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Comparative modeling of combined transport of water and graded-size molecules across the glomerular capillary wall

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HIGHLIGHTS

- Size-selective function of the GCW was described mathematically using three models.
- Fiber Matrix theory, an Extended Fiber Matrix theory, and an Alternative Statistical Physics analysis.
- MWF rat strain develops albuminuria identified by a major quantitative trait locus (QTL) on chromosome (RNO)8.
- The GBM was represented as a homogeneous 3D network of uniform length, radius, total fractional solid volume of fibers and characteristic Darcy permeability.
- We believe that their best-fit numerical values may signify new insights for the diagnosis of human nephropathies.

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ABSTRACT

Chronic kidney disease is a common and growing problem worldwide that necessitates recognition of individual risk and appropriate laboratory testing before its progression to end-stage renal failure, requiring dialysis or transplantation for survival. Clearance studies using various graded-size probe molecules established that the passage of molecules/proteins across the glomerular capillary barrier of mammalian kidneys is increasingly restricted as their size increase. Few mathematical models were developed to describe the dynamics of the size-selective functions of macromolecules across membranes and gelatins. In the present study, we compare the behavior of three mathematical descriptions for the Fiber Matrix theory, an Extended Fiber Matrix theory, and an Alternative Statistical Physics analysis to describe the size-selective function of the glomerular capillary barrier; using mainly its hemodynamic, morphometric and hydrodynamic variables; in two experimental rat models. The glomerular basement membrane was represented as a homogeneous three-dimensional network of fibers of uniform length (L_f), radius (R_f), total fractional solid volume of fibers (V_f) and characteristic Darcy permeability. The models were appropriate for simulating *in vivo* fractional clearance data of neutral Dextran and Ficoll macromolecules from two experimental rat models. We believe that the L_f, R_f and V_f best-fit numerical values may signify new insights for the diagnosis of human nephropathies.

1. Introduction

Chronic kidney disease (CKD) is a growing public health problem worldwide and its identification requires recognition of individual risk and appropriate laboratory testing (serum creatinine and/or urinary protein) (Mohamed and Khalil, 2008; Khalil et al., 2013). Earlier-stage CKD can lead to several complications, such as anemia and bone mineral metabolism disorders, and poor outcomes, including cardiovascular events, morbidity, and mortality (Khalil et al., 2013; Fassi et al., 1998), in addition to progression to end-stage renal disease, requiring dialysis or transplant for survival. The complex function of the human kidney and the intricate permselectivity of the glomerular capillary wall (GCW), which is pivotal for the electrolyte and fluid balance in the body, have fascinated researchers for decades (Fassi et al., 1998; Lubbad et al., 2015; Haraldsson et al., 2008; Johnson and Deen, 1996; Mohamed and De Lorenzo, 2002). The GCW is by far the most complex biological membrane, with properties that allow for high filtration rates of water, non-restricted passage of small and middle-sized molecules, and almost total restriction of serum

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albumin and larger proteins (Haraldsson et al., 2008). This means that the passage of molecules across the GCW is increasingly restricted as a function of their molecular size, shape, deformability, and charge (Lubbad et al., 2015; Haraldsson et al., 2008; Johnson and Deen, 1996; Mohamed and De Lorenzo, 2002).

Considerable attention has been paid to the glomerular basement membrane (GBM), which is built up by a network of mainly collagen, laminin, nidogen, and proteoglycans. We previously developed a mathematical model (Mohamed and De Lorenzo, 2002), based on the Fiber Matrix theory, to describe the dynamics of combined transport of water and graded-size molecules across the GCW, using mainly its hemodynamic and morphometric characteristics. In the present study, we further analyze the size-selective function of the GCW by comparing the original Fiber Matrix (FM) theory (Mohamed and De Lorenzo, 2002; Ogston, 1958) to an extended Fiber Matrix (EFM) theory (Adamson, 1992) and to an Alternative Statistical Physics (ASP) analysis (Schnitzer, 1988); by fitting fractional clearances of neutral test macromolecules of varying sizes in two classical experimental rat models, subjected to micropuncture and morphological analysis in health and disease (Remuzzi et al., 1990; Oliver et al., 1992).

2. Methods

2.1. Model assumptions

A comparative analysis of steric partition and diffusive transport of neutral test macromolecules across the GCW is introduced, taking into account the spatial geometry of our previously developed Fiber Matrix model (Mohamed and De Lorenzo, 2002). The three-dimensional (3D) network of irregular, poorly outlined fibers observed at high magnification has been found to be the characteristic structure of basement membranes (Inoue and Leblond, 1988). A considerable attention has been paid to the GBM, which is built up by a 3D network of mainly collagen, laminin, nidogen, and proteoglycans. Based on these observations and as we detailed earlier (Mohamed and De Lorenzo, 2002), the model's unit element was defined as a collagen type IV tetramer that is, four collagen molecules connected at their 7S domain (Fig. 1A). This unit element forms a scaffold onto which other protein molecules can be integrated to form an ideal symmetric unit element of equivalent uniform fiber radius (R_f) and length per unit volume (L_f) (Fig. 1B). Fig. 2 is a top view of a 3D section of an ideal GBM fibrous network produced by the simple repetition of the unit element along Cartesian coordinates (x, y and z).

