine was too bulky and complicated to be self-operated. Despite the problems, clinical data have shown promising results like satisfactory uremic solutes clearance with stable electrolyte and hemoglobin levels[54]. Monitoring systems are recommended to closely observe parameters like blood pressure, heart rate, fluid flow, and oxygen level. The device should be observed for bubble formation, clearance rate, ultrafiltration rate, and anticoagulant administration[55]. Rambod *et al.* developed a numerical model representing blood flow inside Multiflow M60 hemofilter with 4400 AN69 hollow fibers using Navier-Stokes equation to express laminar Newtonian flow, and Darcy-Brinkman equation for the transport of species inside a porous medium[56]. This study revealed the beneficial characteristics of a WAK pump that offers higher clearance rate of solute and a safer transmembrane pressure range compared to a conventional push-pull hemodiafiltration device.

Modern medical device research utilizes mathematical models to help evaluate the design and treatment performance of the operational unit. The parametric study of mass transport models elucidated the high influence of characteristic times of diffusion on the solute clearance rate. From this, process intensification (PI) is being implemented in the designing and engineering aspects of ETDs. PI is a design approach that utilizes fundamental principles of transport phenomena (i.e., heat, mass, and momentum), and reaction kinetics to redesign processes from the ground up that reduce characteristic times[57,58] or distances, enhance interfacial surfaces, improve processing uniformity, and integrate subprocesses, plus more. In addition to transport and kinetic principle, PI has its own tenets as defined by[59]. The objectives of PI can range from energy reduction, faster processing, change (simplification) of device architecture, waste reduction, modularity, and safety improvement. PI is evident in ETDs by the drive to reduce transport distances of species to a sub-millimeter scale, which can enable a safer and highly efficient device. Although a conventional hemodialyzer has a sub-millimeter solute diffusion length within a hollow fiber, a large volume of dialysate is needed because the 'shell' portion of the cartridge is poorly optimized for transport and fluid flow, the system is not regenerative, and other essential components are not miniaturized. The shell-side deficiencies mentioned are in direct contradiction to the principles of process intensification.

Microscale-based technology utilizes PI principles to significantly reduce the characteristic time of solute diffusion and enhance the rate of clearance, thus drastically lowering the fluid volume within the device and the amount of passes a volume of blood makes through the device. A microchannel hemodialyzer was developed by Tuhy *et al.*[60] demonstrating enhanced mass transfer coefficient. This development was assisted by a mathematical model and accompanying numerical simulations. This model aimed to clarify the impact of various factors, including residence time, pressure, and other parameters, in order to optimize the removal rate. The mathematical model was constructed based on the equations for conservation of mass (i.e., Continuity equation) and momentum (i.e., Navier-Stokes equation), incorporating parameters such as velocity and fluid properties (e.g., density and viscosity). It also coupled the Darcy equation to represent mass transport in the porous membrane, taking into consideration membrane permeability, local oncotic pressure, membrane porosity, and solute diffusivity. The governing equation for conservation of mass in the system at steady state can be expressed in equation (1):

$$\rho\left(u\frac{\partial C}{\partial x}+v\frac{\partial C}{\partial y}+w\frac{\partial C}{\partial z}\right)=D\left(\frac{\partial^2 C}{\partial x^2}+\frac{\partial^2 C}{\partial y^2}+\frac{\partial^2 C}{\partial z^2}\right) \quad (1)$$

Here the primary parameters include diffusivity (D) of solutes and fluid velocity in all three directions. Fig. 3 shows the schematics of the computational domain of the microchannel model. Equation

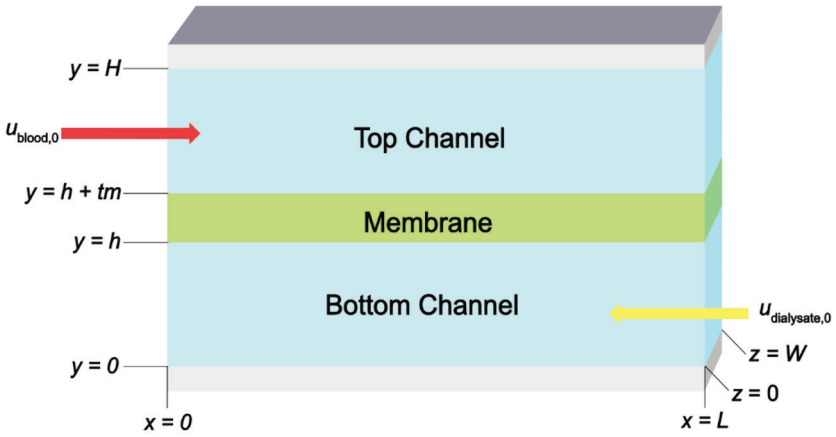


Fig. 3 – *Schematic of the computational domain in the work by Tuhy et al.*[57]

