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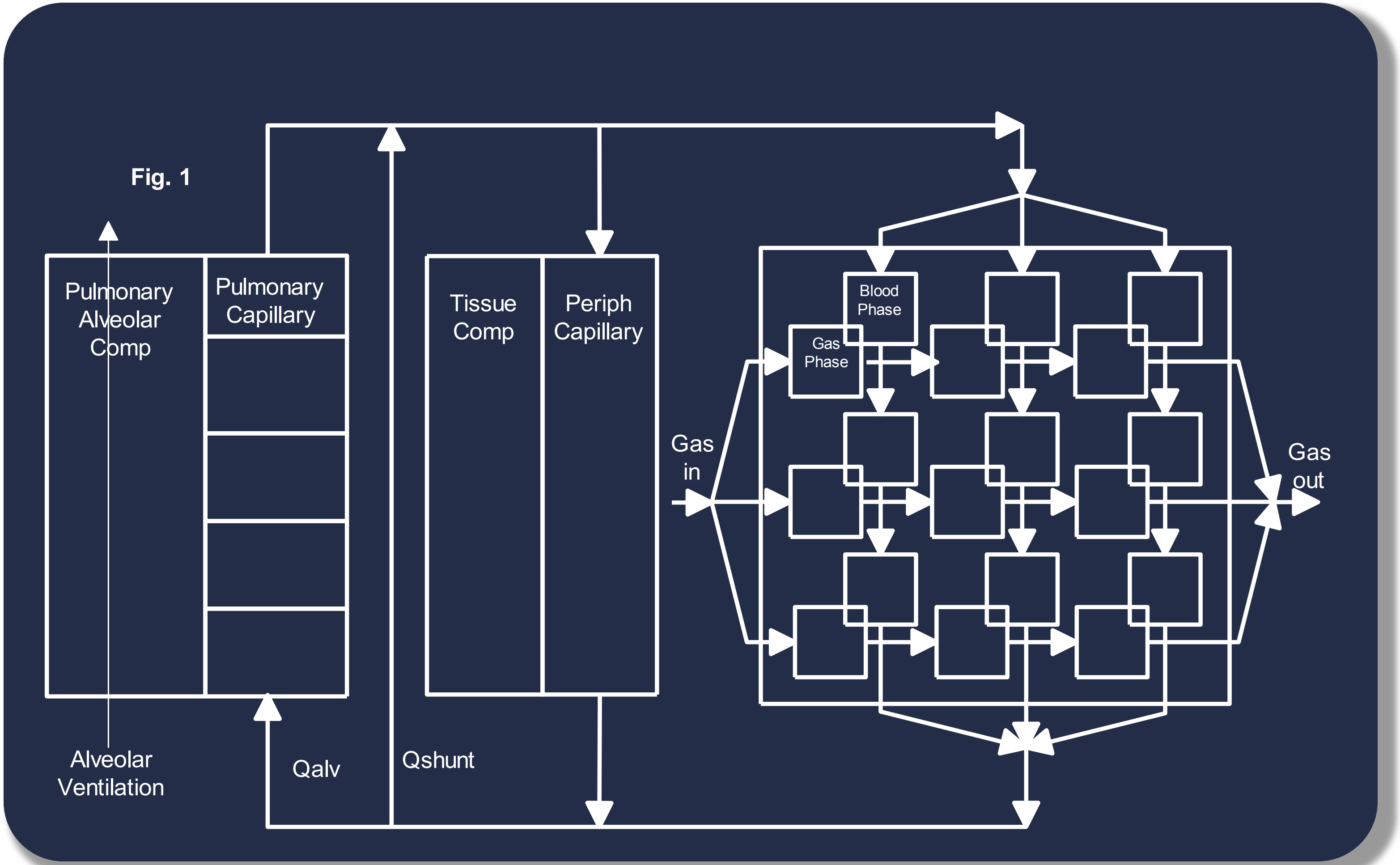
Advanced simulation in medicine and biology: Opportunities for multiphysics modeling

Steven Conrad, MD PhD
Louisiana State University Health Sciences Center
Shreveport, LA

'Traditional' modeling approaches in medicine and biology

- ODE-based lumped compartmental models
  - Mass transport in artificial organs / body systems / intracellular
  - Chemical reactions involving fluids and electrolytes
  - Heat transport in the body
  - Electrostatic discharge from the body
  - …
- Limitations
  - Many underlying assumptions
  - Constrained to specific operating conditions

Arteriovenous carbon dioxide removal model schematic



Mathematical model description

$$Q_{alv} = \int_0^t \left[D_L CO_2 \cdot \frac{\partial PCO_2}{\partial x} - C_{alv} CO_2 \cdot V_E \right] dt$$

$$Q_{pul_i} = \int_0^t \left[\left(C_{pul} CO_{2_{i-1}} - C_{pul} CO_{2_i} \right) \cdot F_{pul_i} - D_L CO_2 \cdot \frac{\partial PCO_2}{\partial x} \right] dt$$

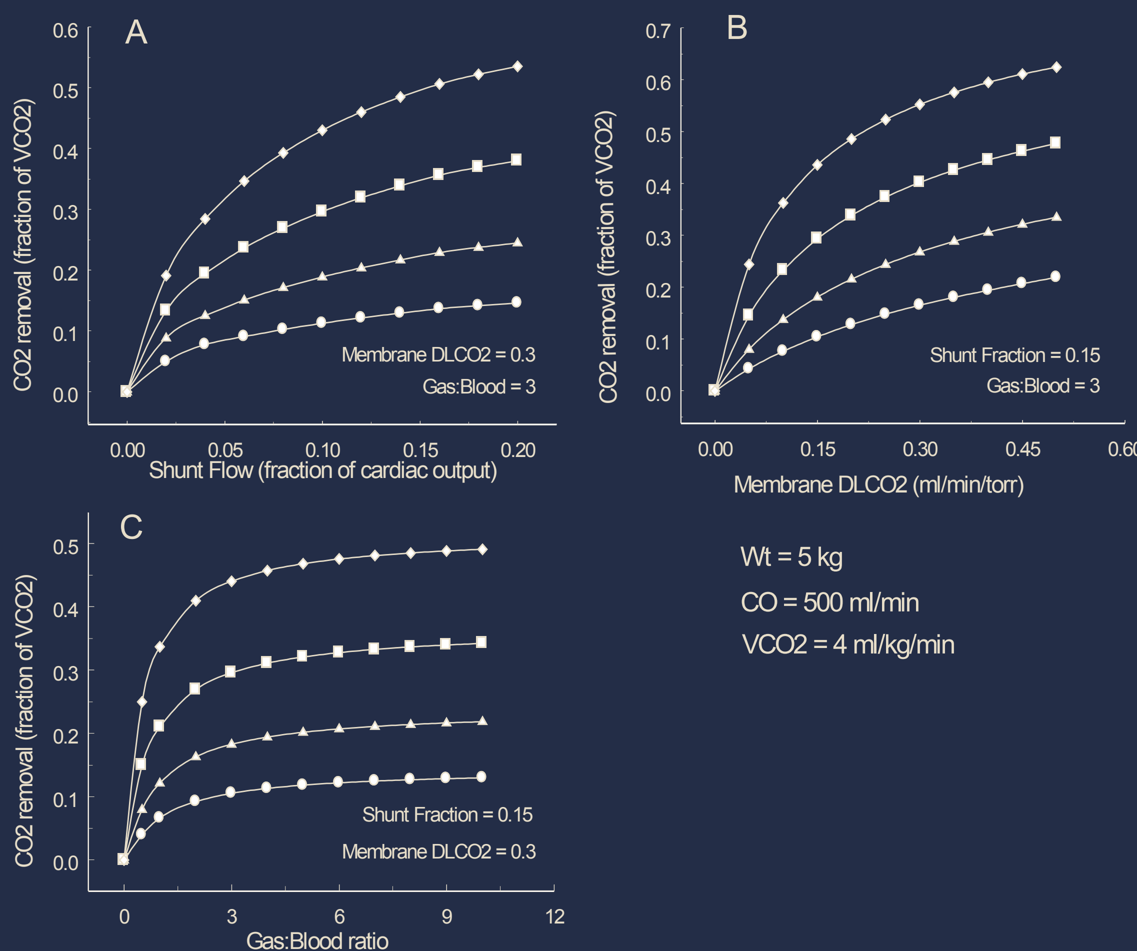
$$Q_{tis} = \int_0^t \left[VCO_2 - D_T CO_2 \cdot \frac{\partial PCO_2}{\partial x} \right] dt$$

$$Q_{cap} = \int_0^t \left[\left(C_{art} CO_2 - C_{ven} CO_2 \right) \cdot F_{cap} + D_T CO_2 \cdot \frac{\partial PCO_2}{\partial x} \right] dt$$

$$Q_{bld_{i,j}} = \int_0^t \left| \left(C_{art} CO_2 - C_{dev} CO_2 \right)_{i,j} \cdot \frac{F_{dev_{i,j}}}{n_b} - \frac{D_D CO_2}{n_b \cdot n_g} \cdot \frac{\partial PCO_{2_{i,j}}}{\partial x} \right| dt$$

$$Q_{gas_{i,j}} = \int_0^t \left| \left(C_{in} CO_2 - C_{out} CO_2 \right)_{i,j} \cdot \frac{F_{gas_{i,j}}}{n_g} + \frac{D_D CO_2}{n_b \cdot n_g} \cdot \frac{\partial PCO_{2_{i,j}}}{\partial x} \right| dt$$

