Transport of Macromolecules through Glomerular Capillary Wall

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ABSTRACT

The main function of human kidneys is to filter blood and remove metabolic waste while retaining the normal blood composition and volume. The first step of this process is blood filtration through the glomerular capillary wall, which consists of multiple layers: endothelium cell layer, the glomerular basement membrane (GBM) and the epithelial foot processes with their interconnecting slit diaphragm. A hydrodynamic model is introduced to describe hindered transport of electrically neutral macromolecules through the slit diaphragm and the glomerular basement membrane (GBM). The glomerular basement membrane is modeled as an isotropic fibrous medium, whereas the epithelial slit is modeled as a row of parallel cylindrical fibers, and the dimensionless flow resistance is calculated using finite element method. The non-uniform cylinder spacing is assumed to follow the gamma distribution. The mean value of the spacing and its standard deviation are calculated from the experimentally obtained hydraulic permeability using the Newton- Raphson's method. The averaged sieving coefficient is calculated by using those distribution functions and is compared with the total sieving coefficient of ficoll from experiments.

Keywords: Renal Transport, Diffusion, Convection, Glomerular Capillary Wall

INTRODUCTION

It is generally believed that the first stage of renal blood filtration occurs at the glomerular capillary wall in the glomerulus (Fig. 1): a capillary wall with its own unique nanostructure. Excess fluid, proteins and metabolic waste are transported from blood stream in the capillary lumen through the three layers into the primary urine in Bowman's capsule. Abnormalities in glomerular capillary wall cause renal diseases. It is desired to relate measurable quantities such as sieving coefficient to structure of each layer.

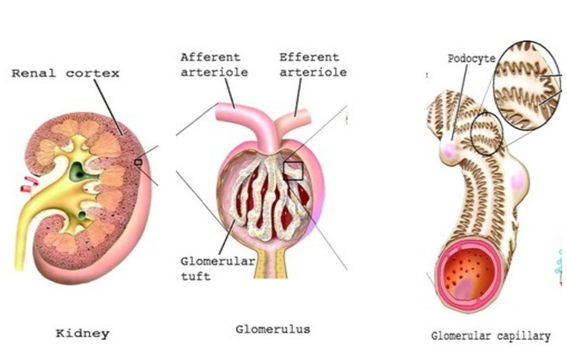


Fig. 1 Schematic drawing of a kidney, a glomuerulus and a glomerular capillary [1]

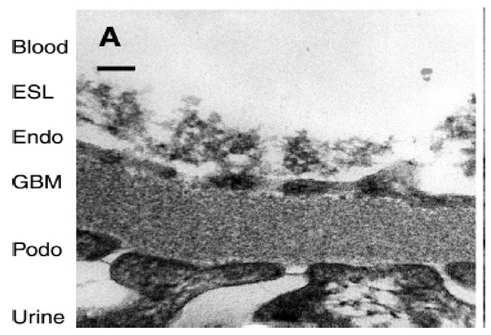


Fig. 2 Structure of glomerular capillary wall from electron microscopy [1]. The scale bar is 100 nm

OVERALL SIEVING COEFFICIENT

The sieving coefficient is the ratio between the downstream and upstream solute concentration (the concentration in blood stream and that in the primary urine). This project focuses on transport of uncharged rigid spherical solutes such as ficolls.

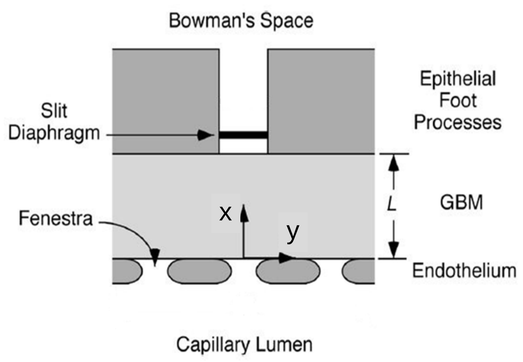


Fig. 3 Idealized structural unit of glomerular capillary wall [2]. The unit width ≈ 360 nm, and the GBM thickness (L) ≈ 200 – 400 nm.