1 could be simplified further assuming no changes in concentration and no fluid velocity with respect to the z-direction. The diffusivity of urea in water (D_{AB}) is defined for the vertical position $0 < y < h$ and $h+t_m < y < H$ (i.e., the channel domains) and the effective diffusivity of urea in water in the membrane (D_{eff}) is defined for the vertical positions $h < y < h+t_m$ (i.e., the membrane domain). The Navier-Stokes equations (not shown) represents conservation of momentum for laminar fluid flow in both channel domains. This work was further progressed using residence time to investigate hydrodynamic behavior and showed potential uses of computational fluid dynamics as a tool for designing lamina plate platform for dialysis[61]. Moreover, microscale-based technology coupling with surface functionalization can help address persisting issues like bubble formation or blood coagulation, as demonstrated in the coating of microchannel plate with polyethylene oxide (PEO)-polybutadiene (PB)-polyethylene oxide surface modification[62] that reduces the bubble stagnation and minimizes the restrictive force in blood flow[63]. This microscale-based operation provides a wide range of functionality for ETD research. The platform can accommodate membranes, bioactive compounds, and therapeutic cells that enhance dialysis performance. From these benefits, progress and understanding in cell therapy and tissue engineering, bioartificial kidneys (BAK) have been developed aiming to replace renal functions of the original native cells with minimal invasion[64].

BAK is developed to be an implantable device or an operational unit for an extracorporeal circuit outside of the body. Wearable bioartificial kidney (WEBAK) utilizes the sorbent-based technology and bioartificial renal epithelial cell system (BRECS) to accomplish the therapeutic functions[64]. BRECS is designed to be a miniaturized cryo-preservable bioreactor with porous niobium-coated carbon disks to accommodate dense cell growth and adhesion[65]. BRECS allows long-term storage by utilizing cryo-preservation to help cells retain viability and renal metabolic functions for up to 3 months. The housings incorporate polycarbonate top and bottom chambers with inlet and outlet to deliver cell culture media through porous disks. An inlet flow separator and baffles are installed to create a homogenous and lamina flow behavior within the system with a fill volume of 30 mL. In previous designs, computer numerical control (CNC) machining is used for producing the components, but the process is too expensive and time-consuming for mass production[66]. In newer designs, stereolithographic rapid prototyping and injection molding of BRECS with a reduced fill volume of only 10 mL were developed with computational fluid dynamics and analyzed for hemodynamics factors like media flow homogeneity, areas of recirculation, and stagnation spots, etc.[66] WEBAK is considered a 'membraneless' design for wearable ETDs utilizing bioactive molecules and cells to perform therapeutic and regenerative functions without the need for an additional phase like dialysate. This configuration allows the device to be miniaturized further using microfluidic systems like microchannel or laminar platforms coupling with cell engineering to maintain reliable clearance performance. The transitioning to the new generation membraneless has miniaturized devices opening up several directions to minimize the disadvantages from mass transfer limited settings. These approaches include but are not limited to Time Scale Analysis (TSA), 2-dimensional laminar platform, and surface functionalization, which will be discussed in the next section.

Future directions towards microscale-based devices

The vision for future ETD progress reflects the ever-present need to reduce risk factors in existing ETD applications (e.g. accidents, mortality, side effects) and enhance the range and scope of therapies.

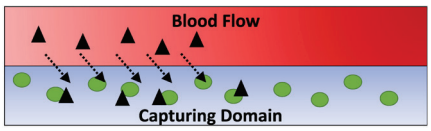
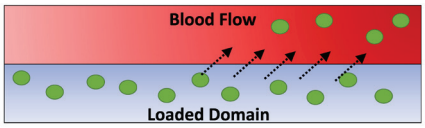
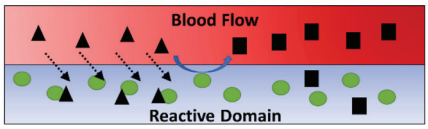
Scientific and engineering developments play a central role in ETD advancements. In line with this objective, the following bioengineering technologies are viewed as the next integral constituent elements of an ETD.

The rates of various transport phenomena such as fluid flow, heat transfer, and molecular diffusion, along with biochemical reaction kinetics and supplementary biological rate processes can be represented by their characteristic times. Characteristic times arise as an intrinsic measure of all rates, fluxes, and biochemical kinetic processes that take place in extracorporeal devices and the human body within the time domain. Characteristic times are developed from fundamental principles embedded in the mathematical models of all processes that occur in ETDs[67,68]. TSA utilizes characteristic times to identify process steps that are imbalanced with other process steps, thus identifying bottlenecks or potential opportunities for process improvement. In traditional biochemical processing, TSA identifies mass transport and bio-kinetic limitations, such as transport of a reactant species to the proximity of immobilized enzymes. Characteristic times and TSA are also used to identify steps in complex biochemical processes, which need to be considered for process intensification improvements. Once a "heat map" of characteristic times pertinent to an ETD's operation is established, one can determine which ETD parameter or operating variable needs to change.

While the current number of ETD applications is modest, the potential future for application development is encouraging. In Table 2, we show three groups of promising functionalities of ETDs, which are in various research stages.

Current research efforts in developing ETD are promising a rapid advent of yet unintroduced technologies. Continuity and sustainability of the new era of therapeutic blood processing innovations will depend on two groups of requirements: The first group of requirements is centered on a continued and robust line of scientific discoveries combined with a pool of creative researchers who will provide a translational effort towards the inception of new medical technologies. The second group of prerequisites is entwined with the development of common technological platforms, which can provide cost-effective and liberated progress of newly conceived ETD applications. Advancements in additive manufacturing and micromachining provide accessible design and fabrication methods for massive low-cost production of the standard platform components. One of these common platforms is the 2D lamina plate. A similar line of progression permeated the development of microscale analytics or lab-on-chip devices where manufacturing advancements of microscale and nanoscale-based technologies were adopted from industries such as semiconductor manufacturing.