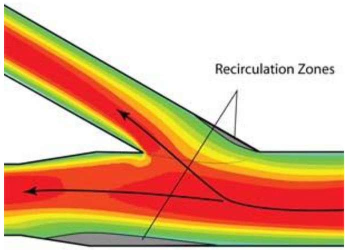
Carbon dioxide removal simulations

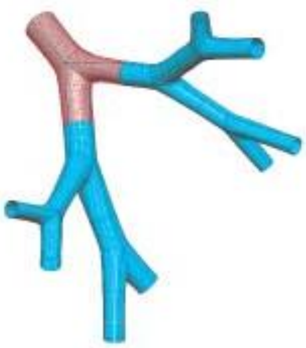


Clinical application

Recent modeling approaches in medicine and biology

- Single physics finite element analysis
  - CFD of blood flow in blood vessels and pumps
  - CFD of gas transport in the lungs
  - Heat transport in organs
  - Fluid-structure interaction in the brain
  - Musculoskeletal stress and strain
- Highly focused studies





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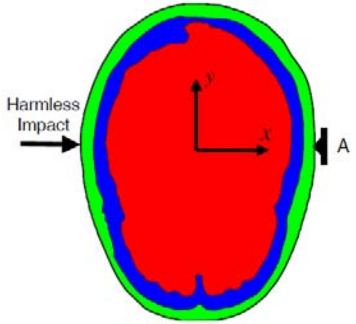
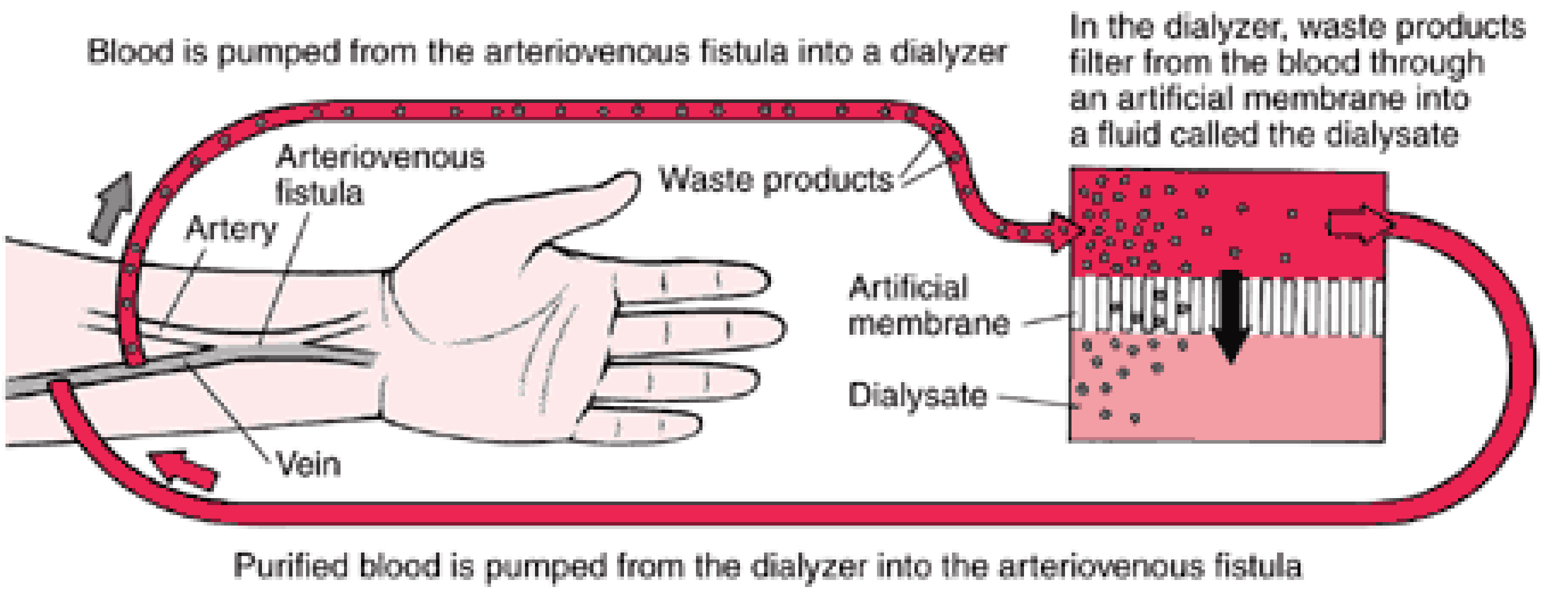
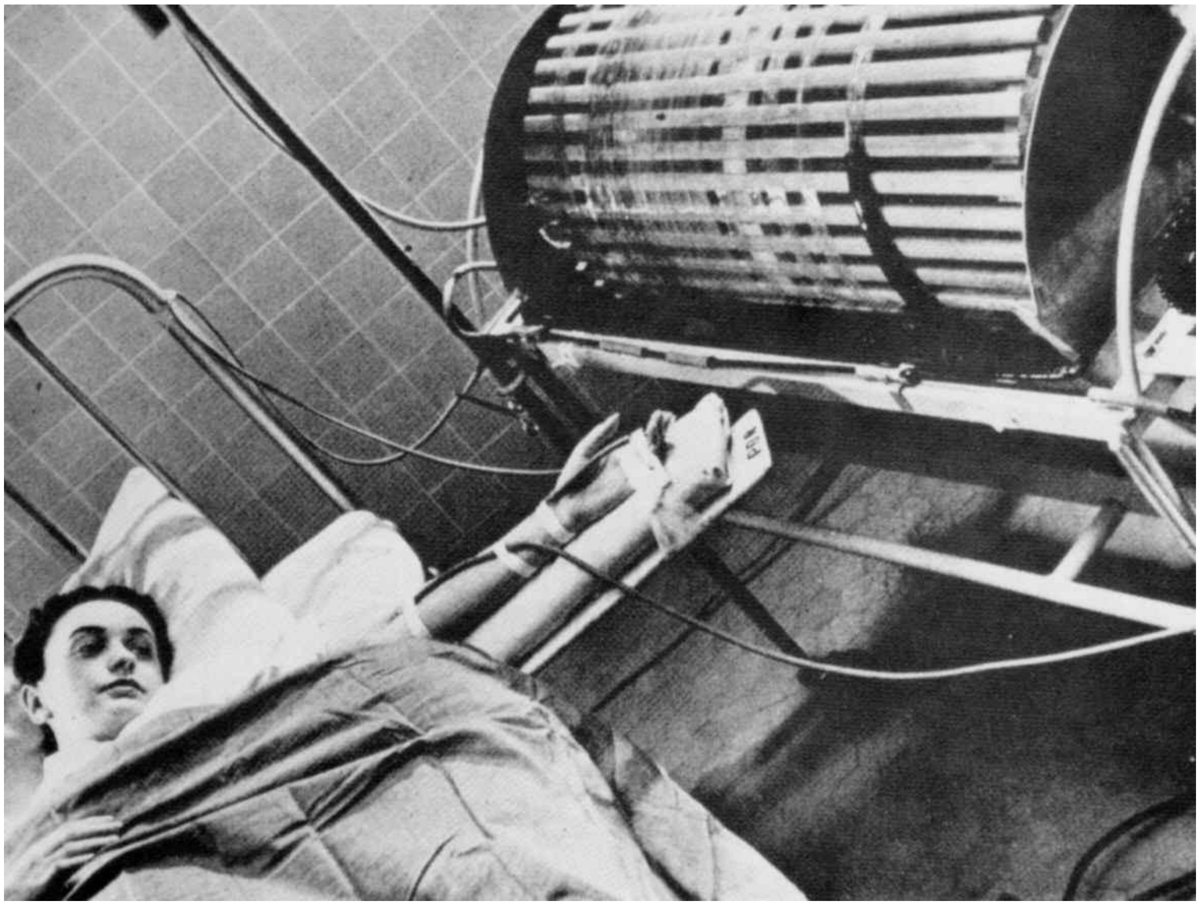


