Comprehensive Multiscale Computational Model of Fluid and Species Transport in Hollow Fiber Membranes

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Abstract

Background: In a previous presentation at this conference, we presented a computational model of simple fluid and single-solute transport in a finite element model of a hollow fiber hemofilter. This model has undergone extensive additional development to include the following capabilities: 1) fluid transport in blood, membrane and dialysate phases, 2) influence of plasma oncotic pressure and concentration polarization on ultrafiltration, 3) transport of charged and uncharged protein fractions, 4) transport of all major electrolytes with constraint of electroneutrality including transmembrane protein charge difference, 5) protein binding of calcium, 6) acid-base equilibrium, 7) citrate and calcium kinetics during regional anticoagulation, 8) body compartment volume and electrolytes, 8) heat transport, 9) restricted convection due large molecular weights, and 10) membrane electrical potential due to membrane charge density.
Model Description: The multiscale model consists of an axisymmetric finite element model of an AN-69 hollow fiber consisting of blood, membrane and dialysate phases incorporating the physics described above. Boundary conditions were blood inflow velocity and outflow pressure, dialysate inflow velocity and outflow velocity or pressure, concentrations of all chemical species at blood and dialysate inlets, and temperature of blood and dialysate. This spatially distributed model was coupled to well-mixed volume-varying reactors representing body compartments (blood, interstitial, and intracellular fluid). The blood inlet of the hollow fiber received the output of the body blood compartment, and the blood outlet of the hollow fiber was fed as an inlet to the body blood compartment. Additional inlet conditions included calcium chloride and sodium citrate infusions. Chemical equilibrium reactions were included that represented acid-base balance, calcium binding to citrate, and calcium binding to protein.
Validation: Validation of ultrafiltration rate was performed against data published for the AN-69 membrane, with excellent agreement. Validation for sodium transport was validated against two clinical cases of hypertonic saline dialysis for controlled hypernatremia following brain injury. Validation of other model components is currently being conducted.
Summary: This comprehensive multiscale model can simulate multiple transport processes simultaneously, providing insight into fluid and species handling during hemofiltration and hemodialysis.

Introduction

Previous mathematical models of hemofilter fluid and solute transport have typically employed lumped compartmental representations of hemofilter phases with uniform membrane processes, with numerous assumptions for analytical efficiency. These models often did not adequately address regional variations in membrane transport, convection-diffusion interaction, and region-dependent processes such as backfiltration. These influences are of particular importance in therapies such as high-volume hemofiltration. In order to overcome these limitations, a comprehensive multiscale model of hollow fiber membrane and body compartment transport that incorporates both momentum and mass transport was developed.

Methods and Materials

A finite element model based on the AN69 hollow fiber membrane used in the M60 hemofilter was developed in COMSOL Multiphysics 6.0. A 2D axisymmetric geometry with blood, membrane and dialysate domains were meshed with quadrilateral elements, with a 1 µm thick boundary layer mesh at the blood-membrane boundary. Fluid flow was determined in blood and dialysate domains using the Navier-Stokes (NS) partial differential equations. The blood phase was modeled as a non-Newtonian fluid with density and viscosity calculated from plasma protein concentration and hematocrit. The dialysate phase was modeled as a Newtonian fluid. The membrane was modeled as a porous medium using the Brinkman equations coupled to the NS equations at membrane boundaries. The Fåhræus–Lindqvist effect on blood viscosity is included. Heat transport was also included, along with temperature-dependence of physical parameters. Species transport was modeled with the convection-diffusion equation

Species included in the blood phase include albumin, globulin, urea, creatinine, sodium, potassium, calcium, magnesium, chloride, bicarbonate, hydrogen ion, carbonic acid, and unmeasured ions. Also included were trisodium citrate and calcium citrate. Equilibrium reactions were set up for acid-base balance and citrate. The same electrolytes and solutes were included in the membrane and dialysate phases except for the protein fractions. Electroneutrality was enforced within each domain.

Boundary conditions included hollow fiber inlet blood flow, blood outlet pressure, dialysate flow and pressure, and inlet concentrations of all species. Ultrafiltration, hemofiltration, hemodialysis, and hemodiafiltration can be simulated. A wall condition was imposed on the dialysate inlet when pure ultrafiltration was being modeled.

Extracellular and intracellular variable volume compartments based on ordinary differential equations were included in the model that provided for citrate metabolism and carbon dioxide generation as well as electrolyte balance outside of the hemofilter.

Model parameters were based on published values. The diffusion coefficient of plasma protein has not been reported, as it is a mixture of different sized proteins. It was determined by an optimization procedure based on published ultrafiltration rates by the M60 manufacturer.

The model can be solved for steady-state conditions, or in a time-dependent manner to investigate the impact of renal replacement therapy on total body electrolytes and solutes.

Results

Sensitivity analysis revealed that ultrafiltration behavior was influenced most by the protein diffusion coefficient. Since plasma protein is a mixture of different sized proteins and therefore variable diffusion coefficients, an effective diffusion coefficient was obtained through SNOPT optimization against published ultrafiltration data and found to be 3.79x10-11 m2/s, about half that of albumin. The behavior of ultrafiltration can be largely explained by the osmotic pressure generated by protein during protein concentration (Figure 1) at clinically relevant UF rates. Membrane fouling may play a role at very high UF rates but is not included in this model.