Table 2 – *Potential therapeutic modalities in microscale-based ETDs*

ETD Functions	Description	Ref.
 Capturing	– Biological chelating agent immobilized inside a biocompatible reactive domain. – Reactant diffuses into and selectively binds to chelating agents. – Method actively reduces plasma concentrations of harmful materials like excess substances, viral or bacterial bodies presented in Sepsis. – Ex. Microchannel device with immobilized iron chelators (e.g. deferoxamine or transferrin) to reduce excess iron due to recurring blood transfusion.	69
 Release	– Controlled release of an active substance (e.g. drug or therapeutic enzyme) via loading within a biocompatible porous layer. Diffusion allows the substance to gradually release into the blood. – Prevents the spiking of drug plasma concentration, often found in transfusion or other routes of drug delivery. – Reduces the risk of drug hypersensitivity while allowing a patient to receive a continuous effective dose. – Example: Plum pudding model: Targeted drug delivery achieved by employing surface-modified nanoparticles as delivery vectors.	70
 Conversion	– Active substance (e.g. enzyme or catalyst) is entrapped inside a biocompatible reactive domain using immobilization techniques (e.g. covalent bonding, physical entrapment). – Substrate diffuses and selectively reacts with immobilized substances inside the reactive domain to form desired products that diffuse back to blood flow. – Ex. conversion of uric acid to allantoin and water using immobilized uricase and catalase.	71

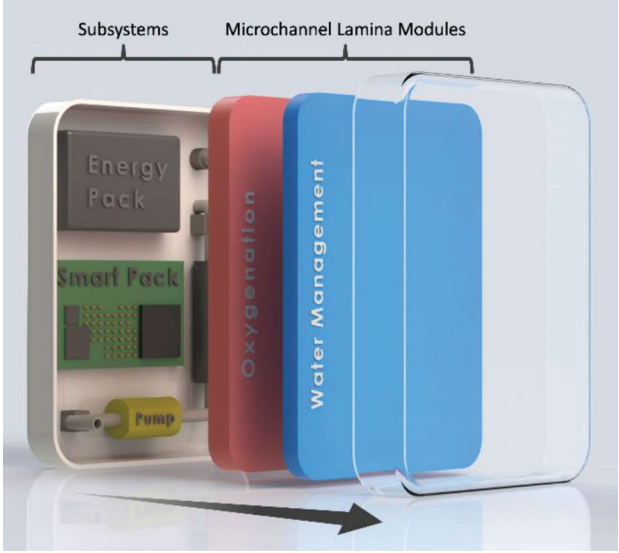


Fig. 4 – *Exploded view schematic representation of a wearable ETD, iCore, showing a multi-lamina plate configuration*

One technological approach in the design and manufacturing of EBPD devices is built around modular microscale-based blood processing units. Fig. 4, courtesy of Oregon State University's *i*Core research group, shows a schematic of a conceptualized ETD, the *i*Core platform. The ETD module consists of multiple microfluidic plates laminated together in a parallel, numbered-up configuration. Laminated plate technology has a strong presence in microscale-based devices deployed in (bio)chemical and petrochemical processing, pharmaceutical manufacturing, energy storage, and water treatment[72,73]. A consistent architectural structure has emerged from these applications, thus forming a common design theme approach, which is now referred to as the 2-D Lamina Plate Platform. In the technological domain of ETDs, this platform will conceptually facilitate three primary roles: 1) Functionalization of the microchannel plate surfaces with an active therapeutic coating pertinent to blood processing. 2) Management of transport phenomena (momentum, energy, and mass transport) via microscale and nanoscale features embedded in the microchannel plate architecture. 3) Process capacity scale-up through numbering-up of lamina plates.

Low-cost manufacturing will further advance applications of the lamina plate platform. Lamina plates can be easily manufactured from various materials, including metals, glass, and polymers. Particularly attractive materials are those already common in biomedical applications such as polycarbonate and polysulfone. Medical-grade polycarbonate is a promising material for blood processing applications due to its FDA approval for medical devices. Large-volume inexpensive fabrication of lamina plates via thermal embossing for disposable application will further improve the prospect of lamina plate platform applications[74,75]. Most recently, additive manufacturing or 3D printing provide an exciting pathway to accelerate prototyping and implement complex, monolithic architectures previously infeasible with subtractive manufacturing and injection molding. The cost of additive manufacturing, along with the capabilities (e.g., materials, tolerances, speed), are only expected to improve in the near future and we can already see companies enter the biomedical device market.