Artificial kidney



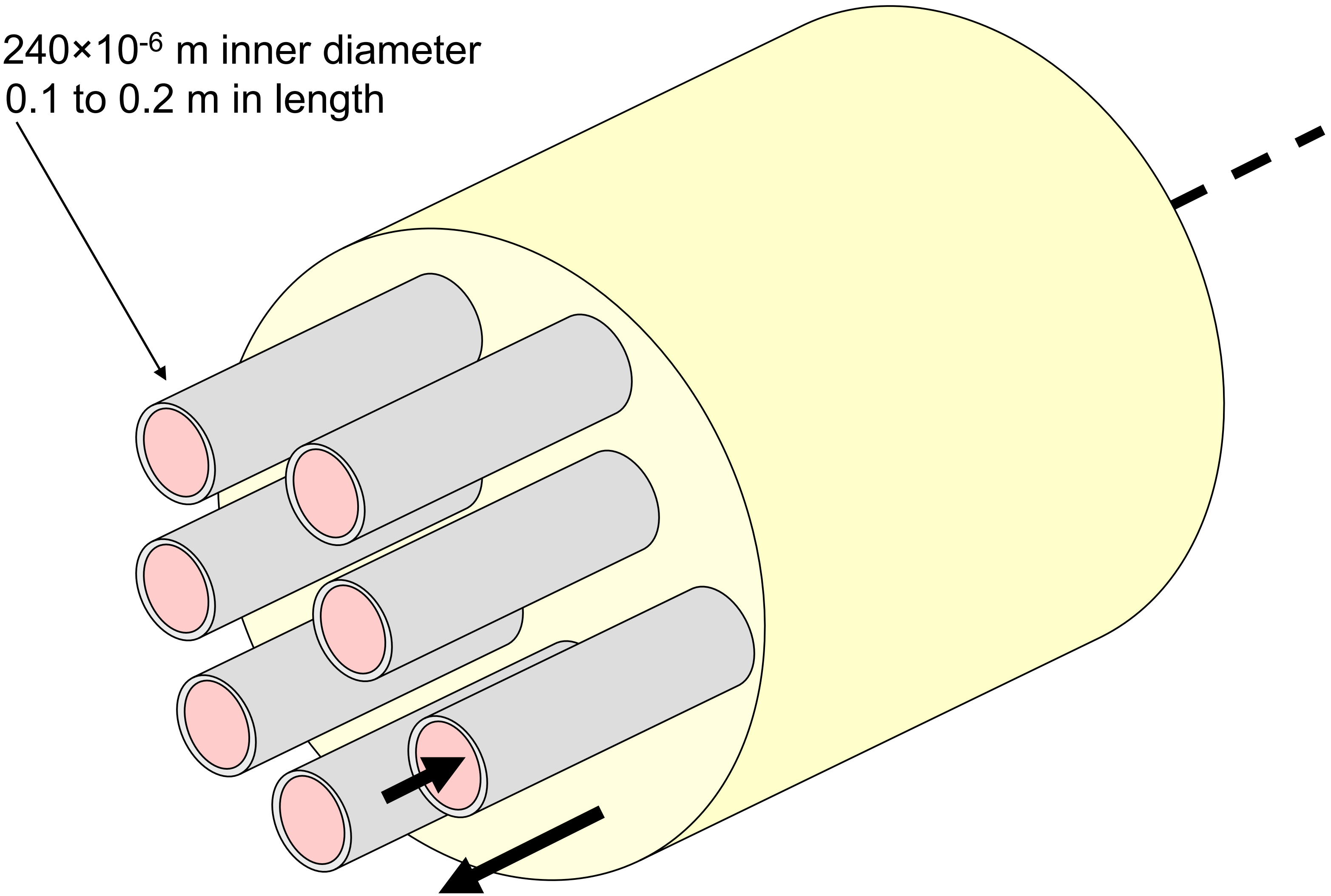
Hemodialysis

Dialysis membrane technologies



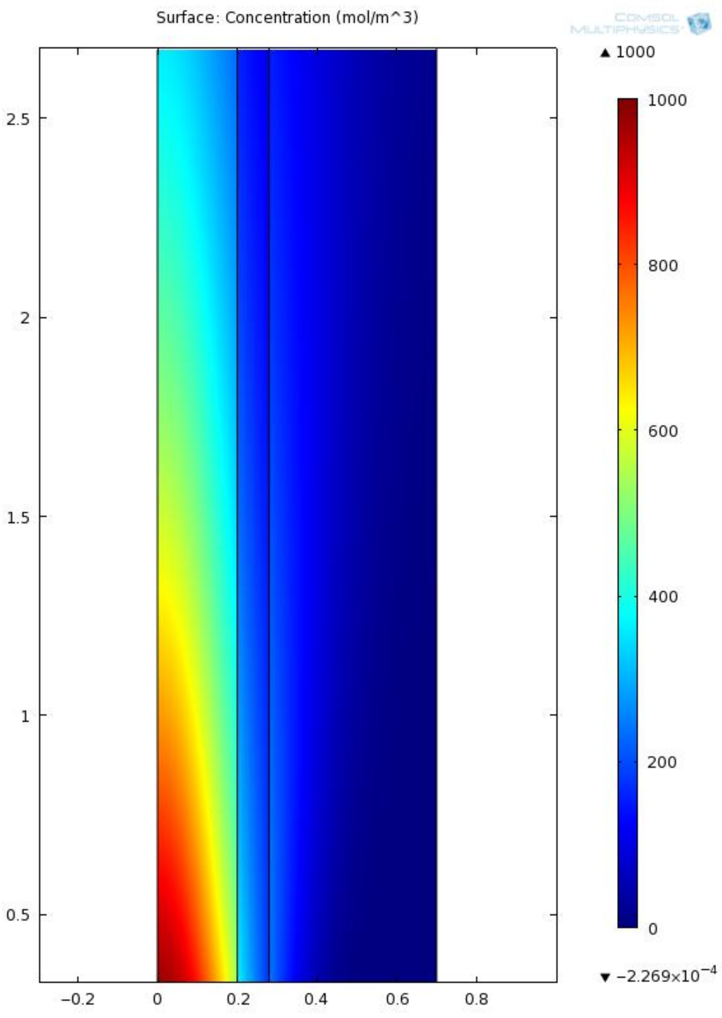
Hemodiafilter Design

HF: 240×10^{-6} m inner diameter
0.1 to 0.2 m in length



COMSOL example – separation through dialysis

- COMSOL model library
- Axisymmetric hollow fiber geometry
- Solute transport through the membrane by diffusion



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Diffusive vs. convective transport

- Hemodialysis (traditional)
  - Focus on diffusive transport
  - Lower porosity membranes
  - Removal of small, readily diffusible solutes thought solely responsible for toxicity of renal failure
- Hemofiltration
  - Focus on convective transport
  - Higher porosity membranes
  - Removal also of larger solutes ('middle molecules') now known to contribute to toxicity of renal failure
- Combined therapies now common

Governing principles for modeling

- Small channel blood flow (r ≈ 120 μm)
  - Applied flows/pressures to blood side
  - Non-Newtonian properties of blood
    - *Blood viscosity varies*
  - Hemoconcentration
    - *Axial alterations in blood density and viscosity*
  - Blood cell skimming behavior (Fahraeus-Lindqvist)
    - *Radial alterations in blood density and viscosity*
- Presence of proteins in blood phase
  - *Influence convection from osmotic pressure*
  - *Additional axial alterations in density, viscosity and osmotic pressure*

Governing principles for modeling

- Solute characteristics
  - *Partitioning between plasma and red blood cell*
  - *Partial solute rejection at membrane surface*
- Membrane factors
  - *Interaction of convective and diffusive transport*
  - *Concentration polarization of blood cells, protein and partially reflected smaller molecules*
  - *Interaction of hydraulic pressure and osmotic effects to produce forward filtration and backfiltration*

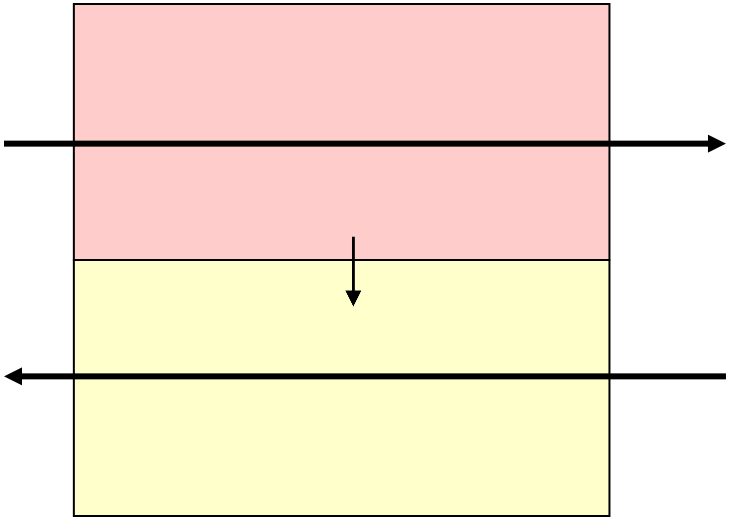
Governing principles for modeling

- Dialysate factors
  - *Applied fluid flows and pressures*
  - *Concentration of solutes in dialysate*
- Dialysate has cooler temperatures than blood
  - *Heat loss to environment*
  - *Temperature dependence of blood density and viscosity*
- Ionic charge on proteins and some solutes
  - *Protein rejection at membrane*
  - *Impairment of solute transport across membrane*

Previous mathematical models

- Single compartment models
- Multiple compartment models
- One-dimensional computational models
- Two/three-dimensional computational model
  - Finite element analysis

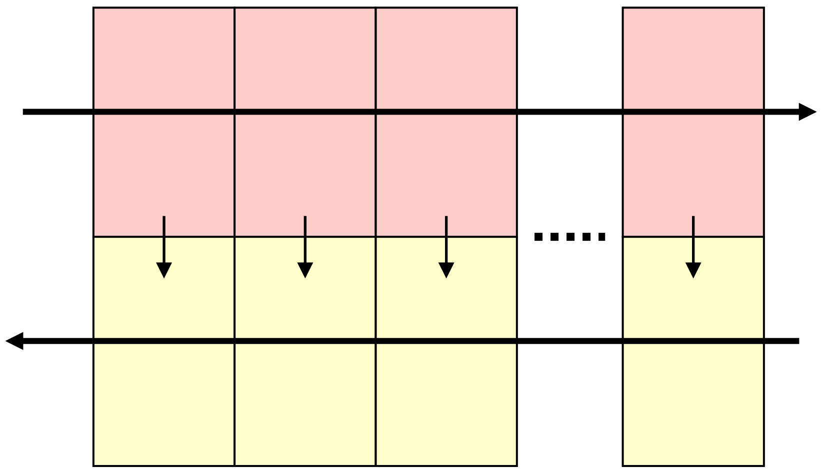
Single compartment analytical model



Pallone TL: *Kidney Int* 1988;33:685-98
Pallone TL: *Kidney Int* 1989;35:125-133

- Single blood and dialysate mass balance compartments
- Used a length-averaged mass transfer coefficient for solutes
  - Dependent upon operating conditions
- Overestimated filtration rate vs. experimental data
  - Could not account for concentration polarization or membrane rejection
- Unable to account for processes such as backfiltration

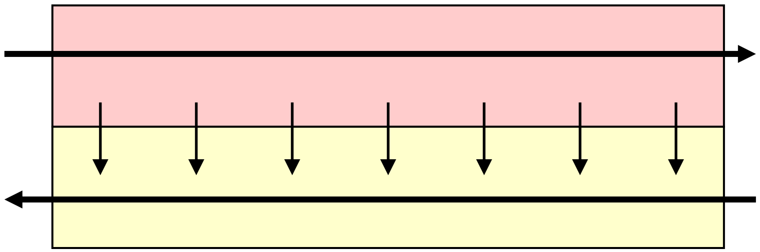
Multiple compartment analytical model



- Accounted for local fluid balance changes (axially only)
  - Pressure drops
  - Viscosity
  - Osmotic effects
- Addressed fluid fluxes only
  - Did not include convective or diffusive solute transport
- Described backfiltration not possible in simpler models
- Does not account for radial effects
  - Concentration polarization