Subsequently, a comparative mathematical formulation of the problem on the basis of the original FM theory (Ogston, 1958), an EFM theory (Adamson, 1992) and an ASP analysis (Schnitzer, 1988) were introduced to describe the dynamics of combined transport of water and neutral test macromolecules across the GCW. These modified formulae of the steric partition and diffusive transport of water and macromolecules were implemented in our Fiber Matrix model (Mohamed and De Lorenzo, 2002), which was then solved analytically and numerically. Computer programming of the whole set of equations was designed and a non-linear least square fitting of mathematical algorithms to experimental fractional clearance data of permeating neutral Dextran in the MWF (Remuzzi et al., 1990) and Ficoll macromolecules in the MW (Oliver et al., 1992) rat strains was carried out.

We previously considered the GBM to be a continuous homogenous network, which is entirely available for filtration (Mohamed and De Lorenzo, 2002) and uniform in density; thus the number of fibers per unit volume (N_{fv}) is constant throughout the network. Since the system of fibrous unit elements is isotropic, for any element of volume, fiber orientation is defined by the angle between the fiber and a given line. The size of spaces is defined by randomly choosing a point of origin in the network and expanding a spherical surface from this point until it makes tangential contact with the nearest point between the joint ends of the arm of a fibrous unit element (Ogston, 1958). Permeation and diffusion of spherical solute molecules across the GBM network depend on their radius (R_s) as well as on the radius (R_f) and length (L_f) of fibers.

2.2. Mathematical formulation

2.2.1. Fiber Matrix theory (Ogston, 1958)

As we detailed earlier (Mohamed and De Lorenzo, 2002), we proposed a symmetric fibrous unit element to provide a simple geometrical means to determine fiber density (N_{fv}) in the network. At any arbitrary point in the network, the fibrous unit element is contained in an imaginary right hexagonal prism and N_{fv} can be calculated by the formula:

$$N_{fv} = 8/\left[3\sqrt{3}L_f^3(\mathrm{Cos}\ 19.5)^2(1+\ \mathrm{Sin}\ 19.5)\right] \qquad (\mathrm{cm}^{-3}) \qquad (1)$$

Moreover, the ideal GBM was based on ideal unit elements of the same R_f and L_f, where the total fractional solid volume (V_f) of the matrix of cylindrical fibers can be given by:

$$V_f = \pi R_f^2 N_{fv} L_f - CF \qquad (2)$$

where $CF = 2/3\pi N_{fv} R_f^3$ is a correction factor for the joined fibrous unit elements.

On the basis of the pre-mentioned assumptions, we derived a form for the probability distribution of spaces of size R_f in an isotropic network of joined fibrous unit elements shown in Fig. 2. The number of fibers with orientation angle Ψ, which lay at tangential distance between R_f and R_f+dR_f from a point of origin in the network is given by:

$$(dN_t)_{R_f,\Psi} = 4\pi N_{fv} R_f^2 dR_f d\Psi / \mathrm{Sin}^2\Psi \qquad (3)$$

We integrated Eq. (3) in the interval between $Cot^{-1}L_f/2R_f$ and $\pi/2$ and expressed the total number of tangential contacts in terms of unit increase in surface area of the sphere as it expands within the network of fibers to obtain the total number of fibers at tangential distance between R_f and R_f+dR_f from the origin, which is given by:

$$dN_t/dS = N_{fv} L_f/4 \qquad (4)$$

According to the original work by Ogston (1958), the size of spaces within the fibrous network is defined by taking an arbitrary origin and expanding a spherical space around it until it reaches the nearest fiber. The probability (δP) that the spherical space lies between R_f and R_f+dR_f is the combined probability that no tangential contact occurs within R_f of the origin ($1-dN_t$) and at least one tangential contact (dN_t) occurs between R_f and R_f+dR_f is given by the binomial distribution:

$$\delta P = n!/(n-1)!(dN_t/dS\delta S)(1-dN_t/dS\delta S)^{n-1} \qquad (5)$$

This is based on the assumption that changes in surface area as R_f expands from the point of origin to R_f are divided into equal increments (δS). In the limit of very large numbers n, Eq. (5) reduces to a Poisson distribution, which represents the probability distribution of spaces of size R_f in a 3D network of joined fibrous unit elements, neglecting the contribution of end-on contacts, since all unit element arm ends are connected to each other, given by the formula:

$$dP/dR_f = 2\pi R_f N_{fv} L_f \mathrm{Exp}\left(-\pi R_f^2 N_{fv} L_f\right) \qquad (6)$$

This is the same as the formula derived on the basis of neglecting the contribution of end-on contacts, when the fiber