A 2-D lamina plate geometry provides an exceptionally high functional surface ratio ~105–107 [$m^2_{functional\ surface}/m^2_{nominal\ surface}$][76], especially if it is enhanced with micro-and nano-architectural features. Enhanced surfaces are ideal for functionalization such as immobilization of therapeutically active substances, modification of surface-free energy towards hydrophilic/oleophilic properties, and the formation of electric/magnetic field gradients. The immobilization of therapeutically active substances is the most common method of surface functionalization. It can take the form of covalent bonding, adsorption or absorption, and entrapment. To effectively immobilize catalysts, drugs, or enzymes on the plate surface, proper bioconjugation chemistry and crosslinker should be cautiously identified to allow active site preservation and high specificity of functionalization[77]. Modifiable functional groups like sulfhydryl (–SH), amine ($–NH_2$), hydroxyl (–OH) or carboxyl (–COOH) are available on the proteins based on their surface residues[78]. Conformal coating of thin films containing microbial or enzymatic active substances is another path to support blood-based therapeutic processing. Functional species can range from immobilizing molecules like chelators in metal-ion affinity columns for protein separation[79–81] to biocatalyst-like enzymes and cells[82,83] to common drugs such as deferoxamine and ferritin. The lamina plates serve as a highly adaptive platform that enables flexible, intensified conversion, high elimination, and delivery rates of ever-increasing blood-resident components without requiring an additional fluid phase or membranes. The design and manufacturing of lamina plates can become a largely simplified and inexpensive platform-like commodity leading to the skills, knowledge, and imaginative creativity of surface functionalization becoming the epicenter of future ETD development.

Lastly, Digital Twin, a virtual entity of a process or equipment resembling the physical unit in operation. Developing and utilizing digital twins once required exorbitant computational resources, bandwidth, and storage, but are now a fast-growing tool across industries. As the fluidity of information transfer becomes more significant, many industries outside of healthcare, are integrating these virtual entities into their operations to mitigate manufacturing obstructions (i.e. risk mitigation). It serves to

simulate numerous scenarios caused by operators and anticipate potential threats and hazards, which often emerge during the device's designing phase but do not manifest themselves until device operation. For self-operated therapeutic blood processing devices, human errors from patients could result in severe consequence such as injury or even death, and employing artificial intelligence to predict user-related hazards could drastically reduce this risk. Like mathematical models, digital twin serves as a tool for designing and functionalizing microscale-based devices that can potentially reduce mortality rate from operations and provide better insights toward the next-generation device development.

Conclusions

A modest number of contemporary applications of ETDs are available in modern medical practice. They intrinsically carry advantages and disadvantages regarding functionality, accessibility, safety, or economics. Additionally, shortcomings and risks found in ETDs adversely impact mortality and fatality rates in patients. These challenges will need to be addressed in developing next-generation ETDs to improve therapeutics performance and safety. Most notably, soon, the potential for new therapeutically disruptive ETD applications could soar via implementation of 2D Lamina Plate platform-technology, coupled with researchers' creativity, artificial intelligence, TSA, process intensification through microscale-based structures, Digital Twin supports, and surface functionalization. These newly conceived ETDSs could be enabled to deliver therapeutic treatment outside of the hospital environment, increasing access and reducing healthcare costs.