Fiore GB: *Contrib Nephrol* 2005;149:27-34

One-dimensional computational models



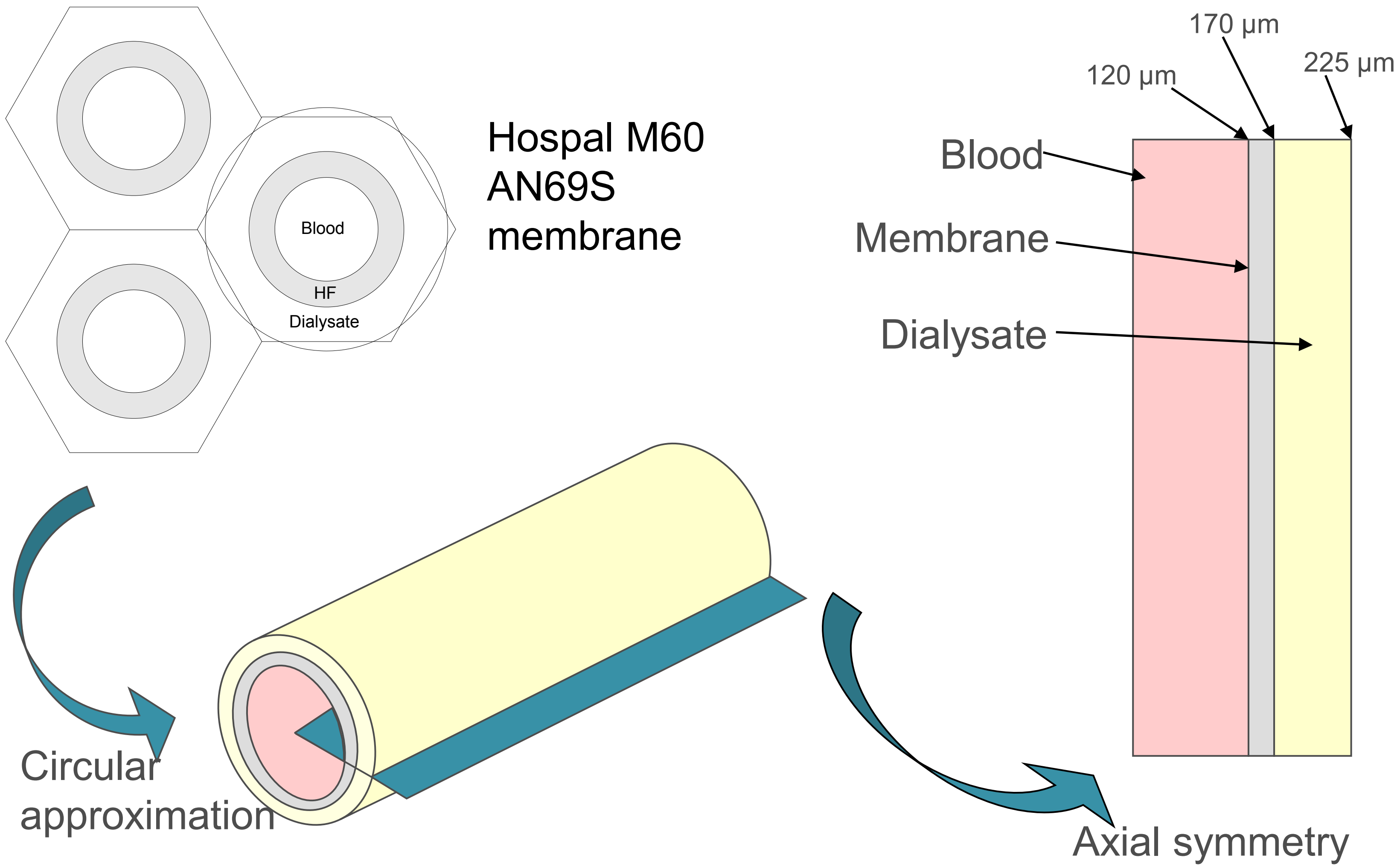
Legallis C: *J Membr Sci* 2000;168:3-15
Raff M: *J Membr Sci* 2003;216:1-11

- Ordinary differential equations solved numerically along the axis
  - Included local viscosity, osmotic pressure, etc.
- Include solute transport with convection-diffusion interaction
  - Formulas of Zydney (extension of Villarroel)
  - Flat membrane
- Included approximations of boundary layer effect on mass transfer coefficient
  - Able to account for concentration polarization

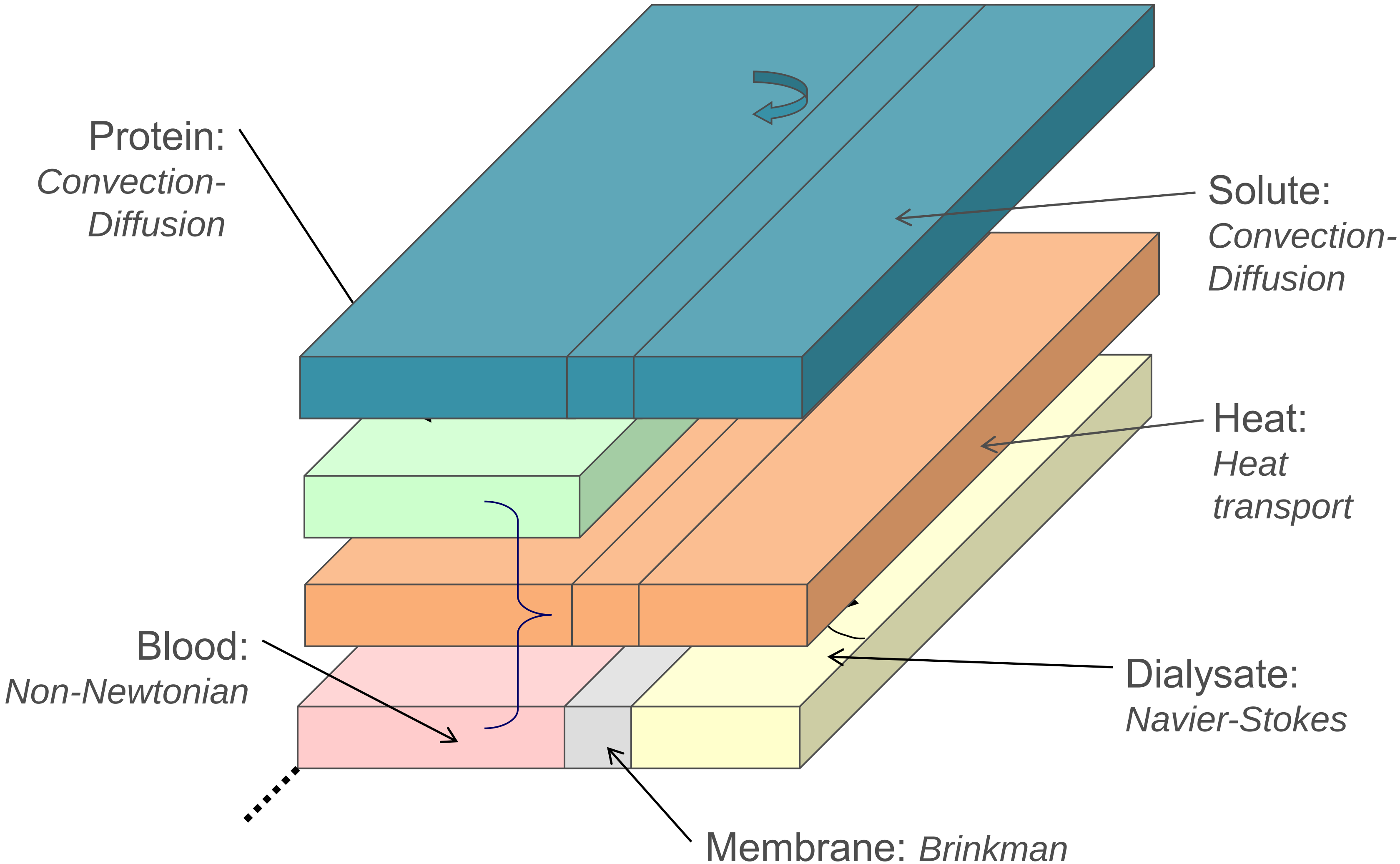
Limitations of previous models

- Simplifying assumptions
  - Overall mass transfer coefficients
  - Approximations to boundary conditions
- Geometrically naïve
  - Single compartments naïve to axis and radius
  - Multiple compartments naïve to radius, and approximate axial conditions
  - One dimensional computational models approximate radial conditions
  - Membranes modeled as boundaries only
- Biased estimates of convection-diffusion interaction
  - Ignored in previous models
  - Based on older flat membrane analysis in advanced models
    - Model geometry based on hollow fiber membranes