Modeling of serum sodium following introduction of hypernatremic replacement fluid for targeted sodium management in the management of intracranial hypertension is shown in Figure 2. The model provides reasonable agreement over time, but data points are limited.

Enforcing the electroneutrality condition on electrolytes and protein, including the presence of an osmotic gradient due to protein in blood and the non-equilibrium conditions of hemofiltration demonstrates the concentration differential across the blood-membrane interface, representing a non-steady state condition of the Gibbs-Donnan effect(Figure 3).

Incorporation of chemical reactions permits the study of Ca dynamics in the hemofilter. Figure 4 shows ionized calcium concentrations during citrate anticoagulation during CVVD with calcium-free dialysate, while Figure 5 shows the same prescription with 2.5 mmol/L calcium in the fluid, with predicted post-filter Ca++ concentrations of 0.43 and 0.51 mmol/L, respectively.

Blood bicarbonate concentration during 32 mEq/L concentration bicarbonate-containing dialysate and effect on blood concentration is shown in Figure 6.

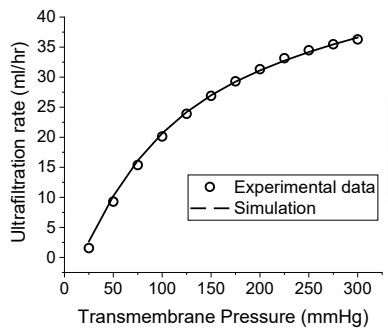

Figure 1. Ultrafiltration optimization against manufacturer's data

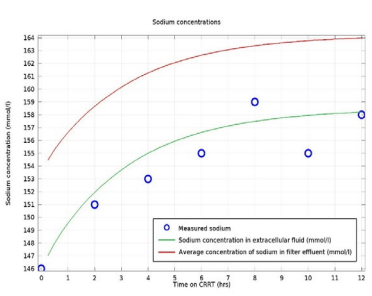

Figure 2. Serum sodium simulation with CVVH with hypertonic replacement fluid

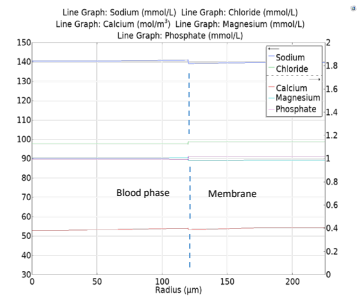

Figure 3. Electrolyte concentrations across the blood-membrane interface

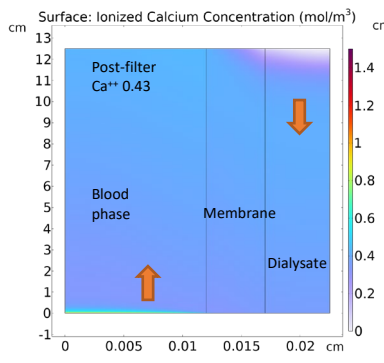

Figure 4. Ionized Ca concentrations with Ca-free dialysate (Inlet Ca++ 1.5, Q_B 100 ml/min, Q_D 2000 mL/hr)

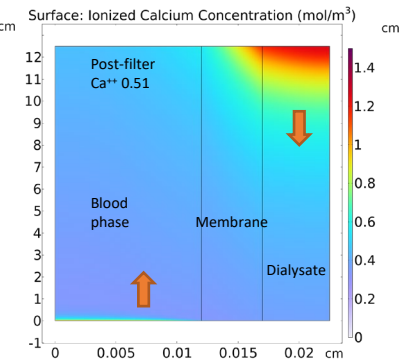

Figure 5. Ionized Ca concentrations with 2.5 mEq/L Ca dialysate (Inlet Ca++ 1.5, Q_B 100 ml/min, Q_D 2000 mL/hr)

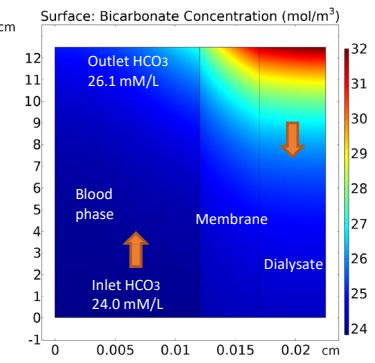

Figure 6. Bicarbonate concentrations with 32 mEq/L Ca dialysate (Inlet HCO_3 24, Q_B 100 ml/min, Q_D 2000 mL/hr)

Discussion

This comprehensive multiscale computational model can simulate steady state conditions in hemofilter membranes that include fluid balance, electrolyte, protein and non-ionic species transport, oncotic pressure, metabolism and chemical reactions (currently acid-base balance and citrate), and heat transport. By incorporating ordinary differential equations representing body compartments coupled to the finite element model, the temporal effect of renal replacement therapy on blood and extracellular fluid concentrations and volume can be determined. Presently, validation of the model is limited to ultrafiltration, and sodium and calcium transport. Further validation studies are planned.

Conclusions

A multiscale computational model that couples finite element analysis of fluid and species reactions and transport in hollow fiber membranes with traditional compartment analysis allows investigation of all relevant factors involved in hemofilter/hemodialyzer function.