References

1. *Jha, V. K., Padmaprakash, K. V.,* Extracorporeal treatment in the management of acute poisoning: What an intensivist should know?, Indian J. Crit. Care Med. **22** (2018) 862. doi: https://doi.org/10.4103/ijccm.IJCCM_425_18
2. *Schanche, T., Kondratiev, T., Tveita, T.,* Extracorporeal rewarming from experimental hypothermia: Effects of hydroxyethyl starch versus saline priming on fluid balance and blood flow distribution, Exp. Physiol. **104** (2019) 13. doi: https://doi.org/10.1113/EP087786
3. *Yaxley, J., Scott, T.,* Dialysis and extracorporeal therapies for enhanced elimination of toxic ingestions and poisoning, Ther. Apher. Dial. **26** (2022) 865. doi: https://doi.org/10.1111/1744-9987.13843
4. *Walpoth, B. H., Walpoth-Aslan, B. N., Mattle, H. P., Radanov, B. P., Schroth, G., Schaeffler, L., Fischer, A. P., von Segesser, L., Althaus, U.,* Outcome of survivors of accidental deep hypothermia and circulatory arrest treated with extracorporeal blood warming, N. Engl. J. Med. **337** (1997) 1500. doi: https://doi.org/10.1056/NEJM199711203372103
5. *Karvellas, C. J., Subramanian, R. M.,* Current evidence for extracorporeal liver support systems in acute liver failure and acute-on-chronic liver failure, Crit. Care Clin. **32** (2016) 439. doi: https://doi.org/10.1016/j.ccc.2016.03.003
6. *MacDonald, A. J., Karvellas, C. J.,* Emerging role of extracorporeal support in acute and acute-on-chronic liver failure: Recent developments, Semin. Respir. Crit. Care Med. **39** (2018) 625. doi: https://doi.org/10.1055/s-0038-1675334
7. *López-Herce, J., Casado, E., Díez, M., Sánchez, A., Nicole, S. F., María J. B., José M. S.,* Renal function in children assisted with extracorporeal membrane oxygenation, Int. J. Artif. Organs **43** (2020) 119. doi: https://doi.org/10.1177/0391398819876294
8. *Prins, K. W., Wille, K. M., Tallaj, J. A., Tolwani, A. J.,* Assessing continuous renal replacement therapy as a rescue strategy in cardiorenal syndrome 1, Clin. Kidney J. **8** (2015) 87. doi: https://doi.org/10.1093/ckj/sfu123
9. *Paolone, S.,* Extracorporeal Membrane Oxygenation (ECMO) for lung injury in severe acute respiratory distress syndrome (ARDS): Review of the literature, Clin. Nurs. Res. **26** (2017) 747. doi: https://doi.org/10.1177/1054773816677808
10. *Lv, J.-C., Zhang, L.-X.,* Prevalence and disease burden of chronic kidney disease, Adv. Exp. Med. Biol. **1165** (2019) 3. doi: https://doi.org/10.1007/978-981-13-8871-2_1
11. *Collister, D., Rigatto, C.,Tangri, N.,* Anemia management in chronic kidney disease and dialysis: A narrative review, Curr. Opin. Nephrol. Hypertens. **26** (2017) 214. doi: https://doi.org/10.1097/MNH.0000000000000317
12. *Himmelfarb, J., Ikizler, T. A.,* Hemodialysis, N. Engl. J. Med. **363** (2010) 1833. doi: https://doi.org/10.1056/NEJMra0902710
13. *Clark, W. R., Dehghani, N. L., Narsimhan, V., Ronco, C.,* Uremic toxins and their relation to dialysis efficacy, Blood Purif. **48** (2019) 299. doi: https://doi.org/10.1159/000502331
14. *Lisowska-Myjak, B.,* Uremic toxins and their effects on multiple organ systems, Nephron. Clin. Pract. **128** (2014) 303–311. doi: https://doi.org/10.1159/000369817
15. *Phadke, G., Khanna, R.,* Renal replacement therapies, Mo. Med. **108** (2011) 45.
16. *Keshavarzi, G., Simmons, A., Yeoh, G., Barber, T.,* Effectiveness of microbubble removal in an airtrap with a free surface interface, J. Biomech. **48** (2015) 1237. doi: https://doi.org/10.1016/j.jbiomech.2015.03.018
17. *Clark, W. R.,* Hemodialyzer membranes and configurations: a historical perspective, Semin. Dial. **13** (2000) 309. doi: https://doi.org/10.1046/j.1525-139x.2000.00081.x
18. *Twardowski, Z. J.,* Dialyzer reuse - Part I: Historical perspective, Semin. Dial. **19** (2006) 41. doi: https://doi.org/10.1111/j.1525-139X.2006.00118.x
19. *Sakai, K.,* Dialysis membranes for blood purification, Front. Med. Biol. Eng. **10** (2000) 117. doi: https://doi.org/10.1163/15685570052061973
20. *Clark, W. R., Rocha, E., Ronco, C.,* Solute removal by hollow-fiber dialyzers, Contrib. Nephrol. **158** (2007) 20. doi: https://doi.org/10.1159/000107232
21. *Hirano, A., Yamamoto, K., Matsuda, M., Ogawa, T., Yakushiji, T., Miyasaka, T., Sakai, K.,* Evaluation of dialyzer jacket structure and hollow-fiber dialysis membranes to achieve high dialysis performance, Ther. Apher. Dial. **15** (2011) 66. doi: https://doi.org/10.1111/j.1744-9987.2010.00869.x