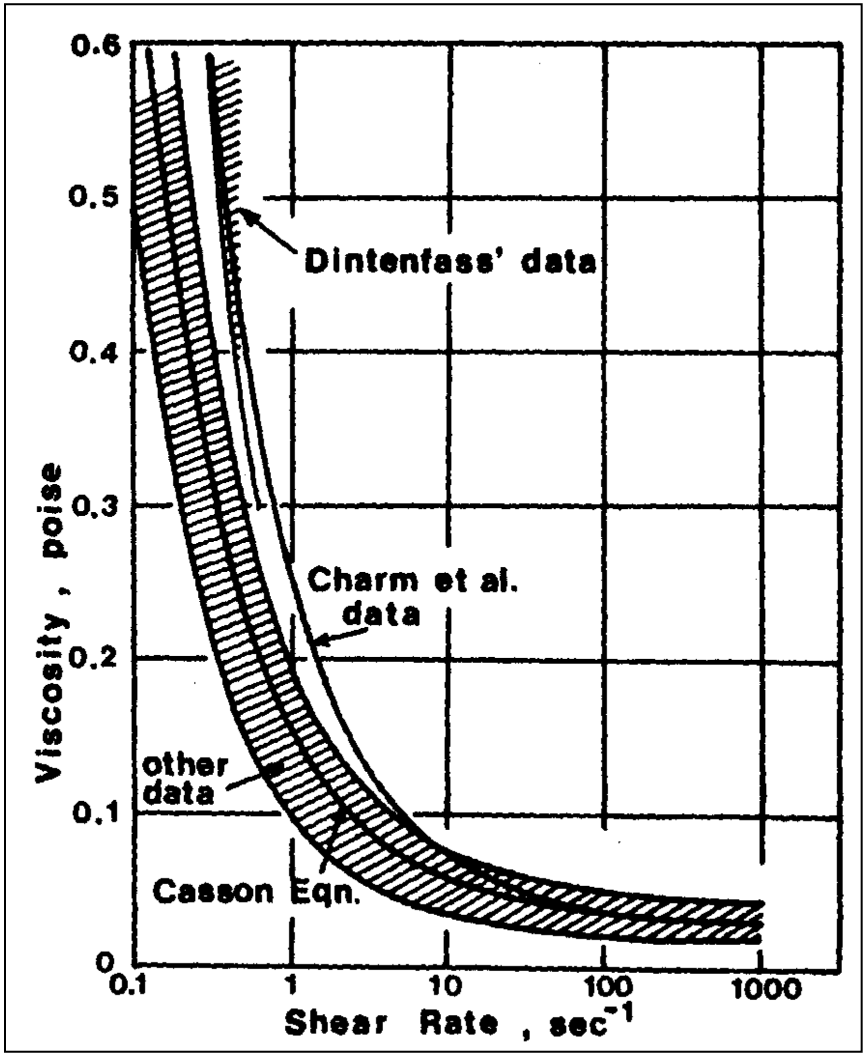
Hollow Fiber Geometry Modeling



COMSOL Application Modes



Non-Newtonian Blood Flow



Carreau equation:

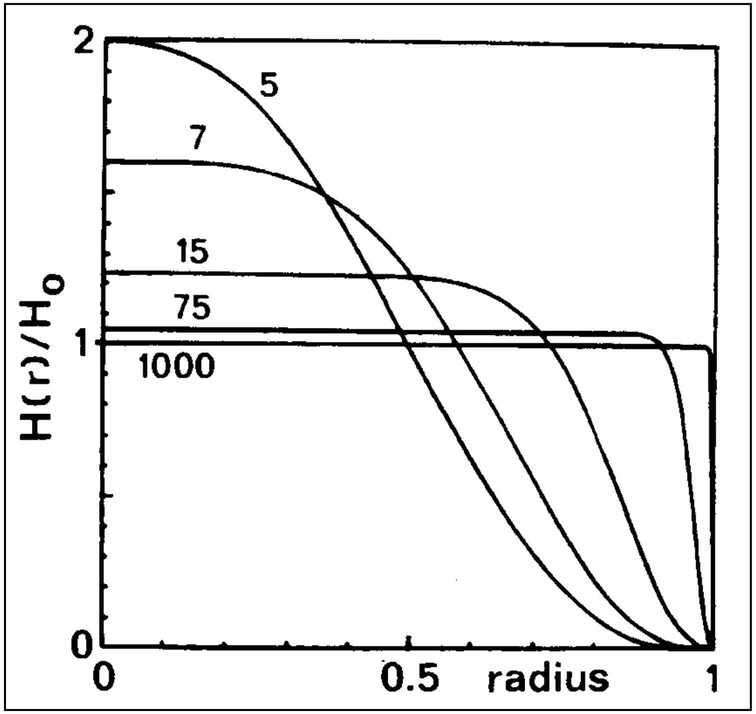
$$\mu = \mu_{\infty} + (\mu_0 - \mu_{inf})[1 + (\lambda\dot{\gamma})^2]^{\frac{(n-1)}{2}}$$

Fahraeus-Lindqvist Effect

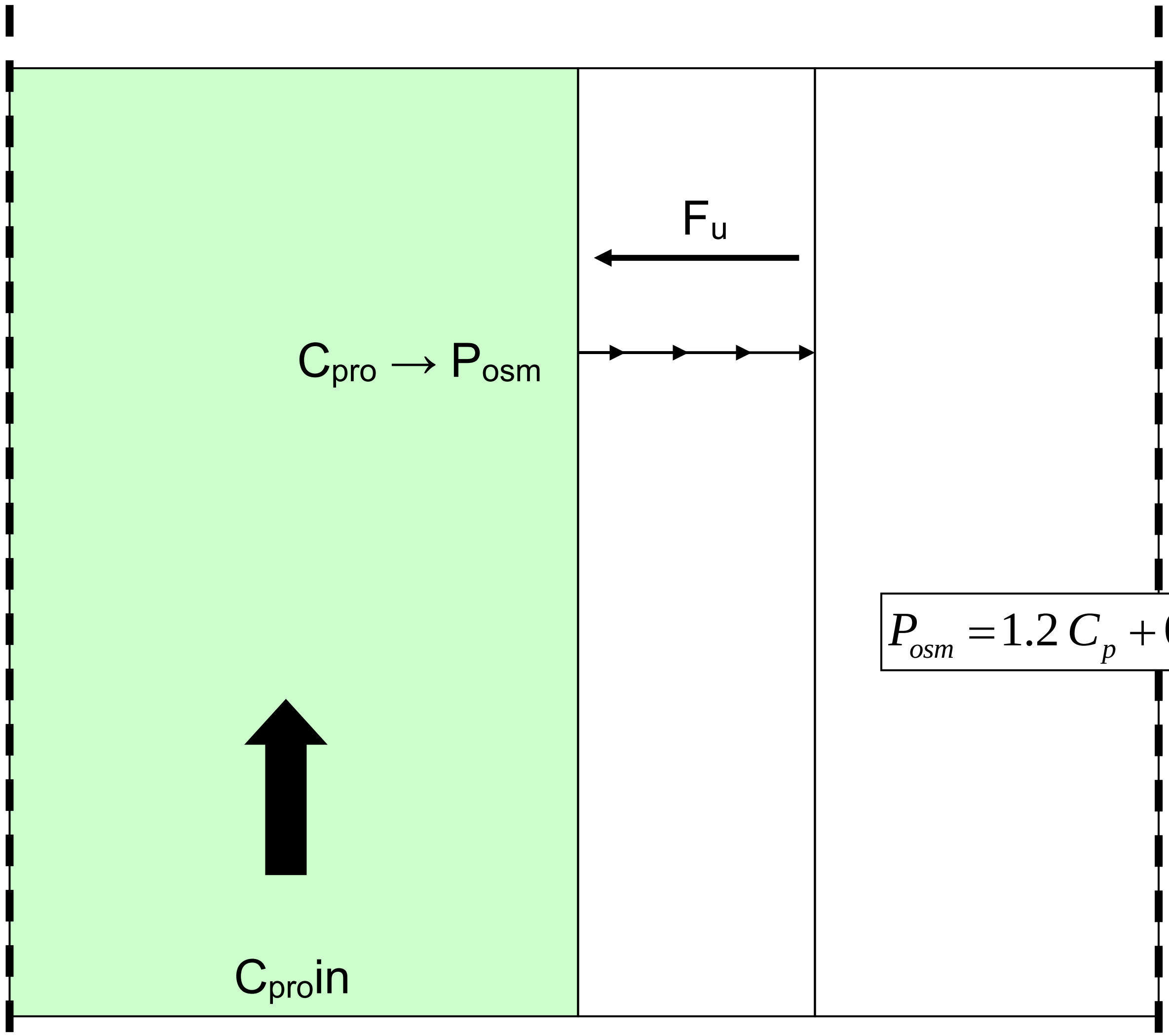
$$H(r) = -H\,\frac{n(n+1)(n-1)}{2}\left[\frac{r^n}{n} - \frac{2r^{n-1}}{n-1} + \frac{r^{n-2}}{n-2} - \frac{2}{n(n-1)(n-2)}\right]$$