Because the endothelial fenestrate openings (diameter ≈ 60 nm) are large compared to the size of ficolls, it does not contribute to the restriction of ficolls. The overall sieving coefficient is simply the product of the sieving coefficient through the GBM and the epithelial slit.

$$\theta = \frac{C_{Urine}}{C_{Blood}} = \theta_{en}\theta_{bm}\theta_{SD} \approx \theta_{bm}\theta_{SD} \qquad (1)$$

($\theta_{en} \approx 1$)

MODEL FOR GBM

GBM is a hydrogel with 90% in volume fraction being water and 10% being cross-linked fibers consisting of type IV collagen ($r_f = 3.5\,\text{nm}$) and GAG ($r_f = 0.5\,\text{nm}$) . It is modeled as an isotropic fibrous medium; the solute concentration is governed by

$$K_d D_\infty \frac{d^2C}{dx^2} - K_c V \frac{dC}{dx} = 0 \qquad (2)$$

where K_d and K_c are the diffusive and convective hindrance factors in the GBM.

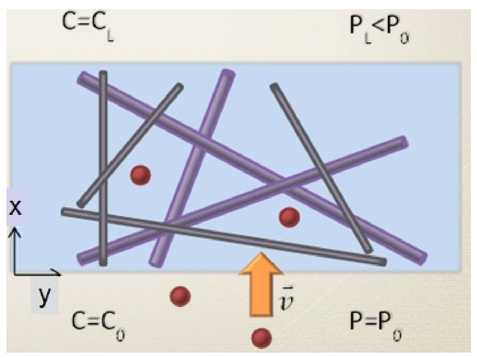


Fig. 4 Schematic drawing of solutes being transported through GBM.

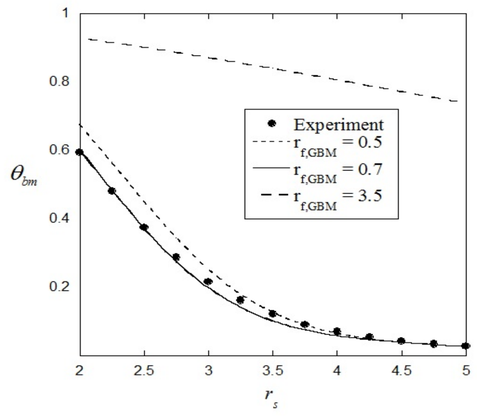


Fig. 5 Sieving coeff. across GBM as a function of solute radii. Also shown is experimental data from ultrafiltration through isolated GBM[4].

MATHEMATICAL MODEL FOR EPITHELIAL SLIT

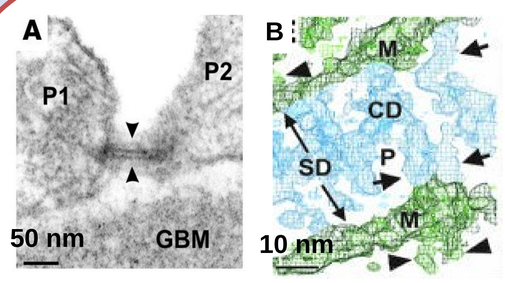


Fig. 6 Structure of epithelial cell layer from electron microscopy [3].

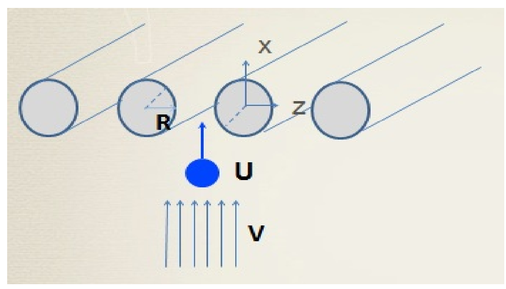


Fig. 7 Schematics of a spherical particle moving through a row of parallel cylindrical fibers.

The constitutive equation for the solute flux is derived in the same approach as that used by Einstein in describing the Brownian motion. Neglecting the fluctuation of solute velocity (**U**), the effective body force(chemical potential gradient per molecule) is balanced by a hydrodynamic force:

$$-kT\ln\nabla C - 6\pi\mu r_s(\mathbf{f}\cdot\mathbf{U} - \mathbf{g}\cdot\mathbf{V}) = 0 \qquad (3)$$

where **f** and **g** are second order tensors containing force coefficients of a translating sphere and flow past a stationary sphere. For instance, f_{ij} is a hydrodynamic force in the i-direction on a sphere moving in the j-direction. The solute concentration and the sieving coefficient through the slit diaphragm are calculated by solving the pseudo-steady convection-diffusion equation:

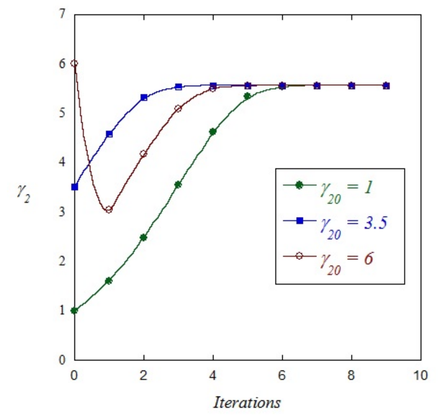
$$\nabla\cdot\mathbf{N} = \nabla^*\cdot\left[-\mathbf{d}\cdot\left(\nabla^* C + Pe\,\mathbf{g}\cdot\mathbf{V}^* C\right)\right] = 0 \qquad (4)$$

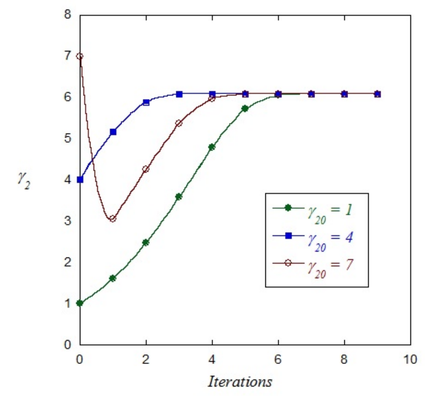
where $\nabla^* = R\nabla$ and $\mathbf{V}^* = \mathbf{V}/V$: V = unperturbed fluid velocity upstream, $Pe = VR/D_\infty$

FIBER SPACING DISTRIBUTION

The non-uniform cylinder spacing is assumed to follow the gamma distribution. The mean value of the spacing and its standard deviation are calculated from the experimentally obtained hydraulic permeability using Newton – Raphson's method.

$$g(u) = \frac{\gamma_2 u^{\gamma_1 - 1}\exp(-\gamma_2 u)}{\Gamma(\gamma_1)} \qquad (5)$$





Figs. 8 and 9 : γ_2 calculated as a function of number of iterations from hydraulic permeability of Wistar rat and human glomerular capillary wall, respectively.

RESULTS

Calculated total sieving coefficients are compared with experimental data from cooled isolated perfused kidney of Wistar rats and urinalysis result in humans [1].

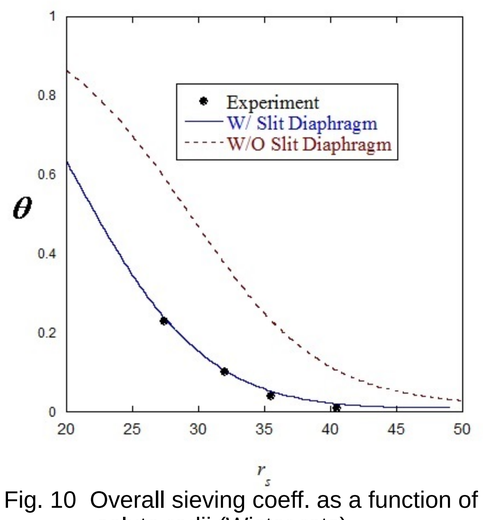


Fig. 10 Overall sieving coeff. as a function of solute radii (Wistar rats).

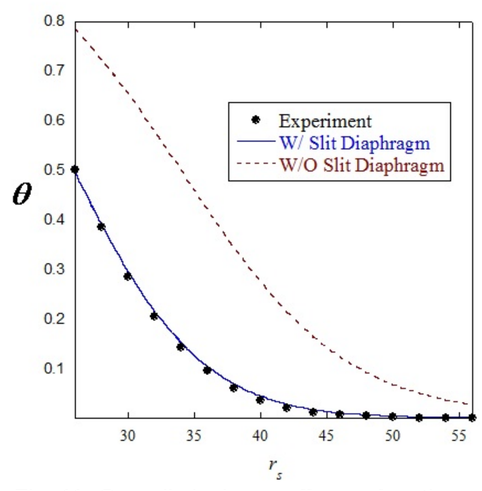


Fig. 11 Overall sieving coeff. as a function of solute radii (humans).

CONCLUSION

The layer in glomerular capillary wall that plays the most crucial role in restricting transport of ficolls is the slit diaphragm, although the significance of the absence of slit diaphragm varies from 40% (in rats) and 60% (in humans) for small molecules to two and three order of magnitudes differences for larger molecules.

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