22. *Hayama, M., Yamamoto, K., Kohori, F., Sakai, K.,* How polysulfone dialysis membranes containing polyvinylpyrrolidone achieve excellent biocompatibility?, J. Membr. Sci. **234** (2004) 41. doi: https://doi.org/10.1016/j.memsci.2004.01.020
23. *Twardowski, Z. J.,* History of hemodialyzers' designs, Hemodial. Int. **12** (2008) 173. doi: https://doi.org/10.1111/j.1542-4758.2008.00253.x
24. *Palmer, S. C., Rabindranath, K. S., Craig, J. C., Roderick, P. J., Locatelli, F., Strippoli, G. F. M.,* High-flux versus low-flux membranes for end-stage kidney disease, Cochrane Database Syst. Rev. **2012** CD005016. doi: https://doi.org/10.1002/14651858.CD005016.pub2
25. *Cheah, W. K., Ishikawa, K., Othman, R., Yeoh, F.-Y.,* Nanoporous biomaterials for uremic toxin adsorption in artificial kidney systems: A review, J Biomed. Mater. Res. B Appl. Biomater. **105** (2017) 1232. doi: https://doi.org/10.1002/jbm.b.33475
26. *Johnson, D. G., Pan, S., Hayden, A., McGrath, J. L.,* Nanoporous membrane robustness/stability in small form factor microfluidic filtration system, Annu. Int. Conf. IEEE Eng. Med. Biol. Soc. **2016** (2016) 1955. doi: https://doi.org/10.1109/EMBC.2016.7591106
27. *Firanek, C. A., Garza, S., Gellens, M. E., Lattrel, K., Mancini, A., Robar, A., Todd, L. B., Sloand, J. A.,* Contrasting perceptions of home dialysis therapies among in-center and home dialysis staff, Nephrol. Nurs. J. **43** (2016) 195.
28. *Masterson, R.,* The advantages and disadvantages of home hemodialysis, Hemodial. Int. **12 Suppl 1** (2008) S16. doi: https://doi.org/10.1111/j.1542-4758.2008.00290.x
29. *Wong, B., Collister, D., Muneer, M., Storie, D., Courtney, M., Lloyd, A., Campbell, S., Pauly, R. P.,* In-center nocturnal hemodialysis versus conventional hemodialysis: A systematic review of the evidence, Am. J. Kidney Dis. **70** (2017) 218. doi: https://doi.org/10.1053/j.ajkd.2017.01.047
30. *Niang, A., Iyengar, A., Luyckx, V. A.,* Hemodialysis versus peritoneal dialysis in resource-limited settings, Curr. Opin. Nephrol. Hypertens. **27** (2018) 463. doi: https://doi.org/10.1097/MNH.0000000000000455
31. *Tolwani, A.,* Continuous renal-replacement therapy for acute kidney injury, N. Engl. J. Med. **367** (2012) 2505. doi: https://doi.org/10.1056/NEJMct1206045
32. *Tandukar, S., Palevsky, P. M.,* Continuous renal replacement therapy: who, when, why, and how, Chest **155** (2019) 626. doi: https://doi.org/10.1016/j.chest.2018.09.004
33. *Cope, G.,* The basic principles of continuous renal replacement therapy, Journal of Renal Nursing (2013) **5** 85. doi: https://doi.org/10.12968/jorn.2013.5.2.85
34. *Tolwani, A. J., Campbell, R. C., Stofan, B. S., Lai, K. R., Oster, R. A., Wille, K. M.,* Standard versus high-dose CVVHDF for ICU-related acute renal failure, J. Am. Soc. Nephrol. **19** (2008) 1233. doi: https://doi.org/10.1681/ASN.2007111173
35. *Saunders, H., Sanghavi, D.,* Continuous Renal Replacement Therapy, StatPearls, StatPearls Publishing, 2022.
36. *AlEnezi, F., Alhazzani, W., Ma, J., Alanazi, S., Salib, M., Attia, M., Thabane, L., Fox-Robichaud, A.,* Continuous venovenous hemofiltration versus continuous venovenous hemodiafiltration in critically ill patients: A retrospective cohort study from a Canadian tertiary centre, Can. Respir. J. **21** (2014) 176. doi: https://doi.org/10.1155/2014/965479
37. *Tan, H.,* Molecular adsorbent recirculating system (MARS), Ann. Acad. Med. Singap. **33** (2004) 329.
38. *Hothi, D. K.,* Designing technology to meet the therapeutic demands of acute renal injury in neonates and small infants, Pediatr. Nephrol. **29** (2014) 1869. doi: https://doi.org/10.1007/s00467-014-2910-8
39. *Ronco, C., Garzotto, F., Ricci, Z.,* CA. R. PE. DI. EM (Cardio–Renal Pediatric Dialysis Emergency Machine): Evolution of continuous renal replacement therapies in infants. A personal journey, Pediatr. Nephrol. **27** (2012) 1203. doi: https://doi.org/10.1007/s00467-012-2179-8
40. *Ronco, C., Garzotto, F., Brendolan, A., Zanella, M., Bellettato, M., Vedovato, S., Chiarenza, F., Ricci, Z., Goldstein, S. L.,* Continuous renal replacement therapy in neonates and small infants: Development and first-in-human use of a miniaturised machine (CARPEDIEM), Lancet **383** (2014) 1807. doi: https://doi.org/10.1016/S0140-6736(14)60799-6
41. *Coulthard, M. G., Crosier, J., Griffiths, C., Smith, J., Drinnan, M., Whitaker, M., Beckwith, R., Matthews, J. N. S., Flecknell, P., Lambert, H. J.,* Haemodialysing babies weighing< 8 kg with the Newcastle infant dialysis and ultrafiltration system (Nidus): Comparison with peritoneal and conventional haemodialysis, Pediatr. Nephrol. **29** (2014) 1873. doi: https://doi.org/10.1007/s00467-014-2923-3
42. *Askenazi, D., Ingram, D., White, S., Cramer, M., Borasino, S., Coghill, C., Dill, L., Tenney, F., Feig, D., Fathallah-Shaykh, S.,* Smaller circuits for smaller patients: Improving renal support therapy with Aquadex™, Pediatr. Nephrol. **31** (2016) 853. doi: https://doi.org/10.1007/s00467-015-3259-3
43. *Askenazi, D. J., Goldstein, S. L., Koralkar, R., Fortenberry, J., Baum, M., Hackbarth, R., Blowey, D., Bunchman, T. E., Brophy, P. D., Symons, J., Chua, A., Flores, F., Somers, M. J. G.,* Continuous renal replacement therapy for children≤ 10 kg: A report from the prospective pediatric continuous renal replacement therapy registry, J. Pediatr. **162** (2013) 587. doi: https://doi.org/10.1016/j.jpeds.2012.08.044
44. *Longmore, D. B.,* A portable artificial kidney, Lancet **276** (1960) 527. doi: https://doi.org/10.1016/S0140-6736(60)91550-6
45. *Briefel, G. R., Galonsky, R. S., Hutchisson, J. T., Hessert, R. L., Friedman, E. A.,* Field trial of compact travel dialysis system, J. Dial. **1** (1976) 57. doi: https://doi.org/10.3109/08860227609039137
46. *Roberts, M.,* The regenerative dialysis (REDY) sorbent system, Nephrology **4** (1998) 275. doi: https://doi.org/10.1111/j.1440-1797.1998.tb00359.x
47. *Agar, J. W. M.,* Review: Understanding sorbent dialysis systems, Nephrology (Carlton) **15** (2010) 406. doi: https://doi.org/10.1111/j.1440-1797.2010.01321.x
48. *Hamm, L. L., Lawrence, G., DuBose, T. D.,* Sorbent regenerative hemodialysis as a potential cause of acute hypercapnia, Kidney Int. **21** (1982) 416. doi: https://doi.org/10.1038/ki.1982.38
49. *van Gelder, M. K., Jong, J. A. W., Folkertsma, L., Guo, Y., Blüchel, C., Verhaar, M. C., Odijk, M., Van Nostrum, C. F., Hennink, W. E., Gerritsen, K. G. F.,* Urea removal strategies for dialysate regeneration in a wearable artificial kidney, Biomaterials **234** (2020) 119735. doi: https://doi.org/10.1016/j.biomaterials.2019.119735
50. *Davenport, A.,* Portable and wearable dialysis devices for the treatment of patients with end-stage kidney failure: Wishful thinking or just over the horizon? Pediatr. Nephrol. **30** (2015) 2053. doi: https://doi.org/10.1007/s00467-014-2968-3