where

$$n = 17.3 + \frac{11.1}{H - .206}$$

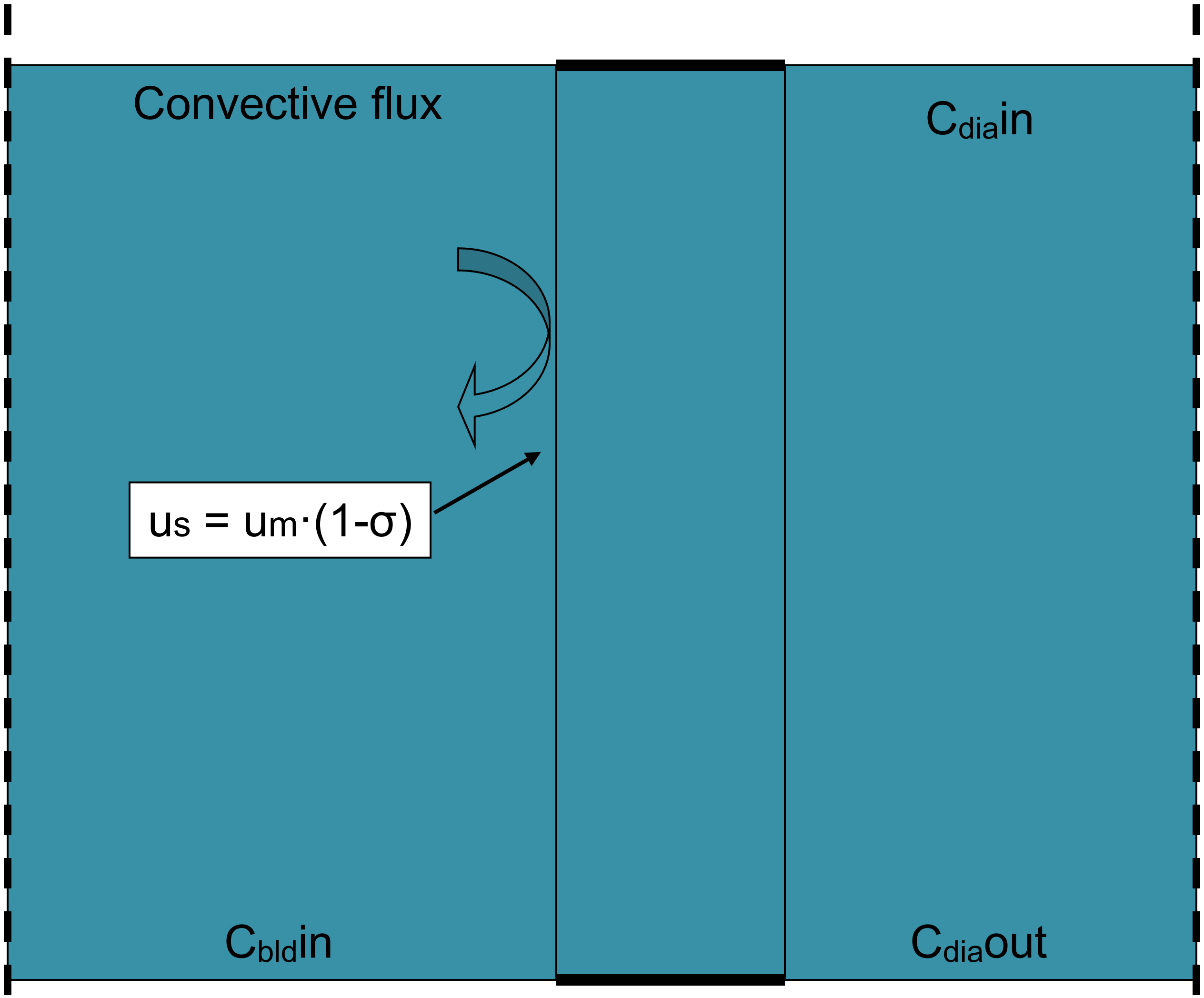


Colloid Osmotic Pressure

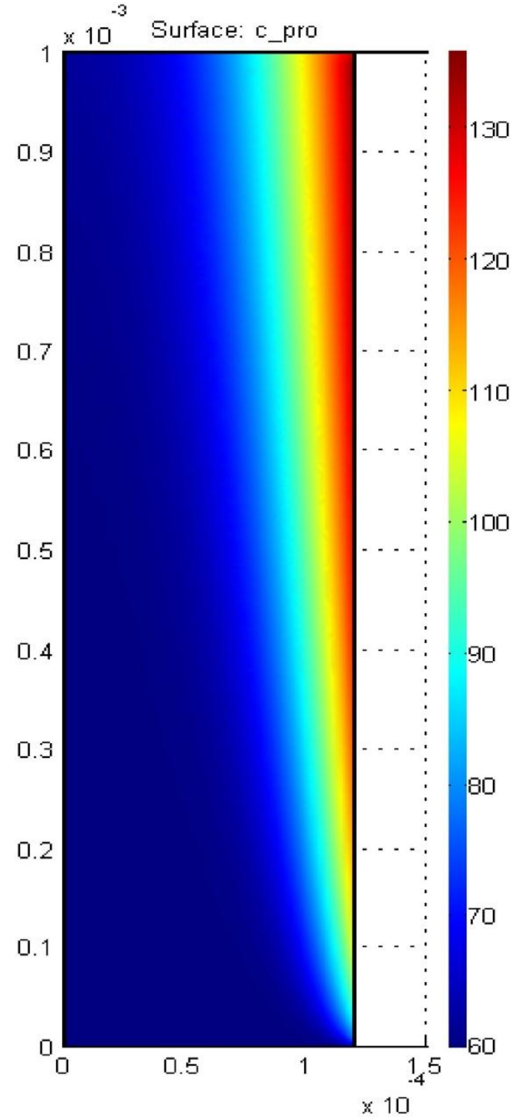


$$P_{osm} = 1.2\,C_p + 0.16\,C_p^{\,2} + 0.009\,C_p^{\,3}$$

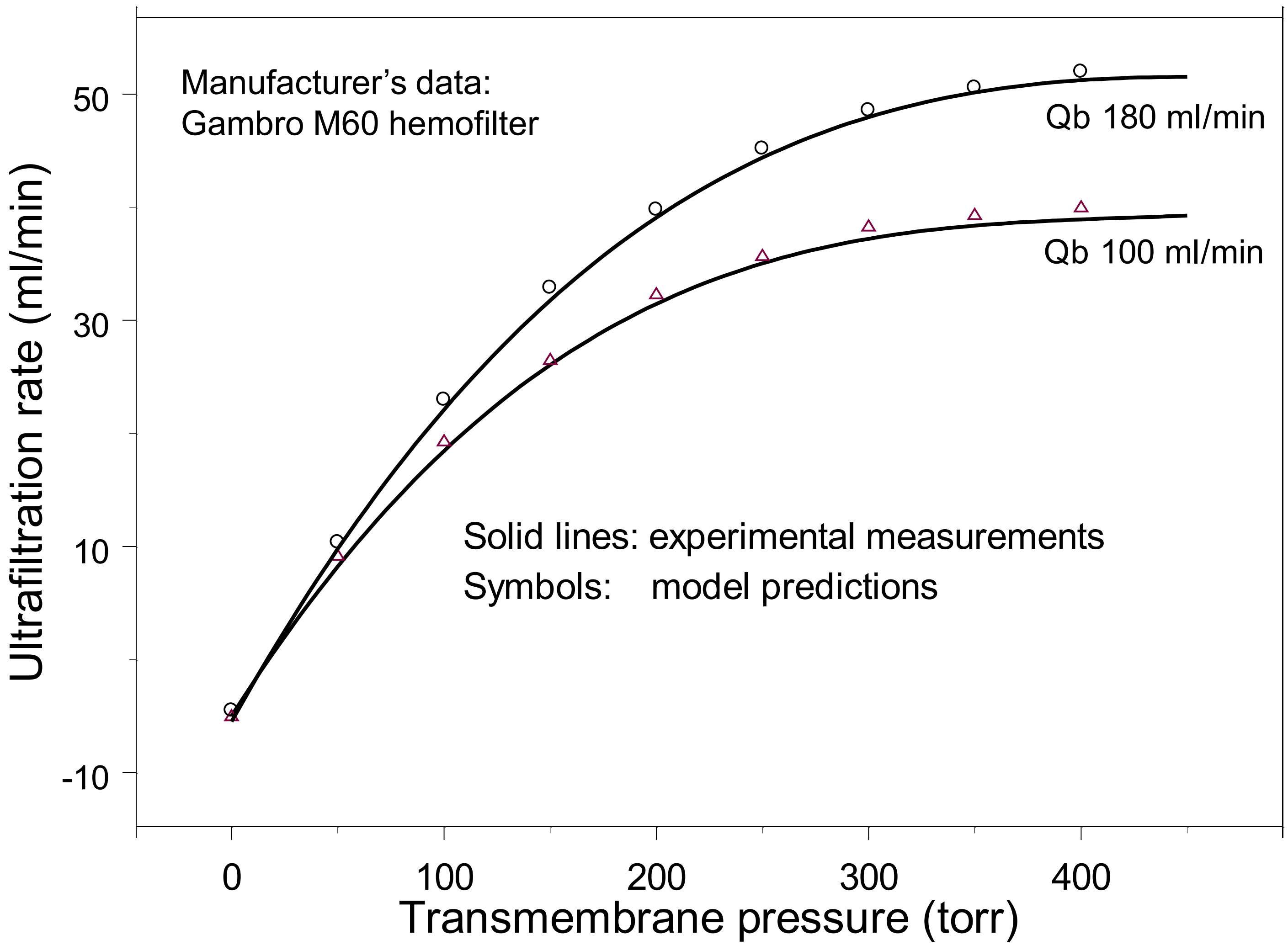
Solute reflection



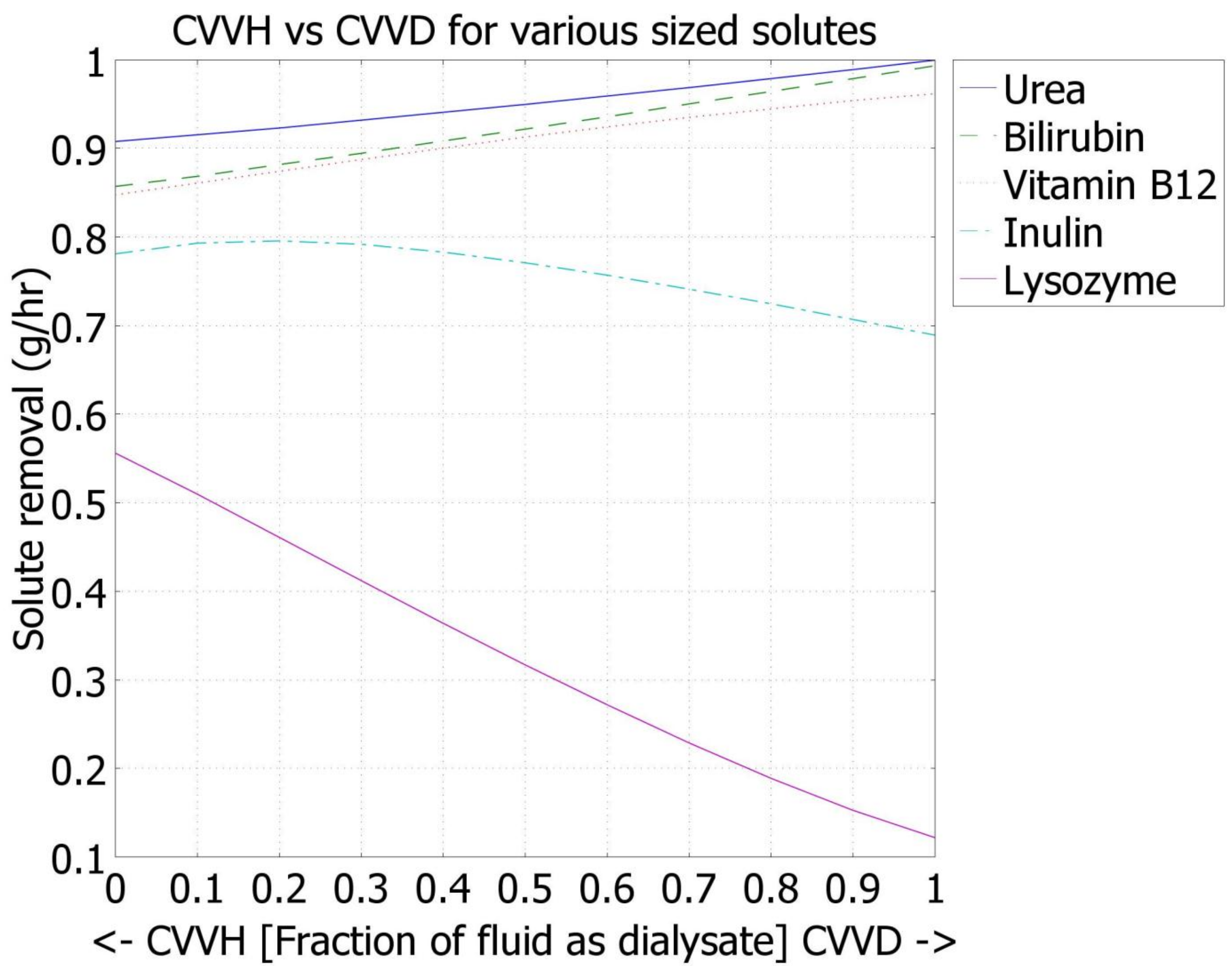
Protein concentration in blood phase