51. *Ronco, C., Davenport, A., Gura, V.,* A wearable artificial kidney: Dream or reality?, Nat Clin Pract Nephrol. **4** (2008) 604.
doi: https://doi.org/10.1038/ncpneph0929
52. *Blaney, T. L., Lindan, O., Sparks, R. E.,* Adsorption: A step toward a wearable artificial kidney, Trans. Am. Soc. Artif. Intern. Organs. **12** (1966) 7.
53. *van Gelder, M. K., Mihaila, S. M., Jansen, J., Wester, M., Verhaar, M. C., Joles, J. A., Stamatialis, D., Masereeuw, R., Gerritsen, K. G. F.,* From portable dialysis to a bioengineered kidney, Expert Rev. Med. Devices **15** (2018) 323.
doi: https://doi.org/10.1080/17434440.2018.1462697
54. *Gura, V., Rivara, M. B., Bieber, S., Munshi, R., Smith, N. C., Linke, L., Kundzins, J., Beizai, M., Ezon, C., Kessler, L., Himmelfarb, J.,* A wearable artificial kidney for patients with end-stage renal disease, JCI Insight **1** (2016).
doi: https://doi.org/10.1172/jci.insight.86397
55. *Rosner, M. H., Ronco, C.,* Remote monitoring for the wearable artificial kidney, Contrib. Nephrol. **171** (2011) 243.
doi: https://doi.org/10.1159/000327229
56. *Rambod, E., Beizai, M., Rosenfeld, M.,* An experimental and numerical study of the flow and mass transfer in a model of the wearable artificial kidney dialyzer, Biomed. Eng. Online **9** (2010) 21.
doi: https://doi.org/10.1186/1475-925X-9-21
57. *Jovanovic, G.*, *Coblyn, M.*, *Plazl, I.*, Time scale analysis and characteristic times in microscale-based bio-chemical processes: Part II – Bioreactors with immobilized cells, and process flowsheet analysis, Chem. Eng. Sci. **236** (2021) 116499.
doi: https://doi.org/10.1016/j.ces.2021.116499
58. *Jovanovic, G., Coblyn, M., Plazl, I.*, Time scale analysis and characteristic times in microscale-based chemical and biochemical processes: Part I – Concepts and origins, Chem. Eng. Sci. **238** (2021) 116502.
doi: https://doi.org/10.1016/j.ces.2021.116502
59. *Stankiewicz*, *A. I.*, *Moulijn*, *J. A.*, Process intensification: Transforming chemical engineering, Chem. Eng. Prog. **96** (1) (2000) 22.
60. *Tuhy, A. R., Anderson, E. K., Jovanovic, G. N.,* Urea separation in flat-plate microchannel hemodialyzer; experiment and modeling, Biomed. Microdevices **14** (2012) 595.
doi: https://doi.org/10.1007/s10544-012-9638-7
61. *Coblyn, M., Truszkowska, A., Jovanovic, G.,* Characterization of microchannel hemodialyzers using residence time distribution analysis, J. Flow Chem. **6** (2016) 53.
doi: https://doi.org/10.1556/1846.2015.00041
62. *Heintz, K., Schilke, K. F., Snider, J., Lee, W. K., Truong, M., Coblyn, M., Jovanovic, G., McGuire, J.,* Preparation and evaluation of PEO-coated materials for a microchannel hemodialyzer, J. Biomed. Mater. Res. B Appl. Biomater. **102** (2014) 1014.
doi: https://doi.org/10.1002/jbm.b.33082
63. *Coblyn, M., Truszkowska, A., Mohammadi, M., Heintz, K., McGuire, J., Sharp, K., Jovanovic, G.,* Effect of PEO coating on bubble behavior within a polycarbonate microchannel array: A model for hemodialysis, J. Biomed. Mater. Res. B Appl. Biomater. **104** (2016) 941.
doi: https://doi.org/10.1002/jbm.b.33440
64. *Humes, H. D., Buffington, D., Westover, A. J., Roy, S. Fissell, W. H.,* The bioartificial kidney: Current status and future promise, Pediatr. Nephrol. **29** (2014) 343.
doi: https://doi.org/10.1007/s00467-013-2467-y
65. *Buffington, D. A., Pino, C. J., Chen, L., Westover, A. J., Hageman, G., Humes, H. D.,* Bioartificial renal epithelial cell system (brecs): A compact, cryopreservable extracorporeal renal replacement device, Cell Med. **4** (2012) 33.
doi: https://doi.org/10.3727/215517912X653328
66. *Pino, C. J., Westover, A. J., Buffington, D. A., Humes, H. D.,* Bioengineered renal cell therapy device for clinical translation, ASAIO J **63** (2017) 305.
doi: https://doi.org/10.1097/MAT.0000000000000485
67. *Jovanovic, G., Coblyn, M., Plazl, I.,* Time scale analysis & characteristic times in microscale-based bio-chemical processes; bioreactors with immobilized cells, and process flowsheet analysis, Chem. Eng. Sci. **236** (2020) 116499.
doi: https://doi.org/10.1016/j.ces.2021.116499
68. *Jovanovic, G., Coblyn, M., Plazl, I.,* Time scale analysis & characteristic times in microscale-based chemical and biochemical processes: Concepts and origins, Chem. Eng. Sci. **238** (2020) 116502.
doi: https://doi.org/10.1016/j.ces.2021.116502
69. *Liu, J., Lu, X., Shu, G., Ni, F., Li, K., Kong, X., Zheng, S., Ma, R., Li, T., Liu, H., Yang, J.,* Structure design and performance study on filtration-adsorption bifunctional blood purification membrane, J. Membr. Sci. **636** (2021) 119535.
doi: https://doi.org/10.1016/j.memsci.2021.119535.
70. *Hoare, T. R., Kohane, D. S.,* Hydrogels in drug delivery: Progress and challenges, Polymer **49** (2008) 1993.
doi: https://doi.org/10.1016/j.polymer.2008.01.027
71. *Cioci, F., Lavecchia, R.*, An innovative extracorporeal membrane system for enzyme-mediated blood purification, Chem. Eng. Sci. **51** (1996) 2823.
doi: https://doi.org/10.1016/0009-2509(96)00159-5
72. *Drost, K., Jovanovic, G., Paul, B.,* Microscale enhancement of heat and mass transfer for hydrogen energy storage (2015).
doi: https://doi.org/10.2172/1225296.
73. *Song, S., Le-Clech, P., Shen, Y.,* Microscale fluid and particle dynamics in filtration processes in water treatment: A review, Water Res. **233** (2023) 119746.
doi: https://doi.org/10.1016/j.watres.2023.119746
74. *Kim, G. D., Rundel, J. T., Paul, B. K.*, UV laser ablation of polyetherimide embossing tools for the packaging of membranes and microchannels using sealing bosses, Int. J. Precis. Eng. Manuf. **11** (2010) 665.
doi: https://doi.org/10.1007/s12541-010-0078-0
75. *Pemg, B. Y., Wu, C. W., Shen, Y. K., Lin, Y.,* Microfluidic chip fabrication using hot embossing and thermal bonding of COP, Polym. Adv. Technol. **21** (2010) 457.
doi: https://doi.org/10.1002/pat.1447
76. *McIlroy, D. N., Zhang, D., Kranov, Y., Norton, M. G.,* Nanosprings, Appl. Phys. Lett. **79** (2001) 1540.
doi: https://doi.org/10.1063/1.1400079
77. *Stephanopoulos, N., Francis, M. B.,* Choosing an effective protein bioconjugation strategy, Nat. Chem. Biol. **7** (2011) 876.
doi: https://doi.org/10.1038/nchembio.720
78. *Hosseini, S., Ibrahim, F., Djordjevic, I., Koole, L. H.,* Recent advances in surface functionalization techniques on polymethacrylate materials for optical biosensor applications, Analyst **139** (2014) 2933.
doi: https://doi.org/10.1039/c3an01789c
79. *Gaberc-Porekar, V., Menart, V.,* Perspectives of immobilized-metal affinity chromatography, J. Biochem. Biophys. Methods **49** (2001) 335.
doi: https://doi.org/10.1016/s0165-022x(01)00207-x
80. *Smith, M. C., Furman, T. C., Ingolia, T. D., Pidgeon, C.,* Chelating peptide-immobilized metal ion affinity chromatography. A new concept in affinity chromatography for recombinant proteins, J. Biol. Chem. **263** (1988) 7211.
doi: https://doi.org/10.1016/S0021-9258(18)68629-6

81. *Yip, T. T., Hutchens, T. W.,* Immobilized metal ion affinity chromatography, Methods Mol. Biol. **11** (1992) 17. doi: https://doi.org/10.1385/0-89603-213-2:17

82. *Datta, S., Christena, L. R., Rajaram, Y. R. S.,* Enzyme immobilization: An overview on techniques and support materials, 3 Biotech **3** (2013) 1. doi: https://doi.org/10.1007/s13205-012-0071-7

83. *Mohamad, N. R., Marzuki, N. H. C., Buang, N. A., Huyop, F., Wahab, R. A.,* An overview of technologies for immobilization of enzymes and surface analysis techniques for immobilized enzymes, Biotechnol. Biotechnol. Equip. **29** (2015) 205. doi: https://doi.org/10.1080/13102818.2015.1008192