Ultrafiltration rate validation

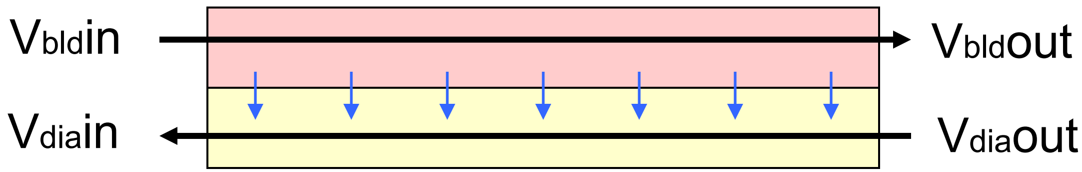


Hemofiltration vs dialysis



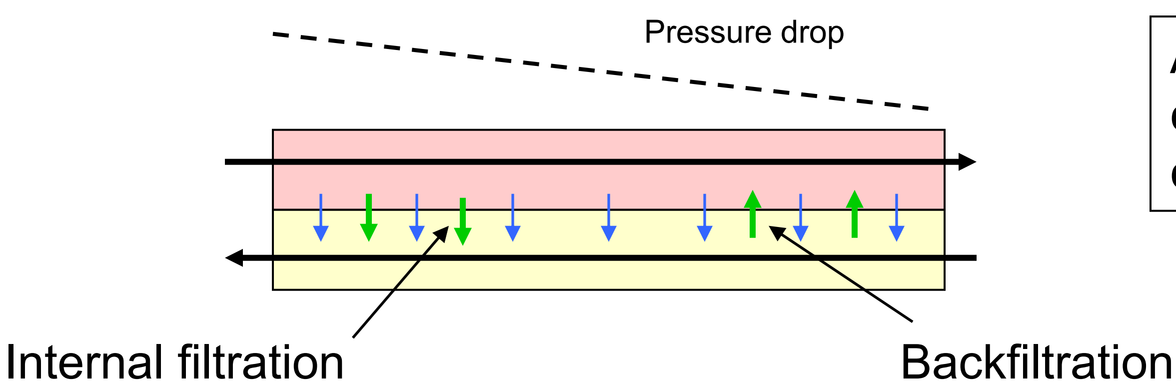
Solute clearance during dialysis

Historical assumption:



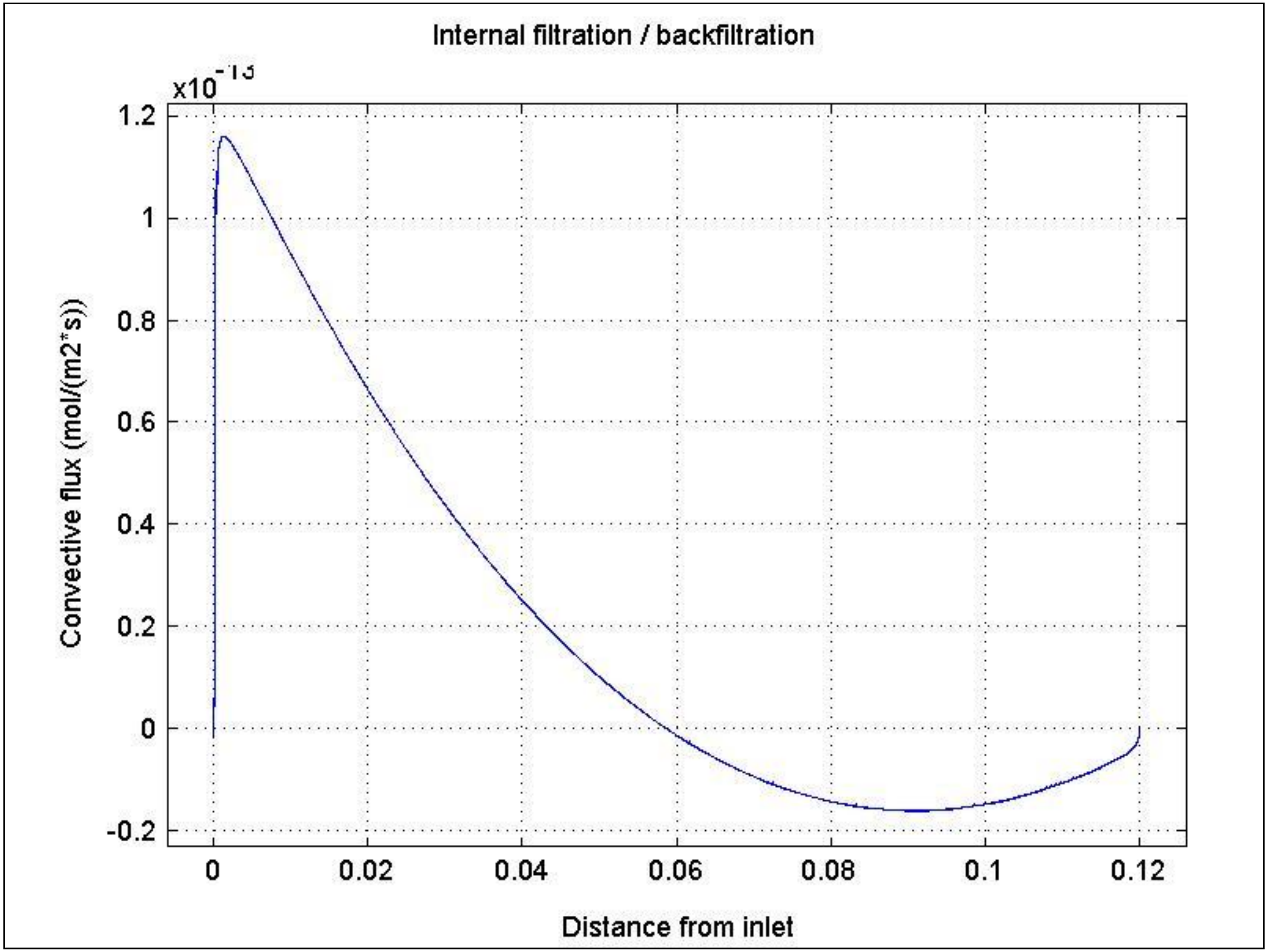
V_{dia}in = Vdiaout → zero net ultrafiltration → diffusive clearance only

Recent recognition:

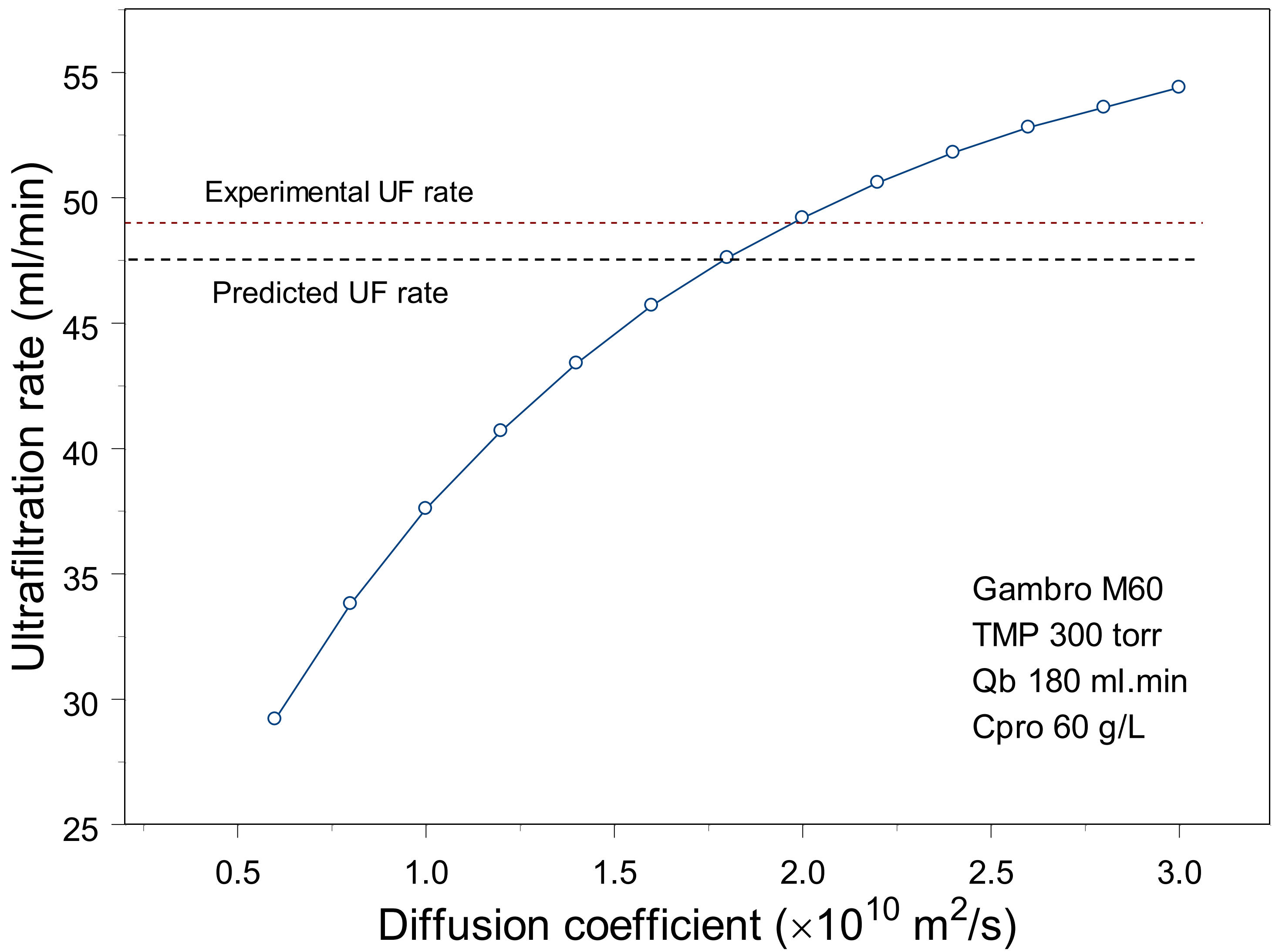


Additional convective clearance

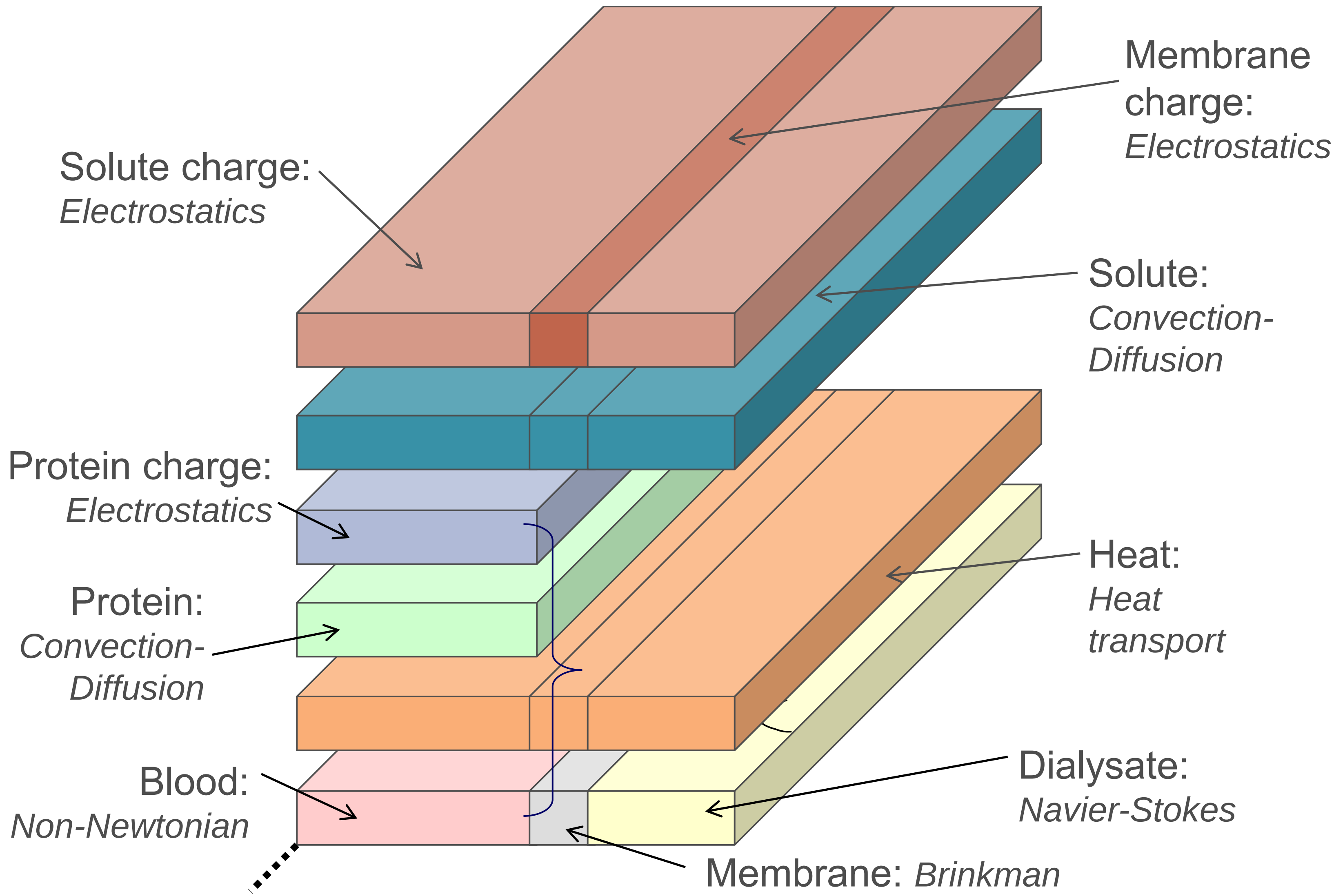
Internal filtration / backfiltration



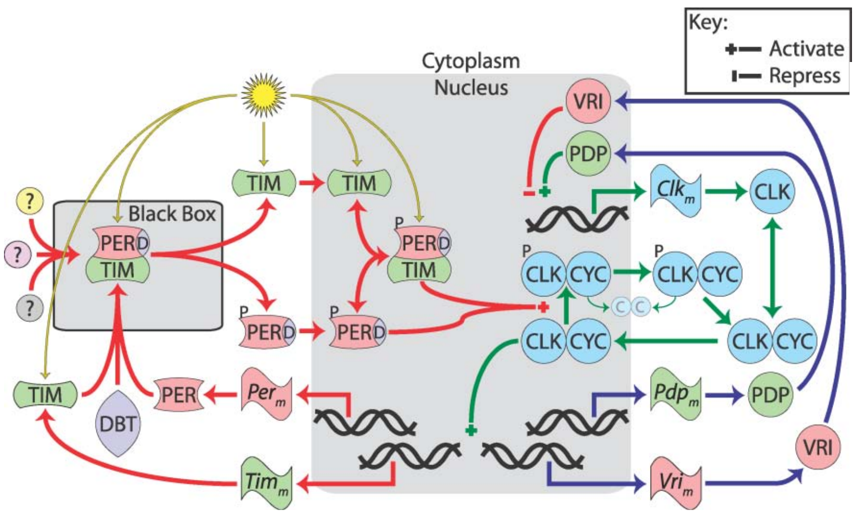
Sensitivity of fluid flux to the protein diffusion coefficient



Expanding the application modes



Modeling the circadian rhythm – existing ordinary differential equation models



$$\frac{d[PER_c]}{dt} = -k_{PTc} \cdot [PER_c] \cdot [TIM_c] \quad (1)$$

$$\frac{d[TIM_c]}{dt} = k_{MA} \cdot [PER \cdot TIM_c] - k_{PTc} \cdot [PER_c] \cdot [TIM_c] - N_T \cdot [TIM_c] + C_T \cdot [TIM_n] \quad (2)$$

$$\frac{d[PER \cdot TIM_c]}{dt} = k_{PTc} \cdot [PER_c] \cdot [TIM_c] - k_{MA} \cdot [PER \cdot TIM_c] \quad (3)$$

$$\frac{d[PER \cdot P_c]}{dt} = k_{MA} \cdot [PER \cdot TIM_c] - N_P \cdot [PER \cdot P_c] + C_P \cdot [PER \cdot P_n] \quad (4)$$

$$\frac{d[PER \cdot P_n]}{dt} = N_P \cdot [PER \cdot P_c] - C_P \cdot [PER \cdot P_n] - k_{PTn} \cdot [PER \cdot P_n] \cdot [TIM_n] + k_{dPTn} \cdot [PER \cdot TIM_n] \quad (5)$$

$$\frac{d[TIM_n]}{dt} = N_T \cdot [TIM_c] - C_T \cdot [TIM_n] - k_{PTn} \cdot [PER \cdot P_n] \cdot [TIM_n] + k_{dPTn} \cdot [PER \cdot TIM_n] \quad (6)$$

$$\frac{d[PER \cdot TIM_n]}{dt} = k_{PTn} \cdot [PER \cdot P_n] \cdot [TIM_n] - k_{dPTn} \cdot [PER \cdot TIM_n] \quad (7)$$

- Cell shape
- Cytoplasmic streaming
- Intracellular organelles
- DNA binding kinetics

- Momentum transport
- Diffusive transport
- Convective transport
- Chemical reactions

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In closing

- Multiphysics modeling has not been widely exploited in medicine and biology
- Most modeling to date has been in the application of technology to medical treatments, such as artificial organs and tissue heating
- Little multiphysics finite element analysis has been applied to study of underlying physiological and cellular processes